2015 ASCO ANNUAL MEETING PROCEEDINGS

Special Award Lecture Abstracts .............................................................. 1s

Plenary Session
(Abstracts LBA1 – LBA4) ........................................................................ 3s

Pathways Clinical Science Symposia
(Abstracts LBA100 - LBA109) ............................................................... 5s

Global Oncology Symposium
(Abstract 200) ..................................................................................... 8s

Breast Cancer—HER2/ER
Scheduled presentations (Abstracts 500 – TPS642) ................................ 9s

Breast Cancer—Triple-Negative/Cytotoxics/Local Therapy
Scheduled presentations (Abstracts 1000 – TPS1113) ............................ 45s

Cancer Prevention, Genetics, and Epidemiology
Scheduled presentations (Abstracts 1500 – 1592) ................................... 73s

Central Nervous System Tumors
Scheduled presentations (Abstracts 2000 – TPS2081) .............................. 96s

Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
Scheduled presentations (Abstracts 2500 – TPS2624) .............................. 117s

Developmental Therapeutics—Immunotherapy
Scheduled presentations (Abstracts 3000 - TPS306) ............................... 148s

continued on following page
Gastrointestinal (Colorectal) Cancer
Scheduled presentations (Abstracts 3500 – TPS3635) ............................................................... 175s

Gastrointestinal (Noncolorectal) Cancer
Scheduled presentations (Abstracts 4000 – TPS4153) ............................................................. 209s

Genitourinary (Nonprostate) Cancer
Scheduled presentations (Abstracts 4500 – 4586) ................................................................. 247s

Genitourinary (Prostate) Cancer
Scheduled presentations (Abstracts 5000 – TPS5084) .............................................................. 269s

Gynecologic Cancer
Scheduled presentations (Abstracts LBA5500 – TPS5619) ......................................................... 290s

Head and Neck Cancer
Scheduled presentations (Abstracts 6000 – TPS6088) .............................................................. 320s

Health Services Research and Quality of Care
Scheduled presentations (Abstracts 6500 – TPS6625) ............................................................... 342s

Leukemia, Myelodysplasia, and Transplantation
Scheduled presentations (Abstracts 7000 – TPS7103) ............................................................... 374s

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
Scheduled presentations (Abstracts 7500 – TPS7586) ............................................................... 400s

Lung Cancer—Non-Small Cell Metastatic
Scheduled presentations (Abstracts 8000 – TPS8111) .............................................................. 422s

Lymphoma and Plasma Cell Disorders
Scheduled presentations (Abstracts 8500 – TPS8614) .............................................................. 450s

Melanoma/Skin Cancers
Scheduled presentations (Abstracts 9000 – TPS9094) .............................................................. 479s

Patient and Survivor Care
Scheduled presentations (Abstracts 9500 – TPS9643) .............................................................. 503s

Pediatric Oncology
Scheduled presentations (Abstracts 10000 – TPS10083) ............................................................. 539s

Sarcoma
Scheduled presentations (Abstracts 10500 – TPS10578) ............................................................. 560s

Tumor Biology
Scheduled presentations (Abstracts 11000 – 11113) ................................................................. 580s

Author Index ................................................................................................................................... 609s
American Society of Clinical Oncology
51st Annual Meeting

2015 Abstracts

Descriptions of Scientific Sessions

**Plenary Session**
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

**Highlights of the Day Sessions**
Highlights of the Day Sessions invite expert discussants to present key findings, put abstracts into clinical context, and provide an overview of the previous day’s Oral Abstract Sessions.

**Oral Abstract Sessions**
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

**Clinical Science Symposia**
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with the presentation of abstracts. Experts in the field serve as discussants to place studies in the appropriate context and critically discuss the conclusions in terms of their applicability to clinical practice. New this year, three special Clinical Science Symposia will be designated around specific pathways that cut across cancer types.

**Poster Discussion Sessions**
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating as panel members. These sessions will be followed by networking with the discussants and authors.

**Poster Sessions**
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track’s Poster Session.

**Publication-Only Abstracts**
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but not to be presented at the Meeting.

All presented and publication-only abstracts are citable to this Journal of Clinical Oncology supplement. For citation examples, please see the Letter from the Editor.

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2015 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

Dates and times are subject to change.
All modifications will be posted on am.asco.org.

The deadline for abstract submission for the 2016 Annual Meeting is Tuesday, February 2, 2016, at 11:59 PM (EST).
Letter from the Editor

The 2015 ASCO Annual Meeting Proceedings Part I (a supplement to the Journal of Clinical Oncology) is an enduring record of the more than 2,800 abstracts selected by the ASCO Scientific Program Committee for presentation at the 51st ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of Journal of Clinical Oncology at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. After the Annual Meeting, abstracts can be accessed online through ASCO University’s Meeting Library (meetinglibrary.asco.org/abstracts). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and presenting author only. The full-text versions of these abstracts will be publicly released through ASCO.org during the Annual Meeting. Late-Breaking Abstracts will also be included in the 2015 ASCO Annual Meeting Proceedings Part II, an online supplement to the June 20 issue of Journal of Clinical Oncology on JCO.org. Print versions of these abstracts will be available onsite at the Annual Meeting in the ASCO Daily News.

All abstracts carry Journal of Clinical Oncology citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 33:5s, 2015 (suppl; abstr LBA1)
J Clin Oncol 33, 2015 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, 2015 ASCO Annual Meeting Proceedings
Journal of Clinical Oncology (ISSN 0732–183X) is published 36 times a year, three times monthly, by the American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314. Periodicals postage is paid at Alexandria, VA, and at additional mailing offices.

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ASCO Abstracts Policy

Public Release of Abstracts

The abstracts published in the 2015 ASCO Annual Meeting Proceedings Part I, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 13, 2015. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts (LBAs), which include all Plenary Abstracts, will be publicly released according to the following schedule:

• Late-Breaking Abstracts presented in a press briefing or scientific presentation on Friday, May 29, will be publicly released Friday, May 29, through ASCO.org at 2:00 PM (EDT). These abstracts will also be available in Section D of ASCO Daily News on the day of their scientific presentation.

• Late-Breaking Abstracts presented in a press briefing or scientific presentation on Saturday, May 30, will be publicly released Saturday, May 30, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of ASCO Daily News on the day of their scientific presentation.

• Late-Breaking Abstracts presented in a press briefing or scientific presentation on Sunday, May 31, will be publicly released Sunday, May 31, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of ASCO Daily News on the day of their scientific presentation.

• Late-Breaking Abstracts presented in a press briefing or scientific presentation on Monday, June 1, or Tuesday, June 2, will be publicly released Monday, June 1, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of ASCO Daily News on the day of their scientific presentation.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

Abstract Notice

All abstracts presented at and published in conjunction with the Annual Meeting are included in online supplements to the Journal of Clinical Oncology. The abstracts released on May 13, 2015, are included in the May 20 (Vol. 33, No. 15S) issue (2015 Annual Meeting Proceedings Part I), and the Late-Breaking Abstracts, released on a daily basis during the Meeting, are included in the June 20 (Vol. 33, No. 18S) issue (2015 Annual Meeting Proceedings Part II).

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In compliance with standards established by ASCO’s Policy for Relationships with Companies (Conflict of Interest; J Clin Oncol. 2013;31[16]:2043–2043) and the Accreditation Council for Continuing Medical Information (ACCME), ASCO’s intent is to promote balance, independence, objectivity, and scientific rigor through the disclosure of financial and other interests, and in the identification and management of potential conflicts. According to the ASCO’s Policy for Relationships with Companies, all authors are expected to provide general disclosure information for 11 disclosure categories of relationships with for-profit health care companies.

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Additional Disclosure Questions for First, Last, and Corresponding Authors of Original Research

The first, last, and corresponding authors are required to answer additional questions specific to their abstract. ASCO will not enforce restrictions listed in ASCO's Policy for Relationships with Companies on first, last, and corresponding authors and will reconsider whether to do so after a period of data gathering and analysis that will continue at least through April 22, 2016. Financial relationships of first, last, and corresponding authors are still required to be disclosed and will be managed in accordance with ASCO procedures.
PD-1 pathway blockade: A common denominator for cancer therapy.
Suzanne L. Topalian, MD; Johns Hopkins Kimmel Cancer Center; Johns Hopkins Kimmel Cancer Center, Baltimore, MD

In the current era in oncology emphasizing personalized therapy, PD-1 pathway blockade is distinguished by its "common denominator" approach. The genetic diversity found in most human cancers creates challenges for therapies directed against individual mutations but exposes a panoply of new targets for potential immune recognition. However, immune cells that recognize and are poised to attack cancer cells are held in check at the tumor site by suppressive molecular pathways (so-called “immune checkpoints”). Nearly twenty years ago, laboratory studies revealed that blocking the prototypical immune checkpoint Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) could mediate tumor regression in murine models, leading to the clinical development and approval of anti-CTLA-4 (ipilimumab) for treating patients with advanced melanoma in 2011. More recently, drugs blocking the distinct checkpoints Programmed Death 1 (PD-1) and its major binding partner PD-L1 have shown great promise in treating diverse cancer types. The realization that non-small-cell lung cancer is susceptible to anti-PD-1/PD-L1 immediately broadened the horizon for cancer immunotherapy as a general treatment modality–lung and other common epithelial cancers had not previously responded to various immunotherapies and were thought to be relatively “non-immunogenic.” Durable regressions of advanced treatment-refractory kidney, bladder, ovarian, and head and neck cancers, as well as melanoma and Hodgkin’s lymphoma, following PD-1 pathway blockade have fueled the intensive examination of predictive biomarkers and a growing cohort of unique checkpoint molecules as potential drug targets. These translational research efforts have provided new treatment options and are revo-lutionizing therapeutic algorithms. The complex biology of immune checkpoint pathways still contains many mysteries, and the full activity spectrum of drugs blocking these pathways, used alone or in combination, is unknown. Armed with a new scientific understanding and unprece-dented clinical opportunities, the field of immunotherapy is now standing on the threshold of even greater advances in the war against cancer.

Immune checkpoint blockade in cancer therapy: New insights and opportunities.
James P. Allison, PhD; University of Texas MD Anderson Cancer Center, Houston, TX

The existence of multiple nonredundant inhibitory pathways that limit T cell responses offers novel strategies for mobilizing the immune system to attack cancer cells. The best characterized of these immune checkpoints is CTLA-4, which inhibits CD28 mediated costimulation. Antibodies to CTLA-4 have proven effective against multiple tumor types in both preclinical and clinical studies. Ipilimumab, an antibody to human CTLA-4, showed long term (>4.5 years) survival benefit in about 23% of patients in a randomized, placebo-controlled trial in late stage melanoma. In 2011 it was approved by the FDA for treatment of late stage melanoma and is now a standard of care for that disease. The mechanism(s) of action of anti-CTLA-4 are still being elucidated. CTLA-4 blockade results in an increase in the frequency of CD4 T cells expression ICOS (inducible costimulator) in both tumor tissues and blood. This population contains that vast majority of tumor-specific cells that produce IFNγ and TNFα. Using mouse models, we have shown that the ICOS/ICOSL pathway is critical for optimal antitumor activity of anti-CTLA-4 and that ICOS is a compelling molecule to develop as a target for agonistic targeting of costimulatory checkpoints. PD-1, another checkpoint, works by interfering with T cell antigen receptor signaling, a completely different mechanism that CTLA-4. It has two ligands, PD-L1 and PD-L2, which are both expressed on dendritic cells. However, many tumor cells also express PD-L1. Antibodies to PD-1 and PD-L1 have both shown objective responses against several tumor types in clinical trials with response rates of about 25%. A recent phase II trial of a combination of anti-PD-1 and anti-CTLA-4 in melanoma showed objective responses in about 50% of late stage melanoma patients. Our studies of the mechanisms involved in the antitumor effects and of more effective combinations will be discussed.
Cancer prevention as our first best hope: Action in prevention research and cancer control.

Ernest Hawk, MD, MPH; Division of Cancer Prevention and Population Sciences, University of Texas MD Anderson Cancer Center, Houston, TX

The global context of cancer is rapidly changing as the population ages and progressively adopts unhealthy lifestyles. It is anticipated that low-to middle-income countries will bear the majority of the future cancer burden. Cancer prevention will be critical to address this growing challenge. But in order to do so, concerted efforts are needed on two fronts: (1) discovery: to better understand at a molecular and cellular level what initiates and drives early cancer development to find effective screening tools and interventions that can be administered much earlier in the disease process; and (2) dissemination: to use existing evidence to formulate and implement effective community-oriented programs involving public policy, public education, and clinical preventive services that reduce cancer risks. NCI-designated cancer centers are in a unique position to collaboratively advance prevention research and cancer control, and the Affordable Care Act is providing unprecedented opportunities to reimburse for clinical delivery of evidence-based preventive interventions. In both the clinical and population contexts, the ultimate goal is safe, timely, effective, efficient, patient-centered or culturally-tailored preventive care, sustainable across time and populations. Together, the two complementary approaches of molecular prevention and cancer control offer an optimal approach to cancer - combining adoption and maintenance of healthy lifestyles, evidence-based screening and early detection, with precision treatment of early-stage lesions. Growing evidence supports the importance of such a strategy, demonstrating significant reductions in cancer risk as well as cardiovascular-, cancer-related, and all-cause mortality in those adhering to cancer prevention recommendations. To this end, we must aspire to elevate cancer prevention and control as the first strategy to address cancer, in every regard, everywhere, and by all means - whether through molecular prevention, lifestyle modifications, screening and early detection, or policy and educational initiatives.

B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology

Sunday, May 31, 9:45 AM

Transforming data into activities designed for older cancer patients.

Silvio Monfardini, MD; Istituto Palazzolo, Fondazione Don Gnocchi, Milano, Italy

Clinical oncologists should be well prepared for the inevitable increase of older cancer patients in the next decades. Extensive data have been provided by many studies on the results of treatment for elderly patients in most tumor types and on the special approach needed to evaluate such patients. As a result, the International Society of Geriatric Oncology issued appropriate guidelines. Tools helping to predict treatment-related toxicity have been studied and a specific methodology for clinical trials in the elderly is now available. To acquire these data the interaction between oncologists and geriatricians has been essential. In the United States, ASCO and NCI-NIA nationwide initiatives have been emphasizing dual training and research, whereas in France a centralized universalistic approach aims to the collaboration between geriatricians and oncologists. In some other European nations, several models of care delivery and cooperation have been developed. The integrated approach built up with these national initiatives needs to be reinforced and spread, providing the background for the implementation of new research projects. Main obstacles to take action in the United States and Europe are the geriatricians shortfall and their time constraint due to being engaged with other multiple tasks at their institutions other than overwhelming numbers of older cancer patients. Local health care situations differ, but the best suited modality of cooperation among oncologists, geriatricians, and allied health professionals should always be found. Innovation through interaction with geriatricians should be brought into surgical oncology and even more in radiotherapy. A greater interaction is also necessary to study how to deliver optimal post-treatment care to older cancer survivors. Studies are also needed for frail cancer patients, the majority of whom are located in nursing homes.

Pediatric Oncology Award and Lecture Childhood cancer survivors: A lifetime of risk and responsibility.

Saturday, May 30, 1:15 PM

An autobiography of “we.”

Stephen E. Sallan, MD; Dana-Farber Cancer Institute, Boston, MA

Simultaneously stunning and yet unsurprising, over the past 40 years the collective endeavors of a relatively small community of pediatric investigators have fundamentally impacted the field of childhood cancer. Cure is expected for the vast majority of affected children. Today’s research focuses on currently intractable variants of disease, more precisely targeted therapies, and diminution of the sequelae of curative treatments. With an emphasis on training and mentorship, and in recognition that every successful endeavor represents the intertwined and inseparable contributions of many individuals, this presentation will encompass the common ground and collective attributes of the pediatric oncology community. The community’s commitment to discovery in the context of clinical trials and the importance of the two-way street between clinical investigators and basic science laboratories will be addressed. In essence, the presentation will consider the too often overlooked “sociology” of our community: Who are we? How did we get here? How do we accomplish our work? Where are we going? — An overview of our collective career journeys as one transitions from “I to We to Them.”
ABSTRACTS
American Society of Clinical Oncology
51st Annual Meeting
May 29–June 2, 2015
McCormick Place
Chicago, Illinois

LBA1 Plenary Session, Sun, 1:00 PM-4:00 PM
Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). First Author: Jedd D. Wolchok, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

LBA2 Plenary Session, Sun, 1:00 PM-4:00 PM
Reduction in late mortality among 5-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Gregory T. Armstrong, St. Jude Children’s Research Hospital, Memphis, TN

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
LBA3  Plenary Session, Sun, 1:00 PM-4:00 PM
Elective versus therapeutic neck dissection in the clinically node negative early oral cancer: A randomised control trial (RCT). First Author: Anil D’Cruz, Tata Memorial Hospital, Mumbai, India

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

LBA4  Plenary Session, Sun, 1:00 PM-4:00 PM
NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. First Author: Paul D. Brown, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
PD-1 blockade in tumors with mismatch repair deficiency. First Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.

Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAFV600E mutated BRAF (BRAFm) metastatic colorectal cancer (mCRC). First Author: Chloe Evelyn Atreya, University of California, San Francisco, San Francisco, CA

Background: BRAFV600E mutations occur in 5–10% of mCRC and confer a poor prognosis. Unlike BRAF melanoma, BRAF and MEK inhibitors have minimal activity in BRAFm mCRC. Preclinical data suggest that combined inhibition of the EGFR and MAPK pathways is required to maximally inhibit growth of BRAFm mCRC. This study evaluates the activity of the combination of P with D and/or T in BRAFm mCRC. Methods: Eligible pts with BRAFm mCRC received doublet, D + P or T, or triplet, D + T + P. Results: Doublet (D + P): 20 pts received the full doublet dose (D 150mg twice daily [BID] + P 6mg/kg every 2 weeks [Q2W]). Triplet: 35 pts received D + T + P including 24 pts that received full triplet dose (D 150mg BID + T 2mg once daily [QD] + P 6mg/kg Q2W). No dose-limiting toxicities were observed. As of October 20, 2014, the most common adverse events were dermatitis acr<a href="#" class="reference">n</a>iform (grade [G] 1/2 55%) and fatigue (G 1/2 45%) for D + P, and diarrhoea (G1/2 60%, G3 9%) and dermatitis acr<a href="#" class="reference">n</a>iform (G1/2 47%; G3 9%) for triplet. The confirmed response rate for D + P was 10% and for D + T + P was 26% (Table 1). Treatment with either regimen reduced levels of pERK in on-treatment biopsies relative to pre-dose biopsies (median reduction D + P 23%; D + T + P 54%). Pts are currently being enrolled to T + P. Updated results including progression-free survival and duration of response will be presented. Conclusions: Encouraging clinical activity with acceptable tolerability is seen with the triplet D + T + P in BRAFm mCRC. Clinical trial information: NCT01790018.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A pharmacokinetic (PK) and pharmacodynamic (PD) biomarker-driven phase I study of intermittent, low dose intensity schedules of the dual MEK BRAF inhibitor, RO5126766 (RO) in patients with advanced solid tumors. First Author: Maria Jose de Miguel Luken, Royal Marsden Hospital/Institute of Cancer Research, Sutton, United Kingdom

**Background:** RO5126766 is a novel dual MEK-RAF inhibitor. A previous phase I study explored high dose intensity schedules that were limited by a t_{1/2} of 60 hours and a challenging toxicity profile. We hypothesised that schedules that achieve significant target modulation but a lower dose intensity due to intermittent dosing would lead to clinically effective, or tolerable schedules of RO5126766. **Methods:** The aims of this investigator-initiated study (EudraCT: 2012-001040-22) were to determine the tolerability, PK, PD and preliminary antitumor activity of 2 dosing schedules: orally once daily on Mon-Wed-Fri (MWF) and Mon & Thu (MT). An expansion cohort mandated patients (pts) with K- or N-RAS/B-Raf mutations. Plasma PK and phosphorylated (p)-ERK in peripheral blood mononuclear cells (PBMCs) were analysed. Tumor PD was assessed in pre- and post-treatment tumor biopsies and diffusion-weighted MRI (DWI). **Results:** To date, 29 pts have been treated. MWF schedule: 3.2 mg and 4 mg (n = 7 each) and MT schedule: 4 mg (n = 8) and expansion cohort (n = 7). Dose-limiting toxicities (DLTs) on the MWF schedule were G3 blurred vision (n = 1) at 4 mg, and G3 skin rash and G4 creatine kinase (CK) elevation (CKx) (n = 2) at 3.2 mg. No DLTs were recorded in the MT schedule. Most common toxicities were rash, CK elevation, fatigue, mucositis and diarrhea. PK profile at 4 mg MT showed a C_{max} of 247 ng/mL and an AUC of 3,580 ng/hr/mL, consistent with growth inhibition in xenograft models. Maximal PD inhibition of p-ERK in PBMCs was 83% at 3.2 mg, thus both 3.2 mg and 4 mg were in the pharmacodynamically active range. Based on the tolerability, PK and PD profiles, 4 mg MT was declared the recommended phase II dose (RP2D). At the RP2D, 3/4 (75%) pts with KRAS-mutant tumors (NSCLC, ovarian and endometrial cancers) achieved RECIST confirmed partial responses and DWI showed increased apparent diffusion coefficient (ADC) at 15 days post-dose in these pts. Recruitment to the expansion cohort is ongoing. **Conclusions:** The RP2D of RO5126766 was defined as 4 mg MT, delivered twice a week, MT, and is associated with preliminary promising single agent activity in KRAS mutant tumors. Clinical trial information: 2012-001040-22.

106 Successful implementation of a novel trial model: The Signature program. First Author: Julio Antonio Peguero, Oncology Consultants PA, Houston, TX

**Background:** Here we describe 8 ongoing single agent clinical protocols under Novartis’ “Signature” program involving buparlisib (BKM120, PI3Ki), dovitinib (TKI258, multi-kinase inhibitor), binimetinib (MEK162, MEKi), encorafenib (LGX818, RAFi), ribociclib (LEE011, CDK4i/6i), BGJ398 (FGFRi), ceritinib (LDK378, ALKi) and sonidegib (LDE225; SmO). These are tissue-agnostic, genetic alteration-specific (mutation, amplification, translocation, etc.) protocols using patients (pts) identified via standard-of-care profiling. This brings the “Protocol to the Patient” approach of the Framework initiative and utilizes multi-drug protocols with actionable genetic alterations and who would like access to drugs targeting those alterations. **Methods:** Pts with advanced solid and hematologic cancers and no standard therapeutic options are eligible. Pts are pre-identified with a local test performed in a CLIA laboratory for an actionable genetic alteration. Indications where existing data showed benefit or key studies were planned, were excluded from accrual. The primary objective is to assess clinical benefit (SD or better for ≥16 weeks) for each compound. A novel adaptive statistical design is used to cluster pts of like indications into cohorts for independent analysis for futility (minimum 10 pts) or efficacy (minimum 15 pts). **Results:** Between March 2013 – January 2015, 16 academic and 151 unique community/network sites have dosed 368 pts; buparlisib (142), dovitinib (73), binimetinib (90), encorafenib (9), ribociclib (30), BGJ398 (12), ceritinib (3) and sonidegib (9) with completed cohorts for buparlisib (CRC, ovarian, sarcomas, HNSCC, cervix), dovitinib (CRC, GIST, thyroid cancer and melanoma) and binimetinib (KRR) and the average startup timeline was 5.2 weeks. The most frequent genetic alterations were RAS mutation (68%), PIK3CA mutation (55%), and PTEN loss (41%). Preliminary activity was observed in various tumors; buparlisib (vaginal, HNSCC), dovitinib (ovarian), and binimetinib (AML, ovarian, thyroid). **Conclusions:** This program allows rapid enrollment of molecularly profiled pts with actionable genetic alterations linked to cognate targeted agents. Early signs of clinical activity suggest potential for detection of new indications using a pt-sparing design that could lead to subsequent confirmatory trials.

107 Prospective evaluation of circulating tumor DNA sequencing in pancreato-biliary carcinomas. First Author: Eric Andrew Collisson, UC San Francisco, San Francisco, CA

**Background:** Pancreato-biliary carcinomas (PC) carry a poor prognosis but have not yet benefitted from the revolution in precision oncology, in part because biopsy tissue is often inadequate for molecular characterization. Cell-free DNA (cfDNA) sequencing tests may provide access to genetic testing and monitoring for advanced PC patients. **Methods:** Twenty-five advanced PC patients were enrolled prospectively in a trial to assess the feasibility, accuracy, cost, and utility of cfDNA sequencing that were not detected by biopsy-based NGS tests, and the concordance of the two was determined. cfDNA sequencing in disease monitoring was compared to changes in secreted tumor markers in a subset of patients. **Results:** The NGS-based cfDNA test detected cancer mutations in 21 of 25 (84%) advanced PC patients and provided actionable findings for four patients. Multi-gene sequencing data was available from both blood-based and biopsy-based methods for 17 patients. Over 90% of mutations detected by the biopsy-based genetic tests were detected in cfDNA in these 17 evaluable patients. Four additional mutations were detected by cfDNA sequencing that were not detected in tumor tissue. Tumor biopsy NGS failed for 8 patients, equating to a considerably higher failure rate (32%) than the overall failure rate reported by commercial vendors. Three cfDNA mutations in these patients suggested a new therapeutic option. An activating EGFR-exon19 deletion was observed in cfDNA for one patient, which was later confirmed by a biopsy test and empowered successful treatment with erlotinib. The average diagnostic accuracy of cfDNA sequencing was 97%, with 92% average sensitivity and 100% specificity across the cohort. Changes in cfDNA mutation frequencies correlated with changes in tumor marker measurements (Pearson’s r = 0.7). **Conclusions:** cfDNA sequencing is a clinically practicable alternative to biopsy-based tumor DNA sequencing in PC. cfDNA from most PCs showed high mutational concordance with tissue biopsy, and showed high tumor-burden concordance with tumor markers. cfDNA sequencing should be considered for prospective therapeutic trials in pancreato-biliary carcinomas.
Circulating tumor cells (CTC) and pathological complete response (pCR) as independent prognostic factors in inflammatory breast cancer (IBC) in a pooled analysis of two multicentre phase II trials (BEVERLY 1 & 2) of neoadjuvant chemotherapy combined with bevacizumab. First Author: Jean-Yves Pierga, Institut Curie, Paris, France

Background: We have reported that CTC detection is an independent prognostic factor in 52 primary HER2+ IBC (Pierga, CCR 2014). We present a pooled analysis of two prospective trials including 152 patients (pts). Predictive and prognostic value of Circulating Endothelial Cells (CEC) for response to bevacizumab was also analyzed. Methods: CTC and CEC were detected in 7.5 ml and 4 ml of blood respectively in the neoadjuvant setting in IBC (T4d) pts enrolled in two phase II multicentre trials, evaluating bevacizumab (15mg/kg q3w) in combination with sequential neoadjuvant chemotherapy (CT) of 4 cycles of FEC followed by 4 cycles of docetaxel in HER2 - tumor (BEVERLY 1) or docetaxel, trastuzumab in HER2 + (BEVERLY 2). The CellSearch System, combining EpCAM immunomagnetic selection followed by anti-cytokeratin (A45B/B3) and anti-HER2 staining for CTC and CD146 IMS and CD105 staining for CEC.

Results: From 10/08 to 09/10, 152 pts were included and 137 were evaluable for CTC and CEC. Median follow-up was 43 months. At baseline, 55 pts had ≥ 1 detectable CTC (39%). After 4 cycles of CT, a dramatic drop in CTC to a rate of 9% was observed. pCR rate was 40% and was associated with absence of hormonal receptor and HER2 + status. No correlation was found between CTC and CEC levels or pCR rate. CTC detection at baseline independently predicted 3-year disease-free survival (DFS): (70% vs. 39% for pts with < 1 vs. ≥ 1 CTC/7.5 mL [p < 0.001, HR 2.80 (1.65-4.76)]) and 3-year overall survival (OS) (92% vs 56% HR 4.28 p < 0.001). At multivariate analysis, independent prognostic parameters for DFS were absence of hormonal receptors, no pCR, and CTC detection at baseline. CEC level at baseline or variations during treatment had no prognostic value. Conclusions: This is the largest prospectives trial in non-metastatic IBC evaluating CTC detection. We observed a high CTC detection rate of 39%, with a strong and independent prognostic value for DFS and OS. Combination of pCR after neoadjuvant treatment, with CTC at baseline, isolates a subgroup of IBC with excellent survival. CTC count should be part of IBC stratification in prospective trials. Clinical trial information: NCT00820547.

Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). First Author: Luis Paz-Ares, Hospital Universitario Virgen Del Rocio, Sevilla, Spain

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.
Randomized controlled trial of comparing gastrectomy (Gx) plus chemotherapy (CTX) with CTX alone in advanced gastric cancer (AGC) with a single non-curable factor: JCOG 0705/KGCA01 study (REGATTA).

First Author: Han-Kwang Yang, Department of Surgery, Seoul National University Hospital, Seoul, South Korea

Background: The prognosis of AGC with non-curable factors is poor. Chemotherapy is the standard-of-care for those patients. However, literatures suggest that Gx may improve patients' survival. Based on these, we conducted an international randomized trial to test the role of Gx in AGC with a single non-curable factor. This trial was performed in Japan, Korea, and Singapore.

Methods: Eligibility criteria included histologically proven gastric adenocarcinoma, cT1-3, presence of a single non-curable factor confined to either liver (H1), peritoneum (P1), or para-aortic lymph node (16a1/b2) confirmed by both CT scan and laparoscopy/laparotomy, no other distant metastasis, aged 20-75, and PS 0-1. Eligible patients were randomized to Gx followed by CTX or CTX alone. Gx with D1 lymph node dissection was recommended without resection of metastatic lesions. CTX regimen was S-1 80 mg/m2/day on days 1-21 plus CDDP 60 mg/m2 on day 8 repeated every 5 weeks. The primary endpoint was overall survival (OS). The planned sample size was 165 cases per arm, with one-sided alpha of 5%, and an 80% power detecting a 2y-survival difference of 10% (20% with CTX alone vs. 30% with Gx and CTX).

Results: Between Feb 2008 and Aug 2013, 175 patients (95 in Japan, 80 in Korea) were randomized. 89 pts were randomized to Gx and CTX, and 86 pts were randomized to CTX alone. The first interim analysis was performed in Sep 2013, with 37% (110/294) of the planned events observed, and JCOG DSMC recommended early termination of the trial based on the overall futile effect. In the updated analysis in Dec 2014 with a median follow-up period of 14.5 months, the 2y-OS were 25.1 (95% CI: 16.2 to 34.9) % with Gx followed by CTX and 31.7 (95% CI: 21.7 to 42.2) % with CTX alone (p = 0.68). However, subgroup analyses suggested gastrectomy might be beneficial especially for patients with L lesion or cN2/N3.

Conclusions: In all randomized patients, Gx followed by CTX has no survival benefit over CTX alone for AGC patients with a single non-curable factor. There is a room to re-evaluate the additional gastrectomy confined to the patients in whom distal gastrectomy suffices for tumor resection. Clinical trial information: UMIN000001012.
The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.

**LBA500**

Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Primary results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) versus tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy. First Author: Richard G. Margolese, NRG Oncology/NSABP, and The Jewish General Hospital, McGill University, Montréal, QC, Canada

**LBA502**

Oral Abstract Session, Mon, 8:00 AM-11:00 AM

PALOMA3: A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. First Author: Nicholas C. Turner, Royal Marsden, London & Surrey, United Kingdom

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Adjuvant endocrine therapy compromises bone health in pre- and postmenopausal breast cancer (BC) patients. Treatment-induced osteopenia, osteoporosis, and fractures are frequent side effects particularly of aromatase inhibitors (AI). Anti-resorptive treatments such as bisphosphonates have been shown to prevent and counteract these side effects of endocrine therapy, and to potentially improve survival outcomes in postmenopausal BC patients. The aim of this trial was to investigate the effects of adjuvant anti-RANK-ligand Denosumab in postmenopausal patients with early hormone receptor (+HR) + BC receiving AI treatment.

Patients and Methods: 3,425 postmenopausal patients with HR+ BC receiving AI were recruited in 58 sites into this prospective, randomized, double-blind controlled study. Placebo arms were randomized 1:1 to Denosumab 60mg or placebo q6mo s.c. The primary endpoint was time from randomization to first clinical fracture, secondary endpoints included outcome (DFS, OS) and bone effects (BMD changes, vertebral fractures).

Results: Denosumab significantly delayed the time to first clinical fracture compared to placebo (HR = 0.5, 95% CI 0.39–0.65, p < 0.0001). The observed reduction in fractures between Denosumab and placebo arm (overall 92 vs 176) was similar in prognostic patient subgroups, e.g. in patients with normal bone health at baseline (n = 1,872, HR = 0.44, p < 0.0001) and in patients who started the trial already osteopenic (n = 1,548, HR = 0.57, p = 0.0021). Denosumab also significantly increased BMD of the lumbar spine (9.99%), total hip (7.88%) and femoral neck (6.49%) at 36 months (compared to placebo, all adjusted p-values < 0.0001). There were no differences between the Denosumab and placebo groups with respect to patient incidence adverse events (3666 vs 1334, p = 0.44), or serious adverse events (521 vs 511). Despite early pro-active adjudication of potential ONJs by an independent expert panel, no ONJ case was observed. Conclusion: Adjuvant Denosumab significantly reduces fractures in postmenopausal BC patients receiving AI, and improves bone mineral density. Adjuvant Denosumab can be administered at this schedule with a favorable safety profile. Clinical trial information: NCT00556374.

Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+HR+ phase II trial. First Author: Nadia HArbeck, University of Munich, Otterting, Germany

Background: Evidence suggests differential efficacy of standard neoadjuvant chemotherapy (cNeoadJ) and neoadjuvant hormone therapy (cEndo) in HER2-positive hormone receptor-positive early breast cancer. The Phase II WSG-ADAPT HER2+HR+ trial aims to identify responders to dual targeted therapy, which has not been widely explored.

Methods: 380 patients (pts) receive 12 weeks of neoadjuvant therapy (1366x T-DM1 (3.6 mg/kg q3w) + endocrine therapy (ET) (pre-tamoxifen; postmenopausal: aromatase inhibitor); Arm C (control); c3w trastuzumab + ET. After surgery, pts are to receive 4 EC – 12 paclitaxel weekly (investigators’ discretion) and complete 1y trastuzumab. Trial tests pCR (ypNO) and ypT0/is in Arms A and B compared to control (C). Biomarkers are measured at baseline and after 3 weeks. Results: Pre-planned interim analysis (n = 130) aimed to identify an early-response biomarker (e.g. Ki-67 drop) and to validate trial assumptions. Median age was 49 years; 55% were pre-menopausal; 40% had cT1 tumors, 51% cT2; 68% had cNO; 27% cN1; 75% had G3. Median baseline Ki67 was 30%. In all arms, 95-100% recorded all 4 therapy cycles. 15 SAEs occurred in 12 patients (A: 4; B: 6; C: 2), majority are CTC grades 2 (9) or 3 (4); all completely recovered without sequelae. Overall pCR rate was 30.8%; A: 40.5%, B: 45.8%, C: 6.7%. The difference between either arm A or B vs C was significant (p < 0.001), but not A vs. B. Exploratory analysis suggests benefit of adding ET to T-DM1 in pre-pCR stage (pCR ≤ 10% in T-DM1 single agent vs. 47.6% with ET) but not in postmenopausal pts (pCR: 64.3% vs. 50%). Ki67 quantification in the 3-week biopsy was not possible in 43.1%, mostly due to low tumor cell counts (< 500); of the remaining tumors, 21.6% (16/74) had Ki67 ≤ 1% after first cycle. Final data set is required to substantiate these findings which may also be impacted by the different ET options (Tam vs AI).

Conclusions: The interim analysis demonstrates for the first time clinically meaningful pCR rates (> 40%) after only 12 weeks of T-DM1 ± ET without systemic chemotherapy in HER2+HR+ BC. Ongoing biomarker analyses include PI3K mutations and intrinsic sub-types. In 12/015, registration phase was completed at 449 pts. Clinical trial information: NCT01745965.

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Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Correlation of PIK3CA mutation with pathological complete response in primary HER2-positive breast cancer: Combined analysis of 967 patients from three prospective clinical trials. First Author: Sybilie Loibl, German Breast Group, Neu-Isenburg, Germany

Background: The predictive value of PIK3CA mutations in HER2+ BC has been shown conclusively. Data on subgroup analyses are lacking. Methods: We combined data from three studies evaluating PIK3CA mutations as predictor for pCR: the neoadjuvant GEPAR studies (n = 504) (Loibl et al. JCO 2014), the Neo-ALTTO study (n = 355) (Majewski et al. JCO 2015) and the CHERLOB study (n = 108) (ESMO 2014). Patients received either trastuzumab (T), lapatinib (L) or the combination T/L in addition to taxane-based chemotherapy. PIK3CA was genotypically detected in tumor biopsies prior to therapy. Results: 967 patients were included. Median age was 48 (range 21-80); 11.3% vs 16.9% for L (p = 0.008). Within the HR group the pCR rate was significantly lower in the PIK3CA mutant group (mut) compared to the wild type (wt) group (16.2% vs 29.6%; p < 0.001). There was no difference in pCR rate whether the mutation was in exon 9 (15.7%) or exon 20 (16.4%). Within the HR group the PIK3CA mutant group (mut) had a pCR rate of 5.5% only when the mutant tumor had a pCR rate of 20.3% vs 27.1% for T (p = 0.034). Conclusions: The impact of PIK3CA mutations on pCR rate in HER2+ BC is dependent on the pCR rate of the wild type group.

Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Meta-analysis of breast cancer expression data using published gene signatures to reveal key cellular processes implicated in chemosensitivity and resistance. First Author: Daniel G. Stover, Dana Farber Cancer Inst, Brookline, MA

Background: Although many pathways and cell states are implicated in therapeutic resistance, predicting response to chemotherapy remains a challenge. Methods: We assembled expression data and pathologic complete response (pCR) versus residual disease (RD) status for 1,507 breast cancer samples collected prior to neoadjuvant chemotherapy. For each sample we evaluated 118 published gene signatures including signaling, lineage, cell state, immune, and microenvironmental processes. Results: Among all signatures, the strongest predictors of pCR or RD were proliferation-related. Microarray data from a breast epithelial cell morphology assay demonstrated that five separate proliferation signatures correlated with in vitro proliferation. To assess how proliferation differences contribute to chemosensitivity, we evaluated genes differentially expressed in patients with pCR versus RD (FDR-adjusted p < 0.05, limma) before and after normalizing data for proliferation using two distinct proliferation signatures. Among ER+ breast cancer and ER+ subsets Luminal A and B, > 95% of differentially expressed genes were proliferation-associated, suggesting that proliferation differences account for most of the variation in ER+ chemosensitivity. In comparison, among triple-negative breast cancers (TNBCs) and the basal-like subset, only 72.0% and 35.4% of differentially expressed genes, respectively, were proliferation-associated. For TNBCs, signatures associated with chemotherapy response clustered into five key areas: proliferation, mesenchymal phenotype, TGF-beta signaling/stromal features, cyclin and Src activation, and ER signaling (possibly low-level not detected by IHC). Stratifying 175 TNBCs with zero (NO) or few positive lymph nodes (N1) by high versus low activity of three signatures—proliferation—mesenchymal transformation, epithelial to mesenchymal—was highly predictive of failure to achieve pCR (negative-predictive value 0.965; 95% CI 0.912-0.990). Conclusions: Interrogating multiple signatures in a large expression data set allows insights into key processes associated with chemoresistance and sensitivity in breast cancer.

Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (NEHERA). First Author: Arlene Chan, Breast Cancer Research Centre - WA & Curtin University, Perth, WA, Australia

Background: Neratinib (N) is an irreversible pan-HR tyrosine kinase inhibitor with clinical efficacy in trastuzumab (T)-treated HER2-positive breast cancer. In HER2+ early breast cancer (EBC), a significant proportion of patients (10%) occur with invasive disease despite T-containing adjuvant therapy. Methods: Women with stage 1–3c EBC with the last T dose <2y (later modified to stage 2–3c and >1y, respectively) and clinically confirmed HER2+ status (HER2+IHC 3+, FISH ratio ≥2.0, ≥46% or HER2+ IHC 2+, FISH ratio ≥1.8, ≥14% by central evaluation) were randomized to N 240mg PO once daily or placebo (P) for 12m, stratified by ER/PR, nodal status and T schedule. A global amendment reduced follow-up to 2y from study entry. A current amendment restores the original 5-y follow-up. Efficacy analyses were ITT using a stratified Cox model and log-rank test (1-sided α = 0.025). Results: 2,821 pts were randomized between 07/2009 and 10/2011 (1,409 N; 1,412 P). Median time from last T was 4.3m N vs 4.7m P. Baseline characteristics were balanced between arms. Efficacy results are shown below. Pre-planned subset analyses showed a lower IDFS HR in ER/P+ pts (n = 1,616; HR = 0.51 [0.33–0.77]) and in a centrally confirmed HER2+ cohort (HR = 0.52 [0.34–0.79]). Diarrhea was the most common adverse event (AE) for N pts with 40% G3 (1pt G4). Other individual AEs ≥G3 occurred in < 4% N pts. Ejection fraction decrease ≥g2 was seen in 1.3% N vs 1.1% P pts. Mean relative dose intensity (RDI) was 88% in N vs 98% in P pts. Conclusions: ExteNET demonstrates that 12m of N following standard chemotherapy is associated with improved BCSS, with an HR of 3.58 (95% CI, 1.48–9.58, p = 0.025). Relative dose intensity (RDI) was 88% in N vs 98% in P pts. Mean baseline characteristics were balanced. Efficacy results are shown below. Pre-planned subset analyses showed a lower IDFS HR in ER/P+ pts (n = 1,616; HR = 0.51 [0.33–0.77]) and in a centrally confirmed HER2+ cohort (HR = 0.52 [0.34–0.79]). Diarrhea was the most common adverse event (AE) for N pts with 40% G3 (1pt G4). Other individual AEs ≥G3 occurred in < 4% N pts. Ejection fraction decrease ≥g2 was seen in 1.3% N vs 1.1% P pts. Mean relative dose intensity (RDI) was 88% in N vs 98% in P pts. Conclusions: ExteNET demonstrates that 12m of N following standard chemotherapy is associated with improved BCSS, with an HR of 3.58 (95% CI, 1.48–9.58, p = 0.025).
512 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM
Predictive biomarkers of everolimus efficacy in HER2+ advanced breast cancer: Combined exploratory analysis from BOLERO-1 and BOLERO-3.

**Background:** Two phase 3 trials BOLERO-1 and BOLERO-3 evaluated the addition of everolimus (EVE) to trastuzumab (TRAS) + chemotherapy in HER2+ advanced breast cancer (ABC). In BOL-3, heavily pretreated patients (pts) derived a significant survival benefit from EVE (HR 0.73). BOL-1 (first-line HER2 ABC) did not meet the primary endpoints. This analysis aimed to identify biomarkers predictive of EVE efficacy using data from both trials. Methods: Exons of 282 cancer related genes were analyzed by next generation sequencing (NGS). PIK3CA mutation (HR 0.44 vs 0.67 in pts with PI3K pathway activation (individual trials). In a combined analysis of 2 trials, pts with PIK3CA mutations (HR = 0.69) or low PTEN (HR = 0.61 vs normal PI3K activity HR = 1.2) and broad def (HR = 0.61 vs normal PI3K activity HR = 1.38). A multivariate analysis, interaction between PIK3 hyperactivity and PFS benefit was observed using both narrow def (HR = 0.67 vs normal PI3K activity HR = 1.2) and broad def (HR = 0.61 vs normal PI3K activity HR = 1.38). In a multivariate analysis, interaction between PIK3 status and treatment effect was statistically significant (p = 0.016). Conclusions: This exploratory analysis suggests that pts with hyperactive PI3K signaling pathway derive greater benefit from adding EVE to TRAS + chemotherapy in HER2+ ABC. Clinical trial information: NCT01079520, NCT00087676.

514 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM
Final analysis of a randomized comparison of letrozole (Lett) vs observation (Obs) as late reintroduction of adjuvant endocrine therapy (AET) for postmenopausal women with hormone receptor positive (HR+) breast cancer (BC) after completion of prior AET: ANZBCTG 0501 (LATER). First Author: Nicholas Zdenkowski, Australia and New Zealand Breast Cancer Trials Group, Newcastle, Australia.

**Background:** AET after postmenopausal women with HR+ early BC has until recently been limited to 3 yrs of tamoxifen, an aromatase inhibitor or a sequential combination of these. However, after 5 yrs of AET, BC events continue to occur at a high rate (2% per yr) for at least another 10 yrs. The LATER trial was designed to compare 5 yrs of tamoxifen (TMX) vs a sequential late reintroduction of AET to Obs (usual care) in postmenopausal women after >= 4 yrs of AET. Methods: LATER was a prospective open label randomized trial for postmenopausal women who were BC free and completed >= 4 yrs of AET for HR+ early BC more than 1 yr prior to study entry. The primary outcome was the rate of invasive BC events (defined as new invasive primary, local, regional or distant recurrence or contralateral BC). No AET arm crossover. Secondary outcomes included disease free survival (DFS), overall survival (OS) and toxicity. To reject the null hypothesis in favor of a 60% reduction in the primary outcome with β = 0.10 and 2α = 0.05, 1700 patients were required. In Oct 2014 the independent data and safety monitoring committee recommended to cease trial follow up and to release the data for analysis due to a low event rate. Results: Between May 2007 and March 2012, 360 patients were randomized (181 Let; 179 Obs), after which enrolment ceased due to a low accrual rate. Patients completed prior AET a median of 2.5 yrs before randomisation. N+ 33.9%, N- 66.0%, unknown 6.1%. Prior AET was aromatase inhibitor only in 11.1%, SERM in 50.6% and a sequential combination in 38.3%. In the ITT population, at a median 3.0 yrs follow-up, 1.1% of patients in the Let arm had experienced an invasive BC event vs 8.4% in the Obs arm (difference 7.3%, 95% CI 2.9-11.6, p = 0.001, conditional binomial test). In the observed cohort the event occurred at a median 3.4 yrs (11.7% p = 0.001) and death in 1.7% vs 2.2% (p = 0.70) in the Let and Obs arms respectively. Conclusion: In postmenopausal women who had completed >= 4 yrs of AET for HR+ early BC, late reintroduction of the AET arm reduced the incidence of late invasive BC events. Clinical trial information ACTRN12607000137493. Clinical trial information: 012607000137493.

515 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM
Ovarian function suppression, symptom burden, and quality of life in young women with breast cancer: A prospective study. First Author: Shoshana M. Rosenberg, Dana-Farber Cancer Institute, Boston, MA

**Background:** Recent clinical trial data have demonstrated that ovarian function suppression (OS) in addition to tamoxifen (T) or aromatase inhibitors (AI) can improve survival in young women with HER2+ breast cancer (HER2+ BC). We evaluated the impact of OS on quality of life (QOL) in young women, a population at risk for worse QOL outcomes and survival. Methods: Patient reported symptom and QOL data were collected 1 year after diagnosis (dx) for patients with HER2+ BC treated with an Ovarian Suppression (OS) regimen at Dana-Farber Cancer Institute (DFCI) between 2000-2003 with HR+ and death in 1.7% vs 2.2% (p = 0.001, conditional binomial test). In the observed cohort the event occurred at a median 3.4 yrs (11.7% p = 0.001) and death in 1.7% vs 2.2% (p = 0.70) in the Let and Obs arms respectively. Conclusion: In postmenopausal women who had completed >= 4 yrs of AET for HR+ early BC, late reintroduction of the AET arm reduced the incidence of late invasive BC events. Clinical trial information ACTRN12607000137493. Clinical trial information: 012607000137493.
Tumor PIK3CA genotype and prognosis: A pooled analysis of 4,241 patients (pts) with early-stage breast cancer (BC). First Author: Dimitrios Zaridakas, Breast International Group, Brussels, Belgium

Background: PIK3CA mutations (mt) are frequently observed in BC but their clinical relevance is unclear. We performed an individual pt data pooled-analysis to evaluate the prognostic impact of PIK3CA status on early-stage BC.

Methods: Participating studies were identified by literature search. Associations of PIK3CA status with clinicopathologic characteristics were tested. Cox regression models were applied adjusting for age, tumor size, nodes, grade, ER, and HER2 status, treatment and study. Invasive disease-free survival (IDFS) was the primary endpoint, followed by distant disease-free survival (DDFS), overall and by BC subtypes.

Results: Data from 16 studies were included. Median age was 56yrs (18-96) and median follow-up was 6.5yrs; 1384 pts (33%) received chemotherapy, 1147 (27%) underwent endocrine monotherapy, 816 (19%) both and 894 (21%) none/unknown. PIK3CA mt occurred in 26.9%; 55.2% exon 20 and 36.2% exon 9. They were associated with ER+ tumors, increasing age, lower grade (all p < 0.001) and smaller size (p = 0.04). Incidence of PIK3CA mt was 15%, 23%, 32% in the ER-/HER2-, ER+ and HER2+ subtypes respectively (p < 0.001). In the univariate analysis, PIK3CA mt were associated with better IDFS: HR = 0.85 [95%CI:0.75-0.96]; p = 0.0009. A statistically significant non-proportional prognostic effect was observed (p = 0.02). During the first 5 yrs: PIK3CA mt (HR [95%CI]: 0.80 [0.67-0.96]) compared to after 5 yrs (IDFS HR = 0.93 [0.81-1.08]; Pinteraction:0.03). There was no significant interaction by BC subtype (p = 0.6) and no significant differences by exon 9 or 20 site (p = 0.7). In the multivariate analysis, PIK3CA status did not remain statistically significant overall (p = 0.94) and only the last 3 yrs (p = 0.6) showed a trend and similar for the DDFS endpoint. In further analyses, a significant interaction between PIK3CA status and age was found, remaining after adjustment (P = 0.04). PIK3CA mt in patients ≤ 50yrs (HR = 0.65 [0.40-0.95]) but not >50yrs (HR = 1.10 [0.91-1.34]; Pint = 0.6) could be observed. Conclusions: PIK3CA mt are associated with improved IDFS and may represent a high risk subgroup for PIK3CA. This effect is greatest in young women for whom PIK3CA status could potentially refine treatment decisions.

OncoType DX in BRCA-associated vs. sporadic breast cancers: Differences based on germline mutation status and potential implications for adjuvant systemic therapy (AST). First Author: Payal Deepak Shah, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Biological differences between BRCA-associated and sporadic breast cancer (BC) could warrant different recommendations for AST among patients (pts) with phenotypically similar cancers. Oncotype DX (Genomic Health Inc., CA) is a prognostic, quantitative, reverse phase protein microarray (RPMA) on pts' primary BCs to identify phosphoproteins associated with recurrence and with outcome on L vs L+D. Methods: 48 pts' FFPE primary breast cancers were acceptable for RPMA at a CLIA-certified laboratory (The University of Texas, MD Anderson). Hematoxylin & eosin staining was carried out with 20 antibodies directed against HER pathway proteins, MET, Src, and Pax. Patient t-test or Mann-Whitney U test and Spearman correlation coefficient (ρ) were used to assess biomarker association with PFS < 6 mos vs > 6 mos by treatment arm (unpaired tailed, p value).

Results: Median PFS for the 48 pts was 19.2 mos for L+D (N = 21) vs 9.2 mos for L (N = 27). -90% of the BCs overexpressed HER3, p-mTOR, p-4EBP1, p-JAK2, p-STAT3 and 50% overexpressed p-Pax. Across all pts, protein linkage Pearson correlations (r) showed strong associations between p-Pax & p-HER2 (r = 0.74), HER3 & p-HER2 (r = 0.79), p-HER1 & p-HER2 (r = 0.82), HER5 & p-HER2 (r = 0.70), and Pax & MET (SR = 0.93). Evaluating all 48 pts, PFS < 6 mos was correlated with HER3 expression (ρ = 0.01), HER3 & HER2 (ρ = 0.02), HER2 (ρ = 0.04) and HER1 (ρ = 0.05). Evaluating L vs L+D pts, PFS < 6 mos was associated with HER3 (ρ = 0.01, p = 0.03), p-HER3 (ρ = 0.07), HER1 (ρ = 0.05, p = 0.02), p-HER2 (ρ = 0.05) and p-4EBP1 (ρ = 0.05) expression in L+D pts vs not in L+D pts. PFS < 6 mos with L+D was associated with p-Src (p = 0.9, ρ = 0.04) and p-Pax (p = 0.71, p = 0.11). p-Pax expression was inversely correlated with prolonged PFS in L alone (p = 0.7, p = 0.04) but not in L+D pts. Conclusions: Primary ER+ HER2- BCs that recurred expressed high levels of HER3 and p-4EBP1. AST-induced treatment failure was associated with p-HER2, p-HER1, p-MET, and p-Pax expression and predicted for short PFS in L alone but not with L+D. These findings suggest that dasatinib may inhibit HER3 signaling in ER+ HER2- MBC pts.
Efficacy of the PARP inhibitor (PI) ABT-888 (veliparib [vel]) either with carboplatin (carb) or as a single agent followed by post-progression therapy in combination with carb in patients (pts) with BRCA1- or BRCA2-(BRCA)-associated metastatic breast cancer (MBC). First Author: George Somlo, City of Hope, Duarte, CA

Background: Based on the concept of synthetic lethality combining platinum agents and PIs should benefit patients (pts) with BRCA-associated MBC. We report mature outcomes with vel alone, or with carb (vel/carb) in pts with germline BRCA4-associated MBC, ECOG performance status of ≤ 2, without prior Pt treatment were included. In phase I the maximum tolerated dose (MTD) of carb (AUC of 5) IV every 21 days, and vel 150 mg BID were defined. In phase II, pts received vel 400 mg BID and upon progression, carb and vel at the MTD. Results: Between 6/2010 and 4/2014, 72 evaluable pts (28 in phase I, 44 in phase II) with BRCA1 (34 patients) or BRCA2 (37 patients) mutations (1 pt had both) and with MBC were enrolled. The median age was 44-years (range; 28-68); 49% of pts had hormone receptor + MBC. Pts received a median of 1 (0 – 5) prior chemo-regimen for MBC. Response rate (RR) for the 28 pts in phase I was 50% [CR rate 18%] and 2 pts remain in CR at 43 + and 34+ cycles, both are on vel maintenance, alone; median progression-free survival (PFS) was 8.5 mos (95% CI 7.3-10.1), and median TTF was 8.3 mos (6.9-9.5). For 44 phase II pts treated with vel, the median PFS was 5.2 months (4.0-6.4) and including their cross-overvel/vel treatment the median PFS was 6.7 months (4.6-8.5); 13/44 (30%) responded to vel; 2 pts are still on vel (1 with a PR at 14 cycles, 1 with a CR at 25 cycles); 1 pt converted to PR after cross-over to carb/vel. OS was 18.8 months (95% CI 15.0-26.3) for the 28 pts treated with the combination of carbvel, and 12.6 months (95% CI 11.7-13.8) for the 44 pts treated with vel followed by carb/vel (OS < 0.1). In phase I, dose delay or adjustment was needed in 1/3 of the pts treated at the MTD within the first 3 cycles due to cytopenias. In phase II, 8/44 (18%) required dose adjustment on single agent vel, and 5 pts required dose adjustment after cross-over to carb/vel. Conclusions: The trend for longer TTF with carb/vel combination of vel/carb/vel, combined with the improved time OS suggest that vel/vel followed by vel maintenance deserves further testing in a randomized prospective trial. Clinical trial information: NCT01149083.

A phase Ib study of abemaciclib with therapies for metastatic breast cancer. First Author: Sara M. Tolaney, Dana Farber Cancer Institute, Boston, MA

Background: Abemaciclib, an inhibitor of cyclin-dependent kinases CDK4 and CDK6, demonstrated safety and clinical activity as a single agent for hormone receptor positive (HR) and HR-like tumors, demonstrated safety and clinical activity as a single agent for hormone receptor positive (HR) and HER2-targeted tumors, and in combination with carb in patients (pts) with HR+ and/or HER2- MBC and in Part F had HER2+ MBC. Eligibility included measurable disease or nonmeasurable bone disease by RECIST v1.1. ECOG performance status ≤ 1, no prior chemotherapy for metastatic disease (Parts A-E), and ≥ 1 chemotherapy regimen for metastatic disease (Part F). Abemaciclib was given continuously until progression. Patients were assessed every 28 days in Parts A-E and every 21 days in Part F. Dose escalation cohorts of ≥ 3 pts receiving abemaciclib at 150 mg and 200 mg Q12H were included in Parts E and F. Results: A total of 65 pts started treatment with abemaciclib (200mg Q12H) by 16-Dec-2014 in Parts A-D. Pts had a median age of 57 years (range; 28-77) and a median of 3 prior systemic therapies (range; 1-8) for breast cancer. The most common (≥ 20% overall in Parts A-D) possibly related treatment-emergent adverse events (TEAEs) (all Grades) were constipation (81%), fatigue (79%), nausea (74%), dyspepsia (59%), diarrhea (53%), vomiting (33%), decreased appetite (29%), and anemia (25%). Diarrhea was manageable with antidiarrheal agents or dose reduction. No G4/5 TEAEs occurred. The disease control rate (CR + PR + SD) was 67% (Parts A + B [nonsteroidal aromatase inhibitors (36 pts)] with 2 confirmed PRs and 75% for Part C [tamoxifen (16 pts)]. Safety, PK, and efficacy results will be updated in a forthcoming presentation. Combining abemaciclib with endocrine therapies demonstrate manageable safety and early clinical evidence of antitumor activity. Clinical trial information: NCT02057133.
Adaptively randomized trial of neoadjuvant chemotherapy with or without the Akt inhibitor MK-2206: Graduation results from the I-SPY 2 Trial. 
First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** A key node of growth and survival signaling pathways is the Akt serine/threonine kinase that activates mTOR and downstream effectors. I-SPY 2 is a randomized neoadjuvant trial to test agents and combinations added to standard chemotherapy. Pathological complete response (pCR) defined as absence of invasive cancer in breast and nodes is the primary endpoint. We report efficacy results for allosteric Akt inhibitor MK-2206. Methods: Women with invasive breast cancer ≥2.5 cm on exam or ≥2 cm on imaging were adaptively randomized to 12 weekly pacitaxel (and trastuzumab if HER2+) cycles (control) or in combination with one of several experimental agents followed by doxorubicin/cyclophosphamide x 4. Patients (pts) are stratified to 8 subsets based on hormone-receptor (HR), HER2, and MammaPrint statuses, with combinations of subsets defining agent signatures. MK-2206 135 mg daily by mouth was evaluated in all 8 subsets. Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control. Graduation by signature and futility stopping was based on Bayesian predictive probability of success in a 2-arm, N=300 Phase 3 randomized 1:1 trial with pCR endpoint. Results: MK-2206 graduated in the first 3 signatures in the table. Accrual ended with 93 patients assigned to that arm and when 56 pts had been concurrently randomized to control, Final posterior and predictive probabilities are shown for all 10 signatures. Conclusions: MK-2206 improves pCR rates compared to standard chemotherapy in several breast cancer signatures, defined mostly by HR- and HER2+, sufficiently for evaluation in a Phase 3 neoadjuvant trial powered for event-free survival. Safety data will be presented. Clinical trial information: NCT01042379.

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**Correlation of Breast Cancer Index HOXB13/L117R (H1/H2, ER, PR and HER2) and prediction of relative endocrine benefit from tamoxifen and anastrozole in HR+ breast cancer: A TransATAC study.**
First Author: Yi Zhang, bioTheranostics, San Diego, CA

**Background:** Estrogen receptor (ER) expression is a critical determinant of endocrine response, however additional biomarkers are needed to complete the molecular picture of treatment benefit, response and resistance to better individualize care. Previous studies have demonstrated that H/I expression ratio predicts benefit for ER+ breast cancer patients from tamoxifen in the Stockholm adjuvant trial and from letrozole in the MA.17 extended adjuvant trial. In this correlative study, H/I was compared with ER, PR, and HER2 expression in assessing relative benefit from adjuvant anastrozole (ANA) vs tamoxifen (TAM) in HR+, LN- patients from the prospective randomized ATAC trial. Methods: Tumor samples from 742 HR+, LN- patients treated with 5 y of TAM or ANA were examined. Expression levels for H/I, ER, PR and HER2 were determined by RT-PCR. Cox proportional hazards models assessed the significance of the interaction between treatment and each biomarker as continuous variables, with 10-year risk of distant recurrence estimated within the 2 treatment arms separately. No adjustment for multiple testing was made. The interaction between H/I and treatment was statistically significant (p = 0.024) whereas the interaction for all other biomarkers was non-significant (ER, p = 0.17; PR, p = 0.054; HER2, p = 0.72). Consistent with this finding, the 10-year distant recurrence rate as a function of continuous H/I index indicated that the endocrine benefit with ANA compared to TAM correlated with increasing H/I. H/I expression was not highly correlated with ER, PR or HER2. Conclusions: In this retrospective study, H/I was the only factor that predicted differential benefit of ANA vs TAM in the adjuvant setting. Consistent with previous IHC results in TransATAC, molecular ER, PR, and HER2 Pathway profile was not predictive of relative benefit or risk from tamoxifen or anastrozole. Previous data suggests that H/I may be a useful indicator of absolute or differential endocrine benefit depending on the clinical setting. Data on utility of H/I for prediction of relative benefit require further validation.

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**Molecular profiling of ER weakly-positive breast cancer.**
First Author: Brandon S. Sheffield, University of British Columbia, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands

**Background:** Recent data suggests that differences in locations of metastases could have implications for tumor characteristics and thus for therapy response. Limited knowledge is available in this respect about heterogeneity of the estrogen receptor (ER). 11β-Fluorooestradiol (FES) uptake on positron emission tomography (PET), reflects ER expression. We aimed to analyze FES uptake in tumor lesions at different sites in metastatic breast cancer patients. Methods: Eligible patients: biopsy proven ER positive breast cancer, post-menopausal, metastases outside the liver, no history of another metastatic malignancy, no use of ER antagonists for ≥ weeks prior to FES PET. They had undergone FES PET with 64-slice mCT within the UMCG (Jan 2009 - Sept 2014). We re-analyzed FES PET and CT scans for metastases. A lesion with maximum absolute standardized uptake value (SUVmax) ≥ 1.5 was considered ER positive. Background tracer uptake was measured for normal tissues. CT lesions with diameter ≥ 10 mm were included. Liver lesions were not evaluated on PET given high background signal. Results: In 67 patients, 1,338 lesions were identified by CT (120 patients), PET (913 patients) or both (305 patients) in bone (79%), lymph nodes (15%), lungs (3%) and liver (2%). SUVmax of FES positive lesions varied maximally 10-fold between patients (median 1.61-15.61), and up to 11-fold within individual patients (range 1.8-19.4). Median SUVmax of bone metastases was 15.6 (range 4.17-82.7), for liver metastases was 10.2 (range 4.4-24.3). Conclusions: Weak ER expression by IHC is a poor correlate of both luminal subtype and ER expression in breast cancer. In the setting of highly sensitive and robust IHC methodology, cutoffs for ER status determination and subsequent systemic therapy may need to be revisited.
Breast cancer recurrence in older patients with clinically node-negative T1-T2 tumors managed without sentinel node biopsy (SNB) and without adjuvant radiation therapy. First Author: Marvat Nabil Saleh, Memorial Hospital of Rhode Island, Pawtucket, RI

**Background:** Older patients (pts) with small breast cancers who receive endocrine therapy can omit radiation without a survival disadvantage. SNB adds additional burden and may not be necessary for pts who are not planning adjuvant radiation or chemotherapy. The objective of our study was to evaluate recurrence rate with or without SNB in those pts. **Methods:** We retrositively reviewed records of pts > 60 years (y) old, diagnosed at our center between 2000 and 2014 with T1-T2, clinically node-negative, estrogen receptor-positive breast cancer, who did not receive adjuvant radiation or chemotherapy. We used Fisher’s exact test to compare characteristics, and Gray’s test for cumulative incidence function (CIF) for cancer recurrence, with 95% confidence intervals. **Results:** We identified 364 pts. Those managed without SNB were significantly older, more often with apocrine, mucinous or papillary histology and less likely to undergo mastectomy, with no significant differences in other characteristics. There were 5 recurrences (4 local, 1 axillary) in pts without SNB and 16 (11 local, 2 axillary, 3 distant) with SNB. CIF for recurrence at 5 years was 4.8% (C1, 2.6-8.0) for all pts, 6.6% (C1, 1.7-16.3) without SNB and 4.3% (C1, 2.1-7.8) with SNB, not significantly different (P = 0.80). Positive SNB (in 12%) was not prognostic for recurrence (P = 0.94). CIF for death from competing causes was twice as high in pts without SNB (24.6 vs 11.1%, P = .0001), resulting in lower overall survival (77.5 vs 89.3%). **Conclusions:** Overall recurrence rate was similar to prior clinical trials. Pts selected for management without SNB have a high risk of death from non-cancer causes, which reflects their advanced age and comorbidities, but they experience no significant increase in the risk of recurrence. Our results, confirmed in a larger dataset, suggest that SNB does not provide useful prognostic information in older pts who are not planning multimodality adjuvant therapy, and could be omitted.

<table>
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<th>SNB N</th>
<th>Median age</th>
<th>Low-risk histology</th>
<th>High grade</th>
<th>HER2-positive</th>
<th>LVI</th>
<th>Mastectomy</th>
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<td>82*</td>
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<td>10%</td>
<td>3%</td>
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* P < .001; 1 Lymphovascular invasion

Evaluation of possible linkage between everolimus benefit in estrogen receptor (ER)-positive breast cancer and genomic alterations of the PI3K/AKT/mTOR pathway. First Author: Esther P. Black, University of Kentucky, Lexington, KY

**Background:** Everolimus, which inhibits mTOR, is used to treat metastatic ER-positive breast cancer after aromatase inhibitor failure. Because not all patients benefit and toxicity can be prohibitive, it is critical to identify biomarkers of sensitivity to this treatment strategy. **Methods:** We studied 36 tumors from patients enrolled on protocol NCT00570921 using fulvestrant and everolimus for estrogen receptor-positive breast cancer. There were 9 out of 11 responders (82%) had at least one genomic alteration in individual components of this pathway, while 2 of the nonresponders had more than one alteration in individual components of this pathway, while 2 of the nonresponders had more than one alteration observed (one with a concomitant PIK3CA mutation and AKT3 amplification, and one with a PIK3CA mutation and RICTOR amplification). Other notable alterations include mutations in PTEN, TP53, and RICTOR, and one with a specific association with everolimus benefit. Additional analysis and frequency of other alterations will be presented in greater detail. **Conclusions:** In this small study, we did not identify predictors for lack of benefit from everolimus, although it appears that the presence of multiple alterations in the PI3K/AKT/mTOR pathway may promote de novo resistance. It is possible that genomic alterations alone may not adequately explain breast cancer response to this strategy without functional signaling analysis. Alternatively, it is possible that everolimus benefit in endocrine resistance may be independent of PI3K/mTOR signaling altogether and its mechanism of action is yet to be fully determined.

Efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/ pertuzumab (TCH-P) in non-metastatic HER2+ breast cancer: The Cleveland Clinic experience. First Author: Shruti Rakesh Tiwari, Cleveland Clinic Foundation, Shaker Heights, OH

**Background:** Pertuzumab is FDA approved for use in combination with trastuzumab and chemotherapy as neoadjuvant therapy in women with non-metastatic HER2+ breast cancer. The TRYPHAENA trial reported a pathologic complete response rate (pCR), i.e. ypT0N0, of 52% in 77 patients (pts) treated with neoadjuvant TCH-P. Aside from this study, there is little data on the role of TCH-P in HER2+ breast cancer. There were 168 patients enrolled; 27 are evaluable for study endpoints. The median age was 58 years. Pts were heavily pre-treated with a mean of 2.6 lines of prior hormone therapy (range 1-6) and 1.6 lines of chemotherapy (range 0-8). Eight pts (30%) stopped treatment due to toxicity including hypertension (HTN), fever, transaminisits, and pulmonary embolism; 6 pts progressed prior to wk 12. The CBR at 12 wks was 44.4% (11 SD, 1 PR), and at 24 wks was 22.4% (4 SD, 2 PR). Median PFS for pts with CB at 12 wks was 30 wks (95% CI 20-40); 6 pts had PFS > 6 months (26, 32, 36, 48, and 78 wks). Three pts remain on study at 20, 32 and 78 wks. The most common adverse events (AE) were neutropenia (52%), fatigue (41%), arthralgia (26%), back pain (26%), Grade 3/4 anemia (23%), Grade 3/4 diarrhea (19%), transaminisits (11%), and headache (7%). **Conclusions:** The addition of P2 to a NSAI resulted in a CBR of 44% at 12 wks, and 22.2% at 24 wks in pts with heavily pre-treated hormone resistant ABC, suggesting that the antiangiogenic TKI P2 can modulate resistance to hormone therapy. Early toxicity disclosures early discontinuation in 30% of pts, which limited drug exposure. Evaluation of biomarkers and immune signatures is ongoing. Clinical trial information: NCT01466972.
Effect of mutations in distinct components of the PI3K/AKT/mTOR pathway on sensitivity to endocrine therapy in estrogen receptor (ER)-positive breast cancer. First Author: Suleiman Alfred Massarweh, University of Kentucky, Lexington, KY

**Background:** Aberrations of the PI3K/AKT/mTOR pathway are common in ER-positive breast cancer and may be associated with endocrine-resistance. We hypothesized that, since the majority of ER-positive breast cancers are actually sensitive to endocrine therapy, the most prevalent aberration in this pathway will more likely be associated with endocrine-resistance rather than resistance. **Methods:** We studied 28 tumors from patients enrolled on protocol NCT00570921 using fuelvestan and everolimus after aromatase inhibitor failure; 19 from 13 patients with endocrine-sensitive disease and 9 from 8 patients with resistant tumors. Resistance was defined as relapse within 3 years of adjuvant use or progression within 6 months in the metastatic setting. DNA was extracted from FFPE tumor tissue and subjected to next-generation-based comprehensive genomic profiling using the FoundationOne assay and alterations were then compared. **Results:** 10 of 13 patients with endocrine-sensitive tumors (77%) had at least one alteration in the PI3K/AKT/mTOR pathway vs. 6 of 8 patients with resistant disease (75%). PIK3CA mutations were more frequent in the sensitive group; 9/13 (69%) vs. 2/8 (25%) in the resistant group (p = 0.08). Interestingly, aberrations of pathway components other than PIK3CA were present in only 1 of 13 patients (8%) with sensitive disease vs. 4 of 8 patients (50%) with resistant disease (p = 0.0475). These aberrations were 1 activating AKT1 mutation in the sensitive group and 2 each of AKT1 activating mutations and PTEN loss in the resistant group. Further analysis of additional alterations will be presented in greater detail. **Conclusions:** Alterations in the PI3K/AKT/mTOR pathway are common in both endocrine-sensitive as well as resistant breast cancer but mutations of specific pathway components may distinguish sensitive from disease that is more likely to be resistant. PIK3CA mutations, which are relatively common, may be associated with more estrogen-dependent tumor biology while non-PIK3CA mutations are potentially associated with endocrine-resistance in ER-positive breast cancer. Further investigation of these findings is warranted.

The vitamin D receptor: A therapeutic target for the treatment of breast cancer? First Author: Alyson M Murray, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

**Background:** Recent studies suggest vitamin D (VD) plays a role in cancer cell growth, with evidence indicating that a deficiency can lead to higher disease risk and a poorer outcome. Activation of the vitamin D receptor (VDR) by the active form of VD (calcitriol) leads to the regulation of anti-cancer genes. Therefore, we propose that VDR could be targeted as a potential therapeutic for treatment of breast cancer. **Methods:** The effects of calcitriol and inecalcitol (Hybrigenics, Paris) on breast cancer (BC) cell line growth were investigated in 16 cell lines (TN of calcitriol and inecalcitol (Hybrigenics, Paris) on breast cancer (BC) cell line growth. Since inecalcitol, which is considerably more potent than calcitriol and has low calcemic potential, and inecalcitol can inhibit breast cancer cell line growth. Since inecalcitol, which is considerably more potent than calcitriol and has low calcemic potential, it should be further investigated as a treatment for breast cancers expressing VDR.

Recurrence score and clinicopathologic characteristics of TAILORx participants by race and ethnicity. First Author: Maria M Zlobin Rubinstein, Memorial Medical Center, New York, NY

**Background:** Black race is associated with worse outcomes in localized breast cancer. We evaluated the characteristics of patients enrolled in the Trial Assigning Individualized Options for Treatment (TAILORx) by race and ethnicity. **Methods:** The analysis included 10,071 evaluable patients with Recurrence Score (RS) data. Eligibility criteria included: (1) T1-2, N0 disease, (2) estrogen receptor (ER) and/or progesterone receptor (PR) positive disease that was also HER2/neu negative, (3) age 75 years or younger and medically appropriate for adjuvant systemic chemotherapy. **Results:** The study population included 8,501 whites (84%), 722 blacks (7%), 423 Asians (4%), and the remainder other/unknown race. With regard to ethnicity, 7,916 were non-Hispanic (79%), 919 were Hispanic (9%), and 1,236 were of unreported ethnicity (12%). There was no significant difference in RS distribution (p = 0.14), median RS (17 vs. 17), and mean RS (19.6 vs. 18.4) in blacks compared with non-blacks. There was likewise no difference in Hispanic vs. non-Hispanic ethnicity for RS distribution (p = 0.53), median RS (17 vs. 17), and mean RS (18.6 vs. 18.4). Blacks were significantly more likely to be younger (39% vs. 30% < 50 years), have larger tumors (37% vs. 31% > 2 cm), poor histologic grade (25% vs. 17%), and PR-negative disease (14% vs. 10%) (Chi square test < 0.05). Hispanic women were also significantly younger (39% vs. 30% < 50 years), and demonstrated marginal but statistically significant differences in tumor size (34% vs. 31% > 2 cm), histologic grade (20% vs. 18% poor), and PR expression (12% vs. 10% negative) (Chi square test < 0.05). In 974 patients with information on body mass index (BMI), there was no correlation between BMI and RS (r = 0.04). BMI was higher for blacks than whites (medians 31.6 vs. 28.9, p = 0.02, Wilcoxon test), but not in Hispanic. **Conclusions:** In patients selected for participation in TAILORx there were no significant differences in RS by race, ethnicity, and BMI. When compared to white patients, black and Hispanic patients were significantly younger, had tumors that were larger, and more likely to be associated with poor grade. Clinical trial information: NCT03011080.

Significance of prospective multicenter decision impact WSG-BCIST Study in premenopausal ER+ HER2- NO early breast cancer (EBC) for molecular testing in intrinsic subtype definition. First Author: Rachel Wuerstlein, University of Munich, Munich, Germany

**Background:** Prosigna is a standardized test measuring expression levels of 50 classifier genes (PAM50) in formalin-fixed, paraffin-embedded (FFPE) breast tumor tissue using nCounter Technology (NanoString Technologies, Inc., Seattle, WA). It provides intrinsic subtype and risk of recurrence (ROR) score predicting 10y recurrence probability. It was retrospectively validated by ABCSG 8 and TransATAC. WSG BCIST evaluates its impact on systemic therapy decisions in EBC. **Methods:** 201 consecutive premenopausal pts. with ER+ HER2- NO were recruited (11 centers; 10/2013-10/2014). Primary objective was to assess impact of Prosigna vs. standard immunohistochemistry (IHC) on adjuvant chemotherapy recommendations and actual therapy received. Secondary objectives include physicians’ confidence in recommendations, patients’ decisional conflict, and rate of chemotherapy-related adverse events. Prosigna testing was performed centrally (university) and repeated de-centrally (community-based pathology) for quality control. **Results:** Intrinsic subtypes were highly concordant (95.5%) between the two pathologies. Risk group differed in only 1/9 discordant cases; underlying tumor heterogeneity is being evaluated. In the total cohort (198 patients evaluated), 58.1% of tumors were classified by PAM50 as Luminal A, 39.9% as Luminal B, 1.5% Basal, 0.5% HER2-E. Local IHC classified 18.3% of PAM50 Luminal A as Luminal B, and 39.2% PAM50 Luminal B as Luminal A (overall 27% discordance). Prosigna results led to a reported change in chemotherapy (CT) indication in 19.2% overall, including 39.2% of PAM50 luminal B patients. Actual CT use and morbidity will be evaluated after scheduled 6-month follow-up. **Conclusions:** In the WSG BCIST prospective decision impact study, Prosigna results led to a 19% change in chemotherapy indication. The 27% discordance in intrinsic subtyping between PAM50 and IHC underlines the importance of molecular testing for optimal systemic therapy indications in EBC. As a pre-planned pooled analysis, WSG BCIST can later be evaluated together with two similar studies currently ongoing in Europe. Clinical trial information: NCT01974856.
Incidence and survival for young women with operable breast cancer: SEER 1992-2011. First Author: Mary Chen Schroeder, University of Iowa, Iowa City, IA

Background: Recent work has shown an increasing incidence of Stage IV breast cancer (bc) in young women (wm). We examined the incidence and survival of young wm with operable bc. Methods: Wm ages 20-39 diagnosed with stages 1-3 bc from 1992-2011 were identified from SEER data and categorized by hormone receptor (HR) status and grade (low = moderately differentiated, high = poorly differentiated). Those with missing information were excluded. Annual percent change (APC) in age-adjusted incidence rates for the SEER 13 registries were calculated. Kaplan Meier survival curves were estimated by HR and grade. Results: We identified 3,566 wm ages 20-29 and 34,508 wm 30-39. For wm 20-29, stages 1, 2, 3 comprised 25.2, 50.5, and 24.3% of the sample versus 30.6, 47.1, and 22.3% for wm 30-39 (all p < 0.001). HR status and grade also differed significantly by age. Wm 20-29 were more likely to have HR- disease (40.4 v 34.2%), less likely to have HR+ low grade disease (25.7 v 35.6%), and more likely to have HR+ high grade disease (33.9 v 30.2%) than wm 30-39 (all p < 0.001). APC in incidence along with 5- and 10-survival is reported in the table. In HR+ disease, regardless of grade, survival decreased more rapidly beyond 5 years from diagnosis for 20-29 than 30-39. This was not seen for HR- disease. Conclusions: Wm age 20-29 presented more frequently with Stage II bc. Wm 20-29, unlike wm 30-39, have not seen a decline in Stage III disease. Low and high grade HR+ disease in wm 20-29 also increased with the highest APC in incidence. 10-year survival for female 20-29 old wm with HR+ disease showed continued late benefits. This was most pronounced for wm 20-29.

B. Satisfaction increased in 38% of patients. After receiving results, 52% of patients recommended for 75% patients pre- and for 55% post-testing. No extended therapy was recommended for 75% patients pre- and for 69% post-testing. A majority of changes were based on identification of patients with low risk of late recurrence and low likelihood to benefit from extended endocrine therapy. Extended therapy was recommended for 75% patients pre- and for 55% post-testing. No extended therapy was recommended for 52% patients pre- and for 45% post-testing. Satisfaction increased in 38% of patients. After receiving results, 52% of patients changed their treatment decision. Patients experienced less anxiety (53%) and depressive (50%) after receiving results. The STAI (p = 0.03) and DCS (p < 0.001) scores decreased significantly post-testing (mean difference of -2 and -3, respectively) compared to baseline scores (31 and 20, respectively). Conclusions: The Breast Cancer Index led to changes in treatment recommendations regarding extended adjuvant endocrine therapy in 27% of cases and resulted in significantly less decision conflict and anxiety for patients. Overall, knowledge of BCI resulted in fewer recommendations for extended therapy and improved patient satisfaction. Clinical trial information: NCT02057029.
Background: TRIO-012 is a double blinded, multinational trial that randomized 1,144 patients with advanced breast cancer to receive first-line docetaxel (Doc) in combination with ramucirumab or placebo. Our objective is to address genetic predisposition to Doc toxicity. In this independent validation study, we selected single nucleotide polymorphisms (SNPs) previously associated with taxane-induced adverse events (AEs), fatigue, myalgia, neuropathy and peripheral neuropathy, including CYP3A5*3 reporting for our group to be strongly associated with Doc toxicity. Methods: Germline SNPs were studied in participants who gave prospective consent for peripheral blood DNA genotyping. All subjects received Doc until unacceptable toxicity or progressive disease. From these, 399 subjects predominantly of Caucasian origin were analysed here. Toxicity grades 0-1 (controls; low toxicity) vs. grade > 2 (cases, high toxicity) were compared. Dominant genotypic model was assumed; Chi-square test with 10000 permutations were employed using SVD v3.3 and p < 0.05 considered statistically significant. Results: Each reported variant conferred risk. CYP3A5*3 allele (rs776746; OR 2.16 [1.18-3.96]), TNF-alpha (rs1800629; NAV1 (rs478472), NOS3 (rs1799983) were associated with fatigue. SNPs associated with myalgia were FADN2 (rs7637888), HIF1-alpha (rs11549465) and NDRG1 (rs2233335). XKR4 (rs4737264) showed association with peripheral neuropathy. SNPs in ABC2C, SLC01B3 and VEGF-1 genes showed associations with all three individual AEs tested. In a combined analysis of all the AEs, CYP3A5*3 allele retained significance (OR 1.9 [1.08-3.37]; as did IL1-beta (rs16944) and CYP2C8. Conclusions: We confirm our previous findings that CYP3A5*3 genotype determines toxicity by its influence on Doc metabolism (EurCancer 9(7),175,2010) and several SNPs previously associated with paclitaxel-induced neuropathy, were now associated with Doc-induced myalgia or neuropathy. In conclusion, we report a subset of variants analysed conferring genetic predisposition to both paclitaxel and Doc AEs. The pleotropic drug effects on multiple genes/pathways appear to contribute to the overall phenotype of taxane toxicity.

542 Poster Session (Board #30), Sat, 8:00 AM-11:30 AM
There are far more to the picture than meets the eye: Population-study based on biopsy verification of suspected breast cancer recurrences. First Author: Ulla Wilking, Department of Oncology and Pathology - Karolinska Institutet and Cancer Center Karolinska, Stockholm, Sweden

Background: Core biopsy/Fine needle aspiration (Bx) is recommended to confirm biopsy verification of suspected breast cancer recurrences. In a population-based cohort in Stockholm, Sweden, of women with suspected RBC, Sites of sample: bone, ascites, lung/pleura, CNS, liver, spleen, GI, gyn, etc. Results of Bx show that suspected RBC may be other malignancy (3%), benign (35%) or inconclusive (6%). Of the 52 lung/pleura samples we had 2 lung cancers, 10 were cancers of unknown primary (CUP) and 6 showed inflammation. Of the 56 liver biopsies one was hemangiomma and one showed inflammation. Also, one of the 185 local biopsies showed to be a neuroendocrine tumor. Tumor trigrrow switch between PBC and RBC in almost one out of three patients as well as between consecutive AEs (see table). Conclusions: For correct clinical management of patients with RBC it is essential to take Bx of any suspected site, since up to 55% of suspected RBC lesions are not RBC. Furthermore, biology changed in around 30% of patients, also between consecutively relapsing.

Table 1. Comparison of RBC and TBC

<table>
<thead>
<tr>
<th>RBC</th>
<th>HR and HER2- Number (%)</th>
<th>HER2+ Number (%)</th>
<th>TNBC Number (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+ and HER2-</td>
<td>38 (36.2)</td>
<td>7 (6.7)</td>
<td>8 (7.6)</td>
<td></td>
</tr>
<tr>
<td>HR+ and HER2+</td>
<td>3 (2.9)</td>
<td>13 (12.4)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>4 (7.7)</td>
<td>12 (21.9)</td>
<td>24 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>48 (45.7)</td>
<td>23 (21.9)</td>
<td>34 (32.4)</td>
<td></td>
</tr>
<tr>
<td>FIRST RBC</td>
<td>CONSECUTIVE RBC</td>
<td>23 (50)</td>
<td>3 (6.1)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>HR+ and HER2+</td>
<td>1 (2.2)</td>
<td>5 (10.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>3 (6.5)</td>
<td>3 (6.5)</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>27 (58.7)</td>
<td>11 (23.9)</td>
<td>8 (17.4)</td>
<td></td>
</tr>
</tbody>
</table>

543 Poster Session (Board #31), Sat, 8:00 AM-11:30 AM
21-gene recurrence score assay (RS) and impact on adjuvant chemotheraphy (CTx) use among lobular (L) and ductal (D) histology hormone receptor positive (HR+) early breast cancers (EBC). First Author: Simon Daniel Baxter, BC Cancer Agency, Vancouver, BC, Canada

Background: RS identifies lower risk HR+ or EBCs that may avoid adjuvant CTx. L histology may influence CTx use in intermediate RS cancers given its association with high HR+ expression and hormone therapy benefit. We examined RS and its use in clinical decision-making related to 9 EBCs. Methods: We identified BC Cancer Agency referred pts with a RS performed on their HR+ EBC between 2007 and 2014, as part of routine care (node negative only) or in clinical trials. Multivariable breast cancer and multivariable histology were excluded. Demographic and histopathological variables and rates of CTx were compared for D and L using univariate and multivariate analyses. Results: After exclusions, 577 cases (89% D, 11% L) were compared. Compared with D, L cases were larger, lower grade, had a lower mean RS (20 vs 16 p < 0.0002), and fewer had high RS (Table 1). These differences were not significant after adjustment for age, degree of HR+ expression, size, grade, nodal status, LVI. Among 289 pts (265 D, 33 L) with treatment not mandated in a trial based on RS, 82 (28.4%) had CTx, including 5 (15.2%) L and 77 (30.1%) D (p = 0.10). Of the 97 with intermediate RS cancers, CTx was given in 31/25% L and 28/65 (30.6%) D cases. Conclusions: The observed frequency of L and D histology in this series mirrors the incidence distribution described in EBC. The overall lower use of CTx in L cancers can be accounted for by lower RS and more favourable histopathological variables. Among intermediate RS cancers, histology did not appear to impact CTx use. In the absence of prospective data, L histology should not influence CTx use for intermediate RS cancers.

Comparison of ductal and lobular cancers.

<table>
<thead>
<tr>
<th>Diastolic</th>
<th>Systolic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts, n (%)</td>
<td>512 (89)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>55 (15-89)</td>
<td>55 (15-87)</td>
</tr>
<tr>
<td>Premenopausal, n (%)</td>
<td>232 (45)</td>
<td>19 (29)</td>
</tr>
<tr>
<td>Grade, n (%)</td>
<td>82 (15)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>3</td>
<td>282 (55)</td>
<td>54 (83)</td>
</tr>
<tr>
<td>2</td>
<td>148 (28)</td>
<td>24 (36)</td>
</tr>
<tr>
<td>1</td>
<td>21 (4)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Size, n (%)</td>
<td>328 (64)</td>
<td>24 (37)</td>
</tr>
<tr>
<td>T1</td>
<td>180 (35)</td>
<td>38 (58)</td>
</tr>
<tr>
<td>T2</td>
<td>158 (31)</td>
<td>42 (63)</td>
</tr>
<tr>
<td>Node negative, n (%)</td>
<td>375 (73)</td>
<td>50 (77)</td>
</tr>
<tr>
<td>LVI</td>
<td>142 (28)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>RS, mean (range)</td>
<td>20 (0-73)</td>
<td>16.4 (4-33)</td>
</tr>
<tr>
<td>HR+</td>
<td>82 (16)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>HER2+</td>
<td>170 (33)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Lum, n (%)</td>
<td>140 (27)</td>
<td>21 (32)</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Prediction of late distant recurrence (DR) using the Prosigna (PAM50) test in a Danish Breast Cancer Cooperative Group (DBCG) cohort of postmenopausal women with hormone receptor-positive (HR+) early breast cancer (EBC) allocated to 5yr of endocrine therapy (ET). First Author: Anne-Vibeke Lænkholm, Department of Pathology, Region Zealand, Denmark

Background: Accurate assessment of the risk of late DR (5-10 yrs after surgery) may be used to tailor the duration of ET for patients with HR+ EBC. The Prosigna (PAM50) risk of recurrence (ROR) score was shown to predict late DR for EBC patients treated with 5yr of ET in clinical trials. Here we assess the ability of PAM50 to predict late DR in a comprehensive nationwide cohort from Denmark consisting of postmenopausal women diagnosed with HR+ EBC allocated to 5yr of ET alone.

Methods: Using the population based DBCG database FFPE primary tumor blocks and follow-up data were collected from all HR+ EBC patients diagnosed from 2000-2003 who by nationwide guidelines were allocated to 5yr of ET alone (N = 2749). The PAM50 test was run on the NanoString nCounter Analysis System. Multivariate analyses tested the ability of PAM50 to predict late DR. Patients were categorized as Low, Intermediate, or High risk based upon prespecified ROR cutoffs varied by number of positive nodes. Results: From 2722 included patients, 2164 were disease free at 5yr and analyzed for risk of late DR. Median follow-up was 4.58 yrs from completion of ET. High risk patients (N = 870) had a late DR risk of 10.2% [95%CI: 8.0-12.7], compared to 6.1% [4.2-8.6] for Intermediate (N = 650) and 2.4% [1.3-4.1] for Low risk patients (N = 644). When ROR was added to a multivariable model including standard clinical and pathological variables it improved the prediction of late DR (likelihood ratio: p < 0.0001; HR for a 20-point change = 1.5 [1.2-1.9]). Luminal B (N = 733), late DR risk = 10.3% [7.8-13.1] and Her2-enriched tumors (N = 1281), late DR risk = 4.4-15.0% (4.4-15.0%) had significantly worse outcome than Luminal A (N = 1281, late DR risk = 4.5% [3.3-5.9]), p < 0.0001 for LumB and = 0.034 for Her2e.

Conclusions: We have confirmed the ability of Prosigna (PAM50) to predict late DR for HR+ EBC patients regardless of nodal status in a real world cohort. Additionally, development of physician selection bias. PAM50 can reliably be utilized to identify patients who need, or most importantly may be safely spared, extended ET beyond 5yr.

Characteristics (N = 853)

<table>
<thead>
<tr>
<th>Grade</th>
<th>N</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<td>58</td>
<td>18</td>
<td>14</td>
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<td>1</td>
<td>88</td>
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<td>3</td>
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Stratification by BCI prognostic (risk of late recurrence) and BCI predictive (Hi/I) risk group.

<table>
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<tr>
<th>BCI Prognostic (Risk of Late Recurrence)</th>
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<tr>
<td>High</td>
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<tr>
<td>Low</td>
<td>Intermediate</td>
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<tr>
<td>Intermediate</td>
<td>High</td>
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Prediction of late DR (10yr) using the Prosigna (PAM50) test in a Danish Breast Cancer Cooperative Group (DBCG) cohort of postmenopausal Danish women with hormone receptor-positive (HR+) early breast cancer (EBC) allocated to 5yr of endocrine therapy (ET) alone. First Author: Anne-Vibeke Lænkholm, Department of Pathology, Region Zealand, Denmark

Background: The Prosigna (PAM50) risk of recurrence (ROR) score has been validated in two randomized clinical trials to predict 10yr DR in EBC allocated to 5yr of ET alone. Here we examine the value of Prosigna for predicting late DR using a comprehensive nationwide cohort from Denmark consisting of postmenopausal women diagnosed with HR+ EBC patients treated with 5yr of ET alone.

Methods: Using the population based DBCG database FFPE primary tumor blocks and follow-up data were collected from all HR+ EBC patients diagnosed from 2000-2003 (N = 2749) by nationwide guidelines were allocated to 5yr of ET alone. The Prosigna (PAM50) test was run on the NanoString nCounter Analysis System. Univariate and multivariate analyses tested the ability of PAM50 to predict DR. Patients were categorized as Low, Intermediate, or High risk based upon prespecified ROR cutoffs varied by number of positive nodes. Results: From 2722 included patients, 2164 were disease free at 5yr and analyzed for risk of late DR. Median follow-up was 4.58 yrs from completion of ET. High risk patients (N = 870) had a late DR risk of 10.2% [95%CI: 8.0-12.7], compared to 6.1% [4.2-8.6] for Intermediate (N = 650) and 2.4% [1.3-4.1] for Low risk patients (N = 644). When ROR was added to a multivariable model including standard clinical and pathological variables it improved the prediction of late DR (likelihood ratio: p < 0.0001; HR for a 20-point change = 1.5 [1.2-1.9]). Luminal B (N = 733), late DR risk = 10.3% [7.8-13.1] and Her2-enriched tumors (N = 1281), late DR risk = 4.4-15.0% (4.4-15.0%) had significantly worse outcome than Luminal A (N = 1281, late DR risk = 4.5% [3.3-5.9]), p < 0.0001 for LumB and = 0.034 for Her2e.

Conclusions: We have confirmed the ability of Prosigna (PAM50) to predict late DR for HR+ EBC patients regardless of nodal status in a real world cohort. Additionally, development of physician selection bias. PAM50 can reliably be utilized to identify patients who need, or most importantly may be safely spared, extended ET beyond 5yr.

Characteristics (N = 853)

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Stratification by BCI prognostic (risk of late recurrence) and BCI predictive (Hi/I) risk group.

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<th>BCI Predictive (Hi/I) Risk Group</th>
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<td>Low</td>
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<tr>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Intermediate</td>
<td>High</td>
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</tbody>
</table>
Impact of combining PgR score and original preoperative endocrine prognostic index (PEPI) score as a prognostic factor of neoadjuvant endocrine therapy using exemestane in postmenopausal ER-positive/HER2-negative breast cancer. First Author: Sasagu Kuruzumi, Division of Breast Surgery, Saitama Cancer Center, Saitama, Japan

**Background:** Neoadjuvant endocrine therapies (NAE) using aromatase inhibitors effectively reduce tumor size in postmenopausal ER-positive breast cancer (BC). The utility of PEPI scoring in predicting of the recurrence-free survival (RFS) after NAE is well-known. On the other hand, PgR can be a prognostic factor of ER-positive BC. We compared original PEPI score with PgR status alone, and modified PEPI score including PgR status, as prognostic factors of NAE in postmenopausal ER-positive/HER2-negative BC.

**Methods:** Our study included 107 Japanese women with invasive ER-positive/HER2-negative BC who were received NAE with exemestane (25 mg/day) for at least 4 months (median follow-up: 47 months).

**Analysis 1:** PEPI score (0-12 points) of each patient was determined using ypT, ypN, Ki67 and ER (Allred score), and patients were divided into 3 risk groups: low (0), moderate (1-3), and high (≥ 4). RFS and cancer-specific survival (CSS) were compared between groups.

**Analysis 2:** Cutoff values of PgR were tentatively defined as, 0, 1, 10, 20, 33, 50 or 66%; an effective cutoff value was determined by analysis of RFS and CSS.

**Analysis 3:** PgR score (3 to low; 0 to high, using cutoff value determined by analysis 2) and original PEPI score were combined, and RFS and CSS of 3 risk groups were analyzed.

**Results:** The PgR staining of 50% was the most significant cutoff value for predicting differences of RFS and CSS (RFS: P = 0.005, CSS: P = 0.003). PEPI score was also significant prognostic factor for CSS and RFS (RFS: P = 0.0009, CSS: P = 0.043).

**Conclusions:** PgR alone using 50% of cutoff value and original PEPI score might be a significant prognostic indicator for NAE using exemestane. However, combining PgR score and original PEPI score might be more potent prognostic indicator in both RFS and CSS.

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**Conclusions:** numerically better results in the no-endocrine therapy group. In multivariate analysis, Overall Survival (OS) were not significantly different with 89.8% in the no endocrine therapy group than in the endocrine therapy group (88.0%). In pT1a,bN0 breast cancer (BC), the utility of PEPI scoring in predicting of the recurrence-free survival (RFS) after NAE is well-known. On the other hand, PgR can be a prognostic factor of ER-positive BC. We compared original PEPI score with PgR status alone, and modified PEPI score including PgR status, as prognostic factors of NAE in postmenopausal ER-positive/HER2-negative breast cancer. First Author: Christophe Perrin, Centre Eugène Marquis, Rennes, France

**First Author:** Christian F. Singer, Medical University of Vienna, Vienna, Austria

**Background:** Elevated intratumoral levels of uPA and PAI-1 in ELISA-based measurements are associated with a high recurrence risk and allow to select patients who might particularly benefit from adjuvant chemotherapy. The clinical utility of ELISA-based uPA/PAI-1 analysis is however, greatly limited by the requirement of fresh tissue. We have therefore evaluated whether immunohistochemical uPA analysis from formalin-fixed paraffin-embedded (FFPE) tumor samples is also suited to identify women with poor clinical outcome. **Methods:** 547 postmenopausal patients with hormone receptor positive early breast cancer who received 5 years of endocrine therapy in the prospective randomized ABCSG-06 trial, and from whom FFPE tumor tissue was available, were included in this analysis. uPA protein expression was evaluated by immunohistochemistry, and was correlated with distant-disease free (DDFS) and overall survival (OS). **Results:** uPA protein was expressed in 296 of 547 (54%) tumors and was associated with size (p = 0.016, Chi Square test) but not with nodal status, grading, age, or receptor status. After a median follow-up of 11.5 years, patients with uPA-positive tumors experienced a significantly shorter DDFS (p = 0.005 log rank test) and OS (p = 0.022). Women with uPA-positive tumors were more likely to experience a shorter DDFS (adjusted HR for distant relapse 1.642; 95% CI 1.046-2.576; p = 0.031 Cox regression analysis) and OS (adjusted HR for death 1.348; CI 0.984-1.846; p = 0.063) than women without uPA expression. **Conclusions:** When measured by immunohistochemistry, intratumoral uPA protein expression predicts poor DFS and OS in postmenopausal women with hormone receptor positive early-stage breast cancer who receive endocrine therapy. Clinical trial information: NCT00309491.
552 Poster Session (Board #40), Sat, 8:00 AM-11:30 AM
Prognostic significance of Focal Adhesion Kinase (FAK) in node-negative breast cancer. First Author: Marcus Schmidt, University Hospital Mainz, Mainz, Germany

Background: Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase playing an important role as a key mediator for signal transduction. We examined the subtype specific prognostic significance of FAK in node-negative breast cancer. Methods: Using microarray based gene-expression data, we analysed the prognostic significance of FAK (208820_at). The subtype specific prognostic role of FAK was analysed in four previously published cohorts (Mainz, Rotterdam, Transbig, Yu) of node-negative breast cancer patients not treated with adjuvant therapy (n = 824). A meta-analysis of previously published cohorts was performed using a random effects model. Prognostic significance of FAK for metastasis-free survival (MFS) was examined in the whole cohort of patients as well as in different molecular subtypes: luminal A (ER+/HER2/AURKA+/aurora kinase A [AURKA])low, luminal B (ER+/HER2/AURKA+)

Results: Prognostic significance of FAK was seen in the whole cohort of patients (HR 1.48, 95% CI 1.16-1.87, P = 0.001). Considering the different molecular subtypes, the prognostic effect was most pronounced in luminal B carcinomas (HR 1.67, 95% CI 1.07-2.62, P = 0.0233). FAK expression was neither significantly associated with MFS in luminal A (HR 1.69, 95% CI 0.96-2.98, P = 0.6962), basal-like (HR 0.98, 95% CI 0.64-1.50, P = 0.9400) nor HER2+ (HR 1.63, 95% CI 0.49-5.46, P = 0.8512) carcinomas of the breast.

Conclusions: A higher expression of FAK was associated with worse MFS in node-negative breast cancer. The prognostic significance was confined to luminal B carcinomas.

554 Poster Session (Board #42), Sat, 8:00 AM-11:30 AM
Detection and functional analysis of estrogen receptor mutations (ESR1-mut) in patients with metastatic breast cancer (MBC). First Author: Shannon Puhalla, University of Pittsburgh Medical Center, Women’s Cancer Program at Magee-Womens Hospital of UPMC, Pittsburgh, PA

Background: Mutations in ESR1 (ESR1-mut) are a potential resistance mechanism to endocrine therapy, especially aromatase inhibitors (AI). Although these mutations are rare in untreated patients with early breast cancer, they have been observed to develop after exposure to hormonal therapy, suggesting a critical functional role for ER signaling in MBC and the potential to use ESR1-mut as a predictive marker and novel treatment target. Methods: Primary (44 patients) and metastatic breast cancers (brain, 38 patients; bone, 15 patients), and plasma (30 patients) samples collected from patients with MBC were examined for the presence of ESR1-mut. D538G, K303R, Y357C, Y357N, S463P and Y357S using digital droplet (dd)PCR and Sanger Sequencing. Ten mL of plasma was collected from patients with MBC were examined for the presence of ESR1 mutation. The allele frequency ranged from 0.01% to 37%. The lowest expression of FAK was associated with worse MFS in node-negative breast cancer patients (P < .0001). More breast cancer survivors used antidepressants (15.3% vs. 12.2%, P = .006) and bisphosphonates and/or calcium/vitamin D (62.2% vs. 54.8%, P < .001). Use of the following classes did not differ: anti-diabetic, cardiovascular, anti-anxiety, and narcotic and non-narcotic analgesics. Medication use at follow-up inventory by adjuvant endocrine therapy are outlined below. Medication use in breast cancer survivors on tamoxifen was lower than controls while those on AIs used more medications.

Conclusions: Reflecting age-related co-morbidities, medication use significantly increases over time in both breast cancer survivors and controls. Overall, breast cancer impact on medication use is limited.

555 Poster Session (Board #41), Sat, 8:00 AM-11:30 AM
Medication use trajectories of postmenopausal breast cancer survivors and matched cancer-free controls. First Author: Kathy Pan, Harbor-UCLA Medical Center, Torrance, CA

Background: While distinct health issues are associated with breast cancer and related therapies, comprehensive assessment of medication use before and after breast cancer diagnosis compared to age-matched, cancer-free controls has not been reported. Methods: From the 93,338 postmenopausal participants in the Women’s Health Initiative, medication inventories by pill container review were serially obtained before and > 3 years (mean 5.3 ± 2.1 SD) after early stage breast cancer in 1730 cases matched with 1730 controls on age, dates of initial and follow-up medication inventories, body mass index, and smoking. Number of medications and medication classes (excluding tamoxifen and aromatase inhibitors [AI]) in cases and controls were compared. Results: Medication use (n) was comparable at baseline in both groups and significantly increased at follow-up in both cases (4.12 ± 2.73 vs 6.47 ± 3.29, P<.0001) and controls (3.92 ± 2.59 vs 5.94 ± 3.37, P < .0001), with clinically marginal but statistically significant additional medication use 0.53 ± 3.93 by breast cancer survivors (P < .0001). More breast cancer survivors used antidepressants (15.3% vs. 12.2%, P = .006) and bisphosphonates and/or calcium/vitamin D (62.2% vs. 54.8%, P < .001). Use of the following classes did not differ: anti-diabetic, cardiovascular, anti-anxiety, and narcotic and non-narcotic analgesics. Medication use at follow-up inventory by adjuvant endocrine therapy are outlined below. Medication use in breast cancer survivors on tamoxifen was lower than controls while those on AIs used more medications.

Conclusions: Reflecting age-related co-morbidities, medication use significantly increases over time in both breast cancer survivors and controls. Overall, breast cancer impact on medication use is limited.

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Effect of tumor infiltrating lymphocytes (TILs) and stromal CD68 on trastuzumab (T) benefit in early stage HER2 positive breast cancer (BC).

First Author: Jacques Raphael, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada

Background: The presence of high TILs has been implicated as a predictor of pathologic complete response (pCR) and decreased recurrence rates in BC patients. However, there is conflicting data for the benefit of T in the adjuvant setting for HER2 positive (HER2+) BC patients with high TILs. In addition, greater numbers of CD68 (+) cells (macrophage marker) in tumor stroma has been shown to be an independent prognostic factor for better OS and specific survival.

Methods: Core biopsies from 52 HER2+ BC patients treated with neoadjuvant (NAT) chemotherapy with or without T were identified. Two pathologists independently quantified stromal TILs and CD68 ratio (inside the TILs population) using Hematoxylin/Eosin and immunohistochemistry respectively. The association of TILs and CD68 with pCR rates, disease free survival and overall survival (OS) was assessed by Kaplan-Meier analysis and log-rank test.

Results: The median age and follow up for the cohort were 52 and 2.8 years, respectively. In the NAT setting, 40 patients received conventional chemotherapy and T (77%) and 12 patients were treated with chemotherapy alone (23%). Overall the pCR rate in the studied population was 40%. Eight patients (15%) had high levels of TILs (≥ 60%) and 20 patients (38%) had low CD68 ratio (≤ 60%). A high percentage of TILs was significantly correlated to low CD68 ratio (p < 0.0001). High levels of TILs and low CD68 ratio were each associated with greater pCR rates for the cohort of patients who received NAT T, respectively (p = 0.05, p = 0.03). Furthermore, pCR was predictive of better OS (p = 0.02) for the patients treated with NAT T. However, these associations were not significant when we performed the analysis on the whole population (p = 0.09, p = 0.32). Conclusions: Our results show that high levels of TILs are associated with low CD68 ratio, and both are predictors of pCR in patients with HER2+ BC receiving NAT T. Importantly, pCR as determined by CD68 and TILs translated into an OS benefit. TILs and CD68 ratio represent potential prognostic and predictive markers in patients with HER2+ BC.

Molecular profiling to identify genetic heterogeneity in synchronous and asynchronous breast cancers.

First Author: Wendy Marie Dean-Colomb, Lafayette General Health, New Orleans, LA

Background: Histologic heterogeneity of tumors is well documented; however, the molecular heterogeneity is not well understood, especially relative to driver mutations within clonal populations and their prognostic and predictive value.

Methods: Molecular profiling of breast cancers (BCs) at a single institution were analyzed for differences in clonal populations within the same breast, bilateral synchronous BCs, and/or within primary and paired locally recurrent or metastatic tumors. Gene alterations (GAs) were identified by next generation sequencing (NGS). GAs were compared in 9 synchronous BCs and 48 primary/recurrent paired BCs. Estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), were evaluated by immunohistochemistry (IHC). HER2 was evaluated by IHC and in situ hybridization (ISH). Results: We identified GAs in 11 of 57 cases (19%); 2 were bilateral and 9 were paired primary/recurrent BCs. The 11 cases included 1 primary, 1 primary locally recurrent, and 9 primary/metastatic pairs. ER, PR, and HER2 status differed in 9 cases (16%), while AR status differed only in 3 (5%); 16% 13/57 were negative for ER, PR, and HER2 (double negative [DN]); of 9 TN BCs with GAs in paired primary/recurrent BCs, 6 of 9 (67%) were TN on both primary and recurrent disease (p = 0.0135). TP53 GAs were identified in 5 of the 11 cases (including the 2 synchronous), PIK3CA GAs were identified in 4 (1 synchronous), and PTEN GAs were identified in 3 (1 synchronous) cases. Other genes in which GAs appeared to be present only in one of the patients included CDH1, MYC, and KRAS (Primary recurrent pair). Of the 2 synchronously profiled cases, 1 had 2 and 1 had 3 different GAs in the bilateral BCs, and 2 GAs in both BCs. In the primary/metastatic pairs, all discordant GAs were wild type in the primary and pathogenic in the metastasis. Conclusions: We identified that common GAs differ in both synchronous primary BCs and in paired primary/metastatic tissues. Such discordance could influence treatment recommendations. These findings highlight the molecular evolution of BC and the importance of evaluating predictive markers of treatment benefit both in synchronous and metastatic BCs.
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Oncotype-DX resection score distribution among breast cancer patients harboring a germline mutation in the BRCA1/2 genes. First Author: Ron Lenard, Davidoff Cancer Center, Robin Medical Center, Petach Tikva, Israel

Background: In about 10% of breast cancer (BC) cases, a genetic mutation in the BRCA1/2 genes can be found. BCs associated with BRCA2 mutations present with positive estrogen receptor (ER) status in about 50% of all cases, whereas BCs associated with BRCA1 mutation are more aggressive and more likely to be ER-negative. Oncotype genetic profiling has become a standard of care to predict recurrence and the benefit from chemotherapy in ER positive BC. The role of Oncotype-DX in BC resection carriers is not clear. To determine the impact of Oncotype-DX in BRCA resection carriers to that of the General Population (GP). Methods: Two different data bases were crossed: the list of BC resection carriers at Robin Medical Center (n=1,191) with the list of all the Oncotype-DX tests which were performed through Kupat Holim Clalit, our HMO (n=5,491), between 2003 and 2015. Results: Patients and tumor characteristics, including Oncotype RS are shown in the Table. Conclusions: Our study indicates that among BC patients with mutations in the BRCA1/2 genes, the distribution of the RS is different from that of the GP. In these patients a larger portion of the population was shifted toward the intermediate- and high-risk groups. This was more pronounced in the BRCA1 carriers. To our knowledge this is the largest BCRA cohort in which the Oncotype-DX RS has been reported.

ORR, n (%) BRCA1 BRCA2 *P-value* BRCA1/2
Age (years) 60 60 54.1 0.015 58.3 0.37
ER index 2.593 2.2/3 0.013 2.53 0.45
PR index 1.653 0.98/3 0.017 1.03/3 0.004
Grade (%): 1 16.7 0 < 0.0001 8.7 0.09
II 66.2 37.5 56.5
III 16.9 62.5 34.7
K167 (%) 14.5 35.9 < 0.0001 19.2 0.13
Tumor size (cm): Low 52.7 6.2 0.0001 25.9 0.0016
Intermediate 39.5 37.5 44.4
High 9.4 56.2 29.6

*All Oncotype tests which were performed for patients at our institute. **The BRCA groups were compared to the non-BRCA group.

Variations in measured ER, PR, and HER2 status in synchronous and asynchronous paired breast cancer (BC) tumors. First Author: Clayton Yates, Tuskegee University, Tuskegee, AL

Background: That tumor heterogeneity exists and evolves over time is well appreciated but how often to biopsy patients’ metastatic BC is not well established. Methods: Immunohistochemical (IHC) and in situ hybridization (ISH) analysis of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and HER2 in 337 cases with > 1 synchronous primary/metastatic BC molecular profiles and in 40 cases with > 1 synchronous molecular profiles were performed at a single institution. We evaluated differences in ER, PR and HER2 status in same or contralateral breast, and in primary vs. locally recurrent or metastatic BC’s. Results: We identified a change in ER or HER2 status in 8 (31%) synchronous BCs and in 55 (16%) primary/recurrent BCs, including in biopsies of distinct tumor foci within the same breast or metastatic organ site. Of the 8 synchronous bilateral primary BC’s, 4 (50%) had discordant ER results (ER, PR, and HER2 negative [TN] vs. ER+; 5 of 18 (28%) with two or more metastatic foci tested within the same organ had discordant ER results; 23% of BCs with biopsies of different organ sites had discordant ER results. Of the 55 paired primary/metastatic BCs, 15% of the discordant findings were in cases with biopsies from the same metastatic site, 19% were in cases with one metastatic and one primary or local recurrent biopsy, and 23% were from 2 primary biopsies or from primary and locally recurrent disease. Discordance was bidirectional from either TN to ER+ or ER+ to TN, and independent of discordance in HER2. Conclusions: Standard systemic treatment of BC relies on reliable assessment by IHC analysis of ER, PR, and HER2. Within a patient, ER and HER2 status are not always concordant between lesions within the same breast, between bilateral BCs, and between distinct foci in a metastatic organ site. Patients are at risk of not being treated for the most clinically important foci of BC if the biopsy(s) obtained are not representative of the more aggressive areas of disease. Profiling should be performed on multiple BC samples both at diagnosis and at each time of recurrence/progression in the cancer continuum, to more accurately reflect the tumor profile at the time of treatment.

Conclusions: Using training data and medical logic, WFO’s machine learning model can assign weights to attributes and features to select therapy for patients that better align with the nuanced decision-making of MSK breast medical oncologists than rules alone. WFO’s machine-learned disease burden score is a useful driver of treatment recommendations for HR+ and/or HER2+ BC.

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**569** Poster Session (Board #57), Sat, 8:00 AM-11:30 AM

**Blinded independent validation of the PAM50-based Chemo-Endocrine Sensitivity Predictor (CESP) in hormone receptor (HR)-positive/HER2-negative (HR+/HER2-) advanced breast cancer (ABC): PALOMA-1/TRIO-18 trial.** First Author: Aleix Prat, Medical Oncology Department, Hospital Clinic, Barcelona, Spain

**Background:** Pathological complete response following NAC is associated with improved survival. CESP is a novel algorithm derived from the GEICAM 2006-03 clinical trial which is based on the association of treatment response with correlation to each PAM50 subtype centroid. CESP has been validated in two datasets consisting of patients with HR+/HER2- disease treated with either NAC or neoadjuvant endocrine therapy (unpublished data). Here, we examined whether CESP score is associated with chemosenstivity in another independent dataset. **Methods:** 216 pre-/post-menopausal patients from the multicenter Spanish cohort, with banked and centrally analyzed FFPE HR+/HER2- pre-treatment breast tumor samples were re-consented. All patients were treated with anthracycline/taxane-based NAC between years 2003-2014. The Prosiga assay was performed on the NanoString nCounter Dx Analysis System at Hospital Universitario Virgen de la Victoria de Málaga and CESP score and cutoffs were determined from those results at Hospital Clinic of Barcelona (blinded from clinical data). Univariate and multivariable analyses were used to evaluate the association of CESP score with centrally determined Residual Cancer Burden (RCB). **Results:** 207 core-needle pre-treatment biopsy samples yielded passing results (95.8%) of which 180 had clinical data including an RCB classification. The overall proportion of RCB-0/I in this patient population was 18.9%. In univariate and multivariable (adjusted for tumor size, age at diagnosis and grade) analyses, CESP as a continuous variable was significantly associated with response (p < 0.001 and p = 0.003). The rates of response in CESP-high, -med and -low groups were 10.3%, 15.2% and 30.4%, respectively (p = 0.006). The odds ratio of the CESP-low group for achieving a RCB-0/I was 3.80 (95% Confidence Interval 1.57-9.18) compared with the CESP-high group. Similar results were obtained after excluding PAM50 non-Luminal disease (n = 23).

**Conclusions:** CESP is a strong and independent predictor of pathological response in patients with HR+/HER2- disease treated with NAC.

**571** Poster Session (Board #59), Sat, 8:00 AM-11:30 AM

**Efficacy and safety of first-line palbociclib plus letrozole compared with letrozole alone in patients aged ≥ 65 years with estrogen receptor-positive, HER2-negative advanced breast cancer: A subgroup analysis by age of the PALOMA-1/TRIO-18 trial.** First Author: John Crown, Irish Cooperative Oncology Research Group, Dublin, Ireland

**Background:** Of the estimated 232,670 new cases of breast cancer (BC) diagnosed in the U.S. in 2014, 40% will have occurred in women ≥ 65 years. In this population, the most common type of BC is estrogen receptor-positive (ER+), HER2-negative (HER2-) for which endocrine treatment (ET) is currently the treatment of choice. The odds ratio of BC-TR, median age (65 years).

**Methods:** Postmenopausal women (N = 165) with advanced ER+, HER2- BC were randomized 1:1 to receive P (125 mg/day for 3 weeks, 1 week off) plus L (2.5 mg/day) or L alone (2.5 mg/day). Of the 76 pts aged ≥ 65 years, 37 were assigned to P + L and 39 were assigned L alone. The primary endpoint was investigator-assessed progression-free survival (PFS). **Results:** In pts ≥ 65 years, the median PFS was 26.6 months (95% CI 12.6 – NR) for P + L, compared to 7.7 months (95% CI 3.7 – 10.7) for L alone (HR = 0.505, 95% CI 0.269 – 0.948; one-sided p = 0.015). In pts eligible for safety analysis, grade 3-4 neutropenia was reported in 56.8% in the P + L arm vs 27.9% in the L arm, leucopenia in 29.7% vs none, and fatigue in 10.8% vs none. In general, neutropenia associated with P + L was short-lived and did not require management with hematopoietic growth factors. **Conclusions:** The median PFS was > 3 times longer in the P + L arm than in the L arm alone for the subgroup of pts ≥ 65 years. The toxicity profile was consistent with that of entire study population. A phase III study evaluating P + L is ongoing; P + L is an important treatment option for elderly, as well as non-elderly, patients with ER+, HER2- advanced BC. Clinical trial information: NCT00721409.

**570** Poster Session (Board #58), Sat, 8:00 AM-11:30 AM

**Long-term safety profile of palbociclib (P) in combination with letrozole (L) as first-line treatment for postmenopausal patients with ER+ and HER2- advanced breast cancer (ABC) (PALOMA-1/TRIO-18).** First Author: Dennis J. Slamon, School of Medicine/Translational Oncology Laboratory, University of California, Los Angeles, Los Angeles, CA

**Background:** P is a selective and reversible oral CDK4/6 inhibitor. In a randomized phase (ph) II/I trial comparing P plus L (P + L) to L alone in patients (pts) with ER+ and HER2- ABC who had not received prior endocrine therapy for their ABC (Study 1003), P + L demonstrated significantly longer progression-free survival (PFS) vs L (20 vs 10 m; HR = 0.488, P = 0.0004). **Methods:** We analyzed reported Adverse Events (AE) from Study 1003 by time interval (0-6m, 6-12m, 12-24, and >24m), cumulatively (12 m, 24 m time points) and assessed latency (event onset) of pertinent Adverse Drug Reactions (ADRs). **Results:** As of Nov 2013, 95 pts received P + L. The median duration of treatment for P was 37.4d (range: 63-1682) for Ph[1] (n = 2420) and 42d (range: 7-1242) for Ph[2] (n = 83). The 6 m interval analysis of the most common (>15%) ADRs (Table 1) indicated that ADRs tend to occur with greater frequency within the first 6 m with some decrease in incidence over time. Comparison of the cumulative incidences between the end of the 2nd year and 1st year shows that the cumulative event rates of the most common ADRs such as neutropenia (76% vs. 76%), fatigue (45% vs 40%), leucopenia (45% vs. 39%) and anemia (34% vs. 30%) were stable. The cumulative event rates for Grade 3/4 events were also stable except for a slight increase in fatigue (5% vs. 3%). The median time to onset of neutropenia was (20d), leucopenia (36d), anemia (168d), and thrombocytopenia (140d). **Conclusions:** Long-term safety analysis suggests no evidence of any specific cumulative or late onset of toxicity with the prolonged treatment with P + L as first-line treatment for ER+ and HER2- ABC. Clinical trial information: NCT00721409.

**Summary of treatment emergent all causes ADRs by 6-m intervals (>15%).**

**572** Poster Session (Board #60), Sat, 8:00 AM-11:30 AM

The effect of palbociclib (P) in combination with letrozole (L) on bone metastases in women with ER+/HER2- metastatic breast cancer (MBC): Subanalysis from a randomized phase II study. First Author: Richard S. Finn, University of California, Los Angeles Medical Center, Los Angeles, CA

**Background:** Bone metastases (BM) are common in MBC. They are often the first and only site of distance disease. Patients with BM only usually have a protracted clinical course though increased bone pain and fractures can be debilitating. PALOMA-1/TRIO-18 was a randomized Phase II study, comparing P plus L (P + L) vs L alone as first-line treatment of advanced ER+ / HER2- BC. At final analysis, P + L doubled progression-free survival (Finn et al. Lancet Oncol 2015). In this sub-analysis, we evaluated the effects of P + L on bone metastases. **Methods:** 165 ER+ and HER2- postmenopausal women who were untreated for their ABC were randomized to receive L (2.5 mg/day) (N = 81) or L (2.5 mg/day) plus P (125 mg/day for 3 weeks on/1 week off) (N = 84). The primary endpoint was investigator-assessed PFS. Tumor assessments were performed every 8 weeks and bone scans every 12 weeks. PFS analysis was performed for those patients (pts) with objective progression determined based on the appearance of new bone lesion(s) and/or progression of existing bone non-target lesion(s). Patient reported outcomes (PRO) on pain severity (PS) and pain interference (PI) were assessed with Modified Brief Pain Inventory-Short Form (mBPI-st); **Results:** 75% of patients had bone disease at baseline (73% P + L vs. 77% L) and 18% had bone only disease (20% P + L vs. 15% L). Median PFS among pts who had objective PD due to the appearance of new BM and/or objective PD in any site (9 months (95% CI 4.7 – 11.3) for T pts vs 7.9 months (95% CI 6.0 – 10.8) for L pts). The median PFS of BM alone was 4 m (95% CI 2.3, 35) for L (n = 16). Among those patients with bone-only disease at baseline, significant prolongation of PFS (NR P + L vs 13.3 m, HR = 0.294, 95% CI 0.092-0.945). Numerical differences in PI and PS scores in favor of P + L over L were observed from the FRO data collected from the randomized phase II study. These findings suggest that the combination of P + L demonstrated a significant improvement in PFS; P + L leads to clinically meaningful delays in progression in the bone. Clinical trial information: NCT00721409.
Impact of locoregional therapy among women 70 years or older with early stage hormone receptor positive breast cancer: A population based study.

First Author: Shaheenah S. Dawood, Dubai Hosp, Dubai, United Arab Emirates

Background: In 2004 the CALGB 39343 trial determined that omission of radiation therapy after lumpectomy in women ≥ 70 years with ER + T1N0 breast cancer did not significantly impact outcome. This retrospective study aimed to determine trends in locoregional therapy practice in this cohort and to determine its impact on outcome. Methods: Using SEER registry we identified 27852 pts who were ≥ 70 years with ptT1-2, N0-1 breast cancer diagnosed between 1990 and 2005. A cutoff of 2005 was chosen to ensure a minimum of 5 years of follow up. Pts were divided into 3 groups based on locoregional therapy received: a) mastectomy, b) lumpectomy plus radiation therapy and c) lumpectomy alone. Breast cancer specific survival (BCSS) was calculated. Both Cox models were then fitted to evaluate the association between type of locoregional therapy and BCSS, adjusted for various pt and tumor characteristics. We expanded the cohort to include pts diagnosed until 2010 to look at practice trends in locoregional therapy. Results: 11533 (41.4%) pts had mastectomy, 13035 (56.8%) pts had lumpectomy plus radiation therapy and 3284 (11.8%) pts had lumpectomy alone. At a median follow-up of 92 months, 5-year BCSS was 97%, 98% and 97% among pts who had undergone mastectomy, lumpectomy plus radiation and lumpectomy alone, respectively (p = 0.0001). Compared to those who underwent mastectomy, there was no significant difference in breast cancer deaths among those who underwent lumpectomy plus radiation (HR 0.89, 95% CI 0.71-1.03, p = 0.056) or lumpectomy alone (HR 1.13, 95% CI 0.94-1.36, p = 0.18). Comparing 1990, 2005 and 2010, the proportion of pts undergoing mastectomy gradually decreased (74.2%, 27.4% and 25% respectively) while proportion undergoing lumpectomy plus radiation increased (21.1%, 53.5% and 52.7% respectively) as did proportion undergoing lumpectomy alone (4.7%, 21.1% and 22.4% respectively). Conclusions: Omission of radiation therapy after lumpectomy in older women did not seem to significantly impact BCSS in this population based analysis. Although the use of lumpectomy without radiation increased over time, post-lumpectomy radiation is still the more favored treatment practice.

Clinical efficacy and safety profile of palbociclib (P) in combination with letrozole (L) as first-line treatment in patients (pts) with ER+ and HER2-advanced breast cancer (ABC) who have not received any systemic treatment (ST): A subgroup analysis of PALOMA-1/TRIO-18. First Author: Richard S. Finn, University of California, Los Angeles Medical Center, Los Angeles, CA

Background: P is an orally active inhibitor of CDK4/6. In a randomized phase II study, P + L significantly prolonged progression-free survival (PFS) vs L alone (20 vs 10 mo; HR = 0.488; P = 0.0004; Finn et al, Lancet Oncol 2015) in ER+/HER2- ABC as first-line treatment. Given that pts who did not receive any systemic treatment (ST) may have different disease biology/course from those treated and relapsed from early stage disease and many pts may initiate endocrine therapy (ET) alone, we investigated the benefit of P + L in this subgroup in the PALOMA-1/TRIO-18 study. Methods: 165 ER+ and HER2- postmenopausal pts who were treatment-naive for their ABC were randomized to receive L (N = 81) or P + L (N = 84). A subset of pts did not receive any ST in the adjuditant setting prior to randomization (P + L = 44, L = 37). The primary endpoint was investigator-assessed PFS. Tumor assessment was performed every 8 weeks. Tumor biopsies were collected for correlative biomarkers. Results: Clinical characteristics at baseline were well balanced on median age (P + L vs. L: 63 vs 62), ECOG PS (0/1 59%/41% vs. 49%/51%) and site of disease (visceral/bone only/other): 55%/14%/32% vs. 51%/14%/35%. Observed mPFS was 24 m (95% CI 13, 35) for P + L vs. 8 m for L (95% CI 6, 13) with HR of 0.35 (95% CI 0.19, 0.67). AUC-calculated ORR was 48% (95% CI 33%, 63%) vs. 41% (25%, 58%), clinical benefit rate (PR + SD ≥ 24 wks) was 84% (70%, 93%) vs. 70% (53%, 84%). The most common treatment emerged adverse events (grades 3/4) for P + L arm were neuropathy (67%), fatigue (49%), leucopenia (49%), and anemia (35%), consistent with the overall safety profile. Tissue samples were available in 73 pts. Loss of BR expression by immunohistochemistry was rare (5.4%). Ki67 baseline did not predict response. Conclusions: The addition of P to L increased by > 2 the PFS in pts who did not receive ST for their ER + MBC. The most common AE's are manageable. Favorable risk benefit profile suggests P + L considered for this group of pts. Clinical trial information: NCT00721409.

A combined screening approach of Fracture (Fx) Risk Algorithm (FRAX) and Trabecular Bone Score (TBS) to identify osteoporotic-range fracture risk (ORFR) in breast cancer patients treated with aromatase inhibitor (AI). First Author: David B. Page, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The NCCN recommends serial bone mineral density (BMD) measurement with dual energy x-ray absorptiometry (DXA) to diagnose and treat AI-associated osteoporosis. The FRAX algorithm identifies additional patients with ORFR who may benefit from anti-resorptive therapies (ART). The TBS, which measures bone microstructure by DXA, is an independent indicator of ORFR. Here, we retrospectively evaluate the utility of a combined screening approach (FRAX + BMD + TBS) in identifying ORFR at baseline and following AI. Methods: Breast cancer patients > 60 years, treated with AI and no ART between 2006-12, who had serial DXA at Memorial Sloan Kettering Cancer Center were identified (n = 744). BMD, FRAX, and TBS were evaluated at baseline (< 3 months from AI initiation) and at 12-24 months, and various screening strategies for identifying ORFR were assessed. Based on National Osteoporosis Foundation criteria and Manitoba TBS study fracture rates, ORFR was defined as: BMD T-score <-2.5; or <-2.0 osteoporosis-associated-10 year fracture risk by FRAX; or TBS score ≥ 1.2 with BMD T-score ≥ -1.0. Results: Following AI, lumbar spine (LS)-BMD declined in 75% of patients (median: -2.9%; SD: 4.3%) and TBS declined in 58% of patients (median: -1.0%; SD: 7.7%). Declines in LS-BMD and TBS were not correlated (Spearman r = -16, p = NS) and were not influenced by age, BMI, ethnicity, or chemotherapy (by Wilcoxon rank-sum). Compared to BMD alone, a combined screening approach (BMD + FRAX + TBS) identified an additional 15% of patients with ORFR at baseline. (Table) Following AI, an additional 29% developed ORFR by BMD alone, versus 4% by BMD + FRAX + TBS. Conclusions: Alcs caused bone loss, leading to ORFR as measured by BMD, FRAX, and TBS. Because FRAX and TBS are derived from DXA and patient history, a combined screening approach may efficiently and cost-effectively identify additional BC patients with ORFR who may benefit from ART.

GHRR-receptor as a new targetable biomarker in breast cancer and its correlation with ER/PR/HER2 status. First Author: Mehrdad Nadji, University of Miami Jackson Memorial Hospital, Miami, FL

Background: In addition to its nominative function as a neurohormone acting on the pituitary, growth hormone-releasing hormone (GHRR) has been shown to modify the growth behavior of numerous cancers, including breast. GHRR is produced by tumor cells, acts in an autocrine/paracrine manner, and requires the presence of the GHRR receptor (GHRR-R) on the tumor cells to exert its effects. The aim of this study was to evaluate the relationship of GHRR-R expression in different subtypes of breast cancer (triple negative, HER2-positive and hormone receptor-positive subsets). Methods: The cohort consisted of 96 primary breast cancers. Immunohistochemistry for GHRR-R was performed on paraffin sections and the staining results were assessed semi-quantitatively from 0 (negative) to 3+ (strongly positive). Patients with 0 or 1+ GHRR-receptor expression were classified as having low expression, and 2+ or 3+ as high expression. The ER/PR/HER2 levels of each tumor were correlated with the GHRR-R IHC results. Results: 62/96 (65%) patients had hormone receptor (HR) positive (ER- and / or PR-positive), 12/84 (14%) had HER2-positive, and 25/84 (30%) had triple negative breast cancers (TNBC). 92% of HER2-positive, 68% of HR-positive, and 44% of TNBC had high expression of GHRR-R. HER2-positive primaries had a significantly increased frequency of high (11/12, 92%) vs. low (1/12, 8%) GHRR-R expression compared to HER2-negative primaries (p = 0.018). There was no difference in GHRR-R expression by HR status (p = 0.85). The TBS was not correlated with the frequency of high (11/25, 44%) vs. low (14/25, 56%) GHRR-R expression compared to non-TNBC (p = 0.041). Conclusions: GHRR-R is expressed by the majority of primary mammary carcinomas regardless of their hormone receptor status. HER2-positive tumors were more likely to express high levels of GHRR-R, which represents a potential target. This finding could potentially serve as a basis for therapeutic approaches using synthetic peptide GHRR-R antagonists that have already shown significant efficacy combined with minimal pharmacologic side effects in experimental models.
577 Poster Session (Board #65), Sat, 8:00 AM-11:30 AM
Activation of PI3K/AKT/mTOR pathway in ER+ breast cancer: Analysis of paired primary and metastatic tumor samples. First Author: Teresa R. Pancamo, Oncology Division, Hospital de Santa Maria - CHLN and Instituto de Medicina Molecular, Lisboa, Portugal

Background: The activation of the mammalian target of rapamycin (mTOR) pathway is associated with resistance to endocrine therapy in breast cancer. Our aim was to evaluate changes in activation of the PIK3/AKT/mTOR pathway between primary and corresponding metastatic tumor samples in estrogen receptor (ER) positive breast cancer patients and to test whether phosphorylated protein levels are predictive of overall survival (OS). Methods: Phosphorylated forms of AKT (p-AKT) and S6 (p-S6) were assessed by immunohistochemistry on archival paraffin embedded samples of primary breast tumors and distant metastases collected from 132 breast cancer patients in two centers. A semi-quantitative scoring system (H-score) was used, combining the intensity of staining and the percentage of stained cells. The difference between expression of p-AKT and p-S6 in primary and metastatic tumor samples was analyzed using the Wilcoxon signed-rank test and the correlation of expression of p-S6 with OS using the Cox’s proportional hazards model.

Results: Overall, 93 cases ER and/or PR positive were analyzed. The median age was 55 years; 66 patients were treated with endocrine therapy in adjuvant and/or palliative setting. The median time to relapse was 42.7 mo and the median follow-up was 73.4 mo. The median OS from time of metastatic sample collection was 26.2 mo. The p-AKT H-score index was higher in primary tumor samples when compared to metastases (p = 0.0003). The p-S6 H-score index of the primary tumor and metastatic samples was not significantly different (p = 0.26); concordance between paired samples was 60% using median as cut-off; only metastatic p-S6 H-score index associated with OS (p = 0.022) and the association was also significant when analyzed by quartiles (p = 0.001). Conclusions: Expression levels of p-AKT and p-S6 are significantly lower in metastatic tumor samples. Metastatic p-S6 higher expression might predict worse prognosis in ER+ breast cancer patients, and deserves further study as a novel predictive breast cancer biomarker.

579 Poster Session (Board #67), Sat, 8:00 AM-11:30 AM
The pattern of somatic mutations and chromosomal copy number variations (CNV) in young breast cancer (BC) patients (pts). First Author: Hatem Abdel Azim, Institut Jules Bordet, Brussels, Belgium

Background: Young age at diagnosis is associated with poor prognosis, different distribution of BC subtypes and unique gene expression patterns. Yet, it is unknown whether young pts have different prevalence of somatic mutations or CNV. Methods: This analysis was performed on The Cancer Genome Atlas dataset. We divided pts according to their age into; young (< 45 years) and old (≥ 45 years). We evaluated the association between age as a continuous variable and number of somatic mutations, CNV (amplification, gain, or deletions) using the chi-square test. We examined the genes showing somatic mutations or CNV in young pts and compared it to older pts using t-test. Results: 959 (138 < 45y) and 788 (124 ≥ 45y) pts were included in the somatic mutation and CNV analyses, respectively. Young age at diagnosis was associated with less number of somatic mutations, mainly in ER- BC (r = 0.21, p = 0.002). Within young ER+ pts, mutations in PIK3CA (32.6%), Q47A3 (16.8%) and TP53 (16.8%) were the most common with prevalence highly comparable in older pts. Of relevance, higher rates of mutations in NTRK2 (5% vs.0%, p < 0.0001) and ARID1A (7% vs.2%, p = 0.03) were observed in young compared to old ER+ pts. No major differences were observed in the pattern of somatic mutations in ER- BC according to age, with mutations in TP53 (67.5%), RYR2 (13.5%) and CSMD2 (10.8%) being the most common in young pts. We found more chromosomal amplifications in young pts with amplifications events decreasing as a function of age but only in ER- BC (r = -0.13, p = 0.007). 22% of young pts showed AXIN2 amplification vs. 4% in older patients (p < 0.0001). No other relevant associations were observed between CNV and age at diagnosis. Conclusions: This is the first analysis to interrogate the impact of young age at BC diagnosis on the pattern of somatic mutations and CNV. We observed that young age at diagnosis is associated with 1) less number of somatic mutations, and 2) more chromosomal amplifications, the latter observed only in ER+ disease. AXIN2, which regulates the Wnt/B-catenin pathway appear to be more amplified in young pts and if further validated could represent a potential treatment target in these women.

578 Poster Session (Board #66), Sat, 8:00 AM-11:30 AM
A prospective comparison of ER, PR, Ki67 and gene expression in paired sequential core biopsies of primary, untreated breast cancer. First Author: Assistant Mark Thompson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Sequential biopsy of breast cancer is increasingly favoured to assess biomarker effects and drug efficacy. The “window of opportunity” in the preoperative setting is recognised as advantageous to test biomarker changes in response to therapeutic agents in previously untreated cancers. However, tissue sampling over time could confound biomarker effects. This study addressed the rate of appearance of paired, sequential biomarker measurements on primary, operable breast cancer in the absence of drug therapy. Methods: Immunohistochemistry was performed for ER, PR and Ki67 on paired preoperative/operative tumor samples taken from untreated patients within 2 weeks of each other. Additionally, microarray analysis on mRNA extracted from formalin fixated paraffin embedded cores was performed using Affymetrix based arrays on paired core biopsies analysed using Ingenuity Pathway Analysis (IPA) and Gene Set Analysis (GSA).

Results: In 41 core/resection pairs, the recognised trend to lower ER, PR and Ki67 score on resected material was confirmed: concordance for ER, PR and Ki67 within status in index of Allard or Quickscore was 90%, 74% and 80% respectively. However, in 23 paired core samples (diagnostic core v on table core), Ki67 used a cut off of 13.25% was concordant in 22/23 (96%) and differences in ER and PR immunohistochemistry by Allred or Quickscore between the pairs did not impact hormone receptor status. IPA and GSA demonstrated substantial gene expression changes between paired cores at the mRNA level, including under expression of ER pathway analysis, despite the absence of drug intervention. Conclusions: This study addresses the potential impact of sampling effects over time in the context of preoperative (window of opportunity) trials. Sequential core biopsy of primary breast cancer (but not core versus resection) was consistent and may be appropriate to assess the effects of drug therapy in vivo on ER, PR and Ki67 using immunohistochemistry. Conversely, studies including mRNA expression may require non-treatment controls to distinguish therapeutic from biopsy differences.

580 Poster Session (Board #69), Sat, 8:00 AM-11:30 AM
Impact on relapse free survival (RFS) of time to hormone therapy (HTx) after diagnosis (Dx) of low risk hormone receptor positive (HR+) early breast cancer (BC). First Author: Wen Yee Chay, BC Cancer Agency, Vancouver, BC, Canada

Background: Retrospective series show worse RFS for adjuvant chemotherapy (CTx) delay. We hypothesized the same effect for delays to HTx in low risk HR+ BC, for which CTx benefit is low. Methods: Histopathologic and demographic data were collected for all patients referred to the British Columbia Cancer Agency with a new dx of stage I or II, grade 1 or 2, HR+, HER2 negative BC from 01/2005 to 12/2009. Neoadjuvant-treated, prior or synchronous bilateral, neo- or adx CTx prior to release, or > 53 weeks (w) to HTx start were excluded. RFS was calculated for three pre and postmenopausal cohorts (C), defined as 1) < 20 w; 2) 20-< 34 w; 3) 34-< dx to HTx, based on first prescription. Multivariable (M) analysis identified factors significant for RFS. Results: Median follow up for the 3737 cases was 6.4 yrs, 80% were stage I: 28% of C1 and 69% of C3 were stage II. 90% were strongly estrogen receptor (ER) positive. Median age was 64, 58, and 51y in C 1, 2, and 3. Most were postmenopausal (71%) and 23% had CTx (< 1%, 27%, and 76% of C 1, 2, 3). HTx was started < 20 w and > 34 w after dx in 1% and 15%, respectively. Five year RFS was 97.3%, 96.4%, and 95.5% for C1, 2, and 3 (p0.018). The table below shows univariate (U) and M results, M hazard ratios (Hz) and 95% confidence intervals. Conclusions: While unnecessary delays to HTx should be avoided, we did not detect a significant impact on RFS of up to 1 year delay in low stage and grade, population-based HR+ HER2 negative BCs. RFS was influenced by stage, PR (low: all grade and ER level independent), and age at dx (premenopausal). If there is an impact on early RFS of HTx delay, it is likely subtle and only in premenopausal women. Our results do not exclude an impact on late RFS or in higher risk disease, or explore impact of longer delays.

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**Correlation between the DCIS Score and traditional clinicopathologic features in the prospectively-designed Ontario population-based validation study. First Author: Eileen Rakovitch, Sunnybrook Health Sciences Centre, Toronto, ON, Canada**

**Background:** In the Ontario population based study, the DCIS Score was significantly associated with 10 year risk of an ipsilateral local recurrence (LR) in women treated with breast conserving surgery (BCS) without radiation (RT) (P < 0.001). Here we evaluate correlation between DCIS Score and clinicopathologic (CP) features in the same cohort, and whether DCIS Score provides independent recurrence risk information. **Methods:** The study population included 571 women diagnosed with DCIS in the province of Ontario from 1994 – 2003 prospectively selected for treatment with BCS without RT. CP variables examined included age at diagnosis, DCIS tumor size, DCIS nuclear grade, comedo necrosis (absent, focal, or extensive), histologic type, multifocality, and surgical margin width. The association between DCIS Score and CP variables was examined by spearman rank correlation, and proportional hazards regression models were used to determine variables significantly associated with LR. **Results:** Tumor size (p = 0.002), multifocality (p < 0.001), histologic type (p = 0.005), and nuclear grade (p = 0.04) were significantly associated with LR. In a multivariable analysis, including grade (rs = 0.02), DCIS Score was statistically significantly associated with LR. Of the 20 pts (median age 54 years), 40% had low cyclin D1 (LCD1) expression vs. 60% with HER2 (n = 12). All but 1 pt in the LCD1 cohort had poorly differentiated (PD) invasive ductal carcinoma (IDC) (87.5%). The remaining pt had moderately differentiated (MD) invasive ductal & lobular carcinoma (mixed). 50% of HCD1 pts had PD tumors while 16.7% were MD. In the HCD1 cohort, 41.7% were IDC, 33% ILC and 25% mixed. Four pts were HER2-neu +, 2 in the LCD1 group & 2 in the HCD1 group. 75% in the LCD1 group were postmenopausal vs. 58% in the HCD1 cohort. TAM exposure was higher in the LCD1 group compared to the LCD1 group (58% vs. 25%). LN positivity was higher in the HCD1 group compared to the LCD1 group (58% vs. 37.5%). Median time to progression (TTP) with F was significantly increased in tumors with LCD1 expression compared to those with LCD1 (1149 days vs. 133 days, respectively; p = 0.027). **Conclusions:** TTP on F is significantly increased for HR + BC compared to HR + BC with LCD1 expression. Clinical trials exploring the use of F in BCs with HCD1 expression may be warranted.

**Docetaxel, cyclophosphamide and trastuzumab as neoadjuvant chemotherapy in HER2-positive primary breast cancer. First Author: Katsuhiko Nakatuka, University of Medicine, Kyoto, Japan**

**Background:** The current standard treatment of primary systemic therapy (PST) in HER2+ breast cancer is antracyclines and/or taxanes combined with trastuzumab which demonstrates high pathological complete response (pCR). The pCR is considered as a predictive marker of prognosis although results are slightly different depending on the hormone receptor status. The efficacy and tolerability of docetaxel, cyclophosphamide and trastuzumab (HER-TCh) as neoadjuvant chemotherapy (NAC) remains unclear. We performed a prospective multicenter study of HER-TCh NAC in HER2+ primary breast cancer. **Methods:** Eligible patients had HER2+ invasive breast cancer that measured more than 1cm, less than 7 cm and NG–N1 clinically between July 2011 and February 2014. Four cycles of HER-TCh (6 mg/kg loading dose 8 mg/kg, 75 and 600 mg/m²) were administered intravenously every 3 weeks as NAC. We investigated the pCR of primary breast tumors; pCR was defined as no histological evidence of invasive carcinoma, or the appearance of only ductal carcinoma in situ. Cardiac toxic effects, defined as a decrease in left ventricular ejection fraction (LVEF), were assessed by echo-cardiography at baseline, at the completion of NAC. **Results:** 42 patients were enrolled. The completion rate for 4 cycles of HER-TCh was 97.6 % (41 of 42). Relative dose intensity was 98.0 % for HER-TCh therapy. Overall pCR rate was 43.9 % (18 of 41). pCR rate for patients with luminal HER2 (ER+, HER2+), and HER2 enriched (ER-, HER2+ ) were 40.0 % (8 of 20), and 47.6 % (10 of 21), respectively. pCR was achieved with about same probability in each subtype. LVEF at baseline and, the completion of NAC were 66.1% and 64.8%, respectively. **Conclusions:** Four cycles of HER-TCh might be one of the NAC options for HER2+ positive breast cancer. There were no patients with decrease in LVEF during the treatment. Clinical trial information: UMIN000013263.

**Cyclin D1 as a biomarker of response to fulvestrant (F) in hormone receptor-positive (HR+) breast cancer (BC). First Author: Krystal Pauline Chevretta, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY**

**Background:** Overexpression of cyclin D1 (CD1) occurs in up to 45% of BCs. High cyclin D1 expression (HC1D) has been shown to significantly increase overall survival yet the opposite is observed in HR+ BC patients (pts) with HCD1 who receive tamoxifen (TAM). TAM is the drug of choice for premenopausal pts with ER+ BC. Numerous studies report an association between CD1 overexpression & TAM resistance. Thus, a large fraction of pts who receive TAM may not benefit from it. F may serve as an alternative approach for these pts. We hypothesized that pts with HCD1 will have a better duration of response to F compared to those with low expression. In order to address the above, we retrospectively analyzed CD1 expression in HR+ metastatic BC (MBC) pts treated with F at our institution. **Methods:** 20 primary BCs were stained for CD1 expression. IHC was scored based on intensity as 0 (negative), 1+, 2+, 3+, & extent as 0 (< 10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), 4 (76-90%) & 5 (> 90%). A total score was subgrouped as low (0 to 4) or high (5 to 8). A retrospective chart review was performed to extract clinical data. The primary endpoint was duration of response to F as it relates to CD1 expression in HR+ MBC. **Results:** Of the 20 pts (median age 54 years), 40% had low cyclin D1 (LCD1) expression (n = 8) vs. 60% with HCD1 (n = 12). All but 1 pt in the LCD1 cohort had poorly differentiated (PD) invasive ductal carcinoma (IDC) (87.5%). The remaining pt had moderately differentiated (MD) invasive ductal & lobular carcinoma (mixed). 50% of HCD1 pts had PD tumors while 16.7% were MD. In the HCD1 cohort, 41.7% were IDC, 33% ILC and 25% mixed. Four pts were HER2-neu +, 2 in the LCD1 group & 2 in the HCD1 group. 75% in the LCD1 group were postmenopausal vs. 58% in the HCD1 cohort. TAM exposure was higher in the LCD1 group compared to the LCD1 group (58% vs. 25%). LN positivity was higher in the HCD1 group compared to the LCD1 group (58% vs. 37.5%). Median time to progression (TTP) with F was significantly increased in tumors with LCD1 expression compared to those with LCD1 (1149 days vs. 133 days, respectively; p = 0.027). **Conclusions:** TTP on F is significantly increased for HR + BC compared to HR + BC with LCD1 expression. Clinical trials exploring the use of F in BCs with HCD1 expression may be warranted.
Background: HannaH (NCT00950300) compared SC and IV trastuzumab (Herceptin SC [H SC] and IV [H IV]) as neoadjuvant–adjuvant therapy for HER2-positive (HER2+) breast cancer. Prior work showed that trastuzumab and chemotherapy also induces HER2 extracellular domain (ECD)-specific immunity. Increased immunity to HER2 was associated with improved long-term outcomes in breast cancer patients who received neoadjuvant–adjuvant therapy for HER2-positive breast cancer. Clinical trial information: NCT00950300.

Methods: In each of HannaH’s two treatment arms, H SC or H IV, all pts receive, after the first cycle, P in a single IV infusion followed by V for 1L of chemotherapy. V was administered at 25 mg/m2 in Cycle 1 followed by 30–35 mg/m2 on Days 1 and 8 of each subsequent cycle. The primary endpoint is investigator-assessed objective response rate (ORR) based on RECIST 1.1. Secondary endpoints include PFS, OS, and safety. Interim analyses for C2 are ongoing. Results: C2 was fully enrolled with 107 pts. At initial diagnosis, 25% of pts had de novo MBC. In (neo)adjuvant settings, 32% had received chemotherapy and 24% had prior T exposure. As of Jan 22, 2015, the median number of cycles received was 15 for P + T and 9 for V (range: 2–28). AEs were reported in 99% of pts. Grade ≥ 3 AEs were reported in 78% of pts. Grade ≥ 3 AEs in ≥ 5 pts were neutropenia (30.8%), hypertension (13.1%), diarrhea (5.6%), leukopenia (4.7%), infections (4.7%), and fatigue (4.7%). EFS rates per subgroup were estimated using the Kaplan–Meier method. Results were consistent for pCR and the efficacy per protocol population.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Brain metastasis (BM) is a serious complication of HER2+ breast cancer (BC). We evaluated prognostic factors for overall survival (OS) in a contemporary cohort of patients (pts) with HER2+ BCBM treated at a tertiary care institution. Methods: The Cleveland Clinic’s IRB approved BM database was used to identify HER2+ BCBM pts treated between 2000 and 2013. OS from the diagnosis of BM was the primary endpoint. Breast-specific GPA (Spenduto et al, 2012), based on age at BM diagnosis (years >60), KPS (90-100 vs 70-80 vs 60 vs <60), and BC subtype (luminal B versus Her2), was correlated with OS. Cox proportional hazards models with and without stepwise variable selection were used for data analysis. Recursive partitioning was used to identify cut points. Results: Data from 215 pts were analyzed. Median age was 52 (23-86); 51% of pts had KPS 90-100, 23% KPS <80; 52% of pts were ER and/or PR+, and 82% had extracranial metastases at BM diagnosis. BM were initially treated with WBRT +/- surgery (62%), or WBRT + stereotactic radiosurgery +/- surgery (17%). Median OS was 16.9 months (95% CI. 13.0-22.5). Using breast specific GPA, 63% of pts had the most favorable profile (scores of 3.5-4), 37% had the second most favorable profile (scores 2.5-3) while a single patient scored 1.5-2. In univariate analysis, breast GPA was associated with OS (p = 0.004) as were 2 of its components, KPS (p <.0001) and age (p < .01); breast subtype was marginally significant (p = .09). Multivariable analysis again identified KPS (p <.0001) and age (p < .003), as independent predictors (with difference categorizations). Bone/ lung metastases (p = .007) rather than BC subtype were predictive of OS. An updated HER2+ specific GPA was thus defined by assigning “points” to each factor: KPS >70 = 2 points; 1 point each for age <50 and no lung or bone metastases. Based on the cumulative number of points, 3 prognostic groups were identified: favorable (3-4 points, 49% pts), intermediate (2 points, 30% pts) and unfavorable (0-1 point, 21% pts) with median OS of 25.7, 13.7 and 5.4 months, respectively. Conclusions: This study confirms the prognostic value of the breast GPA, and proposes a modified HER2+ specific version.

Background: A considerable proportion of patients (pts) with HER2-negative (HER2-) metastatic breast cancer (MBC) present with elevated serum levels of the HER2 extracellular domain (sHER2) and/or HER2-overexpressing circulating tumor cells (CTCs) during their further clinical course. These “occult” HER2-positive (HER2+ ) pts may be candidates for anti-HER2 therapy (Tx) albeit normally not subjected to such treatment. This retrospective study was undertaken to gain more insights into the feasibility of HER2-directed Tx in occult HER2+ MBC pts in the clinical routine. Methods: From our database, we identified 26 pts with heavily pretreated HER2- MBC (ER+ , 21 pts) showing sHER2 values >15 ng/mL (6 pts), HER2+ CTCs (6 pts), or both (14 pts) having failed 2-16 prior systemic treatments (median: 7) who did not qualify for recruitment onto a prospective clinical trial. All pts received anti-Her2 Tx with trastuzumab (H; 14 pts), lapatinib (L; 4 pts), H+L (2 pts), or H+ pertuzumab (H+ P; 6 pts). HER2-targeting Tx was given alone (4 pts), or in combination with endocrine agents (4 pts), cytotoxics (16 pts), or other targeted drugs (2 pts). Responses were scored according to RECIST 1.1, OS was calculated from the start of HER2-directed Ctx until death from any reason or loss to follow-up by using Kaplan-Meier statistics. Results: Anti-Her2 Tx was generally well tolerated and no clinical treatment-related AEs were >16.1 wks (range 1.0-56.1 wks). In 2 pts with L and 1 pt with H+L, Tx was prematurely stopped due to toxicity (diarrhea, fatigue). 10 PR, 10 SD, 5 PD, and 1 non-evaluable (NE) pt accounted for an objective response rate (ORR) of 38.5% and a clinical benefit rate (CBR) of 76.9%. Median OS was 62.9 wks. Conclusions: Our findings indicate that anti-HER2 Tx may be a valid option in pts with heavily pretreated HER2- MBC with pathological sHER2 values and/or HER2+ CTCs in the clinical routine. Thus, results of ongoing randomized trials in this setting are eagerly awaited.
Correlation of trastuzumab treatment benefit with quantitative HER2 expression levels in HER2 positive metastatic breast cancer. First Author: Bernd Bachemier, Institute of laboratory medicine, Ludwig-Maximilians-University, Munich, Germany

Background: The HERmark Breast Cancer Assay (Monogram Biosciences) is used as an adjunct to HER2 immunohistochemistry (IHC) and HER2 fluorescence in-situ hybridization (FISH) to determine the HER2 status of breast cancer (BC). Based on the high degree of concordance of HERmark with centrally determined HER2 status by IHC/FISH, it is expected that HER2-positive BC patients would realize greater benefit from trastuzumab treatment than HERmark negative BC patients. In the current study, this hypothesis was confirmed using a cohort comprised of: (1) HER2 positive BC patients treated before the availability of trastuzumab, (2) trastuzumab-treated HER2 positive BC patients and (3) HER2 negative BC patients. Methods: HERmark was performed retrospectively on paraffin-embedded tumors derived from 305 metastatic breast cancer patients in the Munich Cancer Registry with a median follow up of 10 years. Cases were evenly divided between trastuzumab-untreated HER2 positive (n = 91), trastuzumab-treated HER2 positive (n = 115) and HER2 negative (n = 99) tumors. Cutoffs for HERmark positive and negative status were pre-specified (Huang, Am J Clin Pathol, 134:303 2010). Results: HER2 positive patients treated with trastuzumab had longer overall survival (OS) than those not treated with trastuzumab, as expected (HR = 0.35; p < 0.0001). As reassessed by HERmark, HER2 positive patients treated with trastuzumab experienced longer OS (HR = 0.33; p < 0.0005). In contrast, the benefit of trastuzumab treatment in HERmark negative patients was not statistically significant (HR = 0.55; p = 0.13). Additionally, there was a statistically significant interaction between the degree of trastuzumab benefit and quantitative levels of HER2 expression within the HER2/IHC positive subset (Interaction p = 0.032). Potential correlations between additional markers, including p95HER2 and HER3, and treatment outcome are currently being assessed. Conclusions: The HERmark assay identified breast cancer patients who benefited from trastuzumab treatment. Within this group, increased levels of quantitative HER2 expression correlated with increased degree of benefit from trastuzumab therapy.

Evaluation of the Breast Cancer Index in patients with HER2+/HR+ breast cancer for risk of late recurrence and potential extended endocrine benefit. First Author: Ruth O’Regan, Emory Univ, Atlanta, GA

Background: Hormone-receptor positive (HR+) early stage breast cancer patients (pts) are at risk for late (> 5 year) distant recurrence (DR) and are now considered for extended (10 year) endocrine therapy (EET) to prevent late disease relapse. Approximately 50% of all HER2+ breast cancer pts are HR+ (EET). Clinical trials investigating the benefit of EET to reduce late DR have included HER2+/HR+ pts, but subset analyses in comparison to HER2-/HR+ have been limited. Breast Cancer Index (BCI) is a gene expression based assay validated for advanced stage disease and predicts benefit from EET using the endocrine response biomarker HoxB13/IL17BR (H/I). This study compared BCI results and clinicopathological factors in HER2+/HR+ vs HER2-/HR+ breast cancer. Methods: Consecutive cases with known HER2 status (N = 1182) submitted for BCI clinical testing were analyzed for pt characteristics and BCI reporting rates according to HER2 status. Fisher’s test was used to compare results between subgroups. Results: 10% of BCI testing with positive BCI results on HER2+/HR+ and HER2-/HR+ pts were classified. BCI and H/I categorizations by HER2 status.

<table>
<thead>
<tr>
<th>BCI Risk Classification</th>
<th>HER2+ Cohort (N = 140)</th>
<th>HER2- Cohort (N = 1042)</th>
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<tbody>
<tr>
<td>Low</td>
<td>18 (13%)</td>
<td>564 (54%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>40 (29%)</td>
<td>283 (27%)</td>
</tr>
<tr>
<td>High</td>
<td>82 (59%)</td>
<td>195 (19%)</td>
</tr>
<tr>
<td>H/I Categorization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>45 (32%)</td>
<td>646 (62%)</td>
</tr>
<tr>
<td>High</td>
<td>95 (69%)</td>
<td>396 (38%)</td>
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Conclusions: Molecular subtyping with BluePrint 80-gene profile classification by molecular subtype can aid in the selection of therapy for patients with breast cancer. However, at present, the methodology for molecular subtyping is not standardized. The aim of the prospective NBRST study is to compare chemosensitivity as defined by pathological Complete Response (pCR) using the BluePrint (BP) functional subtype profile vs. conventional IHC/FISH subtype. Methods: The study includes women aged 18–90 with histologically proven breast cancer, written informed consent, no excision biopsy or axillary dissection, and no prior therapy for breast cancer. Neoadjuvant Chemotherapy (NCT) was at the discretion of the physician adhering to NCCN approved or other peer-reviewed regimens. BP in combination with MammaPrint classifies patients into 4 molecular subgroups: Luminal A, Luminal B, HER2 and Basal. Results: 721 patients had definitive surgery. 58/335 (17%) IHC/FISH HR+/HER2- patients were reclassified by BP as Basal (57) or HER2 (2). The 12p22/22q (1%) HER2+/HER2+ patients evaluated re-classification as BP Luminal (67) or BP Basal (25). 7/164 (4%) IHC/FISH triple negative (TN) patients were re-classified as BP Luminal (5) or BP HER2 (2). NCT pCR rates were 3% in Luminal A and 9% in Luminal B patients versus 10% pCR in IHC/FISH luminal patients. The NCT pCR rate was 54% in BP HER2 patients. This is significantly superior (p < 0.001) to the 12p22/22q (1%) HER2+/HER2+ patients. BP Basal and IHC/FISH HER2+ patients (40%). BP Basal and IHC/FISH TN had a pCR rate of 35%. Functional BP subtyping divided the 137 IHC/FISH triple positive patients into two major subgroups: BP Luminal (n = 66, pCR = 11%) and BP HER2 (n = 60, pCR = 45%). 11 patients were re-classified as BP Basal with pCR = 45%, BP HER2 with pCR = 11%. Conclusions: Molecular subtyping with BP leads to a reclassification of 23% of tumors. The reclassification is most prominent in classically assessed triple positive patients where 48% of patients are re-assigned to the less responsive BP Luminal-type group vs. 44% of patients assigned to the responsive BP HER2-type group. These findings confirm the potential of molecular subtyping for treatment decision by BluePrint functional subtype classification. Clinical trial information: NCT01479101.
Effect of ranolazine administered after trastuzumab treatment on cardiotoxicity in mice. First Author: Nicola Maurea, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione Giovanni Pascale- IRCCS, Naples, Italy

Background: Trastuzumab (T), a monoclonal antibody against ErbB2, has improved the prognosis of breast cancer patients, but ErbB2 blockade in cardiomyocytes can produce asymptomatic left ventricular dysfunction and heart failure, whose mechanism has not been elucidated and can include changes in Ca2+ regulation. We aim at assessing whether Ranolazine (R), an inhibitor of the late sodium current, administered after T treatment, blunts T cardiotoxicity in vivo and in vitro. Methods: In vitro, rat H9C2 cardiomyoblasts were treated with T (0.2μM) for 3 days and then treated in the absence or presence of R (1μM or 10μM) for 3 days. In vivo, fractional shortening (FS) and ejection fraction (EF) were measured by M-mode echocardiography and radial and longitudinal strain (RS and LS) were measured using 2D speckle-tracking, in C57/B6L mice, at 0, 2 and after 7 days of daily administration of T (2.25 mg/kg/day). These measurements were repeated after 5 days of T treatment (305 mg/Kg/day) initiated at the end of T treatment. We have divided mice in 4 groups. The first group (G1) was treated with T for 7 days. The second group (G2) was treated with T for 7 days and then treated with R for 5 days. The other 2 control groups: G1 (sham) and G2 (no R). We have evaluated tissue expression of BNP (brain natriuretic peptide) by PCR analysis on heart tissue. Results: R reduced T toxicity in H9C2 cardiomyoblasts as evidenced by higher percentage of viable cells treated with T + R with respect to cells treated with T alone (p<0.01). In vivo, after 7 days with T, FS decreased to 48.7 ± 4.1%, p = 0.01 versus 62.3 ± 0.8% (sham), EF to 81.8 ± 3.5%, p < 0.01 versus 91.7 ± 0.5% (sham), RS to 21 ± 8.1%, p = 0.01 versus 43.2 ± 4% (sham), and LS to -11 ± 3.7%, p < 0.01 versus -38.8 ± 6% (sham). In mice treated with R for 5 days after T treatment, the indices of cardiac function recovered: FS was 61 ± 1.2%, EF was 91 ± 0.7%, p < 0.01; RS was 35 ± 1.8%, p < 0.05 versus T. However the alteration of LS persisted after treatment with R (-15.4 ± 5.1%, p = 0.3 vs. T). R prevents the increased expression of BNP (p < 0.05) on heart tissue Conclusions: R prevents heart function blunts the toxic effects due to T in vivo and in vitro in a mouse model, as demonstrated by the normalization of the values of FS, EF and LS. The first is to impair and may be the last to recover.

Biologic characteristics of breast cancer in male compared to female: SEER analysis. First Author: Mohammed Shaik, Michigan State University, East Lansing, MI

Background: Male (Ma) breast cancer (BC) is a rare disease and information about tumor biomarkers (ER, PR and HER2) is lacking. Since HER2 status was not routinely collected in the population-based cancer registries for patients (pts) diagnosed before 2010, in this study we aim at evaluating the expression of HER2 biomarkers in MaBC compared to female (F) BC. Methods: Using SEER database we analyzed 917(0.84%) MaBC and 108,669 (99.16%) FBC (2010-2011). Data including age, sex, stage, ER/PR status, and HER2 status were analyzed in this variables. These variables were compared between MaBC and FBC. Chi-square and t-test were used for categorical and numerical variables, respectively. Results: The median age at diagnosis was 68 years (F) and 74 years (M) for 3 days. In vivo, fractional shortening (FS) was 61% (sham), EF to 81.8% (sham), RS was 35 ± 1.8%, p = 0.05 versus T. However the alteration of LS persisted after treatment with R (-15.4 ± 5.1%, p = 0.3 vs. T). R prevents the increased expression of BNP (p < 0.05) on heart tissue. Conclusions: R prevents heart function blunts the toxic effects due to T in vivo and in vitro in a mouse model, as demonstrated by the normalization of the values of FS, EF and LS. The first is to impair and may be the last to recover.

Comparison of MaBC and FBC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MaBC(%)</th>
<th>FBC(%)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Median Age (yrs)</td>
<td>68</td>
<td>61</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td>Race</td>
<td>White 742 (84%) 80737 (80%)</td>
<td>0.01</td>
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<tr>
<td>Black 128 (15%) 116317 (12%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Others 47 (5%) 9997 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+ at diagnosis</td>
<td>115 (14%) 207197 (22%)</td>
<td>&lt; 0.0001**</td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>217 (27%) 212281 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-</td>
<td>783 (93.5%) 79145 (82.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Status</td>
<td>19 (2.0% 3365 (0.3%)</td>
<td>&lt; 0.0001**</td>
<td></td>
</tr>
<tr>
<td>Baseline HER2 Status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HER2+ vs HER2-</td>
<td>115 (12.5%) 16418 (15%)</td>
<td>&lt; 0.0001**</td>
<td></td>
</tr>
<tr>
<td>HER2+ Stage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G 27 (24%) 6412 (0.6%)</td>
<td>&lt; 0.0001**</td>
<td></td>
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<tr>
<td>I 63 (55.5%) 1456 (0.2%)</td>
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<tr>
<td>II 141 (12.6%) 2414 (0.2%)</td>
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<tr>
<td>III 218 (19.4%) 2012 (0.2%)</td>
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Comparison of HER2/ER

Effect of high MMP2 and low MMP9 baseline serum levels on outcome in patients with HER2-positive inflammatory breast cancer (IBC) treated with bevacizumab (BEV)- and trastuzumab (T)-based neoadjuvant chemotherapy (NAC) in the BEVERLY 2 study. First Author: Emmanuel Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France

Background: Addition of BEV to TRA-based NAC in HER2-positive IBC has been associated with high pathologic complete response (pCR) rate and favorable outcome in the BEVERLY 2 phase II trial (Piergianni, Lancet Oncol, 2012; Viens, SABCS, 2010). Matrix metalloproteinase (MMP) 2 and 9 are matrix-degrading enzymes involved in tumor growth, invasion and angiogenesis. The plasma levels of which were recently associated with response to BEV in high-grade glioma (Tabouret, Neuro-Oncology, 2014). We examined the prognostic impact of MMP2 and MMP9 serum levels in Beverly 2 patients (pts). Methods: Serum levels of MMP2 and MMP9 were analyzed, using ELISA, in 45/52 samples from pts included in the BEVERLY 2 trial. Serum were analyzed at baseline and before surgical resection, and correlated to pCR, disease-free survival (DFS) and overall survival (OS). Results: Baseline (b) MMP2 and MMP9 serum levels were independent from pts characteristics including age, hormone receptor status, SBR grade, circulating tumor cells and endothelial cells, and were not correlated to pCR. As continuous variables (ROC curves), bMMP2 was significantly associated with relapse (p = 0.002) and death (p = 0.049) risks, while bMMP9 was only associated with death risks (p = 0.035). Using median value as cutoff, univariate analysis of bMMP2 identified high-risk patients with pCR < 50% and better DFS (p = 0.001) and OS (p = 0.032), while low bMMP9 was correlated to better OS (p = 0.022) and tended to be associated to longer DFS (p = 0.071). In multivariate analyses (DFS only, same cutoff), both bMMP2 (p = 0.003, Hazard Ratio [HR]: 1.614) and bMMP9 (p = 0.041, HR: 0.614) remained associated to DFS and pCR. At the median treatment time points, significant increase in MMP2 and decrease in MMP9 levels (p < 0.001 for both) were observed in 100% and 87% of pts, respectively but did not correlate with outcome. Conclusions: High bMMP2 and low bMMP9 serum levels were associated with a better outcome in HER2-positive IBC pts treated with BEV- and TRA-based NAC. Their predictive value should be evaluated in randomized trial.

Skin and subcutaneous tissue disorders (SSTDs) in patients (pts) with HER2-positive metastatic breast cancer (MBC) in the phase III trial CLEOPATRA of pertuzumab or placebo with trastuzumab and docetaxel. First Author: David Miles, Mt Vernon Cancer Centre, London, United Kingdom

Background: CLEOPATRA established pertuzumab (P), trastuzumab (T), and docetaxel (D) as the first-line standard of care for pts with HER2-positive MBC. SSTDs are often reported but detailed prospectively. We assessed the incidence and management of SSTDs from this phase III study. Methods: The safety population in this analysis included 396 pts in the placebo (Pla) arm (Pla +T +D) and 408 pts in the pertuzumab arm (P + T + D). SSTDs included rash, dry skin, alopecia, and nail disorders; incidence, severity (NCI-CTCAE v3.0), and management, and outcome were analyzed in both treatment (tx) arms. Results: See table. The most common SSTDs in both Pla + T + D and P + T + D of pts. SSTDs led to discontinuation of all tx in 0.3% (Pla + T + D) and 0.2% (P + T + D) of pts; and discontinuation of D alone in 1.0% (Pla + T + D) and 3.7% (P + T + D) of pts. Conclusions: SSTDs were common in both Pla + T + D and P + T + D arms, although more frequent during D therapy. SSTDs were mostly low-grade, manageable, and rarely resulting in tx discontinuation. There is no specific tx for SSTDs and tx should be empirical, depending on the nature of the SSTD. These results will further inform clinicians on the nature and management of SSTDs for pts who receive P + T + D for the tx of HER2-positive MBC. Clinical trial information: NCT010567190.

Incidence of SSTDs

**chi-square test. ***data missing for 337 pts.**
Background: Previous studies have shown that basal breast cancers, which may have an inherent “BRCaness” phenotype and sensitivity to inhibitors of poly (ADP-Ribose) polymerase (PARP), express elevated levels of PARP1. Our lab previously reported that HER2+ breast cancers are exquisitely sensitive to PARP inhibitors (PARPi) thru alteration of the NF-κB pathway. In this study, we assessed levels of PARP1 and phospho-PARP1 in a marker of activated NF-κB, in human breast cancer tissues.

Methods: PARP1 and PARP2 copy number, mRNA, and protein expression were assessed by interrogating the PAM-50 defined breast cancer patient set from the TCGA using the cBioPortal. PARP1 and phospho-PARP65 immunohistochemistry and correlation to clinical parameters were conducted using 307 primary breast cancer specimens (132 basal, 82 luminal, 93 HER2+) from univariate and multivariable analyses.

Results: In the PAM50 breast cancer data set, PARP1 and 2 expression was altered in 24/58 (41%) HER2+, 32/81 (40%) basal, and 75/324 (23%) luminal A/B breast cancer patients. This correlated with a statistically significant increase in PARP1 protein levels in HER2+ and basal but not luminal breast cancers (p = 0.003, p = 0.027, p = 0.289, respectively). No change in PARP2 protein level was observed. Interestingly, using breast cancer specimens from 307 patients, HER2 positivity correlated with elevated PARP1 expression (p < 0.0001) and was three times more likely than HER2 negative breast cancers to exhibit high PARP1 levels. No significant differences were noted between race, ER status, or PR status for PARP1 expression. Additionally, we found a significant correlation between HER2 status and phospho-PARP65 expression (p < 0.0001). Lastly, a direct correlation between PARP1 and phospho-PARP65 (p < 0.0001) was noted.

Conclusions: These results indicate a potential connection between HER2 and PARP1, and phospho-PARP65 in human breast tumors. Additionally, these data suggest that the PARP1 sensitivity we previously observed in HER2+ breast cancer cells may be due to elevated PARP1 expression. Future testing of PARPi in HER2+ breast cancer patients is warranted.

Safety of trastuzumab emtansine (T-DM1) in 373 patients 65 years or older with HER2-positive advanced breast cancer: A subgroup analysis of the Kamilla study.

First Author: Carlos H. Barrios, PUCRS School of Medicine, Porto Alegre, Brazil

Background: T-DM1 is approved for HER2-positive metastatic breast cancer (MBC). A pooled analysis of T-DM1 trials (N = 8477) suggested a higher rate of grade ≥ 3 adverse events (AEs) in patients (pts) ≥ 65 yrs (n = 122) vs those < 65 yrs (n = 724, p = 0.027). We report the safety profile of T-DM1 in pts ≥ 65 yrs from the ongoing phase IIIb global safety study Kamilla.

Methods: Kamilla enrolled pts with HER2-positive, locally advanced or MBC with progression after completing adjuvant therapy. T-DM1 3.6 mg/kg was given q3w until unacceptable toxicity, withdrawal of consent or disease progression. Results: As of 20 Oct 2014, Kamilla enrolled 2001 pts; 373 pts ≥ 65 yrs (6.3 yrs vs 4.8 yrs) and basal but not luminal breast cancers (p = 0.003; p = 0.027, p = 0.289, respectively).

Results: As of 20 Oct 2014, Kamilla enrolled 2001 pts; 373 pts ≥ 65 yrs (6.3 yrs vs 4.8 yrs) and basal but not luminal breast cancers (p = 0.003; p = 0.027, p = 0.289, respectively). No change in PARP2 protein level was observed. Interestingly, using breast cancer specimens from 307 patients, HER2 positivity correlated with elevated PARP1 expression (p < 0.0001) and was three times more likely than HER2 negative breast cancers to exhibit high PARP1 levels. No significant differences were noted between race, ER status, or PR status for PARP1 expression. Additionally, we found a significant correlation between HER2 status and phospho-PARP65 expression (p < 0.0001). Lastly, a direct correlation between PARP1 and phospho-PARP65 (p < 0.0001) was noted. These results indicate a potential connection between HER2 and PARP1, and phospho-PARP65 in human breast tumors. Additionally, these data suggest that the PARP1 sensitivity we previously observed in HER2+ breast cancer cells may be due to elevated PARP1 expression. Future testing of PARPi in HER2+ breast cancer patients is warranted.

Conclusions: The incidence of grade ≥ 3 AEs and discontinuation due to AEs were infrequent and similar ≥ 3 AEs in patients (pts) ≥ 65 yrs studied to date, while overall incidence of grade ≥ 3 AEs and discontinuation due to AEs was greater, the most common grade

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
HER2 quantification by mass spectrometry compared to IHC or ISH in predicting clinical benefit from anti-HER2 therapy in HER2-positive breast cancer (BC). First Author: Monica Wu, MD, Department of Radiation Oncology, Vall d’Hebron Institute of Oncology, VHI0, Barcelona, Spain

Background: To be eligible for an anti-HER2 therapy, tumors have to be HER2-positive as determined by IHC or in situ hybridization (ISH) analyses. Although gene amplification is generally considered the main mechanism of HER2 protein overexpression in BC, the biologic regulation of HER2 expression is complex and gene amplification may not always correlate quantitatively with HER2 protein levels and with response to anti-HER2 therapies. Methods: HER2-positive (n = 123) primary BC samples were microdissected, solubilized and digested in trypsin in Liquid Tissue buffer. Absolute quantitation for HER2 protein was performed using selected reaction monitoring (SRM) mass spectrometry. ISH was centrally performed on all cases. HER2 gene copy number (GCN), HER2/Chr17 ratio, and pattern of amplification were evaluated and correlated with HER2 protein levels. The survival benefit according to protein and gene levels was calculated for patients receiving an adjuvant anti-HER2 therapy (n = 68). Results: HER2 SRM levels showed weak positive correlations with HER2 GCN and HER2/Chr17 ratio. Average HER2 protein levels were significantly higher in tumors amplified with homogeneous stained regions (HSR, n = 50) compared to those with double minutes (DM, n = 46). Ten amplified cases showed HER2 protein levels similar to HER2-negative tumors. Eight had a DM and 2 a mixed pattern of amplification. None was amplified in HSR. HER2 protein levels >2.200 amol/μg predicted better disease-free survival and overall survival in patients treated with adjuvant trastuzumab. Neither HER2 GCN, HER2/Chr17 ratio nor pattern of amplification correlated with outcome. Conclusions: By using an objective non-antibody based method we identified a great deal of disparity of HER2 levels in BC patients that are classified as HER2-positive by ISH. Different amplification patterns resulted in significantly different protein levels; with many cases of DM amplification showing no concomitant increase in HER2 protein expression. Our findings indicate that protein abundance rather than gene status predict the clinical benefit from anti-HER2 therapy in HER2-positive BC patients.

Phase II study of weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer (MBC): Updated progression-free survival with overall survival result. First Author: Lilian Mary Smyth, Memorial Sloan Kettering Cancer Center, New York, NY

Background: We previously reported results of the phase II breast cancer (BC) trial of weekly paclitaxel (T), trastuzumab (H) and pertuzumab (P) with its primary endpoint of 6-month (mo) progression-free survival (PFS) of 86% (95% CI, 75% to 92%) in patients (pts) with HER2+ metastatic (M) BC treated in first- and second-line settings. At a median (med) follow-up (FU) of 21 mo, med PFS was 19.5 mo overall. Updated PFS and OS analysis from this fully accrued study is presented here. Methods: Pts with HER2+ MBC with 0-1 prior treatment (Rx) were eligible. Rx was weekly (w) T (80mg/m2), q3w H (loading dose 8mg/kg → 6mg/kg) and q3w P (loading dose 840mg → 420mg), all given intravenously. Primary endpoint was 6 mo-PFS. Secondary endpoints included 6-mo and median OS. Evaluable pts received at least one full dose of Rx. Results: From January 2011 to December 2013, 69 pts were enrolled: 51 (74%) and 18 (26%) treated in first- and second-line metastatic settings, respectively. 67 were evaluable for efficacy. As of 12-01-14, 26/67 pts (39%) remain progression-free (6 CR, 13 PR and 7 SD); 34 pts have progressed and there are 51 survivors. At a med FU of 23 mo (range, 3-40 mo), 6-mo PFS was 85% (95% CI, 74%-92%). Med PFS was 21.4 mo (95% CI, 13.8-NR) overall and 26.1 mo (95% CI, 17.0-NR) and 16.4 mo (95% CI, 8.5-NR) for pts with 0-1 prior Rx, respectively. 6-mo OS was 98% (95% CI, 90%-100%) and med OS was 37.5 mo (95% CI 31-NR). Median duration of ChemRx was 30 weeks. Rx was well-tolerated; there were no febrile neutropenia and no symptomatic left ventricular systolic dysfunction. Conclusions: Updated analysis demonstrates that weekly paclitaxel, when added to H and P, is associated with prolonged PFS and OS and a favourable toxicity profile and should be considered as a therapeutic option in this patient population. Clinical trial information: NCT01276041.

A phase 1b trial of blood-brain barrier (BBB)-penetrant tyrosine kinase inhibitor (TKI) tesevatinib in combination with trastuzumab for patients with HER2+ metastatic breast cancer (MBC). First Author: Komal L. Jhaveri, New York Univ Cancer Inst, New York, NY

Background: Patients with HER2+ breast cancer (BC) have a high incidence of brain metastases (mets). Tesevatinib (formerly KD019) is a TKI with potent activity against EGFR, HER2, and SRC. In contrast to all of the approved anti-HER2 agents in BC, tesevatinib crosses the intact BBB in mouse and rat models and achieves levels in the brain similar to plasma levels of single-agent trials of tesevatinib in NSCLC defined the maximum tolerated dose as 300 mg daily due to QTc prolongation. Methods: This study was designed to define the Recommended Phase 2 Dose for tesevatinib given daily combined with trastuzumab 6 mg/kg IV every 3 weeks. Secondary endpoints include pharmacokinetic evaluation of the combination. Eligible patients have HER2+ MBC with disease progression who are resistant to the HER2 targeted agent trastuzumab. The testing of PARP inhibitors as a novel therapeutic strategy for patients with HER2+ breast cancer.

Crosstalk between PARP-1 and NF-κB signaling pathways as a potential determinant of PARPi sensitivity in trastuzumab resistant HER2+ breast cancer cell lines. First Author: Monicka Wielgos, Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL

Background: We have previously found that HER2+ breast cancer cells, despite being DNA repair proficient, are sensitive to poly (ADP-Ribose) polymerase inhibitors (PARPi). In this study, we investigated whether PARPi susceptibility would be retained in HER2+ breast cancer cells that are resistant to the HER2 targeted agent trastuzumab. Methods: Human HER2+ breast cancer cell lines BT-474, UACC812, SKBR3 and their trastuzumab resistant counterparts were used in this study. Cells were treated with vehicle or 10μM ABT-888 or transfected with scrambled or PARP-1 siRNA. We assessed cell survival by colony formation assays. Western blot analysis was used to measure protein expression. Cell cycle distribution was evaluated by propidium iodide and measured by flow cytometry. NF-κB transcriptional activity was determined via a NF-κB-driven luciferase reporter assay. The nCounter Gene Expression Assay along with qRT-PCR were used to measure the expression levels of NF-κB target genes. Tumor growth delay was assessed in mice bearing tumor xenografts. Results: Similar to parental cells, trastuzumab resistant HER2+ breast cancer cells retained PARPi sensitivity both in vitro and in vivo. The cytotoxicity in these cells was associated with greater than 40% attenuation of NF-κB transcriptional activity. Results were validated with PARP-1 siRNA. Further, re-expression of PARP-1 rescued NF-κB activity in PARP-1 knockdown cells. The expression of several NF-κB target genes, including IL-8, BRCa2, and VEGFC, was reduced with PARP inhibition or knockdown. The effects of PARP inhibition via ABT-888 or PARP-1 siRNA were independent of cell cycle redistribution. Conclusions: Inhibition of NF-κB signaling via pharmacological or genetic modulation of PARP-1 induces a cytotoxic response in trastuzumab resistant HER2+ tumors. This warrants the testing of PARP inhibitors as a novel therapeutic strategy for patients with HER2+ breast cancer.
Characterization of dominant T-cell clones by T-cell receptor (TCR) deep sequencing as a potential predictive biomarker to neoadjuvant trastuzumab (in trastuzumab-positive breast cancer). Authors: David B. Page, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Because TIL quantity by H&E predicts pathologic complete response (pCR) to neoadjuvant trastuzumab and disease, and because clinical responses to trast could be mediated by dominant T-cell clones reactive to the HER2-protein, we hypothesize that the quantity of dominant clones by TCR deep sequencing may predict trast-induced pCRs. Here, we evaluate the influence of specimen age on feasibility of TCR sequencing on breast cancer FFPE-preserved diagnostic core biopsies (bxs), and explore potential associations with pCR in a HER2+ subset. Methods: Two groups with pre-treatment bx’s were selected and sequenced using the ImmunoSEQ platform: 12 neoadjuvant trastuzumab-treated with “archival” HER2+ bxs (median 35mo from procurement, 12-54mo; 6 with pCRs) and 14 women treated on an immunotherapy protocol with “contemporary” bxs (median 10mo from procurement, 4-18mo). Viability was assessed by calculating the proportion of nucleotide sequences yielding productive, in-frame amino acid sequences. T-cell quantity (the proportion of T-cell to total DNA) and dominant T-cell clone quantity (# clones in top decile of reads) were measured by TCR sequencing and evaluated for associations with pCR (Wilcoxon rank sum). Accuracy of T-cell quantity was assessed by comparing with H&E TIL count. Results: TCR sequencing viability was lower in archival compared to contemporary bx (median .67 v .81; p < .0001), and was inversely correlated with sample age (Spearman r = -.062, p = .0008) but not input DNA amount (r = -.05, NS). T-cell quantity by TCR sequencing correlated with TIL quantity by H&E in contemporary (r = .66, p = .033) but not archival bx (r = .21, NS). In the HER2+ group, dominant T-cell clone quantity (median # clones: pCR, 15; no-pCR, 6, p = .003) was not different in archival bx compared to contemporary bx (p < .05). Conclusions: While 50-70% of pts with HER2+ MBC (pts) with extraordinary responses to trast, the vast majority eventually develop resistance, after a median duration of 1 year. In rare cases, pts have exceptionally long durations of response to T. Understanding mechanisms of exceptional responses to antracancer therapies may improve patient selection and rational treatment designs. Methods: We conducted a retrospective screen for pts with HER2+ MBC in the Dana Farber Cancer Institute treated with T in the metastatic setting for more than 60 months. To date, we have identified 3 pts with extraordinary responses to T who provided consent for genomic studies and had sufficient tumor tissue available for study. All pts had histologic response to T. Understanding mechanisms of exceptional responses to trast could be mediated by dominant T-cell clones reactive to the HER2-protein, and no prior treatment for advanced disease were eligible. Pts were randomized to oral N (240mg od) + P or T + P: Dosing; T 4mg/kg iv then 2mg/kg iv weekly, P 80mg/m² iv weekly 3/4w. Primary endpoint: progression-free survival (PFS). Secondary endpoints: overall survival (OS); overall response rate (ORR); duration of response; clinical benefit rate; CNS progression; safety. PFS analysis was ITT by stratified log-rank test. Randomization was stratified by registration in prior T, prior lapatinib, ER/PR status. 304 PFS events were required to detect 30% improvement in median PFS with 80% power (1-sided α = .05). Median 479 pts made up the ITT population (6 pts in NP arm and 12 pts in TP arm had known brain metastases at baseline). Other baseline characteristics were balanced. Most common adverse events (AEs) with NP vs TP: diarrhea 95 vs 33% (G3 30 vs 4%; no G4; G3 median duration of 4.5d); nausea 44 vs 30% (G3 = 2 vs 1%; vomiting 36 vs 16% (G3 = 3 vs 1%); fatigue 32 vs 27% (G3 = 3 vs 3%); rash 31 vs 24% (G3 = 3 vs <1%); cardiac disorders 2.5 vs 5.1% (G3 = 1 vs <1%). Conclusions: NP has similar efficacy to TP; of interest, NP may be more effective than TP in reducing CNS progression. With no prior loperamide prophylaxis, diarrhea was significantly higher with NP than TP. NP AEs occurred at similar rates in both arms. Clinical trial information: NCT0091501B.

Efficacy endpoint N = P (n=242) T + P (n=237) Hazard ratio (95% CI) P-value
Median PFS, months 12.9 12.9 1.03 .0027
(95% CI) (11.0–14.8) (11.1–14.7) (0.83-1.29)
OS, months 19 (79) 183 (15) 0.59 0.85
CNS progression*, n (%) 19 (8) 38 (16) – 0.0037
KM cumulative incidence of CNS recurrence, % 14.4 32.1 0.46 0.006
(0.26-0.81)
*49 events were CNS only.

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Lack of correlation of neoantigens arising from tumor somatic mutations with tumor infiltrating lymphocytes (TILs) or survival in HER2-positive breast cancer (HER2+: BC). TILs were strongly and significantly correlated (R_s = 0.5, p < 0.001) with all gene expression surrogates of immune activation (CD8A, GRZMB, PRFI) and immunosuppression (PD-L1, CTLA4, IDO1). In cohorts 1A and 1B, there was no significant correlation between TILs and total mutation count (R_s = 0.04; R_s = 0.02, respectively), but I Mut (R_s = 0.4 for both) nor the APOBEC mutation signature (R_s = 0). There was no difference in the level of TILs between lowest and highest quartiles of I Mut burden in the cohorts combined (p = 0.7). In the trastuzumab-treated cohort 1, total mutation count (@ 100 vs > 100) and I Mut count (0 vs ≥ 1) was not associated with invasive disease-free survival (ICDFS) p < 0.05 in BC, respectively. The presence of a recently reported melanoma neoantigen signature (Snyder, NEJM 2014) also did not significantly correlate with the presence of TILs (R_s = 0.03) or IDFS (p = 0.6). Conclusions: In HER2+ BC, predicted tumor neoantigens did not correlate with TILs or survival. Other mechanisms seem to be eliciting the anti-tumor immune response in HER2+ BC.

Effect of somatic mutations in the four genes of the HER family on survival in HER2-positive breast cancer (HER2+: BC). TILs comprised mostly CD8+ T cells but the basis for antigen recognition is unclear. We investigated the relationship between somatic mutations and TILs. Methods: Two cohorts of HER2+ early-stage BC were analysed. Cohort 1: 50 cases from the Responsivity-EU project and Cohort 2: 272 cases from TIL Cancer Genome Atlas with whole exome sequencing, gene expression, germline SNP (inferred HLA genotype) and survival. Cohort 1 received adjuvant trastuzumab and chemotherapy. TILs were quantified from H&E slides in both cohorts using our previously defined method. We performed computational prediction of mutant peptide neoantigens binding patient specific MHC Class I. Results: In cohorts 1 and 2, 660/2113 (31%) and 3268/10841 (30%) non-synonymous point mutations were predicted to be immunogenic mutations (I Mut), with a median of 9.5 (IQR 3 – 19), and 9 (IQR 6 – 18) per sample per cohort, respectively. The number of I Mut predicted was strongly correlated with the total number of mutations (Cohort 1: R_s = 0.9; Cohort 2: R_s = 0.8, both p < 0.00001). TILs were strongly and significantly correlated (R_s > 0.5, p < 0.001 for all) with gene expression surrogates of immune activation (CD8A, GRZMB, PRFI1) and immunosuppression (PD-L1, CTLA4, IDO1). In cohorts 1A and 1B, there was no significant correlation between TILs and total mutation count (R_s = 0.04; R_s = 0.02, respectively), but I Mut (R_s = 0.4 for both) nor the APOBEC mutation signature (R_s = 0). There was no difference in the level of TILs between lowest and highest quartiles of I Mut burden in the cohorts combined (p = 0.7). In the trastuzumab-treated cohort 1, total mutation count (@ 100 vs > 100) and I Mut count (0 vs ≥ 1) was not associated with invasive disease-free survival (ICDFS) p < 0.05 in BC, respectively. The presence of a recently reported melanoma neoantigen signature (Snyder, NEJM 2014) also did not significantly correlate with the presence of TILs (R_s = 0.03) or IDFS (p = 0.6). Conclusions: In HER2+ BC, predicted tumor neoantigens did not correlate with TILs or survival. Other mechanisms seem to be eliciting the anti-tumor immune response in HER2+ BC.

Neuromedin U to increase IL-6 levels and to expand cancer stem cells in HER2-positive breast cancer cells. First Author: Vanesa Gabriela Martinez, School of Pharmacy & Pharmaceutical Sciences & Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland

Background: Neuromedin U (NmU) is a neuropeptide belonging to the neuropeptide family. Recently, a significant association between NmU signaling and cancer has been described, particularly correlated with increased aggressiveness and resistance to chemotherapy, although the mechanism through which it exerts this effect remains unclear. Methods: HER2-positive breast cancer cells were stably transfected with NmU and IL-6 levels were measured by ELISA. Migration was evaluated in the presence of anti-NMUR antibodies by wound healing assays, while drug toxicity was assessed by the acid phosphatase assay. Results: Over-expression of NmU increases secreted levels of IL-6 (p = 0.303 ± 0.12 ng/ml, p = 0.027) and increased expression of the lymphocyte activation inhibitor PD-L1, as detected by flow cytometry (49.50 ± 4.21 vs 60.06 ± 1.628, p = 0.0327); Furthermore, NmU-over-expressing cells were shown to display enhanced resistance to antibody-dependent cell cytotoxicity mediated by Trastuzumab (47.13 ± 3.31% lysis of mock-transfected cells vs 36.46 ± 4.34% lysis of NmU-over-expressing cells, p = 0.05). Treatment with antibodies that block NmU receptors NMUR1 and NMUR2 reduces cell migration and enhances toxicity of HER2-targeted drugs in NmU-over-expressing cells, suggesting that interaction of NmU with NMUR1 and NMUR2 are necessary for its effects. Conclusions: Altogether, our results show a new mechanism of action of NmU in HER2-positive breast cancer cells that enhances resistance to HER2-targeted drugs and the anti-tumor immune response, and is at least partially mediated by IL-6. Acknowledgements: Science Foundation Ireland’s funding of MTCI 08/5/R01410; HRB’s Health Research Award (HRA-POR-2014-65); Irish Cancer Society’s Breast-Predict (CCR13GAL); and HEA’s PRTLI-5 Centre 5 support of TBSI.
Background: ALTTO (NCT00490139) is a large adenovirus breast cancer (ABC) study evaluating lapatinib, alone and in combinations with trastuzumab and taxanes. Characterization of hepatic abnormalities during lapatinib treatment in ALTTO was conducted using the lapatinib hepatotoxicity risk biomarker HLA-DRB1*07:01. Methods: Germline DNA collection for HLA-DRB1 genotype determination was achieved for 76% (6323/ 8270) of ALTTO subjects. Association of HLA-DRB1*07:01 allele carriage with ALT elevation during study treatments was evaluated by case-control analysis of NCI CTC AE grade 3 ALT elevation (> 5x ULN, ALT). Results: A higher incidence of ALT elevation (2-5%, n = 6194) was observed in the three lapatinib-containing treatment arms compared with the trastuzumab monotherapy arm (1.5%; p < 0.01). Also, ALT was higher when lapatinib and taxane were administered concurrently. HLA-DRB1*07:01 carriage frequency was enriched in lapatinib-treated ALT cases compared with controls (OR 6.5, 95% CI 4.6-9.3, p = 2x10-36, n = 4568), with overall negative and positive ALT risk predictive values for the HLA allele of 98.6% and 9.7%, respectively. The HLA association was weaker when concurrent taxane was administered to lapatinib-treated patients, suggesting an ALT risk independent of HLA-DRB1*07:01 carriage. Homozygous and heterozygous HLA-DRB1*07:01 genotype carriers exhibited different ALT elevation risk during lapatinib treatment of 12.1% (n = 67) and 8.5% (n = 965), both higher than the risk for non-carriers (1.4%, n = 3286). Furthermore, homozygous carriers exhibited greater severity with significantly higher maximum ALT elevations. ALT elevation risk was significantly correlated with geographic differences in HLA-DRB1*07:01 carriage frequency. Conclusions: Whilst efficacy of lapatinib plus trastuzumab was not significantly impacted by germline HLA-DRB1*07:01, these data suggest a role for HLA variation in ALT risk estimates for HLA-DRB1*07:01 allele carriage that may discriminate causality and support safety management during the use of lapatinib combinations for treatment of metastatic breast cancer globally. Funding: GlaxoSmithKline. Clinical trial information: NCT00490139.

619 Poster Session (Board #109), Sat, 8:00 AM-11:30 AM Association of tumor infiltrating lymphocytes (TILs) with pathologic response in baseline and post-brief exposure HER2+ breast cancer biopsies from BRUG-211B. First Author: Stefanie Avril, Department of Pathology, Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, OH

Background: Increased TILs are prognostic and predictive of therapy response in HER2+ breast cancer (BC). BRUG-211B, a phase II neoadjuvant trial included early stage HER2+ BC pts treated with single-agent trastuzumab (T) or nab-paclitaxel (N) followed by 6 cycles of T, N and carboplatin combination. This correlative study evaluated TILs in both baseline and post-brief exposure biopsies in association with pathologic response. Methods: Stromal (sTILs) and intratumoral (iTILs) TILs were evaluated on H&E sections at baseline (n = 46) and post-brief exposure (n = 43) and scored by deciles (mean of multiple core biopsies) according to the TILs Working Group guidelines. Pathologic response was assessed by residual cancer burden (RCB) index and grouped as responders (R = pCR/RCB 0 & RCB 1) or non-responders (NR = RCB II & III). Results: Of 60 eligible pts 49 were available for analysis (49%). Median iTILs were 10% (range 10-40%) and 20% (10-70%), median sTILs were 30% (10-100%) and 30% (20-100%), at 20% and post-brief exposure respectively. sTILs and iTILs were highly correlated (r = 0.8). Higher iTILs (p < 0.02) and sTILs (p < 0.01) were significantly associated with ER-neg status. Median sTILs were significantly higher in R vs NR at both baseline (35% vs 25%; p = 0.02) and post-brief exposure (50% vs 25%; p < 0.01). iTILs were not significantly different in T vs N responders and not significantly associated with response (70% vs 47% R; p = 0.2). There was a significant change in iTILs or sTILs following brief exposure to T or N, but not significantly for T or N alone. Conclusions: Levels of sTILs do not change significantly in HER2+ BC following brief-exposure to single-agent T or N based on morphologic assessment; however, both baseline and post-brief exposure sTILs significantly predict for pathologic response. Further analyses are needed to determine potential changes in lymphocytic subpopulations.

620 Poster Session (Board #110), Sat, 8:00 AM-11:30 AM Mechanisms of acquired afatinib resistance in HER2-positive breast cancer cells. First Author: Alexandra Canonic, Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland

Background: Afatinib is a potent irreversible ErbB family tyrosine kinase inhibitor. We have previously shown that afatinib has anti-proliferative activity in a panel of 8 HER2 positive breast cancer cell lines (IC50 values 5-80 nM). The aim of this study was to investigate potential mechanisms by which HER2 positive breast cancer cells may develop acquired resistance to afatinib. Methods: SKBR3 cells were continuously exposed to 150 nM afatinib for 6 months. Resistance assays were performed to determine the IC50 values for the parental (SKBR3-P) and the afatinib conditioned cells (SKBR3-A), and to assess sensitivity to lapatinib and neratinib. The molecular profiles of the resistant cells were examined by Reverse Phase Protein Array (RPPA). Results: The SKBR3-A cells were more resistant to afatinib than the SKBR3-P cells (IC50 > 500 nM vs IC50 = 10.9 ± 3.4 nM). Furthermore, the resistant cells were cross-resistant to lapatinib (IC50 = 1.0 µM ± 4.4 µM vs IC50 = 25.9 ± 3.0 nM) and neratinib (IC50 = 287.2 ± 14.0 nM vs IC50 < 10 nM). Of the 73 analytes tested by RPPA, 14 were significantly different in the SKBR3-A cells compared to SKBR3-P (p < 0.05). The level of phosphorylation of 5 proteins, including HER3 (Y1289), Akt (S473 and T308) and ERK1/2 (T202/Y204) was decreased in the afatinib resistant cells. The level of phosphorylation of 9 proteins, including Akt2, EGFR, p38 MAPK, Bcl2 and phospho-Src (Y416) was increased. Conclusion: Analysis of afatinib resistant cells suggests that alternative signaling pathways or alterations in apoptosis may play a role in acquired afatinib resistance. Further investigation of the proteins identified may facilitate the development of novel therapeutic strategies to overcome resistance.

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**Background:** Pretreatment (preRx) biopsies of HER2-amplified breast cancers (BCs) that did not achieve pCR with preop chemotherapy plus H vs L vs HL had PI3K pathway activation with high p-FOXO levels on RPMA (Holmes BMC Res Notes 2013). The RD obtained at surgery in the pts who was enriched for co-mutations in PIK3CA and TP53 (Holmes ASCO 21:26, 625). Here we describe activated phosphoproteins in the HER1/2/3 pathway in the RD from these pts who did not achieve pCR with preop H vs Ls HL and in RD with PIK3CA/TP53 co-mutations.

**Methods:** 15 pts’ FFPE RD BCs were acceptable for RPMA at a CLIA-certified laboratory (Theranosics Health). Immunostaining with 14 antibodies was directed against HER1/2/3 pathway proteins. Spearman correlation (p value) and Mann-Whitney U tests (p value) were performed. **Results:** 7 of 15 RD BCs had PIK3CA/TP53 co-mutations. In the RD with co-mutant PIK3CA/TP53, the strongest Pearson correlations (r) were between HER3 and p-HER1 and each with p-mTOR, p-S6K, p-JAK2 and p-STAT3 (all r > 0.9). In preop L pts (n = 8), the strongest correlations in the RD were pHER2 and HER3, pHER2 and p-mTOR, p-HER1 and pSTAT3, p-HER3 and p-STAT3 (all r > 0.8), and p-AEBP1 and p-JAK2 (r = 0.97). In preop H and HL pts (n = 7), the RD showed strong interactions between HER3 and p-HER1, p-HER2 and p-HER3, HER3 and p-S6K, p-HER1 and p-S6K and p-HER3 and p-JAK2 (all r > 0.9). Comparing L- vs H/L-treated RD, L-treated RD had higher levels of p-Akt (p = 0.08), p-S6 (p = 0.08) and p-MEK1/2 (p = 0.02). Prefx biopsies from pts who had RD all expressed high PI3K or low PTEN ser380 levels and showed strong interactions between p-HER1 and p-HER2 (p = 0.01), p-HR1, p-JAK3, and p-MAPK activation, LC3B (autophagy) and p13K, and Musashi (stem cell regulator) and β-catenin (all p > 0.8) (all p < 0.00006).

**Conclusions:** Prefx biopsies from HER2+ pts who had RD following preop chemotherapy + H, L or HL showed activation of HER1, PI3K and MAPK pathways. Pts’ refractory RD demonstrated HER3, PI3K and MAPK pathways activation under the selective pressure of preop H, L or HL. PIK3CA/TP53 co-mutated RD demonstrated signaling via pHER1/ HER3 to p-mTOR/p-S6K and p-JAK2/p-STAT3.

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Phase III, randomized, double-blind, placebo-controlled study of ribociclib (LEE011) in combination with either tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of pre- or perimenopausal women with HR+ HER2– advanced breast cancer (ABC): MONALEESA-7. First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tamoxifen or NSAI with ovarian function suppression are standard first-line endocrine therapy (ET) options for premenopausal women with HR+ HER2– ABC; however, resistance eventually occurs. The cyclin D- cyclin dependent kinase (CDK)4/6 INK4–Rb pathway is frequently dysregulated in HR+ BC; preclinical data suggest that CDK4/6 inhibition may abrogate endocrine-resistant cell proliferation in BC subsets. Adding ribociclib, a highly selective CDK4/6 inhibitor, to standard ET may provide therapeutic benefit vs ET alone in HR+ HER2– ABC. Methods: A Ph II, randomized, double-blind, placebo-controlled study of continuous tamoxifen (20 mg once daily [QD]) or NSAI (letrozole [2.5 mg QD] or anastrozole [1 mg QD]), with subcutaneous goserelin implant (3.6 mg D1 of each 28-day cycle) and ribociclib (600 mg QD, D1–21 of each 28-day cycle) or matching placebo (MONALEESA-7; NCT02278120). Key inclusion criteria: pre- or perimenopausal women with ER+ and/or PR+ HER2– ABC; ECOG PS ≤ 1. Patients that have received ≤ 1 line of chemotherapy and/or ≤ 14 days of tamoxifen or NSAI (letrozole or anastrozole) with/without goserelin for ABC are eligible, but prior treatment with CDK4/6 inhibitors is prohibited. Patients are randomized (1:1) to receive either ribociclib (Arm 1) or placebo (Arm 2) in combination with tamoxifen + goserelin or NSAI + goserelin. Stratification is based on presence of lung and/or liver metastases; prior chemotherapy for ABC; endocrine combination partner (tamoxifen + goserelin vs NSAI + goserelin). Primary endpoint: PFS (RECIST 1.1); key secondary endpoint: overall survival. Other secondary endpoints include safety, tolerability, response rate, clinical benefit rate, time to response, duration of response. Tumor and blood samples will be collected for biomarker and PK assessments. Approximately 660 patients will be randomized. Global recruitment is ongoing. To our knowledge this is the first Ph III trial investigating a CDK4/6 inhibitor in only pre- or perimenopausal women with ABC. Clinical trial information: NCT02278120.

BRETEL-3: A Phase III study of the pan-phosphatidylinositol 3-kinase (PI3K) inhibitor buparlisib (BKM120) with fulvestrant in postmenopausal women with HR+ HER2– advanced breast cancer treated with aromatase inhibitors (AIs) and refractory to mTOR inhibitor (mTORI)-based treatment. First Author: Angela Di Leo, Ospedale Miserocdicà e Dolo, Prato, Italy

Background: PI3K pathway activation is the most frequent alteration in BC and confers resistance to endocrine and mTORI treatment. The oral pan-PI3K inhibitor buparlisib has shown preliminary activity and a manageable safety profile in patients with HR+/HER2– BC in combination with letrozole or fulvestrant. Buparlisib + fulvestrant exhibits antitumor activity in mTORI-resistant ER + xenograft models, suggesting that buparlisib may potentially bypass mTORI resistance by blocking upstream PI3K pathway signaling. Methods: BRETEL-3 (NCT01633060) is a randomized, double-blind, placebo-controlled, Phase III study of fulvestrant ± buparlisib in postmenopausal women with HR+ HER2– locally advanced/metastatic BC. Key inclusion criteria: prior treatment with AIs, disease progression on or within 30 days of endocrine + mTORI therapy given as the last therapy before study entry, and ≤ 1 prior chemotherapy regimen for advanced disease. Approximately 420 women will be randomized (2:1) to receive buparlisib (100 mg/day) or placebo with fulvestrant (500 mg on CD1, CD15, D1 of subsequent cycles). Randomization will be stratified by visceral disease status. Tumor assessments will be performed at 6-weekly intervals until disease progression per RECIST v1.1. Primary endpoint: progression-free survival (PFS) per local investigator assessment (per RECIST v1.1). Key secondary endpoint: overall survival (OS). Other secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), safety, pharmacokinetics of buparlisib + fulvestrant, quality of life, and time to deterioration of ECOG performance status. Statistical methods: PFS and OS will be analyzed by Kaplan-Meier methods using a stratified log-rank test at 1-sided 2.5% level of significance. Hazard ratios will be estimated by stratified Cox regression with 2-sided 95% confidence intervals (CI). ORR and CBR will be calculated with exact 2-sided 95% CI. Recruitment onto the BRETEL-3 study is ongoing. Clinical trial information: NCT01633060.

LORELEI: A phase II randomized, double-blind study of neoadjuvant letrozole plus taselisib (GDC-0332) versus letrozole plus placebo in postmenopausal women with HER2-negative, early-stage breast cancer. First Author: Evandro De Azambuja, Jules Bordet Inst, Brussels, Belgium

Background: Taselisib is an orally bioavailable, potent, selective inhibitor of Class I PI3-kinase (PI3K) alpha, gamma, and delta isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the alpha isoform showing enhanced activity against PIK3CA mutant breast cancer cell lines. Clinical data have demonstrated confirmed partial responses in patients with PIK3CA mutant breast cancer (BC) treated with single-agent taselisib. Enhanced antitumor activity has been noted when taselisib is combined with either letrozole or fulvestrant in preclinical and Phase Ib clinical studies. Methods: LORELEI is a Phase II, two-arm, randomized, double-blind, multicenter, study of neoadjuvant letrozole and taselisib versus letrozole and placebo in postmenopausal women with newly diagnosed ER+/HER2–, untreated, Stage I-III operable BC. Other eligibility criteria include tumor size ≥ 2 cm by magnetic resonance imaging (MRI), ECOG PS 0-1, and evaluable tumor tissue for PIK3CA genotyping. Patients treated with anti-diabetic drugs are not eligible. Patients are randomized (1:1) to receive continuous letrozole (2.5 mg) with either taselisib (4 mg on a 5 days on/2 days off schedule) or placebo for 16 weeks, followed by surgery. Stratification is based on tumor size and nodal status. The co-primary endpoints are overall objective response rate (ORR) by centrally assessed RECIST criteria and pathologic complete response (pCR) rate in breast and axilla at time of surgery in all randomized patients and PIK3CA mutant patients. Secondary endpoints include ORR by centrally-assessed MRI and pCR rate in PIK3CA wild-type patients. The sample size was calculated to detect an absolute percentage increase of 24% in ORR with 80% power and an absolute percentage increase of 18% in pCR rate. An interim safety analysis will be conducted by an Independent Data Monitoring Committee. As of 28 Jan 2015, 15 of the 330 patients have been enrolled, and global enrollment is ongoing (clinicaltrials.gov NCT02273973). Clinical trial information: NCT02273973.
TPS629  Poster Session (Board #116a), Sat, 8:00 AM-11:30 AM

SANDPIPER: Phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enriched for pts with PIK3CA mutant tumors. First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY

Background: PIK3CA mutations are one of the most frequent genomic alterations in BC, being present in ~40% of ER-positive, HER2-negative breast tumors. PIK3CA mutations promote growth and proliferation of tumors and mediate resistance to endocrine therapies in BC. Taselisib is a potent and selective PI3K inhibitor of the alpha, gamma, and delta isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the alpha isoform. Taselisib has enhanced activity against PIK3CA-mutant BC cell lines, and clinical data include confirmed partial responses in pts with PIK3CA-mutant BC treated with taselisib either as a single agent or in combination with a chemotherapy agent. SANDPIPER, placebo-controlled, randomized, phase III study, is designed to evaluate efficacy and safety of taselisib plus fulvestrant in postmenopausal pts with ER-positive, HER2-negative, PIK3CA-mutant locally advanced or metastatic BC. Methods: Pts with disease recurrence or progression during or after aromatase inhibitor treatment will be randomized 2:1 to receive either taselisib (4 mg qd) or placebo in combination with fulvestrant (500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each subsequent 28-day cycle). Randomization will be stratified by visceral disease, endocrine sensitivity, and geographical region. Pts with PIK3CA-mutant tumors (n = 480) will be randomized separately from pts with non-mutant tumors (n = 120); a valid PIK3CA-mutation result via central assessment is required prior to enrollment. Primary efficacy endpoint is investigator-assessed progression-free survival in pts with PIK3CA-mutant tumors. Other endpoints include overall survival, objective response rate, clinical benefit rate, response duration, investigator-assessed progression-free survival in pts with PIK3CA-mutant tumors, and patient-reported outcomes. Target enrollment is 600 pts from ~165 sites and ~23 countries. The study is active as of February 2015. NCT02340221. Clinical trial information: NCT02340221.

TPS630  Poster Session (Board #116b), Sat, 8:00 AM-11:30 AM

A phase II trial of neoadjuvant aromatase inhibitor therapy and the mTOR inhibitor everolimus in postmenopausal women with hormone receptor positive/HER2-negative locally advanced or metastatic breast cancer (BC) with low intermediate risk (Rx ≤ 25). First Author: Mayra M. Abu-Khalaf, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Breast cancer (BC) patients (pts) with low intermediate Oncotype Dx recurrence scores (Rx ≤ 25) represent a large fraction of BC cases, and a substantial number of distant recurrences occur in this group despite their low to moderate risk and high sensitivity to endocrine therapy. These pts are also the least likely to be sensitive to or benefit from adjuvant chemotherapy. Anatomical risk factors (nodal status, tumor size) continue to define a higher risk group among these endocrine sensitive and molecularly low risk BC pts. The goal of this study is to assess tumor response to a combination of the mTOR inhibitor everolimus and an aromatase inhibitor (AI) in this patient population, utilizing the preoperative endocrine prognostic index (PEPI). Our hypothesis is that everolimus will improve the efficacy of AI in this setting. Methods: This is a phase II study evaluating the efficacy and safety of neoadjuvant AI and everolimus in postmenopausal pts with hormone receptor positive (HR+)/HER2 negative clinical stage II-III BC with low-intermediate risk Rx (≤ 25). Patient enrollment initiated in November 2014 at the Yale Cancer Center/Smow Cancer Hospital and Care Centers. The study will enroll up to 66 pts. Key inclusion criteria are ECOG 0-2, adequate organ function, a fasting cholesterol ≤ 300 mg/dl and triglycerides ≤ 2.5 x IULN. Pts who had prior surgical resection of their BC, uncontrolled diabetes mellitus (HbA1c > 7%), and a prior exposure to mTOR inhibitors are excluded. Eligible pts will receive daily AI therapy (anastrozole 1 mg, letrozole 2.5 mg or exemestane 25 mg) and everolimus 10 mg daily for a total of 26 weeks. The primary objective of the study is to determine the percent of patients achieving complete tumor regression at the end of chemotherapy, post-surgery, and to assess the objectives of everolimus. Eligible pts who achieve a PEPI score of 0 following neoadjuvant AI and everolimus. The secondary objectives are to access the tolerability and side effect profile and to identify biologic markers predictive of a pathologic response (PEPI 0) to neoadjuvant AI and everolimus in this patient population. Clinical trial information: NCT02236572.

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A Phase II study of the safety and efficacy of alpelisib or buparlisib plus letrozole in neoadjuvant treatment of postmenopausal women with HR+/HER2–, PIK3CA-mutant or wild-type breast cancer. First Author: Ingrid A. Mayer, Vanderbilt-Ingram Cancer Center, Nashville, TN

**Background:** The PI3K/AKT/mTOR pathway is the most frequently activated signaling pathway in breast cancer (BC). PIK3CA-activating mutations are the most common genetic alteration observed in hormone receptor-positive (HR+) BC. In preclinical studies of HR+ BC, alpelisib (PI3Kα inhibitor) and buparlisib (pan-PI3K inhibitor) demonstrated significant antitumor effects both in vitro and in vivo when combined with hormone therapy. **Methods:** A Phase II, randomized, double-blind, placebo-controlled trial of alpelisib/placebo (300 mg once daily (QD)) or buparlisib/placebo (100 mg QD; intermittent regimen [5 days on; 2 days off]) plus letrozole (2.5 mg QD) for the neoadjuvant treatment of postmenopausal women with HR+/HER2– BC (NCT01923168). Key inclusion criteria are stage IIC–III, any N, M0 operable BC; measurable disease; HR+/HER2–; BC; known PIK3CA status (mutant vs wild-type [WT]) and Ki67 level; and Eastern Cooperative Oncology Group performance status ≤ 1. Key exclusion criteria are locally recurrent/metastatic disease and prior systemic therapy or radiotherapy for current BC. Patients (pts) will be assigned to 1 of 2 cohorts (PIK3CA mutant or WT) and randomized to 1 of 3 arms (letrozole + alpelisib, + buparlisib, or + placebo), stratified by Ki67 level (≤ 14% vs ≥ 14%) and lymph node status (positive vs negative). Pts will be treated for 24 weeks until surgery, disease progression, unacceptable toxicity, or study discontinuation for any other reason. The primary endpoint is pathologic complete response (pCR; ypT0/Tis, ypN0) at 24 weeks. The secondary endpoints are objective response rate (complete or partial; RECIST v1.1); safety and tolerability; rate of breast-conserving surgery; correlation between pCR and Ki67 changes from baseline to Day 15 and to surgery; response status (central preoperative endocrine prognostic index score of 0); and pharmacokinetic profiles of alpelisib/buparlisib plus letrozole. For each cohort, pCR rates will be summarized by treatment arm with 90% confidence intervals. Proof of concept will be assessed. Global recruitment is ongoing, with planned enrollment of 360 pts. Clinical trial information: NCT01923168.

I-SPY 2 low risk registry: An I-SPY 2 trial sub-study for women with clinically advanced, ER+, HER2- breast cancer and molecular good-prognosis gene signature. First Author: Tufia C. Haddad, Mayo Clinic, Rochester, MN

**Background:** With the increased utilization of molecular gene signatures, clinicians have identified a population of breast cancer patients that have clinically advanced disease associated with a low risk molecular profile. This discordance between tumor stage and molecular prognosis results in a dilemma for which consensus and evidence to guide treatment decisions are lacking. The I-SPY 2 Low Risk Registry (LRR) was therefore developed to capture the critical treatment data and clinicopathologic outcomes of these patients. A correlative biomarker study to characterize the biology and heterogeneity amongst these tumors is also planned. The goals of the LRR are to observe treatment patterns, determine tumor chemoendocrine sensitivity, and monitor clinical outcomes of these patients in order to inform the development of future studies aimed to optimize their management and outcomes. **Methods:** Patients with stage II or III breast cancer are recruited from the ongoing phase 2 neoadjuvant I-SPY 2 TRIAL. In this study, patients with Hormone Receptor-positive, HER2-negative disease are not eligible to be randomized to standard chemotherapy and a novel agent if their tumor has a 70-gene good-prognosis signature; instead, they are encouraged to enroll in the LRR. Treatment on the LRR is not pre-specified and at the discretion of the oncology team and patient. Data collection includes: screening MRI and tumor biopsy specimen, surgical pathology, menopause status, treatment administered, quality of life assessment, recurrence events and survival. Follow up for 15 years is planned. Biomarker analyses will include, but are not limited to, Ki-67, SET Index, GREB1, and HOXB13:IL17BR ratio. As of January 2015, 156 patients across 20 sites were eligible for the LRR, and 72 have enrolled at the Low Risk Registry, Clinical trial information: NCT01042379.

E2112: Randomized phase III trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. First Author: Roisin M. Connolly, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

**Background:** A potential mechanism of resistance to endocrine therapy in breast cancer involves changes in gene expression secondary to epigenetic modifications, which might be modulated with the use of histone deacetylase (HDAC) inhibitors such as entinostat. ENCORE 301, a phase II study evaluating the addition of entinostat to the steroidal aromatase inhibitor (AI) exemestane in patients with hormone receptor (HR)-positive advanced breast cancer who had experienced disease progression after a non-steroidal AI (NSAI), showed a significant improvement in progression-free survival (PFS), and overall survival (OS). Entinostat has been designated a Breakthrough Therapy by the FDA. **Methods:** E2112 is a multicenter randomized double-blind placebo-controlled phase III study (NCT02115282) enrolling patients with advanced HR-positive, HER2-negative breast cancer with prior disease progression on a NSAI (n = 600). Patients receive exemestane 25mg po daily and entinostat/placebo 5mg po every week. Eligibility: Postmenopausal women and men, ECOG 0-1, locally advanced/metastatic invasive adenocarcinoma of the breast: ER/PR-positive, HER2-negative, measurable or non-measurable (20% cap) disease. Disease progression after NSAI use in the metastatic setting OR relapse while on or within ≤ 12 months of end of adjuvant NSAI therapy. **Statistics:** Both PFS (central review) and OS are primary endpoints, and the study is designed to show improvement in either PFS or OS. Secondary endpoints include: Safety and tolerability, objective response rate, changes in lysine acetylation status in peripheral blood mononuclear cells, patient-reported symptom burden and treatment toxicities, adherence. One-sided type 1 error 0.025 split between two hypotheses tests: 0.001 for PFS test and 0.024 for OS. PFS is tested in the first 360 pts, 88.5% power to detect 42% reduction in the hazard of PFS failure (median PFS 4.1 to 7.1 months); OS is tested in all 600 pts, 80% power to detect 25% reduction in the hazard of death (median OS 22 to 29.3 months). E2112 was activated in March 2014 and accrual is anticipated to complete in 40 months. Clinical trial information: NCT02115282.
Brain Metastases in Breast Cancer Network (BMBC; GBG 79): Multicentric, retro- and prospective collection of patient data and biomaterials from patients with brain metastases. First Author: Volkmar Mueller, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: The incidence of brain metastases in breast cancer patients is rising and has become a major clinical challenge in the last years. So far, limited therapeutic options and insights into the biology of brain metastases exist. Most reports include patients with brain metastases from different tumor entities. Few studies so far analyzed exclusively patient data and tumor samples from brain metastases of breast cancer patients. Therefore, an open, multicentric registry and biobank should be helpful for analysis of a large number of breast cancer patients with brain metastases. Therefore we initiated the Brain Metastases in Breast Cancer Network (BMBC; GBG 79) Methods: Registration of patient data is allowed retrospectively as well as prospectively. To enable an easy multicentric access, an internet-based database was chosen ("MedCodes" of the German Breast Group). Captured data include incidence, number and localization of brain metastases, histopathologic characteristics, imaging methods applied, outcome and therapy modalities. Tissue of brain metastases and primary tumors will be collected for translational research projects. Planned analyses include treatment patterns in Germany, patient outcome, as well as validation of prognostic scoring systems in a multicenter setting and in the context of new targeted therapies. Planned translational research projects include the impact of glycosylation, resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, evaluation of markers of radioresistance and specific genomic alterations associated with brain tropism of breast cancer cells. The accrual target is 1000 patients in the database and 400 tissues of brain metastases from participating German centers. The study was opened for documentation in 2013 with 70 participating centers and more than 600 patients with started documentation as of February 2015.

TPS638 Poster Session (Board #120b), Sat, 8:00 AM-11:30 AM
A phase I study of RAD1901, an oral selective estrogen receptor degrader, in ER-positive, HER2-negative, postmenopausal advanced breast cancer patients. First Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN

Background: RAD1901 is a novel, non-steroidal, orally bioavailable selective estrogen receptor degrader (SERD). Preclinical studies demonstrated a favorable tissue selectivity profile, dose dependent ER degradation and potent inhibition of in vitro breast cancer cell proliferation. In an MCF7 xenograft model, significant tumor regression was consistently observed with RAD1901 treatment, compared to Tamoxifen or Fulvestrant. A phase I clinical study conducted in healthy postmenopausal female volunteers evaluated once daily doses up to 1000mg/day for 7 days. All dose levels were tolerated and pharmacokinetic analysis demonstrated good plasma exposure with dose proportional increases. 18F-estradiol positron emission tomography (FES-PET) was performed at baseline and after 6 days of treatment with RAD1901, to assess estrogen receptor engagement. Standardized uptake values (SUV) pre- and post-treatment demonstrated a complete attenuation of FES-PET signal in ER-rich tissues such as the uterus at both the 200mg/day and 500mg/day dose levels. Based on these preclinical and clinical results, RAD1901 is currently being investigated in a phase I study for the treatment of hormone driven and hormone resistant metastatic breast cancers. Methods: RAD1901-005 is phase I study consisting of two phases: a dose escalation phase and a safety expansion phase. The dose escalation will follow a 3+3 design to establish the maximum tolerated dose (MTD), the primary objective of the study. Once the MTD has been established, the expansion will evaluate the safety, tolerability and preliminary efficacy of the recommended phase II dose (RP2D), the secondary objectives of the study. RAD1901 will be administered orally on a continuous once daily schedule until disease progression, unacceptable toxicity or patient’s choice. Key inclusion criteria include post-menopausal women aged 18 years or older, with advanced ER-positive, HER2-negative breast cancer, who have received ≤ 2 prior chemotherapy regimens in the metastatic setting and ≥ 6 months of prior endocrine therapy. Patient enrollment started in early 2015. Clinical trial information: NCT02338349.

TPS639 Poster Session (Board #121a), Sat, 8:00 AM-11:30 AM
Brain Metastases in Breast Cancer Network Germany (BMBC; GBG 79): Multicentric, retro- and prospective collection of patient data and biomaterials from patients with brain metastases. First Author: Volkmar Mueller, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: The incidence of brain metastases in breast cancer patients is rising and has become a major clinical challenge in the last years. So far, limited therapeutic options and insights into the biology of brain metastases exist. Most reports include patients with brain metastases from different tumor entities. Few studies so far analyzed exclusively patient data and tumor samples from brain metastases of breast cancer patients. Therefore, an open, multicentric registry and biobank should be helpful for analysis of a large number of breast cancer patients with brain metastases. Therefore we initiated the Brain Metastases in Breast Cancer Network Germany (BMBC; GBG 79) Methods: Registration of patient data is allowed retrospectively as well as prospectively. To enable an easy multicentric access, an internet-based database was chosen ("MedCodes" of the German Breast Group). Captured data include incidence, number and localization of brain metastases, histopathologic characteristics, imaging methods applied, outcome and therapy modalities. Tissue of brain metastases and primary tumors will be collected for translational research projects. Planned analyses include treatment patterns in Germany, patient outcome, as well as validation of prognostic scoring systems in a multicenter setting and in the context of new targeted therapies. Planned translational research projects include the impact of glycosylation, resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, evaluation of markers of radioresistance and specific genomic alterations associated with brain tropism of breast cancer cells. The accrual target is 1000 patients in the database and 400 tissues of brain metastases from participating German centers. The study was opened for documentation in 2013 with 70 participating centers and more than 600 patients with started documentation as of February 2015.

TPS640 Poster Session (Board #121b), Sat, 8:00 AM-11:30 AM
A phase 2 single-arm study to assess clinical activity, efficacy and safety of enzalutamide (ENZA) with trastuzumab in HER2+ AR+ metastatic or locally advanced breast cancer. First Author: Maureen E. Trudeau, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: Androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) expression have been found to correlate, with one series of breast carcinomas demonstrating AR expression in 77% of HER2+ tumors (Barton V et al. Mol Cancer Res. 2013;11:abstr A047). In vitro, ENZA inhibits proliferation of AR+/HER2+ cell lines and enhances the activity of trastuzumab. ENZA also inhibits proliferation of trastuzumab-resistant HER2+ cells (Micello D et al. Virchows Arch. 2010;457:467-476). Methods: Women with metastatic or locally advanced HER2+/AR+ breast cancer will be enrolled in a phase 2 single-arm study (NCT02091960). Patients will receive daily ENZA (150 mg) continuously and trastuzumab (6 mg/kg) administered every 21 days until disease progression. Patients must have measurable disease per RECIST v1.1 and have received 1–4 prior lines of anti-HER2 therapy in the advanced/metastatic setting. Brain imaging is required to exclude patients with CNS metastases. Patients with a seizure history are excluded. The primary endpoint is clinical benefit rate (CBR), where benefit is defined as complete or partial response or stable disease ≥ 24 weeks according to RECIST v1.1 criteria. Additional endpoints include safety, tolerability, and the relationship between AR expression and ENZA activity. If the CBR is ≥ 3 in 21 evaluable patients, the sample size will increase to 66 patients. The primary endpoint will be analyzed in patients with centrally confirmed AR expression (≥ 10% nuclear staining by immunohistochemistry), who have received at least 1 dose of ENZA and have ≥ 1 postbaseline tumor assessment. The null hypothesis, that the true CBR is 10%, will be tested against a 1-sided alternative. This Simon’s 2-stage design yields 90% power when the true response rate is 25% with a 1-sided type I error rate of 5%. As of the date of abstract submission, 5 patients have been enrolled; enrollment is expected to continue through 2016. Clinical trial information: NCT02091960.
TPS641 Poster Session (Board #122a), Sat, 8:00 AM-11:30 AM
HERMIONE: A Phase 2, randomized, open label trial comparing MM-302 plus trastuzumab with chemotherapy of physician’s choice plus trastuzumab, in anthracycline naïve HER2-positive, locally advanced/metastatic breast cancer patients previously treated with pertuzumab and ado-trastuzumab emtansine (T-DM1). First Author: Kathy Miller, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN
Background: Although HER2-targeted therapies such as pertuzumab and T-DM1 have improved patient outcomes, treatment resistance typically occurs. MM-302 is a HER2-targeted liposomal doxorubicin in development by Merrimack Pharmaceuticals. In a Phase 1 study, patients with HER2-positive metastatic breast cancer (MBC) were treated with MM-302 alone and in combination with trastuzumab with or without cyclophosphamide. MM-302 had an acceptable safety profile and promising efficacy was observed in patients not previously exposed to an anthracycline. Methods: Trial design: HERMIONE (NCT02213744) is a randomized Phase 2, two-arm, open-label trial designed to evaluate if MM-302 can address an unmet medical need in patients with anthracycline naïve, trastuzumab-, pertuzumab- and T-DM1-pretreated HER2-positive locally advanced breast cancer (LABC)/MBC. Patients are randomized 1:1 to receive MM-302 (30mg/m², Q3W) plus trastuzumab (6mg/kg, Q3W) or chemotherapy of physician’s choice (vinorelbine, capecitabine, or gemcitabine) plus trastuzumab (6mg/kg, Q3W). Eligibility criteria: Centrally confirmed HER2-positive LABC/MBC, no prior anthracycline exposure, prior trastuzumab in any setting, prior pertuzumab and T-DM1 in the LABC/MBC setting, unlimited prior lines of therapy, ECOG 0-1 and LVEF ≥50%. CNS metastases are permitted if stable and without symptoms or steroids for 4 weeks. Specific aims: The primary endpoint is independently assessed progression free survival (PFS). Secondary endpoints include investigator assessed PFS, overall survival, response rate, safety and patient related outcomes. Statistics: 250 patients will be enrolled to observe 191 PFS events for 90% power to detect a Hazard Ratio of 0.625. The MM-302 arm will be compared to the control arm on the primary endpoint of PFS using a stratified log-rank test at one-sided 0.025 level. Accrual status: Recruitment began in July 2014 and is expected to be complete in late 2016. Sites will be open in the US, Canada and Western Europe. Clinical trial information: NCT02213744.

TPS642 Poster Session (Board #122b), Sat, 8:00 AM-11:30 AM
PATRICIA: A phase II study of palbociclib and trastuzumab with or without letrozole in previously treated, postmenopausal patients with HER2-positive metastatic breast cancer. First Author: Patricia Villagrasa, SOLTI Breast Cancer Research Group, Barcelona, Spain
Background: Despite the great efficacy of anti HER2-agents, HER2+ metastatic breast cancer remains incurable and in need of additional options. Palbociclib, a CDK4/6 inhibitor, has demonstrated unprecedented clinical activity in HER2-/+ disease. Its potential in HER2+ disease, however, remains to be explored. Preclinical evidence suggests a potentially complementary role with trastuzumab based on their effects on the cell cycle. Our hypothesis is that the addition of palbociclib to trastuzumab-based therapy could offer clinical benefit in this population. Moreover, given that the expression of ER dictates two biologically different HER2+ subgroups, we will explore this activity accordingly, in addition to endocrine therapy. Methods: This is an exploratory, prospective, open-label, multicenter trial of palbociclib plus trastuzumab. Patients must have histologically confirmed HER2+ adenocarcinoma of the breast and have received 2-4 lines of anti-HER2-containing regimens for their advanced disease. The study is based on a Simon 2-stage design comprising three cohorts: cohort A includes ER- patients and cohorts B1 and B2, ER+ patients. All patients receive trastuzumab with an 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks, and 200 mg daily palbociclib for 2 weeks, with 1 week off. Additionally, patients in cohort B2 receive 2.5 mg daily letrozole. A 2-cycle safety run-in with the first 6 patients of each regimen will be performed. The primary objective is to assess clinical efficacy measured as progression-free survival rate at 6 months (PFS6). Assuming an increase of at least 20% in PFS6 by the addition of palbociclib +/- letrozole to trastuzumab, PFS6 should be ≥ 50% for a cohort to be successful, and proceed to stage 2. According to this, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue for up to 46 patients. A treatment regimen will be considered efficacious if ≥ 18 patients are progression-free at 6 months, with an 80% power and α = 0.05. Based on this, a maximum of 138 patients may be included. Translational research searching for predictive biomarkers will be implemented. Clinical trial information: 2014-005006-38.

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1000 Oral Abstract Session, Mon, 3:00 PM–6:00 PM
TITAN: Phase III study of doxorubicin/cyclophosphamide (AC) followed by ixabepilone (Ixa) or paclitaxel (Pac) in early-stage, triple-negative breast cancer (TNBC). First Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN

Background: Ixa is a microtubule stabilizer able to target mechanisms conferring taxane resistance including high β tubulin III expression, seen in TNBC. Here, we present preliminary results of a phase III study of AC followed by Ixa or Pac in patients (pts) with early stage TNBC. Methods: Patients with resected TNBC (ER and PR < 10% by local IHC, HER2 IHC 0-1+ or FISH/ISH negative) and no evidence of distant disease were eligible. Pts were randomized 1:1: AC (60/600mg/m²) q3wks x4 followed by either Ixa (40mg/m² q 3wks x4) or AC/ixa or weekly Pac (80mg/m² x12 weeks) (AC/Pac). Growth factor use was allowed per MD discretion. Following phase II neoadjuvant results that demonstrated no AC/ixa efficacy advantage compared to AC/Pac (including in tumors with high β tubulin levels), the sample size of this study was revised to 590 patients to detect a 30% reduction in risk of recurrence with AC/Ixa. Results: Between December 2008 and March 2011, 614 pts (median age 54, 18% African American, 32% lymph node positive, 50% T2) were randomized (AC/ixa, 306; AC/Pac, 308). 84% AC/ixa and 77% AC/Pac pts completed protocol treatment (tx). 23 (8%) Ixa pts and 47 (16%) Pac pts discontinued tx due to toxicity. Dose reductions/dose delays occurred in 78 (26%)/121 (39%) Ixa pts and in 99 (33%)/158 (52%) Pac pts. Neutropenia was the major reason for dose reduction and tx discontinuation. G3/4 neutropenia rates were low at 11% with Ixa vs 6% with Pac, accompanied by fever in only 4% of patients. At a median follow up of 46 mo, 75 pts have relapsed (AC/ixa, 37; AC/Pac, 38). Median time from initial diagnosis to relapse was 20.8 mo. The 3 year disease-free survival of the Ixa arm was 88% (95% CI: 0.84, 0.91) and 89% (95% CI:0.85, 0.92) for the Pac arm. The hazard ratio (Ixa arm vs Pac arm) was 0.99 (95% CI: 0.63, 1.56, p = 0.98). 51 pts (Ac/ixa 28; AC/Pac, 23) have died, 42 due to disease. Conclusions: AC w/ Ixa or Pac performed well in this early stage TNBC population with no difference in efficacy evident. Pts receiving AC/Pac had higher rates of neutropenia and more dose modifications. Clinical trial information: NCT00789581.

1002 Oral Abstract Session, Mon, 3:00 PM–6:00 PM
Low-dose oral cyclophosphamide-methotrexate maintenance (CMM) for receptor-negative early breast cancer (BC). First Author: Marco Colletti, European Institute of Oncology, Milan, Italy

Background: IBCSG Trial 22-00 was designed to test the efficacy of the CMM regimen, hypothesized to have anti-angiogenic activity, administered following standard chemotherapy in patients (pts) whose tumors are hormone receptor negative. Methods: 1,086 women (ITI 1081) with hormone receptor-negative (< 10% positive cells by IHC) early BC, any nodal and HER-2 status were randomized to CMM (C, cyclophosphamide 50 mg/day orally continuously and M, methotrexate 2.5 mg twice/day orally 1 and 2 of every week for 1 year) vs no further treatment (no CMM). 814 (75%) had triple-negative (TN) BC and 350 (43%) of them had node positive (N+) disease. The primary end point was disease free survival (DFS), and 307 DFS events were required for 80% power. Results: At 82.6 months’ median follow up, 271 DFS events had been observed. Overall, 71 (13%) of 527 pts randomized to CMM did not receive CMM therapy and only 177 (39%) of the 456 pts who started received 75% or more of the scheduled doses. Nevertheless, pts assigned to CMM had a reduced risk of a DFS event compared with no CMM, which was not statistically significant (p = 0.14; table). The magnitudes of effect appeared to be greater for those with TNBC, especially for those with N+ disease. Multivariable allowance for baseline prognostic factors suggested a greater treatment effect within those with TN and N+ BC. A total of 64 pts, 13.5% of those receiving at least one dose of CMM, had a grade 3 or 4 treatment-related AE. Elevated SGOT and/or alkaline phosphatase were most frequently reported, followed by neutropenia. Conclusions: Adding CMM to adjuvant chemotherapy showed a non-significant 16% reduction in risk of a DFS event in the overall population of hormone receptor-negative early BC. Women with TN disease at higher risk of recurrence, for whom no maintenance regimen is currently available, had a greater benefit. Clinical trial information: NCT01229516.

1003 Oral Abstract Session, Mon, 3:00 PM–6:00 PM
Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). First Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The AR may be a therapeutic target for pts with androgen-driven TNBC. ENZA, a potent AR inhibitor, is approved in men with metastatic castration-resistant prostate cancer (mCRPC) and improves median survival (MS) compared with abiraterone (ABR) in mCRPC (15.8 vs 10.8 mos; HR 0.44; p<0.0001). Methods: MVD3100-11 was an open-label, Simon 2-stage study evaluating single agent ENZA in advanced AR+ TNBC (AR >0% by IHC; NCT01889238). Pts could be prescreened for AR, and were enrolled if measurable bone disease and limited brain metastases or seizure history were exclusionary. The primary endpoint was clinical benefit (CR, PR or SD) at 16 wks (CBR16) in ‘evaluable’ pts defined as having both AR IC >10% and a response assessment, CBR24, PFS, response rate, and safety were assessed. An androgen-driven gene signature (Dx) was created from gene profiling and outcomes were assessed accordingly. Stage 2 enrolled if CBR16 was ≥3 in 62 pts receiving 85% risk at 5% significance to test against a 1-sided alternative (CBR16 ≥20%). Results: As of 16 JAN 2015, 404 samples were tested for AR IHC; 79% had AR >0%; 55% had ARIC>10%; 118 pts were evaluable with ENZA; 43 pts were not evaluable (29 AR <10%; 14 AR ≥10% but no response assessment). Key outcomes in the defined populations are shown as shown in the Table. Over 50% received dexamethasone (Dx) in 1’s placebo group. A week was 32% progression or stabilization and 6% disease progression in TNBC. IHC results suggest AR prevalence is higher than previously reported. 47% of pts had an androgen-related gene signature (Dx+) and could appear to have disease superior in this group. AEs from ENZA were consistent with its known profile. ENZA may represent a novel therapeutic option in pts with TNBC who would otherwise receive cytotoxic chemotherapy. Clinical trial information: NCT01889238.
93.5% (p < 0.001). Adding carboplatin to PM increased the pCR rate from 45.2% to 64.9% in HR deficient tumors (p = 0.025). The response rate in HR non-deficient patients was 20% and 40.7% in the PM vs PM plus carboplatin respectively and was not significant (p = 0.146). In patients with non-tmBRCA a high HR score was associated with a higher pCR rate (49.4%) than a low HR score (30.9%; p = 0.050) irrespective of the use of carboplatin. **Conclusions:** HR deficiency in TNBC as well as HR score in non-surgery TNBC patients was found to be predictive of response. **Results:** Among 193 TNBC with PD-L1 results, 26% were PD-L1+ (≥ 1% cancer cell staining). **Conclusion:** The frequency of PD-L1 positivity between BRCA+ and sporadic TNBC (p = 0.35) were similar in BRCA+ than sporadic TNBC (OR, 3.0; 95% CI, 1.1-8.0). PD-L1+ TNBC were more likely to be AR+ (OR, 2.6; 95% CI, 1.1-6.1). **Table 1:** Tumors were randomized to receive PM or PM plus carboplatin with the highest response rate being in the HR-deficient group treated with carboplatin (pCR rate of 64.9%). HR deficiency may be used to identify patients likely to have a high response to DNA-damaging agents. Clinical trial information: NCT01426880.

### Impact of neoadjuvant therapy on breast conservation rates in triple-negative and HER2-positive breast cancer: Combined results of CALGB 40603 and 40601 (Alliance). First Author: Mehran Golshan, Department of Surgery, Brigham and Women’s Hospital, Boston, MA

**Background:** Neoadjuvant therapy (NAT) improves breast conserving therapy (BCT) rates, but the extent by tumor subtype is unknown. To quantify this effect for triple-negative breast cancer (TNBC) and HER2-positive breast cancer (HER2+ BC), we reviewed surgical outcomes from CALGB 40603, a randomized phase II trial of weekly paclitaxel (P) + /- carboplatin (C) followed by doxorubicin (A) + /- bevacizumab (B) for stage (stg) II-III TNBC, and CALGB 40601, a randomized phase III trial of paclitaxel (P) + HER2 blockade with trastuzumab (H), lapatinib (P+L) or both (P+H+L) for stg II-III HER2+ BC, by requiring surgeons to prospectively evaluate BCT eligibility before and after NAT. **Methods:** Patients (pts) with stg II-III TNBC (n = 404) were randomized in CALGB 40603. Pts with stg II-III HER2+ BC (n = 292) were randomized in CALGB 40601. The treating surgeon assessed BCT candidacy based on clinico-radiographic criteria before and after NAT. **Results:** Post- and pre-treatment surgical assessments were received for 94% of 742 pts treated in the two trials. Of 696 evaluable pts, 340 (49%) were considered BCT candidates prior to NAT. Of these, 310 (91%) remained BCT candidates after NAT. **Conclusion:** The rate of successful BCT, as defined by tumor-free surgical margins, was 74% prior to NAT and 85% after NAT. This difference was statistically significant (p < 0.001). **Table 2:** BCT rate for seven subtypes. BCT was successful in 88% of 310 pts who chose this approach; however, a substantial fraction of BCT-eligible pts opted for mastectomy. Clinical trial information: NCT00861705.
Background: There is controversy whether the response to neoadjuvant chemotherapy should be incorporated into the decision-making process for adjuvant radiotherapy in breast cancer. Methods: We present pooled analysis of the randomized neoadjuvant trials GeparTrio, GeparQuattro and GeparQuintoo including 3,481 patients stage III breast cancer for which information on the use of radiotherapy (RT) was available. 94% received any RT. Locoregional recurrence was defined as a recurrence in the breast, at the chest wall or in the regional lymph nodes. The overall risk of locoregional recurrence (LR) was 8.3% after a median follow-up of 55.9 months. RT conferred a significant benefit in terms of 5-year LR-free survival (LRFS, 95.4% vs. 67.4%, logrank p < 0.001) and 5-year disease-free survival (DFS, 75.4% vs. 64.7%, logrank p < 0.001). The absolute advantage of RT regarding both LRFS and DFS was highest among patients with clinically positive lymph nodes at first diagnosis (HR 2.32, 95% CI 1.54-3.50; p < 0.001; HR 1.97, 95% CI 1.48-2.62; p < 0.001 respectively). In patients with pCR, the 5-year LRFS was 95.7% with RT vs. 86.6% without RT (HR 3.32, 95% CI 1.00-11.08; p = 0.041) and 5-year DFS was 86.9% and 56.1% (HR 3.52, 95% CI 1.82-6.83; p < 0.001). In patients without pCR, the LRFS was 88.6% with RT vs 80.7% without RT (HR 1.86, 95% CI 1.29-2.67; p < 0.001) and 5-year DFS was 72.6% vs 65.7% (HR 1.39, 95% CI 1.07-1.81; p = 0.014). Multivariate analyses with additional clinical parameters as well as for pathologic tumor stage and pCR confirmed RT as an independent prognostic factor for LRFS (HR 0.54, 95% CI 0.35-0.82; p = 0.004) and DFS (HR 0.69, 95% CI 0.51-0.93; p = 0.016). Conclusions: This retrospective analysis suggests that patients managed without RT after neoadjuvant chemotherapy for breast cancer have a significantly worse outcome even if they achieved a pCR.

1010 Poster Discussion Session: Displayed in Poster Discussion Session (Board #124), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM


Background: 5 year disease specific survival (DSS) improvement among breast cancer (BC) patients has been observed over the past two decades. It is not known if this improvement extends to elderly women. Methods: Retrospective cohort study of BC patients from a dedicated BC registry database, years 1990-2007 (N = 1889). Chi square tests for bivariate proportional differences and Kaplan Meier survival analysis were used. The disease specific survival (DSS) endpoint was death from breast cancer. Results: Invasive breast cancer in patients age 65 and older was 62% mammography detected between 1990 and 2007 with no difference in detection method or stage by age (61% stage I, 27% stage II, 12% stage III). As age increased, patients were more often treated with surgery and radiation only [65-69 = 60%, 70-74 = 72%, 75-79 = 79%, 80+ = 82% (p < .001) and less often with chemotherapy [65-69 = 32%, 70-74 = 19%, 75-79 = 12%, 80+ = 82% (p < .001)] or hormonal therapy [65-69 = 63%, 70-74 = 71%, 75-79 = 66% vs. 80+ = 70%] than younger patients. In all patients, 5-year OS was similar between groups, but OS may become a common choice for adjuvant chemotherapy among older patients. In all patients, 5-year OS was similar between groups, but may be higher for patients with stage III disease receiving ACT.

1011 Poster Discussion Session: Displayed in Poster Discussion Session (Board #125), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Contralateral prophylactic mastectomy decision-making in the population-based iCanCure study of early-stage breast cancer patients: Knowledge and physician influence. First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI

Background: Contralateral prophylactic mastectomy (CPM) use is increasing in women who are not at increased risk of contralateral cancer development and will experience no survival benefit from the more morbid procedure. Little is known about treatment decision-making and other interactions. Methods: We surveyed patients newly diagnosed with breast cancer in 2013-14, identified through the population-based SEER registries of Los Angeles and Georgia, about 6 months after diagnosis, to determine receipt of diagnostic tests and factors related to the decision about surgery (including knowledge and perceived physician recommendation). Survey return is ongoing with an expected final response rate > 70%; current response rate 68%. Results: Nearly half of 1949 respondents with unilateral cancer considered CPM (20% very strongly, 6% strongly, 9% moderately, 10% weakly). Only 37% of those who considered CPM knew that it does not improve survival for the contralateral breast (20% believed it does, 49% didn’t know). Among women receiving CPM, 36% believed it generally improves survival. Ultimately, 1138 (58%) received BCS and 811 (42%) mastectomy (387, or 20% overall, with CPM). On multivariable analysis, pts who received CPM were younger, more likely to be white, less likely to be married, and less likely to have private insurance, compared to those who received BCS (p = 0.013). Conclusions: Contralateral prophylactic mastectomy use is widespread and is associated with clinical and demographic differences but results are not yet available. We examined temporal trends and clinical associations with CPM and compared the overall survival of patients receiving adjuvant ACT vs. TC. Methods: We used the SEER-Medicare database for women over 65 diagnosed 2004-2009. Women receiving ACT were compared to women receiving TC, ACT, and other (including anthracycline without taxane and cyclophosphamide, mitomxetrexate, and 5-fluorouracil). We excluded women who received trastuzumab. We used chi-square and logistic regression to identify factors associated with ACT vs. TC receipt and Cox proportional hazards models to assess survival differences by treatment. Results: We identified a total of 4391 patients: 1577 (36%) received ACT, 1174 (22%) received TC, and 1640 received other regimens. Use of ACT decreased from 26% in 2004 to 21% in 2009, whereas use of TC increased from 1% to 43% in the same period. Receipt of ACT vs. TC was associated with younger age; fewer comorbidities; lack of history of coronary artery disease or congestive heart failure; higher stage and lymph node involvement; and living in the Northeast United States (as compared to the West or South). Five-year overall survival (OS) estimates were 81% for patients receiving ACT and 86% for patients receiving TC (p = .21); 3-year unadjusted survival for stage III patients was 61% for ACT and 79% for TC (p =.02). The Cox proportional hazard ratio for all patients, adjusted for stage, comorbidities, and other significant associations, was 1.10 (95% CI 0.64-1.91). The hazard ratio for ACT vs. TC was not significant for stage I/I patients, but for stage III patients was 0.59 (95% CI 0.40-0.89). Conclusions: TC has been a common option for adjuvant chemotherapy among older patients. In all patients, 5-year OS was similar between groups, but may be higher for patients with stage III disease receiving ACT.
Conclusively demonstrate that CSM halves the (considerations; however, CSM resulted in a significantly lower re-excision rate endpoint of the study. Not all (margin rate than SPM (18.3% vs. 33.6%, p = 0.014). After randomization, those randomized to CSM had a significantly lower (+) margin rate than SPM (18.3% vs. 33.6%, p = 0.006). This was the primary endpoint of the study. Not all (+) margins were re-excised due to anatomic constraints; however, CSM resulted in a significantly lower re-excision rate than SPM (9.5% vs. 20.8%, p = 0.014). Conclusions: This is the first RCT to conclusively demonstrate that CSM halves the (+) margin and re-excision rate of SP. The routine implementation of CSM may significantly reduce morbidity and the necessity for re-operation for margin clearance. Clinical trial information: NCT01452399.

A phase II, open-label, neoadjuvant, randomized study of LCL161 with paclitaxel in patients with triple-negative breast cancer (TNBC). First Author: Marina Parton, The Royal Marsden Hospital, London, United Kingdom

Background: LCL161 is a small molecule that induces apoptosis by inactivating inhibitor of apoptosis proteins (IAPs). LCL161 preferentially synergizes with paclitaxel in TNBC models with a defined genetic signature that reflects the biology of IAP antagonists. Here we present preliminary safety and efficacy data from a completed Phase II study of neoadjuvant LCL161 with paclitaxel in patients with GS+ and GS– TNBC (NCT01617668). Methods: Women with operable, newly diagnosed TNBC (T2, N0–N2, M0) were stratified into GS+ and GS– patients and treated with paclitaxel (60 mg/m² weekly) + LCL161 (1800 mg/m²) for 12 weeks. Patients then received surgery to assess pathological complete response (pCR), followed by investiga-
tor’s choice of adjuvant therapy. Primary objective: To assess whether LCL161 enhances the efficacy of paclitaxel in patients with GS+ or GS– TNBC, defined by a ≥ 7.5% increase in pCR rate after 12 weeks of combination treatment vs paclitaxel alone. Results: All 209 treated patients completed the study: 171/106 patients (16.0%) in the combination arm and 171/103 patients (16.5%) in the control arm achieved pCR. In the GS+ group (30.1% of patients), 13/45 patients (29.2%) in the combination arm achieved pCR vs 6/22 patients (27.3%) in the control arm achieved pCR; the posterior probability of a ≥ 7.5% increase in pCR rate was 88.8%. In the GS– group, 4/72 patients (5.6%) in the combination arm achieved pCR vs 1/46 patients (2.2%) in the control arm. Conclusions: Neoadjuvant LCL161 with paclitaxel shows promising signs of efficacy in a GS+ subset of TNBC (~30%) of patients, but with some toxicity at the 1800 mg/m² dose. Clinical trial information: NCT01617668.

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Therapy of refractory relapsed metastatic triple-negative breast cancer (TNBC) with an anti-Trop-2 SN-38 antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132): Phase II/III clinical experience. First Author: Aditya Bardia, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Patients with metastatic TNBC have an aggressive disease with limited therapy options. The duration of response with standard chemotherapy is usually short, with median survivals of 3-6 months, and there is an unmet need for better therapies. Trop-2 is highly expressed in most epithelial cancers, including TNBC (>90%). IMMU-132 is a conjugate of a humanized anti-Trop-2 (trophoblast cell-surface antigen) mAb coupled site-specifically to SN-38 (7.6 moles SN-38/g), the active metabolite of irinotecan. The study used a modified response assessment criteria to assess efficacy. Methods: 57 patients with metastatic TNBC were treated: median age 61 years (range 31-81), median duration of therapy 9.4 months (range 1-11). In TNBC, Grade 3/4 toxicities included neutropenia (G3, 24%; G4, 6%) and febrile neutropenia (G4, 3%). Other G3 toxicities included diarrhea (3%), anemia (3%), leucopenia (3%), lymphopenia (3%), caecitis (3%). No pt developed antibodies to the conjugate, no one discontinued therapy due to toxicity. Thirty-four TNBC pts had at least 1 response assessment, with an objective response rate (ORR) of 21% (including 1 complete response), a disease stabilization rate (CR+PR+SD) of 74%, and a clinical benefit ratio with CR+PR+SD ≥ 60% = 37% (7 of 15 pts with SD are still on treatment). Conclusions: IMMU-132 therapy is associated with encouraging clinical activity, limited toxicity, and a multiple pt/tumor classification. Clinical trial information: NCT01631552.

Combined Homologous Recombination Deficiency (HRD) scores and response to neoadjuvant platinum-based chemotherapy in triple-negative and/or BRCA1/2 mutation-associated breast cancer. First Author: Melinda L. Teoh, Stanford University School of Medicine, Stanford, CA

Background: The HRD-LOH (loss of heterozygosity) score is significantly associated with favorable response to neoadjuvant platinum-based therapy in PREDICT G0105. We set out here to assess the combined HRD score, an unweighted sum of LOH, telomeric allelic imbalance (TAI), the HRD status, in identifying responders lacking a deleterious BRCA1/2 mutation. When BRCA1/2 mutation status was no longer significantly associated with RCB 0/1 or pCR; however, power was limited. Results: As of Feb 2, 2015, a total of 174 pts with relapsed/refractory diverse epithelial tumors have been treated with IMMU-132. Forty-eight pts with TNBC were treated: median age 61 years (range 31-81), median duration of therapy 9.4 months (range 1-11). In TNBC, Grade 3/4 toxicities included neutropenia (G3, 24%; G4, 6%) and febrile neutropenia (G4, 3%). Other G3 toxicities included diarrhea (3%), anemia (3%), leucopenia (3%), lymphopenia (3%), caecitis (3%). No pt developed antibodies to the conjugate, no one discontinued therapy due to toxicity. Thirty-four TNBC pts had at least 1 response assessment, with an objective response rate (ORR) of 21% (including 1 complete response), a disease stabilization rate (CR+PR+SD) of 74%, and a clinical benefit ratio with CR+PR+SD ≥ 60% = 37% (7 of 15 pts with SD are still on treatment). Conclusions: IMMU-132 therapy is associated with encouraging clinical activity, limited toxicity, and a multiple pt/tumor classification. Clinical trial information: NCT01631552.

Concordance of intrinsic subtyping and risk of recurrence (ROR) scores between matched primary and metastatic tissue from Triple Negative Breast Cancer Trial (TNT). First Author: Maggie Chon U Cheang, Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU), London, United Kingdom

Background: The majority of triple negative breast cancers are of basal-like subtype (BLBC). There is uncertainty about concordance of intrinsic subtypes and ROR scores by PMD50 between matched primary and metastasis samples. We sought to examine agreement of intrinsic subtypes and ROR groups using tissue in the TNT trial. Methods: TNT is a phase III, multicentre, randomized trial of carboplatin vs docetaxel in women with ER-Pgr-HR2- metastatic/recurrent locally advanced breast cancer. Using Prosigna test on Naboxing(r) Countour, intrinsic subtyping was performed on a central laboratory on primary tumour (PT) from 216 patients, 66 positive lymph nodes (PLN) and 13 recurrent tissue samples (RC). The ROR-5 (ROR based on subtype contents) and ROR-P (ROR based on subtype contents and proliferation index) were calculated using research-based PMD50 classifier (Park JCD 2009). Agreement on classification was assessed by kappa statistics and agreement between ROR subtypes and intrinsic subtypes was assessed. Results: Of 216 PT; 75 (35%) were BLBC, 25 (11%) HER2-negative (HER2E), 25 (12%) Luminal A (LumA), 5 (2%) Luminal B (LumB). Of PLN 49 (74%) were BLBC, 12 (18%) HER2E, 2 (3%) LumA, 3 (5%) LumB. Of RC, majority were BLBC (12/13, 92%) with 1 HER2E. There were 63 matched PT and PLN pairs, with substantial agreement between subtypes (k = 0.74 (95% CI 0.56-0.92), p < 0.0001; Table 1). 1 BLBC PT was classified HER2E in PLN. Of the 8 LumA PT, 5 (63%) were HER2E, 1 (12.5%) LumA, 2 (25%) LumA in their matched PLN. Comparing ROR risk groups, all high risk cases remained high risk (Table 1), while low/med switched to med/low/high risk groups. Conclusions: Our study confirms that BLBC and high risk ROR assignments in PT were substantially conserved with matched PLN and RC. None of the PT/non-BLBC was classified as BLBC in matched PLN or RC. LumA appeared to switch to aggressive subtypes or higher ROR-defined risk groups in matched PLN and RC. Gene expression profiles of matched samples will be presented.

Comparison of intrinsic subtypes and ROR groups between matched PT/PLN.
Background: A significant number of triple-negative breast cancer patients achieve pathological complete response (pCR) and improved relapse-free survival from neoadjuvant taxane-anthracycline (AT) based chemotherapy. However, the 3-year distant relapse free survival (DRFS) probability for AT-treated TNBC patients is only about 0.50. A test is needed that identifies the AT-insensitive patients who are candidates for an alternative therapy. Methods: Gene expression measurements of 242 AT-treated TNBC patients were divided into training and validation sets balanced for clinical traits and pCR. An innovative multistate gene methodology was used to identify predictors of pCR in the training set and confirmed in validation set, along with higher DRFS in the predicted TF-sensitive group. Results: Analysis of the training set (n = 129; 38 pCR) identified 15 genes that were most predictive of pCR. RespondR Score was developed using these genes to continuously stratify patients by probability of pCR. In the validation set (n = 133; 60 pCR), RespondR stratifies patients into groups of low (RR-low, 55%), moderate (RR-moderate, 21%) and high (RR-high, 24%) sensitivity with rate of pCR 0.24 (RR-low), 0.29 (RR-moderate), 0.62 (RR-high) and 5-year DRFS probability 0.49 (RR-low), 0.61 (RR-moderate) and 0.80 (RR-high). In the RR-high group mitosis-related genes are up-regulated and genes involved in extracellular matrix organization and cell adhesion are down-regulated. Conclusions: The RespondR Score accurately predicts those TNBC patients likely to achieve pCR and improved survival using AT neoadjuvant chemotherapy. RespondR can provide critical information to patients and physicians deciding between AT and an alternative therapy.

Background: CALGB 49907 compared cabazitabine (X) with standard (S) chemotherapy in BC patients (pts) 65 yrs and older. Initial results: inferiority of X for both RFS and OS at 2.4 yrs median follow-up (NEJM 2009;360:2055). Current median 9 yrs. Methods: Pts ≥ 65 years with Stage I-IIIB BC. Randomization: Xx6 vs S (physician choice: CMFx6 or ACx4) . Endocrine therapy recommended for hormone receptor (Hr) positive. Endpoints: relapse-free (RFS) and overall survival (OS). We now include recurrence-free interval (RFI) and BC-specific survival (BCSS) to separate competing risk from other-cause mortality. All endpoints defined by the STEEP. Primary analysis: Bayesian probability of X inferiority in RFS for early stopping and final. Results: At first interim analysis, after 633 pts (9/2001–12/2006), met the criterion for early stopping. Final Bayesian probability of inferiority of X to S was > 99% for both RFS and OS. Accrual closed (2006) and results published (2009). At 7-ys for S vs X: RFS 60% vs 52%; RFI 83% vs 75%; OS 79% vs 68%; BCSS 91% vs 83% - all p < .05. Table shows hazard ratios (HR) of X and 95% confidence intervals (CI). The magnitude of S effect and its interaction with Hr status has decreased, its benefit in Hr-neg tumors remains. There are 45 new primary cancers (S: 29; X: 16); breast 13 (S: 8; X: 5). H11022 MDS 6 (CMF: 2; AC: 3; X: 1). Conclusions: Long-term follow-up shows X inferior to S. Competing risks are important contributors to mortality in this population. Clinical trial information: NCT00224302.

HR of X (95% CI) by time of analysis and Hr status.

<table>
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<th>Hr status</th>
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Significant at P < .05.

Background: Anthracycline is one of the most effective and commonly used chemotherapy agents in patients with breast cancer, Hodgkin and non-Hodgkin lymphomas. However, it is associated with cardiomyopathy that is accumulative dose related and irreversible. We performed a meta-analysis to determine the efficacy of β-blocker or angiotensin antagonist to prevent early-onset anthracycline-induced ventricular dysfunction and cardiac events. Methods: Relevant articles were searched in PubMed, EMBASE and Cochrane database. Eligible studies were limited to randomized controlled trials comparing cardioprotective agents (β-blocker and angiotensin antagonist) to control in adult patients treated with anthracycline based regimens. Relative risks and 95% CI were calculated using random effect model and statistical analysis was performed by using RevMan 5.3 software. Results: The combined estimate demonstrated an association of β-blocker and angiotensin antagonist treatment with higher post-chemotherapy LVEF with 63.61% vs. 56.19% (MD 7.15, 95% CI, 0.47 to 13.84, p = 0.04). Cardiac events rate in experimental group was non-significantly lower than control with 9.7% vs. 27.4% (RD -0.15, 95% CI, -0.38 to 0.08, p = 0.2). In a subgroup analysis, the benefit of experimental agents on LVEF preservation was significant in patients treated with higher anthracycline accumulative dose (MD 14.61, 95% CI, 12.26 to 16.97, p < 0.00001), however not in lower dose (MD 1.79, 95% CI, -3.11 to 6.70, p = 0.47). Conclusions: In a meta-analysis of randomized controlled trials in patients treated with anthracycline, β-blocker and angiotensin antagonist treatment was associated with significantly better LVEF preservation, and the benefit was prominent in patients with higher anthracycline accumulative dose. Collectively, these results suggest that routine use of β-blocker or angiotensin antagonist should be encouraged in patients undergoing anthracycline based chemotherapy, especially when higher accumulative dose is expected.

Background: Brain Derived Neurotrophic Factor (BDNF) is important for neuronal survival and repair. We hypothesized that a disregulated neuronal and peripheral BDNF may enhance vulnerability to Paclitaxel-Induced Peripheral Neuropathy (PIPN). Methods: 21 women with breast cancer were examined for peripheral neuropathy at baseline and during paclitaxel treatment, using the Total Neuropathy Score (TNSr) and the neurotoxicity subscale; Fact/GOG-NTx. Allelic discrimination of val66met BDNF polymorphism, which is reported to cause a deficit in the cellular distribution and regulated secretion of neuronal BDNF, was done by PCR and DNA sequencing. Peripheral BDNF was studied by analyzing the delta between peripheral BDNF and baseline after 8 weeks of treatment in each patient as was measured by ELISA. Results: Seven of the patients (33.3%) had TNSr ≥ 2 at baseline and identified to have pre-existing peripheral neuropathy (PEX-PN). The remaining 14 patients (66.7%) were identified as non-pre-existing peripheral neuropathy (NPX-PN). The frequency of BDNF-SNP in the study population was Val/Val in 13 patients (62%) and Val/Met in 8 patients (38%). None of the patients were Met/Met (0%). We found a significantly higher incidence of the Val/Met genotype in the PEX-PN group than in NPX-PN (5 out of 7 (71.4%) vs. 3 out of 14 (21.4%) respectively). Correspondingly, patients carrying the Val/Met genotype reached higher maximal TNSr and Fact/GOG-NTx scores in response to paclitaxel compared to Val/Val patients (4.69 ± 0.74 vs. 8.87 ± 2.54 respectively, prob > 0.02); and 8.69 ± 1.96 vs. 20.37 ± 3.24, respectively, prob > 0.002). As regards peripheral BDNF we found that BDNF decreased in patients with PEX-PN along their treatment with paclitaxel while it increased in NPX-PN (~1.58 ± 2.80 ng/ml vs. +6.16 ± 2.58 ng/ml, respectively, prob > 1.03). Conclusions: BDNF may play a protective role in PIPN, and exhaustion of its peripheral resources may lead to the exacerbation of PIPN. The genetic data presented here suggests that dysfunctional neuronal BDNF-induced repair mechanism due to BDNF-SNP may be a predisposing condition that exacerbates PIPN.
Hippocampal memory impairment in breast cancer survivors after chemotherapy measurement using covert testing. 

**First Author:** Anthony J. Ryals, Northwestern University Feinberg School of Medicine, Chicago, IL

**Background:** Cognitive impairments are frequently reported following adjuvant chemotherapy, yet potential neuropathological substrates remain uncertain. Chemotherapy and anti-estrogen therapy have neurotoxic effects in rodent models, with disproportionate impairment of the structure and function of the hippocampus, a critical structure for long-term declarative and relational memory. To date, there have been no detailed assessments of human hippocampal function following adjuvant chemotherapy.

**Methods:** We used a specialized test of covert long-term memory processing sensitive to hippocampal impairment, involving eye-movement tracking coupled with functional MRI (fMRI). We compared 13 premenopausal breast cancer survivors on tamoxifen who were within 18 months of completing adjuvant chemotherapy to 14 healthy controls.

**Results:** Relative to controls, patients were not impaired on standard delayed overt recognition memory testing or on neuropsychological tests. In contrast, patients were impaired in eye-movement-based discrimination of repeated visual scenes matched on configurational similarity. Impairments were associated with less recruitment of hippocampal activity during covert memory testing. The location of hippocampal relative hypoactivity co-localized with regions of hippocampus that showed significant local volume reductions in survivors, demonstrating concurrence of structural and functional measures of hippocampal impairment.

**Conclusions:** We identified hippocampal and memory abnormalities in breast cancer survivors that were not evident using standard testing. These deficits mapped onto structural measurements of hippocampal atrophy, possibly indicating a neurologic basis of self-reported cognitive difficulties frequently experienced by cancer survivors.

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**1026**  
Poster Session (Board #140), Sat, 8:00 AM-11:30 AM

The utility of bi-weekly eribulin therapy for metastatic breast cancer: A Japanese multicenter phase II study (JUST-STUDY). 

**First Author:** Tetsuhiro Yoshimizu, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

**Background:** The EMBRACE study established eribulin as a standard therapy for metastatic breast cancer (MBC). However, eribulin at the standard dose and schedule (1.4 mg/m² on days 1 and 8 every 3 weeks) frequently leads to adverse events. The aim of this study was to investigate a new approach to control eribulin toxicity by schedule modification rather than dose modification.

**Methods:** We conducted a multicenter phase 2 study to evaluate the efficacy and safety of bi-weekly eribulin. Eligibility criteria included MBC treated with both anthracycline and taxane, and up to three prior regimens of chemotherapy for MBC. Eribulin was started at the standard dose and schedule, but the schedule was changed to bi-weekly without dose reduction, if any of administration criteria were not satisfied by day 8 of the 1st cycle or day 1 of the 2nd cycle, or remained bi-weekly without dose reduction, if any of administration criteria were not met at both time points. The primary endpoint was the primary tumor (T) pathological complete response (pCR) rate, and 268 pts were planned to be recruited. In the pre-planned interim analysis after recruitment of 60 pts, the independent data monitoring committee decided to stop the recruitment because the difference between the two arms was too small to continue this study.

**Results:** From April 2009 to March 2014, a total of 161 pts were enrolled. 78 and 83 of them were randomized to control arm and tailored arm, respectively. Median age was 49, 111 (68.9%) pts were ER positive, 65 (40.4%) pts were stage III. Among the tailored arm, 58 (69.8%), 41 (49.4%), and 64 (77.1%) of pts were positive for tumor, tailo II α, and ERCC1, respectively. The results of efficacy were listed in table. There were significantly higher incidence of grade 3/4 leukopenia (11.7% vs. 4.4%) and febrile neutropenia (2.9% vs. 0.0%) in control arm. In terms of response, tailo II α and ERCC1 did not influence the efficacy of eribulin in METBC.

**Conclusions:** The JUST-STUDY investigators concluded from the National Cancer Data Base, which contains 70% of incident cancers across the US. Logistic regression was used to examine factors associated with NST use. Results: Among 474,333 women, NST use increased by clinical stage: IIA (15%), IIB (39%), IIIA (52%), and IIIB (77%). Use for inflammatory breast cancer was 89%. NST use was also varied by age and receptor status (Table). Mastectomy rates in patients who did not receive NST were: stage IIA (50%), IIB (69%), and IIIA (75%). On multivariable analysis, age, stage and receptor status remained significantly associated with NST. Compared to hormone receptor (HR)/HER2- patients, adjusted odds ratios (aOR) for other groups were: HR+/HER2+ (1.91, 95% CI 1.83-2.00), HR-/HER2+ (2.56, 2.43-2.72), triple negative (2.62, 2.51-2.74). There was lower use of NST in the community (vs academic centers, aOR 0.58, 0.55-0.61) and in patients with higher vs lower Charlson comorbidity score (aOR 0.77, 0.74-0.81). There was higher use in Black vs White patients (aOR 1.11, 1.06-1.16). Medicaid and uninsured patients did not have lower NST use compared to private insurance. NST use increased over time (2012 vs 2010, aOR 1.20, 1.15-1.24). Conclusions: NST is an increasingly common approach, particularly for high risk clinical and biologic subtypes. However, many stage IIA-III patients undergo mastectomy without attempting NST to downstage their cancers.
A comparison of toxicity profiles between standard and lower dose capcitabine (CAP) in breast cancer (BC): a meta-analysis. First Author: Tomohiro Funakoshi, The Univ of Tokyo, Tokyo, Japan

Background: CAP 1,250 mg/m² BID x 14 days every 21 days (14/21) as monotherapy is the FDA approved dose and schedule for metastatic breast cancer (MBC). In trials of CAP 1,250 mg/m² BID (14/21), 26%–65% of patients required a dose reduction due to toxicities. A more favorable toxicity profile has been reported in trials of CAP 1,000 mg/m² BID (14/21). We performed a systematic review and meta-analysis to compare a safety profile between CAP starting dose of 1,250 mg/m² and 1,000 mg/m².

Methods: Studies were identified using PubMed, and ASCO and San Antonio Breast Cancer Symposium abstract databases from 1966 to November 2014. Eligible studies included phase II and III trials of CAP monotherapy at 1,250 or 1,000 mg/m² BID (14/21) for BC patients that reported detailed, individually patient-reported grade 3-4 adverse events. We performed a meta-analysis, using random-effects models, to calculate summary incidence estimates and 95% confidence intervals (CI) for grade 3-4 adverse events between the two doses. Incidence estimates for each event were compared using a random-effects model.

Results: A total of 4,283 patients from 32 trials (12 phase II and 20 phase III) of CAP monotherapy were included. 29 trials were in the locally advanced or MBC setting, 2 trials were neoadjuvant, and 1 trial was adjuvant. 3,065 and 1,218 patients were treated with CAP 1,250 and 1,000 mg/m², respectively. A significantly lower incidence of dose reductions, high grade HFS, diarrhea, neutropenia and anemia as well as grade neutropenia was seen in CAP 1,000 mg/m² compared to 1,250 mg/m². (Table)

Conclusions: CAP monotherapy at 1,000 mg/m² BID (14/21) has a clinically meaningful and significantly better toxicity profile compared to 1,250 mg/m² BID (14/21).

Efficacy of 12 weeks neoadjuvant nab-paclitaxel combined with carboplatinum vs. gemcitabine in triple-negative breast cancer: WSG-ADAPT TN randomized phase II trial. First Author: Oleg Gluz, West German Study Group, Moenchengladbach, Germany

Background: Pathological complete response (pCR) is associated with improved prognosis in TNBC, but optimal chemotherapy remains unclear. Neoadjuvant weekly nab-paclitaxel (Nab-Pac) has higher efficacy than conventional paclitaxel, with maximum benefit in TNBC. Both gemcitabine (Gem) and carboplatinum (Carbo) are interesting partners for taxane combined regimens, as metastatic BC data suggest that taxane + Gem is more active than taxane + Carbo. The aim of this phase II study was to compare toxicity and activity of nab-paclitaxel alone and in combination with Gem or Carbo to identify the most favorable regimen for higher Nab-P doses (arm C). No stat. differences in NP rates were observed (small sample size); numerically arm C had higher risk of G3 NP. EPHA-n3749683 SNP is associated with higher NP risk. Detailed genomic data and EMG results will be presented. Clinical trial information: NCT01763710.

A randomized phase III study of vinflunine versus an alkylating agent of physician’s choice in metastatic breast cancer (MBC) previously treated with or resistant to an anthracycline, a taxane, an antimetabolite and a vinca-alkaloid. First Author: Javier Cortes, Vall D’Hebron University Hospital, Barcelona, Spain

Background: There is currently no consensus on the efficacy of chemotherapy (CT) beyond 3rd line in MBC and only eribulin (which has been characterized properly. Methods: Studies were identified using PubMed, and ASCO and San Antonio Breast Cancer Symposium abstract databases from 1966 to November 2014. Eligible studies included phase II and III trials of CAP monotherapy at 1,250 or 1,000 mg/m² BID (14/21) for BC patients that reported detailed, individually patient-reported grade 3-4 adverse events. We performed a meta-analysis, using random-effects models, to calculate summary incidence estimates and 95% confidence intervals (CI) for grade 3-4 adverse events between the two doses. Incidence estimates for each event were compared using a random-effects model.

Results: A total of 4,283 patients from 32 trials (12 phase II and 20 phase III) of CAP monotherapy were included. 29 trials were in the locally advanced or MBC setting, 2 trials were neoadjuvant, and 1 trial was adjuvant. 3,065 and 1,218 patients were treated with CAP 1,250 and 1,000 mg/m², respectively. A significantly lower incidence of dose reductions, high grade HFS, diarrhea, neutropenia and anemia as well as grade neutropenia was seen in CAP 1,000 mg/m² compared to 1,250 mg/m². (Table)

Conclusions: CAP monotherapy at 1,000 mg/m² BID (14/21) has a clinically meaningful and significantly better toxicity profile compared to 1,250 mg/m² BID (14/21).
1033 Poster Session (Board #147), Sat, 8:00 AM-11:30 AM
Clinical predictors of failure of granulocyte colony stimulating factor (G-CSF) prophylaxis in patients with breast cancer treated with dose dense epirubicin (E), cyclophosphamide (C), and docetaxel (T) Adriamycin (A) Ctx followed by Ctx protocol: subgroup analysis of the NCIC CTG MA.21 study. 
First Author: Ravi Ramjeesingh, NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, ON, Canada

Background: Administration of prophylactic GCSF is recommended for curative chemotherapy regimens with an estimated incidence of febrile neutropenia of < 20% (Smith et al., JCO 24:3187-3205, 2006). Clinical predictors of failure of prophylaxis are poorly understood. We retrospectively analyzed data pertaining to patients treated with dose dense EC-T chemotherapy (E: 120 mg/m² IV Day 1 + C: 830 mg/m² IV Day 1, q14days x 6 cycles followed by T: 175 mg/m² IV q21days x 4 cycles) and primary prophylaxis with GCSF (5 μg/kg subcutaneously, days 2-13) on the NCIC CTG MA21, phase III study which compared 3 different anthracycline-based chemotherapy regimens. An interim analysis has been published (Burnell et al., JCO, 2010). Results: 695 patients were randomized to the EC-T arm and received at least one dose of protocol therapy and primary GCSF prophylaxis. 139 (20.0%) patients experienced a febrile neutropenic event, of which 46 (33.1%) were hospitalized. There were no deaths secondary to febrile neutropenia. In a multivariate analysis, no significantly detrimental role of the covariates, including the ones listed, were identified.

Conclusions: In the context of the MA.21 study, the failure rate of primary prophylaxis with GCSF therapy for prevention of febrile neutropenia in patients treated with dose dense EC-T therapy was 20% with an associated hospitalization rate of 30%. In multivariate analysis, none of the patient variables analyzed was significantly associated with failure of GCSF prophylaxis.

1034 Poster Session (Board #148), Sat, 8:00 AM-11:30 AM
A nomogram to predict axillary response to neoadjuvant chemotherapy in clinically node positive breast patients. First Author: Jose Vila, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Background: Many clinically node positive breast cancer patients receive neoadjuvant chemotherapy (NAC), with 40% converting to node negative. Recent trials suggest a potential role for limiting axillary surgery in these patients. This study was undertaken to develop a nomogram predicting the likelihood of axillary pathologic complete response (pCR) in biopsy-proven cN1 patients receiving NAC. Methods: Patients with cT1-4N1M0 disease who underwent NAC and underwent axillary lymph node dissection were identified. Patients received anthracycline- and/or taxane-based therapy with trastuzumab in HER2+ patients. Estrogen receptor (ER) was recorded as the percentage of cells staining positive. Univariate and multivariate logistic regression analyses were performed to determine factors predictive of nodal conversion. A nomogram to predict the likelihood of nodal pCR was constructed. Results: A total of 614 cN1 patients were included: 93 (15%) cT1, 367 (60%) cT2, 107 (17%) cT3, and 47 (8%) cT4. Imaging showed multifocal disease in 24% (146/614). Receptor status was ER+ in 75% (458/614), PR+ in 64% (394/612), and HER2+ in 20% (124/614). Axillary pCR was achieved in 37% (228/614). On univariate analysis, nuclear grade (OR 13.67 grade 3 vs. 1, p < .0001) and HER2 status (OD 4.6, p < .0001) were predictive of nodal pCR. Significant negative factors included multifocality on imaging (OR 0.67, p = 0.045), lobular histology (OR 0.53, p < .0001), PR+ (OR 0.24, p < .0001). ER percentage as a continuous variable (OR 0.98, p < .0001) as well as ER+ categorized as > 1% staining (OR 0.29, p < .0001). Nomograms to predict nodal pCR were created using these variables in addition to the clinically significant factors of T stage and number of abnormal nodes on US (≤ 4 vs. > 4). The discrimination of the nomogram using ER positive (> ≥ 1% staining versus negative (OR = 0.775) was improved using the percentage of ER staining (AUC = 0.789).

Conclusions: Multifocality, histology, nuclear grade, ER, PR, and HER2 status predict the ability to achieve nodal pCR with NAC. A nomogram incorporating these factors predicts the likelihood of nodal pCR with NAC which may help guide decisions regarding surgical management of the axilla in these patients.

1035 Poster Session (Board #149), Sat, 8:00 AM-11:30 AM
Direct effects on bone metabolism induced by perioperative anthracycline- and/or taxane-based chemotherapy depend on the menopausal status of patients with primary breast cancer. First Author: Nadine Rauschenbach, Gynecologic Center Bonn-Friedensplatz, Bonn, Germany

Background: Whereas cancer therapy-induced bone loss (CTIBL) is among the well-known sequelae of adjuvant endocrine therapy in patients (pts) with primary breast cancer (PBC), the knowledge about direct effects of modern perioperative Ctx protocols on bone metabolism is limited. This translational project was initiated to gain detailed insights into the influence of anthracycline (A)- and/or taxane (T)-based Ctx on bone turnover of both pre- and postmenopausal PBC pts in the clinical routine. Methods: Data of 109 pts (premenopausal: 49; postmenopausal: 60) receiving A- and/or T-based neoadjuvant or adjuvant Ctx were included. Serum bone markers including the C-telopeptide of type I collagen (ICTP) indicating osteoclast activity, the N-propeptide of type I collagen (PINP) measuring osteoblast activity, and bone alkaline phosphatase (BALP) were determined at baseline and prior to each subsequent Ctx cycle (C) up to C6. Changes of ICTP, PINP, and BALP over time were analyzed by repeated-measure ANOVA. Results: 600 Ctx cycles were analyzed. Baseline levels of ICTP (p = 0.0027), PINP (p = 0.0063), and BALP (p = 0.0007) were significantly higher in post- versus premenopausal pts. BALP levels remained largely unchanged during Ctx. Trends showing an increase of ICTP from baseline until C6 in premenopausal pts and a decrease in postmenopausal pts did not reach statistical significance. In contrast, PINP and BALP significantly decreased in postmenopausal pts to baseline by C6 (p = 0.0152). In premenopausal pts, PINP declined from baseline to C3 and thereafter increased to C6. These changes were highly significant (p = 0.0024).

Conclusions: Our study represents one of the first systematic evaluations of bone turnover in pts exposed to A- and/or T-based Ctx for PBC in the clinical routine. In postmenopausal pts, Ctx was associated with a sustained suppression of osteoblast activity whereas osteoblast suppression recovered until the end of Ctx in premenopausal pts. Whether these effects will translate into an increased risk of CTIBL remains a matter of further investigations which should clearly focus on the individual menopausal status.

1036 Poster Session (Board #150), Sat, 8:00 AM-11:30 AM
Death during study treatment: An evaluation of events in 31 German clinical trials. First Author: Jenny Furlanetto, German Breast Group, Neu-Isenburg, Germany

Background: Information on deaths occurring during oncological clinical trials has never been systematically assessed to describe patient, tumor, and treatment characteristics. Methods: Information on patients’ deaths during German Breast Group (GBG) led breast cancer (BC) trials was prospectively captured. In addition to the trial databases, data were derived from death narratives that included autopsy results if performed. All deaths were evaluated for possible causes, underlying conditions, treatment relatedness, time point and rate of autopsies. Results: From 12/1996 to 12/2014 23,570 patients were treated within 31 trials. Of those 75 (0.3%) died on therapy within 14 trials. 29/12,956 patients died in neoadjuvant (0.2%), 35/9,851 in adjuvant (0.3%) and 11/763 in metastatic studies (1.4%). Median age was 64 yrs (range 35-84), 63.5% of patients had an abnormal BMI (25.7% underweight, 32.4% overweight, 5.4% obese); 60% had I-3 and 13.3% ≥ 4 comorbidities; 56% had ≥ 2 cardiovascular risk factors (CRFs); 45.3% took ≥ 3 drugs; 80% had an ECOG 0. Over 50% of patients had a stage III tumor at baseline with a luminal B-like BC subtype (HR+/Her2-). Most patients with advanced disease had a high BMI (p = 0.024), ≥ 3 comorbidities (p = 0.013) and CRFs (p = 0.001) compared to early stage patients. Main causes of death were infections (34.7%); febrile neutropenia (4%); cardiac (14.7%) and respiratory disorders (12%). 13% of patients (4 in metastatic BC, 6 in early BC) died of disease progression. Aty1% of patients received treatment (A)-based chemotherapy (CT) and the event mostly occurred in the first 4 cycles. Relatedness to chemotherapy was declared in 55% of patients, mainly when a T-based CT was given (51.2% for T-based CT, 14.6% for anthracycline (A)-based CT, 22% for A-based CT, 12.2% for other regimens (capetibarine, bevacizumab, lapatinib, CMF, celecoxib), none for hormone therapy); p = 0.001. An autopsy was performed in 13% of patients.

Conclusions: Death during study treatment was mainly related to infections, and patients with advanced disease, high BMI, underlying comorbidities and CRFs. If considered for study participation these patients need careful monitoring due to their higher risk for death on study.
Background: Assessment of TILs has gained interest in oncologic pathology especially as a predictor of outcome in HER2+ and triple negative breast cancer (BC). Recently, a standardized approach to assess TILs on routine histopathology slides as a biomarker in BC was recommended by an international panel of experts. Using this approach, we assessed the inter rater reliability and predictive value of TILs in HER2+ locally advanced BC cases.

Methods: Core biopsies from 52 HER2+ BC patients obtained prior to neoadjuvant (NAT) chemotherapy with or without trastuzumab (T) were reviewed. Two pathologists independently quantified stromal TILs, intratumoral heterogeneity (ITH), presence of lymphocyte predominant (LPBC), and ISH of SPAG5 using H&E-stained slides following 2014 international guidelines. Discordant results were resolved by reviewing on a double headed microscope. The association of TILs as a continuous and categorical (LPBC) variables with complete pathological response (pCR) rates was determined by Mann-Whitney Wilcoxon test. Inter rater reliability was measured using Cohen’s Kappa coefficient. Results: An average of 4 cores per case were assessed. 8/52 (15%) cases had LPBC. Heterogeneity was mild in 30, moderate in 16 and severe in 6 cases. The pathologists agreed on 90%, 96% and 88% of the cases for quantitative TILs, LPBC (≥60%) and (ITH, inter rater reliability was excellent (Cohen’s Kappa 0.89, 0.85 and 0.81 respectively). On univariate analysis, high levels of TILs and LPBC were associated with greater pCR rates for the cohort of patients who received NAT with T (p = 0.004, p = 0.05 respectively).

Conclusions: Our results show that the levels of TILs can be reliably assessed on breast core biopsies. High levels of TILs as a continuous variable and LPBC are candidate predictors of pCR in HER2+ BC patients receiving NAT.

Background: Adjuvant trials have demonstrated that addition of trastuzumab (T) to chemotherapy reduces risk of recurrence and death in women with HER2 overexpressed or gene amplified early breast cancer (BC). Central testing of specimens from patients in NSABP B-31 demonstrated that ~10% of patients without overexpression/gene amplification of HER2 had similar benefit from adjuvant T. Aim of this study was to assess pathologic complete response (pCR) when T is added to neo-adjuvant (NA) chemotherapy in women not exhibiting HER2 FISH amplification but had low level of protein (IHC) expression (1+ or 2+). Methods: Single arm phase II trial of clinical stage II/III operable BC with HER2 expression of 1+ or 2+ by IHC and FISH negative (Ratio < 2). All clinically suspicious axillary nodes were biopsied. Eligible women were treated with 12 weeks of nab-paclitaxel (100mg/m2) + weekly T (4mg/kg LD then 2mg/kg) followed by 4 cycles of dose dense AC (60/600), followed by surgery. Women with + axillary nodes at diagnosis had ALND. Results: 32 subjects were enrolled between 7/2009-9/2013. Median age was 53, 59% were postmenopausal. 6% had grade 1, 41% grade 2 and 53% had grade 3 tumor. All but 1 were ER + (97%) with average ER expression of 85% (range 50-99%). 22 tumors (70%) were 1+ by IHC; 10 (30%) were 2+. Median tumor size was 4.1 cm (range 1.5 to 8.5cm). 17 (53%) had biopsy proven + axillary nodes. 14 subjects had clinical CR after 12 weeks of nab-paclitaxel/trastuzumb. 18 had cCR at completion of AC. 8 (25%) demonstrated higher pCR and ISH of SPAG5 when OR was ≥ 3.0, 95% CI = 1.3-7.1, p = 0.01) and ER- cases (OR = 4.2, 95% CI = 1.3-13.0, p = 0.01). In the paclitaxel arm there was no statistical association between pCR and SPAG5 mRNA level. SPAG5-protein+ was shown to be an independent predictor for pCR (OR = 2.4, 95% CI = 1.6-3.9, p < 0.001). In a vitre cell line models, SPAG5+ expression was linked to cell response to CT drugs, irrespective of ER and TP53 status. For instance, T47D and BT549 cell lines with SPAG5+ expression were sensitive to Doxorubicin and knocking-down of SPAG5 made cells resistant to CT agents. Conclusions: SPAG5 is a novel amplified gene on chr17q11.2 and is an independent prognostic factor. SPAG5 could help in the selection of patients who will benefit from AC-CT, and its interaction with TP53 need to be explored.
A model-based approach to dose optimization of neurotoxic chemotherapy for metastatic breast cancer (MBC). First Author: Manish Sharma, The University of Chicago Medicine, Chicago, IL

Background: CALGB 40502 (Alliance) randomized patients (pts) with MBC to paclitaxel 90 mg/m², nab-paclitaxel 150 mg/m², or ixabepilone 16 mg/m² on days 1, 8, and 15 every 28 days, with or without bevacizumab. The aims of this analysis were to develop a model of chemotherapy-induced peripheral neuropathy (CIPN) using dosing data and patient-reported symptoms, and to use this model to inform a dose adjustment algorithm to reduce CIPN. Methods: FGSUM4 is the fourth follow-up of the FACT/GOG Neurotoxicity subscale, which are scored 0-4 on a Likert scale and inquire about numbness/tingling and discomfort in the hands and feet. Of 799 pts, data from 655 with baseline FGSUM4 ≤ 4 were used to develop a kinetic-pharmacodynamic model of CIPN. Baseline height, weight, age, race and prior taxane therapy were evaluated as covariates. The model was evaluated by standard diagnostic plots and bootstrapping. Simulations evaluated the model’s ability to predict later CIPN from early CIPN data. Simulations were also used to explore dose adjustments to minimize later CIPN. Results: The model identified paclitaxel as the least neurotoxic drug in the study; for paclitaxel, the median average dose per day divided by SDK₅₀ (a parameter that reflects clearance and intrinsic toxicity) was 0.56, compared to 0.95 for nab-paclitaxel and 1.02 for ixabepilone. Using the first 3 cycles of data, the model predicts mean FGSUM₄ ≤ 5 at later time points with 73% sensitivity and 73% specificity. Simulations support a dose adjustment algorithm in which pts with 4 ≤ FGSUM₄ < 8 after 3 cycles skip the day 8 dose in subsequent cycles, while pts with FGSUM₄ ≥ 8 skip the day 8 dose and reduce the day 1 and 15 doses by 50%. This algorithm reduces the number of pts with FGSUM₄ ≥ 8 after 6 cycles by 33% compared to no dose adjustment. Conclusions: A model of CIPN in pts with MBC treated with neurotoxic chemotherapy was developed using patient-reported symptoms from CALGB 40502. The model can use early CIPN assessments to predict later CIPN with good sensitivity and specificity. Simulations support a dose adjustment algorithm after the first 3 cycles of therapy that reduces later CIPN. Validation of the model with an independent data set is necessary before clinical use.

Gene expression of metastatic biopsies for prediction of response to palliative chemotherapy in breast cancer. First Author: Theodoros Foukakis, Karolinska University Hospital, Stockholm, Sweden

Background: To date, no clinically useful predictive tests for chemotherapy in breast cancer (BC) are available. Several studies have tried to identify predictive gene expression signatures in the neoadjuvant setting, but no data are available for metastatic BC. Methods: We evaluated with advanced BC who were treated with epirubicin and paclitaxel with or without capecitabine as first-line treatment in the Swedish Phase 3 TEX trial. For 111 patients, a metastatic biopsy was obtained at baseline for gene expression profiling (Affymetrix array GPL10379). PAM50 molecular subtypes and published gene modules related to immune response or proliferation were investigated as predictors of objective response to chemotherapy (by RECIST tumor response criteria) in patients with (PET) or without (PST) prior chemotherapy. Patients were divided according to HER2 status. Results: Of 111 patients, 45 were HER2 positive and 66 were HER2 negative. Non-disruptive TP53 mutations were more common in non-luminal (16.5 vs. 8 months, hazard ratio 2.2, 95% confidence interval 1.4-3.4, p = 0.001 by log-rank test). A high immune response module was predictive of response to chemotherapy for the whole cohort (Odds ratio (OR) 1.61, 95% CI 1.02-2.64) and for luminal tumors (OR = 2.91, 95% CI 1.32-7.75), but not for basal-like tumors (OR = 0.87; 95% CI 0.34-2.25). The PAM50 proliferation index was positively associated with response in patients with estrogen receptor (ER) negative tumors (OR = 2.58; 95% CI 1.06-7.83). Conclusions: A high immune gene module was predictive of chemotherapy response in metastatic breast cancer, but this was restricted to the subgroup of luminal tumors. ER negative tumors with high proliferation rate had a higher probability to respond to chemotherapy. Clinical trial information: nct01435614.

Objection response within PAM50 molecular subtypes.

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<thead>
<tr>
<th>PAM50 subtype</th>
<th>Objective Response</th>
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<tr>
<td>Non-responders</td>
<td>responders</td>
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<tr>
<td>Basal-like</td>
<td>10 (40.0%)</td>
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<tr>
<td>Her2 enriched</td>
<td>15 (51.7%)</td>
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<tr>
<td>Luminal A</td>
<td>6 (60.0%)</td>
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<tr>
<td>Luminal B</td>
<td>11 (34.4%)</td>
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<tr>
<td>Normal-like</td>
<td>10 (33.3%)</td>
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Proteomic analysis of primary and metastatic breast cancers and expression of the folate receptor as a potential drug target. First Author: Todd A. Hemmingsh, OncostePlex Diagnostics, Rockville, MD.

Background: The folate pathway is a critical nucleotide biosynthetic pathway in many tumor cells, and blockade of this pathway with antifolates has demonstrated clinical utility in NSCLC and mesothelioma. The folate receptor alpha (FRA) is reported to be highly expressed in triple negative breast cancer (TNBC). However, targeting this pathway with permetrexed in metastatic breast cancer (MBC) has been a modest success (~20% response rate in unselected patients). We used multiplex mass spectrometry (MS) to assess the expression of the FRA and other biomarkers in TNBC to identify patients who may be responsive to antifolate therapy. Methods: In our clinical lab, primary and metastatic BC tissues were microdissected, solubilized and enzymatically digested following CAP/CLIA guidelines. Archived BC tissues (n = 270) were analyzed following GLP protocols. Absolute quantitation of protein targets was performed using selected reaction monitoring (SRM) mass spectrometry. Results: Using quantitative proteomic analysis, we found ~40% of TNBC tumors express high levels of FRA. In contrast, among 247 hormone receptor-positive and HER2-positive tumors, only 8% expressed FRA. FRA showed a 10-fold range of expression in both sample sets; a range that is most likely indiscernible by IHC. Correlation analysis between FRA and several other markers of chemotherapy sensitivity in the TNBCs showed only weak correlations suggesting that the FRA pathway is not influenced by other known pathways. Conclusions: Multiplex MS data confirm that FRA expression is more common in TNBC than other BC subtypes, and demonstrate that there is a wide dynamic range of FRA expression. Further analyses are warranted to identify a cutoff which predicts for antitumor activity of antifolate drugs. Proteomic screening should be performed to identify TNBCs which highly overexpress FRA to enrich for a population most likely to benefit from antifolate therapy. Prospective evaluation of permetrexed and other FRA-targeted agents is warranted in metastatic TNBC pts whose cancers express high levels of FRA.

Pre-treatment Near-Infrared Spectroscopic Tomography (NIRST) to predict pathologic complete response to neoadjuvant chemotherapy (NAC) in women with locally advanced breast cancer (LABC). First Author: Peter Kaufman, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background: NIRST has a potential role for easily integrated monitoring and prediction of therapeutic response in women with LABC undergoing NAC. It captures biophysical changes in tissue occurring in the vascular as well as prediction of therapeutic response in women with LABC undergoing NAC. It

Results: Using quantitative proteomic analysis, we found ~40% of TNBC tumors express high levels of FRA. In contrast, among 247 hormone receptor-positive and HER2-positive tumors, only 8% expressed FRA. FRA showed a 10-fold range of expression in both sample sets; a range that is most likely indiscernible by IHC. Correlation analysis between FRA and several other markers of chemotherapy sensitivity in the TNBCs showed only weak correlations suggesting that the FRA pathway is not influenced by other known pathways. Conclusions: Multiplex MS data confirm that FRA expression is more common in TNBC than other BC subtypes, and demonstrate that there is a wide dynamic range of FRA expression. Further analyses are warranted to identify a cutoff which predicts for antitumor activity of antifolate drugs. Proteomic screening should be performed to identify TNBCs which highly overexpress FRA to enrich for a population most likely to benefit from antifolate therapy. Prospective evaluation of permetrexed and other FRA-targeted agents is warranted in metastatic TNBC pts whose cancers express high levels of FRA.

Impact of sequencing weekly paclitaxel (T) and dose-dense doxorubicin/cyclophosphamide (DDAC) on tolerability and relative dose intensity (RDI) in breast cancer (BC) patients (pts) receiving neoadjuvant chemotherapy (NAC). First Author: Nicholas Martin LeCroy, Memorial Regional Hospital - Department of Pharmacy, Hollywood, FL.

Background: A preferred NAC regimen for HER2-negative BC is DDAC for 4 cycles followed by 12 weeks of T. RDI of 1 indicates that all intended doses are given at the scheduled interval. While large randomized studies are lacking, a few studies indicate improved pCR and RDI when T is given first. We hypothesize that tolerability and RDI are improved when T is given before DDAC. To our knowledge, this is the first study evaluating the impact of the sequence of paclitaxel and RDI on systemic therapy at diagnosis of BM, continuation of anti-HER2 agents prolonged TTP-B (HR 0.41 CI 0.23–0.72, p < 0.001) and OS (HR 0.41 CI 0.28–0.59, p < 0.001). Lapatinib-based was not superior to trastuzumab-based therapy and capecitabine was not superior to other cytotoxic agents. Pts who were on systemic therapy at diagnosis of BM and had controlled extra-cranial disease, local therapy to the brain, less than 3 lines of therapy prior to diagnosis of BM. Disease progression in the brain was documented in 359 pts (40.7%). Median TTP-B was 6.8m (3.7–12.1). Systemic therapy prolonged TTP-B (7 vs 4.5m; HR 0.58 CI 0.40–0.84 p = 0.005). Other factors associated with OS: ER+, HER2+, single BC, and local therapy to the brain. In pts receiving anti-HER2 based therapy at diagnosis of BM, continuation of anti-HER2 agents prolonged TTP-B (HR 0.41 CI 0.23–0.72, p < 0.001) and OS (HR 0.41 CI 0.28–0.59, p < 0.001). Lapatinib-based was not superior to trastuzumab-based therapy and capecitabine was not superior to other cytotoxic agents. Pts who were on systemic therapy at diagnosis of BM and had controlled extra-cranial disease did not benefit from switching to non-cross-resistant agents. Conclusions: In patients with breast cancer metastatic to the brain, systemic chemotherapy was associated with better control in the brain and longer survival.

Impact of systemic therapy on the outcomes of patients with metastatic breast cancer to brain: MD Anderson Cancer Center (MDACC) experience 1999-2012. First Author: Bugano Dizogomes, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Management of metastatic breast cancer to the brain (MBC-B) is mainly surgery and/or radiation. The efficacy of systemic therapy remains controversial. Methods: Out of 1514 consecutive patients (pts) with MBC-B treated at MDACC October 1999-December 2012, 882 had complete data and were included in this retrospective study. We used a Cox multivariate model to identify the effect of systemic therapy on time-to-progression in the brain (TTP-B) and overall survival (OS). Results: Disease subtypes: ER+/HER2- (26%) ER+HER2+ (17%); ER-/HER2+ (20%); ER-/HER2- (33%), missing (4%). Number of breast metastasis (BM): 1 (24%), >1 (67%), concurrent LMD (8%), missing (1%). Local treatment: metastasectomy (5%), stereotactic radiosurgery (SRS) (14%), whole-brain radiation (WBRT) (58%), combination S/SRS with WBRT (12%); no treatment (11%). Subsequent systemic therapy was given to 679 pts (77%). Median OS was 9.7 months (m) (4.0–21.9). Systemic therapy prolonged OS (HR 0.44 CI 0.36–0.52 p < 0.001) for all subgroups: HER2+ (17.8 vs 3.3m); ER+HER2+ (10.7 vs 2.3m); ER-/HER2- (8.4 vs 2.4m). Other factors associated with OS: ER+, HER2+, age < 60, ECOG 0-1, single BM, controlled extra-cranial disease, local therapy to the brain, less than 3 lines of therapy prior to diagnosis of BM. Disease progression in the brain was documented in 359 pts (40.7%). Median TTP-B was 6.8m (3.7–12.1). Systemic therapy prolonged TTP-B (7 vs 4.5m; HR 0.58 CI 0.40–0.84 p = 0.005). Other factors associated with OS: ER+, HER2+, single BC, and local therapy to the brain. In pts receiving anti-HER2 based therapy at diagnosis of BM, continuation of anti-HER2 agents prolonged TTP-B (HR 0.41 CI 0.23–0.72, p < 0.001) and OS (HR 0.41 CI 0.28–0.59, p < 0.001). Lapatinib-based was not superior to trastuzumab-based therapy and capecitabine was not superior to other cytotoxic agents. Pts who were on systemic therapy at diagnosis of BM and had controlled extra-cranial disease did not benefit from switching to non-cross-resistant agents. Conclusions: In patients with breast cancer metastatic to the brain, systemic chemotherapy was associated with better control in the brain and longer survival.

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Clinical evaluation of germline polymorphisms (SNPs) associated with capetible (C) toxicity (tox) in metastatic breast cancer (MBC).  
First Author: Peter H. O’Donnell, The University of Chicago, Chicago, IL

**Background:** C is associated with sometimes severe tox affecting patient (pt) adherence and quality of life, which can result in dose disruption/reduction potentially attenuating effectiveness. We sought to identify pharmacogenomic (PGX) markers of C tox using a novel prospective tox assessment method in a large, multi-institutional study of women with MBC.  

**Methods:** pts were prospectively identified prior to C monotherapy initiation at 2000 mg/m²/d, 14 d on/7 off. Pts completed a 32-item self-reporting tox questionnaire (SP) on d1 of each cycle (cy) and automated phone-in q on d8, d15 for 4 cy, but met study endpoint earlier if C was dose-reduced or suspended. Genetic analysis of 50 prespecified markers and a separate genome-wide association study (GWAS) were conducted with phenotypes immediate (cy 1) and overall diarrhea or hand-foot syndrome (HFS).  

**Results:** N = 259 pts enrolled from 14 institutions (median age 57 yrs, range 25-85). Pt adherence with tox reporting was robust, with 86% (cy 1) and 71% (cy 4) of q completed. Rates of any-grade diarrhea and HFS were 52% and 69%, respectively, including 17% reporting grade 3 diarrhea and 9% grade 3 HFS. Worst tox was identified solely via at-home phone reporting in 39% of pts. Only 29% of pts completed 4 cy without C interruption, dose change, or early discontinuation. In candidate PGx analysis, 3 SNPs associated with development of diarrhea: **DPYD** (OR 4.9; P = 0.0005, significant after multiple test correction), missense SNP in **MTHFR** (OR 3.3; P = 0.02), and upstream SNP of **MTRR** (OR 3.0; P = 0.03). For HFS, GWAS elucidated a novel SNP (OR 3.0; P = 0.0007) upstream of **TNSF4A**, a gene implicated in systemic sclerosis and graft-versus-host disease of skin, never before implicated in HFS.  

**Conclusions:** To our knowledge, this is the first PGx study to use phone-in pt self-reporting, permitting increased accuracy of tox-phenotype characterization. Three germline SNPs previously associated with fluorouracil sensitivity in preclinical/clinical models were identified, and a novel SNP having strong functional relevance was discovered. If further replicated, these markers could improve prediction of pts at highest risk for C tox, reducing morbidity and enhancing outcomes.  
Clinical trial information: NCT00977119.
1053 Poster Session (Board #167), Sat, 8:00 AM-11:30 AM

Breast cancer with extensive regional lymph node involvement: Toward optimizing local management. First Author: Lior Zvi Braunstein, Harvard Rad Onc Prag, Boston, MA

Background: Extensive lymph node (LN) involvement portends significant risk for distant metastasis (DM) among breast cancer patients. As a result, local management may be of secondary import to systemic control in this population. We analyzed patients with ≥10 involved LNs (N3) to evaluate the outcomes of breast conserving surgery (BCS) vs modified radical mastectomy (MRM) in this high-risk cohort. Methods: From 1973-2011, 98 women with N3 disease were treated at our institution. Of these, 46 (46.9%) underwent BCS and 52 (53.1%) received MRM. Adjuvant chemotherapy was administered in 79 (80.1%) cases, and hormonal therapy in 56 (57.1%). Nearly all patients (92%) received comprehensive radiotherapy including axillary and supraclavicular fields. The Kaplan-Meier method was used to estimate local regional control (LRC), disease-free survival (DFS) and overall survival (OS). Results: At a median age of 51.5 years (range 26-82), 54% of patients had disease in 10-14 nodes, 26% in 15-19, and 20% had >19 involved nodes. Median follow-up was 76 months, with a 5-year DFS of 64.9% and OS of 71.9% among the cohort. Multivariate Cox regression revealed that age <50 years was unfavorable with regard to LRC (p = 0.02), although young age did not influence DFS (p = 0.12) or OS (p = 0.31). However, poorly differentiated (p = 0.007), ER-negative tumors (0.015) heralded adverse DFS outcomes. 10-year LRC was 91.4% following MRM and 89.3% following BCS (p = 0.15). Notably, treatment groups did not differ with regard to 10-year DFS (45.4% for MRM vs 57.6% for BCS; p = 0.31), or OS (61.4% vs 63.7%; p = 0.79). Though only 12 local regional recurrences were observed, 47 patients developed DM with a DM-free survival of 48.9% following MRM and 60.6% following BCS (p = 0.19). The use of contemporary chemotherapy improved 5-year OS (82.0% following doxorubicin, cyclophosphamide and taxol vs 61.3% for other regimens; p = 0.04). Conclusions: Patients with ≥10 involved LNs have similar outcomes following BCS or MRM, suggesting that radiotherapy may obviate the need for more-extensive surgery. While local regional control is comparably-favorable regardless of surgical approach, systemic control remains a challenge in this population.

1055 Poster Session (Board #169), Sat, 8:00 AM-11:30 AM

The efficacy and efficiency of half frozen section assessment of breast cancer sentinel lymph nodes: A retrospective analysis of 1116 cases. First Author: Houpu Yang, Peking University People’s Hospital, Beijing, China

Background: Sentinel lymph node (SLN) biopsy became the standard of care for the staging of clinically negative axillary lymph node in patients with invasive breast cancer. Surgeons often request intra-operative frozen section assessment of SLN to guide treatment decision during the operation. This study was to assess whether this protocol was accurate and efficient. Methods: We retrospectively reviewed pathology records for consecutive breast cancer patients with frozen section of SLNB examined from 2012 to 2014. We defined paraffin section diagnosis as gold standard. Sensitivity, specificity, false negative rate, and false positive rate were calculated. The waiting time for frozen section analysis was record. Results: In total, 1116 cases involved frozen section evaluation of sentinel lymph nodes. The sensitivity, specificity of frozen section was 79.9%, 99.6% respectively. In 49 cases (20.1% of positive patients), the SLN was called negative during the intra-operative evaluation but positive on final examination (false negative). Furthermore, in another 3 patients, malignancy was only detected on frozen but not on paraffin sections (false positive). The waiting time for frozen diagnosis, unnecessary for true negative patients (77.8%), was 51 ± 17 minutes, which is approximately 1.5 times the duration of a secondary axillary dissection (33 ± 15). Only 17.4% patients from intra-operative half frozen section assessment. Conclusions: We do not recommend intra-operative frozen section to guide further axillary surgery, as the protocol of freezing half of SLN is not an accurate or an efficient method, with a relatively high false negative rate and some false positive cases which might make the axillary staging complicated.

1056 Poster Session (Board #170), Sat, 8:00 AM-11:30 AM

Cosmetic outcome after breast conserving surgery and either external beam or intraoperative radiotherapy for early breast cancer: Objective assessment of patients from a randomized controlled trial in Lublin, Poland. First Author: Norman R. Williams, University College London, London, United Kingdom

Background: The international randomised controlled TARGeted Intraoperative radioTherapy (TARGIT A) trial demonstrated non-inferiority between the technique of TARGIT (Intra-Operative RadioTherapy (IORT) with Intrabeam) and whole-breast external beam radiotherapy (EBRT) in women with early breast cancer. The aim of this study was to determine if the single high dose of TARGIT leads to impaired cosmesis in a group of patients in Lublin, Poland. Methods: Frontal digital photographs were taken of women participating in the TARGIT Trial at the Medical University in Lublin and analysed, blinded to treatment received, by BCCT.core software which produced overall Harris scores, and scores for various measures of symmetry, colour and scar. Results: 29 women (16 EBRT, 13 IORT), median age 56 years (range 49 to 79) had photographs taken at baseline (up to 2 days prior to surgery), then at 12m (median 364d). There were no differences in overall classification or measures of symmetry apparent between treatment groups. At 12m there was a significant difference in cEMDL, cEMDb and cX2b (see Table); these differences indicate more “redness“ in the EBRT group compared with the IORT group. Conclusions: This objective assessment of aesthetic outcome in patients from a randomised trial demonstrates that “redness”, a surrogate for radiation induced erythema grade 1 or 2, is significantly worse in patients receiving EBRT compared with those receiving IORT. This study provides further evidence that the objective scoring of cosmesis using BCCT.core is feasible and may be an approach for standardisation, and confirms an early beneficial effect of TARGIT on cosmesis.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase I dose escalation trial using stereotactic body radiation therapy (SBRT) for partial breast irradiation (PBI). First Author: Asal Shoushtari Rastegari, Moncrief Radiat Onc, Irving, TX

Background: To evaluate tolerability of escalating doses of 5 fraction SBRT PBI in treating early stage breast cancer after partial mastectomy on a phase I dose escalation trial. The primary objective was to escalate the PBI dose utilizing a robotic stereotactic radiation system treating the lumpectomy cavity without exceeding the maximum tolerated dose (MTD).

Methods: Eligible patients included DCIS or invasive ductal histologies, AJCC stage 0-II with tumor size < 3cm, minimal lumpectomy margins ≥ 2mm. Prior simulation 3-4 four gold fiducials were placed around the lumpectomy cavity for real-time respiratory tracking. Dose limiting toxicity (DLT) equaled grade ≥ 3 toxicity by CTC-AE deemed definitely related to treatment for: skin, bone (fracture), pulmonary, neurological (intercostal or brachial plexus nerves) or any grade 4/5 toxicity definitely attributed to therapy. Both patients and physicians completed baseline and subsequent cosmesis questionnaires using a four point scale – excellent, good, fair, poor. Starting dose was 30 Gy in 5 fractions. Dose was escalated by 2.5 Gy total, provided 4 or fewer of 15 patients experienced a DLT within 90 days of treatment within each dose group. If more patients had DLT in a given dose cohort, the MTD would be exceeded. Results: 68 patients (15 per dose cohort (5-8 patients)) enrolled with median age 62 years. Median follow-up for cohorts 1,2,3,4, and 5 were 36, 26.4, 16, 8.8, and 2.3 months. The first 3 dose cohorts completed 90 day follow-up without DLTs. There was 1 focal grade 3 dermatitis DLT at 37.5 Gy. DLT follow-up is still ongoing in cohort 5. There were 72 grade 1 toxicity events, 2 grade 2 toxicities (rib fracture and breast pain), and 2 grade 3 radiation dermatitis toxicities. Physicians scored cosmesis as excellent or good in 94.9%, 100%, 97.7%, and 100% respectively (p = 0.28), at baseline, 6, 12, and 24 months post SBRT, while patients scored the same periods 82.7%, 96.2%, 95.4%, and 92.8% (p = 0.04). Conclusions: Dose is escalated to 37.5 Gy in 5 fractions without MTD thus far. Soon we are completing dose escalation for 40Gy in 5 fractions PBI, hoping to increase the likelihood of long term tumor control while evaluating toxicity and cosmesis of this innovative therapy. Clinical trial information: NCT01162200.

Breast cancer brain metastases: Comprehensive review of tumor extent, histology and treatment on survival. First Author: Jennifer A. Crozier, Mayo Clinic, Ponte Vedra Beach, FL

Background: Breast cancer brain metastases (BCBM) are associated with poor overall survival (OS) and no treatment guidelines exist. Localized treatments include neurosurgery (ns), stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBT). We studied the association of OS with patient (pt) characteristics, ns and radiation (rad). Methods: 196BCCBM pts who received brain rad from 2009-2013 at three Mayo Clinic sites were retrospectively studied. Data included primary tumor histological subtype: ER+, HER2+, and triple negative (TN). ECOG status at BCBM diagnosis, number of brain lesions, ns and rad treatments were also studied. Results: In single variable analysis (Table), TN pts had 1.8 fold (p = 0.004) increased hazard of death, compared to ER+, while HER2+ had improved OS (HR 0.6, p = 0.008). Hazard of death in pts with leptomeningeal disease was 2.5 fold higher (p = 0.003) than pts with 1-3 brain lesions. Poor ECOG status was associated with poor OS. Pts who received WBT and SRS had an improved OS (HR 0.37, p < 0.001) compared to WBT alone. Combining ns, WBT and SRS had better OS (HR 0.29, p < 0.001) than WBT alone. Conclusions: In this large dataset, pts with the best OS had an ECOG score of 0, HER2+ disease, 1-3 brain lesions, and the combination of ns and rad.

Conclusions: Dose is escalated to 37.5 Gy in 5 fractions without MTD thus far. Soon we are completing dose escalation for 40Gy in 5 fractions PBI, hoping to increase the likelihood of long term tumor control while evaluating toxicity and cosmesis of this innovative therapy. Clinical trial information: NCT01162200.

Breast cancer brain metastases: Comprehensive review of tumor extent, histology and treatment on survival. First Author: Jennifer A. Crozier, Mayo Clinic, Ponte Vedra Beach, FL

Background: Breast cancer brain metastases (BCBM) are associated with poor overall survival (OS) and no treatment guidelines exist. Localized treatments include neurosurgery (ns), stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBT). We studied the association of OS with patient (pt) characteristics, ns and radiation (rad). Methods: 196BCCBM pts who received brain rad from 2009-2013 at three Mayo Clinic sites were retrospectively studied. Data included primary tumor histological subtype: ER+, HER2+, and triple negative (TN). ECOG status at BCBM diagnosis, number of brain lesions, ns and rad treatments were also studied. Results: In single variable analysis (Table), TN pts had 1.8 fold (p = 0.004) increased hazard of death, compared to ER+, while HER2+ had improved OS (HR 0.6, p = 0.008). Hazard of death in pts with leptomeningeal disease was 2.5 fold higher (p = 0.003) than pts with 1-3 brain lesions. Poor ECOG status was associated with poor OS. Pts who received WBT and SRS had an improved OS (HR 0.37, p < 0.001) compared to WBT alone. Combining ns, WBT and SRS had better OS (HR 0.29, p < 0.001) than WBT alone. Conclusions: In this large dataset, pts with the best OS had an ECOG score of 0, HER2+ disease, 1-3 brain lesions, and the combination of ns and rad.

Conclusions: Dose is escalated to 37.5 Gy in 5 fractions without MTD thus far. Soon we are completing dose escalation for 40Gy in 5 fractions PBI, hoping to increase the likelihood of long term tumor control while evaluating toxicity and cosmesis of this innovative therapy. Clinical trial information: NCT01162200.

Effect of the use of immediate reconstruction on the rates of bilateral mastectomy and adjuvant radiation therapy use in women with node-negative breast cancer treated with neoadjuvant chemotherapy on ACOSOG Z1071 (Alliance). First Author: Judy Caroline Boughey, Mayo Clinic, Rochester, MN

Background: Each treatment decision can impact other multidisciplinary treatment recommendations. Herein we evaluate the interaction of surgery, reconstruction and radiation in node-negative breast cancer treated with neoadjuvant chemotherapy in a contemporary clinical trial. Methods: ACOSOG Z1071 (Alliance) was a prospective study evaluating sentinel node surgery after chemotherapy in patients with initial node-positive disease. We reviewed breast operation, use of immediate reconstruction and radiation on all patients who underwent mastectomy. Differences in proportions/rates were assessed with a chi-square test. Results: Of 686 eligible patients with data available, 409 underwent mastectomy (72% bilateral). Bilateral mastectomy rate was higher at 67% (117/176) in women undergoing immediate reconstruction compared to 33% (75/233) in women without reconstruction (p < 0.0001). Use of immediate reconstruction varied by clinical tumor stage at presentation, with reconstruction rates being higher in cT1-2 tumors, similar in cT2 tumors and lower in cT3-4 disease (p < 0.0001) compared to no reconstruction. Immediate reconstruction did not vary by approximated tumor subtype, pathological tumor stage or nodal stage after chemotherapy. Adjuvant radiation was used less often in patients with immediate reconstruction (76% vs 88%, p = 0.0009) and those patients with node-positive disease. Multivariable analysis, use of immediate reconstruction was significantly associated with absence of adjuvant radiation (p = 0.009). Conclusions: A majority of node-positive patients treated with neoadjuvant chemotherapy undergoing mastectomy received adjuvant radiation. Bilateral Mastectomy rates are higher in women electing immediate reconstruction. We found that radiation therapy was less commonly used in patients with immediate reconstruction. Since radiation therapy in node-negative breast cancer may impact local control and survival, multidisciplinary input in surgical and reconstructive planning decisions is recommended. Clinical trial information: NCT00081361.

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60s Breast Cancer—Triple-Negative/Cytotoxics/Local Therapy

1061 Poster Session (Board #175), Sat, 8:00 AM-11:30 AM
Residual breast tissue after mastectomy in non high risk and BRCA mutated patients. First Author: Georg Pfeifer, Med Univ of Vienna, Vienna, Austria

Background: Skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM) and immediate reconstruction by an implant are widely used in patients with breast cancer and in high risk patients for prophylaxis. Surgical procedure is guided by oncological aspects on the one hand – meaning cutaneous/subcutaneous envelope as thin as possible – and by cosmetic aspects on the other hand – meaning envelope as thick as possible. Pre-operative MRI might help the surgeon to choose the right thickness of this envelope. In this retrospective analysis we investigated the presence of residual breast tissue and the thickness of the envelope after SSM and NSM. Methods: Patients treated with SSM or NSM for prophylaxis or after breast cancer at a single university hospital, who had at least one post-operative MRI, were included. MRI’s were retrospectively analysed by two independent radiologists. Analyses included (a) the detection of residual breast tissue (yes/no) and (b) the maximum thickness of the envelope directly above the implant. Results: 39 patients of which 19 had bilateral SSM/NSM were included. 14 patients with BRCA 1/2 mutation had prophylactic bilateral SSM/NSM. Residual breast tissue could be detected in all 58 reconstructed breasts. The medium thickness of the envelope was 11.2mm (1-35mm). In patients with bilateral SSM/NSM, a strong correlation between the thickness of left and right breast envelope could be observed (r = -0.79, p < 0.05). Conclusions: Thickness of the envelope of the reconstructed breast does not appear to be the major determining factor of residual breast tissue.

1062 Poster Session (Board #176), Sat, 8:00 AM-11:30 AM
Detrimental effect of blood-product transfusion on survival for patients with breast cancer in Florida (1996-2007). First Author: Hattan Alghamdi, University of Miami Hospital, Miami, FL

Background: The effect of marital status (MS) on survival varies according to cancer type and gender. To our knowledge there has been no report on the impact of MS on survival in male breast cancer patients. This study aims to determine the influence of MS on tumor characteristics at diagnosis and 5-year specific survival (SS) in MBC using the SEER database. Methods: We included patients (pts) with MBC diagnosed after the year 1999. On multivariate analysis being unmarried was associated with increased hazard of death (HR = 1.95, p < 0.0001) after adjusting demographic, clinical, and comorbidity factors. Conclusions: Our study concludes that blood transfusion is a significant independent risk factor for survival in female breast cancer patients.

1063 Poster Session (Board #177), Sat, 8:00 AM-11:30 AM
Impact of neoadjuvant chemotherapy to surgery interval on survival outcomes in breast cancer patients. First Author: Rachel Ann Sanford, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Retrospective analyses have sought to identify the optimal interval between surgery and initiation of adjuvant chemotherapy in breast cancer, with conflicting results. No studies have examined the impact of the interval from conclusion of neoadjuvant chemotherapy to surgery. We evaluated the relationship between survival outcomes and the time interval between neoadjuvant therapy and surgery. Methods: Retrospective review of the prospectively maintained Breast Medical Oncology Institutional database at The University of Texas MD Anderson Cancer Center identified 1101 women diagnosed with stage I-III breast cancer between June 1995 and April 2007 who received any neoadjuvant chemotherapy. We examined the effect of the interval from completion of neoadjuvant chemotherapy to surgery, defined as < 4 weeks, 4-6 weeks, > 6 weeks after neoadjuvant chemotherapy to surgery, on pathologic characteristics, compared with an interval of 4-6 weeks. Results: Three hundred thirty five of 1101 patients (30.4%) had surgery within 4 weeks of their last dose of neoadjuvant chemotherapy, 524 (47.6%) within 4-6 weeks, and 242 (22%) after more than 6 weeks. Median age was 50 years, median time to surgery was 33 days (range 8-159 days) and median follow-up was 94 months (range 3-178 months). Patients whose interval was < 4 weeks were more likely to have more advanced stage (p = 0.003) and higher grade (p = 0.04) disease. The 5-year overall survival (OS) estimate was 79%, 87%, and 81% in patients who received surgery in 0-4, 4-6, and > 6 weeks after neoadjuvant chemotherapy, respectively (p = 0.04). The three groups did not differ in five-year locoregional recurrence-free survival (LRFS) or recurrence-free survival (RFS). In multivariate analysis adjusting for important clinical and pathologic characteristics, compared with an interval of < 4 weeks, patients who underwent surgery at 4-6 weeks or at > 6 weeks had equivalent OS (4-6 weeks HR = 0.88, 95% CI 0.68 – 1.16; > 6 weeks HR = 1.12, 95% CI 0.83 – 1.53), LRFS and RFS. Conclusions: Our results suggest no relationship between the neoadjuvant chemotherapy to surgery interval and overall survival, LRFS, or RFS. This data should prove reassuring to clinicians coping with ever-increasing patient volumes.

1064 Poster Session (Board #178), Sat, 8:00 AM-11:30 AM
Influence of marital status on tumor characteristics and survival in male breast cancer. First Author: Shourya Tadasina, McLaren Flint, Flint, MI

Background: The effect of marital status (MS) on survival varies according to cancer type and gender. To our knowledge there has been no report on the impact of MS on survival in male breast cancer (MBC). This study aims to determine the influence of MS on tumor characteristics at diagnosis and 5-year specific survival (CSS) in MBC using the SEER database. Methods: We included patients (pts) with MBC diagnosed after the year 1999. Pts with unknown MS or survival data were excluded. Kaplan-Meier method was used to estimate the 5-year CSS. Multivariate regression models were used to determine the independent covariates of cancer specific mortality and metastatic disease (stage IV) at diagnosis (Cox and logistic respectively). Results: We included 3,761 pts; 2,647 (70.4%) were married. Mean age was 64.9 years with no significant difference between the married and unmarried. Unmarried pts were more often diagnosed with advanced MBC (Stage III & IV) compared to married pts (33.3% vs. 22.1%, p<0.0001) but there was no significant difference in hormone receptor status, histologic grade or subtype. Unmarried pts were significantly less likely to undergo surgery compared to married pts (92.4% vs. 96.7%, p<0.0001). Overall unmarried pts with stage II, III & IV MBC have significantly worse 5-year CSS compared to married (Table). The survival difference between the two groups was significant only in MBC diagnosed after the year 1999. On multivariate analysis being unmarried was associated with increased hazard of death (HR=1.44, p<0.0001) and increased likelihood of metastatic disease at diagnosis (OR=1.95, p<0.0001). Conclusions: It is known that males with breast cancer (BC) have worse survival compared to females. Our study showed that unmarried males with BC are at an even greater risk for advanced disease at diagnosis and poorer outcomes compared to married males.

5-year cancer specific survival.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Married</th>
<th>Unmarried</th>
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<tr>
<td>I</td>
<td>98%</td>
<td>96%</td>
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<tr>
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<td>71%</td>
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<td>Overall</td>
<td>88%</td>
<td>77%</td>
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*Log rank test.
1065 Poster Session (Board #179), Sat, 8:00 AM-11:30 AM
Phase II study of panitumumab, nab-paclitaxel, and carboplatin followed by FEC neoadjuvant chemotherapy for patients with primary HER-2 negative inflammatory breast cancer (IBC). Naoko Matsuda, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: EGFR overexpression is an independent poor prognostic factor in patients with inflammatory breast cancer (IBC). Our IBC animal model indicates that EGFR targeted therapy inhibited IBC tumor growth. It will reverse epithelial mesenchymal transition. Historically, the pathological complete response (pCR) rate in IBC has been 15%. We determined the effect of an anti-EGFR monoclonal antibody and anti-HER2- neoadjuvant chemotherapy by determining the pCR rate. Methods: In this single-arm, phase II prospective study, the patients received 4 cycles of combination panitumumab (2.5 mg/kg), nab-paclitaxel (100 mg/m²), and carboplatin (AUC 2) on a weekly schedule (PN2). After the PNC regimen was completed, 4 cycles of FEC (5-flourouracil, 500 mg/m²; epirubicin, 100 mg/m²; cyclophosphamide, 500 mg/m²) was administered followed by surgical resection, radiation and hormonal therapy (ER +). The primary end point was the pCR rate. The secondary objectives were disease-free survival, safety and identification of biomarkers. Results: We analyzed 25 IBC patients. Median age was 57 years (range 23-68 years). 15 were HR+/HER2- and 10 were HR-/HER2-. The median follow-up time was 11.7 months (range, 8.7-33.9 months). The pCR rate was 36% (95% CI: 0.18-0.58). Six (60%) TNBC patients and 3 (20%) HR+/HER2- patients achieved pCR. Five patients experienced disease recurrence, and 4 died. The frequency of grade 3 or 4 hematological events was 18 (72%); and grade 3 nonhematological adverse events were seen in 9 (36%) patients, (n = 5): fatigue, n = 2; infection, n = 1; anorexia, n = 1; stomatitis, n = 1; pleuritic pain, n = 1) and grade 4 was 0 during the PNC regimen. The association between pCR and subtype has trending for significance (p = 0.087). The area under the probability-time function was lower for TNBC (EGFR, COX2, Nodal, E-Cadherin, Vimentin, ALDH1 expression) in 14 samples. Conclusions: Our data show that this novel treatment, based on the biological characteristics of IBC, produced unprecedentedly high pCR rates in TNBC. We plan to conduct a randomized study to determine the role of this regimen compared with standard regimens. Clinical trial information: NCT01306087.

1066 Poster Session (Board #180), Sat, 8:00 AM-11:30 AM
MHC II antigen presentation pathway expression in triple-negative breast cancer. First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL

Background: The purpose of this study was to identify gene expression differences between triple negative breast cancer (TNBC) tumors from patients who did or did not have disease relapse. Methods: 47 snap frozen macro-dissected primary TNBC tumors from treatment-naïve patients, with an adequate follow up (greater than 24 months), were analyzed using RNA-seq to identify gene expression differences between patients with disease relapse and patients who did not relapse. In addition, archived de-identified primary TNBC tumors underwent standard immunohistochemical analysis with anti-CD74 and anti-HLA-DPB1 antibodies. Results: Database included 22 patients with disease relapse and 25 who did not relapse. 24 genes had significantly higher expression in tumor tissue from patients who did not relapse and 11 of these genes were integral members of the MHC II antigen presentation pathway. The 24 gene signature was significantly associated with progression free survival (PFS) (HR = 0.24; log rank p = 0.00016). Individually expression of CIITA and CD74, key components of the MHC II pathway, were significantly associated with PFS (HR values of 0.17 and 0.35; log rank p = 0.0002 and 0.0164. A large meta-analysis of microarray data from 199 patients with TNBC (Breast Cancer Res 2013; 140: 219) validated that 10 of the 24 genes (including 6 MHC II genes) were prognostic for PFS with a HR = 0.31; log rank p = 0.000009 and CD74 alone was similarly prognostic with a HR = 0.31; log rank p = 0.0000019. Immunohistochemical analysis of patient primary tumors detected CD74 and HLA-DPB1 protein in TNBC tumor cells (greater than 20% of the cells), suggesting the MHC II pathway may be aberrantly expressed in tumor cells. The expression MHC II pathway genes correlated strongly with a tumor infiltrating lymphocyte gene signature. Conclusions: The role of the MHC II antigen presentation pathway is likely an important component of the anti-tumor immunity associated with good prognosis TNBC.

1067 Poster Session (Board #181), Sat, 8:00 AM-11:30 AM
A study of triple-negative breast cancer patients tested with a 25-gene panel of hereditary cancer genes. First Author: John F. Sandbach, Texas Oncology Central Austin, Austin, TX

Background: Although triple-negative breast cancer (TNBC) accounts for 15% to 20% of all breast cancers diagnosed in the US, its epidemiology is not well understood. Previous studies have shown a high incidence of BRCA1 and, more recently, BRCA2 mutations in patients with TNBC. As panel testing becomes more prevalent, these studies can be extended to other genes with a known breast cancer risk and improve understanding of the genetic origin of TNBC. Here we examined the gene distribution of other genes with a known breast cancer risk and improve understanding of the genetic origin of TNBC. Methods: We queried a commercial laboratory database for patients affected with breast cancer who were tested with a 25-gene panel from September 2013 through December 2014. All patient data was obtained by health care provider report on test requisition forms. Patients affected with TNBC were analyzed separately. All patient data was obtained by health care provider report on test requisition forms. Results: We identified 2,535 patients with a personal history of TNBC and 17,304 patients with a personal history of other breast cancers. Of the TNBC patients, 14.5% (367) were identified as having a pathogenic mutation, obtained by health care provider report on test requisition forms. The highest, tested dose with a first-cycle DLT rate of 40% was 200 mg/m². The secondary objectives were disease-free survival, safety and identification of biomarkers. Results: We analyzed 25 IBC patients. Median age was 57 years (range 23-68 years). 15 were HR+/HER2- and 10 were HR-/HER2-. The median follow-up time was 11.7 months (range, 8.7-33.9 months). The pCR rate was 36% (95% CI: 0.18-0.58). Six (60%) TNBC patients and 3 (20%) HR+/HER2- patients achieved pCR. Five patients experienced disease recurrence, and 4 died. The frequency of grade 3 or 4 hematological events was 18 (72%); and grade 3 nonhematological adverse events were seen in 9 (36%) patients, (n = 5): fatigue, n = 2; infection, n = 1; anorexia, n = 1; stomatitis, n = 1; pleuritic pain, n = 1) and grade 4 was 0 during the PNC regimen. The association between pCR and subtype has trending for significance (p = 0.087). The area under the probability-time function was lower for TNBC (EGFR, COX2, Nodal, E-Cadherin, Vimentin, ALDH1 expression) in 14 samples. Conclusions: Our data show that this novel treatment, based on the biological characteristics of IBC, produced unprecedentedly high pCR rates in TNBC. We plan to conduct a randomized study to determine the role of this regimen compared with standard regimens. Clinical trial information: NCT01306087.

1068 Poster Session (Board #182), Sat, 8:00 AM-11:30 AM
Phase I dose-finding study of the gamma secretase inhibitor PF-03084014 (PF-4014) in combination with docetaxel in patients (pts) with advanced triple-negative breast cancer (TNBC). First Author: Giuseppe Curigliano, Istituto Europeo di Oncologia, Milan, Italy

Background: Gamma secretase is a key component of the Notch signaling pathway, which is involved in cancer cell biology and survival in various tumor types including breast cancer. PF-4014 demonstrated synergistic anti-tumor activity with docetaxel in preclinical models, supporting clinical development of this combination. Methods: Pts received PF-4014 orally, twice daily (BID) in combination with docetaxel Q3W, following a matrix design with the modified toxicity probability interval method. The purpose was to estimate the maximum tolerated dose (MTD); the primary endpoint was first-cycle dose-limiting toxicity (DLT). The MTD was defined as the highest, tested dose with a first-cycle DLT rate < 0.33. Results: In all, 22 female pts received treatment, mean age 50 yrs (27-76 yrs). The most common treatment-related adverse events (AEs) were neutropenia (91%), fatigue (77%), leukopenia (68%), nausea (64%), alopecia (59%), diarrhea (59%), and anemia (50%), which were generally mild to moderate in severity. We also noted G3 leukopenia (41%), hypophosphatemia (14%), and pneumonia (14%); and G4 neutropenia (16%), leukopenia (23%) and febrile neutropenia (FN) (18%). One G5 treatment-related AE, septic shock, occurred. DLTs are listed in the table, by treatment cohort. One pt, previously treated with paclitaxel, had a confirmed partial response in first-line treatment for advanced TNBC. Six pts had stable disease. PK and pharmacodynamic evaluations of pathway modulation in surrogates (CD74 and tumor tissues are ongoing. Co-administration with PF-4014 did not affect exposure to docetaxel. Conclusions: The MTD estimated for the combination in pts with advanced TNBC was PF-4014 100 mg BID/ docetaxel 75 mg/m². Antitumor activity will be assessed in an expansion cohort of pts with advanced TNBC (first-line setting). Clinical trial information: NCT01876251.

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Lymphopenia after adjuvant radiotherapy (RT) to predict poor survival in triple-negative breast cancer (TNBC). First Author: Anooshleh Ashghahi, Stanford Univ Med Ctr, Stanford, CA

Background: The immune system is increasingly recognized as critical in cancer development, progression, and treatment response. Intense lymphocytic infiltration in pre-treatment biopsies predicts improved survival in TNBC; lymphopenia after RT correlates with poor prognosis in other solid tumors. We investigated the prognostic impact of RT-associated lymphopenia in early-stage TNBC. Methods: Diagnostic and treatment data from electronic medical records of Stanford University Hospital (SU) and Palo Alto Medical Foundation (PAMF), a nearby community practice, were linked at an individual patient level with demographic, staging and survival data from the California Cancer Registry. A Cox proportional hazards model (adjusted for patient age, race, insurance, marital and neighborhood socioeconomic status, and for tumor stage, grade, and chemotherapy receipt) was used to analyze the relationship between immunologic measures obtainable from complete blood counts (CBC) treated as continuous variables (minimum absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and white blood cell count [WBC]) and overall survival (OS). Results: 1211 TNBC patients (pts) seen at SU and/or PAMF were identified from 2000-2011; 218 pts with stage I-II TNBC received adjuvant RT and CBC within 12 months of starting radiation. 190 of these 218 pts (87.2%) received neoadjuvant or adjuvant chemotherapy, 58.3% of treated pts were lymphopenic (ALC < 1.0 x10^9/L) with median ALC of 0.9 (interquartile range: 0.66-1.23). On multivariable analysis, lower ALC immediately after RT was strongly associated with worse OS (hazard ratio [HR] for death with an increase of 0.1 K/uL in ALC = 0.70; 95% confidence interval [CI]: 0.55–0.91); lower ANC (HR = 0.98; 95% CI: 0.95–1.01) and WBC (HR = 0.99; 95% CI: 0.97–1.00) were not associated with OS. Conclusions: Among curable TNBC pts, a low ALC after RT was independently associated with a substantial increase in the risk of death; no such effect was observed with other blood counts. These results build on tumor-based studies implicating lymphocytic function as a key determinant of treatment response and survival, and may guide development of targeted immunotherapies for TNBC.

Enzalutamide: A new hormonal treatment for triple-negative breast cancer? First Author: Francesco CanaZZa, Education and Research Centre, St.Vincent’s University Hospital and School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

Background: Like the estrogen receptor (ER), the androgen receptor (AR) is present in approximately 80% of invasive breast cancer. However, in contrast to the ER which is never expressed in triple-negative breast cancer (TNBC), the AR can be present in up to 30% of patients with this molecular subtype of breast cancer. The aim of this study was therefore to investigate the targeting of AR with the second generation anti-androgen enzalutamide as a possible new hormonal approach for the treatment of breast cancer. Methods: IC50 values for enzalutamide were determined for 14 breast cancer cell lines (8 TN; 6 non-TN), using the colony formation assay. AR engagement was determined using Boyden chamber assays in 4 TN cell lines. Results: enzalutamide IC50 values across 14 breast cancer cell lines varied from 4 μM to > 50 μM. Response to the anti-growth activity of enzalutamide was similar in TN and non-TN cell lines but depended on the presence of AR. In addition to blocking cell growth, enzalutamide also inhibited cell migration and invasion in 3 out of 4 TN cell lines, again in an AR-dependent manner. Similar to enzalutamide, the first generation anti-androgen flutamide also blocked cell growth, migration and invasion in TNBC cell lines. The addition of doxorubicin to enzalutamide enhanced growth inhibition in 4 of 5 breast cancer cell lines investigated, including 2 TN cell lines. In contrast to doxorubicin, no enhancement of growth inhibition was found with cisplatin, carboplatin or 5-FU. Conclusions: We conclude that targeting AR with enzalutamide may represent a new approach to breast cancer treatment, especially for patients with AR-positive TN disease. The current availability of anti-androgens for the treatment of metastatic prostate cancer should facilitate their clinical application in TNBC. Finally, the AR is expressed in several different types of cancer, targeting with enzalutamide may have wide application in cancer treatment.
Neoadjuvant chemotherapy with dose-dense doxorubicin, cisplatin, and paclitaxel in patients with early triple-negative breast cancer (TNBC). First Author: Mona Frolova, N.N. Blokhin Russian Cancer Research Center, Moscow, Russia

Background: TNBC is characterized by aggressive behavior and poor prognosis. It has been shown that achievement of pathological complete regression (pCR) after neoadjuvant chemotherapy improved survival of patients (pts) with TNBC. Rates of pCR with standard antiracine- and taxane-based chemotherapy regimens don’t exceed 20-27%. There are strong phenotypic and molecular similarities between BRCA1-related breast cancers and triple-negative sporadic tumors. Markers of BRCA1 dysfunction may predispose sensitivity to specific agents such as platinum salts. We performed a prospective trial to evaluate efficacy of dose-dense schedule of doxorubicin, cisplatin and paclitaxel in correlation with breast cancers and triple-negative sporadic tumors. Markers of BRCA1 dysfunction in pts with early TNBC (NCT01672671).Methods: Pts with early TNBC (cT1-2N0-1M0) were treated with doxorubicin 25 mg/m2 iv weekly, cisplatin 30 mg/m2 iv weekly and paclitaxel 100 mg/m2 iv weekly for planned 8 weeks with G-CSF 300 mcg 2-4 days followed by surgery. Pathologic response was assessed in correlation with BRCA1 dysfunction in 17 pts. Results: Forty one pts were included in the study. Median age was 44 years (23-72), 45% of pts had tumor Grade 3, Ki67 was > 20% in 95% of cases. Forty pts completed chemotherapy (median treatment duration 8.9 weeks) and underwent surgery. Twenty-six pts (65%) achieved pCR. With median follow-up of 19.7 months, 3 pts had a disease progression and 2 pt died (one from disease progression and one from pulmonary embolism after 6 injections of chemotherapy). 1-year DFS was 95,1% and OS was 97,5%. The disease-limiting toxicities were neutropenia (53.7% grade 3-4) and mucositis (19.5% grade 3). In 8 pts treatment was discontinued early due to toxicity. Somatic BRCA1 5382insC mutation correlated with achievement of pCR (p = 0.004). All pts with somatic 185delAG and C61G mutations had residual disease (p = 0.2 and 0.2, accordingly). Conclusions: Dose-dense doxorubicin, cisplatin and paclitaxel regimen shows high activity as neoadjuvant treatment of early TNBC with acceptable toxicity. Somatic BRCA1 mutations may determine different responses to platinum-based chemotherapy. Clinical trial information: NCT01672671.

Rampant centrosome amplification and aggressive disease course of triple-negative breast cancers. First Author: Vaishali Pannu, Georgia State University, Atlanta, GA

Background: Centrosome amplification (CA) is a cell biological trait characteristic of pre-neoplastic and pre-invasive lesions has empirically been associated with tumor aggressiveness suggesting an early and causal role of excess centrosomes in driving tumor progression. Recent studies provide convincing evidence that CA leads to malignant transformation and promotes invasion in mammary epithelial cells. Given that supernumerary centrosomes occur in a variety of breast cancers, we hypothesize that CA can serve as a predictor of breast cancer aggressiveness. Triple (ER/PR/Her2) negative (TN) breast cancer, a histologically-aggressive breast cancer subtype, commonly affects African-American (AA) women and is characterized by high recurrence, metastases, and mortality rates. TN and non-TN breast tumors follow variable kinetics of metastatic progression, and thus constitute a test bed to explore if the severity and nature of CA can distinguish the two subtypes. Methods: Utilizing formalin-fixed paraffin-embedded and fresh-frozen breast cancer tissues, we quantitatively assessed extent of structural and numerical centrosomal aberrations for each patient sample in a large-cohort of grade-matched TNBC (n = 30) and non-TNBC (n = 98) cases employing multi-color immunofluorescence confocal imaging and immunoblotting. Results: Our data establish previously unrecognized differences in incidence and severity of CA between TNBC and non-TNBC cell lines and clinical specimens. We found strong correlation between CA and markers of aggressiveness associated with breast cancer metastasis in 20 pairs of grade-matched TNBC and non-TNBC clinical specimens (p < 0.02). Time-lapse imaging of MDA-MB-231 cells stably-transfected with GFP-tagged centrosome harbored amplified centrosomes demonstrated that CA confers enhanced migratory ability. Conclusions: Our study is the first to identify centrosome amplification as a clinical predictor of breast cancer aggressiveness. Organellar disparity between breast cancer subtypes harboring different metastatic potential has immense translational value as it may allow early-risk prediction and explain higher tumor aggressiveness in TNBC patients.

expression, AR mRNA expression, clinical information and survival data of TNBC patients with different levels of AR expression was compared using Cox-proportional hazards model and Kaplan-Meier method in Statistical Analysis System (SAS. v9.3). Results: Ten retrospective studies including 2463 breast cancer patients were included in the meta-analysis. AR was expressed in 590 (24,1%) patients. Expression of AR was associated with significantly better DFS (HR = 0.70, 95% CI = 0.54-0.89, P = 0.005) in TNBC. Although there was a trend toward longer OS in TNBC patients with AR expression, it was not statistically significant (HR = 0.76, 95% CI = 0.58-1.00, P = 0.06). The TCGA dataset (N=236) showed a trend toward longer OS in TNBC patients expressing AR compared to non-expressing patients (P = 0.0001). Again although there was a trend toward longer OS in cases with higher AR expression, the difference was not statistically significant (HR = 0.71 for > 10% vs ≤ 10% AR expression, P = 0.583; HR = 0.66 for > 15% vs ≤ 15% AR expression, P = 0.470; and HR = 0.70 for > 50% vs ≤ 50% AR expression, P = 0.452). Conclusions: Expression of AR in TNBC is associated with better DFS. There is a trend for better OS in patients with high levels of AR expression, this requires validations by additional large studies.
Nuclear HSET as a negative prognostic indicator and racial disparity biomarker in breast cancer patients. First Author: Angela Ogden, Georgia State University, Atlanta, GA

**Background:** The kinesin HSET (human spleen, embryo, and testes) is a negative prognostic indicator in cancer. Specifically, increased expression levels are associated with brain metastases in lung cancer, and increased nuclear levels are associated with worse overall and progression-free survival in breast cancer. HSET is overexpressed in triple-negative breast cancer, which is associated with African American (AA) race; however, a definitive role for HSET in health disparity has not been established.

**Methods:** To probe associations between HSET levels, race, and prognosis, formalin-fixed paraffin-embedded breast tumor biopsies from 149 AA and 109 European American (EA) patients were immunostained for HSET. Staining intensity (0-3) and extent (0-100%) in nuclei and cytoplasm were determined by blinded pathologists. Weighted indices were calculated as the products of the staining intensity and extent and were stratified into low, moderate, and high groups. Associations of these groups with negative prognostic indicators and overall and progression-free survival were determined using Cox proportional hazards and Kaplan-Meier analyses.

**Results:** High nuclear HSET was associated with more advanced grade and a higher percentage of Ki67-positive cells than low nuclear HSET regardless of race (P < 0.05 for all). However, high nuclear HSET was only associated with triple-negative receptor status (P < 0.001) and worse overall survival (P = 0.02) in AAs. In multivariate analysis, AA breast cancer patients with high nuclear HSET had a 5.05-fold increased risk of worse overall survival after adjusting for grade, stage, and triple-negative receptor status (95% CI = 1.77-14.40). They also had a 2.72-fold increased risk of worse progression-free survival in multivariate analysis (95% CI = 1.00-7.39). Cyttoplasmic HSET was not significantly associated with survival in either race. These data suggest that nuclear HSET is a valuable negative prognostic biomarker in AA breast cancer patients. Determination of nuclear HSET levels may help to risk-stratify AAs with breast cancer, who suffer disproportionate disease-specific morbidity and mortality relative to their EA counterparts.

Conclusions: DNA methylation profile is an interesting predictive tool for response to neoadjuvant CT in TNBC.

DNA methylation signature to identify treatment response in triple negative breast cancer. First Author: Begona Pineda, INCLIVA, Valencia, Spain

**Background:** The triple negative breast cancer (TNBC) subtype is an aggressive phenotype with limited treatment options. Chemotherapy (CT) is only effective in about 40% of patients. DNA methylation could play a role in this differential response between TNBC. The objective of our work was to define a DNA methylation profile with potential to predict response to CT in TNBC patients. Methods: Tumor samples from patients diagnosed with a TNBC stage I to III and considered candidate for neoadjuvant CT with anthracycline and taxane were identified. DNA was extracted from FFPE samples obtained by pre-surgery biopsy. Patients were classified according to residual cancer burden (RCB) index in responders (RCB = 0, n = 10) vs. non-responders (RCB > 0, n = 14). DNA methylation was performed by the Infinium HumanMethylation450 array (Illumina) that allows interrogating more than 485,000 methylation CpG sites over sample. The selection criteria were: p < 0.05 and mean difference between methylation groups of ≥ 20%. The functions associated to genes were analyzed using the Gene Ontology FDR. Results: We identified 24 samples from TNBC patients. Median age was 58.4 (48.5-69.0) years. Most patients presented T1-2 tumors (72%), no axillary lymph involvement (93%). Proliferative scores were high with 53% of patients with ki67 > 60% and 88% of grade 3 tumors. We have detected 133 differentially methylated CpGs allowing clearly separate the responders from the non-responders. Thirty five were located at CpG islands (CGIs) or CGI shores at promoter regions. We selected 11 CpGs corresponding to 11 genes with the least variation intragroup (standard deviation ≤ 20%). Nine of them showed a consistent DNA methylation profile of consecutive CpGs. Of these, 5 genes (genes 1 to 5) increased and 4 genes (genes 6 to 9) decreased methylation in non-responding patients compared to those who responded to treatment. The increase ratio varied between 0.20 and 0.27, and the decrease ranges between -0.21 and -0.22. Some of these genes were related to Wnt and Hedgehog pathways, epithelial-mesenchymal transition and cell migration.

Conclusions: DNA methylation profile is an interesting predictive tool for response to neoadjuvant CT in TNBC.

A Phase II study of cabozantinib for metastatic triple-negative breast cancer (TNBC). First Author: Sara M. Tolaney, Dana Farber Cancer Institute, Boston, MA

**Background:** Data suggests that MET expression and activation are important for initiation and progression of TNBC. We evaluated the efficacy of cabozantinib (XL184), a novel inhibitor of multiple receptor tyrosine kinases, including MET and VEGFR2, in patients with metastatic TNBC.

**Methods:** In this single-arm, two-stage Phase 2 study, patients with metastatic TNBC with measurable disease by RECIST v1.1 and up to 3 lines of prior chemotherapy in the metastatic setting received cabozantinib 60 mg daily on a 21-day cycle. Patients were restaged 6 weeks following treatment initiation and every 9 weeks thereafter. The primary endpoint was objective response rate (ORR). If ≥ 1/3 pts responded at stage 1, 22 more will be enrolled. If < 4/35 responded, the null rate (5%) would be rejected in favor of a 20% rate of activity. Predefined secondary endpoints included progression free survival (PFS) and toxicity. Results: Thirty-five patients (median age 50 years, range 31-78) initiated protocol therapy and were included in this analysis. Patients had 0 (n = 6, 17%), 1 (n = 18, 51%), 2 (n = 4, 11%), or 3 (n = 7, 20%) prior lines of chemotherapy for metastatic disease. Two patients achieved confirmed PR (ORR 9% [95% CI 1-25%]) and 3 achieved unconfirmed PR; 18 patients (51%, 95% CI: 40.3-61.1%) achieved stable disease (SD) and 12 patients (34%, 95% CI: 22.0-46.5%) had SD as their best response. The clinical benefit rate at 15 weeks was 31% (95% CI 17-49%) and the median PFS was 1.9 months (95% CI 1.3-3.3). The most common toxicities (all grades) were fatigue (77%), diarrhea (51%), nausea (43%), arthralgia/ myalgia (37%), hand-foot syndrome (HFS) (37%), and peripheral sensory neuropathy (PSE) (37%). There were no grade 4 toxicities. Twelve (34%) patients required dose reduction, 4 due to PPE and 8 due to other toxicities. Ongoing studies are exploring MET expression and amplification in archival tumor samples, MET amplification in circulating tumor cells, and plasma biomarkers of response to cabozantinib.

Conclusions: In patients with metastatic TNBC, cabozantinib monotherapy showed evidence of antitumor activity. Adverse events requiring dose reduction occurred in about one-third of patients. Biomarker changes and their association with outcome will be presented at the meeting. Clinical trial information: NCT02260531.

Contribution of immune system and tumor-related interferon signaling to epirubicin response in triple-negative (TN) breast cancers. First Author: Giampaolo Bianchini, San Raffaele Scientific Institute, Milan, Italy

**Background:** In HER2+ patients treated with HER2-targeted monoclonal antibodies in the NeoSphere trial, multivariate analysis showed a complex interplay between immune system and response (Gianni L SABCS 2012). High STAT1 and IGG metagens were associated with pCR, whereas high MHC1 and Interferon-inducible (IF.I) metagens were associated with resistance. We sought to assess in TN tumors if there is a similar relationship between immune system and response to anthracyclines, which leads to immunogenic cell death. Methods: We selected Affymetrix GEPS for 87 TN breast cancers (BCs) treated with neoadjuvant epirubicin monotherapy in the TOP trial (Desmedt C JCO 2011). Association between four previously define immune metagens (IGG, STAT1, IF1 and MHC1), PCR and distant metastasis free survival (DMFS) were assessed. We assessed in 51 BC cell lines (25 TN) if isolated cells themselves express these immune-related genes. Results: In TOP trial, immune metagens were not associated with pCR in univariate analysis. In multivariate analysis, high STAT1 (OR 5.17 (1.66-16.1); p = 0.004) and low MHC1 (OR 0.19 (0.07-0.51); p = 0.001) were associated with pCR. Significance was retained when clinical variables and TOP2A amplification/deletion were included. In univariate analysis for DMFS, only high STAT1 was associated with lower risk of relapse (HR 0.62 (0.43-0.90); p = 0.012). In multivariate, high STAT1 (HR 0.26 (0.12-0.59); p < 0.001) and low IF1 (HR 0.57 (0.30-1.09); p = 0.07) were associated with lower risk of recurrence. Results were similar when only patients with residual disease were considered in the analysis. In BC cell lines, expression of MHC1-related genes was very heterogeneous from low to very high. A group of cell lines, TN and HER2+ in particular, expressed also some IF1. STAT1-related genes. Conclusions: Multivariate analysis is needed to uncover the contribution of immune components to the response and prognosis of TN tumors treated with anthracyclines, which was similar to the involvement with response of HER2+ tumors to monoclonals. Interferon signaling, defined by STAT1 and IF1 metagens, and MHC1 expression are related to both the immune system status and tumor cells.
Cisplatin with or without rucaparib after neoadjuvant chemotherapy in patients with triple negative breast cancer: Final efficacy results of Moosier Oncology Group BREDS01. First Author: Georges Azzi, University Of Miami/Sylvester Cancer Ctr, Miami, FL

**Background:** Patients (pts) with triple negative breast cancer (TNBC) with residual disease after neoadjuvant therapy have a high risk of recurrence. **Methods:** Pts with BRCA mutations and/or TNBC with lymph node (LN) or > 2 cm of invasive disease after anthracycline (A) and/or taxane (T) neoadjuvant therapy were assigned 1:1 to cisplatin (C: 75 mg/m² q3 wks X 4) +/- rucaparib (R: 24-30 mg IV D1,2,3 X 3 wks) or 100 mg orally wkly for 24 wks. BROCA analysis identified deleterious germline mutations. Pharmacokinetic sampling to assess R exposure was obtained during IV and oral dosing. The primary objective was to study was substantially less than the current phase II monotherapy dose (600 mg orally twice daily) and may not have been sufficient to inhibit this study was significantly improved with CR (55.9% vs. 69.9%; p = 0.04). Mutation status did not impact DFS. **Conclusions:** The addition of low dose R did not impact the toxicity of cisplatin or improve 2-yr DFS. The dose of R used in this study was substantially less than the current phase II monotherapy dose (600 mg orally twice daily) and may not have been sufficient to inhibit PARP activity. Clinical trial information: NCT01704970.

**1083** Poster Session (Board #197), Sat, 8:00 AM-11:30 AM

A novel biomarker to predict sensitivity to enzalutamide (ENZA) in TNBC. First Author: Joel S. Parker, UNC Chapel Hill, Chapel Hill, NC

**Background:** TNBC is a heterogeneous disease with multiple subtypes and driven by HER2, a potential growth factor for TNBC (pts) whose expression correlates with ER (~0%) by IHC (NCT01889238). However, AR expression may not confer ENZA sensitivity. Gene profiling was therefore explored to determine whether this could be superior to IHC in predicting benefit from ENZA. **Methods:** Consent and tissue for AR testing was collected from 404 pts. Next-Gen RNA-sequencing analysis was performed on 170 tissue samples; 122 samples came from pts treated with ENZA (118 unique pts) (ITT); 55 were from untreated pts. A Training Set (TrS, n = 122) and a Validation Set (VS; n = 55) were created. TrS consisted of 80 samples from ENZA treated pts (77 unique pts) + 42 from untreated pts (29 AR + 13 CR > 0%). VS consisted of 42 samples from ENZA treated pts (41 unique pts) + 13 from untreated pts (10 AR + 3 CR > 0%). A gene expression model of biological subtype (GES) was built directly from the response data in the TrS. Model development utilized the elastic-net algorithm in the context of 500 rounds of Monte-Carlo cross-validation. Tuned parameters were used to validate the gene expression model in the VS, outcomes were blinded during model validation. **Results:** The selected GES achieved 80% sensitivity and 65% specificity in prediction of 16 week clinical benefit (CBR16). Utilization of this model to define Diagnostic positive (Dx+) and Dx- populations showed the following results in pts treated with ENZA are shown in the Table. Highest accuracy was demonstrated in pts receiving ENZA as their 1st or 2nd line of treatment. **Conclusions:** A genomic signature, associated with androgen biology, has been identified that demonstrates the potential to predict clinical response to ENZA in pts with TNBC. Nearly half of the pts enrolled in the phase 2 were classified as Dx+, suggesting a reasonable prevalence of pts who may benefit from this hormonal therapy. This assay may be useful to select TNBC pts for future studies evaluating ENZA. Clinical trial information: NCT011889238.

**1084** Poster Session (Board #198), Sat, 8:00 AM-11:30 AM

Rac1 inhibition to sensitize triple negative breast cancer to EGFR inhibition. First Author: Georges Azzi, University Of Miami/Sylvester Cancer Ctr, Miami, FL

**Background:** Triple Negative Breast Cancer (TNBC) a subtype of breast cancer with the poorest prognosis lacks expression of estrogen progesterone receptor and does not overexpress HER2. Currently, there are no effective targeted therapies. TNBC frequently overexpresses EGFR, a member of the ErbB family of transmembrane receptor tyrosine kinases. Although EGFR targeted therapies are approved and used widely in lung cancer and head and neck cancer, their use in breast cancer has not revealed significant activity. Previous studies in lung cancer have shown that Rac1 overexpression results in resistance to EGFR inhibition. Rac1, a Rho GTPase, is frequently overexpressed in breast cancer. We have previously reported that Rac inhibition may be an effective therapeutic strategy in breast cancer. Furthermore, we have previously shown that EGFR overexpression results in resistance to Rac inhibition in breast cancer. The aim of the current study was to assess the activity of gefitinib (an EGFR tyrosine kinase inhibitor) and a Rac inhibitor (EHT1864) alone or in combination in TNBC. **Methods:** Using proliferation and clonogenic assays we assessed the activity of gefitinib (2.5 μM) and EHT1864 (25 μM), and their use in combination on the growth of TNBC breast cancer cell lines (MDA 231, MDA 468, MDA 436, HS578T). We also confirmed the pharmacological effect of gefitinib on EGFR with molecular knockdown of EGFR in HS578T cells. **Results:** All 4 cell lines tested did not show any significant growth inhibition with gefitinib alone. 61% difference in colony formation with Rac inhibitor alone but the combination was effective in significantly reducing both growth and colony formation potential in 2 of the TNBC cell lines (HS578T and MDA468). The combination of shEGFR knockdown and Rac inhibition phenocopied the results of pharmacological inhibition with gefitinib plus EHT1864. **Conclusions:** Our results suggest that Rac inhibition sensitizes a subset of TNBC to EGFR inhibition and the combination of Rac and EGFR inhibition is a promising therapeutic strategy for a subset of TNBC that warrants further studies.

**1085** Poster Session (Board #199), Sat, 8:00 AM-11:30 AM

Protein activation mapping and exploratory predictive markers for pCR in triple-negative breast cancer patients treated with neratinib in the I-SPY 2 TRIAL. First Author: Julia Dianne Wulfkuhle, George Mason Univ, Columbus, MD

**Background:** In the I-SPY 2 trial, the pan-ERBB inhibitor, neratinib (N) arm was open to all HR/HER2 subtypes but graduated in the HR-/HER2+ signature. Exploratory analysis of protein signaling was performed to identify biomarker candidates correlated with pCR in the TN population. We evaluated 110 key signaling proteins using reverse phase protein array (RPPA) data from pre-treatment (LUM) or purified tumor euthyroidism. **Methods:** Of 59 TN patients, 49 (N: 30, concurrent controls; 19) had RPPA and pCR data. RPPA data was correlated to pCR in both the treated and untreated patients using parametric (t-test) or non-parametric (Wilcoxon) statistical analysis, depending on data distribution. Only analyses whose levels were associated with response in the N but not the control arm were selected for further analysis. Markers are analyzed individually; p-values are descriptive and were not corrected for multiple comparisons. ROC analysis identified an optimal cut point and pCR rates of biomarker positive patients were assessed using that cut point. **Results:** Out of 110 analytes analyzed, only activation of HER2 Y1248, p = 0.03, A-RAF Y1173, p = 0.009; were found to be positive predictors of pCR, and 3 proteins, TIE2 Y992, p = 0.02; LC3B, p = 0.02, and A-RAF S299, p = 0.0008, were found to be negative predictors of pCR. pCR rates in the biomarker positive group of 62.5% (10/16), 66% (11/16), 55% (10/18), 67% (10/15) and 71% (10/14) were found to be significant. **Conclusions:** Our sample size is too small to draw definitive conclusions. However, activation of HER2-EGFR in HER2- tumors may identify patients who respond to N. Levels of activated A-RAF and LC3B also correlated with response. The results imply that there is a subset TN patients that paradoxically exhibit HER family signaling activation and may achieve clinical benefit with N. These findings merit future consideration as we develop trials for patients with suboptimal response to neoadjuvant therapy where biomarkers could be used as the basis for treatment reassignment. Clinical trial information: NCT01042379.
Clinical utility of in depth RNA sequencing for non-metastatic triple negative breast cancers. First Author: Benoit Thouvenot, GENCLIS, Van-.

Background: KCNK9 is a maternally imprinted and functionally mono-allelic 2-pore domain K+ channel proto-oncogene. It has been postulated that loss of KCNK9 methylation (LOM) is associated with more aggressive triple negative (TN) phenotype breast cancer. Epidemiological data characterizing KCNK9 is sparse and was the rationale for this study.

Methods: Publically available breast cancer data from The Cancer Genome Atlas on clinical factors and KCNK9 gene methylation (HM450 beta values), amplification (putative copy-number alterations (CNA) from GIS-TIC), and mRNA expression Z-scores (RSEM) was examined in 818 women. Multivariable (MV) logistic regression models with model-based standard errors (QIF) was used to estimate risk ratios (RRs) with 95% confidence intervals (CIs).

Results: Overall, KCNK9 gene amplification was more common than deletion (58% vs. 6%, respectively). Bivariate results for KCNK9 LOM (highest tertile loss vs. others), gene amplification (CNA gain vs. normal), and mRNA expression (highest tertile vs. others) are provided in the table below. Median overall survival for women with gain was 103 vs. 140 months (log-rank test, p = 0.011), and 96 vs. 130 months for higher vs. lower expression (p = 0.014), but was not different for LOM. Conclusions: KCNK9 gene LOM, amplification and higher mRNA expression occur more frequently in black women, and ER/PR-negative and TN disease, and amplification and expression are associated with worse survival outcomes.

Prognostic markers in triple-negative breast cancer (TNBC): The role of androgen receptor, e-cadherin, and Ki67. First Author: Giuseppina Rosaria Rita Ricciardi, Medical Oncology Unit AOOR Paparo-Piemonte, Department of Human Pathology, University of Messina, Messina, Italy

Background: TNBC represents a group of tumors with poor prognosis owing to aggressive tumor biology and lack of targeted therapies. However, TNBC is clinically and biologically heterogeneous and no clear prognostic bio-

marker has been identified. We evaluated the prognostic value of various clinical-pathological variables, including androgen receptor (AR), E-cadherin (CDH1) and Ki67 (Ki) expression.

Methods: This is a retrospective study of 99 patients (pts) with TNBC diagnosed during 2000–2010 in two Italian hospitals. All pts received neo/adjuvant chemotherapy (mostly anthracycline/taxane-based). Immunohistochemistry (IHC) of the primary tumors was performed in formalin-fixed paraffin-embedded primary tumor samples. CDH1 expression was considered positive as > 30% of the membrane cells staining. AR positivity was defined as > 10% of positive tumor cells. High Ki67 was defined as > 14% positive tumor cells. Cox proportional hazard univariate and multivariable models were used to evaluate the associations of each variable with relapse-free survival (RFS) and overall survival (OS). Distribution of samples within groups was compared using a Chi-square test.

Results: Median age was 61 years (range 33-83). The majority of tumors were ductal (n = 85, 85.8%), node-negative (n = 49, 58.3%), grade 3 (n = 58, 66.7%) and showed high Ki67 (n = 74, 74.7%). The distribution of tumor stage was I (n = 32, 32.3%), II (n = 37, 37.4%), III (n = 18, 18.2%) and IV (n = 2, 2.0%). CDH1 was expressed in 30.3% of the cases, was found in 17.1% and 50.5% of the cases. Only 26.6% of AR-positive cases were grade 3 compared with 68.2% of grade 3 in AR-negative cases (p = 0.01). At median follow-up of 62.0 months (range 3.0-118.0), 95 pts were evaluable for RFS and OS. Univariate analyses showed that lack of expression of CDH1, tumor size and nodal status were significantly associated with worse RFS and OS (p < 0.05). AR expression and low Ki67 showed a trend towards better RFS and OS. Multivariate analysis showed an independent association between CDH1 expression and better RFS and OS (p < 0.05) beyond tumor size, nodal status and grade. Conclusions: Our findings support the potential prognostic value of molecular biomarkers such as CDH1 that might be useful to classify subgroup of TNBC.

Clinical utility of in depth RNA sequencing for non-metastatic triple negative breast cancers. First Author: Benoit Thouvenot, GENCLIS, Van-.

Background: KCNK9 is a maternally imprinted and functionally mono-allelic 2-pore domain K+ channel proto-oncogene. It has been postulated that loss of KCNK9 methylation (LOM) is associated with more aggressive triple negative (TN) phenotype breast cancer. Epidemiological data characterizing KCNK9 is sparse and was the rationale for this study.

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Prognostic markers in triple-negative breast cancer (TNBC): The role of androgen receptor, e-cadherin, and Ki67. First Author: Giuseppina Rosaria Rita Ricciardi, Medical Oncology Unit AOOR Paparo-Piemonte, Department of Human Pathology, University of Messina, Messina, Italy

Background: TNBC represents a group of tumors with poor prognosis owing to aggressive tumor biology and lack of targeted therapies. However, TNBC is clinically and biologically heterogeneous and no clear prognostic bio-

marker has been identified. We evaluated the prognostic value of various clinical-pathological variables, including androgen receptor (AR), E-cadherin (CDH1) and Ki67 (Ki) expression.

Methods: This is a retrospective study of 99 patients (pts) with TNBC diagnosed during 2000–2010 in two Italian hospitals. All pts received neo/adjuvant chemotherapy (mostly anthracycline/taxane-based). Immunohistochemistry (IHC) of the primary tumors was performed in formalin-fixed paraffin-embedded primary tumor samples. CDH1 expression was considered positive as > 30% of the membrane cells staining. AR positivity was defined as > 10% of positive tumor cells. High Ki67 was defined as > 14% positive tumor cells. Cox proportional hazard univariate and multivariable models were used to evaluate the associations of each variable with relapse-free survival (RFS) and overall survival (OS). Distribution of samples within groups was compared using a Chi-square test.

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Programmed cell death 1 (PD-1) receptor and programmed death ligand 1 (PD-L1) expression in primary breast cancer (BC), correlations with clinical characteristics and patient outcomes. First Author: Neelima Vidula, UC San Francisco, San Francisco, CA

Background: The interaction of the PD-1 receptor on tumor infiltrating lymphocytes and PD-L1 on tumor cells dampens antitumor immunity. Two phase I trials suggested efficacy of anti-PD-1/PD-L1 antibodies in triple negative (TN) BC. This study investigated associations between primary BC PD-1 and PD-L1 expression, clinical characteristics, and patient outcomes in publicly available databases.

Methods: We evaluated PD-1 and PD-L1 expression using microarray data from the neoadjuvant I-SPY 1 study (n = 149). Associations with clinical features and chemotherapy response were assessed by Kruskal-Wallis and Wilcoxon rank sum tests, respectively. Recurrence free survival (RFS) associations were assessed by the Cox proportional hazard model. PD-L1 expression and correlations between PD-1 and expression of PD-L1, HAVCR2, STAT5A, FOXP3, MYC, and ESR1 were determined in I-SPY 1 and 2 other datasets: METABRIC (n = 1492) and TCGA (n = 817). Results: In I-SPY 1, PD-1 expression was significantly higher in HER2+ and TNBC (p = 0.003), and in grade 2/3 tumors (p = 0.043); this association was also seen in METABRIC. PD-1 expression was associated with pathologic complete response (p = 0.006) but not with tumor stage, nodal status, lymphovascular invasion or RFS. While PD-L1 did not correlate with tumor features, patients with PD-L1 expression in the lowest quintile had worse RFS, even after subtype adjustment (HR 2.33, p = 0.01). In all 3 datasets, PD-1 significantly correlated with PD-L1, HAVCR2 and STAT5A, and inversely with ESR1. In the TN subset of METABRIC and METABRIC, PD-1 significantly correlated with PD-L1, HAVCR2, and STAT5A. In TCGA and METABRIC, PD-1 significantly correlated with HAVCR2 and STAT5A, and this was also seen in the TN subset. In TCGA alone, PD-1 and PD-L1 significantly correlated with FOXP3 and PD-1 with MYC. Conclusions: PD-1 expression is higher in TN and other aggressive BC subtypes. PD-1 and PD-L1 correlate with immune related genes HAVCR2 and STAT5A. Low PD-L1 expression may be an adverse prognostic factor. Trials are underway to investigate the activity of anti-PD-1/PD-L1 antibodies in TNBC and to elucidate markers of response.

Outcomes with neoadjuvant versus adjuvant chemotherapy for T1-2 node negative triple negative breast cancer. First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS

Background: Randomized studies have demonstrated that Neoadjuvant Chemotherapy (NAC) is equivalent to adjuvant chemotherapy (AdjC) in operable breast cancer (BC). However, the differential impact of NAC vs AdjC on outcomes in various BC subtypes is not known. Specifically, the impact of AdjC vs NAC BC outcomes in small (T1-2) clinically node negative (NN) triple negative breast cancer (TNBC) is not known. Aim: To evaluate the impact of NAC vs AdjC on BC recurrence and RFS in NN T1-2, TNBC utilizing data from a prospective registry. Methods: 316 stage I-III NN T1-2 TNBC patients enrolled in a multisite IRB approved registry between 2011 and 2014. Clinical, demographic, chemotherapy and recurrence information was collected. This study was restricted to analysis of registry participants with T1-2, NN disease. RFS was estimated according to the Kaplan-Meier method and compared among groups with log-rank statistic. Results: 146 patients with NN T1-2 TNBC enrolled on the registry since 2011. Patients underwent either NAC (67/146, 46%) or AdjC (79/146, 54%) at the discretion of treating physician. For the 146 eligible patients, median age was 55 yrs (range 24-80), 14%: African American, 49% had T1 and 51% had T2 disease. Almost all patients received Anthracycline and/or taxane containing chemotherapy (AdjC: 95%, NAC: 100%). Compared to AdjC patients, NAC patients were younger (median age 52 vs 58 yrs, p = 0.015), more likely to have T2 tumors (76% vs 29%, p < 0.001), more likely to have recurrence (24% vs 7%, p = 0.043) and received more cycles of chemotherapy (85% vs 53%, p = 0.001). PCR was observed in 55% of NAC cohort (37/67). Overall, at a median follow of 37 months (6-89) there were 8 (5%) recurrences (1/67 in NAC group & 7/79 in AdjC group). RFS in NAC group was 98% vs. 91% in AdjC group (p = 0.07). On multivariate Cox regression analysis, AdjC (compared to NAC) was the only factor demonstrating a trend towards worse RFS (p = 0.080). Conclusions: Patients with NN, T1-2 TNBC demonstrate excellent outcome when treated with NAC (98% RFS). Compared to AdjC, NAC was associated with a trend towards better RFS in NN T1-2 TNBC. In patients with clinically node negative TNBC, NAC should be compared to AdjC prospectively.

Reproducibility of homologous recombination deficiency (HRD) scores in biopsies of triple negative breast cancer (TNBC) tumors. First Author: Kirsten Timms, Myriad Genetics, Inc., Salt Lake City, Utah

Background: The HRD score is the sum of three previously described tmBRCA mutations (tmBRCA) and response to DNA damaging agents in TNBC. This study assesses the consistency of the HRD score in multiple biopsies obtained from the same cancer to examine the impact of spatial heterogeneity and sampling on the results. We included 32 tumors (46 total biopsies) from patients with clinical and/or taxane containing chemotherapy (AdjC: 95%, NAC: 100%). Comparisons between first and second biopsy samples exhibited lower scores (mean 1.1 vs 0.8, p = 0.001), more likely to have T2 tumors (76% vs 29%, p = 0.001), and patients with HAGE mRNA expression exhibited lower risk of death compared to HAGE- tumors (HR 0.54 (0.36-0.85), p = 0.031) compared to HAGE- residual tumours. HAGE expression was associated with immune-related genes in TNBC (p = 0.003), and significantly associated with prolonged survival (HR 0.54 (0.41-0.85), p = 0.0005). Following AC-Neo-ACT, loss of HAGE protein expression was found (p = 0.002) and patients with HAGE+ residual disease exhibited no TiLs and had two fold increase in the risk of death (HR (95% CI) = 1.66 (1.10-2.52), p = 0.0018) compared to HAGE- residual tumours. HAGE interactome included genes that involved in protein degradation and antigen presentation. Conclusions: The expression of HAGE is a potential prognostic marker and predictor of response to AC-CT in TNBC.
In germline BRCA1 or BRCA2 mutation carriers, restoration of tumor BRCA1/2 function by a secondary mutation in these genes has been recognized as a mechanism of acquired resistance to platinum and PARP inhibitors, primarily in ovarian cancer. We set out to evaluate this mechanism of resistance in newly diagnosed BRCA1/2-mutant BC patients (pts) with a poor response to platinum-based therapy. BRCA1/2 genotyping using pre-treatment biopsies. For mutation carriers with an unfavorable response (moderate or extensive residual disease at surgery), tumor BRCA1/2 status was re-sequenced in the residual surgical tissue. All testing was performed at Myriad Genetics. Results: 19 pts had a deleterious germline BRCA1/2 mutation, and of these 4 had moderate residual disease at surgery. BRCA1/2 sequencing of residual tissue was available in 2 of 4 pts (no consent in 1 case; inadequate DNA extraction in 1 case). These 2 pts had BRCA1 1479delAG and W1712X mutations with LOH at these loci in the pre-treatment tumor. In the first case, a new BRCA1 mutation (a 42 base pair (bp) deletion that overlapped with the original 2 bp deletion) was detected in the residual tissue. This resulted in a 14 amino acid deletion and restoration of the BRCA1 reading frame. A relapse biopsy 4 months later revealed the identical reversion mutation and the pt subsequently died of metastatic TNBC. No reversion mutation was observed in the residual tissue of the second BRCA1 carrier, who notably had ER/PR+ BC. Conclusions: We report a BRCA1 reversion mutation in a newly diagnosed TNBC pt that developed over the course of 18 weeks of platinum-based neoadjuvant therapy. This was associated with poor neoadjuvant therapy response, early relapse and death from metastatic BC.

High glycolytic metabolism in breast cancer is known to support tumor progression and metastasis, and a unique glycolysis signature has been identified in ER- and triple-negative (TNBC) breast tumors. Here, we investigated the therapeutic effect of the anti-Warburg agent BPM 31510 in xenograft models of triple-negative breast cancer (TNBC). Methods: In vitro models were used to define mechanistic underpinnings. Results: BPM 31510 or chemotherapy alone improved survival; however, BPM 31510 monotherapy was associated with more than a 6 week increase in survival compared to TAC alone. Cleaved caspase 3 levels were higher in tumors from BPM 31510-treated mice, demonstrating activation of apoptosis in response to this treatment. A panel of primary, non-tumorigenic, and breast cancer cells was used to determine IC50 values for BPM 31510 in vitro. At doses comparable to circulating levels achieved in vivo, BPM 31510 exposure was associated with decreased viability in tumor cells, and was antagonistic to the cytotoxic effects of cyclophosphamide in MDA-MB231 cells demonstrating maximal sensitivity to cell death. Interestingly, although cellular proliferation rate was not predictive of anti-cancer responses to BPM 31510, a bioenergetic signature characterized by high glycolytic flux and low mitochondrial respiration was highly correlated with sensitivity to BPM 31510-induced cell death. Conclusions: These data demonstrate that BPM 31510 is effective as a single agent in breast cancer. When used in combination with chemotherapy, BPM 31510 augments survival, particularly in distinctly glycolytic TNBC, a sub-type for which prognosis is poor and few therapeutic options exist.
Background: Patients with triple-negative breast cancer (TNBC) are ineligible for endocrine and HER2-targeted therapy and remain at high risk for relapse after treatment. Most TNBC are basal-like (BL) but recent studies identified additional subtypes of TNBC. Immunohistochemistry (IHC) for various markers has been reported to correlate with clinical outcomes, but many studies are based on relatively limited IHC panels. We applied a large IHC-based marker set in a TNBC cohort to evaluate their potential for prognostic and predictive modeling. Methods: Archived tissue samples from a prospectively maintained registry of 145 TNBC patients (mean age 57.2 years; median follow up 3.8 years) were used to investigate associations between marker expression and time-to-progression. Progression-free survival was defined as local, regional, or distant recurrence. IHC for EGFR, HMWCK, (high molecular weight cytokeratin), TOP2A, BCL2, and AR was performed. Simple data imputation was used for missing protein data as complete case analysis (no missing data) resulted in a sample size of 82. Positive was defined as > 10% for AR and > 0% (any staining) for EGFR and HMWCK TOP2A and BCL2 staining was recorded in 5% increments and optimal cut-points relative to time-to-progression were used to define positivity and negativity. Cox proportional hazard models were used to examine associations between expression and progression. A random forest classification tree approach was used to identify potential co-expression between proteins. Results: TNBC expressed HMWCK, EGFR, AR, TOP2A and BCL2 in 76.6, 86.2, 13.1, 58.6, and 12.4% of cases, respectively. With an optimal derived cutoff of 40%, TOP2A expression was associated with shorter time to progression (HR = 2.01; p = 0.059) while the expression of BCL2 (optimal cut-off: 60%) was not (HR = 0.18; p = 0.087). Sixty-seven (46.2%) cases showed co-expression of HMWCK, EGFR, and TOP2A. TOP2A was consistently correlated with HMWCK (66% agreement in positivity) and c-MET (43% agreement in positivity) per the classification tree. Conclusions: Results indicate a potential co-expression of TOP2A with the BL phenotype of TNBC and provide a rationale for further investigation into tailored therapy for TNBC.
Phase 3 randomized, placebo-controlled trial of carboplatin (C) and paclitaxel (P) with/without veliparib (ABT-888) in HER2-BRCA-associated locally advanced or metastatic breast cancer (NCT02163694). Methods: Phase 3 randomised, double-blind, placebo-controlled, multicentre trial. Eligible patients (female or male: ≥ 18 years) have HER2– metastatic/locally advanced unresectable BC with (suspected) deleterious BRCA1/2 germline mutations and received 2 or fewer prior lines of DNA-damaging chemotherapy for metastatic BC. In addition, patients must have received ≤ 1 prior line of platinum therapy (any setting) without progression within 12 months of completing treatment. Patients are randomized 2:1 to C/P with veliparib or C/P with placebo, stratified by HER2- BRCA-associated locally advanced or metastatic BC (NCT02163694).

Background: BRCA-mutated tumors are more susceptible to platinum therapy and PARP inhibitors due to underlying defects in homologous recombination repair of DNA damage. Preclinical models the potent oral PARP1/2 inhibitor veliparib was shown to enhance sensitivity to C and to have single-agent activity in BRCA+ cell lines. Phase 1 trials suggest promising antitumor activity and acceptable toxicity of veliparib plus C/P in triple-negative BC (Puhlala et al. Cancer Res 2012;72(24 suppl):PD09-06) and single-agent activity of veliparib in BRCA+ BC (Sommol et al. J Clin Oncol 2014;32(15 suppl):abstr. 1021). This phase 3 trial assesses efficacy and toxicity of veliparib plus C/P vs C/P alone in patients with HER2- BRCA-associated locally advanced or metastatic BC.

Primary endpoint is SSE-free survival. Eligible pts are pre- or postmenopausal with estrogen receptor– HER2+ breast cancer patients (pts) with bone metastases (mets). First Author: Robert E. Coleman, University of Sheffield, Weston Park Hospital, Sheffield, United Kingdom

Background: Treatment of bone-metastatic breast cancer (MBC) is limited. Multimodality therapy may improve symptom control and survival. In a phase 2a study of advanced breast cancer pts with bone-dominant and no visceral disease, Ra-223, a first-in-class α-emitter selectively targeting bone mets, reduced baseline bone biomarker levels with favorable safety. (Coleman et al. Breast Cancer Res Treat 2014). This study (NCT02258464) evaluatesRa-223 efficacy and safety vs placebo (pbo) in HER2+ hormone receptor– breast cancer pts with bone mets receiving single-agent HT. Methods: Pts receive (1:1) Ra-223 50 kBq/kg IV or pbo q4w k( 6 cycles) + concurrent single-agent HT + best supportive care. Stratification is by geographic region, prior lines of HT for MBC, and number of prior skeletal events. Pts are assessed for efficacy and safety, and followed to symptomatologic event (SSE), radiologic progression, death, or withdrawal. Primary endpoint is SSE-free survival. Eligible pts are pre- or postmenopausal with estrogen receptor–, HER2+, bone-dominant MBC with > 2 bone mets and ≥ 1 or 2 prior SSEs (external beam radiotherapy for bone pain, pathologic bone fracture, spinal cord compression, orthopedic surgery). Pts had ≥ 1 line of HT for MBC; are taking bisphosphonates or denosumab for ≥ 1 month before study; are eligible for endocrine treatment; and have not received adjuvant systemic therapy. Women with mildly symptomatic bone disease (Brief Pain Inventory), ECOG score 0-1, and adequate hematologic, renal, and liver function. Pts may not have had visceral or brain mets or leptomeningeal disease, need for chemotherapy for mets, and untreated spinal cord compression. Assuming a 1-sided α of 0.1, power of 90%, ~ 119 SSEs are required for the analysis. Time-to-event variable analysis will use a log-rank test, accounting for stratification. Kaplan-Meier estimates and survival curves will be given for each treatment group. Safety analyses will be descriptive. Target enrollment is 227 pts. First pt first visit is expected in early 2015. Clinical trial information: NCT02258464.

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**TPS1106** Poster Session (Board #217a), Sat, 8:00 AM-11:30 AM

Weekly nab-paclitaxel (nab-P) plus gemcitabine (gem) or carboplatin (carbo) vs gem/caro as first-line treatment for metastatic triple-negative breast cancer (mTNBC) in a phase 2/3 trial (MyloBRCA). First Author: Denise A. Yardley, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN

Background: Treatment of mTNBC is an unmet clinical need. First-line nab-P with gem or carbo/bevacizumab has demonstrated efficacy and safety in female patients (pts). In the phase III, nab-P vs nab-P+gem was a non-inferiority-based-paclitaxel in pts with early TNBC. The phase II/III trial (TRiAct: triple-negative Albumin-bound paclitaxel combination international treatment study) trial will compare efficacy and safety of 2 nab-P-containing regimens (with gem or carbo) vs gem/caro as a control first-line treatment for mTNBC. Methods: 790 female pts ≥ 18 yrs with measurable mTNBC will be enrolled at ~150 sites globally per major eligibility criteria (Table 1). In phase II, 240 pts will be randomized 1:1 to receive nab-P 125 mg/m² + gem 1000 mg/m² (arm A), nab-P 125 mg/m² + carbo arm under the curve (AUC) 2 (arm B), or gem 1000 mg/m² + carbo AUC 2 (arm C). Pts 1 D and 8 qw. Pts will be treated until disease progression. Stratification factors are disease-free interval (≤ 1 yr vs > 1 yr) and prior taxane exposure (phase III only). A rank ordering of 5 efficacy and safety parameters will be used to identify the nab-P combination for the phase III portion in which 550 pts will be randomized 1:1 to receive the selected nab-P regimen (arm A or B) or gem/caro. In pts in phase II will not be the phase III population. The phase III primary endpoint is PFS by independent radiological assessment. Study design provides ≥ 90% power to detect an HR of 0.70 for PFS with a 2-sided 5% significance level. Secondary endpoints: ORR, OS, disease control rate, duration of response, and safety. Exploratory analyses include tumor biomarkers and circulating tumor cells analyses. Current enrollment as of submission: 128 pts. Clinical trial nCT01881230. Clinical trial information: NCT01881230.

Key eligibility criteria.

ER and PgR expression both < 1% of tumor cell nuclei

HER2 IHC 0 or 1 + or FISH +, or IHC 2 + and FISH - ECOG PS 0-1

Peripheral neuropathy grade < 2

No prior choemo for metastatic disease

Prior adjuvant/neoadjuvant anthracycline treatment required unless contraindicated

Prior taxane, gem, or platinum treatment permitted if completed ≥ 12 months before randomization

**TPS1108** Poster Session (Board #216a), Sat, 8:00 AM-11:30 AM

A phase 2 study (2-stage, 2-cohort) of the oral PARP inhibitor talazoparib (BMN 673) in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer (ABRAZO). First Author: Nicholas C. Turner, Royal Marsden, London & Surrey, United Kingdom

Background: Poly-ADP-ribose polymerase (PARP) represents a family of enzymes of which at least two (PARP1 and PARP2) play important roles in DNA repair. PARP inhibition induces synthetic lethality in tumor cells bearing deleterious mutations in the genes BRCA1/2. Talazoparib (BMN 673) is a novel, dual-mechanism PARP inhibitor that potently inhibits the PARP enzyme and effectively traps PARP on DNA [1]. Methods: 229 patients (pts) with advanced breast cancer at high risk of recurrence will be randomized in 2 stages and 2 cohorts: arm A (n=115) to receive nab-paclitaxel 125 mg/m² q4w + gem 1000 mg/m² q4w for 12 cycles, followed by talazoparib 80 mg/day for as long as progressing and tolerable; arm B to receive nab-paclitaxel 125 mg/m² q4w + gem 1000 mg/m² q4w for 12 cycles, followed by talazoparib 80 mg/day for as long as progressing and tolerable (arm A or B) or gem/carbo. Pts in phase II will not be in the phase III population. The phase III primary endpoint is PFS by independent radiological assessment. Study design provides ≥ 90% power to detect an HR of 0.70 for PFS with a 2-sided 5% significance level. Secondary endpoints: ORR, OS, disease control rate, duration of response, and safety. Exploratory analyses include tumor biomarkers and circulating tumor cells analyses. Current enrollment as of submission: 128 pts. Clinical trial nCT01881230. Clinical trial information: NCT01881230.

Key eligibility criteria.

ER and PgR expression both < 1% of tumor cell nuclei

HER2 IHC 0 or 1 + or FISH +, or IHC 2 + and FISH - ECOG PS 0-1

Peripheral neuropathy grade < 2

No prior choemo for metastatic disease

Prior adjuvant/neoadjuvant anthracycline treatment required unless contraindicated

Prior taxane, gem, or platinum treatment permitted if completed ≥ 12 months before randomization

**TPS1109** Poster Session (Board #218b), Sat, 8:00 AM-11:30 AM

Olympia: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm). First Author: Andrew Nicholas James Tutt, King’s College London School of Medicine, London, United Kingdom

Background: In a Phase II proof-of-concept study (NCT00494234), treatment with the PARP inhibitor olaparib (Lynparza; 400 mg twice daily [bid]; capsules) resulted in antitumor activity in patients (pts) with advanced BC harboring a gBRCAm (objective response rate: 41%; Tutt et al Lancet 2010). An AstraZeneca-sponsored Phase III trial (Olympia; NCT02032823; co-supported by BIG, NRG Oncology, Frontier Science and AstraZeneca) of olaparib as adjuvant monotherapy has been initiated in pts with gBRCAm-associated triple negative BC (TNBC) who have completed local treatment and neoadjuvant or adjuvant chemotherapy (CT). Methods: Olympia is a double-blind trial in which pts with TNBC at high risk of recurrence are currently randomized (1:1) to receive treatment with olaparib (300 mg tablets bid [x 150 mg]) or placebo for a maximum of 12 months. Eligible pts must have completed definitive local treatment and at least 6 cycles of either neoadjuvant CT (without a pathological complete response) or adjuvant CT. Pts must also have a known or suspected deleterious gBRCAm, which will be retrospectively confirmed by Integrated BRACAnalysis (Myriad Genetic Laboratories) before entering the trial. Stratification factors include prior neoadjuvant versus adjuvant CT, and whether pts have received prior platinum therapy for current BC. The primary objective is invasive disease-free survival (iDFS). Efficacy assessments will be made by matched tumor/breast cancer (BC) (both DC and distant BC), progression-free survival (PFS), and overall survival (OS). Health-related quality of life assessments are an exploratory objective. Patient eligibility includes ≥ 18 yrs, locally advanced and/or metastatic disease, deleterious BRCA1/2 mutation, and ECOC performance status ≤ 1. Eligible patients will receive oral talazoparib (Olaparib) 400 mg/day, 21-days on/7-days off until disease progression, toxicity. This trial is enrolling patients in the United States, France, Germany, Spain, and the United Kingdom. (NCT02034916). [1] Murali J et al. Cancer Res. 2012;72(21):5588-5599. [2] Murali J et al. Mol Cancer Ther. 2014;13:433-443. [3] Wainberg ZA et al. J Clin Oncol. 2014;32(suppl):5; abstr 7522 Clinical trial information: NCT02034916. [4] Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**TPS1110** Poster Session (Board #219a), Sat, 8:00 AM-11:30 AM

**METRIC: A randomized international study of the antibody-drug conjugate glembatumumab vedotin (GV or CDC-011) in patients (pts) with metastatic gastric/gastroesophageal adenocarcinoma (GEA) not otherwise eligible for palliative care**

**First Author:** Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN

**Background:** The internalizable transmembrane glycoprotein NMB (gpNMB) is overexpressed in 20% of BC, including 40% of TNBC (Yardley JCO, in press), where it is a poor prognostic marker (Rose CCR 2010). gpNMB enhances tumor invasion and metastasis and promotes angiogenesis in preclinical models. GV is a novel antibody-drug conjugate containing the potent cytotoxin monomethylauristatin E (MMAE) to gpNMB + tumor cells. In a Phase I/II study (Bendell JCO, 2014) and the Phase II “EMERGE” study (Yardley JCO, in press), GV demonstrated promising activity, particularly in pts with TNBC and gpNMB overexpression, and was well-tolerated (treatment related toxicities: rash, neutropenia and neuropathy). In subset analyses, for GV vs. “investigator’s choice” (IC) single-agent chemotherapy, objective response rate (ORR) was 30% (7/23) vs. 9% (1/11) in pts with gpNMB overexpression (in ≥ 25% of tumor epithelium); 18% (5/28) vs. 0% (0/11) in TNBC, and 40% (4/10) vs. 0% (0/6) in gpNMB-overexpressing TNBC, with apparent improvements in progression-free survival (PFS; hazard ratio (HR) = 0.11) and overall survival (OS; HR = 0.14). **Methods:** The international (US, CA, Aus) “METRIC” study (NCT01997333) is recruiting up to 300 pts with metastatic, gpNMB-overexpressing TNBC. Eligibility criteria include: ≥ 25% tumor epithelium gpNMB + by central IHC prescreening of archival tissue; ER and PR < 10% and HER2(-)(0-1+ IHC, or ISH copy number < 4.0 / ratio < 2.0) by local assessment; ECOG 0-1; taxane resistance; and tamoxifen resistance (if indicated); ≥ 2 chemotherapy regimens for advanced BC; measurable disease; no persistent Grade ≥ 2 toxicity; and capcitabine naive. Pts are randomized (2:1) to GV (1.88 mg/kg IV q 21 days) or capcitabine, a current standard for this population (2500 mg/m2 daily for d1-q14, q21 days) until progression or toxicity. Crossover is not permitted. Endpoints are PFS (primary), ORR, duration of response, OS, safety, PK, PD (immune dynamics) and quality of life. Imaging will be centrally assessed per RECIST 1.1. The trial has 85% power to detect a PFS HR of 0.64 with α = 0.05. Clinical trial information: NCT01997333.

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**TPS1111** Poster Session (Board #219b), Sat, 8:00 AM-11:30 AM

**LOTUS: A randomized, phase II, multicenter, placebo-controlled study of ipatatasertib (Ipat, GDC-0068), an inhibitor of Akt, in combination with paclitaxel (Pac) as first-line therapy for patients (pts) with metastatic triple-negative breast cancer (TNBC)**

**First Author:** Sung-Bae Kim, Asan Medical Center, Seoul, South Korea

**Background:** The PI3K/Akt pathway is often activated in TNBC through loss of PTEN expression, low INPP4B expression, and/or amplification of AKT3. Activation of Akt may then lead to chemoresistance; thus, inhibition of Akt signaling may result in improved efficacy of chemotherapy in TNBC. Ipatatasertib (GDC-0068) is an oral, potent ATP-competitive small molecule inhibitor of all three isoforms of Akt. In preclinical breast cancer models, the combination of Ipat with taxanes enhanced efficacy. In a Phase Ib clinical study, the combination of Ipat with Pac was well-tolerated; the most commonly reported adverse events associated with Ipat were Grade 1-2 diarrhea, nausea, fatigue, vomiting, decreased appetite, and rash. **Methods:** The international (US, CA, Aus) LOTUS study (Yardley JCO, in press), where it is a poor prognostic marker (Rose CCR 2010). gpNMB is overexpressed in 20% of BC, including 40% of TNBC (Yardley JCO, in press), where it is a poor prognostic marker (Rose CCR 2010). gpNMB enhances tumor invasion and metastasis and promotes angiogenesis in preclinical models. GV is a novel antibody-drug conjugate containing the potent cytotoxin monomethylauristatin E (MMAE) to gpNMB + tumor cells. In a Phase I/II study (Bendell JCO, 2014) and the Phase II “EMERGE” study (Yardley JCO, in press), GV demonstrated promising activity, particularly in pts with TNBC and gpNMB overexpression, and was well-tolerated (treatment related toxicities: rash, neutropenia and neuropathy). In subset analyses, for GV vs. “investigator’s choice” (IC) single-agent chemotherapy, objective response rate (ORR) was 30% (7/23) vs. 9% (1/11) in pts with gpNMB overexpression (in ≥ 25% of tumor epithelium); 18% (5/28) vs. 0% (0/11) in TNBC, and 40% (4/10) vs. 0% (0/6) in gpNMB-overexpressing TNBC, with apparent improvements in progression-free survival (PFS; hazard ratio (HR) = 0.11) and overall survival (OS; HR = 0.14). **Methods:** The international (US, CA, Aus) “METRIC” study (NCT01997333) is recruiting up to 300 pts with metastatic, gpNMB-overexpressing TNBC. Eligibility criteria include: ≥ 25% tumor epithelium gpNMB + by central IHC prescreening of archival tissue; ER and PR < 10% and HER2(-)(0-1+ IHC, or ISH copy number < 4.0 / ratio < 2.0) by local assessment; ECOG 0-1; taxane resistance; and tamoxifen resistance (if indicated); ≥ 2 chemotherapy regimens for advanced BC; measurable disease; no persistent Grade ≥ 2 toxicity; and capcitabine naive. Pts are randomized (2:1) to GV (1.88 mg/kg IV q 21 days) or capcitabine, a current standard for this population (2500 mg/m2 daily for d1-q14, q21 days) until progression or toxicity. Crossover is not permitted. Endpoints are PFS (primary), ORR, duration of response, OS, safety, PK, PD (immune dynamics) and quality of life. Imaging will be centrally assessed per RECIST 1.1. The trial has 85% power to detect a PFS HR of 0.64 with α = 0.05. Clinical trial information: NCT01997333.

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Full updated results of the NRG Oncology/NSABP Protocol P-2: Study of Tamoxifen and Raloxifene (STAR) in preventing breast cancer. First Author: Donald Lawrence Wickerham, NRG Oncology, and Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA

Background: NSABP P-2 (STAR) was a randomized, double-blinded trial of tamoxifen vs raloxifene for the reduction of breast cancer incidence. The initial report from 2006 found raloxifene to be as effective as tamoxifen in preventing invasive breast cancer, but with fewer associated toxicities. In 2010 updated results indicated that raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer and remained less toxic. Methods: May 31, 2012, STAR was permanently closed to followup. This current and final update is based on data through the end of followup for invasive and noninvasive breast cancer, other cancers, vascular events, and deaths. The final analysis comprises the same 19,490 women (9736 in the tamoxifen group and 9754 in the raloxifene group) as the 2010 update report. The median time of followup as of May 31, 2012, was 9.7 yrs. Results: Similar to the previous update, raloxifene remains less effective in preventing invasive breast cancer than tamoxifen (RR = 1.19, 95% CI = 1.04–1.37). For noninvasive breast cancer, the borderline statistically significant difference between treatment groups seen in the original findings continues to decrease (RR = 1.09, 95% CI = 0.88–1.36). Raloxifene also continues to have a better profile than tamoxifen re thromboembolic events (RR = 0.80, 95% CI = 0.66–0.96) and uterine cancer (RR = 0.56, 95% CI = 0.40–0.79). There were no statistically significant differences between treatment groups for any other site of cancer. There was, however, a borderline statistically significant all-cause mortality difference between the treatment groups. The death rates per 1000 in the raloxifene and tamoxifen groups were 4.10 and 4.73, respectively (RR = 0.87, 95% CI = 0.75–0.99). Conclusions: Raloxifene has retained approximately 81% of the effectiveness of tamoxifen in preventing invasive breast cancer and continued to grow closer to tamoxifen in preventing noninvasive breast cancer. Raloxifene has also maintained a better profile with respect to uterine disease, thromboembolic events, and death. Support: U10CA137377, 69974; 180968-180922; 189867; 44066; Eli Lilly and Company; AstraZeneca Clinical trial information: NCT0003906.

Estrogen alone and health outcomes in black women by African ancestry. First Author: Rowan T. Chlebowski, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA

Background: Disparities are seen in breast cancer outcome in black compared to white women. However, in black women in the Women’s Health Initiative (WHI) randomized trial, estrogen alone significantly reduced breast cancer incidence, but its comprehensive influence on health outcomes in black women in this trial has not been reported. Therefore we examined, in post-hoc analyses, the risks and benefits of estrogen alone use in black women in the WHI randomized trial overall and by African ancestry. Methods: Of 10,729 postmenopausal women with prior hysterectomy randomized at 40 US centers, 1,616 were black, including 1,061 with >5% African ancestry determined using information from 656,852 single nucleotide polymorphisms. Participants received daily conjugated estrogen (0.625 mg) or placebo for 7.2 years (median intervention) with 13 years cumulative follow-up. Coronary heart disease (CHD) and breast cancer were primary efficacy and safety outcomes. A global index of outcomes under potential hormone influence also included stroke, colorectal cancer, hip fracture, pulmonary embolism and death. Results: Entry, black women had more diabetes, hypertension, and prior myocardial infarctions compared to white women. Black women in the estrogen alone compared to the placebo group had fewer breast cancers (17 vs. 40, hazard ratio [HR] 0.43 [95% confidence interval [CI] 0.26-0.72] and somewhat fewer thromboembolism events (23 vs. 40, HR 0.63 [95% CI 0.36-1.10], p = 0.08) (pregnancies = 0.95) and other outcomes including CHD, stroke, overall survival and the global index (HR 0.95 [95% CI 0.77-1.17]) were null without racial differences. In women with >80% African ancestry, breast cancer HR was lower (0.32 [95% CI 0.12-0.86], trend p = 0.04 for effect modification by ancestry). In black women, the estrogen global index effect was more favorable in younger (50-59 years) (HR 0.65 [95% CI 0.43-0.98] than in older women. Conclusions: In black postmenopausal women with prior hysterectomy, estrogen alone significantly reduced breast cancers with no apparent adverse influence on CHD, stroke, or mortality. Favorable estrogen alone effects were more pronounced in younger black women warrant further study. Funding: National Institutes of Health. Clinical trial information: NCT0000611.
1504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Uterine cancer (Ut Ca) following risk-reducing salpingo-oophorectomy (RRSO) in women with BRCA mutations (BRCA+): A multicenter, prospective study. First Author: Catherine A. Shiu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While RRSO is key in management for BRCA+ women, concomitant hysterectomy is not standard. Here we estimate the risk of Ut Ca in BRCA+ women following RRSO and examine the distribution of specific histologic subtypes. Methods: Data on 718 women from 35 centers who underwent RRSO with retention of the uterus were prospectively followed from latest of ascertainment, BRCA testing, or RRSO. Censoring occurred at hysterectomy, Ut Ca diagnosis, last follow-up or death. Expected cancer incidence was determined using age and race-specific SEER data, adjusted for prevalence of hysterectomy. Ut Ca were categorized into endometrioid endometrial cancer (E-EC) [e.g. endometrioid, serous endometrial cancer (SE)], and sarcoma. The observed-to-expected (Obs/Exp) ratios and lower 95% CI were calculated using a Poisson distribution test. Results: 1083 BRCA+ women were followed for a median 5.2 years. 8 incident Ut Ca were observed [4.2 Exp; Obs/Exp = 1.9, p = .06]. When stratified by subtype, there was no increased risk of E-EC [2 Obs vs 3.7 Exp; p = .29] or sarcoma [1 Obs vs 0.14 Exp; p = .13]. E-EC were observed 7.2 – 12.9 years after RRSO (0.33 Exp; Obs/Exp = 15.2, p < .0001). Tumor tissue was available from 4 BRCA1+ women. LOH and/or IHC analyses confirmed loss of BRCA1 function in 3 of 3 E-EC. In the sarcoma, BRCA1 function was retained.

Conclusions: While the overall risk of Ut Ca following RRSO does not appear to be increased, there is a small absolute increased risk of more aggressive S-EC (1.1% at 10 yrs in BRCA1+ women). Further studies are needed to define the risk/benefit of hysterectomy at time of RRSO.

1506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Statin use and all-cancer mortality: Prospective results from the Women’s Health Initiative. First Author: Ange Wang, Stanford Univ School of Medcin, South Palo Alto, CA

Background: Statin medications are widely used for lipid lowering and heart disease prevention. Retrospective studies and basic scientific evidence have suggested that statins may also reduce cancer mortality. Data from the Women’s Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) were used to investigate the association between statin use and all-cancer mortality in a prospective cohort of postmenopausal women.

Methods: The WHI-OS enrolled women aged 50-60 with no prior cancer who were enrolled in 40 U.S. clinical centers. Among 146,326 participants with median 14.6 follow-up years, 23,067 incident cancers and 3,152 cancer deaths were observed. Cox proportional hazards models were used to investigate the relationship between statin use (as a time-dependent exposure) and cancer mortality. Analyses were adjusted for age, race, ethnicity, education, smoking, body mass index, physical activity, family history of cancer, current health care provider, hormone use, age at menarche, solar irradiance, and history of heart disease/diabetes.

Results: Compared with never users, current statin use was associated with significantly decreased cancer mortality (HR 0.78; 95% CI 0.71-0.86). Use of other lipid lowering medications was associated with a similar reduction in cancer deaths compared to monotherapy statin use (p-het = 0.57). The reduction in cancer death associated with statin use was not dependent on statin potency (p-het = 0.22), lipophilic/hydrophilic (p-het = 0.43), type (p-het = 0.34) or duration (p-het = 0.33). Current statin use was associated with significantly decreased mortality of multiple cancer types, including breast, colorectal, ovarian, digestive, and bone/connective tissue cancer deaths, but not lung cancer. However, past statin users were not at lower risk of cancer death compared to never users (HR 1.06; 95% CI, 0.88-1.25). In the observational WHI-OS and Clinical Trial (WHI-CT), there were 1,958 cases of NSCLC (stage I-IV) diagnosed between 1994-2013.

Conclusions: For postmenopausal women, statin use was associated with a reduction in cancer deaths.

1507 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Post-diagnosis BMI and physical activity in association with triple-negative breast cancer prognosis: Results from 5 prospective cohorts. First Author: Sarah Jean Nychuta, Vanderbilt University Medical Center, Nashville, TN

Background: Triple negative breast cancer (TNBC), defined as ER-/PR-/HER2-, has a poor prognosis and limited targeted treatment options. Modifiable lifestyle factors, including body mass index (BMI) and physical activity (PA), have been well-studied for overall breast cancer prognosis. However, no prospective study has investigated BMI and PA in TNBC prognosis; we conducted such an analysis using data from 5 breast cancer survivor cohorts in the US, UK, and China. Methods: The pooling project included 12,240 stage I-III breast cancer cases with known ER/PR/HER2 status from 5 cohorts, with 1,695 TNBC cases (13.9%). Clinical characteristics including treatment, and lifestyle factors collected on average 1.8 years after diagnosis, were pooled and harmonized. Self-reported recreational PA, summarized in MET-hours/week, was available for 4 cohorts; weight and height were available in all cohorts. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using delayed-entry Cox regression models; stratified by cohort and adjusted for known prognostic factors. Outcomes were breast cancer-specific survival (BCSS) and overall survival (OS). Results: Among TNBCs, mean follow-up was 9.5 years (401 deaths). In adjusted models, increasing BMI (MTI-hr/wk) was associated with improved BCSS; HRs (95% CIs) by tertile (reference: < 4.1) were: 0.80(0.56-1.15) for 4.1-5.9 and 0.61(0.41-0.92) for >16.0; Ptrend = 0.02. Similar results were observed for OS (HRs (95% CIs): 0.86(0.64-1.16) for 4.1-5.9 and 0.52(0.32-0.85) for >16.0; Ptrend = 0.009). In adjusted models, a U-shaped association was observed for BMI (kg/m2) and OS (ref. = 21.5-24.9). Only the HR for BMI <21.5 was statistically significant, HR (95% CI): 1.60(1.02-2.52), however, the HR was no longer significant after exclusion of the Chinese cohort, HR (95% CI): 1.27(0.78-2.08). Conclusions: In this prospective evaluation of PA and BMI in TNBC, a trend for increasing PA and improved BCSS and OS was observed, which was not significant only for high levels of PA (equivalent to ≥ 4 h of moderate intensity PA/wk). A U-shaped pattern was observed for BMI; however, obesity was not significantly associated with survival.
Alcohol consumption and prognosis in patients with stage III colon cancer: A correlative analysis of phase III trial NCT0147 (Alliance). First Author: Amanda I. Phipps, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Alcohol consumption is associated with a modest increased risk of colon cancer (CC). The relationship between alcohol and survival after CC, however, has not been well elucidated. Using data from N0147, a phase III randomized adjunctive trial in stage III CC, we assessed the association of alcohol consumption with CC outcomes. Methods: Patients completed a risk factor questionnaire before randomization. Patients receiving FOLFOX + cetuximab (N = 19844). Information was collected on lifestyle factors, including smoking, physical activity, and the frequency and extent of alcohol consumption. Separate information was collected for different alcohol types. Multivariate Cox models assessed the association between alcohol consumption and outcomes of disease-free survival (DFS), time-to-recurrence (TRT) and overall survival (OS), adjusting for age, sex, study arm, body mass index, smoking, physical activity, and performance status. Results: Overall, 70% of patients had ever consumed alcohol regularly. There was no statistically significant difference in outcomes between ever and never drinkers in multivariate analyses [hazard ratio (HR) = 0.86, p = 0.11, HRTR = 0.87, p = 0.18, HROS = 0.86, p = 0.14]. However, when considering alcohol type, ever consumers of red wine (n = 639) had significantly better outcomes than never consumers (HRROS = 0.81, p = 0.01; HRTR = 0.81, p = 0.02; HROS = 0.78, p = 0.01). Favorable outcomes were confirmed in patients who consumed 1-30 glasses of red wine per month (n = 612): HR = 0.81 to 0.83, p = 0.03 to 0.04); there was a suggestion of more favorable (but not statistically significant) outcomes in patients who consumed >30 glasses of red wine per month (n = 27; HR = 0.3 to 0.38, p = 0.05 to 0.06). For white wine, better OS was observed in patients who consumed 1-30 glasses per month (n = 538) compared to never consumers (HR = 0.75, p = 0.007), but no association was noted for other outcomes. Beer and liquor consumption were not associated with improved outcomes. Conclusions: Although alcohol consumption was not associated with CC outcomes overall, mild to moderate red wine consumption was suggested to be associated with longer OS, DFS, and TRT in stage III CC patients.

Prevalence of incidental actionable germline mutations in 1,000 advanced cancer patients on a prospective somatic genomic profiling program. First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Next generation sequencing is increasingly used in cancer research and precision oncology. This practice may also reveal germline variants of potential clinical significance. We here report patient preferences for return of results as well as the prevalence of incidental deleterious germline mutations. Methods: Targeted exome sequencing of 202 genes was performed on tumor and normal DNA in a research laboratory. This panel included 18 genes for which return of incidental deleterious findings is recommended by The American College of Medical Genetics and Genomics. Mutations in these genes, as well as PALB2, were considered actionable. Results were confirmed with an orthogonal CLIA assay. A companion protocol determined patient preferences for return of incidental germline results. Return of results was initiated with genetic counseling and repeat CLIA testing. Results: Of 1,000 advanced cancer patients who underwent sequencing, 999 had at least one germline variant in one of the 19 “actionable” genes and 43 had likely pathogenic mutations: BRCA1 (11), BRCA2 (10), TP53 (10), PTEN (6), PALB2 (2), PTEN (2), TSC2 (1), and RBL1 (1). Only 20 (49%) of 43 mutations were known based on clinical genetic testing. The ratio of somatic to pathogenic germline mutations differed by gene; for TP53, 375 patients had somatic mutations and 10 had pathogenic germline TP53 mutations (38 to 1); for BRCA1, 96 patients had 1-30 germline mutations (5 to 1). The 22 previously unrecognized mutations identified in the research environment were re-tested with an orthogonal CLIA platform with 100% concordance of mutation and interpretation. Of 1,167 patients who consented for a germline testing protocol, 1,157 (99%) stated they would like to be informed of incidental germline results. Initial experience with return of results will be presented. Conclusions: Most patients undergoing genomic testing are comfortable with germline testing and desire return of incidental results. A significant number may have unknown pathogenic mutations. Thus, genomic testing must be accompanied by a plan for return of germline results, in partnership with genetic counseling.

Characteristics of high risk breast cancer patients with mutations identified by multiplex panel testing. First Author: Kara Noelle Maxwell, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background: Multiplex panel testing studies evaluating cancer susceptibility in breast cancer (BC) patients suggest that between 4-11% of BRCA1/2 negative individuals have a deleterious mutation in a high or moderate penetrance gene. The range in mutation positivity is likely due to heterogeneity of the studied patient populations. Methods: We performed targeted, massively parallel sequencing of 795 BRCA1/2 negative BC patients in a research laboratory and analyzed 18 cancer susceptibility genes. The high risk groups were studied: multiple primary cancers (MP, n = 315), early onset breast cancer (EOBC, n = 323), and familial breast cancer (FBC, n = 415). MP was defined as at least one BC and at least one other primary malignancy excluding non-melanoma skin cancer, EOBC was defined as BC under age 40, and FBC was defined as at least three first to third degree relatives with BC under age 75. Results: Overall, 78 patients (10%) were found to have a deleterious mutation. Mutations were found most commonly in CHEK2 (n = 32, 4.0%), ATM (n = 14, 1.8%), TP53 (n = 10, 1.3%), and MSH6 (n = 4, 0.5%). One to two patients each had deleterious mutations in BARC1, BRIPI, CDKN2A, MRE11A, MSH2, BRCA1 and 2, PTFEN, PTEN, PM52, and RAD50, no mutations were identified in CDH1, MLH1, or STK11. Deleterious mutations were more common in MP patients versus FBC patients without MP (12% versus 7%, p = 0.04) but not EOBC patients without MP (10%, p = NS). CHEK2 and MSH6 mutations were more common in EOBC patients than FBC patients (4% versus 1%, p = 0.05) whereas ATM mutations were more common in non-MP patients (6% versus 2.5%, p = 0.05). The most common cancers in mutation carriers were a second primary breast cancer, sarcoma, melanoma, hematological malignancies, ovarian, thyroid and uterine cancer. There was a similar distribution of malignancies in MP mutation carriers versus non-mutation carriers. Sequencing is ongoing for 276 additional MP patients to validate these findings. Conclusions: Our results indicate that multiplex panel testing may find a higher rate of mutations in patients with MP malignancies as compared to patients with FBC alone; however, the type of second primary malignancy may not be predictive of mutation status.
**1512 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

Identification of ERCC2 as novel susceptibility gene for hereditary breast and ovarian cancer. First Author: Pauline Wimberger, University Hospital Carl Gustav Carus, Dresden, Germany

**Background:** Breast and ovarian cancer (BC/OC) predisposition has been associated with several high-, moderate-, and low-penetrance susceptibility genes. Despite comprehensive testing by next-generation sequencing (NGS), there is still a large portion of high-risk cases with absence of mutations in any of the known susceptibility loci. Therefore, it is essential to extend the diagnostic spectrum by screening novel candidate genes.

**Methods:** Inclusion criteria for study patients (n = 717, German and Lithuanian) were defined by the German Consortium for Breast and Ovarian Cancer. NGS was performed on the Illumina MiSeq sequencer and with the Tru-Signature Cancer Panel. The mean age was 51 years (range 18-92) and 10.4% were male.

**Results:** In 19.7% of the patients, the BRCA1 or BRCA2 variants were found. These were either pathogenic-loss-of-function mutations (43%) or rare, unclassified missense variants with high probability of a deleterious effect (57%). In 17.9% of the patients we found null-mutations and rare, unclassified missense variants in the acknowledged BC/OC susceptibility genes ATM, CDH1, CHEK2, NBN, PALB2, RAD51C/D, and TP53. Analysis of the non-BC/OC genes on the NGS panel identified the "excision repair cross-complementing rodent repair deficiency, complementation group 2" gene (ERCC2) as a promising BC/OC predisposition candidate. We found 3-frame-shift mutations and 1 splice-site mutation in 24 different BC/OC families. In all individuals tested so far, ERCC2 mutations co-segregate with the occurrence of BC and OC. Additionally, we found 20 rare unclassified ERCC2 sequence variations with a cumulative allele frequency of 2.9%, which is 14.5-fold overrepresented compared to the general population (0.19%).

**Conclusions:** Our data suggest ERCC2 as a novel BC/OC susceptibility gene and provide clinical rationale for ERCC2-mutational analysis in high-risk patients with confirmed absence of mutations in known BC/OC predisposition genes.

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**1513 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

Clinical impact of multi-gene panel testing for hereditary breast and ovarian cancer risk assessment. First Author: Leif W. Ellis, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

**Background:** Genetic testing for hereditary breast and ovarian cancer is evolving with the recent introduction of multi-gene panels, although the clinical impact of such panels is not yet fully defined. For patients without BRCA1/2 mutations management is guided by personal and family history, although additional (non-BRCA) mutations can contribute additional information regarding risk for both the patient and their family members. It is unknown how often finding such mutations, including those that lack gene-specific guidelines, will potentially alter clinical management.

**Methods:** We used similar 25 or 29 gene panels to test 1112 patients enrolled prospectively as appropriate candidates for HBOC evaluation at three academic medical centers. We applied uniform criteria to analyze the clinical impact of the non-BRCA1/2 mutations observed in these patients and also in comparable patients at these centers. Primary outcome measures included the frequency and types of potential management changes based on each patient’s gene-associated cancer risks given personal/family history and established risk-based practice standards.

**Results:** The prevalence of BRCA (9.0%, CI 7.1-11.3%) and non-BRCA (3.9%, CI 2.7-5.6%) mutations was in line with previous studies and suggests that this was a representative population. The most common non-BRCA findings involved known breast/ovarian cancer genes (BRCA1, ATM, and CHEK2) and Lynch syndrome genes. Among 61 patients in all groups with non-BRCA findings, the majority would result in consideration of additional disease-specific screening and/or prevention measures for the patient (56%, 34/61) or mutation-positive first-degree relatives (76%, 47/61).

**Conclusions:** In appropriately-referred patients, multi-gene panel testing yields clinically relevant findings with potential management impact for substantially more patients than does BRCA1/2 testing alone. Thus, this approach may improve care for many mutation-affected individuals in the short term, and in the long term should lead to the development of additional evidence-based guidelines for at-risk individuals.

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**1514 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

Assessment of the clinical presentation of patients with at least two deleterious mutations on multi-gene panel testing. First Author: Jeffrey N. Weitzel, City of Hope, Duarte, CA

**Background:** Technical advances have upended the established paradigm of testing high penetrance cancer predisposition genes based on syndromic features. National guidelines now include discussion of multi-gene panels. However, significant gaps in our knowledge of gene-specific phenotypes have been identified, and thus effects of gene combinations are unknown.

**Methods:** We examined results from patients tested with a 25-hereditary cancer gene panel in a CLIA approved laboratory. Clinical history was obtained from test requisition forms completed by ordering healthcare providers. We used similar 25 or 29 gene panels to test 1112 patients enrolled prospectively as appropriate candidates for HBOC evaluation at three academic medical centers. We applied uniform criteria to analyze the clinical impact of the non-BRCA1/2 mutations observed in these patients and also in comparable patients at these centers. Primary outcome measures included the frequency and types of potential management changes based on each patient’s gene-associated cancer risks given personal/family history and established risk-based practice standards.

**Results:** Of 55,803 patients tested, 3,953 (7.1%) had a single deleterious mutation, and 106 (0.19%) had mutations in at least two genes. Breast or colon cancer was the most common diagnosis among the probands (42.8-46.8% and 23.1-26.8%, respectively), although additional (non-BRCA) mutations can contribute additional information regarding risk for both the patient and their family members. It is unknown how often finding such mutations, including those that lack gene-specific guidelines, will potentially alter clinical management.

**Conclusions:** Our data suggest ERCC2 as a novel BC/OC susceptibility gene and provide clinical rationale for ERCC2-mutational analysis in high-risk patients with confirmed absence of mutations in known BC/OC predisposition genes.

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**1515 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

Outcomes of clinical testing for 50,000 patients utilizing a panel of 25 genes associated with increased risk for breast, ovarian, colorectal, endometrial, gastric, pancreatic, melanoma, and prostate cancers. First Author: Eric T. Rosenthal, Myriad Genetic Laboratories, Inc., Salt Lake City, UT

**Background:** Genetic assessment for inherited risk is a key tool for cancer prevention. Genetic testing strategies are evolving in response to expanding information about gene associations and available technologies for the cost-effective simultaneous screening of large numbers of genes. Here we provide outcomes data from clinical testing of a large, diverse cohort of US patients using a panel of 25 genes known to be associated with an increased risk for 8 common cancers with known genetic associations. Among 61 patients in all groups with non-BRCA findings, the majority would result in consideration of additional disease-specific screening and/or prevention measures for the patient (56%, 34/61) or mutation-positive first-degree relatives (76%, 47/61).

**Conclusions:** In appropriately-referred patients, multi-gene panel testing yields clinically relevant findings with potential management impact for substantially more patients than does BRCA1/2 testing alone. Thus, this approach may improve care for many mutation-affected individuals in the short term, and in the long term should lead to the development of additional evidence-based guidelines for at-risk individuals.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Sarcoma: A Lynch syndrome (LS)-associated malignancy? First Author: John M. Kaczmar, Temple Univ/Fox Chase Cancer Ctr, Philadelphia, PA

Background: Lynch syndrome (LS) is a well characterized hereditary cancer syndrome caused by mismatch repair (MMR) deficiency of epithelial tumors. Uncertainty remains as to whether several less common non-epithelial cancers such as sarcomas may also be associated with LS. We sought to describe the incidence and characteristics of sarcomas within a sample of LS families assembled through a multi-institutional collaboration. Methods: Participating sites (n = 7) queried their databases for molecularly proven and clinical LS families with sarcoma reported in a close relative (1st, 2nd, 3rd-deg). Information on the familial underlying MMR gene mutation (MLH1, MSH2, MSH6, PMS2, or EPCAM) was collected. Results: Of 3500 LS families, 7 sarcomas were identified: 5 sarcomas in adults with no pancreatic cancer and 2 soft tissue sarcomas. Especially 2 soft tissue sarcomas. Evaluable families, 7 thyroid cancers (2 early-onset, 5 late-onset) were included. Other pedigree findings included: Muir-Torre variant LS in 14/38 (37%) families. MLH1 mutation was considered likely. In total, from 958 LS families, 55 LS-sarcoma families (5.7%) contained 58 individuals with possible (n = 16) or likely (n = 42) sarcomas. Mean age of sarcoma diagnosis was 47.1 years (range 4-87 years), with a 1:1 male to female ratio. Nearly two-thirds (62%, 35/58) of sarcomas were in MSH2+/EPCAM+ families, in contrast to the ~40% of all LS that are MSH2+. Other LS-sarcoma families were: MLH1+ (n = 12), MSH6+ (N = 3), PMS2+ (n = 3) and unknown (n = 4). Sarcoma histologies were diverse: liposarcoma, synovial sarcoma, pleomorphic stromal sarcoma, and osteosarcoma. Recurrent MSH2 mutations in presumed unrelated LS-sarcoma families included 2 known founder mutations dMLX1-6 and c.942+3A>T as well as c.1216C>T, c.2135insT, and c.1906G>C. Of the 194 evaluable patients, 7 thyroid cancers (2 early-onset, 5 late-onset), 1 adult retinoblastoma, and an MSH-H thymoma in a 55-year-old woman with 2 soft tissue sarcomas. Conclusions: From a sample of nearly 1000 LS families, our findings suggest sarcomas may be a rare manifestation of LS, especially MSH2+ LS. More research of genotype-phenotype correlations in LS is needed.

Usefulness of the patient self-administered cancer family history questionnaire in identification of gynecological cancer patients suspected of Lynch syndrome: KCOG-G1302 study. First Author: Ryutaro Nishikawa, Nagoya City University, Nagoya, Japan

Background: Detailed family history collection is necessary to detect gynecological cancer patients suspected of Lynch syndrome (LS). However, clinicians have little time for family history interviews. In addition, there is a lack of genetic counselors in Japan. Therefore, information from medical records on the first visit (MR) is insufficient to determine if a patient may be at risk of LS. We showed that using the self-administered cancer family history questionnaire (SACFHQ) improves identification of patients suspected of LS. Methods: We recruited endometrial or ovarian cancer patients already diagnosed or newly diagnosed from research participating institutions. After consent was obtained, participants completed the questionnaire. By referring to the cancer family history obtained from MR and SACFHQ, we referred to cases that met the Amsterdam criteria II (AMSII), the SGO20-25% criteria (SGO20), ACOG’s clinical bulletin 2014 criteria (ACOG2014), and the SACFHQ criteria. Results: Among 455 patients, 38 patients were excluded by exclusion criteria. Finally, 455 were eligible. Median age at diagnosis was 56 (range 21-84). 243 participants were endometrial cancer patients, and 213 were ovarian cancer, including peritoneal and tubal cancer. 12 cases had either synchronous/metachronous endometrial cancer and/or endometrial cancer and colorectal cancer, and 12 cases had either synchronous/metachronous endometrial cancer and either synchronous/metachronous ovarian cancer and colorectal cancer. Among these 16 cases, endometrial or ovarian cancer was sentinel in 8 cases. By using MR, 0/455 (0%), 4/455 (0.9%), and 170/455 (37%) cases met AMSII, SGO20-25%, ACOG2014 criteria, respectively. By using SACFHQ, 6/455 (1.3%), 9/455 (2.0%), and 217/455 (48%) cases met AMSII, SGO20-25%, ACOG2014 criteria, respectively. All 6 cases that met AMSII were endometrial cancer patients. 8 of 9 patients who met SGO20-25% were endometrial cancer patients, and one patient was ovarian cancer. Conclusions: Family cancer history obtained from MR was shown to be insufficient to identify individuals at risk of LS. SACFHQ improves identification of gynecological cancer patients suspected of LS. Clinical trial information: 000013192.
Modifiable metabolic markers c-peptide (C-PeP), highly sensitive c-reactive protein (hsCRP), leptin (LEP) and lung cancer (LC) risk: A matched case-control study nested in the prostate, lung, colorectal and ovarian (PLCO) cancer screening study. First Author: Pamela Jean Goodwin, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada.

Background: LC is not associated with obesity; however, metabolic factors have been inconsistently associated with LC risk or death in previous small studies (involving <100 LC cases). We investigated pre-diagnosis (C-PeP, hsCRP and LEP) and LC risk in EVER and NEVER smoking PLCO participants. Methods: 986 LC cases and 2054 controls (matched for age, gender, race/ethnicity, study center, duration in study, smoking status (never, former and current smoker) and provider billing zip code) were included. Pre-diagnosis data was used (≥3 yrs in 75%). After storage at -80°C, C-PeP, hsCRP and LEP were assayed using Luminex xMap Multiplex immunoassays. Log transformed continuous blood markers were analyzed using multivariable conditional logistic regression (that included family history LC (FH), COPD, and smoking intensity, duration and quit-time). Tail P ≤ 0.05 was considered significant. Results: Cases (854 NSCLC, 132 SCLC) and controls had similar age (64 yr) and ethnicity (90% white); cases had more smoking pack years (57.4 vs 39.6, P < 0.001). In EVER smokers (89.2% of total), LC cases (vs controls) had higher mean C-PeP (976.9 vs 939.4 pmol/l, P = 0.02), hsCRP (22.6 vs 18.3 mg/L, P = 0.001) and LEP (7.7 vs 8.1 ng/ml, P = 0.001). Multivariably, higher C-PeP (p = 0.049) and hsCRP (p = 0.001) but lower LEP (p = 0.001) were associated with LC (Odd Ratios (OR) for upper vs lower quartiles 1.23, 1.4-3.3, P = 0.0003). Metabolic markers were not associated with LC in NEVER smoking EVER vs NEVER smokers. Conclusions: In EVER smokers, higher pre-diagnosis C-PeP and hsCRP were associated with higher LC risk; inverse associations were seen with LEP. This suggests an underlying genetic mechanism may predispose persons with these traits to develop LC. Future research should replicate our findings and investigate biologic mechanisms. Because these factors are potentially modifiable, intervention studies may be warranted.

Family history of breast cancer in Hodgkin disease and future risk for breast cancer. First Author: Sarah Violet Colonna, George E. Whalen VA, Salt Lake City, UT

Background: Women with Hodgkin disease (HD) who undergo thoracic radiation have an extremely high risk of breast cancer (BC), up to 5x6 that of the average woman. family history (FH) of BC is also associated with an increased risk of BC. However, we do not know if increased risk is observed in family members. We investigated BC risk among HD patients and relatives of women with HD. Methods: Using a genealogical database linked to Utah cancer data from 1966-2011, hazard ratios from Cox models were used to estimate BC risk among first-degree relatives (FDR) of women with HD. Using a separate database, we compared female HD probands with BC (N = 43) and HD probands without BC (N = 837) to population-based controls age-matched to 10:1. Results: The ‘baseline’ BC risk in FDR among BC patients in the Utah population (with no HD) is 1.8-fold (95% CI: 1.7-1.8, P < 0.0001). Among women with HD diagnosed before 2000 (higher radiation exposure) and with subsequent BC, their FDRs are at 4-fold BC risk (95% CI: 1.9-8.1, P < 0.0001) compared to controls. Conversely, women with HD have markedly higher BC risk if they have FDR with BC compared to controls (HR = 9.1, 95% CI: 6.1-13.7, P < 0.0001) and 2-fold BC risk compared to HD patients with no FDR with BC (95% CI: 0.96-5.2, P = 0.06). Conclusions: FDRs of women with HD and BC are at increased risk to develop BC beyond the general population risk seen in women with HD. Consistently, we found a very pronounced increase in BC among HD patients with FDRs with BC and 2x BC risk compared to HD patients with no BC in FDRs. This suggests an underlying genetic mechanism may predispose women with HD and their relatives to an increased risk for BC. Obtaining a family history at HD diagnosis may help personalize treatment around radiation therapy. Future investigation into HD treatment details related to familial and genetic for BC risk is warranted.

BC risk among relatives and HD probands vs. controls.

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Clinical outcomes based on multigene profiling in metastatic breast cancer patients. First Author: Reva Kakkar Basho, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Identifying the clinical impact of mutations in cancer-related genes can help define their role in cancer. Here, we aim to classify frequent hotspot mutations in metastatic breast cancer (MBC) patients and determine how they may affect clinical outcomes. Methods: Hotspot mutation testing was conducted in 500 MBC patients using an 11 gene Sequenom (N 126) and/or 46 or 50 gene Ion AmpliSeq Panel (N = 391). Patients were stratified by hormone receptor (HR) and HER2 status, type of therapy (chemo, endocrine or targeted therapy) and line of therapy. Clinical outcomes including recurrence-free survival from diagnosis (RFS) and time to treatment failure due to progression (TTP) were retrospectively collected, and comparative analysis between patients who did and did not harbor mutations in certain genes was conducted. Results: The most frequent genes with hotspot mutations were TP53 (30%), PIK3CA (26%) and AKT1 (4%). Triple-negative breast cancer patients had the highest incidence of TP53 (58%) and the lowest incidence of PIK3CA (8%) mutations. TP53 mutation was associated with significantly shorter RFS (median 19 vs 41 months; P < 0.001) and second-line (median 4 vs 7 months; P = 0.006) therapy and TTP with chemotherapy (median 6 vs 8 months; P = 0.005) and targeted therapy (median 4 vs 14 months; P = 0.009) in the first-line setting. Conversely, presence of PIK3CA mutation did not significantly affect RFS or TTP, first-line or second-line. In HR-positive tumors, TP53 (N = 6) was associated with significantly shorter RFS (median 24 vs 46 months; P < 0.001), distant RFS (median 30 vs 46 months; P = 0.002) and local-regional RFS (median 51 vs 131 months; P < 0.001). However, there was no significant association between TTP and mutation status of TP53, PIK3CA or AKT1 in HR-positive patients treated with endocrine therapy in the first- or second-line setting. Conclusions: Correlating clinical outcomes with the presence of hotspot mutations in cancer-related genes can help define the clinical significance of these mutations. In this cohort of MBC patients, TP53, the most frequent hotspot mutation, was associated with worse clinical outcomes, both overall and in HR-positive patients. Clinical trial information: NCT01772771

Amplification of CRKL in human cancer: A rare event associated with potential sensitivity to targeted therapy. First Author: Kai Wang, Foundation Medicine, Inc., Cambridge, MA

Background: CRKL amplification (amp) has been linked to tumor progression and resistance to targeted therapies in solid tumors. Recent evidence suggests that CRKL amp may mediate resistance to EGFR inhibitors and may be associated with exceptional tumor response to Src kinase inhibitors. Moreover, germline-based comprehensive genomic profiling (CGP) using hybridization capture of 236 cancer-related genes was applied to > 50 ng of DNA extracted from 33,000 FFPE specimens and sequenced to high, uniform median coverage (> 600X) and assessed for base substitutions, INDELs, copy number alterations and rearrangements. Clinically relevant genomic alterations (CRGA) were defined as those for which a causal role in cancer could be attributed, either through germline or somatic testing. Methods: CGP results were collected from a laboratory database. Sanger sequencing was performed to confirm mutations identified through sequencing. Results: CRKL amp was identified in 274 (0.8%) patients of median age 62 years (range 19-92) with 137 females and 63 males. There were 18 distinct tumor types featuring CRKL amp as shown in the table below. Co-existent CRGA associated with CRKL amp cases with CRKL amp as show in the table below. Co-existent CRGA associated with CRKL amp cases with CRKL amp treated with targeted therapies will be presented. Conclusions: CRKL amp is a newly described cancer driver that may mediate resistance to EGFR inhibitors. Identification of specific somatic and potentially germline CRGA in cancer patients treated with EGFR inhibitors may provide therapeutic opportunities for personalized treatment of patients carrying CRKL amp.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Comparison of genotyping performance in DNA extracted from matched FFPE tumor, FFPE lymph node, and whole blood for pharmacogenetic analyses. First Author: Daniel Louis Hertz, University of Michigan, Ann Arbor, MI

Background: Pharmacogenomics requires genetic information from patients’ germline DNA. There is concern that DNA extracted from formalin-fixed paraffin embedded (FFPE) tumors may not accurately represent germline DNA due to somatic genetic alterations and technical challenges. Our objective was to compare genotyping performance for DNA isolated from FFPE tumor (T), FFPE non-cancerous lymph node (LN), and whole blood (WB) to determine the extent and source of genotyping inaccuracy in FFPE tumors (T). Methods: Single nucleotide polymorphisms (SNPs) from genes that affect drug elimination, efficacy, and toxicity were genotyped on Sequenom MassArrays using DNA isolated from matched T, LN, and WB samples obtained from patients with early stage breast cancer. The no-call rate was calculated for each tissue type and the discordant call rate was calculated for T and LN by comparison with the WB genotype. Results: After quality control, matched samples from 114 patients were genotyped for 247 SNPs in 80 genes. The no-call rate in T (4.3%) was greater than LN (3.0%) and both were greater than WB (0.5%). The discordant rate in T (1.1%) was greater than LN (0.3%). Samples with heterozygous genotypes were more likely to be no- or discordantly-called than homozygous samples (all p < 0.001, Table). Conclusions: FFPE T no- and discordant-call rates were acceptable (<5%), though higher in heterozygous samples, suggesting that somatic genetic alterations and FFPE storage have minimal effect and/or FFPE T samples contain sufficient normative tissue for germline genotyping. FFPE T samples can be used in pharmacogenetic research, however, certain genes that are highly altered in somatic tissue require germline specimens and inaccurate genotyping of heterozygous samples precludes use of FFPE T for clinical pharmacogenomics.

No and discordant call rates in each sample type.

<table>
<thead>
<tr>
<th></th>
<th>T</th>
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<tr>
<td>No Calls</td>
<td>4.3% (122/2815)</td>
<td>3.0% (843/2815)</td>
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<td>9.5% (264/2815)</td>
<td>4.0% (112/2815)</td>
<td>0.5% (14/2815)</td>
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<tr>
<td>Discordant</td>
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<td>0.3% (85/2815)</td>
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Discordant Calls

<table>
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<tr>
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<td>All Pts (n = 236)</td>
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<td>176 (93.6%)</td>
<td>22 (43.8%)</td>
<td>22 (43.8%)</td>
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<tr>
<td>Any Trial</td>
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<tr>
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<td>176 (93.6%)</td>
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<td>NCI-MATCH</td>
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<td>22 (43.8%)</td>
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</table>

Patient-reported outcomes associated with population-based Jewish genetic testing for BRCA1 and BRCA2. First Author: Kelly A. Metcalfe, University of Toronto, Toronto, ON, Canada

Background: Population based genetic testing for common Jewish mutations in BRCA1 and BRCA2 has been proposed, however it is unclear what the outcomes associated with population-based testing are. Methods: 6108 unselected Jewish women in Ontario were offered genetic testing for three common Jewish BRCA mutations. Cancer-related distress was measured prior to testing, and at one and two years post-testing. Information on uptake of cancer risk reduction options was collected at two years post-testing. Results: Of the 6108 Jewish women tested, 1.1% were found to have BRCA mutation (0.4% BRCA1 and 0.7% BRCA2). None of these women had a previous cancer diagnosis and 62% of the women would not have been eligible for testing based on current criteria. Of the 68 women identified with a BRCA mutation, 3 breast cancers and 1 ovarian cancer were identified on first screenings. Within two years of testing, 28% of women had prophylactic mastectomy and 72% had a prophylactic oophorectomy. Cancer-related distress was significantly higher at one-year post-testing for those with a mutation (mean 20.0, SD = 15.3) compared to those without (mean 9.8, SD = 13.9) (p < 0.0001). For women with a BRCA mutation, cancer-related distress declined significantly from one year to two-years post genetic testing (p = 0.01). Satisfaction with population based genetic testing was high (mean 4.1; 1 = extremely satisfied to 5 = extremely satisfied). After identification of the 68 women with carcinogenic mutations, 29 (43%) women with 128 additional BRCA1 and 2 BRCA2 mutations, of which 90 were tested (70%) and 32 additional BRCA carriers were identified. Conclusions: Population based Jewish genetic testing for BRCA1 and BRCA2 is effective at identifying unaffected women with mutations who otherwise would not be eligible for testing, in addition to their first degree relatives. The majority of women elect for risk reduction surgeries after learning of their BRCA mutations. Increased levels of cancer-related distress in BRCA carriers are transient and decline at two years post genetic testing. We propose that population based genetic testing for BRCA1 and BRCA2 be made available for Jewish individuals who wish to be tested.
Somatic mutation profiling of advanced breast and ovarian cancers according to germline BRCA1/2 mutation status.

**Background:** The risk of breast cancer (BC) and ovarian cancer (OC) is increased in germline BRCA1/2 mutations carriers (BRCA+). We investigated the somatic mutation profile and clinical impact of targeted sequencing in advanced BC and OC patients (pts) according to germline BRCA1/2 status.

**Methods:** Targeted sequencing with Illumina MiSeq TruSeq AmpliSeq Cancer Panel (48 non-homologous 5’ transcripts, 212 amplicons, ≈500x coverage) was performed using archival tumor and germline DNA from advanced BC and OC pts through an ongoing institutional molecular screening program (NCT01505400). Medical records were retrospectively reviewed for clinical, pathological and germline BRCA1/2 testing results.

**Results:** From May 2013 to Oct 2014, somatic TSACP testing was completed in 257 pts (106 BC and 151 OC). Germline BRCA1/2 testing was performed in 118 pts (35 BC [33%] and 83 OC [55%]), primarily in those with family history and/or young age at diagnosis. Among these, 25 pts were BRCA+ (21%), including 4 BC (11%; 25 triple negative [TN] and 21 OC [25%, all type 2]) pts. The BRCA-lunked group (BRCA/-UK) comprised 102 BC (24% TN and 76% non-TN) and 130 OC (31% type 1, 68% type 2) pts. Using the TSACP, 188 pts (73%) had ≥1 somatic hotspot mutation with no difference in the number of somatic mutations detected in BRCA+ vs BRCA/-UK (median 1, range 0-3; p = 0.85). More BRCA+ pts had TP53 hotspot mutations compared with BRCA/-UK pts (76% vs 50%, p = 0.01). Somatic hotspot mutations in PIK3CA were more frequent in BRCA/-UK vs BRCA+ (22% vs 4%, p = 0.04). After a median follow up of 8 months, 12 BRCA/-UK pts vs no BRCA+ pts were enrolled in somatic genotype matched targeted clinical trials (53% vs 0%, p = 0.62). Seven BRCA+ pts received PARP inhibitors on clinical trials. **Conclusions:** In pts with BRCA+ BC and OC, TP53 mutations are common while PIK3CA or other hotspot somatic mutations are rare. Whether the association between germline BRCA1/2 and hotspot mutation status is causal or confounded by histological subtypes should be evaluated in larger cohorts. Broadger genetic profiling may further highlight biological differences amongst BRCA+ and BRCA- tumors and provide more opportunities for genotype-treatment matching.

Evaluation of rapid whole-body magnetic resonance as screening strategy for early cancer detection in 57 Brazilian Li-Fraumeni syndrome patients.

**Background:** Li-Fraumeni Syndrome (LFS) is a rare autosomal dominant syndrome associated with germline mutations in TP53 gene. Carriers have a high risk for developing multiple early onset cancers, most commonly breast cancer, sarcomas, brain and adrenocortical carcinomas. Screening strategies for early diagnosis in carriers constitute a major challenge due to genetic modifiers, tumours occur at a later age in p.R337H carriers. Due to genetic modifiers, screening for early cancer detection in 57 Brazilian Li-Fraumeni syndrome patients. Evaluation of rapid whole-body magnetic resonance as screening strategy for early cancer detection in 57 Brazilian Li-Fraumeni syndrome patients.

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Do women with BRCA1 or BRCA2 mutations have reduced ovarian reserve?  
First Author: Kelly-Anne Phillips, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia

Methods: Eligible women were from families segregating BRCA1 or BRCA2 mutations enrolled in the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (KCoFab). Each woman had been tested for the family mutation and had completed an epidemiological questionnaire and provided a blood sample at cohort entry. Women aged 25-45 years, had no personal history of invasive cancer, had two intact ovaries and were not pregnant or breastfeeding at the time of blood draw. AMH was tested on stored plasma samples using an electrochemiluminescence immunoassay platform. Higher AMH levels are associated with greater ovarian reserve. Associations between AMH level and carrier status were tested by linear regression, using the natural logarithm of AMH as the outcome variable, carrier status as the explanatory variable, and adjusting for age at blood draw, oral contraceptive use, BMI and cigarette smoking. Robust standard errors were estimated to account for the inclusion of multiple members from the same family.

Results: AMH level was measured for 172 carriers and 216 non-carriers from families carrying BRCA1 mutations, and 147 carriers and 158 non-carriers from families carrying BRCA2 mutations. Within both groups, mutation carriers were younger at blood draw than non-carriers (p = 0.031). Age was negatively associated with AMH level for carriers and non-carriers of BRCA1 and BRCA2 mutations (p < 0.001). BRCA1 mutation carriers had, on average, 25% lower AMH levels than non-carriers (p = 0.022). There was no evidence of an association for BRCA2 mutation carriers (p = 0.349). Results did not change substantially after excluding women who were post-menopausal or taking oral contraceptives at blood draw. Conclusions: This study suggests that women with a germline mutation in BRCA1 have reduced ovarian reserve. This could have implications for their fertility and family planning.
Germline variation in NFE2L2/CUL3/KEAP1 and risk of head and neck squamous cell carcinoma (HNSCC). First Author: Siddharth Sheth, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) is a key transcription factor regulating oxidative stress. Activated NFE2L2 translocates to the nucleus and binds anti-oxidant response elements in the promoter regions of cytotoxic protective genes. It is negatively regulated by its protein complex partners, CUL3 and KEAP1. Recent HNSCC genome profiling studies identified NFE2L2, CUL3 and KEAP1 as recurrent somatically altered genes, suggesting an important role in HNSCC carcinogenesis. We hypothesized that germline variation in NFE2L2, CUL3 and KEAP1 affects risk of HNSCC. Methods: The study population consisted of 751 cases (459 oral cavity, 292 oropharynx; 69% smoker) and 862 controls (50% smoker) from the University of Pittsburgh HNSCC case-control study. Subjects were genotyped for 22 single nucleotide polymorphisms (SNPs) located in or near NFE2L2 (10), CUL3 (8) and KEAP1(4) using Sequenom's iPLEX assay. Odds ratios (OR) for HNSCC risk and corresponding 95% confidence intervals (CI) were calculated using logistic regression models. Additive and dominant genetic models were evaluated; common allele homozygotes were used as the reference group. All analyses were adjusted for age (continuous), sex (male, female), smoking status (never, ever) and alcohol use (never, ever). Results: Two SNPs in NFE2L2 (rs13001694, rs6726395) and two SNPs in CUL3 (rs14666723, rs3738952) were significantly associated with HNSCC risk in our study population (p<0.05). The minor alleles of these SNPs were associated with increased risk of developing HNSCC (rs13001694, OR: 1.16, 95%CI: 1.00-1.35; rs6726395, OR: 1.17, 95%CI: 1.02-1.35; rs14666723, OR: 1.27, 95%CI: 1.03-1.56; and rs3738952, OR: 1.54, 95%CI: 1.20-1.98). Conclusions: Our results suggest that germline variation in the NFE2L2/CUL3/KEAP1 pathway affects risk of developing HNSCC. Improved understanding of the role of genetic variation in HNSCC carcinogenesis may aid the development of more effective, personalized prevention and diagnostic strategies.

Genetic testing decisions of breast cancer patients: Results from the iCanCare study. First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI

Background: Breast cancer pts at high risk for pathologic genetic mutations should consider testing. Even those without elevated risk may have concerns about genetic predisposition. Little is known about cancer pts' decisions to undergo genetic testing as access to multiple gene panels and rising awareness transforms the decision-making context. Methods: We surveyed a population-based sample of early-stage breast cancer pts diagnosed in 2013-14, identified by 2 SEER registries (Los Angeles and Georgia), about experiences with genetic testing after diagnosis. Surveys were completed about 6 months after dx. A “high risk” subgroup was determined based on age, family history, and ancestry, and receptor status. We evaluated patterns of receipt of counseling and correlates of testing in a preliminary sample (response rate 68%). Results: Among 2,051 pts analyzed, 728 (35%) were “high risk.” Most high risk pts (67%) and half (50%) of others desired testing. Most high risk pts (63%) and 38% of others spoke to a physician or other health care professional about testing. Overall, 23% reported formal genetic counseling (34% of high risk pts, 18% of others), and 28% received testing (46% of high risk pts, 19% of others). On multivariable analysis, test receipt was more common in pts with high risk, invasive vs in situ disease, and higher education. Among high risk pts, non-receipt of testing was associated with situ vs. invasive disease (OR 1.8, p = .02), no family hx of breast cancer/OR 2.4, p < .005), no family hx of colorectal cancer (OR 1.9, p < .001), inverse association with Medicaid insurance (OR 0.5, p = .05), and Medicaid insurance (OR 2.0 vs private, p = .03). Of 362 high risk pts who did not get tested, 54% indicated their doctor didn’t recommend it, 10% didn’t want it, and 12% said it was too expensive.

Conclusions: Most newly diagnosed breast cancer pts desire genetic testing, but many do not discuss it with providers. Most high risk pts do not report formal genetic counseling; a substantial number report no discussion of genetic risk at all. Test receipt is reassuringly correlated with risk but also with SES. Providers must ensure that breast cancer patients with interest in genetic risk have adequate discussion, especially as access to more expensive testing soars. Funding: P01-CA-163233.

Assessment of functional impact of germline BRCA1/2 variants located in noncoding regions in families with breast-ovarian cancer predisposition. First Author: Elizabeth Santana dos Santos, Hospital Sírio Libanés, São Paulo, Brazil

Background: The molecular mechanism of cancer susceptibility remains unclear for the majority of breast and/or ovarian cancer patients. The screening of the key genes BRCA1 and BRCA2 identifies a causal mutation in less than 15% of the families tested. Even if some germline mutations in the regulatory non-coding regions of these genes have been described, their screening is still limited to the coding regions and intron-exon junctions. The aim of this study was to evaluate the potential contribution of non-coding variants on the BRCA1/2 promoter activity and then in breast-ovarian cancer predisposition. Methods: The variants tested were selected from the ENIGMA database (Evidence based Network for the Interpretation of Germline Mutant Alleles) and from the screening of 2 co-horts of patients with BRCA1/2 negative status and whose personal and/or family history suggested a breast-ovarian cancer predisposition. The latter was performed on 4 BRCA1/2 non-coding regions (promoter regions and intronic regions). The impact of the variants on the BRCA1/2 gene expression was tested in vitro, after transient transfection in MCF-7 and MDA-MB231 breast cancer cells, by Luciferase gene reporter assay. Results: A total of 12 BRCA1 and 8 BRCA2 variants were tested. We delimited a BRCA1 promoter region with 3 functionally active variants with a clear repressor impact on the promoter activity. This DNA sequence region corresponds to a R-spondin (DPI2/F) transcription factor binding site, which has never been described before. One BRCA2 variant in the promoter also showed a significant reduction in the transcriptional level. Two BRCA1 in the promoter and in intron 2 and 2 BRCA2 variants in the promoter increased the promoter activity. All the others were shown to have no impact in our functional assay. Conclusions: Through Luciferase gene reporter assay, we identified 8 non-coding and rare variants with a significant impact on BRCA1/2 promoter activity, 3 of them showing a significant reduction in the transcriptional levels. As further investigation is needed, this approach has helped us to prioritize the studies on those variants.

Transgenerational genomic effect of chemotherapy exposure in testicular cancer survivors. First Author: Eliezer Mendel Van Allen, Dana-Farber Cancer Institute, Boston, MA

Background: Cancer survivors who receive chemotherapy express concern that these exposures may induce germ cell mutations that lead to transmissible genetic damage in post-treatment children. Preclinical models suggest these regimens induce mutations in critical cellular pathways involved in the remodeling phase of spermatogenesis (e.g., elevated mutation rates, chromosomal abnormalities). Epidemiological studies have not demonstrated a significant increase in congenital abnormalities or genetic syndromes in post-treatment children of cancer survivors, although comprehensive genomic assessments have not yet been performed in this patient population. Methods: We identified two testicular cancer survivors who were cured with chemotherapy and had children before and after therapy without cryopreserved sperm. We acquired saliva from patients and their families and performed whole genome sequencing (WGS) from extracted DNA. Genome analysis and de novo mutation discovery were performed using established methods. Results: Genomes were sequenced to 50X mean depth. There was no increase in the de novo mutation burden of post-exposure children compared to their pre-exposure counterparts (Table). In fact, post-exposure offspring born two years after treatment had fewer de novo mutations than pre-exposure counterparts. There were no differences in recombination frequency or rearrangements between offspring. Conclusions: In two families of male cancer survivors, there was no genomic alteration increase in post-exposure children. The lower de novo mutation rate in early post-treatment children may indicate heightened selective pressure, especially when accounting for increasing paternal age. This study provides possibly reassuring evidence for patients undergoing chemotherapy who are unable to have pre-treatment sperm cryopreservation. Broadly, this study illustrates the potential for using WGS to identify environmental cancer treatment effects on the inherited genome.

Offspring data.

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Posterior Session (Board #368), Mon, 1:15 PM-4:45 PM

Somatic mutations in Luminal HER2 negative tumors from young breast cancer patients. First Author: Giselly Encinas, Departamento de Radiología e Oncología, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background: Early age patients less than 36 years represent 4% of breast cancer cases and have a higher probability of being BRCA1/2 mutation carriers. There are indications that tumors from young patients are biologically distinct from older women, however, these tumors have been less studied. Our aim was to identify somatic mutations in luminal tumors from BRCA1/2 wild type young breast cancer patients.

Methods: Seventy-nine unselected young patients were enrolled. BRCA1/2 mutations were screened by Sanger sequencing and Multiplex Ligation-Dependent Probe amplification (MLPA). Tumor and blood samples from eight patients (hormone receptor positive, HER2 negative) were selected for whole exome sequencing using Nextera Rapid Capture Enrichment in an Illumina HiSeq 1000, analyzed through MuTect (v1.14), SomaticSniper (v1.0.2) and Strelka (v1.0.12). Results: Median age of the 79 patients was 32 years (22-35) and luminal subtype was the most frequent (63.1%). Deletions in BRCA1/2 genes were detected in 13 patients (BRCA1, n = 4 and BRCA2, n = 9). One novel mutation was detected in BRCA1 gene; a stop codon in exon 6 (c.483T > A; p.Cys161Ter). Somatic mutations were evaluated in eight luminal samples and a median of 60 alterations/tumor was detected, varying from 49 to 113. A total of 537 individual genomic alterations were found, comprising 77 non-synonymous and four nonsense based on mutation in 26 different non-synonymous codons.

Conclusions: Besides BRCA1/2 mutation, which is the most frequent alteration in luminal tumors, and TP53 mutation, at least five other different driver genes may be mutated in tumors from young breast cancer patients.

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Posterior Session (Board #370), Mon, 1:15 PM-4:45 PM

Evaluation of family history in newly diagnosed children with cancer. First Author: Kinley Garfield, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT.

Background: The collection of cancer family history (FH) is a key component for risk assessment in adult cancer patients, but is not routine in pediatric oncology. We collected FH on all newly diagnosed pediatric cancer (PC) patients presenting to a single children's hospital to determine the feasibility of FH collection and risk prevalence for hereditary cancer syndromes.

Methods: Parents of newly diagnosed children (age 0 to 20) were approached for enrollment and given a FH questionnaire to complete and return by mail assessing FH in first- and second-degree relatives. A genetic counselor contacted all participants by phone to review the reported history or to obtain a FH from those who did not return the form. Criteria for genetic referral were based on NCI guidelines and reviewed criteria. Results: Of the 91 families that completed a FH, 24 (26%) were considered eligible for further genetic risk evaluation. 16 (17%) warranted referral based on the child's tumor type or personal/FH criteria, 8 (9%) children did not meet criteria but had a first- or second-degree relative who met criteria for referral. 10 of 16 children meeting criteria were seen for genetic counseling.

Conclusions: Collecting FH at the time of diagnosis is feasible and identifies at risk individuals for cancer predisposition. Approximately 30% of newly diagnosed PC patients meet criteria for further genetic risk evaluation. This is consistent with data from a survivorship clinic reported by Knapke et al. (2011), although our study enrollment occurred at diagnosis and is not biased by patient mortality. These findings support a high rate of genetic predisposition related to childhood cancer (at least 1 in 4), and highlight the importance of obtaining an accurate FH at the time of initial diagnosis.

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Posterior Session (Board #369), Mon, 1:15 PM-4:45 PM

Patient interest and willingness-to-pay (WTP) out-of-pocket (OOP) for comprehensive tumor genetic profiling (CGP). First Author: Julie Innocent, Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA.

Background: CGP via multiplex gene panels has emerged as a novel technology to identify mutations in pathologically relevant cancer genes for therapy targeting. While CGP is anticipated to alter the course of standard cancer care, its current clinical role remains ill-defined, and thus its perceived value for patients is unclear. In an effort to understand patient awareness and perceived value of CGP, we explored interest and WTP OOP for CGP among cancer patients receiving active treatment. Methods: Fox Chase patients were recruited to complete a 20 min survey. In addition to assessing demographics, cancer stage/treatment, and financial items (income, health insurance, co-pays), we queried awareness of CGP, and interest in CGP to guide therapy using items adapted from previous research by our group. We specifically assessed interest in CGP only if covered by insurance vs interest conditional on paying an OOP cost: (< $200, $500, and > $1000). All p-values are significant at α = 0.05 using two-sided Fisher’s exact tests. Results: Participants were 88 patients of diverse cancer histology, time since diagnosis (51% > 2yrs), therapy line (60% > 2nd line) age (mean 58.9 yrs), sex (38%) female, race/ethnicity (20% non-White), family structure (64% married; 21% no children), education (27% < high school (HS)), and financial status (37% income < $50,000; 38% Medicare/85% Medicaid; 40% reporting difficulty paying co-pays). 61% were aware of CGP, and 67% believed it could improve their treatment. In total, 79% were interested in CGP, with interest higher in younger (p < 0.005) and privately insured (p = 0.01). Patients with < HS education were less WTP OOP for any costs for CGP beyond those covered by insurance (p = 0.05). Those with income > $50K (p = 0.06) and private insurance (p = 0.001) were more WTP. Of those WTP OOP, 44% were WTP < $200, while 24% were WTP $500 and 32% WTP > $1000. WTP $500 or > $1000 for CGP was associated with White race (p = 0.05), education > HS, income > $50K, and private insurance (all p < 0.001).

Conclusions: Patients are interested in CGP and believe it can improve their cancer treatment. Those with lower income, less education and non-private insurance may be less likely to pursue CGP if accompanied by OOP costs.
Rare germline TP53 variants in lung adenocarcinoma. First Author: Erin Michelle Parry, Osher Medical Housestaff Training Program, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

Background: TP53 is one of the most commonly altered genes in lung adenocarcinoma, with as many as 50% of all cases possessing somatic inactivating mutations. Germline mutations in TP53 predispose to a wide variety of cancers in Li-Fraumeni syndrome. While lung cancer is generally not considered a classic Li-Fraumeni malignancy, several studies have indicated it may appear at an earlier age in this cancer-prone syndrome.

Methods: We tested the frequency of germline TP53 mutations in an unselected cohort of lung adenocarcinoma cases sequenced as part of The Cancer Genome Atlas (TCGA) project. At the time of data access (October 1, 2014), germline exome and genome data were available for download from 531 subjects, and clinical information was available on 94% of these cases (n = 497). After Data Access Committee approval, we extracted raw bam files that included the TP53 sequence, called and annotated the variants. We considered variants with high (greater than 20x) coverage, and then excluded those with a minor allele frequency of 0.005 or greater in control populations. Suspected pathogenic variants were then confirmed by examining the matched tumor sequence data or a replicate normal tissue sample using the same methods.

Results: Four cases carried germline missense variants in TP53 (0.8%), and all of them fell in the DNA binding domain. Three of the mutations were previously described in Li-Fraumeni syndrome and all of mutations have been reported as somatically mutated in various cancers. The mean age at lung cancer diagnosis was 58 years (range 41-73) and one individual was male. One of the cases was a never smoker (female), and another subject had a prior history of thymic carcinoma, a diagnosis that has been documented in Li-Fraumeni syndrome.

Conclusions: Our data suggest that a subset of lung adenocarcinoma patients carry germline mutations in TP53, pointing to a role for inherited factors in lung cancer susceptibility. This diagnosis may be overlooked in cases where genomic data is filtered for background germline variants, and is relevant for genetic counseling and screening decisions.

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1550 Poster Session (Board #374), Mon, 1:15 PM-4:45 PM

The impact of a molecular tumor board on treatment decisions for 35 patients: The Dartmouth experience. First Author: Laura J. Tafe, The Geisel School of Medicine at Dartmouth and Dartmouth Hitchcock Medical Center, Lebanon, NH

Background: Genetic profiling of tumors is a powerful approach to predict drug sensitivity and resistance. However, oncologists are often unfamiliar with interpretation of genetic data. We established a Molecular Tumor Board (MTB) at our Cancer Center to interpret individual patients’ tumor genetic profiles and provide treatment recommendations. Methods: DNA from tumor specimens was sequenced in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory to identify coding mutations in a 50-gene panel (n= 34), or a 255-gene panel (n= 1). Cases were evaluated by a MTB composed of molecular and anatomic pathologists, medical oncologists, basic research scientists, and genetic counselors.

Results: Thirty-five cases were evaluated in one year by the MTB. The most common reason for MTB referral was a request for recommendations on targeted therapies (91.9%), and for potential germline mutations. Tumors exhibited a wide range of genetic heterogeneity: 71 different mutations were found across 50 genes, and 63 mutations were observed only once. In 56.3% of cases (18/32) of advanced/metastatic disease, MTB recommended non-standard therapy with a specific targeted agent (11 clinical trials; 7 off-label use) based on evaluation of tumor genetic profile, and disease and treatment histories. Four patients were subsequently treated with a MTB-recommended targeted therapy; 3 of these 4 patients remain on therapy. 2 of whom have experienced tumor regression > 10 months. The remaining 14 patients continued on current therapy because disease was stable (n= 4), were treated with non-MTB-recommended standard therapy (n= 4), declined conventional therapy (n= 5), or died prior to receiving further therapy (n= 1).

Conclusions: Case evaluation by a multidisciplinary group of individuals in the context of a MTB frequently shapes treatment options and decisions. Importantly, anticipated obstacles to capitalizing on the benefits of a MTB such as access to drugs were rarely encountered. Instead, the most commonly encountered reasons that MTB-recommended therapy was not administered stemmed from patient preferences, and genetic profiling at a very late stage of disease.
Genetic testing for hereditary breast cancer: The decision to decline. 
**First Author:** Brook White, CMC, Charlotte, NC

**Background:** Genetic testing is an important component of comprehensive cancer care. Testing for hereditary breast and ovarian cancer syndrome is well established, as commercial analysis of the BRCA1/2 genes has been available since 1996. The National Comprehensive Cancer Network (NCCN) guidelines identify those individuals appropriate for BRCA1/2 analysis, and define management recommendations for mutation carriers. Despite recommendations, not all who meet NCCN criteria undergo genetic testing. We assessed the frequency that individuals meeting NCCN criteria decline BRCA1/2 analysis, as well as factors that affect the decision making process.

**Methods:** A retrospective chart review was performed from September 2013 through August 2014 of individuals who had genetic counseling at the Levine Cancer Institute (LCI).

**Results:** 1083 individuals identified through the retrospective chart review met NCCN criteria for BRCA1/2 analysis. 268 (24.5%) of the 1083 individuals did not pursue genetic testing. Of those who did not undergo testing, 21.3% (N = 57) did not desire testing and 40.3% (N = 108) were advised to gather additional genetic or medical information prior to genetic analysis. The remaining 38.4% (N = 103) had insurance and desired testing but did not pursue due to expense. The majority of the 103 individuals (N = 88) were responsible for the total cost of the test, although some (N = 15) had a prohibitive co-pay expense.

**Conclusions:** Our analysis reveals that 38% of patients who meet NCCN guidelines for BRCA testing do not undergo testing based on financial barriers. This highlights the need to address public policy initiatives in this high-risk population.

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Identification of tropomyosin kinase receptor (TRK) mutations in cancer. 
**First Author:** Nisha Nanda, Loxo Oncology, San Francisco, CA

**Background:** TRK A, B and C, (encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) localize to a subset of receptor tyrosine kinases that mediate tumorigenesis and survival of neurons. Chromosomal rearrangements resulting in kinase fusions have been described across the NTRK gene family, and may contribute to tumorigenesis in diverse clinical settings. We searched for potentially activating mutations in the NTRK gene family by applying biologically driven ranking criteria to an anonymized next-generation sequencing dataset, sourced from Foundation Medicine (FM) and Compenda BioSciences (Compenda).

**Methods:** Approximately 10,000 patient samples were analyzed for mutations in NTRK1, NTRK2 or NTRK3. Mutation data in other known cancer-related genes were also captured for these tumors. Data were reconciled across the disparate sources by mapping mutations to the canonical transcript for each gene where possible, or to a representative non-canoncal transcript when the mutation occurred in a region not contained within the canonical transcript. Mutations were clustered together based on sequence proximity. Mutation groups were ranked by likelihood of oncogenic-activating potential using six biologically-driven component scores.

**Results:** 732 distinct mutation clusters were identified across > 20 tumors. NTRK1, NTRK2 and NTRK3 represented 33%, 30% and 37%, respectively, of these mutation clusters. A disproportionate number of the most promising mutation clusters were in NTRK3: 59% of the top 5%, 58% of the top 10%, and 46% of the top 25%. In addition, the top 3 mutation clusters were in the NTRK3 gene domain, and were observed in head and neck, lung, upper gastrointestinal, melanoma and colon cancers.

**Conclusions:** This heuristic identified mutations in the NTRK family, especially in NTRK3, that hold promise as oncogenic activating mutations. The highest ranked mutations deserve further study, as they are clonally present in the kinase domain, exist in the absence of other known oncogenic drivers, and are infrequent in germline databases.

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Next-generation sequencing as an informing phenotype: A TP53 example. 
**First Author:** Rosie O’Shea, The Mater Hospital, Dublin, Ireland

**Background:** Li-Fraumeni (LFS) and Li Fraumeni like (LFL) syndromes are characterized by early onset cancers such as breast cancer, leukaemia, sarcoma, brain tumours and adrenocortical carcinoma, and are defined traditionally by clinical criteria such as Chompret and Eeles. Genetic testing for TP53 germline mutation is typically undertaken in families that satisfy these clinical criteria. Next generation sequencing and gene panel testing has resulted in more frequent TP53 testing to include families that don’t meet classic testing criteria. We investigated testing criteria and result outcome in a cohort of Irish probands undergoing TP53 full sequencing.

**Methods:** All TP53 test requests processed thought the national genetic testing laboratory between 2012 and 2014 were retrospectively reviewed. Family history data including diagnoses and age at diagnosis was ascertained through hospital charts or electronic patient record systems. Management decision making was to compare cancer risk management decisions among women with BRCA VUS to those of women with negative results.

**Results:** Between 1/2006-12/2012, we identified patients whose genetic testing results yielded a VUS and those who had definitively negative results at a single institution. VUS patients were matched with negative patients of the same age and testing date. $\chi^2$ analyses were used to assess differences between the groups.

**Conclusions:** Three hundred and seventy-one patients underwent genetic testing during the study period. Eighty-two (22%) patients had a VUS. These were matched with 82 control patients with negative genetic testing. The median age of study patients was 47 years for the 164 patients evaluated. Women with a VUS were more racially diverse than those with negative testing (38% of B2, 46% non-Caucasian vs. 17% of B2). Patients with VUS were more likely to be referred to a gynecologic oncologist (42% of 82, 51% vs. 29% of B2, 35%, $p = 0.002$). VUS patients were less likely to be of Ashkenazi descent (14 of 82, 20% of B2, 32 of 82, 39%, $p = 0.002$). Patients with VUS were more likely to be referred to a gynecologic oncologist (42% of 82, 51% vs. 29% of B2, 35%, $p = 0.058$). Among VUS patients, 21% of (7 of 82) were recommended to undergo ovarian cancer screening and 28% of (23 of 82) risk-reducing bilateral salpingo-oophorectomy (RRBSO) vs. 15% (12 of 82) and 28% (23 of 82), respectively in controls ($p = 0.28$). Ultimately, RRBSO was performed in 20% (32 of 164) of all patients, with no significant difference in rate of surgery based on the presence of a VUS.

**Conclusions:** At our institution, patients with VUS are managed similarly to those with negative BRCA testing. In these groups of patients, screening and prevention strategies need to be individualized. The numbers of patients with VUS are likely to increase with the implementation of multi-gene testing. Our findings underscore the importance of genetic counseling in the management of genetic testing results.
First one thousand families: Our multidisciplinary experience in the heredo-familial cancer unit from a Spanish University Hospital. First Author: Ivan Marquez Rodas, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Background: Patients with hereditary cancer syndromes (HCS) need a multidisciplinary approach: Different organs and systems may be involved and different risk reducing strategies (medical and surgical) should be provided. In 2010 we implemented a multidisciplinary heredo-familial cancer unit (HFCU) in Hospital General Universitario Gregorio Marañón (Madrid, Spain). Methods: A retrospective analysis of the first 1000 families attended in our HFCU (2010-2014). Results: 1167 patients, from 1000 different families were attended. In 936 cases (79.6%) fulfilled international criteria for HCS; 84 are pending of gathering more information. Genetic test results were available for 426 patients, with 136 cases bearing pathological mutations. New mutation detection rate (first time diagnosis in a family) was 44/235 (18.7%). Two patients with no HCS criteria were diagnosed with BRCA1 and MSH2 mutations respectively. For the 136 patients with a pathological mutation, prophylactic surgery and/or follow up were offered according to international recommendations and patient’s preferences (Table). In two BRCA1 mutation carriers, an early ovarian cancer was detected in prophylactic surgery. Conclusions: The first one thousand families attended in our HFCU demonstrate that a multidisciplinary assistance is the core of this clinical activity. The intervention resulted in risk reduction surgery in 31% of cases and intensive surveillance in all cases. A longer follow up is warranted in order to evaluate the long-term impact of these interventions and for improving the different steps of the cancer genetic counseling process.

**MUTATION CARRIERS (%)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prophylactic surgery (%)</th>
<th>Only follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>12/96 (70.6)</td>
<td>36 (38)</td>
</tr>
<tr>
<td>MLH1/MSH2/MSH6</td>
<td>18 (13.2)</td>
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<tr>
<td>APC/MYH</td>
<td>6 (4.4)</td>
<td>2 (33.3)</td>
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<tr>
<td>p53</td>
<td>2 (1.5)</td>
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<tr>
<td>CDH1</td>
<td>2 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>PTEN</td>
<td>1 (0.8)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>MEN1</td>
<td>2 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>RET</td>
<td>3 (2.2)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>VH1</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>CDH1</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>NF1</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>PTEN</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>FH</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>RB</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>136 (100)</td>
<td>42 (30.9)</td>
</tr>
</tbody>
</table>

1558 Poster Session (Board #382), Mon, 1:15 PM-4:45 PM

Intratumoral heterogeneity of cancer driver genomic alterations across several tumor types. First Author: Kai Wang, Foundation Medicine, Inc., Cambridge, MA

Background: Intratumoral heterogeneity (ITH) or variations in genomic alterations (GA) between different areas of primary tumors or in their metastases has been an area of intense investigation and is often cited as a reason for failure of targeted therapies. We used an NGS-based comprehensive genomic profiling assay (CGP) to examine 5 tumor types across 10 tissue sections in 5 patients to determine the impact of ITH on GA relevant to cancer biology (cancer "drivers"). Methods: 250 FFPE 40u sections from 25 patients were processed successfully, obtaining coverage depth >700x, with all classes of GA (substitutions, indels, copy number alterations - CNA) assessed. Heterogeneity in cancer driver GA was evaluated including raw data review, and associated with clonal architecture. Results: 837 total substitutions or indels (short variants - SV) were observed in 245 sections, with 217 assessed to be subclonal based on mutant frequency (MAF) and tumor content. Only 20 SV were not detected in paired sections from the same PT, for a discordance rate of 2.3% (20/857). All discordances were in subclonal variants, with avg MAF <6%. CNA concordance was 90.2%, with half of discordances associated with low tumor purity or coverage bias. Findings were similar across tumor types (Table), with key targetable GA including EGRF mutation in lung cancer and ERBB2 amplification in breast cancer across all sections. Conclusions: Our analysis reveals that intratumoral heterogeneity of cancer driver GA is limited. The data supports CGP of a single biopsy section as appropriate in most patients with advanced solid tumors, provided sufficient sensitivity is attained for subclonal events in impure clinical tissue.

1555 Poster Session (Board #381), Mon, 1:15 PM-4:45 PM

DNA repair landscape of discordant sibling pairs from hereditary breast cancer families. First Author: Yongli Ji, University of Vermont, Burlington, VT

Background: DNA repair plays a significant role in carcinogenesis. The aim of this study is to describe the landscape of germline DNA sequence variation among discordant sister pairs (one with and one without breast cancer) from breast cancer families with a strong presence of DNA repair variation on DNA repair pathways. Methods: Six sister-pairs were identified from a cohort of high-risk women at University of Vermont Cancer Center. To be eligible for inclusion families must have at least 3 cases of breast cancer, 1 diagnosed under age 50. The unaffected sister must be older than the affected sister’s age at diagnosis. Germline DNA was isolated and full exome sequencing was performed for all 12 women. Computational genomics were utilized to identify putative single nucleotide polymorphisms in DNA repair pathway associated genes. Candidate variants were identified based on the quality of the variant call, distribution among sibling pairs, frequency in the general population, and predicted functional consequences. Results: We obtained high-quality exome sequences for each individual. We identified deleterious mutations in several known cancer-associated pathways, including DNA repair. The genetic variants and pathways include (see Table): TSC1 (tuberous sclerosis complex) is a tumor suppressor gene; WRN is a member of the RECQ helicase family involved in DNA repair and maintaining genomic stability; PM2 (postmenotic segregation increased 2) is involved in mismatch repair; POLG is a DNA polymerase; POLE is a DNA replicative polymerase.

Conclusions: Using 6 discordant sister pairs from high-risk families we were able to deconstruct high-quality sequences and identify several interesting variants in DNA repair pathways. We have enrolled additional sister pairs and are funded to sequence and analyze 8 additional pairs. Future studies will focus on identification of rare familial variants and understanding the functional significance of identified variants.

**Variant finding**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Findings</th>
<th>Rare?</th>
<th>Predicted Damaging?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1</td>
<td>R37H</td>
<td>Het in one case</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WRN</td>
<td>M1187V</td>
<td>Hets in 2 cases</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WRN</td>
<td>C1367R</td>
<td>4/6 cases; p = 0.0625</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PM2</td>
<td>N355S</td>
<td>Het in one case</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>POLQ</td>
<td>Q1546X</td>
<td>Het in one case</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>POLQ</td>
<td>A252V</td>
<td>Hets in 2 cases</td>
<td>✓</td>
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</tr>
</tbody>
</table>

1559 Poster Session (Board #383), Mon, 1:15 PM-4:45 PM

Feasibility of using memantine in smoking cessation among cancer survivors. First Author: John Spangler, Wake Forest University, School of Medicine, Winston-Salem, NC

Background: Memantine, an N-methyl-D-aspartate receptor noncompetitive antagonist, has been proposed for smoking cessation by virtue of opposing the effects of glutamate in the CNS “addiction center,” the nucleus accumbens. This study evaluated Memantine’s feasibility and preliminary efficacy for quitting smoking among cancer survivors. Methods: A prospective randomized feasibility trial was conducted by the Wake Forest CCOP Research Base, grant number U10CA081851. Clinical trial information: NCT01535040.

Results: Six sites attended. All patients (79.6%) fulfilled international criteria for HCS; 84 are pending of evaluation following randomization. Other options for smoking cessation could remain smoke-free for one week prior to the 12 week evaluation. Only two patients reported being smoke-free at 12 weeks, while patients were on study (86% M, 93% C). Four serious adverse events occurred in the two arms. Similar in the two arms. Only two patients reported being smoke-free at 12 weeks, both in the Control arm. The number of cigarettes smoked at 12 weeks was similar in the two arms. Characteristics were similar in the two arms. Results: Over 20 CCOP sites participated; accrual was approximately 10 patients per month. Retention at 12 weeks was poor (54% M, 68% C). Self-reported adherence was good while patients were on study (86% M, 93% C). Four serious adverse events were noted (3 M, 1 C), none related to treatment. Toxicities were similar in the two arms. Only two patients reported being smoke-free at 12 weeks, both in the Control arm. The number of cigarettes smoked at 12 weeks was similar in the two arms. Conclusions: While accrual was robust and patients reported good adherence, 40% dropped out by 12 weeks and very few patients could remain smoke-free for one week prior to the 12 week evaluation following randomization. Other options for smoking cessation need to be assessed. (Funding for this study was provided by NCI to the Wake Forest CCOP Research Base, grant number U10CA081851).
Hormonal and lifestyle factors as modifiers of risk of breast cancer (BC) in *BRCA1* and *BRCA2* carriers. First Author: Asunción Torres, Servicio de Oncología Médica, Hospital Universitario de Almansa, Albacete, Spain

**Background:** Mutations in the *BRCA1*/*2* genes confer a high lifetime risk of BC. Penetrance varies among populations and individuals suggesting that non-genetic factors may modify the inherited risk. Knowledge of modifiable factors will help to develop preventive strategies. **Methods:** The study was carried out in 874 women (W) with a *BRCA1/2* germ-line mutation (511 with BC, 51% *BRCA2* from 414 families, followed at three Spanish Genetic Counseling Units. Participants gave their consent and the study was approved by the ethics committee. The association between BC, hormonal and lifestyle factors was studied using logistic regression. Huber-White robust estimators of variance were employed to take into account correlations between family members. Age, menopausal status and specific mutated gene were included as co-variables. **Results:** While late menarche (≥ 14 years) was associated with a reduction in BC risk in *BRCA1* C (OR:0.48; 95%CI:0.42-0.88, p = 0.016), no similar effect was observed for *BRCA2* W (p = 0.252). Moreover, although pregnancy increased BC risk in both *BRCA1* and *BRCA2* C (OR:2.38; 95%CI:1.26-4.49, p = 0.007; OR:1.89; 95%CI:1.91-3.95, p = 0.09 respectively), a deleterious effect of spontaneous abortion was found only in *BRCA1* C (OR:1.66; 95%CI:0.92-3.01, p = 0.09). Furthermore, oral contraceptive (OC) use was also associated with an increased BC risk in the *BRCA1* group (OR:1.65; 95%CI:0.98-2.78, p = 0.058). BMI also increased the risk of BC among *BRCA1* C (p-trend = 0.014). Finally, breastfeeding, smoking, alcohol intake and exercise did not significantly modify BC risk. **Conclusions:** Our preliminary data suggest that the hormonal changes associated with pregnancy increases BC risk in mutation C. Obesity and the use of OC also exert a deleterious effect in *BRCA1* germline mutation C and could be considered as potential modifiable factors for BC prevention in these group of W.

Impact of prior knowledge of mutation status on tumor stage in *BRCA1*/*2* mutation carriers with newly diagnosed breast cancer. First Author: Clinton Yam, Bassett Research Center for BRCA at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

**Background:** *BRCA1*/*2* mutation carriers have an elevated lifetime risk of developing breast cancer. Knowledge of one’s *BRCA1*/*2* mutation status may aid earlier detection of breast cancers due to increased awareness and screening with breast MRIs. **Methods:** Retrospective analysis of tumor characteristics of *BRCA1*/*2* mutation carriers known to our institution who were diagnosed with breast cancer from 1/1/2009 - 12/31/2013. **Results:** 106 *BRCA1*/*2* mutation carriers were diagnosed with breast cancer during the first study period and 56 patients received care primarily at our clinical sites and were included in the study. 19.5% (16/82) were known *BRCA1*/*2* mutation carriers prior to breast cancer diagnosis and the remaining 66 patients had genetic testing after cancer diagnosis. There were no differences in the median age at cancer diagnosis (p = 0.87) or distribution of *BRCA1* vs *BRCA2* mutation carriers between the 2 groups (p = 0.18). 62.5% (10/16) of known carriers diagnosed with breast cancer following an abnormal MRI vs 0/66 of those identified as carriers only after breast cancer diagnosis (Table 1). Patients who knew their *BRCA1*/*2* mutation status were more likely to have smaller tumors (p = 0.008) and node negative disease (p = 0.004). There were no differences in the ER, PR or Her2 statuses between the 2 groups. **Conclusions:** *BRCA1*/*2* mutation carriers who have knowledge of their genetic status are more likely to have early stage disease at the time of breast cancer diagnosis, demonstrating the utility of identifying unaffected carriers who benefit from enhanced screening for early detection.

<table>
<thead>
<tr>
<th>Summary of findings:</th>
<th></th>
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<tbody>
<tr>
<td>Known at diagnosis</td>
<td>Unknown at diagnosis</td>
</tr>
<tr>
<td>N</td>
<td>106 (100)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>40 (25-70)</td>
</tr>
<tr>
<td>N</td>
<td>66 (100)</td>
</tr>
<tr>
<td>Number (%)</td>
<td>42 (62-74)</td>
</tr>
<tr>
<td>p value</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Development and external validation of a melanoma risk prediction model using self-assessed risk factors. First Author: Kylie Vuong, University of Sydney, Camperdown, Australia

**Background:** Melanoma incidence rates have been increasing in fair-skinned populations, with Australia having the world’s highest melanoma incidence rates. By providing individuals with their overall risk instead of relying on individual risk factors, melanoma risk prediction models may lead to improved risk perception and sun protection behaviours. In addition to their clinical uses, these models may assist in planning intervention trials and population prevention strategies that target particular risk groups. We aimed to develop and validate a melanoma risk model predicting lifetime absolute risk of primary melanoma using self-assessed risk factors. **Methods:** We used unconditional logistic regression with backward selection to develop the melanoma risk model using the Australian Melanoma Family Study, a population-based case-control family study with 629 population-based cases with first primary melanoma diagnosed before age 40 years and 535 controls from 2001 to 2005. Relative risk estimates from the model were combined with Australian melanoma incidence and mortality data using the Gail method to obtain lifetime estimates from the model, which is based on self-assessed risk factors, discriminates well between those with and without melanoma and may be useful in the design of melanoma prevention interventions.
Aspirin has been identified as reducing cancer incidence, especially colorectal cancer (CRC), distant metastasis and mortality. Secondary cancer prevention has not been investigated. To examine the potential effects of aspirin on non-colorectal SPMs prevention among patients with previous CRC Methods: We enrolled 92,392 patients with newly diagnosed CRC between January 1, 1997 and December 31, 2011 from the Taiwan’s National Health Insurance database. Participants with more than 90 cumulative defined daily doses (cDDD) of aspirin exposure are defined as aspirin users (n = 7,488) compared with non-users (n = 84,904). Development of non-colorectal SPMs was obtained from the Taiwan’s National Health Insurance database. The Cox proportional hazards model, and the Fine and Gray’s proportional hazards model were used to estimate the cause-specific hazard ratios (HRs) and subdistribution HRs, respectively. Data analysis was conducted in April, 2014. Results: During the 15-year study period, 3,880 patients developed non-colorectal SPM among 92,392 recruited CRC participants. We compared 7,488 aspirin users with 84,904 non-users. Overall, the difference for risk of SPM was not significant. The cause-specific hazard ratios (HRs) and subdistribution HRs were 0.99 (95% CI 0.88–1.12) and 1.00 (95% CI 0.88–1.12), respectively. Propensity score analyses were done and matched 6,728 aspirin users with 26,912 non-users. The cumulative incidence of SPM showed no difference (p = 0.824).

Conclusions: Among patients with prior CRC, aspirin use did not provide chemoprevention in non-colorectal SPMs.

The influence of inflammation on mammographic breast density in women at increased risk of breast cancer. First Author: Samir S. Ambracle, University of Vermont, Burlington, VT

Background: Mammographic density is an important risk factor for breast cancer but the etiology of density is not well understood. Studies suggest that inflammation may play a role in density. We evaluated the association between serum inflammatory markers and breast density in women at increased risk for breast cancer. Methods: Women previously enrolled in the University of Vermont IRB-approved High-Risk database were eligible for inclusion if they had a baseline serum sample and a mammogram available within 120 days of each other (N = 174). A subset of eligible women also had a paired serum sample and mammogram at 4 years from study entry (N = 38). Blood samples were analyzed for C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1b (IL-1b) and tumor necrosis factor-α (TNF-α).

Breast density was calculated using 2 methods: the Cumulus method and fully automated University of Pennsylvania (UPenn) method. Results: Mean age of the cohort was 46.2 (range 24-71 years) and 63.8% were premenopausal. Mean baseline density was 35.8% and 31.8% using the Cumulus and UPenn method respectively. Mean baseline values were 20,005 ng/ml for CRP, 10.6 pg/ml for TNF-α, 0.78 pg/ml for IL-1b and 0.84 pg/ml for IL-6. Body mass index correlated with CRP (spearman correlation coefficient [r] = 0.58; p < 0.0001), IL-6 (r = 0.17; p = 0.003) and TNF-α (r = 0.19; p = 0.02). Linear regression adjusted by age and BMI found that baseline IL-6 had significant association with breast density calculated by either density methods (Cumulus: β coefficient 1.62, p = 0.04; UPenn: β coefficient 1.95, p = 0.01). No other biomarker had a statistically significant relationship with density. There was no significant correlation between change in inflammatory marker levels and change in density at 4 years. Conclusions: Mammographic breast density was found to be elevated among women with higher serum IL-6 levels, a finding that supports prior data suggesting a relationship between inflammation and density. This study strengthens the evidence for consideration of anti-inflammatory agents as chemoprevention for breast cancer. Further research is needed to elucidate the mechanism by which IL-6 is associated with breast density.

Impact of a risk model based on routine lab results on colorectal cancer screening in average risk population. First Author: Shimam Ben Boursi, University of Pennsylvania, Philadelphia, PA

Background: Risk scores for colorectal cancer (CRC) screening use limited variables and have low predictive values. We sought to develop and validate a novel CRC risk prediction model based on routinely available data from electronic medical records including laboratory results. Methods: We conducted a nested case-control study using a population-based database. The cohort was randomly divided into test and validation datasets. Cases were defined as those with a diagnostic code of CRC, aged 50-85. Subjects with CRC syndromes or IBD were excluded. For every case, 4 controls matched on practice site and duration of follow-up were selected using incidence-density sampling. Lifestyle parameters, medical history, medications, and lab results were examined as CRC risk factors using univariate conditional logistic regression. Variables with p-value < 0.25 were evaluated in the multivariate model, after correcting for linearity, using backward elimination. Discrimination ability was calculated using receiver operator curve (ROC). Goodness of fit was evaluated using the McFadden’s R2. For the final model we calculated the net reclassification index (NRI) compared to a model including lifestyle parameters only. Results: Our study cohort included 45,498 subjects in the test set (n = 9,299 (20.44%) cases) and 22,490 subjects in the validation set (n = 4,580 (20.36%) cases). A multivariate model based on lifestyle parameters only (age, sex, height, obesity, ever smoking, alcohol dependence and previous screening criteria) had an AUC of 0.79 (95%CI 0.77-0.81). The model was validated using the NRI and McFadden’s R2. The model was also validated in the validation set.

Conclusions: The model was able to improve risk prediction of CRC screening in average risk population.

Background: Since 2001, Medicare has covered colorectal cancer (CRC) screening for average-risk enrollees. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against routine CRC screening of the average-risk over age 75. Although Medicare CRC screening policy has no age limit on screening eligibility, there are concerns about inappropriate use of CRC screening services. Methods: The data consist of a 1998-2010 5% non-cancer sample of Medicare enrollees residing in 147 cancer registry areas. We constructed 9-year panel data from 2002 to 2010. Each panel was assembled in the similar fashion. For illustration purpose, average-risk Medicare beneficiaries were included in the 2010 panel if they were 76 years or older in 2010; enrolled in FFS plans and Part A&B benefits in every single month in 2010 and the previous year. Then they were diagnosed with any indications for higher risks in 2010 and the previous 4 years. The outcomes are the up-to-date overall adherence status, and the specific modality (conditional on adherence). Chi-squared tests were used for statistical analyses. Results: The sample size of 9-year panel data of average-risk Medicare enrollees over age 75 ranges from 23,536 in 2002, 19,847 in 2008, to 19,609 in 2010. The overall CRC screening adherence rates increased from 12.69%, 17.44% and 20.88%, respectively. For the adherence rates by modality, the rates of adherence to colonoscopy increased from 2.18%, 14.67%, and 19.03%, respectively, while the rate of adherence to other modalities decreased rapidly. There was variation in overall adherence rates. Blacks were less likely than whites to be adherent (P < 0.01); women were less likely than men to be adherent. For the subpopulation over age 85, the rates of adherence to colonoscopy were .74%, 7.14%, and 11.24%, respectively. The differences in colonoscopy adherence according to race and gender among the subpopulation were consistent to those among the population over age 75 (P < 0.01). Conclusions: Overall adherence rates have risen rapidly since 2002, largely driven by 2001 Medicare coverage decision on colonoscopy. The high proportion of the average-risk over age 75 who received screening colonoscopy services, a practice against USPSTF recommendation, warrants more research.

Beliefs and behavior regarding e-cigarettes in a large cross-sectional survey.

First Author: Sebastien Couraud, Acute Respiratory Medicine and Thracic Oncology Department, Lyon Sud Hospital and Lyon University Cancer Institute, EMR 3738 “Therapeutic Targeting in Oncology”, Lyon Sud, Pierre Benite, France

Background: The use of e-cigarettes has developed dramatically in recent years. However, the role of e-cigarettes in helping cigarette cessation or in lowering social stigma of tobacco use remains controversial. It is therefore useful to assess beliefs and behavior about e-cigarettes. Methods: The 4th French nationwide observational survey, EDIFICE 4, was conducted among a representative sample of 1602 subjects aged 40 to 75 years, using the quota method, from June 12 to July 10, 2014. Profile, beliefs and behavior were assessed by phone interviews of the general population with no history of cancer (n = 1463), and compared with those of cigarette smokers and e-cigarette users (eC-). Results: Of the 1463 individuals analyzed, 93 (6%) were e-cigarette users (74 current and 19 former cigarette smokers), with a mean daily consumption of 9.9 ± 11.0; 88% used nicotine-based e-liquid. Among cigarette users (C+), current C+/eC+ were more likely to be men, to have a lower socioeconomic status (56% vs 39%), and to be more dependent on nicotine according to the Fagerström test (58% vs 46%), in comparison with cigarette smokers alone (C+/eC-). In the general population, 58% believed that e-cigarettes are potentially useful in helping to reduce cigarette smoking, and for 31%, they can help to quit smoking. In contrast, these proportions were 24% and 65% respectively, among e-cigarette users (C+/eC+). In the general population, 58% believed that e-cigarette smoke is less toxic than cigarette smoke for the user and for passive smokers, respectively. These figures were both greater among e-cigarette users (C+/eC+), reaching 68% and 87% respectively. Of the total population, 12% felt that e-cigarettes are likely to be effective for controlling lung cancer mortality (18% among current smokers vs 9% and 12% in former- and never-smokers), compared to 33% of e-cigarette users (C+/eC+). Lastly, current C+/eC+ smokers believed they have a higher risk of lung cancer than that of current C+/eC- smokers. Conclusions: Current cigarette smokers and current e-cigarette smokers both tend to have a lower awareness of e-cigarette toxicity and to emphasize the potential benefit of e-cigarettes for quitting smoking.

Prediction models for primary melanoma: an independent external validation study in an Australian population.

First Author: Kylie Vuong, University of Sydney, Camperdown, Australia

Background: There are a growing number of melanoma risk prediction models; however few assessed model external validity. External validation refers to the process of establishing model performance in an external, independent population and provides an indication of generalizability. Model performance tends to be poorer when measured in an external, independent data set compared with the data set that was used to develop the model. To help clinicians decide which models are potentially most useful, we assessed the external validity of six published melanoma models on an independent population. Methods: The Australian Melanoma Family Study, a population-based, case-control family study with 629 population-based cases with first primary melanoma diagnosed before age 40 years and 535 controls from 2001 to 2005 were used to validate the models. We compared performance using discrimination (separation of those with and without melanoma) by calculating the area under the receiver operating curve (AUC). Results: Model performance ranged from fair to good. The models of Mar (AUC = 0.79 (95% CI 0.73 – 0.79)) and Fears for men (AUC = 0.79 (0.71 – 0.86)) showed comparable discrimination. Other models yielded lower discrimination: Guther (AUC = 0.70 (0.67-0.72)), Williams (AUC = 0.66 (0.64-0.69)), Cho (AUC = 0.63 (0.61-0.65)) and Fears for women (AUC = 0.63 (0.56-0.69)). Conclusions: The six models discrimi- nate well between those with and without melanoma in the Australian population suggesting potential for these models to be developed for use in targeted melanoma prevention interventions. However further external validation in different populations and prospective evaluation of efficacy is required before they can be routinely used in clinical settings.

Omentin as a potential biomarker related to exercise and cancer risk.

First Author: Michaela Onstad, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Omentin is a protective adipokine whose circulating levels are inversely related to BMI, waist circumference, and insulin resistance. Serum levels are lower in women with endometrial and ovarian cancers compared to healthy controls. In our vitro studies demonstrate that exogenous omentin suppresses ovarian cancer cell motility and invasion potential and inhibits tumor growth indirectly. Given its inverse relationship with obesity and insulin resistance, we hypothesized that serum omentin can be increased with exercise. Methods: We conducted a pilot study of healthy individuals participating in a 10 week community exercise program aimed at training beginning runners for a 5K race. At the start of the program, anthropometric measures were taken, serum collected, and a whole body dual-energy x-ray absorptiometry (DXA) was done to measure percent body fat (%BF) and percent lean body mass (%LBM). These were repeated at completion of the program. Spearman’s rank correlation was used to analyze the association between omentin, anthropometric mea- sures and body composition. Paired t-tests and Wilcoxon signed-rank test were used to analyze changes in omentin. Results: 40 participants were enrolled and 28 completed all follow-up studies. Baseline omentin was negatively associated with waist circumference (p = 0.03) and %BF (p = 0.01), and positively associated with %LBM (p = 0.009). 11 participants decreased their %BF at completion of the program, whereas 17 had no incidence. The %BF in the 11 participants who decreased their %BF had an increase in serum omentin (median = 89.23ng/mL), whereas those who had no improvement or increased their %BF showed a decrease in omentin (median = 69.98ng/mL). The change in omentin was different between these groups, approaching statistical significance (p = 0.06). Conclusions: Omentin is inversely associated with waist circumference and %BF, and positively associated with %LBM. Changes in serum omentin due to exercise may be reflective of changes in body composition. As the correlation between omentin and cancer risk is further established, it may serve as a useful biomarker for patients to receive specific interventions. Omentin warrants inclusion in future research involving energy balance and cancer.

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1572 Poster Session (Board #396), Mon, 1:15 PM-4:45 PM
Effect of green tea catechins in prostate cancer chemoprevention. First Author: Nagi B. Kumar, H Lee Moffitt Cancer Ctr At Univ of S Florida Coll of Medicine, Tampa, FL

Background: Preclinical, epidemiological and prior clinical trial data suggest that green tea catechins may reduce prostate cancer (PCa) risk. Methods: We, therefore, conducted a placebo-controlled, randomized clinical trial of one of Polyphenon E (PolyE), a proprietary mixture of green tea catechins containing 400 mgs of epigallocatechin-3-gallate (EGCG) per day, in 97 men with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) on prostate biopsy. The primary study endpoint was the total number of PCa diagnoses on the PolyE versus placebo arm at one year. Results: No differences in prostate cancer rates were observed in the two groups (4/49 PolyE vs 6/48 placebo, P = 0.25). A prespecified analysis comparing the combined rates of PCa + ASAP in the subgroup of men with HGPIN-only at baseline, showed a decrease in this composite endpoint (3/26 PolyE vs 10/25 placebo, P < 0.024). This was largely driven by a reduction in ASAP (0/26 PolyE vs 5/25 placebo). In another prespecified analysis, a decrease in serum PSA was observed the PolyE arm (-0.90 ng/ml; 95% CI: -1.67, -0.12; P < 0.05). Adverse events related to the study agent did not significantly differ between the two study groups. Conclusions: Daily intake of a standardized, decaffeinated catechin mixture containing 400 mgs EGCG per day for 1 year accumulated in plasma and was well tolerated, but did not reduce the likelihood of a subsequent PCa diagnosis in men with baseline HGPIN or ASAP over this period of time. Clinical trial information: NCT00596011.

1574 Poster Session (Board #398), Mon, 1:15 PM-4:45 PM
Association between geriatric assessment findings and clinical depression in 1092 older patients with cancer: The ELCAPA Cohort study. First Author: Christophe Tournigand, APHP, Henri-Mondor Hospital, Oncology department, Creteil, France

Background: Few studies assessed jointly geriatric and oncological factors associated with clinical depression in older patients with cancer. Methods: We studied a prospective cohort of cancer patients aged ≥ 70 years and referred to geriatric oncology clinics between 2007 and 2012. A multidimensional geriatric assessment (GA) was performed before treatment. Clinical depression was diagnosed by senior geriatricians by a semi-structured interview. It encompassed criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th edition, DSM-IV) and of the International Classification of Diseases (10th edition, ICD-10). Multivariate analysis was based on multivariate logistic regression. Systematic adjustment for gender was done. Results: Of 1121 consecutive patients, 1092 had available data (mean age, 80.4 years; women, 48.8%; metastases, 51.3%; cancer location: colorectal 21.1%, breast 16.8%, kidney bladder or urinary tract 14.0%, and prostate 11.4%). The overall prevalence of clinical depression was 28.4% (95% confidence interval, 25.7-31.2). Factors independently associated with clinical depression by multivariate analysis adjusting for all following factors and gender were impaired mobility (adjusted OR [aOR], 2.41; 1.64-3.54), impaired functional status defined as ECOG-PS ≥ 2 (aOR, 2.42; 1.83-3.76), impaired status (aOR, 1.66; 1.18-2.32), metastatic status (aOR, 1.42; 1.01-2.01), inadequate social support (aOR, 1.58; 1.12-2.25), cognitive impairment (aOR, 1.73; 1.23-2.43), polypharmacy defined as five or more nonantineoplastic drugs (aOR 1.70; 1.18-2.44), and multimorbidity (aOR additional CHS-G_score, 1.07; 1.04-1.11). Conclusions: In older patients with cancer at various sites and stages, clinical depression was highly prevalent. Clinical depression was independently associated with several GA findings (impaired mobility and function, inadequate social support, cognitive impairment, polypharmacy, and multimorbidity) independently from with gender, tumor site, and metastatic status.
Factors associated with early mortality in metastatic breast cancer (MBC) in a population based cohort. First Author: Ines Maria Vaz Duarte Luis, Dana Farber Cancer Inst, Boston, MA

Background: Significant improvements in survival time have been achieved for patients (pts) with MBC. Nevertheless, some still die soon after diagnosis. Data regarding features associated with early death are limited. Methods: Using Surveillance, Epidemiology, and End Results (SEER) data, we studied 30,862 pts diagnosed between 1/1/2010-6/30/2011 (when Human Epidermal Growth Factor Receptor 2 (HER2) status started to be recorded) with follow up of at least 6 months. Multivariate logistic regression models assessed features associated with death within 1 and 6 months of diagnosis, adjusting for the variables in the table. Results: The median age was 62 (22-99), 75% were white, 95% were insured. Disease subgroups were the following: hormone receptor (HR)+HER2- (61%); HR-HER2+ (1%); HR-HER2- (9%) and triple negative (15%). Approximately 8% died 1 month and 20% died by 6 months. Older age, lack of insurance, and triple negative subtype were associated with early death. See Table. Conclusions: Among a population based cohort, one fifth died within 6 months. This study highlights that both clinical factors and insurance type seem to impact early death. These data suggest the importance of studying how differences in insurance reform and other disease characteristics may modify risk for early death and may also inform interventions aimed at those at risk for early death.

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Malignancy incidence and prevalence in adult lung transplant recipient.

<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>1-Year follow up</th>
<th>Entire follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types combined</td>
<td>247 (2.3%)</td>
<td>1,471 (13.5%)</td>
</tr>
<tr>
<td>Other than Skin</td>
<td>174 (1.6%)</td>
<td>1,321 (12.1%)</td>
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* per 1,000 person-year.
deed, 58.9% of pts with malnutrition had a PS alteration was significantly more frequent in malnourished patients. In- (1,132 men and 1,046 women, 19 not evaluable) were included. PS BMI systematically assessed in out-pts and in-pts. Malnutrition was defined as a respectively (chi2 (166/249), and 69.8% (44/63) of the pts with a PS ranging from 2 to 4, without malnutrition. Malnutrition was found in 48.1% (276/574), 66.7% (158/240) in PS1 pts. Almost one third of the patients with high risk of severe acute toxicity.

Background: The association between calcium channel blockers (CCBs) and breast cancer. The long-term use of CCBs is not associated with an increased rate of breast cancer overall, and to assess whether this risk varies with cumulative duration of use. Methods: A cohort of 273,152 women newly treated with antihypertensive drugs between January 1, 1995 and December 31, 2009, and 6.5%, 10.1%, and 12.7%, respectively. This occurrence was signifi-
cantly different between IBC and NI-IDC pts (p = 0.0037). However, multivariate competing risk regression models looking at 18 variables in IBC and NI-IDC pts including patient, tumor, and treatment characteristics showed no statistically significant associations with the risk of developing CNS metastasis. In terms of survival, with a median follow up of 7.2 years, median post CNS metastasis OS was not significantly different between IBC (7.6 months) and NI-IDC (5.6 months) pts. At last follow up, 190 pts with CNS metastasis have died. HER2 positive pts had better OS with a median of 11.1 months vs 4.3 months (p = 0.0001). In addition, age > 50 (p = 0.012) but not IBC status (p = 0.49) was a significant predictor of post CNS metastasis survival. Conclusions: IBC pts have a higher incidence rate in the development of brain metastases but OS following brain metastases is similar to its NI-IDC counterpart. Only HER2 status and age appears to play a role in prognosis.

Prevalence of malnutrition in PS 0-1 cancer patients: Results of the NutriCancer2 one-day national survey in 2,197 cancer patients. First Author: Jean-Philippe Durand, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France

Background: The performance status (PS) measured by the ECOG scale, and malnutrition are both prognostic and risk factors for treatment-related toxicities in cancer patients (pts). In the medical literature, pts characteristics are usually limited to PS without description of the nutritional status. There is a serious issue concerning the under-estimation of the risk prior to anticancer treatments initiation. The prevalence of malnutrition in "fat" PS 0-1 pts remains unknown. Methods: We conducted a prospective one-day prevalence survey, NUTRICANCER 2, in 283 wards of private or public hospitals in France in 2012. Height, present and usual body weight were systematically assessed in out-pts and in-pts. Malnutrition was defined as a BMI < 18.5 or < 21 in pts older than 75 years, or a loss of body weight > 10% since the diagnosis of malignancy. Results: A total of 2197 patients (1,132 men and 1,046 women, 19 not evaluable) were included. PS alteration was significantly more frequent in malnourished patients. Indeed, 58.9% of pts with malnutrition had a PS > 2 versus 31% of pts without malnutrition. Malnutrition was found in 48.1% (276/574), 66.7% (158/240), and 69.8% (44/63) of the pts with a PS ranging from 2 to 4, respectively (chi2 = 223.95; p < 0.001). In pts assumed as fit for chemotherapy, the prevalence of malnutrition was 17.3% (76/440) in PS0 and 33.2% (262/790) in PS1 pts. Almost one third of the patients with apparent good general status were already malnourished and therefore at high risk of severe acute toxicity. Conclusions: This national prevalence survey indicates that Performance Status is not sensitive enough for risk assessment in oncology, requiring a systematic nutritional status assessment prior to anticancer treatments initiation.

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Overall survival in solid tumor patients with abnormal renal function or renal insufficiency. First Author: Vincent Launay-Vacher, Pitie Saipetriere Hospital, Paris, France.

Background: Data still remain scanty on the potential impact of renal insufficiency (RI) on the mortality of cancer patients. The results of 3 clinical studies we conducted (IRMA-2, CANDY and MARS) were pooled. In all 3, methodology and definitions of RI were the same regarding RI. Pooling analysis was thus allowed to study the potential association between RI and overall survival (OS), and to stratify the risk, if any, depending on the GFR Methods: The KDIGO definition and classification of CKD was used. GFR was estimated with the MDRD formula. RI was defined as GFR<60 ml/min/1.73 m². Results: Population included 5908 solid tumor patients (2181 breast, 854 colorectal, 556 lung, 366 ovarian, 293 prostate for the main tumors). Median age 59.2, mean BMI 24.4, 64.0% were women. 70.7% of these patients were alive at the end of the follow-up period of one year. Univariate analysis reported that RI was strongly linked to mortality (p<0.0001), when analysing together all types of patients and tumors. Furthermore, Hazard-Ratio became statistically significant at a GFR of 85 ml/min/1.73 m². For non-metastatic patients (n = 4671), RI was also significantly associated with mortality (p < 0.008), with a significant higher risk of death starting at a GFR of 86. Finally, multivariate Cox model adjusted for sex, age, metastasis and the 5 main types of tumor reported that GFR was significantly associated with OS with an increased risk of mortality at a GFR of 75. This risk gradually increased along with the decrease in GFR. Conclusions: The IRMA studies already reported the high prevalence of RI in cancer patients. But our pooled analysis reported that the reduced OS began at an early stage of CKD, for a GFR<75. These results underline that assessing, monitoring and managing renal function in cancer patients is crucial in prevent or at least minimise renal dysfunction because of its potential impact on survival.

Multivariate Cox model regression.

<table>
<thead>
<tr>
<th>GFR cut-off</th>
<th>HR [95% CI], p-value</th>
</tr>
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<tbody>
<tr>
<td>GFR &lt; 90</td>
<td>HR = 1.03 [0.93-1.14], p &lt; 0.05</td>
</tr>
<tr>
<td>GFR &lt; 85</td>
<td>HR = 1.06 [0.96-1.17], p &lt; 0.05</td>
</tr>
<tr>
<td>GFR &lt; 75</td>
<td>HR = 1.13 [1.02-1.26], p &lt; 0.01</td>
</tr>
<tr>
<td>GFR &lt; 60</td>
<td>HR = 1.15 [1.03-1.27], p &lt; 0.01</td>
</tr>
<tr>
<td>GFR &lt; 30</td>
<td>HR = 1.53 [1.23-1.86], p &lt; 0.0001</td>
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GFR = Glomerular Filtration Rate (mL/min/1.73m²); HR = Hazard-Ratio

Effect of current smoking on risk of triple negative breast cancer. First Author: Diviyya Prabhakar, University Hospital/Case Western Reserve University, Cleveland, OH.

Background: A number of lifestyle factors have been associated with risk of breast cancer. Studies have suggested that risk factors for triple negative breast cancer (TNBC) are different from other forms of breast cancer, and have suggested that parity, family history and body mass index (BMI) are associated with risk of TNBC. Here we sought to explore these associations and investigate the association of previously unexplored variables with risk of TNBC Methods: Newly diagnosed breast cancer patients (N = 1236) were recruited from University Hospitals Case Medical Center (UHCMC) from 2007 to 2014. Patients were ineligible if they had a prior cancer or were recruited from University Hospitals Case Medical Center (UHCMC) and were eligible if they were not former and current smoking at risk of TNBC (p = 0.34). We did not note a statistically significant association between current smoking with risk of TNBC (OR = 2.67, 95% CI = 1.05-6.76, p = 0.038 in multivariate regression). There was no association between former smoking at risk of TNBC (p = 0.28). There was no association between current smoking at risk of non-TNBC (p = 0.34). Our data suggests that current smoking is a risk factor for TNBC, but not other subtypes of breast cancer. The lack of association between former smoking and TNBC suggests quitting smoking may reduce risk.
Tumor Treating Fields (TTFields): A novel treatment modality added to standard chemotheraphy in newly diagnosed glioblastoma—First report of the full dataset of the E14 randomized phase III trial

**Methodology**

This prospective phase 3 trial randomized patients with newly diagnosed glioblastoma, after completion of concomitant chemoradiotherapy, to receive either adjuvant temozolomide (TMZ) chemotherapy alone, or TMZ with TTFields (TTFF/TMZ). The primary endpoint of the trial, survival, with overall survival, safety, cognitive function and quality of life as secondary endpoints. **Results:** (ITT) From 2009 to 2014, 700 Grade IV astrocytoma (glioblastoma) patients (68% male) were randomized 2:1. Patient characteristics were well balanced: median age was 56 and 57 years in the TMZ and TTFF/TMZ arms, respectively. Tumor was resected in 87% of patients. MGMT was centrally assessed in 77% of patients, 35% and 39% of the tumors had a methylated promoter; 10% and 8% of the results were invalid. Median time from diagnosis to randomization was 3.8 and 3.7 months. Progression-free survival was 7.1 for TTF/TMZ vs 4.2 months for TMZ alone, hazard ratio (HR) 0.694 (95% CI 0.558-0.863) log rank p = 0.0010; overall survival 19.4 vs 16.6 months, HR 0.754 (0.595-0.955), p = 0.0222. This translates into 2-year survival rates of 43% (CI 36-50%) vs. 29% (CI 21-38%). No significant added toxicity was seen in the TMZ/TTF arm. Quality of life and gross cognitive function were comparable in the two arms. **Conclusions:** This is the first randomized trial demonstrating improved progression-free and overall survival of patients treated with Tumor Treating Fields. It sets a new standard of care for patients with glioblastoma, and warrants further investigation into clinical trial information. NCT00916409.

**2003**

**CABARET is a prospective randomized Phase 2 study of pts at first recurrence of GBM (rGBM) who had previously been treated with surgery, radiotherapy and temozolomide. Pts were randomized to carboplatin plus etoposide or supportive care; according to clinician choice. Part 2 endpoints included response rate (RR), progression-free survival (PFS) and overall survival (OS).** **Results:** Of 120 pts who received treatment in Part 1, 48 (40%) continued to Part 2, with 23 pts continuing Bev and 25 pts ceasing Bev. The median time on treatment was 1.2 months. There were no radiological responses in either arm. Median PFS (Bev vs no Bev) was 1.8 versus 2.0 months (HR 1.08, 95% CI 0.95–1.20, p = 0.81). Median OS was 3.4 versus 3.0 months (HR 0.84, 95% CI 0.47–1.50, p = 0.56). There were no treatment-related deaths or unexpected serious drug-related adverse events. Preliminary assessment of quality of life scores shows no difference between arms. **Conclusions:** Continuing Bev after progression of rGBM did not improve PFS or OS in this prospective study. Clinical trial information: ACR1300020009150555.
**2004**

**Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

**NCCN N0872 (Alliance): A randomized placebo-controlled phase II trial of bevacizumab plus dasatinib in patients with recurrent glioblastoma (GBM).**

**First Author:** Evanthia Galanis, Mayo Clinic, Rochester, MN

**Background:** Preclinical data indicate that Src kinase signaling is markedly upregulated at the invasive GBM front following administration of the anti-VEGF antibody bevacizumab (Bev). The broad spectrum Src kinase inhibitor dasatinib can effectively block Bev-induced glioma invasion (Huveldt et al, 2013). We therefore hypothesized that combining dasatinib with Bev could increase Bev efficacy in the recurrent GBM setting.

**Methods:** Eligible patients (pts) who progressed on GBM therapy, up to 1st line chemotherapy regimen, were allowed for recurrent disease. Following a 16 pt phase I dose escalation trial that established Bev 10 mg/kg every 2 weeks in combination with dasatinib 100 mg PO bid as the phase II dose of the combination, the randomized placebo-controlled phase II portion of the trial was initiated. The study followed a 2:1 randomization procedure with 85% power to detect a 20% difference in progression-free survival at 6 months (mo) (primary endpoint) between the two arms, and a type I error rate of 0.15.

**Results:** This analysis includes 121 evaluable patients. Median follow-up was 6.8 mo for Arm A (Bev/dasatinib, N = 83 pts), and 7.8 mo for Arm B (Bev/placebo, N = 38 pts). Although a higher percentage of Arm A patients were progression free at 6 mo (27.16% vs 18.42%), this difference did not reach statistical significance (p = 0.30). There was no significant difference in OS (7.2 mo vs 7.9 mo; HR 0.86, 95% CI 0.56-1.31, p = 0.48). Response rate was 18.3% in Arm A and 26.5% in Arm B (p = 0.48). The overall incidence of grade 3+ hematologic and non-hematologic toxicity was comparable in Arms A and B (19.3% vs 16.7% for hematologic toxicity and 45% vs 43.4% for non-hematologic toxicity). Grade 2+ treatment-related hypophosphatemia and diarrhea were more common in the dasatinib arm than in the placebo arm (21.7 vs 5.3% and 19.3 vs 2.6%, respectively).

**Conclusions:** The combination of the Src kinase inhibitor dasatinib with Bev did not improve the outcome of recurrent GBM pts as compared to single agent Bev. Ongoing correlative analysis in baseline tumor samples is exploring associations between src family kinase expression (c-Sarc, Lyn, c-Yes) and activation of downstream signaling pathways and outcome. Clinical trial information: NCT00892177.

**2006**

**Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

**Radiotherapy in relation to temozolomide: Subgroup analysis of molecular markers of the randomized phase III study by the EORTC/NCICT-CRG/ MRC-CTU (EORTC 22033-26033) in patients with a high risk low-grade glioma.**

**First Author:** Brigitta G. Baumert, University of Bonn Medical Centre, Bonn, Germany

**Background:** A subgroup analysis based on molecular markers of patients randomized between standard radiotherapy (RT) and temozolomide (TMZ) alone in the phase III randomized EORTC 22033 trial. Molecular analysis of RT and TMZ treatment arm was done for 407 patients (of 477 randomized). The IDH status was determined by immunohistochemistry for the most common IDH mutant, complemented by sequencing of IDH1 and 2 for all negative cases. The status of 1p/19q co-deletion was evaluated by LOH or FISH, the MGMT promoter methylation status on the HM450k beadchip (Illumina) and classified by MGMTSTP27.

**Results:** IDH1 and IDH2 mutations were detected in 327/392 (83%) and 11/392 (2.8%) (n = 9). Co-deletions of 1p/19q were identified in 33% (n = 117/357), MGMT was methylated in 90% (315/357), of which 86% were IDH mutant (128/140). For 318 patients the status for both IDH1/2 and 1p/19q co-deleted was available - 269 (85%) were IDHmt, 104 (39%) IDHmt/cod and 49 (15%) IDHwt. Mutation of the IDH 1 or 2 (IDHmt) regardless of 1p/19q co-deletion was a positive prognostic factor. Exploratory analysis of these 318 patients showed that patients with IDHmt/non-cod tumors had a shorter DFS after treatment with TMZ than after RT (HR 1.86; 95% CI, 1.21-2.87; logrank p = 0.008). While no difference was observed between these treatments for patients with IDHwt, and IDHmt/cod tumors. **Conclusions:** Subgroup analysis suggests that DFS is longer in patients with IDHmt/non-cod tumors when treated in first-line RT compared to first-line TMZ. With still only a few events no such difference is visible in 1p/19q co-deleted patients. However, maturation of survival data is needed to derive more firm conclusions. Clinical trial information: NCT00182819.

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<th>Median (95% CI) [Mths]</th>
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**2007**

**Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

**Molecular classification of diffuse cerebral gliomas using genome- and transcriptome-wide profiling.**

**First Author:** Michael Weller, Department of Neurology, University Hospital Zurich, Zurich, Switzerland

**Background:** WHO grade II and III cerebral gliomas represent a major challenge for histological classification and clinical management. Here, we aimed to improve prognostically relevant patient stratification by characterizing genomic and transcriptional profiles in a prospective patient cohort of the German Gliona Network. Methods: We performed microarray-based genome- and transcriptome-wide molecular profiling of primary tumor samples from 137 patients with cerebral gliomas. Integrative bioinformatic analyses were employed to define molecular subgroups, which were then related to histology, molecular biomarkers, including isocitrate dehydrogenase 1 or 2 (IDH1/2) mutation, 1p/19q co-deletion and telomerase reverse transcriptase (TER1) promoter mutations, and patient outcome. Results: Genetic profiling identified five distinct glioma groups, including three IDH1/2 mutant and two IDH1/2 wild-type groups. Expression profiling revealed eight transcriptionally different tumor groups (five IDH1/2 mutant, three IDH1/2 wild-type), which were only partially linked to the genomic groups. Correlation of DNA-based molecular stratification without outcome allowed for the definition of three major prognostic groups with characteristic genomic aberrations. The best prognosis was found in patients with IDH1/2 mutant and 1p/19q co-deleted tumors. Patients with IDH1/2 wild-type gliomas and glioblastoma-like genomic alterations, including gain of chromosome arm 7q and loss of chromosome arm 10q (TER1 promoter hypermethylation, displayed the worst outcome. Intermediate survival was seen in patients with IDH1/2 mutant but 1p/19q intact, mostly astrocytic gliomas, and in patients with IDH1/2 wild-type gliomas lacking the 7q+10q genotype and TER1 promoter mutation. **Conclusions:** DNA-based molecular subgroup stratification patients into prognostically distinct groups better than histological classification, whereas addition of gene expression data did not further improve prognostic stratification.
Background: Lower grade gliomas (LGGs, WHO grade II/III gliomas) account for approximately one third of all gliomas. Although LGGs are typically slowly progressive, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to glioblastoma, our knowledge about the genetic lesions and clonal evolution in LGG is still incomplete. Methods: To obtain a complete registry of gene mutations involved in LGG pathogenesis and their role in clonal evolution, we analyzed whole exome sequencing and/or targeted sequencing of 757 LGG cases from Japan and the Cancer Genome Atlas consortium. Clonal evolution in LGG was investigated using multi-time point/regional sampling in 14 cases with LGGs. Results: Massive parallel sequencing revealed LGGs were clearly grouped into three subgroups with or without IDH1/2 mutation and 1p/19q loss of heterozygous (LOH). Type I tumor with IDH1/2 mutation and 1p/19q LOH had a most favorable survival and harbored mutations in TERT promoter, CIC, FUBP1 and NOTCH1. Type II tumor with IDH1/2 mutant/1p19q intact subtype represented TPS3 biallelic inactivation and/or ATRX mutation. Type III tumor with IDH1/2 intact showed GBM-like mutation profile and poor prognosis. Multi regional/time-points sampling analysis supported mutational order and revealed a close correlation of regional heterogeneity with the history of clonal evolution, illustrating the way by which a tumor expands from its origin to surrounding regions, while increasing intratumor heterogeneity and spatially intermingling different evolutional branches in periiphery. Conclusions: Our findings delineated the landscape of gene mutations in LGG. LGG had mutually exclusive mutational patterns with hierarchical order in discrete subtypes. LGGcontiguously developed and generated heterogeneity through acquiring new mutations in a complex but ordered fashion.

2010
Clinical Science Symposium, Sun, 8:00 AM-9:30 AM
Phase II multicenter study of gene mediated cytotoxic immunotherapy as adjuvant to surgical resection for newly diagnosed malignant glioma. First Author: Laura K. Aguilar, Advantagene Inc, Auburndale, MA

Background: New therapies are desperately needed for malignant gliomas since aggressive standard of care (SOC) treatment with surgery, radiation, and temozolomide leads to median survival of less than 15 months. Gene Mediated Cytotoxic Immunotherapy (GMCI) generates a polyvalent anti-tumor immune response through local delivery of aglatimagene besadenov (Adv-Ik) plus prodrug, synergizing with SOC to improve patient outcomes. Methods: A Phase II open-label multicenter trial was designed to assess safety and overall survival (OS) after GMCI+SOC compared to a concurrent matched control group meeting protocol criteria and SOC at an institution not active in the treatment trial. Adv-Ik was injected into the resection bed followed by oral valacyclovir for 14 days. Primary efficacy analysis was planned on the null hypothesis of no improvement in the 2-year survival over the SOC group with planned subset analysis of significant disease prognostic factors. Results: From 2006 to 2010, 48 patients completed SOC+GMCI and 134 SOC in the matched cohort. There were no dose-limiting toxicities. Fever, fatigue, and headache were the most common GMCI-related symptoms. Median OS increased by 3.6 months, from 13.5 to SOC for 17.1 months for GMCI+SOC (p = 0.0417). Survival at 1- and 2-years increased from 57%, 22%, and 8% to 67%, 35%, and 19%, respectively. The improvement was mostly in patients that underwent gross total resection: median OS increased from 16.9 to 25 months (p = 0.0492); 1- and 2-year survival increased from 24%, 21% to 6% to 90%, 53% and 32%. Conclusions: GMCI can be safely combined with SOC in newly diagnosed malignant gliomas. Survival rates compared favorably to historical reports and a matched control group. Survival outcomes were significantly improved in patients with minimal residual disease after total resection. The 2-year survival rate met the planned statistical threshold for significance. No significant differences were observed for subtotal resections. This is the first study to demonstrate a correlation between maximum debulking and a survival advantage using immunotherapy. These data strongly support further evaluation of GMCI for malignant gliomas. Clinical trial information: NCT00589978.

2011
Clinical Science Symposium, Sun, 8:00 AM-9:30 AM
Newly diagnosed glioblastoma patients treated with an autologous heat shock protein peptide vaccine: PD-L1 expression and response to therapy. First Author: Orin Bloch, Northwestern University, Chicago, IL

Background: Standard therapy for glioblastoma (GBM) consists of surgical resection followed by concurrent chemo and radiotherapy with a median overall survival of 16 months. In this phase II, single arm study, addition of an autologous heat shock protein peptide vaccine was evaluated for newly diagnosed GBM. Expression of PD-L1 on peripheral monocytes has been shown to be elevated in GBM patients and was evaluated as a predictor of survival. Methods: Adult patients with GBM underwent surgical resection followed by chemoradiotherapy. Vaccine was generated from tissue obtained at surgery. Key eligibility criteria included ≥ 90% tumor resection and collection of sufficient tumor tissue to generate at least four 25 μg doses of vaccine. Within 5 weeks of completing radiotherapy, patients received weekly vaccinations, followed by adjuvant temozolomide with monthly vaccinations until depletion of vaccine or tumor progression. The primary endpoint was overall survival. Relative PD-L1 expression on circulating monocytes was measured from peripheral blood obtained at surgery. Results: A total of 46 patients from eight centers received the vaccine in addition to standard therapy. Median progression-free survival was 17.8 months (95% Confidence Interval [CI], 11.3-21.6) and median overall survival was 23.8 months (95% CI, 19.8-30.2). The vaccine was well-tolerated with no severe (grade 3 or 4) events attributed to vaccination. The median overall survival for patients with high PD-L1 expression (above the average of 18.0% of tested patients; n = 24; 18.0% median, 8.3% max) was 47.3 months (95% CI 32.3-62.3) as compared to 44.7 months (95% CI not calculable) for low PD-L1 expressers (hazard ratio for death 3.35; 95% CI, 1.36 – 8.23; p = 0.003). A multivariable proportional hazards model revealed MGMT methylation status and PD-L1 expression as the greatest independent predictors of survival. Conclusions: Vaccination with autologous tumor-derived heat shock proteins improves survival compared to standard therapy for newly diagnosed GBM. Systemic immunosuppression driven by peripheral monocyte expression of PD-L1 is a previously unidentified factor that may mitigate vaccine efficacy. Clinical trial information: NCT00905060.
Brain Tumor Trials Collaborative Bayesian Adaptive Randomized Phase II trial of bevacizumab plus vorinostat versus bevacizumab alone in adults with recurrent glioblastoma (BTCCT-1102). First Author: Vinay K. Puduvalli, Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Bevacizumab (Bev) is approved in the US for patients (pts) with recurrent glioblastoma based on response rate. However, adaptive resistance to antiangiogenic agents can result in tumor recurrence. Deacetylase inhibitors such as vorinostat (Vor) have pleiotropic effects against several pathways potentially relevant to adaptive resistance to Bev. Methods: We conducted a phase II multicenter trial with Bayesian adaptive randomization of patients to Bev alone or Bev+Vor with a primary endpoint of progression-free survival (PFS) and secondary end points of overall survival (OS) and safety. All patients had recurrent glioblastoma (GB), ECOG PS 1, 93.7% had primary GB. The median number of cycles for Bev was 2 (range 1-158 pts). Results: Of the 90 pts (Bev + Vor, 49; Bev, 41) enrolled between Oct 2012 and Oct 2014, 83 were evaluable for the primary endpoint (Bev + V: 46; Bev, 37). MDASI-BT scores were available for 81 pts. There was no significant difference between the two arms in median PFS (4.2 vs 3.6 months, p = 0.53) or median OS (8.3 vs 7.0 months, p = 0.93). Analysis of the MDASI-BT scores showed no significant differences between the two arms in overall symptom burden or intermediate symptoms (p = 0.71 respectively). Overall, 61 pts had died by the time of analysis (Bev + V: 35, Bev: 26) with one treatment related death due to pulmonary embolism. Toxicity ≥ grade 3 included hypertension (n = 17), neurological changes (n = 2), infections (n = 2), wound dehiscence (n = 2), DVT/PE (n = 2), and colitis (n = 1). Conclusions: In this phase II comparator study with Bayesian adaptive randomization of patients to Bev alone or Bev+Vor, no significant difference in PFS between bevacizumab and placebo was observed. Grade 3 or higher hematologic toxicity was lower in the bevacizumab arm (43.9% vs 68.8%, p = 0.0012) primarily due to lower rates of lymphopenia. Grade 3 or higher non-hematologic toxicities were similar between arms (53.8% vs 41.3%, p = 0.1384). Analysis by MGMT status will be forthcoming. Conclusions: This study demonstrates the feasibility of conducting studies with adaptive trial designs in a multicenter setting. Clinical trial information: NCT01266031.

A phase II study of galunisertib monotherapy or galunisertib plus lomustine compared to lomustine monotherapy in patients (pts) with recurrent glioblastoma (GB). We report safety, population pharmacokinetics (PK), and efficacy final results. Methods: G (300 mg/day) was given as intermittent dosing (each cycle = 14 days on/14 days off). L was given on day 7 of cycle 1 every 6 weeks as 6.7mg/m2. L was 6.7 mg/m2 for 42 days, beginning with the first day of RT (total dose 60 Gy) and first dose of TMZ (75 mg/m2/d). Following a 24 - 42 day rest, patients then received 6 cycles (28 days cycles) of dasatinib or placebo (days 1-28) and TMZ (days 1-5). At the completion of 6 cycles of TMZ + dasatinib/placebo, patients continued on dasatinib/placebo only (28 day cycles) until progressive disease. Results: Data from 187 of 196 patients enrolled were available for analysis. Median follow-up was 12.6 months (G = 113 pts, 144 for placebo (P = 63 pts). Cox proportional hazards: no significant difference in PFS between dasatinib and placebo (6.7m vs 7.8m, respectively; HR 0.80 favoring placebo, 95% CI 0.57-1.1; p = 0.18) or OS (15.5m vs 20.6m; HR 0.71 favoring placebo, 95% CI 0.46-1.1, p = 0.12). Response rate (CR + PR) was 10.5% for dasatinib and 5.3% for placebo. For the overall survival endpoint, the hypotheses of superiority and non-inferiority of an improved PFS or OS or clinical benefit in terms of reduced symptom burden compared with Bev alone in patients with recurrent GB and does not warrant further investigation. To our knowledge, this trial represents the first prospective Bayesian adaptive randomized therapeutic study against glioblastoma that demonstrates the feasibility of conducting studies with adaptive trial designs in a multicenter setting. Clinical trial information: NCT01266031.

2013 Poster Presentation Session; Displayed in Poster Session (Board #2), Mon, 1:15 PM-4:45 PM, Discuss in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Randomized, placebo-controlled, phase II study of dasatinib with standard chemoradiotherapy for newly diagnosed glioblastoma (GBM), NCCTG N0877 (Alliance). First Author: Nadia N. Laack, Mayo Clinic, Rochester, MN

Background: Dasatinib is a potent oral ATP competitive multi-targeted kinase inhibitor of multiple members of the Src kinase family known to be involved in gliomagenesis, tumor invasion, and radiosensitivity. N0877 is a phase II, open-label, randomized trial evaluating the combination of dasatinib, radiation (RT) and temozolomide (TMZ) in newly diagnosed GBM. Methods: Following a 13 patient phase I dose escalation trial which established the MTD and phase II dose of dasatinib to be 150 mg PO daily when given with RT and TMZ, the randomized placebo-controlled phase II portion of the trial was initiated. The study was approved by the NCI. Randomization was stratified by race (Asian and non-Asian) and extended PFS (HR 0.46, 95% CI 0.25-0.84; p = 0.0137). In the absence of a high powered trial, the treatment plan was designed to detect a hazard ratio of 1.6 or higher in overall survival (OS) between the two arms and a type I error rate of 0.10. Dasatinib or placebo was given orally for 42 days, beginning with the first day of RT (total dose 60 Gy) and first dose of TMZ (75 mg/m2/d). Following a 24 - 42 day rest, patients then received 6 cycles (28 days cycles) of dasatinib or placebo (days 1-28) and TMZ (days 1-5). At the completion of 6 cycles of TMZ + dasatinib/placebo, patients continued on dasatinib/placebo only (28 day cycles) until progressive disease. Results: Data from 187 of 196 patients enrolled were available for analysis. Median follow-up was 12.6 months (G = 113 pts, 144 for placebo (P = 63 pts). Cox proportional hazards: no significant difference in PFS between dasatinib and placebo (6.7m vs 7.8m, respectively; HR 0.80 favoring placebo, 95% CI 0.57-1.1; p = 0.18) or OS (15.5m vs 20.6m; HR 0.71 favoring placebo, 95% CI 0.46-1.1, p = 0.12). Response rate (CR + PR) was 10.5% for dasatinib and 5.3% for placebo. For the overall survival endpoint, the hypotheses of superiority and non-inferiority of an improved PFS or OS or clinical benefit in terms of reduced symptom burden compared with Bev alone in patients with recurrent GB and does not warrant further investigation. To our knowledge, this trial represents the first prospective Bayesian adaptive randomized therapeutic study against glioblastoma that demonstrates the feasibility of conducting studies with adaptive trial designs in a multicenter setting. Clinical trial information: NCT00869401.

2014 Poster Presentation Session; Displayed in Poster Session (Board #3), Mon, 1:15 PM-4:45 PM, Discuss in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Onartuzumab plus bevacizumab versus placebo plus bevacizumab in recurrent glioblastoma (GBM): HGF and MGMT biomarker data. First Author: Timothy Francis Cloughesy, UCLA, Los Angeles, CA

Background: The phase II G027819 study assessed the monovariant MEGF inhibitor, onartuzumab, plus the anti-VEGF antibody, bevacizumab (O+B) versus placebo plus bevacizumab (P+B) in recurrent GBM. Exploratory univariable biomarker analyses correlated efficacy with levels of the MET ligand HGF and MGMT methylation (77). The GBM patients (pts) at 1:1 randomization after chemoradiation were randomized 1:1 to receive O (15 mg/kg, q3w) + B (15 mg/kg, q3w) or P + B until progression. Primary endpoint: progression-free survival (PFS); secondary endpoints: overall survival (OS), objective response rate (ORR), safety, exploratory endpoint: biomarker analysis. Baseline tumor HGF levels were quantitatively assessed by cobas PCR; MGMT methylation was assessed by Quantitative Methylation Specific PCR. Results: In the ITT group (64 O+B, 65 P+B) no difference in PFS, OS or ORR was seen between the arms. A total of 119 pts (58 O+B, 61 P+B) had HGF-PCR results and 110 (56 O+B, 54 P+B) had MGMT data. Assessing the P+B arm only showed that GBM pts may have a higher tumoral expression of hHGF. Conclusions: The hypotheses of superiority and non-inferiority of an improved PFS or OS or clinical benefit in terms of reduced symptom burden compared with Bev+TMZ did not improve the outcome of newly diagnosed GBM patients as compared to standard therapy alone. Clinical trial information: NCT00869401.

2015 Poster Presentation Session; Displayed in Poster Session (Board #4), Mon, 1:15 PM-4:45 PM, Discuss in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase I study of ABT-414 mono- or combination therapy with temozolomide (TMZ) in recurrent glioblastoma (GBM). First Author: Hui K. Gan, Austin Health and Ludwig Institute for Cancer Research, Melbourne, Australia

Background: GBM remains almost universally fatal and new therapies are needed. The epidermal growth factor receptor (EGFR) is a key oncogenic target. ABT-414, an antibody-drug conjugate with a toxic payload (monomethylauristatin E) targeted to activated EGFR, showed efficacy in preclinical models. We report the data of patients (pts) with recurrent GBM (Arms B + C) from an ongoing phase 1, open-label, 3-arm study (NCT01800695). Methods: Eligible pts (≥ 18 years) had recurrent supratentorial GBM and KPS ≥ 70. ABT-414 was given i.v. every 2 weeks combined with TMZ re-challenge (150–200 mg/m2) in Arm B, or Arms B + C. MTD for ABT-414 doses were escalated using a modified continual reassessment method. Primary objectives were safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of ABT-414; secondary objectives included antitumor activity.

Results: As of Jan 15, 2015, accrual included 18 pts in Arm B treated in 4 dose arms (0.5, 1.0, 1.25, 1.5 mg/kg) and 28 pts in Arm C treated at 1.25 mg/kg. Median age was 51/57 years (Arms B/C); 50%/50% were male, 57/65% had KPS ≥ 80, and 11/7 pts had amplified EGFR. Treatment-emergent adverse events (AEs) occurring in ≥ 25% of pts either in Arm B or C were: blindness (n = 1/115), fatigue (n = 6/10), foreign body sensation in the eyes (n = 5/7), periorbital and eyelid edema (n = 5/7), constipation (n = 5/7), and GGT increase (n = 1/5). Grade 3/4 AEs in ≥ 10% of Arm B or C or pts were keratitis (n = 1/3), GGT increase (n = 3/0), fatigue (n = 2/0), and thrombocytopenia (n = 2/0). Dose-limiting toxicities in Arm B were corneal deposits and GGT increase (n = 1 each); none occurred in Arm C during the dose escalations. ABT-414 MTD was 1.25 mg/kg for both arms. Best objective responses were complete response (CR) in 1 pt and partial responses (PR) in 4 pts in Arm B, and 1 CR and 1 PR in Arm C. EGFR amplification was found in all pts with confirmed responses. Confirmed responses were durable, ranging from 5–16 months from first response. Conclusions: The RP2D of ABT-414 in Arm B is 1.25 mg/kg for both arms. The unique ABT-414 safety profile included ophthalmic AEs. ABT-414 appears to have antitumor activity in recurrent GBM pts, particularly those with amplified EGFR. Clinical trial information: NCT01800695.

Impact of bevacizumab added to temozolomide-chemoradiation on time to health-related quality of life deterioration in unresectable glioblastoma: Results of a phase II randomized clinical trial. First Author: Franck Bonnetain, Methodology and Quality of Life Unit, Department of Oncology, EA 3181, University Hospital of Besançon, French National Platform Quality of Life and Cancer, Besançon, France

Background: Two clinical trials investigating the addition of bevacizumab (BEV) to TMZ for glioblastoma (GB) reported promising antitumor activity. The first phase II study was conducted in children, and to assess the toxicity profile.

Methods: EORTC QLQ-C30 and its BN20 brain cancer module were used at baseline, during treatment and every 4 weeks until progression. Time until definitive HRQoL score deterioration (TUDD) was used as a modality of longitudinal HRQoL analyses (Bonnetain et al., EJC 2010), with a 10-point Minimal Clinically Important Difference including or not death as an event. TUDD was estimated with the Kaplan-Meier method. Cox model was used to estimate Hazard Ratios (HR) and its 95% confidence interval (CI). Multivariate Cox model investigated factors associated with TUDD. Results: Among the 134 patients included from 2009 to 2011, 101 patients (75%) filled the baseline HRQoL questionnaires (51 in BEVIRI arm, 50 in TMZ arm). For TUDD or death, patients in BEVIRI arm presented a longer TUDD than those of TMZ arm for 10/15 dimensions of the QLQ-C30 and 10/11 dimensions of the BN20. For example, patients in BEVIRI arm presented a longer TUDD of motor dysfunction than those of TMZ arm (Median 4.6 months (95%CI 3.2-9.4) for BEVIRI vs. 3.3 (95%CI 2.8-6.7) for TMZ, HR = 0.70 (95%CI 0.45-1.08)). A sensorial deficit was associated with shorter TUDD of Weakness of legs dimension or death (HR = 2.74 (95%CI 1.41-5.30). Conclusions: Patients in BEVIRI arm presented a longer TUDD than those of the TMZ arm. These HRQoL results are consistent to those obtained with AVAGLIO trial suggesting HRQoL benefit for patients with BEV. Clinical trial information: 2008-002775-28.

Defining the cutoff value of MGMT gene promoter methylation and its predicative capacity. First Author: Andrea Rocca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Background: Adult glioblastoma (GBM) is the most common type of malignant primary brain tumor. Despite advances in treatment, median survival is between 12 and 15 months. Standard care is concomitant radiotherapy (RT)chemotherapy (CT) and adjuvant temozolomide (TMZ) for 5 cycles. At progression, subsequent treatments are at the discretion of the patient’s physician. MGMT gene promoter methylation status is acknowledged worldwide as a predicative marker. When MGMT promoter values fall into a “methylated” range, a better response to TMZ treatment is expected. Methods: We retrospectively analyzed data from 105 patients with GB treated from January 2014 with bevacizumab (BEV) combined with the wide catchment area of Romagna, Italy. MGMT promoter methylation status was determined by analyzing 10 CpG islands by pyrosequencing. We evaluated whether variability in the methylation profile of each patient can influence the predictive capacity of MGMT promoter methylation and also aimed to identify the best cutoff value. Results: All patients were treated by RT followed by TMZ. MGMT promoter methylation status was classified into three types: unmethylated 0 – 9%, methylated 10 – 29% and methylated 30 - 100%. Statistical analysis showed that an assumed methylation cut-off of 9% led to an overestimation of responders. All of the patients in the 10 – 29% methylation group relapsed before the 18th month. Patients with a methylation status > 30% showed a median overall survival (OS) of 25.2 months compared to 15.2 months in all other patients, indicating that this is the best methylation cut-off. We also analyzed the methylation status of each CpG island in patients’ profiles but, despite observing a great variability in patients’ profiles, none of the CpG islands showed a correlation between single CpG island values and relapse or death (Wilcoxon test and ROC curves). Conclusions: Our results did not highlight an impact of specific CpG island methylation status on the predictive value of MGMT. The predictive role of MGMT promoter methylation was maintained only when 30% was used as cut-off value.

Outcome of neurofibromatosis type 1 patients treated with first line vinblastine for optic pathway gliomas: A Canadian multicenter study. First Author: Alvaro Lassaletta, The Hospital for Sick Children, Toronto, ON, Canada

Background: To date, the first line chemotherapy treatment in the majority of countries for children with NF-1 and OPG is vincristine + carboplatin. Toxicity of this regimen consists mostly in neuropathy, allergic reactions, and hearing loss. Vinblastine has shown promising activity in a phase II study in children with recurrent/refractory low grade glioma (LGG). The aim of this study was to assess the activity of vinblastine in chemotherapy naive children, and to assess the toxicity profile. Methods: Patients < 18 years old with unresectable or progressive LGG were eligible if they had not received any previous treatment with chemotherapy or radiation. Vinblastine was administered weekly at a dose of 6 mg/m2 over a period of 70 weeks. Patients who showed progression on 2 consecutive imaging studies or evidence of clinical progression were removed from treatment. Results: Overall, the study enrolled 54 patients with LGG. A total of 13 patients (24.1%) had NF-1. Patients < NF-1 were younger (median age 3.8 by (range, 1.74-16.36 y) vs. 7 years in non-NF-1. Tumor location in all NF-1 patients was the optic pathway. Treatment was very well tolerated, however, 5 patients (38%) needed dose reductions. Most common toxicity was hematological: only 1 patient who experienced grade 3 + neutropenia (NF-1). None of the non-NF-1 patients developed episodes of febrile neutropenia, no RBC transfusions and no toxic death. Best response to chemotherapy was assessed centrally by an independent radiologist: 2 PR, 1 MR, 8 SD, and 2 PD, for a response rate of 23.1%. At a median follow-up of 5.37 years (3.45 – 6.57 years): Only two NF-1 patients had progression. Five year progression free survival (PFS) was 85.1 ± 9.7% (vs. 42.7±9.3% for all non-NF-1, p = 0.01; and 41.7±14% for non-NF-1 with OPG, p = 0.01). None of the NF1 patients received radiation (0 vs. 6 patients non-NF-1). None patients died of progression (0 vs. 3 patients non-NF-1). Conclusions: Weekly vinblastine is well tolerated and can be used in NF-1 children with OPG as first line chemotherapy with good results. The toxicity profile is lower than with other chemotherapies, offering a better quality of life to these patients. Clinical trial information: NCT00575796.
A multi-institutional prospective observational study of stereotactic radiosurgery (SRS) for patients with multiple brain metastases (BM): Updated results of the JLGK0901 Study—Long-term results of irradiation-related complications and neurocognitive function (NCF). First Author: Masaaki Yamamoto, Katsura Hospital Mito GammaHouse, Hitachi-Naka, Japan

Background: The JLGK0901 study (UMIN ID: 00001812) showed the non-inferiority of SRS alone as initial treatment for patients with 5-10 BMs as compared to those with 2-4 in terms of overall survival at disease secondary endpoints (Lancet Oncol 2014;15:387-95). However, a study weakness was that observation periods were not long enough to allow confirmation of the long-term safety of SRS alone in patients with 5-10 BMs.

Methods: This was a prospective observational study of SRS-treated patients with 1-10 newly-diagnosed BMs enrolled at 23 facilities between 3-1-2009, and 2-15-2012. Results: The 1194 eligible patients (471 females, 723 males, mean age 66 [range; 30-91] years), enrolled from March 2009 to February 2012, were categorized into three tumor number groups, i.e., A: 1 (435), B: 2-4 (531) and C: 5-10 (208). During observation periods ranging from 0.3 to 67.5 (median; 12.0, IQR; 5.8-26.5) months as of the end of 2014, SRS-induced complications occurred in 145 patients (12.1%) with the median post-SRS period being 9.3 (IQR; 4.1-17.4) months; 46, 54, 29, and 11, and 5 for CTCAE grades 1, 2, 3, 4, and 5, respectively. Cumulative incidences of complications determined with a competing risk analysis (group B vs C) were 8.3% vs 5.8%, 10.9% vs 10.6%, 11.3% vs 12.1% and 12.2% vs 12.9% at the 12th, 24th, 36th and 48th post-SRS months, respectively.

These statistical results were confirmed to be similar even with missing data analyses. Conclusions: There were no significant differences in the incidences of post-SRS complications and NCF maintenance between groups A and C. We concluded that the already-reported non-inferiority hypothesis of SRS alone for patients with 5-10 versus 2-4 BMs gains further support, in terms of treatment safety, from this longer-term follow-up study. Clinical trial information: NCT0001812.

A phase 1I study of temozolomide in the treatment of adult patients with supratentorial low-grade glioma. First Author: Michael Traut Wahl, UC San Francisco, San Francisco, CA

Background: Optimal adjuvant management of low-grade gliomas (LGGs) remains controversial. Radiotherapy has been shown to improve progression-free survival compared to observation, but carries the potential for substantial late toxicity. In an effort to delay or obviate the need for radiation, there has been increasing interest in the use of adjuvant chemotherapy in LGGs. However, there is a dearth of prospective studies with long-term follow-up elucidating the efficacy of adjuvant chemotherapy without radiation in patients with newly diagnosed LGGs. Methods: Patients over the age of 18 with histologically proven supratentorial LGG (WHO grade II) who underwent subtotal resection or biopsy were eligible for enrollment. Daily temozolomide (TMZ) was administered at 200 mg/m² for 5 days, and repeated every 28 days for up to 12 cycles or until disease progression. Patients were assessed for radiographic response and progression with MRIs every two months during and after treatment. The primary outcome was objective radiographic response rate; secondary outcomes included progression-free and overall survival. Results: 120 patients were enrolled in the trial (57 oligodendrogliomas, 20 oligoastrocytomas, 43 astrocytomas), with a median follow-up of 6.9 years. Objective responses were seen in 7 patients (6%), and 86% demonstrated stable or improved disease during treatment with TMZ. Median progression-free survival was 4.2 years, and median overall survival was 9.7 years. Univariate analysis demonstrated that aged ≥65 years (HR 1.62, p = 0.025), IDH negative histology (HR 2.45, p = 0.009) and lack of tumor crossing midline (p < 0.001) were associated with improved overall survival. Treatment was well tolerated with minimal toxicity. Conclusions: This high-risk cohort of newly diagnosed LGGs undergoing subtotal resection or biopsy, adjuvant TMZ alone achieved progression-free survival comparable to that seen in similar cohorts treated with adjuvant radiation. TMZ was very well tolerated, and could be considered as adjuvant therapy in appropriately selected patients. Work is ongoing to determine the demographic, pathologic and molecular characteristics of patients who are optimal candidates for adjuvant TMZ. Clinical trial information: NCT00313729.

A randomized, global, multi-center study of whole-brain radiation therapy (WBRT) plus veliparib or placebo in patients (pts) with brain metastases (BM) from non-small cell lung cancer (NSCLC). First Author: Pierre Chabot, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada

Background: Veliparib (V) is a potent, orally bioavailable PARP inhibitor that crosses the blood-brain barrier. Phase 2 trials in BRCA-mutant metastatic unselected pts in combination with platinum-based chemotherapy have demonstrated efficacy of V. Plus radiation has shown promising efficacy in preclinical models and in clinically colonized with SRS. Methods: Patients were randomized 1:1:1 to WBRT plus V 50 mg BID (V50), V 200 mg BID (V200), or placebo BID. Treatment began within 28 days (d) of diagnosis. Pts received 30 Gray WBRT in 10 fractions, V50, V200, or placebo was self-administered starting on day 1 of WBRT and continuing until 1 d after completion. The primary endpoint was overall survival (OS). Survival was assessed at 2 month (m) intervals for 6 m then every 3 m (≥6 m). Pts who received ≥1 dose were included in the safety analyses; AEs were compared across arms using Fisher’s exact test. Results: 507 pts were randomized. OS, intracranial response rate, and time to or radiographic progression were not statistically significantly different between any of the V arms and the P arm. There were no differences in all grade adverse drug reactions (ADRs) across arms and a modest improvement in grade 3/4 AEs in the V arms. Conclusions: Although preclinical and early clinical data suggested that V might synergize with radiotherapy, there was no difference in multiple study endpoints between V50 or V200 and P in this setting. Safety parameters observed in the V arms were generally similar to the P arm; no new safety signals of V were identified. Clinical trial information: NCT01657799.
A phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma. First Author: Xuehe Cai, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA

Background: Tivozanib, an oral, pure VEGFR tyrosine kinase inhibitor is an anti-angiogenesis drug which aims to modulate the tumor blood supply. This phase II study was designed to test the effectiveness of tivozanib on tumor vasculature in patients with recurrent GBM. Methods: Ten adult patients with recurrent GBM, median age of 62 (range 51-73), were enrolled on a Simon 2-stage design study and treated with tivozanib 1.5mg daily, 3 weeks on/1 week off in 28 day cycles. Brain MRI was done at baseline and after each cycle. The enhancing tumor and surrounding area of abnormal FLAIR hyperintensity were outlined and median tumor cerebral blood flow (CBF) and cerebral blood volume (CBV) values were derived from dynamic susceptibility contrast MRI to assess the performance of tivozanib. Vascular architecture (VAI) was used to measure tumor vessel calibers and relative oxygen saturation. A t-test was used to compare baseline MRI parameters to the pre-cycle 3 visit. A univariate Cox model was used to test the association of each MRI parameter with time to progression. Results: Best MacDonald criteria responses were: CR (1), PR (1), SD (4), PD (4) and the median duration of response was only 3.6 mo (1.7-3.8mo) so the study was stopped per planned stopping rule. One patient was taken off study for unacceptable skin toxicity and nine patients for progressive disease. Given the dropout rate, only data up to cycle 3 was included in this analysis. There was no statistically significant change in enhancing tumor volume (p = 0.70), FLAIR volume (p = 0.31), or median CBV (p = 0.13) or median CBF (p = 0.54) within the enhancing tumor. Within the FLAIR hyperintensity, median CBV (p = 0.12) and median CBF (p = 0.41) also did not change significantly. No parameter was associated with time to tumor progression. VAI showed no change in vessel calibers or tumor vascularity. Conclusions: Tivozanib was well tolerated but limited impact on brain tumor vasculature. Clinical trial information: NCT01846871.
Conclusions: Expression of the enzyme alkylpurine-DNA-N-glycosylase (APNG) has been associated with poor outcome in patients with glioblastoma multiforme (GBM). APNG is part of the base excision repair system, and expression of APNG is related to resistance towards temozolomide (TMZ). This study evaluates the prognostic value of APNG in a population-based cohort of 185 GBM patients diagnosed between 2005 and 2009. Due to GBM’s cellular heterogeneity, APNG contribution from non-tumor cells was excluded. Methods: APNG expression was evaluated using image analysis and a novel quantitative immunohistochemical (IHC) assay (qIHC, Dako), where APNG protein levels were represented through dots. Non-tumor cells, which were found to express APNG, were excluded using an IHC/qIHC double-staining. To verify the qIHC results, APNG was measured in 177 of the patients using a quantitative in-house developed APNG immunofluorescence (IF) assay. MGMT methylation status was obtained in 152 patients by pyrosequencing. Results: Using qIHC, median expression of APNG was 0.31 dots/cell (range 0.039-0.96). An optimal cut-point was identified dichotomizing the patients at an APNG value of 0.24 (25% vs. 75% of the patients). In Cox regression high expression of APNG was associated with better overall survival (OS) (HR 0.53, p = 0.001) adjusting for the effect of age, performance status, tumor crossing midline, treatment and gender. APNG was associated with better OS (HR 0.57, p = 0.012) when adjusting for MGMT status. Retesting the cohort using IF, demonstrated similar results (HR 0.81, p = 0.2). Patients with methylated MGMT promoters and high APNG expression demonstrated a better OS, than with non-methylated MGMT promoters and low APNG expression (HR 0.55, p = 0.042). Conclusions: APNG measured by qIHC was found to be an independent significant prognostic factor for OS in GBMs. This was supported by IF measurements. Removing bias associated with APNG expression in non-tumor cells in both assays has, in this study contributed substantially to analyze the prognostic value of APNG in GBM patients. We expect that APNG qIHC can potentially identify patients who will not benefit from treatment with TMZ.

Differential molecular expression profile according to glioblastoma (GB) location. First Author: Emilie Denicolai, AMU, Marseille, France

Background: Initial GB topography occurred throughout the brain without established specific molecular profile. Our previous study suggested that cortical and subventricular regions exhibit distinct transcriptome profile. Based on these preliminary results, our objective was to evaluated the expression of ten selected genes (VEGFC, FLT4, MET, HGF, CH3L1, PROM1, NOTCH1, DLL3, PDGFRa, and BDNF) according to GB locations. Methods: Fifty nine patients with newly GB were retrospectively included according to the availability of pre-surgery MRI and frozen tumors. Tumor locations were classified into cortical and periventricular (PV) locations, which were next segregated according to cerebral lobes: cortical fronto-parietal (N = 19), cortical temporal (N = 5), PV fronto-parietal (N = 12), PV temporal (N = 12), and PV occipital (N = 12). Expression levels of the selected genes were determined using real-time quantitative PCR, and were correlated with tumor locations. Results: Cortical GB were characterized by a lower expression of two mesenchymal genes, VEGFC (p = 0.001) and HGF (p = 0.001), than periventricular GB. Among cortical GB sub-groups, genes expressions were homogenous. In contrast, PV locations exhibit distinct expression profiles. PV temporal tumors were associated with higher expression of two proneural and cancer stem cell genes, NOTCH1 (p = 0.028) and PROM1 (p = 0.033) while PV fronto-parietal tumors were characterized by a higher expression of FLT4 (p = 0.037) and CH3L1 (p = 0.006). PV occipital GB were associated with a lower expression of VEGFC (p = 0.032) than other PV GB and an over-expression of MET correlated to MET amplification. Finally, VEGFC and HGF expressions were correlated (p < 0.001) as well as NOTCH1 and PROM1 expressions (p < 0.001).

Conclusions: Our results suggest a differential expression profile of the selected genes according to initial GB location. These results should be validated in a prospective study.

A phase I trial of intravenous liposomal irinotecan in patients with recurrent high-grade gliomas. First Author: Jennifer Leigh Clarke, UC San Francisco, San Francisco, CA

Background: Treatment options for recurrent malignant glioma are limited. Preclinical activity of irinotecan has been seen in glioma models but only modest efficacy has been noted in clinical studies, perhaps related to drug distribution and/or pharmacokinetic limitations. In preclinical testing, liposomal irinotecan (nal-IRI, also MM-398, PEP02) demonstrates prolongation of drug exposure and higher tissue levels of drug due to slower metabolism. A Phase I study was undertaken in advanced solid tumor patients in Taiwan, and the MTD was 120 mg/m²; UGT1A1 genotyping was not prospectively undertaken in that solid tumor study. Objectives: To assess the safety and pharmacokinetics (PK) of nal-IRI and to determine the maximum tolerated dose (MTD) in patients with recurrent malignant glioma stratified based on UGT1A1 genotyping. Methods: This Phase I study in recurrent malignant glioma stratified patients by UGT1A1 status, to homozygous WT (“WT”) vs heterozygous WT/28 (“HT”). Patients who were homozygous 28 were ineligible. Eligibility criteria included age > = 18, KPS > = 60, not on enzyme-inducing drugs (including enzyme-inducing seizure medications), and no prior treatment with irinotecan. The design was a standard 3 + 3 Phase I design. Patients who were WT were started at 120 mg/m² (the MTD from the Taiwanese study) with dose increases in 60 mg/m² increments. Patients who were HT were started at 60 mg/m², with dose increases in 30 mg/m² increments. Dosing was given IV every 3 weeks. The DLT assessment period was 1 cycle (21 days).

Results: In the WT cohort, the MTD was 120 mg/m². In the HT cohort, the MTD was 150 mg/m². DLTs in both cohorts included diarrhea, some with associated dehydration and/or fatigue. Analysis of PK data is in process, and will be presented at the meeting. Conclusions: Nal-IRI had no unexpected toxicities when given via IV. The toxicity profile of the drug was felt acceptable to move forward with additional testing using convention-enhanced delivery into intracranial tumors, and such a Phase I study is currently enrolling at our institution. Clinical trial information: NCT00734682.
Long-term survival in patients with primary CNS lymphoma: Results from the G-PCNSL-SG1 trial. First Author: Patrick Roth, Department of Neurology, University Hospital of Tübingen, Tübingen, Germany

Background: Although potentially curable, primary CNS lymphoma (CNS) is still a therapeutic challenge and only a minority of patients survive longer than 5 years. The factors which define the prognosis of PCNSL patients have only been partially elucidated. A more detailed insight into the parameters which promote long-term survival in PCNSL may allow for more patient-tailored therapies. Methods: We analysed the dataset of patients enrolled into G-PCNSL-SG1, the largest phase 3 study performed in PCNSL evaluating the role of whole-brain radiotherapy after high-dose methotrexate-based chemotherapy. Out of 459 patients with sufficient data quality, we identified 89 patients who had survived for five years or more after surgery and diagnosis of PCNSL. This long-term survival (LTS) cohort was compared with two different control groups: first, patients who had died within one year of diagnosis for any reason (control 1 = C1 patients) and second, all patients who had survived for more than one year, but who did not reach a survival of 5 years from diagnosis (control 2 = C2 patients). Results: We compared baseline characteristics and treatment of the 89 patients surviving for 5 years or more with the C1 and C2 control populations. Patients within the LTS cohort were younger and had a higher performance score at diagnosis. Furthermore, they had less frequently multiple tumor manifestations, better renal function and were less often affected by cardiovascular disease. High-dose methotrexate-based treatment resulted in a higher complete response rate and was associated with less toxicity, particularly a reduced frequency of myelosuppression. Within the group of LTS patients, age at diagnosis is the only prognostic factor for conditional survival from 5 years on. Conclusions: Within this large patient population, survival of 5 years or more was reached by approximately a fifth of the patients. Young and fit patients with single lesions are most likely to survive for 5 years or more following diagnosis of PCNSL.

Phase II study of bevacizumab and vorinostat for recurrent glioblastoma. First Author: Ashley Ghiaiseddin, Duke University Medical Center, Durham, NC

Background: Prognosis for recurrent glioblastoma (GBM) remains dismal with a 9-15% 6-month progression-free survival (PFS). However, the addition of bevacizumab (BEV), a humanized monoclonal IgG1 antibody with effects at human vascular endothelial growth factor, has improved 6-month PFS to 40-50% and median overall survival (OS) to 9.2 months. Vorinostat (VOR) is a small molecule derivative of hydroxamic acid that crosses the blood-brain barrier and has anti-tumor effects directly by inhibition of histone deacetylase and indirectly by anti-angiogenic promotion. In light of VOR’s mechanism of action and favorable toxicity/safety profile, we sought to evaluate the efficacy of VOR combined with BEV in recurrent GBM. Methods: A phase II single-center open-label, single arm study was performed to evaluate VOR and BEV in recurrent GBM. Primary endpoint was 6-month PFS. Secondary endpoints were safety/tolerability, radiographic response, PFS, and OS. Major eligibility criteria included age ≥18 years, KPS = 70 and ≤2 prior progressions. Dosing regimen of BEV was 10mg/kg IV q2weeks combined with VOR 400mg PO daily for 7 days, then 7 days off in a 28 day cycle. Forty patients with GBM path had been enrolled. To date, median follow-up time is 13.2 months with 6-month PFS of 30% (95% CI: 16.8%, 44.4%). Median OS is 10.4 months (95% CI: 9.3-13.1 months). Objective radiographic responses included 9 partial responses, 29 stable responses, and 1 radiographic progression with 1 patient death noted. Most common treatment-related adverse events were neutropenia (55%), febrile neutropenia (43%), neutropenia (33%) and hypertension (33%). Most common treatment-related grade 3-4 toxicities were lymphopenia (55%), leukopenia (43%), neutropenia (33%) and hypertension (33%). Grade 4 toxicities were leucopenia (3%), neutropenia (3%), sinus bradycardia (3%), and thromboembolic event (3%). Two deaths occurred on study; one due to disease progression and the other was a sudden death of vascular origin. Conclusions: Initial findings of this study suggest that VOR and BEV combination therapy was well-tolerated in recurrent GBM, although it did not improve 6-month PFS when compared to BEV monotherapy. There was a trend towards improved OS in VOR and BEV in comparison to BEV monotherapy. Continued follow-up and research is needed to delineate better the role of chemotherapy in combination with BEV. Clinical trial information: NCT01738646.

Timed-sequential therapy with mibefradil and temozolomide in patients with recurrent high-grade gliomas: A phase I Adult Brain Tumor Consortium study. First Author: Matthias Holdhoff, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Mibefradil (MIB) is a selective T-type calcium channel blocker that had previously been approved for treatment of hypertension. MIB has shown significant preclinical activity in many cancers, including high-grade gliomas (HGG). MIB was found to impact cell cycle activity with arrest at G1/S in tumor cells, suggesting a possible chemo-sensitizing effect of the drug if given prior to cytotoxic therapy. This was a multi-center open label phase I study to determine the maximum tolerated dose (MTD) of MIB followed by temozolomide (TMZ) in recurrent HGG and to assess the safety and tolerability of MIB, particularly its myelosuppressive effects, in a timed-sequential combination with TMZ. Methods: Adult patients with recurrent HGG (WHO grade III and IV) who were selected to likely have a benefit from repeat treatment with TMZ (no progression ≥ 3 months from their last dose of TMZ) were eligible. MIB was given in 4 daily doses (QID) for 7 days followed 24 hours later by standard TMZ at 150-200 mg/m² for 5 days per 28-day cycle. Dose escalation of MIB was done using a modified 3 + 3 design, followed by an extension cohort of 10 patients at the MTD. Results: 27 eligible patients with recurrent HGG participated (at time of enrollment, 21 with WHO grade IV, 6 with grade III; median age 50y; median KPS 90). The MTD of MIB was determined as 87.5 mg po QID. Most common side effects (grade 1 and 2) were fatigue, nausea, constipation and anorexia. Grade 3 elevation of ALT/AST was observed in one patient. Dose limiting toxicities were elevation of ALT/AST and sinus bradycardia. 5 partial and 1 complete responses were observed based on response by the sites (response rate 22%; 95% CI:9.4-42%). Plasma concentrations of MIB achieved a steady-state after 4 days of dosing with a mean peak concentration of approximately 1,700 ng/ml. The MTD was determined at a ratio of 1.1 at the MTD. Conclusions: MIB followed by TMZ was well tolerated in patients with recurrent HGG. The MTD for MIB in this setting was determined as 87.5 mg po QID. The lack of toxicity, including extensive myelosuppression, and the presence of responses in this selected patient population suggests that this regimen deserves further investigation. Clinical trial information: NCT01480050.

Patterns of response and relapse of primary central nervous system lymphomas (PCNSL) following first line of high-dose methotrexate-based chemotherapy (hdMTX): Analysis of a prospective ANOCEF randomized phase II trial. First Author: Emeline Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France

Background: Detailed neuro-imaging analyses of PCNSL are limited. Our objective was to evaluate MRI findings in PCNSL patients treated with hdMTX without radiotherapy, with a particular emphasis on T2-FLAIR MRI abnormalities. Methods: We reviewed MRI (T1, T1 post-gadolinium and T2 FLAIR) findings of approximately 1,700 patients enrolled in a randomized multicenter phase II trial (NCT00503594) evaluating two hdMTX regimens (MPV-A and MTX-temozolomide), conducted in patients aged 60 and older. Response rate (IPCG criteria, number and volume of enhancing lesions, anatomical site, site of relapse and patterns of relapse were analyzed and correlated with outcome. Landmark analyses were performed at 2 and 4 months. Results: Objective responses (OR) were: complete response (CR): 56%, uncertain CR: 4%, partial response: 18%, stable disease: 7%, progressive disease: 15%. On multivariate analysis, location in the posterior fossa (p = 0.008) and tumor volume (p = 0.006), but not lesion number, were significantly associated with survival. OR at the first MRI (2months) and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both. Progression rates were 15% at 2months and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both. Progression rates were 15% at 2months and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both. Progression rates were 15% at 2months and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both. Progression rates were 15% at 2months and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both. Progression rates were 15% at 2months and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis (p < 0.001 and p = 0.004 respectively). Early versus delayed CR did not impact survival.
Comparative impact of treatment on clinical benefit in patients with glioblastoma (GBM) enrolled in the phase II trial of ICT-107. First Author: Terris S. Armstrong, The University of Texas Health Science Center School of Nursing, Houston, TX

Background: This study was a randomized double blind placebo-controlled phase 2 trial of dendritic cell(DC) Vaccine ICT-107 following standard treatment in newly diagnosed patients with GBM. Although OS was not different, PFS was longer in those receiving the vaccine. To evaluate the clinical benefit of this prolonged DFS, Karnofsky Performance Status (KPS) and steroid dosing, as well as patient reported QOL using the Functional Assessment of Cancer Therapy –Brain (FACT-BR) were evaluated during the progression free period. Methods: The FACT-BR was completed by patients at baseline, and longitudinally during the maintenance phase after four induction vaccinations and at the end of study visit. Corticosteroid dosing and KPS were evaluated throughout the progression free period at monthly timepoints for 12 months and every 6 months thereafter. Between arm differences were evaluated using Fisher test or ANOVA statistics. A p-value of 0.05 was considered significant when comparing the two treatment groups for all analyses. Results: Participants (81 patients in the ICT-107 arm and 43 patients in the control arm) completed baseline FACT-BR assessment (97% compliance), with 84% and 68% completing end of cycle 1 and end of study assessments respectively. Quality of life, as measured by the FACT-BR, was maintained equally until progression for end of cycle 1 and end of study assessments respectively. Quality of life, as measured by the FACT-BR, was maintained equally until progression for end of cycle 1 and end of study assessments respectively. The maximum “tumor-to-brain ratio” (TBRmax) and the minimum “time-to-peak” (TTPmin) were analyzed as FACT-BR parameters. Clinical outcome measures were progression free survival (PFS) and overall survival (OS). Results: Vessel density varied from 1 to 25% and did not have an impact on OS or PFS (p = 0.09/0.6); furthermore, it was not intercorrelated with IDH1 mutation status or with TTPmin. 54% of all patients showed no IDH1 mutation. The IDH 1 status did not correlate with TBRmax (2.9 vs. 3.2 without vs. with IDH 1 mutation; p = 0.24), but with TTPmin (p < 0.001): 37/41 (90%) patients with a TTPmin < 12.5 min had a significantly shorter PFS (10.0 vs. 37.4 months vs. 37.4 months and 9.8; p < 0.001) and OS (20.5 and 22.0 months versus median not reached, respectively; p < 0.001). In the multivariate analysis, both TTPmin and IDH 1 status were independent factors of OS. Conclusions: Anaplastic gliomas, early TTPmin < 12.5 min is associated with a lack of IDH 1 mutation, but not with vessel density, MGMT mutation status or LOH 1p/19q. TTPmin and IDH1 mutation are both independently associated with clinical outcome.

Prognostic model of lower grade gliomas. First Author: Kosuke Aoki, Department of Neurosurgery, Nagoya University School of Medicine, Nagoya City, Japan

Background: Lower grade gliomas (LGGs, WHO grade II/III glioma) account for one third of all gliomas. Most LGGs generally show a slow progression, but some show a more aggressive clinical course. Large-scale and comprehensiveness in genetical and clinical studies enables establishment of a reliable prognostication system. Methods: Status of somatic mutations and copy number variations (CNVs) generated by whole exome targeted sequencing and SNP array were investigated for 653 patients combined 269 Japanese patients with publically available 384 patients from the Cancer Genome Atlas, who were randomly divided into training (327 patients) and validation sets (326 patients). LGGs were genetically classified into 3 types according to IDH1 mutation and 1p/19q loss of heterozygosity (LOH): Type 1 (mutated IDH with 1p/19q LOH), Type 2 (mutated IDH without 1p/19q LOH), and Type 3 (IDH wild type) which also well correlated with overall survival (OS) (Nature Genetics, in press). In the current study, we sought significant risk factors in each LGG type contributing OS using Cox regression analysis and Akaike information criterion. We validated the accuracy of this classifier in the validation set. Results: In the training set, significant risk factors were extracted in Types 1 and 3, but not in Type 2. These types were sub-grouped into low- and high-risk groups (HR = 3.13, 2.81 and 95% CI = 1.36-7.19, 1.25-6.32 respectively). Eventually, all LGGs were divided into low- and intermediate- and high-risk group, showing significantly different OS. The performance of the new model was evaluated by receiver operator characteristic analysis, which showed significantly higher accuracy than previously reported clinical/histological parameters, in particular for long-term prognosis. Conclusions: We established a new classifier based on genetic parameters, which provides a reliable tool for predicting OS in LGG patients and should be useful to guide an individual molecular-targeted therapy.

Phase I study of vorinostat combined with isotretinoin and temozolomide in adults with recurrent malignant gliomas. First Author: Marta Penas-Prado, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Vorinostat (Vor), a histone deacetylase inhibitor, has shown promising activity in recurrent GBM. Preclinical studies demonstrated that Vor can overcome resistance to isotretinoin (cRA) and temozolomide (TMZ). We hypothesized that Vor could overcome resistance to cRA and TMZ in the treatment of recurrent gliomas. Carboplatin (CBP) was originally selected as the cytotoxic drug since eligible patients would have failed prior standard TMZ therapy. Methods: We conducted a Phase I study of combination of these agents preceding a proposed adaptive randomized 3-arm Phase II study. Adults with recurrent malignant glioma were enrolled into one of 3 arms. Arm 1: Vor + cRA, Arm 2: CBP + cRA, or Arm 3: Vor + cRA + CBP. A total of 38 patients were enrolled. In an interim analysis of 53 cases, patients without IDH 1 mutation or with a TTPmin < 12.5 min had a significantly shorter PFS (10.0 vs. 37.4 months vs. 37.4 months and 9.8; p < 0.001) and OS (20.5 and 22.0 months versus median not reached, respectively; p < 0.001). In the multivariate analysis, both TTPmin and IDH 1 status were independent factors of OS. Conclusions: In anaplastic gliomas, early TTPmin < 12.5 min is associated with a lack of IDH 1 mutation, but not with vessel density, MGMT mutation status or LOH 1p/19q. TTPmin and IDH1 mutation are both independently associated with clinical outcome.

Correlation of dynamic 18FET-PET with IDH 1 mutation for prediction of outcome in anaplastic astrocytoma WHO II independently from tumor vascularity. First Author: Tadashi Soga, Nagoya University School of Medicine, Nagoya, Japan

Background: Patients with an anaplastic glioma (WHO II) without IDH1 mutation have a comparable disease course to glioblastoma. Dynamic 18FET-PET has been shown to provide prognostic information in malignant glioma independent of other clinical parameters. Here, we analyzed whether dynamic parameters acquired from 18FET-PET imaging correlate with IDH1 mutation status or tumor vessel density regarding the clinical course in anaplastic astrocytoma. Methods: 96 patients with a glioma WHO II who received a 18FET-PET at primary diagnosis were analyzed with respect to IDH1/2 mutation, MGMT promoter methylation, LOH 1p/19q status and vascularity (vessel density quantified by CD34-positive tumor area). The maximum “tumor-to-brain ratio” (TBRmax) and the minimum “time-to-peak” (TTPmin) were analyzed as 18FET-PET parameters. Clinical outcome measures were progression free survival (PFS) and overall survival (OS). Results: Vessel density varied from 1 to 25% and did not have an impact on OS or PFS (p = 0.09/0.6); furthermore, it was not intercorrelated with IDH1 mutation status or with TTPmin. 54% of all patients showed no IDH1 mutation. The IDH 1 status did not correlate with TBRmax (2.9 vs. 3.2 without vs. with IDH 1 mutation; p = 0.24), but with TTPmin (p < 0.001): 37/41 (90%) patients with a TTPmin < 12.5 min had a significantly shorter PFS (10.0 vs. 37.4 months vs. 37.4 months and 9.8; p < 0.001) and OS (20.5 and 22.0 months versus median not reached, respectively; p < 0.001). In the multivariate analysis, both TTPmin and IDH 1 status were independent factors of OS. Conclusions: In anaplastic gliomas, early TTPmin < 12.5 min is associated with a lack of IDH 1 mutation, but not with vessel density, MGMT mutation status or LOH 1p/19q. TTPmin and IDH1 mutation are both independently associated with clinical outcome.
Effectiveness of transcranial magnetic stimulation in neurooncological patients. First Author: Dmitry P. Atmachidi, Rostov Scientific Research Institute of Oncology, Rostov-on-Don, Russia

Background: Development of technologies of neurooncological treatment has not solved the problem of treatment for malignant brain tumors. Neurological and somatic complications reduce the length and quality of life of patients. Development of systemic therapeutic approach showed the effectiveness of multisystem influence factors. They include low-intensity extremely low frequency variable and static magnetic fields (ELFMF and SMF). The purpose of this study was to improve the results of complex treatment for malignant brain gliomas using transcranial magnetic stimulation (TMS). Methods: 30 patients received TMS during adjuvant chemoradiotherapy (CRT) on days 1-20 of the treatment: ELFMF to hypothalamus projection with frequency 0.03; 3; 9 Hz, induction from 5 to 0.8 mT, exposure 7 min.; and in 20 min. - SMF to the area of operation with induction 20 mT, exposure 15 min. X-ray computed tomography was performed using Toshiba-Asteinium 2002. Toxicity was evaluated according to CTC-NCI criteria, cerebral symptoms and somatic status (ECOG-WHO performance status) - according to the scale, Karnofsky Performance Score and identification of integral reactions of the body. Results: Remission maintained in CRT + TMS in 93.2% of 4.6 patients vs. 40-91% in the control, 2-year survival increased by 2.4 times. Rate and severity of toxic complications, especially neurological ones (cerebral symptoms, disturbances of speech and motor functions) reduced significantly. Dynamics of somatic status improved (0.32 vs. 0.18), as well as Karnofsky index (9.3 vs. 2.6% in the control, p<0.05). Rate of stress development decreased by 10.8 times after TMS, antistress responses prevailed. Conclusions: TMS in complex treatment for malignant brain gliomas provides protective effect on homeostatic regulation systems, increases body resistance, optimizes rehabilitation and improves quality of life of patients.
A phase 2 study on efficacy, safety and intratumoral pharmacokinetics of oral selinexor (KPT-330) in patients with recurrent glioblastoma (GBM).

**Background:** Patients (pts) with recurrent GBM have few treatment options and a poor prognosis. Selinexor is an oral inhibitor of XPO1 mediated nuclear export resulting in nuclear retention of multiple tumor suppressor proteins (TSPs) including p53, pRB, CDKN2A, p21 and FOXO. Mean IC_{50} of selinexor in pt derived GBM neosphere cultures was 1.33 nM. In a pt derived orthotopic murine xenograft model, selinexor demonstrated marked inhibition of tumor growth in vivo and prolongation of survival (>2x). **Methods:** This study (NCT01986348) is an open label, multicenter, two-arm phase II trial enrolling pts with recurrent GBM after radiation therapy with concurrent and adjuvant temozolomide. Pts in Arm A received 3 doses (50 mg/m^2) of selinexor prior to surgery, and resumed selinexor after surgery. Pts in Arm B received selinexor alone (50 mg/m^2 BIW) until disease progression. **Results:** (Jan 22, 2015) 7 pts (6/1/0.1, median age 57, 1–2 prior treatment regimens) were treated on Arm A and 15 pts (11/4, M/F, median age 62; 1–3 prior treatment regimens) were treated on Arm B. Mean plasma PK concentration was 999 nM (311-2071 nM) and mean tumor concentration was 136 nM (40-291 nM) in 6 pts. Grade 1/2 AE’s (Arm B) included thrombocytopenia (27%/27%), anorexia (13%/33%), fatigue (7%/40%), and hyponatremia (47%/0%). One Grade 3 AE was reported in ≥ 2 pts (fatigue) and no Grade 4 AEs were reported. Investigator reported best responses for 12 evaluable pts (Arm B): 2 partial responses (17%), 4 stable disease (33%) and 6 progressive disease (50%). Analysis of XPO1 and TSP expression in tumor tissue is ongoing. **Conclusions:** Oral selinexor at 50 mg/m^2 BIW achieves concentrations in GBM tissue exceeding the IC_{50} in pre-clinical models. Main toxicities are fatigue and anorexia. Partial responses and stable disease were observed. Clinical trial information: NCT01986348.

**2046 Poster Session (Board #35), Mon, 1:15 PM-4:45 PM**

**IDH 1/2 status and low grade gliomas (LGG): Correlation with outcome upfront Pignatti criteria and molecular profile in a retrospective analysis of a single-centre cohort.**

**First Author:** reli Bezu, University of Bonn, Germany, Bonn, Germany

**Background:** Current therapy of LGG is based on clinical, radiologic and histologic (Pignatti prognostic classification) features. In the last years genomic profile of LGG has been investigated showing a new tool to guide therapy. **Methods:** IDH analysis was performed by IDH1 and IDH2 genes sequencing in a series of 58 LGGs diagnosed from 1991 to 2012 and correlated with histology, Pignatti classification, molecular profile (p53 expression, 1p19q deletion status and MGMT promoter methylation) and outcome. **Results:** 56.9% of the pts were male and mean age was 45 years. Histological distribution was 39.7%, 22.4% and 37.9% for Astrocytoma (A), Oligodendroglioma (OD) and Oligoastrocytoma (OA), respectively. Surgical resection was total in 41.4%, subtotal in 19% and only biopsy in 39.7% of the cases. Pts were classified by Pignatti criteria. Immediate post-surgery therapy was administered performed in 41.4% of pts. IDH alterations were found in 61.9% (26/42), 1p19q codeletion in 46.3% (25/54), overexpression of p53 in 17.3% (9/52) and MGMT methylation in 40.4% (19/47) of the cases. Median TTP was 61.6 months (95% CI 25.3-97.9) and median OS was 109.7 months (95%CI 73.0-146.5). In univariate analysis, 1p19q codeletion (p = 0.045) and IDH mutation (p < 0.001) were associated with better TTP. Median OS was correlated with Pignatti classification (p = 0.024) and IDH mutation (p < 0.001). A trend to a better OS was observed with 1p19q codeletion (p = 0.052) and MGMT methylation (p = 0.068). In multivariate analysis, IDH mutation was the only independent prognostic factor after adjustment for histology, molecular profile and Pignatti criteria in terms of OS (HR = 0.120, 95%CI 0.030-0.459, p = 0.002) and TTP (HR 0.237, 95%CI 0.072-0.779, p = 0.018). **Conclusions:** Our findings confirmed the favorable prognostic independent value of IDH mutation in LGG over other criteria.

**2047 Poster Session (Board #36), Mon, 1:15 PM-4:45 PM**

**Time to response (TTR) and early tumor shrinkage (ETS) in recurrent glioblastoma patients treated with bevacizumab: an exploratory analysis of the prospective randomized AVAREG (ML25739) phase II study.**

**First Author:** Enrico Franceschi, Bellaria Hospital, Bologna, Italy

**Background:** The treatment of recurrent glioblastoma (GBM) remains an open issue, and the role of bevacizumab (BEV) has been widely debated since a few studies compared this agent with the standard treatments. **Methods:** a multicenter, randomized (2:1), phase II study (EudraCT: 2011-001363-46) with BEV 10 mg/kg iv every 2 weeks or fotemustine (FTM) 75 mg/m^2 iv day 1-8-15 followed, after a 35 days interval, by fotemustine 100 mg/m^2 every 3 weeks, was conducted. The primary endpoint was overall survival at 6 months (OS-6). ETS was assessed with central review exploratory analysis. TTR contrast enhancing area at first disease assessment (p = 0.05, HR = 0.46, 95%CI:0.21-1.00) and ETS > 15% in T1 contrast enhancing area at first disease assessment (p = 0.040, HR = 0.51, 95%CI:0.269-0.971) could predict OS in patients treated with BEV but not with FTM. OCR in the FTM arm was: 30% (95%CI:18-42) and 9% (95%CI:2-25) for patients treated with BEV and FTM, respectively. TTR (p = 0.05, HR = 0.46, 95%CI:0.21-1.00) and ETS > 15% in T1 contrast enhancing area at first disease assessment (p = 0.040, HR = 0.51, 95%CI:0.269-0.971) could predict OS in patients treated with BEV but not with FTM. OCR in the FTM arm was: 30% (95%CI:18-42) and 9% (95%CI:2-25) for patients treated with BEV and FTM, respectively. Patients achieving an ETS > 15% had significantly longer OS than those achieving an ETS < 15% (84 vs 5.2 months). **Conclusions:** BEV and FTM are both active drugs in recurrent GBM. TTR and ETS might be helpful predictors of GBM outcome in patients treated with BEV. Clinical trial information: NCT01474239.
2049
Poster Session (Board #38), Mon, 1:15 PM-4:45 PM
Graded prognostic assessment index for colorectal cancer with brain metastases. First Author: Vidhya Kaniedu, Fairview Hospital Cleveland Clinic, Cleveland, OH
Background: Brain metastasis (BM) is a rare but serious neurologic complication of colorectal cancer (CRC). The Disease Specific Graded Prognostic Assessment (DS-GPA) which is based solely on Karnofsky performance scale (KPS) is a commonly used prognostic index in patients with BM. We evaluated DS-GPA and other potential prognostic factors for overall survival (OS) in CRCBM at our institution.
Methods: With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify CRCBM patients treated between 2002 and 2014. OS from the diagnosis of CRC BM was the primary endpoint. Cox proportional hazards models with stepwise variable selection were used to identify independent prognostic factors. Results: Ninety-four patients were eligible for evaluation with median age of 60 years (range; 32-87), were included for analysis. KPS was 90-100 in 35 patients (38%), 70-80 in 35 (39%) and <70 in 20 (23%) patients. Single BM was noted in 53 (56%), 2-3 BM in 25 (27%) and >3 BM in 16 (17%) patients. Eighty nine patients (95%) were symptomatic at diagnosis. Forty nine (52%) patients had supratentorial BM, 25(25%) had infratentorial BM and 20 (21%) had both supra-and infratentorial BM at diagnosis. Initial therapy included whole brain radiation (WBRT) in 31 (33%), stereotactic radiosurgery (SRS) in 22(23%), WBRT + SRS in 11 (12%), surgery (S) in 2 (2%), S + SRS in 6 (6%), S + WBRT in 14(15%), S + SRS + WBRT in 1 (1%), while 2 patients received only chemotherapy and 5 underwent observation. Median OS from diagnosis of BM was 5.5 months (95% C.I. 3.5-7.5). In multivariate analysis, factors independently associated with shorter OS included KPS, age, and individual lesion number. Conclusions: A revised DS-GPA for CRCBM based on KPS (performance status) and number of BM is proposed.

Factors No. of points Hazard ratio P value
Number of BM
1 1.271 (0.2-1.5) 0.032
2 2 2
3 3 >3
Colorectal cancer specific GPA (KPS)
100 4 0.760 (0.3-1.5) 0.015
90 3
80 2
70 1
<70 0
Revised GPA No. Points OS (mo)
Unfavorable ≤3 2.8
Intermediate 4-5 6.1
Favorable ≥6 14.7

2050
Poster Session (Board #39), Mon, 1:15 PM-4:45 PM
Phase II trial of dovitinib in recurrent glioblastoma. First Author: Manmeet Singh Ahluwalia, Cleveland Clinic, Cleveland, OH
Background: Glioblastoma (GBM) is a vascular tumor and bevacizumab (an anti-VEGF antibody) failed to provide meaningful improvement in progression-free survival (PFS). Mechanisms of resistance to anti VEGF therapy include up-regulated FGF signaling and increased PDGF-mediated pericycle coverage. Dovitinib is an oral, small-molecule tyrosine kinase inhibitor of FGF-1, -3, PDGFR β, and VEGFR 1-3. Methods: This was a phase II trial in adults with GBM, stratified by prior anti-angiogenic therapy (naive – arm A, refractory – arm B). Arm A’s primary endpoint (PE) was PFS in a 2-stage adaptive design to test the hypothesis that PFSF was 36% vs. 55%. Arm B’s PE was time to progression (TTP) and a one-stage design to test the hypothesis that median TTP could be increased from 1.5 to 3 months. Type I and II error was 10% and 20%, respectively in both arms. Extracellular vesicles (EV) were measured at study enrollment, at the end of cycle 1 (day 28), and at progression (PD) to evaluate response to therapy. Results: Nineteen patients enrolled in Arm A and 14 in Arm B. Accrual in arm A was stopped after the first stage due to futility. Overall 64% (21/33) of patients were male, median age at on-study was 57 years (range 26-68), and median KPS was 90 (range 60-90). In Arm A, PFSF was 3% (1/33), median PFS was 1.8 months (95% C.I. 1.3-2.8) and median OS was 7.9 months (95% C.I. 3.6-11.7). In arm B, median TTP was 1.8 months (95% C.I. 1.0-1.8), median PFS was 1.8 months (95% C.I. 0.7-1.8) and median OS was 3.0 months (95% C.I. 0.8-4.7). In arm A, patients with PD had significantly higher levels of CD14+ EV (median 85329 vs 27750, p = 0.027) and CD14+ EV (median 38855 vs 4675, p = 0.042) compared to stable disease at end of cycle 1. Overall 5 patients (15%) reported grade 4 toxicities and 22 (67%) reported grade 3 reactions, primarily elevated lipids/lipase (42%), fatigue (21%), thromboembolic events (18%), hyper- trophic heart (18%), and lymphopenia (6%). In 9 patients (28%) appendicitis/collitis (n = 1), oral pain and proteinuria (n = 1), and delirium (n = 1). Conclusions: Dovitinib is not active in recurrent GBM, regardless of prior anti-angiogenic therapy. In arm A, elevated pre-treatment levels of CD14+ and CD14+ EV were associated with PD, suggesting their potential role as a predictor of poor response to Dovitinib. Clinical trial information: NCT01753713

2051
Poster Session (Board #40), Mon, 1:15 PM-4:45 PM
Incidence of pseudo-progression in low-grade gliomas treated with radiotherapy. First Author: Sophie E. van West, Erasmus MC, Rotterdam, Netherlands (The Netherlands)
Background: Pseudo-progression (psPD) is a well-known phenomenon in high-grade gliomas (HGG) after treatment with radiotherapy/temozolomide. However the incidence of psPD in low-grade glioma (LGG) after radiotherapy (RT) is unknown. Therefore, we retrospectively investigated the occurrence of psPD in a cohort of low grade glioma patients treated with RT. Methods: All patients with histologically proven LGG treated with RT between 2000 and 2011 were reviewed. MRI scans were reviewed by 3 independent reviewers before and after RT in periods of 3-6 months until progression leading to the start of a new treatment as judged by the treating physician. Furthermore clinical data including dexamethasone dose and epileptic activity was taken into account. Pseudo-progression was scored when a new enhancing lesion occurred after RT, and this disappeared or remained stable for at least a year without therapy. Results: Seventy-one patients were treated with RT for LGG. Sixty-four patients were deemed eligible for evaluation (3 were lost to follow up and 4 patients were not evaluable, due to a missing scans). The median follow-up was 7 years (range 1-22 years). The median progression free survival was 3.1 years. The median overall survival time was 5.3 years. Sixty-three patients were evaluable for psPD (1 patient was evaluated for response only, because of gadolinium allergy). psPD was seen in 13 patients (20.6%). In two of these patients epilepsy may have played a role. Pseudo-progression occurred after a median of 10 months in a period of 3 – 78 months. The median duration of psPD was 6 months with a range of 2 – 26 months. It always occurred within the RT fields. The area of the enhancement at the time of pseudo-progression was significantly smaller compared to the area of enhancement during ‘true’ progression (median size 54 mm² (range 12 – 340 mm²) versus 270 mm² (range 30 – 3420 mm²), respectively; p = 0.009). Conclusions: psPD occurs frequently in LGG patients treated with RT. This supports the policy to postpone a new line of treatment until further progression is evident, especially when patients have small contrast enhancing lesions in the RT field.

2052
Poster Session (Board #41), Mon, 1:15 PM-4:45 PM
Delineation of MGMT promoter hypermethylation as a predictive biomarker for the A071102 clinical trial of veliparib combined with temozolomide (TMZ) using patient-derived xenograft (PDX) GBM models. First Author: Jann Nagina Sarkaria, Mayo Clinic, Rochester, MN
Background: Poly-ADP-ribose polymerase inhibitors have potent sensitizing effects in pre-clinical models. This study was focused on identifying potential biomarkers of response to TMZ combined with veliparib in GBM. Methods: The efficacy of 3 cycles of TMZ alone or combined with veliparib (dosed days 1-5 every 28 days) was evaluated in 27 PDX models grown as orthotopic xenografts, with 8-10 mice randomized to each treatment group. Results: The combination of veliparib and TMZ was associated with significant survival prolongation (p < 0.05 by log-rank) in 8 of 20 MGMT methylated PDXs lines (range: 20 to 150 d increase vs. TMZ alone), as compared to 1 of 7 MGMT unmethylated lines (GBM6: 7 d increase). Comparing the survival ratios (median survival with treatment vs. placebo) across all lines, veliparib/TMZ was associated with a greater efficacy in MGMT methylated lines, as compared to TMZ alone, with an average survival ratio of 4.0 ± 2.0 and 3.0 ± 1.1, p = 0.0002 respectively, as compared to 2.4 ± 1.7 and 2.4 ± 1.5, p = 0.41 in unmethylated tumors. For the 8 responsive methylated lines, treatment with veliparib/TMZ resulted in an average median survival of 188 days (d) as compared to 121 d with TMZ alone. Exogenously expressed MGMT in GBM12 (MGMT methylated; 75 d prolongation in survival with veliparib/TMZ) resulted in a complete loss of TMZ efficacy with or without veliparib (36 d vs. 34 d, p = 0.03). In similar association for MGMT expression and occurrence was observed in GBM28 sublines with an intact vs. homozogous deleted MGMT locus. In comparing in vivo DNA damage signaling, co-treatment with veliparib/TMZ, relative to TMZ alone, resulted in greater phosphoryla- tion of Kap1 (SB24), Chk1 (S345), Chk2 (T68), and HAX2 (S139) only in MGMT methylated GBM12 (39) lines. Conclusions: While veliparib combined with TMZ conferred profound sensitizing effect in MGMT hypermethylated tumors, the combination was ineffective in unmethylated tumors. Based on these data, MGMT methylation is a predictive biomarker and entry criteria for the randomized Phase II/III A071102 clinical trial testing this combination in newly diagnosed GBM.

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The role of temozolomide (TMZ) in the management of anaplastic astrocytoma (AA): A comparison of survival in the era prior to and following TMZ.

**Methods:** This single-institution retrospective study was conducted to determine survival trends in patients with AA. All patients ≥18 years with newly diagnosed AA treated at Johns Hopkins from 1966-2012 were analyzed. As we incorporated TMZ into high grade glioma treatment regimens in 2004, patients were divided into pre-2004 and post-2004 groups for analysis. Clinical, radiographic, and pathologic data were collected. Results: A total of 196 patients were identified; 74 with pre-2004-AA, 74 with post-2004-AA, and 48 with post-2004 AM/MM. Median age was 54 (23-81) years. Median number of BEV infusions was 16 (2-62). Multivariate analysis controlling for age, Karnofsky performance status, and extent of resection revealed a 37% reduced risk of death (HR 0.63, 0.44-0.91, p = 0.015) in patients with AA receiving BEV. Conclusions: This retrospective analysis suggests a significant improvement in the survival of patients with AA receiving BEV with RT. Until prospective phase III data is available, our findings support the use of TMZ in the management of newly diagnosed AA.

**Background:** Adding TMZ to radiation therapy (RT) is common clinical practice for patients with AAs despite the lack of prospective studies documenting a survival advantage. Two retrospective studies, each with methodologic limitations, provide conflicting advice regarding the optimal treatment strategy. Methods: This single-institution retrospective study was conducted to determine survival trends in patients with AA. All patients ≥18 years with newly diagnosed AA treated at Johns Hopkins from 1966-2012 were analyzed. As we incorporated TMZ into high grade glioma treatment regimens in 2004, patients were divided into pre-2004 and post-2004 groups for analysis. Clinical, radiographic, and pathologic data were collected. Results: A total of 196 patients were identified, 74 with pre-2004-AA, 74 with post-2004-AA, and 48 with post-2004 AM/MM. Median age was 54 (23-81) years. Median number of BEV infusions was 16 (2-62). Multivariate analysis controlling for age, Karnofsky performance status, and extent of resection revealed a 37% reduced risk of death (HR 0.63, 0.44-0.91, p = 0.015) in patients with AA receiving BEV. Conclusions: This retrospective analysis suggests a significant improvement in the survival of patients with AA receiving BEV with RT. Until prospective phase III data is available, our findings support the use of TMZ in the management of newly diagnosed AA.
Significant PD-L1 and CTLA4 expression was not identified in primary cancer suggests that further investigation of the immune response in BM low sTILs expression. The expression of PD1 and FOXP3 in BM from breast sTILs (p<0.05) compared to BM (p<0.001). PD1 and FOXP3 expression and PAM50 subtype or BM sTILS (p<0.001). Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

Methods: For other profiling methods, i.e. IHC (IDH-1 R132H mutation), RT-PCR (EGFR amplification, 1p/19q co-deletion) was performed. Participation in clinical trials was recorded. Results: N = 104 pts were enrolled (48 glioblastomas, 39 grade III, 9 grade II and 3 grade I gliomas). The mutational landscape was in line with TCGA, including mutations in TERT (59%), TP53 (55%), IDH-1 (53%), ATRX (27%), Pten (12%) EGFR (7%), PIK3CA (12%) and BRAF (2%); four pts displayed a hypermutator genotype. MSK-IMPACT identified all IDH1/2 mutations, including one IDH2 R172K in an IDH-1 R132H IHC-negative tumor. All pure oligodendrogliomas (N = 13) displayed 1p/19q co-deletion on MSK-IMPACT. Three pts had 1p/19q co-deletion on FISH but not on MSK-IMPACT, but mutational profiling favored non-codilete glioma, suggesting false-positive FISH results. All FISH EGFR amplifications were detected by MSK-IMPACT. Among EGFR amplified tumors, MSK-IMPACT disclosed EGFRVIII in 55%. To date, 33 pts have been enrolled in trials, including 4 extreme responders in whom resistance to treatment has allowed drug development. Conclusions: NGS is becoming increasingly available but its relevance in clinical practice has been questioned. In this prospective, IRB-approved study (NCT01775072), we utilized the MSK-IMPACT assay to analyze gliomas in a routine practice setting. The MSK-IMPACT, performed in a CLIA-competent laboratory, is a multiplexed assay (Illumina HiSeq) providing toll exon coverage of 341 cancer related genes, excluding gene substitutions, small indels, copy number and select gene rearrangements.

Tumor infiltrating lymphocytes associated with brain metastasis in breast cancer. First Author: Nicole Olivia Williams, University Hosp/Case Western Reserve Univ, Cleveland, OH

Background: Breast cancer represents the second most common cause of brain metastasis (BM). Though tumor-infiltrating lymphocytes (TILs) and immunotherapies have been studied in primary breast cancer, little is known about TILs in BM from breast cancer. The aim of this study is to characterize the immune response to BM in breast cancer. Methods: The cohort included 75 initial and recurrent BM samples and 20 matched primary breast tumors from our tumor bank. MSK-IMPACT (transcriptome Array 2.0 microarrays), PAM50 subtypes were assigned by confrontational clustering, and scored according to international TILs working group guidelines and categorized as having no, low (1-5%), moderate (6-20%) or high (> 20%) TILs. Tumor DNA/RNA was extracted on corresponding archival FFPE material. Gene expression profiling was performed using Affymetrix Human Transcriptome Array 2.0 microarrays. PAM50 subtypes were assigned by clustering samples using median-subtracted PAM50 gene expression levels. Gene expression levels of programmed cell death 1 (PD1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and forkhead box P3 (FOXP3) were compared in this cohort. Results: Of the 25 BM evaluated, 34 (4IIs) had no stILs; 20 (EGFR) had low stILs, 10 (13%) had moderate stILs, and 1 (1%) had high stILs. stILs were significantly lower in the BM when compared with matched primary tumors (p = 0.0025). When comparing the level of BM vs. stILs in the PAM50 subtypes, the HER2-enriched subtype more commonly exhibited higher (p = 0.025) and high stILs compared luminal A, luminal B, and normal breast (p = 0.065). No association was seen between time to develop BM and % stILs (p = 0.68). Though primary and BM were found to express both PD1 and FOXP3, only FOXP3 expression was found to be higher in primary tumors compared to BM (p = 0.0023). There was no association between PD1 and FOXP3 expression and PAM50 subtype or BM stILs (p = 0.06). Significant PD1-L and CTLA4 expression was not identified in primary tumors or BM. Conclusions: Overall, BM from breast cancer have relatively low stILs expression. The expression of PD1 and FOXP3 in BM from breast cancer suggests that further investigation of the immune response in BM and clinical trials with immune checkpoint inhibitors should be considered for this poor prognosis population.

Tumor profiling on 1245 gliomas and paired tumor study on 19 high grade gliomas. First Author: Joanne Xi, Caris Life Sciences, Phoenix, AZ

Background: Gliomas are molecularly heterogeneous with genetic alterations driving the growth of recurrent tumors differing from the initial tumor. Previous reports showed molecular changes during progression of lower grade gliomas to GBM, driving tumor growth and treatment resistance; however changes during progression of high-grade gliomas have not been systematically reported. Methods: 1245 gliomas (934 GBM) were tested with multiple platforms including sequencing (SEQ), immunohistochemistry (IHC), fluororescent/chromogenic in-situ hybridization (FISH/ CISH), fragment analysis (FA) and promoter methylation (Me) assay. Metachronous paired tumors from 19 patients (pts) were assessed for biomarker changes over time. Results: EGFRVIII was seen exclusively in GBM (16% of GBM) while amplification was more common in GBM than grade II-III tumors (56% vs. 20%, p<0.001). MGMT Me was seen in 47% of all, and was more common in grade II-III (64% vs. 42%, p<0.001). PD-L1 expression on tumor cells was seen in 27% and was more common in tumors without MGMT Me (36% vs. 18%, p = 0.01). PD-1 expression on tumor-infiltrating lymphocytes was seen in 48% and was higher in GBM than grade II-III (54% vs. 30%, p = 0.005). 38 of 48 sequenced genes had mutations, including BRCA1 (8%) and BRCA2 (6%). 1p19q co-deletion was seen in 26% of grade II-III and 2.9% of GBM. Paired tumors from 19 pts (18 GBM and 1 grade III in both samples) taken at an average of 469 days apart (91-1400) showed that 17 pairs (89%) had one or more biomarker changes of 13 (22%) capable of explaining reduced MGMT Me, potentially indicating acquired resistance to temozolomide. EGFR aberrations including amplification (N = 1), mutations on the extracellular (EGFRVIII, N = 1) and intracellular domains (T970M, N = 1; Exon 20 insertion N = 1) were acquired in 3 pairs. One pt, presenting with a PTEN mutation, acquired three additional mutations (E535K, PTEN 12 (A72T) and PIK3CA (D434N). Conclusions: Multipletumor profiling on a large cohort of gliomas confirms tumor heterogeneity. Changes in MGMT Me and EGFR of potential therapeutic importance are frequently observed in high grade gliomas at the time of recurrence, suggesting the need for a re-biopsy for tumor profiling to direct the next line of therapy.

Tumor profiling of brain metastases from NSCLC, breast cancer, and melanoma. First Author: Santosh Kesari, UC San Diego, La Jolla, CA

Background: An estimated 70,000 diagnoses of brain metastases (BM) occur each year in the U.S., with an incidence of 5-7% in breast and melanoma and 20% in lung cancer. Despite its prominence, the biology of BM remains poorly understood. Several theories of BM development exist, including the linear progression model, which states that metastatic cells develop at primary sites following the accumulation of alterations. The parallel progression model argues that tumor cells disseminate early and accumulate changes independently at the secondary site. We compare the tumor profiles of BM from common cancers to understand the biology and to identify differential treatment strategies. Methods: Tumor samples were profiled using a multiplatform (Caris Life Sciences, Phoenix, AZ), including sequencing (Sanger, NGS), protein expression (IHC) and amplification (ISH). Results: 5,391 NSCLC (293 BM, 5,058 lung), 3,595 breast cancer (99 BM, 3496 breast) and 761 melanoma (101 BM, 660 skin) unpaired samples were included. No significant differences were found in 48 genes between BM and the primary tumor sites, with the exception of PIK3CA in breast cancer, which was mutated less in BM vs. the primary tumors (10% vs. 25%, p = 0.005). Similar expression of TOP2A, TOP1 and TS, and amplification of EGFR, were more prevalent in BM as compared to the primary sites (Table). Conclusions: A similar genetic landscape with limited differences was seen in BM of NSCLC, melanoma and breast cancer compared to primary tumors. The limited differences are more consistent with a linear progression model of cancer metastasis. Additionally, this suggests that both primary tumor and BM would respond to similar chemotherapeutics with the consideration of effective blood-brain barrier-penetrant drugs. Small molecule inhibitors of EGFR should be considered due to increased EGFR amplification and the higher TOP2A. TOP1 expression prompts consideration of topoisomerase inhibitors like etoposide or irinotecan.

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A phase I trial everolimus and sorafenib in patients with recurrent high-grade gliomas: Brain Tumor Treatment Collaborative trial O9-01.

**Background:** Limited treatment options exist for patients with recurrent Malignant Gliomas (MG), especially after failing Bevacizumab (BEV). Signal transduction pathways involved in gliomagenesis provide therapeutic targets. Everolimus targets mTOR which is an important node downstream from PI3K and Akt. Sorafenib targets Raf, as well as VEGF and PDGF. The rationale for combining these agents is to inhibit two parallel pathways simultaneously. We performed a phase I trial of Everolimus and Sorafenib in patients with recurrent malignant gliomas in preparation for a phase II study. **Methods:** Patients with recurrent MG > 18 yrs, KPS ≥ 60, adequate hematologic, renal and hepatic function and no history of HIV or hepatitis were eligible. No limit on prior relapses and BEV exposure was allowed. Enzyme inducing seizure drugs were not allowed. A 3 + 3 dose escalation was used to determine the MTD, defined as the highest dose combination resulting in 0/3 or 1/6 patients experiencing a DLT. The starting dose was Everolimus 5 mg a day + Sorafenib 400 mg twice a day with a plan to increase to a maximum dose of 10 mg a day and 800 mg twice a day over several defined dose levels. A DLT-decascation level was Everolimus 5 mg/day + Sorafenib 400 mg twice a day for 7 days on and 7 days off. **Results:** 11 men and 2 women were enrolled with a median age of 50 years (19-66) and median KPS of 80 (70-100). All patients had a GBM with 7 receiving prior BEV therapy. In cohort 1, 3 of 6 patients experienced a DLT which were grade 3: fatigue, chest pain, HTN, elevated ALT, hypercholesterolemia and hyperglycemia and one grade 4 hypertriglyceridemia. Dose de-escalation occurred with 1 of 7 patients having a DLT of myositis, nausea, fatigue, hypertension and hypercholesterolemia—all grade 3. All patients died due to disease progression with a median PFS of 4 weeks and OS of 20.9 weeks. **Conclusions:** This phase I study determined the phase II dose in patients with recurrent malignant glioma to be Everolimus at 5 mg daily + Sorafenib at 400 mg twice a day for 7 days on and 7 days off. A phase II trial is on-going investigating this regimen in Bev naive recurrent anaplastic gliomas and GBMs as well as recurrent GBM who failed BEV. Clinical trial information: NCT01434602.

**Decision support needs analysis in newly diagnosed malignant glioma.**

**Background:** Standard treatment pathways exist for malignant glioma, but are largely palliative. Patients face difficult non-curative treatment decisions. Oncologists may misinterpret patient goals or communicate ineffectively the risks/benefits of treatments. Shared Decision Making in which the patients’ values and goals are incorporated into informed consent is ideal in this situation. **Methods:** Ten patients, caregivers and two treating physicians participated in a questionnaire- and interview-based investigation exploring patient perceptions and understanding of standard of care treatment recommendations in the outpatient clinical setting after receiving a post-surgical diagnosis of malignant glioma. Cognitive dysfunction was evaluated with neuropsychological examination, Trail Making Test and Hopkins Verbal Learning Test. Physical and emotional distress was scored with the FACT-BR and KPS. **Results:** Ten patients participated. Common themes in the patients’ interviews were 1. Fear of “doing nothing”, “chemotherapy”, “loss of function/QOL”; 2. Misperception of improvement in prognosis with treatment; 3. Loss of autonomy in decision making to physician and family members; 4. Lack of perception of any options; 5. Need for validation in decision making; 6. Lack of perception of dis/advantages of treatment. All patients and caregivers desired more information than was provided. Patients and caregivers who expressed interest in a second opinion did so with the goal of validating what the treating physician was recommending to improve confidence that the question was making the right treatment decision. The patients emphasized the expected advantages of improved survival. Physicians and caregivers perceived increased patient independence in decision making than did patient. **Conclusions:** Patients had difficulty formulating and discussing the treatment information provided in a verbal format. While the information given met criteria to form the basis for informed consent and the physicians believed that Shared Decision Making occurred, in fact there was poor understanding of prognosis, advantages and disadvantages of standard of care treatment and patients felt little autonomy. A decision tool to incorporate patients’ concerns is under development.

Clinical outcome of adult brainstem glioma treated with concurrent chemoradiotherapy: An institutional experience.

**Background:** Brainstem glioma (BSG) is an aggressive tumor of adulthood. Treatment outcomes remain dismal and role of concurrent chemoradiotherapy (CRT) is not established in these patients. We intended to study the clinical characteristics along with outcome of adult BSG patients treated with CRT. **Methods:** We retrospectively evaluated 29 patients, age more than 18 years, with BSG treated at our department in the period Jan 2007 to December 2012. Demographic and disease characteristics in this patient cohort were recorded, and their progression free survival (PFS) was analyzed with respect to sex, age, use of CRT and adjuvant chemo-therapy. **Results:** Median age at presentation was 35 years (range 22-66 years), with a male: female ratio of 2:1.18 patients presented with gait ataxia and 16 presented with cranial nerve palsies. Patients were diagnosed radiologically as low grade. None of the patient underwent surgery. Radiotherapy dose was 56-60 Gray over 5.5 -6 weeks at 1.8-2 gray/fraction. All patients completed their radiotherapy. 11 patients received concurrent Temozolomide (75 mg/m2), 10 patients received adjuvant Temozolomide (150-200 mg/m2 D1-5 q4 weeks for 3-6 cycles) and 6 patients received both concurrent and adjuvant Temozolomide. Median follow up duration was 9.77 months (range 0.3-54.82 months). At last follow up, 27 patients had progressive disease. Median PFS for the entire group was 64.19 months. PFS was significantly poorer in the patients who received concurrent Temozolomide than those who did not (Median PFS 64.19 vs. NR months; p = .016) on Univariate analysis. Sex, grade, and adjuvant chemotherapy did not statistically alter treatment outcomes. **Conclusions:** Outcome of adult BSG is better in our cohort compared to reported results. CRT with Temozolomide has detrimental effect on survival and its use should be discouraged. Radiotherapy along with standard fractionation remains the treatment of choice in inoperable adult BSG.
A phase II study of the combination of BKM120 (buparlisib) and bevacizumab in patients with relapsed/refractory glioblastoma multiforme (GBM).

First Author: Kent C. Shih, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN

Background: BKM120 is an orally bioavailable, pan-class I PI3K inhibitor that is known to cross the blood brain barrier. The PI3K pathway is frequently dysregulated in GBM patients causing abnormal cell growth and proliferation. This phase II multicenter study evaluated the combination of BKM120 with bevacizumab in patients with relapsed/refractory GBM.

Methods: Patients with relapsed/refractory GBM following 1st-line therapy were randomized to receive BKM120 and surgery and surgical resection were treated with BKM120 60 mg PO daily and bevacizumab 10 mg/kg IV every 2 weeks of each 4 week cycle. Following an amendment, responses were evaluated every 8 weeks per RANO criteria; prior to this amendment, responses were assessed by MacDonald criteria. Treatment continued until disease progression or intolerable toxicity. The primary endpoint was median PFS. Secondary endpoints included RR, OS and toxicity. Results: Sixty-eight patients were treated with a median age of 57 years (range, 19-77). 13 patients (19%) had received prior bevacizumab. Median treatment duration was 16 weeks (range, 1-120); 6 patients (9%) remain on treatment. Disease progression (51%) and toxicity (13%) were the most common reasons for treatment discontinuation. Overall RR was 32% (CR, 2; PR, 20); 18 patients (26%) had stable disease. In patients who received prior bevacizumab, 1 patient each experienced a CR and a PR and 4 experienced SD for a clinical benefit rate (CR + PR + SD) of 46%. Median PFS and OS (95% CI) were 3.5 months (3.8, 7.5) and 10.8 months (9.1, 22) respectively. Treatment-related toxicities included fatigue (37%), hyperglycemia (26%) and increased ALT (25%); 1 patient experienced grade 4 hyperglycemia. Forty patients (59%) experienced CNS symptoms while on study, 5 (13%) of which were treatment-related grade 3 toxicities: mood alteration, suicidal ideation, altered mental status, confusion, and psychosis (1 patient each).

Conclusions: The combination of BKM120 and bevacizumab was well-tolerated and clinical activity was observed, including 6 patients who received prior bevacizumab. Accrual to this study in patients previously treated with bevacizumab continues. Clinical trial information: NCT01349660.

Poster Session (Board #54), Mon, 1:15 PM-4:45 PM

Oncolytic polio/rhinovirus recombinant (PVSRIPO) against recurrent glioblastoma (GBM): Optimal dose determination.

First Author: Annick Desjardins, Duke University Medical Center, Durham, NC

Background: The live attenuated oral (SABIN) serotype 1 poliovirus vaccine was modified to contain a heterologous internal ribosomal entry site stemming from human rhinovirus type 2, creating PVSRIPO. PVSRIPO recognizes nectin-like molecule-5, an oncocyte cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We report results of a dose finding study evaluating PVSRIPO delivered intratumorally by convection-enhanced delivery (CED). Methods: Eligible patients were adults with recurrent supratentorial GBM; solitary tumor 1-5cm in diameter, ≥ 4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS > 70%; and positive anti-polio titer. The original two-step continual reassessment method dose escalation was amended to decrease to dose level -1 after observing prolonged steroid use in patients treated on higher dose levels. Results: Thus far, 20 patients have been treated (1 each at dose levels 1 and 3, 7 at level 2, 2 at level 4, 4 at level 5 and dose level -1). One dose-limiting toxicity was observed; a grade 4 intracranial hemorrhage at catheter removal (dose level 5). Adverse events possibly related to study include: pyramidal tract syndrome (grade 3; n = 5; grade 2; n = 1; grade 1; n = 1), seizure (grade 3; n = 3; grade 2; n = 2; grade 1; n = 8), lymphenopia (grade 3; n = 1), headache (grade 2; n = 4), fatigue (grade 1; n = 5), dysphasia (grade 2; n = 3; grade 1; n = 6), paresthesia (grade 2; n = 3; grade 1; n = 5), concentration impairment (grade 2; n = 1; grade 1; n = 1), hypothermia (n = 1), anemia, nausea and vomiting. Twelve patients remain alive, with pts #1 and #2 now more than 33 and 31 months post-PVSRIPO, respectively. Conclusions: Infusion of PVSRIPO via CED is safe thus far and encouraging efficacy results are observed. We are determining optimal phase II dosing. Clinical trial information: NCT01491893.

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Targeting dopamine receptor 2 (DRD2) signaling in combination with temozolomide chemotherapy as a novel therapeutic concept in glioblastoma. First Author: Tor-Christian Aase, Johannesnessen, Kristin Bjørn-Jensen, and Ole-Johan Jebsen Brain Tumor Research Centre, Department of Biomedicine, University of Bergen, Bergen, Norway

**Background:** Glioblastomas are highly resistant to therapy and carry a poor prognosis. Novel therapeutic strategies are urgently needed to improve patient outcome. This study was designed to identify drugs that would sensitize glioblastoma cells to temozolomide (TMZ) chemotherapy. **Methods:** A genome-wide RNAi synthetic lethality screen was performed in glioblastoma cells to identify functional gene sets that would potentiate the effect of TMZ. The Connectivity Map database was then interrogated to identify potential drug candidates that would induce corresponding changes in gene expression. The highest ranked prospective compounds were validated in combination with TMZ in low-throughput cytotoxicity assays. Based on these findings, the most promising compound, the established anti-psychotic agent Thioridazine, was evaluated further in combination with TMZ in vivo in a clinically relevant orthotopic xenograft model. **Results:** Thioridazine significantly improved TMZ sensitivity in established glioblastoma cell lines as well as patient-derived cells. The specific chemosensitizing effect of Thioridazine was due to antagonism of dopamine receptor 2 (D2 receptor; DRD2). Inhibition of D2 receptor signaling by Thioridazine decreased MAPK and PI3K/AKT/mTOR pathway activity through a DRD2/β-arrestin-2/AKT signaling complex. Inhibition of this complex induced non-apoptotic cell death caused by impaired autophagy leading to catastrophic vacuolization. The combination of TMZ and Thioridazine significantly decreased intracranial glioblastoma growth, and improved survival of tumor-bearing mice compared to treatment with TMZ alone. **Conclusions:** Our findings demonstrate that the DRD2/β-arrestin-2/AKT signaling complex connects dopamine signaling to tumor cell survival. We have also identified a novel strategy to inhibit autophagy in glioblastoma cells by antagonizing the D2 receptor. Due to the low toxicity of Thioridazine and its advantageous pharmacological properties, the presented work suggests that Thioridazine plus TMZ could be used for glioblastoma treatment in an adjuvant setting.

**Identification of glioblastoma patients who stand to benefit from PARP inhibitor therapy. First Author:** Kerrie Leanne McDonald, University of NSW, Kensington, Australia

**Background:** The development of effective targeted drugs for the treatment of glioblastoma (GBM) represents a major unmet need. Veliparib (ABT-888; Abbvie) inhibits both PARP1 and PARP2 (poly(ADP-ribose) polymerase). The successful clinical application of veliparib and other PARP inhibitors (PARPi) will be assisted by the identification of predictive biomarkers. **Methods:** Efficacy of veliparib in combination with radiotherapy (RT) was tested on a panel of primary and recurrent GBM patient-derived cell lines (PDCLs). In order to screen for potential biomarkers for PARPi we performed whole genome sequencing (WGS) on sensitive and resistant PDCLs and also measured the expression of 96 candidate DNA repair pathway genes using the RT2 Profiler PCR Array (Human DNA Repair; Qiagen). We also detected mutations in other genes involved in DNA maintenance such as XRCC4, FANCA, FANCD2, ATR, RPA1, REV3L and PARP1 only in the sensitive PDCLs. **Conclusions:** Mutations in DNA maintenance pathways may be a method for selecting patients for therapies involving the combination of DNA damaging agents such as radiotherapy and PARP inhibitors. Additionally, the signature associated with genomically unstable GBM may be a method of identifying potential responders to PARP inhibitor therapy.

**A phase 1b/2 study of the combination of the IDO pathway inhibitor indoximod and temozolomide for adult patients with temozolomide-refractory primary central nervous system tumors: Safety data and preliminary efficacy of the phase 1b component. First Author:** Howard Colman, Huntsman Cancer Inst Univ of Utah, Salt Lake City, UT

**Background:** Indoleamine 2, 3-dioxygenase (IDO) is a key immune-modulatory enzyme within the IDO pathway that inhibits CD8+ T cells and enhances the suppressor activity of Tregs. IDO is expressed in a large proportion of solid tumors including 50 to 90% of glioblastomas (GBM). High IDO expression is correlated with poor prognosis in GBM. IDO pathway inhibitors such as indoximod (1-methyl-D-tryptophan / D-1MT) can improve anti-tumor T cell response slowing the tumor growth in vivo. We have demonstrated a synergistic effect of indoximod when combined with temozolomide (TMZ) and radiation in a syngeneic orthotopic brain tumor model. This phase 1b/2 study is designed to determine the safety profile and maximal tolerated dose (MTD) of indoximod in combination with TMZ in recurrent refractory malignant brain tumors with subsequent expansion into a phase 2 portion evaluating efficacy of the combination. **Methods:** After progression to standard front line-therapy with TMZ, patients were enrolled in a 3+3 dose escalation study of indoximod (600, 1000 or 1200 mg twice daily orally) with a standard dose of TMZ (150mg/m^2 x 5 days). Indoximod was administered for all 28 days of each treatment cycle. **Results:** 12 patients were required to fully enroll all three dose cohorts with no DLTs requiring cohort expansion at lower doses. Median age was 48.5 years (27-62) with 5 female and 7 male. 83% had a diagnosis of GBM. 6 patients remain on study, the longest on cycle 12. Best responses in these previously TMZ-refractory patients to date include SD in 3 patients lasting between 5 and 10 months duration (ongoing) with one patient demonstrating a progressive, ongoing substantial reduction in tumor size, approaching RANO criteria for PR. No patients to date have experienced a reduction or delay in temozolomide dosing due to the addition of indoximod nor an indoximod related serious adverse event. **Conclusions:** The MTD for indoximod in this combination and setting was 1200mg twice daily. Expansion into the phase 2 portion is proceeding to evaluate the exciting preliminary observations made in this trial. Clinical trial information: NCT02052648.
IDH1 mutation status and outcome in clinical trials for recurrent glioblastoma. First Author: Jacob Joseph Mandel, Baylor College of Medicine, Houston, TX

Background: IDH1 mutated glioblastoma (GB) has a better prognosis than IDH1 wildtype GB. Clinical trials for recurrent GB currently do not stratify patients (pts) based on IDH1 status. It is not known if pts with IDH1 mutated GB on clinical trials are more likely to have a higher 6-month progression free survival (PFS6) or radiographic response (RR) rate.

Methods: A retrospective review of GB pts treated at MD Anderson Cancer Center between 2006-2012 identified 330 pts enrolled in recurrent GB trials. 93 pts (28%) either had PFS6 or a complete or partial RR per RANO criteria. 49/93 (53%) pts with PFS6 or a complete or partial RR were found to have tumor tissue available for IDH1 testing. A matched cohort of pts on the same recurrent GB clinical trials with tissue for IDH1 testing but no PFS6 or RR was identified based on the specific clinical trial, age and KPS. 49 pts were identified for comparison resulting in a total of 98 patients.

Results: IDH1 status was obtained in 92 (94%) pts of which 17 (18%) had an IDH1 mutation. Recurrent GB trial was at 1st-4th recurrence with 62% at 1st, 26% at 2nd, 8% at 3rd and 4% at 4th recurrence. Median time from GB diagnosis to recurrent trial was 8.4 months (mo) for IDH1 wildtype GB vs. 10.9 mo for IDH1 mutated GB (p < 0.06). PFS6 was seen in 26/49 (53%) pts of which 2 pts IDH status was unknown. 5/24 (21%) pts with PFS6 had IDH1 mutations compared to 5/24 (21%) pts of their matched cohort without PFS6. RR was found in 46/49 (94%) pts of which 4 pts IDH status was unknown. IDH1 mutation was present in 7/42 (17%) pts with RR compared to 10/42 (24%) pts of their matched cohort without RR (p < 0.49). For all patients, median PFS on a recurrent trial was 3.68 mo for IDH1 wildtype GB vs. 3.52 mo for IDH1 mutated GB (p < 0.72). Median OS on recurrent trial was 8.64 mo for IDH1 wildtype GB vs. 9.59 mo for IDH1 mutated GB (p < 0.49). Conclusions: IDH1 mutation status does not appear to be predictive of PFS6 or RR in recurrent GB trials. However, further examination in larger randomized prospective studies is needed.

Targeting PTBP1 as a therapeutic strategy to reverse lineage-specific splicing of ANXA7 and ensuing EGFR activation in glioblastoma. First Author: Markus Breider, University of Alabama at Birmingham School of Medicine, Birmingham, AL

Background: Tissue-specific splicing involves evolutionarily conserved, alternative exons many of which have functional features that influence cell signalling. The membrane-binding tumor suppressor ANXA7 belongs to a family of proteins involved in endosomal organization and function. ANXA7 contains an alternative cassette exon that shows high prevalence in GBM and astrocytoma progression. PTBP1, a ribonucleoprotein that is normally repressed during neuronal development, contains an alternative cassette exon that shows high prevalence in glioblastoma (GB) and astrocytoma. PTBP1 mediates lineage-specific splicing of the cassette exon in ANXA7 during glioblastomagenesis. We examined the cellular and genomic effects of a new class of PTBP1 modulators and pharmacologic targeting of PTBP1 on ANXA7 splicing. Results: Lineage-specific splicing of the cassette exon in ANXA7 diminished endosomal targeting of the EGFR Oncoprotein and enhanced glioblastoma (GBM) progression, ANXA7 splicing was mediated by PTBP1, which was highly expressed in GBMs due to loss of brain-enriched microRNA miR-124 and to PTBP1 amplification. The alternative ANXA7 splicing trait was present in precursor cells, suggesting that GBM cells inherit the trait from a potential tumor-initiating ancestor. PTBP1 overexpression perturbed a poor clinical outcome in patients with GBM. Targeting PTBP1 with an FDA-approved compound, identified by a cell-based high-throughput assay revealed the splicing repression by PTBP1 reduced PTBP1 levels and reversed ANXA7 splicing and ensuing EGFR activation. It revealed a significant inhibitory effect on GBM cell viability that was enhanced by the addition of radiation. Drug derivatives exerted even more potent effects on cell proliferation alone and when combined with radiation. Conclusions: PTBP1 mediates lineage-specific splicing of ANXA7 and eliminates its tumor suppressor function, thereby promoting GBM progression. Pharmacologic targeting of PTBP1 reverses the splicing event and exhibits anti-proliferative effects that are augmented by concurrent radiation, offering a potential new avenue for future therapeutic modulation in glioblastoma.

Analysis of BRAF alterations and molecular profiling in glioblastoma and astrocytoma. First Author: Nadia Faqir, UC San Diego Moores Cancer Center, San Diego, CA

Background: Although well characterized in pilocytic astrocytoma and pleomorphic xanthoastrocytoma, the prevalence of BRAF alterations in glioblastoma (GBM) and astrocytoma is not well established. Characterization of BRAF mutations in glioblastoma and astrocytoma may identify a subgroup of patients with sensitivity to BRAF inhibitors. Methods: DNA was extracted from 95 diffuse gliomas (grade II-IV) at our institution and an independent set of 714 gliomas, and was subjected to hybrid capture for 315 or 265 cancer-related genes plus select intronic regions. Sequencing was performed to a mean coverage depth of > 500x and analyzed for the presence of base substitutions, insertions/deletions, copy number alterations, and rearrangements. Results: 7 of 95 gliomas (7.4%) analyzed harbored BRAF alterations; 6 (6.3%) were identified with either a V600E mutation (3 GBM + 1 gliosarcoma) or a D594G mutation (2 GBM). One glioma with a BRAF rearrangement was identified (astrocytoma grade II). There were no alterations found in oligodendrogliomas. Molecular profiles in all 6 tumors with BRAF point mutations were similar; all were wild type for IDH1/2 and exhibited CDKN2A/B loss. Conversely, the BRAF rearrangement was IDH1 mutated and CDKN2A/B intact. To confirm the frequency of BRAF alterations, an independent database of 714 gliomas was queried. Thirty-four (4.8%) tumors were found to have BRAF alterations, including 24 BRAF point mutations. Of those, 96% (n = 23) were IDH1/2 wild type and 83% (n = 21) harbored CDKN2A/B loss. Conversely, BRAF rearrangements and amplifications (n = 10) did not share this profile. 40% harbored IDH1/2 mutations and only 40% displayed CDKN2A/B loss. In our patients, 5 of the 6 with BRAF point mutations are alive. The median overall survival is 28.8 months (10.7-40.6). One patient with recurrent GBM and created V600E mutation was treated with the BRAF inhibitor vemurafenib with a PFS > 12 months. Conclusions: BRAF alterations occur in GBM and astrocytoma. BRAF point mutations are associated with a specific molecular profile, specifically IDH1/2 wild-type and CDKN2A/B loss. This profile identifies a molecular subgroup of gliomas that may exhibit improved survival and are amenable to targeted therapy with BRAF inhibitors.

A phase I study of TPI 287 concurrent with fractionated stereotactic radiotherapy (FSRT) in treatment of brain metastases from advanced breast and non-small cell lung cancer (NSCLC). First Author: Solmaz Sahetpyam, Moffitt Cancer Center, Tampa, FL

Background: TPI 287, a member of taxanes diterpenoid (taxoid) family, is a microtubule-inhibitor with significant cytotoxic activity. TPI 287 is not a P-glycoprotein substrate and therefore is able to circumvent resistance associated with the expression of the multidrug-resistance-1 (MDR-1) gene. Preclinical studies have demonstrated that TPI 287 crosses the blood-brain barrier into brain metastases and reduces the formation of large brain metastases. The radiosensitizing effect of taxanes is well established. This report describes an ongoing phase I trial of TPI 287 concurrent with FSRT in patients (pts) with 1-3 brain metastases from histologically or cytologically confirmed advanced breast or NSCLC cancer. Methods: This phase I study employs a standard 3 + 3 dose escalation design exploring 6 sequential dose escalation cohorts (NCT02187822). Pts with up to 3 untreated brain metastases (maximum diameter of each brain lesion ≤ 5 cm, maximum tumor volume ≤ 120 cc) from breast cancer or NSCLC are eligible. Eligible patients will be treated with FSRT to target brain metastases (25 Gy in 5 daily fractions). TPI 287 is administered intravenously once per week, for a total of 3 doses. The first dose of TPI 287 is given concurrently with the first fraction of FSRT. Once the recommended phase II dose (RP2D) is determined, 3 additional patients will be treated at the RP2D with concomitant FSRT to 75% of the RP2D. For safety, a second FSRT safety cohort, for a planned total enrollment of 36 patients. The primary study objectives are to determine safety and the RP2D of TPI 287 administered concurrently with FSRT to brain metastases. Secondary endpoints include determination of the pharmacokinetics of TPI 287, preliminary antitumor activity (local control rate, distant intra-cranial control rate, progression-free survival) and evaluating effect of treatment on measures of quality of life. Study Progress: At deadline for abstract submission, 2 patients have been enrolled onto this study. Clinical trial information: NCT02187822.
Phase II study to evaluate the clinical efficacy and safety of MEDI4736 in patients with glioblastoma (GBM). First Author: David A. Reardon, Dana-Farber Cancer Center Institute and Harvard School of Medicine, Boston, MA

Background: Programmed cell death ligand-1 (PD-L1) is widely expressed on antigen presenting cells (APC) and other immune cells. PD-L1 binds two important regulatory receptors on T-cells: programmed cell death-1 (PD-1) and CD80/B7. Targeting Programmed Death-1 (PD-1) and its ligand, PD-L1, have demonstrated promising anti-tumor activity among other challenging solid tumors and growing data implicates PD-L1/PD-L1 interaction as a significant contributor to immunosuppression in glioblastoma (GBM). PD-1 is expressed by many GBM infiltrating lymphocytes while PD-L1 is expressed by 61-100% of GBM tumors. Furthermore, loss of the PTEN tumor suppressor gene, which occurs in 40-50% of GBM tumors, leads to increased transcription and expression of PD-L1 in GBM. These findings indicate that PD-L1 is an attractive and important therapeutic target in GBM. MEDI4736 (M), a human IgG1 blocking monoclonal antibody against PD-L1, represents a compelling immune-mediated anti-tumor treatment for GBM. Methods: Phase II, multicenter, open-label study (NCT02336165) is evaluating the clinical efficacy and safety of M in GBM patients. Eligible patients include those who are newly diagnosed with unmethylated MGMT GBM scheduled for standard radiotherapy (Cohort A); Bevacizumab-naive patients with recurrent GBM (Cohort B); and Bevacizumab-refractory patients with recurrent GBM (Cohort C). Cohort A patients will receive M at 10 mg/kg i.v. Q2W for up to 12 months beginning with standard radiotherapy. Cohort B will receive M at 10 mg/kg i.v. Q2W for up to 12 months as monotherapy. Cohort C will receive M at 10 mg/kg i.v. Q2W for up to 12 months in combination with continued bevacizumab at 10 mg/kg Q2W. Primary endpoints include overall survival (OS) at 12 months (cohort A), progression free survival rate at 6 months (cohort B) and OS-6 (cohort C). Secondary endpoints are safety/tolerability, PFS, median OS, radiographic response, and quality of life (QoL) by EORTC QLQ-C30/BN20. Exploratory endpoints are patient neurologic function using the Neurologic Assessment in Neuro-Oncology (NANO) scale, as well as immune-correlative biomarkers and pharmacokinetics. Clinical trial information: NCT02336165.

An oxygenation agent and radiation sensitizer, dodecafluoropentane, for tumor treatment for GBM. First Author: Susanne Antje Kuhn, Hospital Ernst von Bergmann, Potsdam, Germany

Background: Venous thromboembolism (VTE) is a preventable complication in cancer and represents the second most frequent death cause, despite widely available anticoagulants. Further, VTE was proven as a significant contributor to immunosuppression in glioblastoma (GBM). MEDI4736 (M), a human IgG1 blocking monoclonal antibody against PD-L1, represents a compelling immune-mediated anti-tumor treatment for GBM. Methods: Phase II study of plerixafor and bevacizumab in recurrent high-grade glioma. First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA

Background: Although anti-angiogenic therapy for high-grade glioma is promising, responses are not durable. The SDF-1/CXCR4 axis may help mediate resistance to VEGFR inhibition. Plerixafor is a reversible CXCR4 inhibitor that has demonstrated growth inhibition in glioblastoma xenografts. Methods: We are conducting a Phase I study to determine the safety and tolerability of plerixafor in combination with bevacizumab in patients with recurrent HGG. In Part 1 of the study, a 3 x 3 dose escalation design, with an increase in the maximum planned dose level of plerixafor 320 µg/kg on Days 1-21 and bevacizumab 10 mg/kg on Days 1 and 15 of each 28 day cycle was used. DLTs were determined during the initial 4 weeks of therapy and included drug-related Grade ≥ 3 non-hematologic toxicities and Grade ≥ 4 hematologic toxicities. Prior to the study, a surgical study to determine if plerixafor penetrates tumor tissue. Results: Part 1 of the study has been completed with 23 patients enrolled. Part 2 of the study is now open with 3 patients enrolled to date. For all 26 patients, the median age is 59 (23-72), median KPS 90 (70-100), 11 women (42.3%). In Part 1, no DLTs were seen at the maximum planned dose level of plerixafor 320 µg/kg + bevacizumab. Treatment has been well tolerated to date with one grade 3 hypophosphatemia and one grade 3 rectal fistula. Preliminary pharmacokinetic data on plerixafor from the first two cohorts compares well with historical PK data. Conclusions: Combination treatment with bevacizumab and plerixafor is well tolerated in HGG patients. No DLTs were encountered at the maximum planned dose level. To date, 3 of 10 planned patients have enrolled in the surgical cohort to examine tumor tissue penetration. Updated results as well as preliminary circulating biomarker analysis will be presented. Clinical trial information: NCT01399039.
A phase I study of convection-enhanced delivery of nanoliposomal irinotecan using real-time imaging in patients with recurrent high grade glioma.

First Author: Nicholas A. Butowski, University of California, San Francisco, San Francisco, CA

**Background:** Cytotoxic drug delivery to high grade glioma (HGG) is limited by the blood brain barrier (BBB). Convection-enhanced delivery (CED) improves chemotherapy delivery by utilizing fluid convection, obviating the challenges of crossing the BBB while minimizing systemic toxicity. CED of a highly concentrated formulation of nanoliposomal irinotecan (MM-398, nal-IRI) has been optimized in animal models of brain tumors and shows superior anti-tumor activity compared to systemic delivery. A major advance in the application of CED is the development of real time CED, which utilizes an interventional MRI suite to visualize the CED process with the aid of a co-convected contrast agent, and thus allows for real time monitoring of drug delivery to the target.

**Methods:** With support from a R21 grant, a Phase I study of CED of concentrated nal-IRI using real-time imaging in patients with recurrent HGG is currently open for enrollment. This is a 3+3 dose escalation trial, with dose levels of 20 mg, 40 mg, 60 mg, and 80 mg of nal-IRI, given via up to 3 catheters surgically placed in an intra-tumoral location. The MRI contrast agent gadoteridol (2 mM) will be co-infused via the same catheters. Interim safety, efficacy, and imaging response results will be presented. From the imaging data, the correlation of pre-infusion modeling of drug distribution with post-infusion imaging will be analyzed. This will also allow for determination of the total volume of distribution to volume of infusion (Vd:Vi) ratio for each infusion. Clinical trial information: NCT02022644.
A pharmacokinetically (PK) and pharmacodynamically (PD) driven phase I trial of the pan-AKT inhibitor AZD5363 with expansion cohorts in PIK3CA mutant breast and gynecological cancers was presented. The MTDs of 7/7, 4/7 and 2/7 were established, two expansion cohorts of PIK3CA-mutant breast (B) and gynecological (G) cancers were explored: results: 47/21 and 22 patients were treated on the 7/7, 4/7 and 2/7 schedules respectively, with a further 27 and 18 patients recruited to the B and G cohorts to date. The MTDs of 7/7, 4/7 and 2/7 were 320mg BID, 480mg BID and 640mg BID respectively. The dose limiting toxicities (DLTs) were rash and diarrhea for 7/7, and hyperglycemia for 2/7. No DLTs were identified for 4/7. The most common causally-related adverse events ≥ CTC Grade 3 were hyperglycemia (20%), diarrhea (10%), rash (10%), nausea (3%) and fatigue (1%). PK profiles at the RP2D of 480mg BID (4/7) showed a multi-dose C_{max} of 1426ng/mL and AUC_{0-24h} of 7952ng.hr/mL, which were consistent with exposures that gave tumor regression in preclinical models. Pre- and post-treatment biopsies confirmed target engagement in tumor tissue, with an increase in pAKT and reductions in pGSK3β and pPRAS40. Based on toxicity, PK and PD profiles 480mg BID (4/7) was chosen as the RP2D for single agent AZD5363, with the option of using 640mg BID (2/7) as a pharmacologically active dose for future expansion cohorts. Tumor lesion shrinkage was observed in 7/5 and 4/14 for the B and G cohorts respectively, and with RECIST responses in evaluable patients of 3/15 (20%) and 1/14 (7%). Conclusions: Based on toxicity, PK and PD data two intermittent schedules of AZD5363 have been identified for further exploration. Promising single agent activity has been seen in PIK3CA-mutant breast cancer providing support for ongoing combination studies. Clinical trial information: NCT01226316.

**Phase I studies of anti-ENPP3 antibody drug conjugates (ADCs) in advanced refractory renal cell carcinomas (RRCC).** First Author: John A. Thompson, Seattle Cancer Care Alliance, Seattle, WA

Background: ENPP3 is expressed in greater than 90% of clear cell (CC) and 70% of papillary (PAP) RCC and represents an interesting target in this disease. Hybridoma-derived AGS-16M8F and CHO-derived AGS-16C3F are fully human IgGκ monoclonal antibodies (mAbs), containing the tubulin micelle-targeting agent MMAF via a plasma-stable linker, which bind to ENPP3. The 2 ADCs have similar pharmacokinetic and toxicologic profiles. Methods: Two phase I studies were conducted sequentially to test safety, PK, and antitumor activity in patients with v1.1) of AGS-16M8F and AGS-16C3F in CC and PAP RCC (median prior systemic therapies = 3). ADCs were given q3w until PD or unacceptable toxicity. Results: AGS-16M8F and AGS-16C3F were studied in 15 and 34 subjects in dose range 0.6 - 4.8 and 1.8 - 4.8 mg/kg, respectively. Fatigue was the most common adverse event (AE) in both studies. In the AGS-16M8F study, maximum tolerated dose (MTD) was not reached, but 3/8 subjects at 4.8 mg/kg discontinued for ocular toxicity (OT). OTs were most commonly reversible keratopathy. In the AGS-16C3F study, the initial dose of 4.8 mg/kg exceeded MTD; 2/2 subjects had dose-limiting toxicities (DLTs). The MTD was 3.6 mg/kg. DLTs were also observed at lower doses, usually after 2 doses. This led to a successive de-escalation to 3.6, 2.7, and 1.8 mg/kg. Thrombocytopenia (TCP) was frequently reported but a DLT in only 1 subject at 3.6 mg/kg (AGS-16C3F). PK of both ADCs was comparable. Serum concentrations decreased multi-exponentially; exposure was dose proportional. In both studies, the mean terminal half-life was approx. 7-8 days for the main PK parameters C_{max} and AUC_{0-24h}. In the AGS-16C3F study, the median Tmax of ~4 h and a dose-dependent increase in exposure with incremental weight gains was observed. The PK variability was moderate-high (mean %CV on AUC0-24h ~50–70%); wkly dosing resulted in only 1 subject at 3.6 mg/kg (AGS-16C3F). PK of both ADCs was comparable. Results: At data cut-off, 76 pts had enrolled; 34 and 34 pts in AGS-16M8F and AGS-16C3F studies, respectively. Clinical trial information: NCT01672775.

**Therapy of advanced metastatic lung cancer with an anti-Trop-2- SN-38 antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132): Phase II clinical experience.** First Author: Michael J. Quinn, Helen F. Graham Cancer Center at Christiana Care Health System, Newark, DE

Background: Sacituzumab govitecan (IMMU-132) is a new ADC comprising SN-38, the active metabolite of the topoisomerase inhibitor, camptothecin (irinotecan), conjugated to an anti-Trop-2 antibody. In vitro and in vivo preclinical data suggest that IMMU-132 is the most efficacious with a high drug-antibody ratio (DAR) of 7.6, and capable of delivering up to 136-fold more SN-38 than its parent drug, irinotecan, in a human cancer xenograft. Trop-2 is widely expressed in most epithelial cancers, including non-small and small cell lung cancers (NSCLC and SCLC). Therefore, the safety and efficacy of this new ADC is being examined in advanced metastatic lung cancers. Methods: A phase II clinical trial (ClinicalTrials.gov, NCT01631552) is ongoing in subsets of previously-treated patients with metastatic lung cancer, administering IMMU-132 on days 1 and 8 of 21-day treatment cycles. Treatment is continued based on tolerability until progression, with safety and response assessments made every week and at 8-12 weeks, respectively. Dose reductions and delays allowed most patients to continue treatment until progression. Results: Thirty-four lung cancer (15 NSCLC and 19 SCLC) patients with a median of 3 (range, 1-7) prior therapies were given IMMU-132 doses at 8 mg/kg (N = 22), 10 mg/kg (N = 10), 12 mg/kg (N = 2). Tumor responses, including squamous and adenocarcinoma NSCLC types having PR, are summarized in the table below. Neutropenia was the only Grade 3/4 toxicity (G3, 15%; G4, 3%). Other drug-related G3 toxicities included diarrhea (9%), anemia (6%), leucopenia (5%), lymphopenia (3%), pneumonia (3%), vomiting (3%), dizziness (3%). No differences were found between 8 and 10 mg/kg dosing. No pt developed antibodies (ELISA) to the conjugate. Conclusions: Repeated cycles of IMMU-132 monotherapy are well tolerated. Objective responses in previously treated metastatic lung cancer encourage further study of IMMU-132 in these cancers. Clinical trial information: NCT01631552.
A new anti-CEA-SN-38 antibody-drug conjugate (ADC), IMMU-130, is active in controlling metastatic colorectal cancer (mCRC) in patients (pts) refractory or relapsing after irinotecan-containing therapies. This is a phase II/III study. First Author: Eftat Dolan, Fox Chase Cancer Center, Philadelphia, PA

Background: Combination chemotherapies with 5-FU, irinotecan, oxapilatin, anti-VEGF, and anti-EGFR agents have improved the outcome of mCRC pts. However, there is still an urgent need for better therapies to control this disease. IMMU-130 (labeluzumab govtacian), a conjugate of a humanized anti-CEA (chimeric) antibody coupled site-specifically to SN-38 (7.6 moles SN-38/lg) using a proprietary linker, is an attractive therapeutic option for mCRC pts. Methods: A phase II clinical trial (NCT016053318) was initiated in irinotecan-refractory/multiresistant mCRC pts with an elevated CEA (> 5 ng/ml), treated with IMMU-130 once- or twice-weekly at escalating 4-10 mg/kg dosages on weeks 1 and 2 of 3-week cycles. The primary objective of the study was determination of MTD, with secondary objectives of efficacy (by RECIST 1.1), PK and immunogenicity. Treatment was continued until disease progression or intolerance. Results: Between Feb 2013 and Nov 2014, 66 patients were enrolled. Median age was 57 years [39-82]. Median prior therapies were 5 [1-9], with 76% and 36% pts receiving prior bevacizumab and an EGFR inhibitor, respectively. Median number of cycles per pt was 2 [1-15]. Fifty-eight patients were evaluable for toxicity, with 3 DLTs (G3 lymphopenia, G4 neutropenia and G3 anemia/vomiting > 48h) in all pts. Grade 3/4 drug-related toxicities were found in 25% pts, including neutropenia (G3, 7%; G4, 3%), diarrhea (G3, 2%), anemia (G3, 3%) and lymphopenia (G3, 3%). The dose selected for further study was 10 mg/kg weekly or 6 mg/kg biw. No pt developed antibodies to the conjugate. Tumor reductions were seen in 23/66 (35%) pts, including one PR with 88% best tumor shrinkage still being treated for 52 + weeks, 6 pts with 20-30% tumor reductions, and 16 pts with 0-20% tumor reductions. Conclusions: Repeated cycles of IMMU-130 monotherapy had an acceptable toxicity profile. Tumor reductions were noted in 35% of patients despite prior relapse to irinotecan-containing therapies. These results encourage further evaluation of IMMU-130 in combination with other agents in mCRC. Clinical trial information: NCT01605318.

Phase II study with Wee1 inhibitor AZD1775 plus carboplatin in patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard first line therapy. First Author: Suzanne Leijen, The Netherlands Cancer Institute, Amsterdam, Netherlands

Background: AZD1775 (formerly MK-1775) is a potent and selective inhibitor of Wee1, a kinase that phosphorylates CDC2. Phosphorylation of CDC2 inactivates the CDC2/cyclin B complex and is therefore essential for normal G2 checkpoint function. As most p53-deficient tumors lack a functional G1 checkpoint, they rely on the G2 checkpoint for cell cycle arrest in response to DNA damage. G2 checkpoint abrogation, using a functional G1 checkpoint, they rely on the G2 checkpoint for cell cycle arrest in response to DNA damage. Using a Wee1 inhibitor may therefore sensitize p53 deficient tumor cells to DNA-damaging anti-cancer agents. In a phase I study the maximum tolerated dose (MTD) of AZD1775 in combination with carboplatin demonstrated target engagement (NCT00648648). Methods: Patients (pts) with p53 mutated ovarian cancer refractory or resistant (< 3 months) to standard first line therapy (carboplatin plus paclitaxel) were re-exposed to carboplatin (AUC 5), plus 5 bi-daily doses of 225 mg AZD1775 in a 21 day cycle (MTD) (NCT01164995). p53 mutation status was analyzed by both sequencing analysis (TP53 exons 2-10) and AmpliChip TP53 array (TP53 exons 2-11). Response evaluation was performed according to RECIST 1.0. Volumetric tumor measurement (enhanced RECIST) and CA-125 blood levels. Results: Bone marrow toxicity, fatigue, diarrhea, nausea and vomiting were the most common adverse events. Out of 24 pts enrolled, 22 pts were evaluable for study endpoints. As best response (RECIST 1.0), 6 pts (27%) showed confirmed partial response (PR) with a median progression-free survival (PFS) of 10.9 months. Nine pts (41%) had stable disease and 7 pts (32%) had progressive disease as best response, with a median PFS of 5.3 and 1.3 months, respectively. Conclusions: AZD1775 is a first in class Wee1 inhibitor that in combination with carboplatin is well tolerated and shows promising anti-tumor activity in p53 mutated ovarian cancers refractory or resistant (< 3 months) to standard first line therapy. Clinical trial information: NCT01164995.
Preliminary results of TATTON, a multi-arm phase Ib trial of AZD9291 combined with MED14736, AZD6094 or selumetinib in EGFR-mutant lung cancer. First Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA

Background: AZD9291 is an irreversible, mutant-selective EGFR tyrosine kinase inhibitor (TKI) developed to have potency against EGFR mutations, including T790M. Inhibiting the TK domain of T790M, the wild-type EGFR was retained, in the previously published phase I study of AZD921, EGFR-mediated toxicity was reduced compared to available EGFR-TKIs. We hypothesized that the safety profile of AZD9291 would permit combinations with other targeted therapies in a tolerable fashion.

Methods: TATTON (NCT02143466) is a multi-arm phase Ib trial studying AZD9291 in combination with MED14736 (anti-EGFR mAb), AZD6094 (MET inhibitor) or selumetinib (MEK1/2 inhibitor; AZD6244, ARRY-142886). Eligibility required advanced EGFR-mutant lung cancer, progression on any prior EGFR-TKI, measurable disease, adequate PS (0-1) organ function, and tissue for correlates. In each combination, AZD9291 was dosed at 80 mg daily and the 2nd agent was escalated from a dose below the phase II monotherapy dose. Using a rolling 6 design, patients (pts) were randomly allocated to a combination arm. Data included here are preliminary and will be updated for presentation.

Results: As of 8 January 2015, 42 pts have been enrolled on combination therapy (MED14736 = 14 pts; AZD6094 = 7 pts, selumetinib = 21 pts). All 3 combination arms were escalated to their phase II monotherapy doses; an additional arm continues to explore intermittent dosing of selumetinib. Adverse event (AE) data is currently available for 20 pts from all arms and cycles and includes mild/moderate AEs in 16 pts (6 skin, 5 laboratory, 2 gastrointestinal, 2 psychiatric, 2 other) and severe AEs in 5 pts (1 skin, 1 gastrointestinal, and 1 metabolism); 2 DLTs were reported (fatigue; AZD9064 arm; transaminase elevation – selumetinib arm). To date, 3 partial responses (PR) have been seen with AZD9291/MEDI4736, 2 PR with AZD9291/AZD6094, and 2 PR with AZD9291/selumetinib. Combination dose finding is expected to complete by May 2015. The toxicity profile of AZD9291 makes rational combinations with potentially synergistic targeted therapies feasible at biologically active doses. Expansion cohorts are planned for pts with acquired resistance to third-generation EGFR-TKI. Clinical trial information: NCT02143466.

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A first-in-human dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of oral 2-hydroxyoleic acid (2-OHOA) in adult patients (pt) with advanced solid tumors including grade III/IV glioblastoma multiforme (GBM). First Author: Desamparados Roda, The Institute of Cancer Research and The Royal Marsden, London, United Kingdom.

Background: 2-OHOA, a synthetic hydroxylated lipid that activates sphingomyelin synthase (SGMS) and regulates the lipid content of cell membranes resulting in translocation of Ras to the cytoplasm and inactivation of Ras/MAPK, PI3K/Akt and PDK1/CDK signaling pathways. 2-OHOA reduces tumor growth in xenograft mouse models of prostate, leukemia, breast, colon, breast cancer, and GBM, and also crosses the blood brain barrier. This first-in-human study was designed to determine the safety, tolerability, and recommended phase 2 dose (RP2D), alongside the PK, PD and anti-tumor profile of 2-OHOA. Methods: Eligible pts with advanced solid tumors or grade (G) III/IV GBM received 2-OHOA as a PO suspension, BID in 21-d cycles using a 3+3 dose escalation design. Adverse events (AE) were assessed by Common Terminology Criteria for AE v4; tumor response was assessed every 2 cycles using RECIST 1.1/RANO criteria.

Results: 17 pts (median age 59 years; range 19-71; 7 GBM and 10 solid tumors) were treated at 5 dose levels: 250-, 500-, 1000, 2000 and 4000-mg BID. Treatment was well tolerated with toxicities limited to grade 1-2 nausea (n = 4), vomiting (n = 6) and diarrhea (n = 6). The PK profile was dose-proportional with no accumulation up to 2000mg BID; t1/2 = 4h. No effect of food was observed. One pt with GBM treated at 500mg BID had a confirmed and ongoing partial response and is currently at cycle (C) 23 of treatment; a 2nd GBM pt has SD after 2 cycles and continues on study. A 3rd pt with progressive melanoma demonstrated TCR to C15.

Conclusions: 2-OHOA can be safely administered up to doses of 4000mg BID. Clinical benefit was observed in 3 patients including 1 PR in a pt with GBM. Dose escalation continues to determine a RP2D, followed by a RP2D expansion in patients with both solid tumors and grade III/IV GBM. Clinical trial information: NCT01792310.

TP53 mutations emerge in circulating cell-free DNA obtained from patients undergoing treatment with the HDM2 antagonist SAR405838. First Author: James Wilson Watters, Sanofi, Cambridge, MA.

Background: SAR405838 is an oral antagonist of HDM2 that results in p53 activation. In preclinical studies, SAR405838 is active in p53 mutant tumors. In an ongoing Phase I study, p53 activation was demonstrated at 100mg BID, with p53 stabilized in the majority of treated pts.

Methods: Tumor and plasma samples were available from 18 patients (pts) undergoing treatment with SAR405838 for different solid tumors. Baseline and post-hoc tumor and plasma samples were analyzed by a tissue-agnostic genetic alteration–specific protocol that matches pts to treatments that target tumors harboring PI3K pathway–activated tumors. The pts are identified via standard of care physician-directed profiling.

Results: Commonest AEs (greatest in cervix and sarcomas: 2; highest in colorectal and vaginal: 5) were: neutropenia (16), vomiting (10), fatigue (13), elevated ALT (2). 25 SAEs were ‘possibly/probably related’ to study drug, and 2 > G2; elevated ALT (4) and lung infection (3). Commonest AEs = G3 ‘possibly/probably related’ were: neutropenia (16), fatigue (13), elevated GGT (10). SAR405838 was stable, with plasma half-life of 8.3 hours. High intracellular levels of the active anti-tumor agent dT-dC(T) (Cmax = 475±86 µM) were rapidly achieved and maintained for 24 hours. Notable efficacy results were observed: 5 RECIST partial responses (10%); 33 Stable Disease (67%) for an ITT disease control rate (DCR) of 97%. Median (MD) treatment duration of OATAs was 22 weeks. PRs and SDs were observed in pts refractory/refractory to prior nucleoside analogue therapy and were durable, mean PFS 6.1 months (range 2 – 20 mths). The RP2D was 825mg/m2 given on days 1, 8, 15, q4w. Conclusions: SAR405838 has demonstrated considerable clinical activity in pts with PI3K or PIKK pathway–dependent tumors (ITT 56%; OATAs 78%) in a wide range of patients with advanced and progressing disease. SAR405838 is well-tolerated at the RP2D. Phase II clinical studies in ovarian, pancreatic and biliary cancers are planned this year and combination studies are currently recruiting. Clinical trial information: NCT01621854.
First-in-human phase I study assessing imalumab (Bax69), a first-in-class anti-oxidized macrophage migration inhibitory factor (oxMIF) antibody in advanced solid tumors. First Author: Devalingham Mahalingham, Cancer Therapy and Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: MIF is a pleiotropic cytokine involved in tumor proliferation, invasion, angiogenesis, and pro-inflammatory microenvironment. oxMIF is the patho genetic form mainly in tumor and its surrounding stroma. Imalumab (Bax69) is a novel recombinant, fully-human, monoclonal antibody that targets oxMIF, inhibiting tumorgenesis. Preclinical data demonstrated that Imalumab has antitumor activity and acceptable toxicities. Methods: The primary endpoint of this dose-escalation study (3+3 design) was to assess maximum tolerated dose (MTD). The secondary endpoints were to assess antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics (PD). Patients (pts) received intravenous (IV) Imalumab (28-d cycles; 2 dose schedules (DS); biweekly in all solid tumors (DS1), weekly in metastatic colorectal cancer (mCRC) (DS2)). Results: As of Dec 2014, 28 pts were analyzed. DS1 = 19 pts in 6 cohorts (1, 3, 10, 25, 37.5, and 50 mg/kg). AUC and C\text{max} increased with dose. Dose escalation was stopped at 50 mg/kg (DS1) and 25 mg/kg (DS2). An MTD was not reached for either DS. One pt reported dose-limiting toxicities: hypersensitivity pneumonitis (DS1; 50 mg/kg). There were no other grade 3 or 4 treatment related adverse events (trAEs). Grade 2 trAEs included: fatigue (n = 2), peripheral edema (n = 1), infusion reaction (n = 1), urticaria (n = 1). About 86% of pts had no trAE > G1. Stable disease (SD) = 4 mo was seen in 7 heavily pre-treated pts, including 1 pt with NSCLC who achieved SD > 13.4 mo. In DS2, DLTs and on-tumor biologic responses were consistent with preliminary data of Imalumab with regulation of PI3K-AKT-mTOR downstream signaling, TNF-α signaling, anti-inflammatory cytokines (IL-1 and IL-10), and apoptosis in all 5 biopsy evaluable patients. Due to non-clinical PK & PD study, 10mg/kg weekly was considered a biologically active dose and sufficient to reach > 95% target binding by the end of first cycle. Conclusions: Imalumab was well tolerated and showed single agent antitumor activity in heavily pre-treated pts. An MTD was not reached. Recommended phase II dose (RP2D) is 10mg/kg IV weekly. NCT01765790 Clinical trial information: NCT01765790.
2521 Poster Session (Board #237), Sat, 8:00 AM-11:30 AM
Phase I study of ontuxizumab, a humanized monoclonal antibody (mAb) recognizing endosialin in Japanese patients (pts) with hepatocellular carcinoma (HCC). First Author: Masafumi Ikeda, National Cancer Center Hospital East, Chiba, Japan

Background: Endosialin is a cell surface glycoprotein that is expressed on cells involved in the development of tumor vasculature, primarily pericyte and stromal fibroblast. Ontuxizumab is a humanized IgG1x mAb that is the first clinical stage agent to target Endosialin. Based on the safety profile obtained in the dose escalation portion of this study, 3 dosage cohorts were explored to further characterize the safety, pharmacokinetics (PKs), and preliminary efficacy of Ontuxizumab in advanced HCC pts. Methods: HCC pts with Child-Pugh (CP) A who have no other appropriate treatment were enrolled at 4 study sites to 3 dosage cohorts; and 4 and 8 mg/kg weekly, and 12 mg/kg biweekly as 4 weeks a cycle. Primary objective was to safety. Efficacy endpoints were Response rate by RECIST v1.1, Disease Control Rate (DCR) and Time to Progression (TTP). Results: Fifteen pts with advanced HCC pre-treated at minimum with sorafenib have been enrolled. Of these, 11 and 4 pts presented with ECOG 0 and 1 respectively, while 10 and 5 pts presented with CP A5 and A6 respectively. The PK profile from the HCC cohort was consistent with those of the dose escalation cohorts with other solid tumors. There were no significant differences for Cmax and AUC of Ontuxizumab between HCC and other solid tumors. Mean t1/2 was 99.0 - 216 hours after multiple administrations. Safety profile was mainly characterized by Gr 1-2 events. Treatment related adverse events (AEs) were observed in 10 of 15 pts. The most common AEs were hiccups (20%) after ALT increased, AST increased, blood bilirubin increased, hypoalbuminemia and malaise (each 13%). There were 3 treatment related Gr 3-4 AEs (ALT increased, AST increased and hyperglycaemia), and no treatment related serious AEs. No CRs or PRs were reported; DCR was 60% with TTP ranging from 11 to 12.9 months. Five pts (33%) showed tumor shrinkage (over 6 months) SD was observed in 3 pts (20%). Conclusions: Ontuxizumab appears generally well tolerated in this HCC population with a PK profile consistent with the profile in other solid tumors. Preliminary efficacy results suggest that Ontuxizumab at minimum 4 mg/kg weekly warrants further investigation for clinical activity in HCC. Clinical trial information: NCT01773434.

2523 Poster Session (Board #239), Sat, 8:00 AM-11:30 AM
Molecular characteristics in breast cancer tumors treated with neoadjuvant chemotherapy with and without bevacizumab: Results from NeoAvA—Randomized phase II study. First Author: Olav Engebretsen, Oslo University Hospital, Oslo, Norway

Background: The molecular characteristics of responding and non-responding breast cancers when treated with antiangiogenic therapy are largely unknown. Methods: To investigate molecular alterations in tumors treated with antiangiogenic therapy, the NeoAvA study included patients with HER2 negative primary tumors of ≥ 25 mm that were randomized (1:1) to 12 chemotherapy alone (A; n = 108) vs chemotherapy and bevacizumab therapy (A+B; n = 108) arms, where the median follow-up time was 3 years. Results: mRNA expression profiling was performed. In the A+B arm, 103 of the 120 patients were evaluable for tumor response. Results: PCR in breast and axilla were obtained in 14 (21.1%) patients in the chemotherapy arm and in 7 (10.6%) patients in the chemotherapy-only arm. The overall PCR rates were higher in the ER negative tumors compared to ER positive tumors (19 of 23 (vs 12 of 108)). Addition of bevacizumab seemed to improve PCR in the ER positive patient group (9 vs 3) and not in ER negative patient group (5 vs 4). Tumors that achieved PCR showed a significant higher expression of genes (n = 362) enriched for immune response related pathways, compared to the tumors that did not achieve PCR in the ER positive group. The identified immune gene signature predicted response independent of the PAM50 proliferation signature and VEGF pathway signature, particularly in the breast cancer treated with bevacizumab (A+B; p < 0.001). Immunohistochemistry analysis across time points in response to therapy (p < 0.001), and bevacizumab treatment accelerated the reduction of the proliferation score in the ER positive tumors. In response to therapy, tumors achieved a better prognosis profile, i.e. Luminal A or Normal-like profile. ER positive tumors, particularly Luminal B showed significant differences in gene expression and associated pathways between two treatment arms (chemo only and chemo+b-bev), while minimal change was observed for ER negative/Basal-like tumors. Conclusions: The immune signature was found to be a strong predictor of response in ER positive tumors, particularly in tumors treated with chemotherapy combined with bevacizumab. Clinical trial information: NCT00773695.

2524 Poster Session (Board #240), Sat, 8:00 AM-11:30 AM
Bevacizumab plus Letrozol (LEA clinical trial phase III). Using hypertern-sion for finding biomarkers of efficacy. First Author: Juan de la Habac-Rodriguez, Medical Oncology Department University Reina Sofia Hospital. Biomedical Research Institute Maimonides, Cordoba, Spain

Background: The LEA study compares the combination of endocrine therapy plus bevacizumab (ET-B) against endocrine therapy (ET), as first line treatment in patients (pts) with advanced breast cancer. It failed to demonstrate superiority for the combination (JCO 2015 in press). Some retrospective studies have shown that pts developing hypertension (HT) whilst on antiangiogenic treatment have a better outcome. Polymorphisms in several HT-related genes might contribute to inter-individual differences in response to these treatments. The aim of this study is to analyze the predictive value of HT for bevacizumab efficacy. Associations between polymorphisms in genes related with HT and bevacizumab efficacy were assessed. Methods: The LEA study randomized 380 pts in two treatment arms, ET-B (191 pts) and ET (189 pts). We collected Grade 1-4 HT in all pts, genotyped 117 of these pts (ET-B:67/ ET:50). A higher rate of HT was found in the ET-B arm, p < 0.01. Pts developing HT had a better response rate (45% vs. 27% in pts with HT vs no HT, p < 0.001) and a longer progression free survival (PFS) (21.9 vs 12.0 months, HR = 0.55 (95%CI:0.34–0.71), p < 0.001) and overall survival (OS) (48.6 vs 41.6 months, HR = 0.55 (95%CI:0.35–0.83), p < 0.01). The association was stronger in the ET-B and ET, and between HT and efficacy was maintained in the genotyped subpopulation. The variant in the angiotensin converted enzyme (ACE) rs1799752 (287pbIN/DEL) and in the angiotensin receptor type 1 (AGTR1) rs5186 (M235T) were associated with HT (p < 0.05). In the ET-B arm, we found a correlation between rs1799752 ACE IN/DEL and PFS (p = 0.04), and between VEGF2578 and OS (p = 0.0045). Conclusions: HT is correlated with better clinical outcomes in pts treated with the ET-B combination. These results provide preliminary evidence of the predictive role of polymorphisms in HT-related genes in bevacizumab efficacy. The real interest of these polymorphisms should be further elucidated in larger prospective studies.
A phase 1 trial of a potent and selective VEGF receptor inhibitor, apatinib, in patients with advanced solid tumors. First Author: Sunil Sharma, University of Utah Huntsman Cancer Institute, Salt Lake City, UT

Background: VEGF-mediated signaling pathways are critical to tumor growth. Apatinib mesylate is a novel, oral angiogenesis inhibitor that potently and selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR-2). Methods: Apatinib mesylate was administered once daily as an oral monotherapy starting at 100 mg/day and escalating to 250, 500, 750, or 850 mg/day, with dose expansion at the up to 850mg/day or maximum tolerated dose level. PD primary objective was to determine the safety and tolerability of continuous oral Apatinib mesylate in patients with recurrent solid tumors. A secondary endpoint was response to treatment. Results: In this Phase 1 trial, 25 patients were treated and evaluated for safety and tolerability. The dose levels were: 100 mg/day (n = 5); 250 mg/day (n = 9); 500 mg/day (n = 4); 750 mg/day (n = 4); and 850 mg/day (n = 3). Median age was 62 years (range, 33–76 years), and median prior number of therapies was 3.5 (range, 0–8 therapies). There was 1 dose-limiting toxicity (malignant hypertension, 250mg/day). Among 19 evaluable patients, after 2 cycles, there was 1 (5.3%) partial response, 11 (57.9%) stable disease, and 7 (36.8%) disease progression. Pharmacokinetic data will be presented. Conclusions: Apatinib mesylate monotherapy was well tolerated in patients with recurrent solid tumors in this phase 1 trial with preliminary evidence of promising antitumor activity. The recommended phase 2 dose for further development was 850 mg/day. Clinical trial information: NCT01497704.

First-in-human Phase 1 safety, PK, and PD study of the CDK4/6 inhibitor G1T28. First Author: Renger G. Tiessen, PRA Health Sciences, Groningen, Netherlands

Background: G1T28 is a highly potent and selective CDK4/6 inhibitor being developed as an IV agent for targeted bone marrow chemoprotection and as an oral antineoplastic agent. The CDK4/6 pathway is critical in regulating cell proliferation of certain tumors. In addition, hematopoietic stem and progenitor cells (HSPCs) are dependent upon CDK4/6 for proliferation. Transient G1T28-induced G1 cell cycle arrest of HSPCs renders them resistant to the cytotoxic effects of chemotherapy. Thus, G1T28 could be used for chemoprotection (reduction of chemotherapy-induced myelosuppression) in patients with CDK4/6-independent tumors, or as an antineoplastic agent in patients with CDK4/6-dependent tumors. Methods: The objective of this study was to assess the safety and tolerability of G1T28, as well as to characterize PK and PD. Part 1 was a single-blind, placebo-controlled, single escalating dose study in healthy volunteers of both sexes, where subjects were randomized (3:1) to receive G1T28 or placebo as a single 30-minute IV infusion. Part 2, 8 subjects will receive single escalating oral doses of G1T28 in three dosing periods. PD assessments included evaluation of ex vivo stimulation of lymphocytes and bone marrow cell cycle analysis. Results: 45 subjects have enrolled in the study to date. In Part 1, G1T28 was administered at doses of 6, 12, 24, 48, 96 and 192 mg/m². G1T28 was well tolerated, with no dose limiting toxicities or serious adverse events reported. In Part 1, G1T28 exposure (Cmax and AUC) increased proportionally with dose, while clearance was relatively constant. G1T28 at 96 and 192 mg/m² demonstrated a robust pharmacodynamic effect with a dose-dependent decrease in phytohemagglutinin (PHA)-stimulated lymphocyte proliferation ex vivo. Conclusions: G1T28, a novel CDK4/6 inhibitor, is well tolerated and demonstrates predictable PK and robust PD activity. Based on these results, IV G1T28 will be investigated in Phase 1b/2a studies in patients with CDK4/6-independent tumors to evaluate its potential as a targeted bone marrow chemoprotectant. In addition, the oral formulation will be assessed as an antineoplastic agent in patients with CDK4/6-dependent tumors. Clinical trial information: NCT02243150.

Overcoming the proliferation rate paradox: Clinical evaluation of a continuous dosing scheme of the novel oral Eg5 inhibitor 4SC-205. First Author: Klaus B. Mross, Klinik für Tumtorheologie, Freiburg, Germany

Background: Mitotic proteins, like Eg5, are exclusively expressed during mitosis. Targeted therapy directed against such proteins prevents side-effects like peripheral neuropathies. However, mitosis is a timely restricted event and doubling times of human solid tumors (~120d) largely exceed the ones observed in preclinical models. Therefore, continuous exposure at the target site is mandatory. Here we present a clinical dosing scheme for the Eg5i 4SC-205 to address these challenges. Methods: Time-dependent anti-proliferative effect of 4SC-205 on spindle check point (SAC) deficient (H929, HT29) and proficient (HCT116, NCCIT) cell lines was investigated. Apoptosis induction was assessed by western blot analysis for Noxa, Mcl-1 and caspase 3. 59 patients (pts) with solid tumors were enrolled in a Phase I study and dosed either once weekly (ow) at days 1 and 8 or twice weekly (tw) at days 1, 4, 8, and 11 or continuously (con) within a 21-day cycle. Results: Effects on proliferation and apoptosis induction in SAC deficient/proficient cell lines was time-dependent. SAC deficient cells required up to 96h incubation to establish the full IC50. 46 pts were enrolled in the discontinuous dosing arms with either once weekly (ow) or twice weekly (tw) dose levels: 25mg (N = 3), 50mg (N = 3), 100mg (N = 6), 150mg (N = 6) and 200mg (N = 13) ow; at 50mg (N = 3), 75mg (N = 7), and 100mg (N = 5) tw. 13 patients were evaluated for con. dosing at 10mg (N = 3), 20mg (N = 6), and 30mg (N = 4). Response acc. to RECIST 1.1 was not observed in any of the 29 evaluable pts at follow-up after 6 weeks. One patient is still on treatment at 20mg daily. The median time on study of pts receiving continuous dosing of 20 mg was 162 days. In contrast, the overall median time on study was 42 days under ow or tw dosing. Conclusions: Prolonged exposure is needed for 4SC-205 to inhibit proliferation and to induce apoptosis in SAC deficient cell lines. This requirement was translated into the clinic utilizing a continuous dosing scheme. 4SC-205 can be safely administered at an oral daily dose of 20mg (= RP20). Promising long-term disease stabilization is observed under continuous dosing. Clinical trial information: NCT01065025.
2529 Poster Session (Board #245), Sat, 8:00 AM-11:30 AM
Evaluation of targeted bone marrow arrest by G1T28, a CDK4/6 inhibitor in clinical development to reduce chemotherapy-induced myelosuppression.
First Author: Patrick J. Roberts, G1 Therapeutics, Inc, Research Triangle Park, NC

Background: Myelosuppression is the major dose-limiting toxicity of chemotherapy, which limits dose intensity. G1T28 is a highly potent and selective CDK4/6 inhibitor in development as an IV agent to provide targeted bone marrow chemoprotection in patients with CDK4/6-independent tumors. Hematopoietic stem and progenitor cells (HSPCs) are dependent upon CDK4/6 for proliferation. G1T28 induces a transient G1 cell cycle arrest that renders HSPCs resistant to the cytotoxic effects of chemotherapy. In preclinical models, this results in faster recovery of all blood cell counts following chemotherapy and preservation of long-term hematopoietic function. Methods: To rationally design tolerable and active chemotherapy combination regimens with reduced multi-lineage myelosuppression, the magnitude and duration of G1T28-induced HSPC G1 arrest in human bone marrow was characterized. Data from 3 species (mouse, rat, dog) were used to evaluate dose response relationships for HSPC G1 cell cycle arrest and to construct a cross-species allometrically-scaled PK/PD model. Model simulations and human PK/PD data from a Phase I trial (NCT02243150) were used to predict the biologically effective dose (BED) in humans. In this trial, the BED was assessed by obtaining bone marrow aspirates and evaluating G1 arrest of HSPCs by flow cytometry. Results: Preclinical PK/PD modeling outputs and clinical data predicted the BED in humans to be 192 mg/m². Specifically, a 15mg/kg dose of G1T28 in dogs produced robust and sustained bone marrow arrest for ~24 hours and had a similar PK exposure to the predicted human BED. A single bone marrow aspirate from 12 subjects following 192 mg/m² (baseline, n = 5; 24 h post-G1T28, n = 3, or 24 h post-G1T28, n = 4) demonstrated a robust G1 arrest of multiple progenitor subsets at 24 h, with early progenitors persisting in G1 arrest to ~32 h. Conclusions: A single IV administration of G1T28 at the BED of 192 mg/m² produced robust inhibition of HSPCs within the bone marrow for >24 hours. Based on these results, Phase Ib/2a studies are planned to evaluate the potential of G1T28 in reducing multi-lineage chemotherapy-induced myelosuppression. Clinical trial information: NCT02243150.

2530 Poster Session (Board #246), Sat, 8:00 AM-11:30 AM
SLC1A5 to predict outcome with chemotherapy in early triple-negative breast cancer.
First Author: Anna Maria Affan, St Vincent Charity Medical Center, Cleveland, OH

Background: TNBC are high grade tumors which have a poor prognosis. SLC1A5 is a neutral amino acid transporter found in these tumors and high levels correlate with aggressive biological behavior. By targeting SLC1A5 function, tumor cell growth can be inhibited and autophagy activated which should result in improved survival benefit for patients with TNBC. We evaluated the role of SLC1A5 on tumor death rate in patients who were treated with chemotherapy in TNBC cell lines. Methods: A retrospective, cohort study of patients with TNBC was performed to evaluate survival compared with the level of expression of SLC1A5. A histogram was constructed to determine a median point which could be used to define a “high” versus “low” score. Five was used as the average cut-point. Thereafter to determine overall survival (OS) and progression free survival (PFS) the log rank test was compared using the following cut points. Results: The cohort consisted of 171 patients with TNBC. The median age was 51 years with similar distribution between male and female patients. Survival information was available for 112 patients with data available on the SLC1A5 score. There was a significant association of the outcome of interest, overall survival, with the SLC1A5 score with a worse outcome noted in tumors with higher expression (p = 0.00189). Additionally, 80 patients with TNBC who received chemotherapy with higher levels of SLC1A5 showed worse survival (p = 0.00056). The relationship of CAIX with SLC1A5 is also of significance, there was a significant association of the outcome of interest, overall survival, with the SLC1A5 score. There was a significant association of the outcome of interest, overall survival, with the SLC1A5 score with a worse outcome noted in tumors with higher expression (p = 0.00189). Additionally, 80 patients with TNBC who received chemotherapy with higher levels of SLC1A5 showed worse survival (p = 0.00056). The relationship of CAIX with SLC1A5 implies that the latter may be involved in tumor hypoxia that needs further exploration in additional cohorts and clinical trials.

2531 Poster Session (Board #247), Sat, 8:00 AM-11:30 AM
Phase I dose-escalation study with extended daily administration of Debio1143, an oral inhibitor of apoptosis protein inhibitor, in patients with solid tumors.
First Author: Henry C. Pilot, Mayo Clinic, Rochester, MN

Background: Inhibitors of apoptosis proteins (IAPs) play a critical role in modulating multiple processes, including caspases activation and NF-κB signaling. Because high expression of IAPs represent a frequent oncogenic event in human cancers, therapeutic targeting of IAPs is considered as a promising approach. The small molecule Debio 1143 is a novel oral, active IAP antagonist able to promote apoptosis in tumour cells by restoring the balance between pro- and anti-apoptotic IAPs, and it has also been shown to affect NF-κB signaling. This study was conducted to evaluate the potential of G1T28 in reducing multi-lineage chemotherapy-induced myelosuppression. Clinical trial information: NCT02243150.

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Conclusions: The cohort of 171 patients with TNBC. The median age was 51 years with similar distribution between male and female patients. Survival information was available for 112 patients with data available on the SLC1A5 score. There was a significant association of the outcome of interest, overall survival, with the SLC1A5 score with a worse outcome noted in tumors with higher expression (p = 0.00189). Additionally, 80 patients with TNBC who received chemotherapy with higher levels of SLC1A5 showed worse survival (p = 0.00056). The relationship of CAIX with SLC1A5 implies that the latter may be involved in tumor hypoxia that needs further exploration in additional cohorts and clinical trials.
First-in-human study of LY3039478, a Notch signaling inhibitor in advanced or metastatic cancer. First Author: Christophe Massard, Gustave Roussy Cancer Campus (Cedex), Groupe蹋s Fleurie, France

Background: LY3039478 (LY) is an orally bioavailable, potent, and highly selective Notch inhibitor (Notch 1-4). We report on safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of LY. Methods: Eligible pts (ECOG ≤ 1) had relapsed solid tumors, adequate hematologic, renal, and hepatic functions. Using a predictive pre-clinical PK/PD model and non-clinical toxicity data, a dose range of 2.5-100 mg was selected. LY was given three times a week (TIW) on a 21-day cycle to assess dose-dependent inhibition of disease progression. Dose escalation used 3+3 design with probability toxicity band modelling. Safety assessments were based on CTCAE V4.0. Primary objective: to define the recommended phase 2 dose of LY; additional objectives: PK, PD (AUC in plasma and a panel of genes expressed in skin), and preliminary antitumor activity. Results: 55 pts were treated. The most common related toxicities (≥ 10% of pts) included diarrhea (42%); vomiting (40%); nausea (36%); asthenia (33%); decreased appetite (25%); hypophosphatemia (18%); mucosal inflammation (16%); weight decrease (15%); hair color changes and dry skin (13% each); dry mouth (11%); 5 dose-limiting toxicities were observed in cycle 1: thrombocytopenia grade 4 in 3 pts (20mg, 30mg, and 60mg), nausea and asthenia grade 3 in one patient (100mg) and colitis grade 3 (100mg). Other observed grade 3/4 toxicities related to LY in > 1 patient included hypophosphatemia (5 pts) and vomiting (2 pts). Maximum tolerable dose (MTD) was defined as 75 mg TIW, AUC and Cmax appeared to increase in a dose proportional manner. There was no accumulation with multiple dosing with an elimination half-life of approximately 6-8h. Dose dependent inhibition of plasma Aβ and target genes (in skin) was observed. At the recommended dose of 75mg TIW, preliminary data indicate approximately 80% inhibition of Aβ, > 50% inhibition of HES1, N-RARP, and NCNID. Additional inhibited genes included HES2, HES4, HES5, HEY1 and MYC. 6 pts received ≥ 6 cycles (range 6-18). Best observed response is PR in a patient with ER+/PR+/HER2-breast cancer. Conclusions: The recommended dose for LY monotherapy is 75 mg TIW with manageable toxicities and significant target inhibition. Further exploration of LY monotherapy is ongoing. Clinical trial information: NCT01695005.
Early anti-tumor activity is seen. Dose-escalation on a 6-day infusion was well tolerated in monotherapy or in combination with chemotherapy agents.

**Conclusions:**

- Disease, decrease in tumor markers, QOL improvements.
- Integrated multi-tumor reductions, decrease FDG, arrested tumor progression, stable disease, evaluable for efficacy after cycle 2 showed various responses including:
- One MPN pt decreased WBC and increased hemoglobin.
- Grade 1-2 thrombo-related AEs in all 4 arms were grade 1-2 INR prolongation that resolved.
- No bleeding reported.
- MTD has not yet been established.
- Most frequently reported (140 mg/m2), 8.3% in a triple negative breast cancer pt (300 mg/m2), 25.6% in an ER positive breast cancer pt (400 mg/m2), 20.8% in a penile cancer pt (500 mg/m2).
- Plasma levels measured both ways were in close concordance.
- Concentrations measured both ways were in close concordance.
- Related grade 3 anemia, 1 pt grade 2 intolerable headache. Related grade 3 ALT, 1 pt grade 3 nausea/vomiting.
- Preliminary data from 22 patients treated with 10-40 mg/day during the dose escalation phase of the trial indicate that Debio 1347 is rapidly absorbed with a median tmax occurring at 3-10 x ULN) HI received C dose escalation at 25, 10 or 10 mg/m2 respectively. Endpoints were cycle 1 (C1) dose-limiting toxicities (DLTs), safety, and PK. Plasma PK were derived by non-parametric analysis. HI effect was assessed by linear mixed-effects modeling on clearance normalized to body surface area (CL/BSA) and exposure normalized to dose. Results: Pts (43 (6 NHF, 18 MIHI, 12 ModHI, 7 SHI)) had a median age of 60 years (range 18–79); 52% were male; 81% had ECOG performance status 1. Colon and liver tumors were most common (19%; prostate), Maximum tolerated doses (MTD) were 20 (MIHI) and 15 mg/m2 (ModHI). The SHI cohort was discontinued early (first pt treated at 20 mg/m2 died). Median number of C cycles (range) at MTD were: NHF 3 (1–4); MIHI 2 (1–3); ModHI 2 (1–3).

**Conclusion:**

- A phase I dose-escalation study (NCT01140607) assessed the effect of HI on C PK and safety in pts with advanced solid tumors.

**Methods:**

- Pts with normal hepatic function (Child Pugh A or B) on long-term steroidal (A) or non-steroidal (B) anti-inflammatory doses (ASIA) were enrolled.
- Mild (MIHI; B < 1.5 x ULN or AST > 1.5 x ULN), moderate (ModHI; B < 1.5 – 3 x ULN) or severe (SHI; B > 3–10 x ULN) HI received C dose escalation at 25, 10 or 10 mg/m2 respectively. Endpoints were cycle 1 (C1) dose-limiting toxicities (DLTs), safety, and PK.

**Methods:**

- To date, 40 pts have received PU at doses from 124I-PU-H71 (*PU) PET imaging, 124I without altering its biochemical properties. Intratumoral drug concentrations measured both ways were in close concordance.
- In evaluable pts, C1 DLTs were seen in 3/4 NHF, 3/11 MIHI and 1/6 ModHI pts at MTD, and 0/6 SHI pts at 10 and 15 mg/m2. The most frequent DLT was grade 4 febrile neutropenia (FN). The most frequent C-related, grade 3–4 toxicities were neutropenia (42%), FN (16%) and anemia (12%).
- PK was assessed in 36 pts (6 NHF, 15 MIHI, 9 ModHI, 6 SHI). CL/BSA was lower (mean 13.4 L/h/m2) than typical values (26.4 L/h/m2) in NHF, but similar in MIHI (23.5 L/h/m2) and ModHI (27.9 L/h/m2). CL/BSA in SHI was 18.1 L/h/m2. HI with or without C increased C CL.
- HI received C dose escalation at 25, 10 or 10 mg/m2 respectively. Endpoints were cycle 1 (C1) dose-limiting toxicities (DLTs), safety, and PK.

**Methods:**

- Preliminary clinical pharmacokinetics and pharmacodynamics of Debio 1347 (CHS183284), a novel FGFR inhibitor. First Author: Claudio Zanna, Debiopharm International SA, Lausanne, Switzerland.

**Background:**

- Deregulated fibroblast growth factor receptor (FGFR) signaling is associated with tumorigenesis. Debio 1347 is an orally-available ATP competitive inhibitor of FGFR 1, 2 and 3 with preclinical data showing high target-specificity and antitumor activity across models of FGFR amplified, mutated or translocated tumors for various human malignancies.
- Debio 1347 is currently investigated in selected patients harboring FGFR genetic aberrations. Methods: Eligible patients (pts) aged >18 yrs had previously treated relapsed/refractory ST. Pts in the monotherapy arm received IV BPM 31510 for 4 di n continuous infusion in 28-d cycles. Pts in the combination arms were primed for 3 wks and then started in a weekly dosing (either gemcitabine, 5-FU or Docetaxel).

**Methods:**

- Eligible patients (pts) aged >18 yrs had previously treated relapsed/refractory ST. Pts in the monotherapy arm received IV BPM 31510 for 4 d in continuous infusion in 28-d cycles. Pts in the combination arms were primed for 3 wks and then started in a weekly dosing (either gemcitabine, 5-FU or Docetaxel). The SHI cohort was discontinued early (first pt treated at 20 mg/m2 died). Median number of C cycles (range) at MTD were: NHF 3 (1–4); MIHI 2 (1–3); ModHI 2 (1–3).

**Conclusion:**

- Preclinical data indicate BPM 31510 causes this shift resulting in tumor regression and enhances the antitumor activity in combination with chemotherapy agents in a priming schedule. This is the first clinical study to evaluate BPM 31510 at a 4-days (d) continuous infusion in four arms; as a single agent, and in combination with Gemcitabine, 5-FU or Docetaxel.

**Methods:**

- 126s Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics

**Conclusion:**

- The trial is ongoing to determine the recommended phase II dose Clinical trial information: NCT01957735.
A phase I study of BI 853520, an inhibitor of focal adhesion kinase (FAK), in patients with advanced or metastatic solid tumors. First Author: Alona Zerin, Princess Margaret Hospital, Toronto, ON, Canada.

Background: BI 853520 is a potent and highly selective inhibitor of FAK. In the dose-finding part of this study in patients (pts) with advanced or metastatic solid tumors, the maximum tolerated dose (MTD) was determined as 200 mg in a continuous oral daily dosing schedule in 28-day cycles. Dose limiting toxicities included proteinuria grade 3 and fatigue grade 3. Preliminary pharmacokinetic (PK) data support the once-daily dosing schedule. BI 853520 is now being evaluated at the MTD in expansion cohorts of selected tumor types. Methods: Pts with metastatic or advanced-pancreatic adenocarcinoma (PAC), platinum-resistant ovarian cancer (OC), esophageal cancer (EC) and soft tissue sarcoma (STS) are treated with 200 mg of BI 853520. Selection criteria: radiologically demonstrated progressive disease in 6 months, have not been treated with targeted therapy or immunotherapy, and consent for tumor biopsies for biomarker assessment. Endpoints include further determination of safety profile (NCI Common Terminology Criteria for AEs (v4.03)), PK, pharmacodynamics (PD) and efficacy, determined according to RECIST v1.1 criteria. Results: To date, 41 pts have been treated: 8 PAC, 11 OC, 8 EC, 14 STS. Male/female ratio: 12/29, median age 62 years (range, 21-78 years), ECOG PS 0/1:10/31. Drug-related adverse events (AEs) in > 10% of pts included proteinuria (58.5%), nausea (58.5%), diarrhea (48.8%), vomiting (36.6%), fatigue (19.5%), decreased appetite (14.6%), dyspepsia and dysgeusia (both 12.2%), in the majority of grade 1–2. Proteinuria grade 3 was reported in 8 pts and reversible upon treatment interruption. Ten pts underwent dose reduction. Three drug-related serious AEs have been reported of which none were fatal. Preliminary PD analysis in fresh tumor biopsies (pFAK) shows target engagement. Preliminary efficacy: of 30 evaluable pts 8 pts had stable disease lasting 2-6 cycles in PAC (3 pts), OC (1 pt), EC (1 pt) and in STS (3 pts), and 22 progressed. Conclusions: The safety profile of BI 853520 is favorable. Preliminary analysis shows anti-tumor efficacy in pts with progressive disease. Recruitment is ongoing and an update on all study endpoints will be provided at the meeting. Clinical trial information: NCT01335269.

Predicting outcomes in patients with advanced malignancies treated on Phase 1 clinical trials. First Author: Kit Man Wong, University of Colorado, Denver, CO.

Background: Appropriate selection of patients fit for Phase 1 trials is critical to avoid harm and maximize the potential for benefit, yet this can be challenging. Previous studies of prognostic factors demonstrated mixed results and many were limited by small cohorts. There is no consensus on the optimal prognostication strategy. We analyzed outcomes and prognostic factors of a large cohort of Phase 1 patients treated at an academic center. Methods: 779 patients with advanced solid malignancies enrolled on Phase 1 trials from 2001-2009 at the University of Colorado were included. Baseline patient, disease and lab parameters, trial characteristics and outcomes were extracted from a prospective IRB-approved database. Associations between clinical factors and 90-day mortality (90DM, overall survival (OS), progression-free survival (PFS) with a MTD not yet reached. In EC, TAS-114 was administrated at the dosage of 120 and 160 mg/m² for 14 days followed by 7 days rest at the starting dosage of 5 mg/m² with the fixed dosage of S-1 (30 mg/m²). Dose-limiting toxicity (DLT) was evaluated during the 1st cycle in dose escalation cohort (DEC), using a 3 + 3 design. Expansion cohort (EC) is conducted in parallel with DEC at the dosage which was confirmed tolerable in DEC. Results: As of 25 September 2014, 56 pts were enrolled with 36 pts in the DEC and 20 pts in the EC. In DEC, dosage of TAS-114 was escalated up to 240 mg/m² with a MTD not yet reached. In EC, TAS-114 was administrated at the dosage of 120 and 160 mg/m² for the fixed dosage of S-1 (30 mg/m²). Currently, we are planning the dose escalation of TAS-114 with a pharmacogenomic-guided approach. Conclusions: Dose-escalation of SXR is ongoing on S2 and S3 with more G3 AEs seen in S3. Promising antitumor activity was observed. Clinical trial information: NCT02078349.

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**2545 Poster Session (Board #261), Sat, 8:00 AM-11:30 AM**

**Phase 1, first-in-human study of ARQ 087, an oral pan-Fibroblast Growth Factor Receptor (FGFR) inhibitor, in patients (pts) with advanced solid tumors. First Author: Kyriakos P. Papadopoulos, START Center for Cancer Care, San Antonio, TX**

**Background:** ARQ 087 is a novel, orally bioavailable, ATP-competitive inhibitor of multiple kinases, including FGFR1-3. It has potent in vitro and in vivo inhibitory effects on a variety of human tumor cell lines and xenograft models dependent on FGFR signaling. **Methods:** This first-in-human 2-step study was initiated in pts with advanced solid tumors. Step 1: dose escalation followed by expansion cohorts in pts with characterizable tumors, safety, manageability, and recommended Phase 2 Dose (RP2D; unsolicited for selected FGFR aberration). Step 2: expansion cohort to assess safety and clinical activity of ARQ 087 in selected tumor types, including FGFR gene amplification, translocation and mutation. Assessments included tumor molecular status, response by RECIST v.1.1 every 8 weeks (wks), plasma concentrations of FGFR19, 21, 23, fasting glucose and phosphate. **Results:** 61 pts were treated (dose range 25-425mg QOD or QD) in Step 1; the majority were female (61%), mean age 64 yrs (34-78). The RP2D was defined as 300 mg QD continuous dosing. Dose-limiting toxicities included increased liver enzymes (reversible Grade (G) 3 AST increase). Common drug-related adverse events (AEs; mostly G 2) were fatigue (53%), elevated LFTs (45%), nausea (45%), vomiting (20%) and diarrhea (20%). Only 2 pts (3%) experienced G1 drug-related hyperphosphatemia. Drug t1/2 was 2-11 days, PK was unaffected by food. FGF 19/21/23 concentrations post-treatment were increased 1.5-6 fold. Ten pts in Step 1 had confirmed stable disease (SD) ≥ 16 wks (adenocerebral [2], endometrial, ovarian, NSCLC, choroidal melanoma, carcinoid, sarcoma [3]). A squamous NSCLC pt with Src amplification had SD (24% tumor reduction) for 32 wks. One adenocerebral carcinoma pt with FGFR1 amplification remains on study > 22 months. Two ongoing pts with intracranial metastases and FGFFR2 fusions demonstrated a partial response and SD ≥ 24 wks with 26% decrease in target lesions, respectively. **Conclusions:** ARQ 087 has manageable, mostly G ≤ 2 AEs. It has demonstrated preliminary antitumor activity in pts with FGFR-pathway aberrations. Further evaluation of ARQ 087 in pre-defined tumor types is ongoing. Clinical trial information: NCT01752920.

**2546 Poster Session (Board #262), Sat, 8:00 AM-11:30 AM**

**Dermatologic toxicities of 3,517 solid tumor patients on phase I clinical trials of the National Institutes of Health Cancer Therapy Evaluation Program (CTEP). First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY**

**Background:** Dermatologic adverse events (AEs) can be key determinants of overall drug tolerability, and the maximum tolerated and recommended phase II doses of therapy on phase I trials. We present the largest dedicated analysis of dermatologic AEs on phase I trials to date. **Methods:** Data from a prospectively maintained database of solid tumor patients (pts) enrolled on CTEP-sponsored phase I trials from 2000 to 2010 was analyzed. Cumulative incidence, site, type, and timing of drug-related dermatologic AEs were described and compared between pts who received molecularly targeted agents (MTAs), cytotoxic therapy, or a combination of both. **Results:** 3,517 solid tumor pts and 6,165 unique drug-related dermatologic AEs were described. Phase I trials were analyzed for 5 MTAs, 37 cytotoxic agents, and 10 combination MTA and cytotoxic trials. Percent grade 1, 2, 3, and 4 dermatologic drug-related AEs were 75.5%, 22.6%, 1.9% and < 0.1%, respectively. Most common drug-related dermatologic AEs were alopecia (23%) and maculopapular rash (21%). Of 1,270 pts with drug-related dermatologic AEs, timing of worst drug-related toxicity was: 743 pts (cycle 1), 303 (cycle 2), and 224 (cycle 3 or later). While cumulative incidence of ≥ grade 3 drug-related dermatologic AEs increased to 2.4% by cycle 6, it was only 1.6% at the end of cycle 1. Cumulative incidence of drug-related dermatologic AEs was highest in pts with MTA only therapy, and significantly differed by dose level (p < 0.001). In pts who received MTA only therapy, drug-related dermatologic toxicity was most common for combination kinase inhibitor-containing therapy (p < 0.001). **Conclusions:** A substantial proportion of drug-related dermatologic AEs occurs after the traditional DLT monitoring period. Future phase I trial designs should account for delayed toxicities to avoid defining intolerable doses of study therapy.

**2547 Poster Session (Board #263), Sat, 8:00 AM-11:30 AM**

**A first in human Phase I/Ii study of NUC-1031 in patients with advanced gynecological cancers. First Author: Sarah Patricia Blagden, Ovarian Cancer Action Research Centre, London, United Kingdom**

**Background:** Acquired resistance to chemotherapy hampers patients’ survival from many gynecological malignancies. NUC-1031, a first-in-class nucleotide analogue, utilises phosphoramidate chemistry to overcome key drug resistance mechanisms and enhance anti-cancer activity. **Methods:** NUC-1031 was given as a single injection either 1) on days 1, 8, & 15 of a 28 day cycle (q4w) in doses ranging from 500mg/m2 to 1000mg/m2, or 2) a sa 1031 was given as a single injection either 1) on days 1,8, & 15 of a 28 day cycle. **Results:** Fourteen of the 18 pts had received at least 2 cycles of NUC-1031 and 128s Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics. 7.5 months. A Phase Ib study of NUC-1031 in combination with carboplatin in refractory gynecological cancers. Clinical trial information: NCT01621854.

**2548 Poster Session (Board #264), Sat, 8:00 AM-11:30 AM**

**Biomarker analysis from a Phase I study of copanlisib with expansion cohorts in solid tumors with and without PIK3CA mutations and NHL. First Author: Carol Elaine Pena, Bayer HealthCare Pharmaceuticals, Whippany, NJ**

**Background:** Copanlisib is a novel, selective, reversible, pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibitor with potent activity against both the δ and α isoforms. Safety and tumor response data from the first-in-man phase I trial have been reported (Patnaik et al., 2012, ASH), with two patients with follicular lymphoma ongoing as of January 2015, with partial responses lasting 1380 and 909 days. A secondary objective of the study was to identify biomarkers associating with copanlisib response. **Methods:** After dose escalation, expansion cohorts were enrolled and treated at the maximum tolerated dose (0.8 mg/kg, iv, on days 1, 8 and 15 of a 28-day cycle), including solid tumors (n = 25) with and without PIK3CA mutations. N = 15 of 25 pts had PIK3CA mutations. Non-Hodgkin lymphoma (NHL) (n = 9), PIK3CA, BRAF, and KRAS mutations were tested using digital PCR on archival tumor samples and circulating tumor (ct) DNA from plasma (BEAMing). Next generation sequencing (NGS) of tumor genes and IHC for PTEN were performed on archival tumor samples. **Results:** Ten of 25 solid tumor patients (40%) had mutations in PIK3CA (5/10) and/or BRAF (5/10; NGS: 4/9) and/or PIK3CA MTA and/or KRAS mutations. None of the NHLs tested had PIK3CA or KRAS mutations. PTEN loss was identified by IHC in 9 of 18 (50%) solid tumors, and in 1 of 7 (14%) NHLs tested. PTEN mutations were detected in 2 of 11 cases, both had PTEN loss. Of 11 patients tested, 4/11 had a complete radiological response (CR) lasting more than one year and 2 extended stable disease (SD) (≥ 4 cycles); conversely, of the 9 without PTEN loss, none had an objective response (OR) or extended SD. The CR was in an endometrial cancer patient with PTEN loss and both PIK3CA and PIK3CA mutations. However, PIK3CA mutations alone did not seem to enrich response rate, as 3 of 10 (30%) patients with PIK3CA mutations and 4 of 15 (27%) without had either an OR or extended SD. Conclusions: PTEN loss, but not PIK3CA mutations alone, may enrich for response to copanlisib in this mixed solid tumor expansion cohort. The CR to copanlisib in the presence of both PTEN and PIK3CA aberrations may be due to multiple mechanisms leading to PI3K pathway activation. Clinical trial information: NCT00962611.
Phase I trial of tivantinib in combination with carboplatin and paclitaxel as first-line treatment in patients with advanced nonsquamous non small cell lung cancer or malignant pleural mesothelioma: update of a phase I trial

**Background:** Tivantinib (T) is a selective non-ATP competitive oral inhibitor of MET receptor. Preclinical data showed that MET inhibition blocks Malignant Pleural Mesothelioma (MPM) and Non Small Cell Lung Cancer (NSCLC) cell growth and migration. Adding T to standard first-line chemotherapy may improve efficacy. MPM or non-squamous NSCLC were eligible to receive escalating doses of T combined with carboplatin (C) AUC 5 i.v. d1-q21 and pemetrexed (P) 500 mg/m2 i.v. d1-q21 as first-line treatment. After 6 cycles of CP, T is continued as maintenance therapy until progression. Pts must be chemonaive with ECOG Performance Status (PS) ≤ 2 and adequate bone marrow, liver, and kidney functions. A standard 3+3 dose-escalation design was employed starting from dose level 0 (T 240 mg BID). The primary endpoint of the phase I study was to assess the maximum tolerated dose (MTD), defined as the highest dose level at which no more than 1 of 6 pts experiences a dose limiting toxicity (DLT) during the first cycle. To evaluate the anti-tumor activity (MPM pts: 3-month PFS%; NSCLC pts: 5-month PFS%) and the pharmacokinetics of the combination, a phase Ib trial is still ongoing.

**Results:** From April 2013 to September 2014, 12 pts were enrolled in the phase I study; mean age was 69 years (range, 37-73 years), M/F: 9/3, ECOG PS 0-1: 5/7, MPM/NSCLC: 6/6. The MTD was reached at dose level 0 (T 240 mg BID). DLTs (2 neutropenia G4, 1 thrombocytopenia G4) were observed in 2 pts, both at dose level 1 (T 360 mg BID). The most common all-grade toxicities were nausea/vomiting (67%), anemia (58%), neutropenia (50%), and asthenia (50%). G3/4 treatment-related AEs were reported in 6 pts (50%). EC1456 caused complete tumor regression without significant toxicity. Enhanced anti-tumor activity was observed when EC1456 was combined with platinum, taxanes, and topotecan in preclinical models. These data led to this clinical evaluation of EC1456 in advanced CA pts. **Methods:** The primary objective is to determine the MTD of EC1456 administered on 2 schedules (BIW: days 1, 4, 8, 11 q 21 or 28 days). Pharmacokinetic (PK) analyses were performed on days 5, 14 and 29 combined with explorative PD assessment of E by FDG-PET on days 1, 5 and 14 of therapy. Efficacy was assessed by CT (RECIST 1.1) every six weeks of combination treatment. **Results:** 31 patients (mean age 58.5 years) were enrolled and evaluable from October 2009 to December 2013, of which 16 (51.6%) had NSCLC. DLT was not observed according to protocol definition in the dose finding phase (18 patients), however the MTD for treatment of further patients was defined at 7.5mg/d E + 800mg/d S due to toxicities at 10mg/d occurring after the DLT-defining interval (neutropenia I/II; thrombocytopenia III and pneumonia IIIII). The median PFS of all treated patients was 99 days (95% CI 85.7 - 112.3), the median OS was 178 days (95% CI 116.9 - 239.1). In 24 of 29 evaluable patients (82.8%) a decrease in SUVmax of the hottest lesion could be observed in PET, the best response as assessed by RECIST criteria was CR in 7 (21.4%) and SD in 21 (72.4%) patients. No patient reached PR in CT scan whereas 8 of 21 (38.1%) evaluable patients showed confirmed SD over at least 14 weeks. **Conclusions:** Treatment of patients with relapsed solid tumors with a combination of 7.5mg/d E and 800mg/d S is safe and feasible. Most tumors show a moderate metabolic decrease in PET, however, we observed a pharmacodynamic effect than long term disease control observed in this group of patients. Clinical trial information: NCT00933777.
Conclusions: Days. Plasma and IP PK data are summarized below in the Table. Over the four plasma. The inter- and intra-patient variability appears to be low. The plasma treatment delay is.

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Pharmacologic advantage (PA) of intraperitoneal (IP) nab-paclitaxel in patients with advanced malignancies primarily confined to the peritoneal cavity. First Author: Mikaela C. Cristea, City of Hope, Department of Medical Oncology and Therapeutics Research, Duarte, CA

Background: nab-Paclitaxel is albumin-bound paclitaxel that achieves higher intratumoral concentrations and undergoes receptor-mediated transcytosis across cell membranes. Previous clinical trials have demonstrated an advantage to IP chemotherapy. A phase I study was undertaken to evaluate the safety, tolerability, and pharmacokinetics of IP nab-paclitaxel. Methods: Eligible pts received IP nab-paclitaxel on D1, 8, 15 of a 28-day cycle with a 3+3 dose-escalation design. Plasma and peritoneal (IP) nab-paclitaxel was administered as a 3-hour dose, immediately upon completion of infusion, 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose on C1D1 and C1D15. Results: The trial is complete with 27 pts with peritoneal carcinomatosis secondary to GYN (n=14), GI (n=15) malignancies and 1 pt with peritoneal mesothelioma. The starting dose level was 35mg/m2 and escalated to 170mg/m2. The MTD of IP nab-paclitaxel was established at 140 mg/m2. DLTs included grade 3 neutropenia resulting in treatment delay >15 days, grade 3 abdominal pain and grade 4 neutropenia ≥ 7 days. Plasma and IP PK data are summarized below in the Table. Over the four dose levels, the data show a ~150-fold PA to IP nab-paclitaxel with low intra-pt variability. The lowest PA was 50-fold. Conclusions: PK results suggest a significant PA to IP nab-paclitaxel (i.e. higher peritoneal exposure compared to plasma). The intra- and inter-patient variability appears to be low. The plasma AUC resulting from IP nab-paclitaxel at the MTD of 140 mg/m2 are similar to plasma AUC’s associated with IV nab-paclitaxel at 100 mg/m2. In addition to achieving high local drug levels in the peritoneum, patients are also exposed to therapeutic systemic drug levels. This study was funded by the National Comprehensive Cancer Network (NCCN) with support from Celgene Corporation. Clinical trial information: NCT00825201.

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First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with in transit melanoma. First Author: Christophe Le Tourneau, Institut Curie, Department of Medical Oncology, Paris, France

Background: DT01 is a double stranded DNA oligonucleotide conjugated to cholesterol, which mimics "false" double strand breaks (DSB). DT01 triggers DNA repair proteins trapping, thereby inhibiting their repair activity. In non-clinical studies, DT01 showed antitumor activity as a single agent and in combination with radiotherapy (RT) in several tumor types including melanoma. Novel methods: Subcutaneous, peritoneal and intratumoral injections of DT01 were evaluated in combination with RT in a first-in-human phase I trial in patients (pts) with unresectable in-transit metastases of melanoma. Each pt received RT at a standard dose (3Gy/d 5 days/week for 2 weeks) on all selected tumor lesions, with one or two additional lesions treated with DT01 3 times a week during both weeks of RT. A 3+3 dose escalation design was used. DT01 dose levels explored were 16, 32, 48, 64, and 96 mg. RT was given using a rectangular field by a linear accelerator. Tolerance was assessed using NCIC CTCAE v4.3 and efficacy using modified RECIST criteria 1.1. Results: Seventeen pts (16 eligible) were included in the trial, of whom received RT alone in 31 and RT + DT01 in 31 tumor target lesions. As no dose-limiting toxicity was observed, the maximum tolerated dose was not reached. Most frequent adverse events were reversible grade 1 and 2 injection site reactions. PK analyses suggested a systemic passage of DT01 in a non-linear fashion. Overall response rates (ORR) were 68% and 48% in tumor lesions treated with RT + DT01 and RT alone, respectively. Notably, ORR correlated with blood AUC (p = 0.01), suggesting 1) an anti-tumor activity of DT01, and 2) a systemic effect of DT01. Conclusions: DT01 in combination with RT is safe in patients with metastatic in-transit melanoma, and provides anti-tumor activity in DT01 treated and non-treated lesions possibly explained by a systemic distribution of the drug. Clinical trial information: NCT01469455.

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A phase I study of ARQ 197 in combination with temsirolimus in advanced solid tumors. First Author: Christos Kyniakopoulos, University of Wisconsin Cancer Center, Madison, WI

Background: A wide variety of human cancers exhibit dysregulated c-Met activity which has implications in oncogenesis. Phosphorylation of c-Met results in activation of the PI3K/Akt/mTOR pathway. Combined blockade of c-Met and mTOR pathways has shown efficacy in preclinical studies. ARQ 197 (tivantinib) is a c-Met inhibitor and temsirolimus is a selective mTOR inhibitor. We aimed to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), adverse events (AEs), clinical activity and pharmacokinetic (PK) parameters of the above combination. Methods: This open-label phase I study used a 3+3 dose escalation design. Patients (pts) in cohorts of 3 were treated with escalating doses of ARQ 197 (120-360 mg tablets orally twice daily) and temsirolimus (20 mg iv weekly) followed by dose expansion at MTD. Separate cohorts were planned for poor and extensive ARQ 197 metabolizers based on CYP2C19 genotypes. Cycles were 28 days besides cycle 1 that was 35 days to allow for PK analysis. Results: 21 pts (median age 57 [range 29-71]) were enrolled for dose escalation. All were extensive CYP2C19 metabolizers. The most common types of cancer were colorectal (6 pts), ovarian (4 pts), renal (2 pts) and pancreatic (2 pts). In the dose escalation cohort, 16/21 pts were evaluable per protocol. They remained on study for a median of 73.6 days (range 15-296). The MTD was ARQ 197 240 mg bid and temsirolimus 20 mg once weekly. DLTs included grade (gr) 4 neutropenia (2 pts; 1 with gr 3 febrile neutropenia) and gr 3 abdominal pain (1 pt). The most common AEs at least possibly related to therapy included: fatigue (62%; gr 1-2 in 12 pts, gr 3 in 1 pt), anemia (48%; gr 2 in 9 pts, gr 3 in 1 pt), nausea (48%; gr 1 in 9 pts, gr 3 in 1 pt), vomiting (48%; gr 1-2 in 9 pts, gr 3 in 1 pt) and diarrhea (48%; gr 1-2 in 9 pts, gr 3 in 1 pt). 1 pt with ovarian cancer had a confirmed partial response and 1 pt remained on study for 9 months. A second pt with ovarian cancer has stable disease and remains on study at 5 months. 4 of 6 pts have been enrolled to the dose expansion cohort and are in cycle 1. Data from the dose expansion will be presented. Conclusions: The combination of ARQ 197 with temsirolimus appears to be well tolerated with evidence of clinical activity. The MTD expansion and PK analysis are ongoing. Clinical trial information: NCT01625156.

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Rationale for the combination of veliparib with platinum-based chemotherapy. First Author: David Maag, AbbVie, North Chicago, IL

Background: Owing to the role of PARPs in DNA damage repair, PARP inhibitors (PARPi) are under clinical investigation as anticancer therapies with a focus on tumors with repaired homologous recombination or regimens containing DNA damaging chemotherapies. Pre-clinical evidence indicates that PARPi potentiate the cytotoxicity of platinum. A recent Phase II study suggested evidence of a benefit in both progression and survival when veliparib was added to carboplatin and paclitaxel in the treatment of advanced NSCLC. Methods: In vitro efficacy was evaluated in GFP-overexpressing cell lines cultured as 3D spheroids. In vivo efficacy was determined in xenograft tumor-bearing SCID mice. PARPi trapping was evaluated by cellular fractionation and immunoblotting. Bone marrow toxicity was determined with CFU assays. Results: We have developed a method to monitor the growth of 3D spheroids in vitro in real time. In this system, veliparib potentiated the activity of platinum in numerous models. Likewise, veliparib potentiated the activity of platinum in multiple xenograft models in vivo. PARP trapping was undetectable when PARPi were combined with cisplatin, PARPi differed in the extent to which catalytic inhibition and trapping could be resolved. PARPi with more potent trapping activity induced greater cytotoxicity in bone marrow CFU assays than equipotent inhibitors with weaker trapping activity. Conclusions: Veliparib potentiates the activity of platinum agents in vitro and in vivo; however the mechanisms underlying this activity remain unclear. PARP trapping is a recently utilized method to measure the synergistic cytotoxicity of PARPi and temozolomide. In contrast, our results suggest that PARP trapping is not required for the combination activity of PARPi and cisplatin. Our observation that potent trapping activity is associated with cytotoxicity towards myeloid and erythroid progenitors suggests that trapping may contribute to the anemia and myelosuppression observed in patients treated with PARPi. As such, PARPi capable of catalytic inhibition at concentrations where trapping is undetectable may be more suitable for combination regimens in which trapping is not required for activity.
Genomic landscape of DNA repair genes in cancer: Mutation and copy number variation (CNV) frequencies. First Author: Jonathan Anker, Northwestern University, Chicago, IL

Background: DNA repair genes are frequently mutated in cancer, with different cancers linked to specific repair pathways. However, much remains unknown, including whether these mutations drive cancer or are a result of the disease. We have performed genome-wide mutational analysis of DNA repair genes to identify DNA repair genes that are frequently mutated or display high CNV. Methods: We created a comprehensive list of DNA repair genes and indirectly involved caretaker genes. The mutation and CNV frequencies of these genes were recorded from the COSMIC database (cancer.sanger.ac.uk). Results: Of the 193 genes analyzed, 24 had a mutation frequency of greater than 1.0% across all cancers. Table 1 lists the 10 genes most frequently mutated (overall and by common cancer types; n = 197,950 for each overall) or with a high CNV gain or loss frequency. There was a strong correlation as genes with a high CNV gain displayed a low CNV loss frequency, and vice versa (p < 0.001). Conclusions: Multiple DNA repair pathways were affected in each cancer type. Interestingly, genes with high frequency CNVs were either predominantly CNV gain or loss, but not both, providing evidence that these are functional alterations. This study displayed a low CNV loss frequency, and vice versa (p < 0.001).

2559 Poster Session (Board #275), Sat, 8:00 AM-11:30 AM Using gamma-H2AX and H2AX quantitative ELISA for monitoring DNA damage induced by chemotherapeutic agents and irradiation exposure. First Author: Jiaying Jin Ji, National Clinical Target Validation Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Gamma-H2AX (γH2AX) is a biomarker for DNA double-strand breaks and programmed cell death, but variable relative amounts of H2AX in different samples causes ambiguity in the meaning of the γH2AX level unless it is related to total H2AX levels. We developed a 96-well plate-based ELISA for quantifying γH2AX and H2AX levels in crude extracts of tumor cells, CTCs and biopsy tissues and are validating it for applications in irradiation exposure monitoring and in pharmacodynamic evaluation of anti-cancer agents. Methods: The ELISA was used to analyze extracts of several NCICD10 tumor cell lines that had been exposed to a variety of agents, including ionizing radiation, inhibitors of Top-1 (CPT, SN-38, Topotecan), PARP (ABT-888, AZD-2010, MK-4827), and ATR (VE-821, VE-822, AZD-6738, Compound 45, NU-6027), and their combinations. Combination regimens of CPT-11 with PARP inhibitors (ABT-888, AZD-2281, MK-4827) were further evaluated in vivo in the A375 xenograft mouse model. Patient samples obtained for research purposes were also examined by ELISA for feasibility and utility. Results: In vitro, dose-dependent increases in the ratio of γH2AX to H2AX were detected after escalating ionizing radiation exposure and concentration-dependent increases after Top-1 exposure. Treatment with inhibitors of PARP or ATR alone did not significantly influence γH2AX. Combinations of Top-1 inhibitors with PARP or ATR inhibitors led to synergistic induction of DNA damage. Among 5 ATR inhibitors evaluated in combination with Top-1 inhibitors, VE-822 and AZD-6738 were observed to have the highest synergy for γH2AX induction, while NU-6027 showed none. Combinations of CPT-11 with ABT-888, AZD-2281 or MK-4827 showed synergistic induction of γH2AX in A375 xenografts in vivo. Additional testing of human specimens including PBMCs, bone marrow and tumor biopsies proved the assay's clinical suitability and potential advantages. Conclusions: A newly developed quantitative ELISA for measuring both γH2AX and H2AX is ready for clinical validation for monitoring DNA damage induced by chemotherapeutic agents or irradiation exposure. Funded by NCI Contract No. HHSN261200800001E.

2558 Poster Session (Board #274), Sat, 8:00 AM-11:30 AM Phase I clinical trial of temozolomide and methoxamine (TRC-102) in patients with advanced solid tumors. First Author: Jennifer Rachel Eads, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Temozolomide (TMZ) is an alkylating agent that generates DNA adducts that are repaired by direct DNA and base excision repair mechanisms. Methoxamine (MX, TRC-102) is a small molecule that potentiates TMZ by binding to apurinic and apyrimidinic sites after removal of N3-methyladenine and N7-methylguanine, inhibiting site recognition of apurinic/apyrimidinic (AP) endonuclease. We conducted a phase I trial to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of intravenous MX when given with oral TMZ. Methods: Patients (pts) with advanced solid tumors, progression on standard treatment, and no CNS involvement were enrolled. A standard 3+3 design was used to target TZM (150-200 mg/m2 orally) and MX (15-150 mg/m2 IV). Dose Levels (DL) 1-3: TMZ day 1, MX day 4 in first 14 day cycle (C), TMZ days 1-5, MX day 1 in subsequent 28 day C; DL 4-7: TMZ days 1-5, MX day 1 of 28 day C. DLT period was 42 days for DL 1-3 and 28 days for DL 4-7. Tumor response assessed per RECIST and AEs by CTCv4. Pharmacokinetics (PK) of 1-hour MX infusion and comet assays on peripheral blood mononuclear cells were performed. Results: 38 pts were enrolled: 45% male, 82% white, 16% African American, 2% Asian, median age 59.5 years (38-76), mean number of C2.9 (1-11.3). No DLTs were observed. Grade 3 AEs: fatigue (n = 2), lymphopenia (n = 2), anemia (n = 1), INR (n = 1), leukopenia (n = 1), neutropenia (n = 1), allergic reaction (n = 1), constipation (n = 1), psychosis (n = 1) and paranoia (n = 1). Late grade 4 AEs: thrombocytopenia (n = 2) and confusion (n = 1). Partial response was seen in 1 pt with pancreatic adenocarcinoma (PAC) (8 mo); prolonged stable disease in 1 pt with PAC (4 mo), pancreatic neuroendocrine tumor (NET) (9 mo), small bowel cancer (12.5 mo), lawret cancer (12.5 mo) and non-small cell lung cancer (5.5 mo). MX PK was linear with dose and was not affected by concomitant TMZ. Geometric means (SD) were: 1/45.6 (11.5) h, CI 31.7 (15.6) L/h/m2; and 33.0 (22.9) L/m2. Conclusions: TMZ 200 mg/m2 may be safely administered with MX 150 mg/m2 with minimal toxicity. Evidence of antitumor activity was seen in pancreatic adenocarcinoma and pancreatic neuroendocrine tumors. Further studies assessing this drug combination are warranted. Clinical trial information: NCT00892385.

2557 Poster Session (Board #273), Sat, 8:00 AM-11:30 AM A phase I study of pazopanib (PAZ) in combination with abexinostat (ABX) in patients (pts) with metastatic solid tumors. First Author: Rahul Raj Agrawal, UC San Francisco, San Francisco, CA

Background: PAZ is a tyrosine kinase inhibitor of VEGFR, PDGFR, and C-KIT approved for use in renal cell carcinoma (CRC) and soft tissue sarcoma (STS). ABX is a potent pan-HDAC inhibitor (HDACi). Pre-clinical models suggest that HDACi-mediated epigenetic modulation of VEGF expression potentiates PAZ’s efficacy and may reverse therapeutic resistance. We therefore designed a Phase I clinical trial combining ABX with PAZ in pts with advanced solid tumors. Methods: The primary objective was to determine the maximal tolerable dose (MTD) of PAZ plus ABX. Secondary objectives included pharmacokinetics (PK) and efficacy. Altered histone acetylation post treatment denoted HDACi activity and served as a pharmacodynamic (PD) marker in peripheral blood mononuclear cells. PAZ was dosed days 1-28 and ABX days 1-5, B-12, and 15-19 of 28-day cycle (schedule A) at a starting dose of 400 mg/day and 45 mg/m2 orally twice daily respectively. An alternate ABX dosing schedule of days 1-4, 8-11, and 15-18 was also investigated (schedule B). Results: 36 patients with advanced solid tumors were enrolled (N = 22 schedule A; N = 14 schedule B). There were six dose-limiting toxicities (DLTs) (5 on schedule A, 1 on schedule B), including fatigue (N = 2), thrombocytopenia (N = 2), and elevated AST/ALT (N = 2). The most common grade ≥ 3 related adverse events observed included thrombocytopenia (8%), fatigue (8%), and diarrhea (6%), the majority of which occurred with schedule A. The MTD was PAZ 15 mg/m2 BID and ABX 250 mg/m2 BID. Additional DLTs included grade 3 related adverse events in 5 pts (17%) (including 2 RCC pts) experienced a partial tumor response (PR). All 6 pts with prior disease progression on PAZ monotherapy had reduction in tumor burden on study, 12 out of 29 evaluatable pts (41%) experienced stable disease or better for > 6 months, and two pts with PRs remain on study for > 2 years. PK and PD analyses are ongoing. Conclusions: In the first trial to explore the combination of ABX with PAZ in CRC and other solid tumor malignancies, the combination was well tolerated, particularly with schedule B ABX dosing. Preliminary evidence of anti-tumor activity was observed, notably in pts with progression on prior PAZ monotherapy. The promising efficacy in RCC is being further evaluated. Clinical trial information: NCT01543763.
**2561**

**Poster Session (Board #277), Sat, 8:00 AM-11:30 AM**

Pharmacokinetics/pharmacodynamics (PKPD) of blinatumomab in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). First Author: Ming Zhou, Amgen, Thousand Oaks, CA

*Background:* Blinatumomab is a CD19-directed bispecific T-cell engager antibody construct indicated for treatment of Ph-negative r/r ALL. We evaluated blinatumomab PK/PD and explored their associations with efficacy/safety in 189 r/r ALL patients in a phase 2 study (Topp et al. Lancet Oncol 2015;16:57).

*Methods:* Blinatumomab was given by continuous IV infusion (4 wk on/2 wk off) for ≤ 5 cycles (Cycle 1: 9 μg/day 1–7; then 28 μg/day 8–21). Association between exposure and measures of efficacy (complete response [CR]/CR with partial hematologic recovery [CRh]) within the first 2 cycles and safety (cytokine release syndrome [CRS]; neurologic events [NE]) was evaluated by logistic regression. Impact of covariates on exposure-response was assessed in multivariate analyses.

*Results:* Blinatumomab PK was linear; mean (SD) serum steady state concentration ([C]ss) at 28 μg/dL was 621 (502) μg/mL in Cycle 1. IL-6, IL-10 and IFNγ were transiently elevated in >50% of pts on days 1–2 of Cycle 1, much less in later cycles; interpatient variability was high. In Cycle 1, mean peripheral B cells fell from 4660 to ≤ 10 cells/μL. Responders had lower percentages of CD19+ B cells and bone marrow (BM) blasts and higher percentages of CD3+ T cells and granulocytes at screening than nonresponders (P < .001); absolute counts were not associated with response. In multivariate analyses, higher [C]ss (OR, 1.90 [95% CI, 1.12–3.21]; P = .017), higher peak IL-10 levels (1.59 [1.23–2.22]; P = .007) and lower percentage of BM blasts at screening (0.90 [0.84–0.97]; P = .004) and [C]ss (1.40 [1.01–1.94]; P = .046) were associated with CR/CRh. No association between [C]ss and time to CR/CRh was found after adjusting for percentage of blasts and B/T cell ratio. Higher plateau counts (0.996 [95% CI, 0.992–1.0]; P = .03), CD19+ B cell counts at screening (0.90 [0.84–0.97]; P = .004) and [C]ss (1.40 [1.01–1.94]; P = .046) were associated with time to NE. Cytokine peaks were not associated with NE or CRS. [C]ss was not associated with CR/S. *Conclusions:* We found empirical associations of blinatumomab PK, PD and disease-related prognostic factors with CR/CRh and NE. Confounding factors and confirmation of the associations deserve further evaluation. Clinical trial information: NCT01466179.

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**2562**

**Poster Session (Board #278), Sat, 8:00 AM-11:30 AM**

Pharmacogenetic variants associated with differential sirolimus clearance in pediatric patients. First Author: Jordan Wright, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

*Background:* Sirolimus inhibits the mammalian Target of Rapamycin (mTOR) pathway and is widely used in organ transplantation and treatment of malignancy. CYP3A5*3 polymorphisms have been shown to influence sirolimus clearance in solid organ transplant patients, but effects of other drug metabolism enzyme and transporter (DMET) gene polymorphisms have not been investigated thoroughly. We hypothesized that additional variants alone or in combination, would better predict sirolimus clearance in pediatric and young adult patients with neurofibromatosis type 1 (NF1) associated plexiform neurofibromas and complex vascular malformations (CVM).

*Methods:* Patients treated with single agent sirolimus (N = 74) had pharmacokinetic parameters including clearance measured in two studies of NF1 and CVM. Patients were genotyped for 1,931 known polymorphisms using the DMET Microarray (Affymetrix). Initial statistical analysis included univariate linear regression on SNPs with a minor allele frequency of >0.05 for each of the clinical trials. Subsequently, the datasets were combined and a univariate regression analysis was obtained on the combined data. SNPs for which the association was strengthened in the combined dataset were then placed in a final multivariate regression model.

*Results:* The final multiple regression analysis included five SNPs that were significant at p < 0.05: rs776746 (CYP3A5*3 6986 A > Gj, rs8909530 (FG3 855 C > T), rs1339067 (SLC15A1 1347 T > C), rs2276299 (SLC22A6 723 T > A), and rs774801 (CYP8B1 6468 A > C). The model had an overall F-value of 7.83, p-value < 0.0001, and R-square of 0.38. *Conclusions:* Our analysis identified a multivariate model with five SNPs, of which four are novel and not previously described in the literature. The CYP3A5*3 allele, which has been identified in other studies, was significant in our data. Our findings provide support for the role of this SNP in sirolimus metabolism. Future studies in larger populations are needed to confirm this model, and will lead to potential pharmaco-genetically-guided dosing for the safe and effective use of sirolimus.
Effect of itraconazole and rifampin on the pharmacokinetics of olaparib tablet formulation in patients with advanced solid tumours: Phase I open-label studies. First Author: Palani, Clinical Pharmacology, Biotechnology Clinical Development, Pfizer Inc., Los Angeles, CA

Background: The metabolism of olaparib (Lynparza) is mediated predominantly by CYP3A4/5 enzymes. Two Phase I studies are reported here investigating pharmacokinetic interactions between olaparib (tablet formulation) and itraconazole, a potent CYP3A4 inhibitor (Study 1, NCT019299603), and rifampin, a potent CYP3A4 inducer (Study 2, NCT019299603). Methods: In Study 1, 59 eligible patients received a single oral dose of olaparib 100 mg on Day 1 and olaparib 100 mg plus itraconazole 200 mg on Day 9; itraconazole 200 mg was administered once daily (qd) on Days 5–11. In Study 2, 22 pts received a single oral dose of olaparib 300 mg on Day 1 and single oral dose olaparib 300 mg plus rifampin 500 mg on Day 14; rifampin 600 mg qd was administered on Days 5–17. Results: Co-administration with itraconazole in Study 1 resulted in a significant increase in mean Cmax (treatment ratio 1.42; 90% CI: 1.33, 1.52) and mean AUC (treatment ratio 2.70; CI: 2.44, 2.97) compared with olaparib alone. Olaparib absorption was slightly slower in the presence of itraconazole (median [range] 1.50 [0.5–12] hours) vs olaparib alone (1.03 [0.5–8.25] hours). In Study 2, a significant decrease in olaparib bioavailability was observed when co-administered with rifampin (decrease of 71% in Cmax [treatment ratio: 0.29; 90% CI: 0.24, 0.33] and 87% in AUC [0.13, 90% CI: 0.11, 0.16]) vs olaparib alone. Median tmax was reduced in the presence of rifampin (0.78 [0.27–5.98] hours compared with 1.49 [0.57–3.05] hours for olaparib alone). In both studies, the majority of adverse events were of mild or moderate severity; safety data were consistent with the known safety profile of olaparib. Conclusions: It is recommended that potent CYP3A enzyme inhibitors (eg. itraconazole, telithromycin, clarithromycin, ketoconazole, posaconazole, ritonovir, lopinavir, indinavir, saquinavir, nelfinavir, boceprevir, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, ritonovir, lopinavir, indinavir, saquinavir, nelfinavir, boceprevir, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, rifter, phenytoin, rifampin, carbamazepine, St John’s Wort) be avoided during olaparib treatment. Clinical trial information: NCT01990028/NCT019299603.
Background: Antibody-drug conjugates (ADCs) provide unique challenges during clinical development, as these products are a heterogeneous mixture of a monoclonal antibody and a small molecule payload. As such, the current paradigm has been to conduct studies that characterize the clinical pharmacology of both the antibody and small molecule components of the ADC. We have compiled a database of ADCs approved and under development to assess the study designs and outcomes to guide future FDA regulatory recommendations on evaluation of the clinical pharmacology for ADCs. Methods: Investigational New Drug (IND) applications, Biologics License Applications (BLA), product labeling and published literature were reviewed to develop the database. A description of the indication, antibody target, payload, linker, clinical pharmacology studies, and available study results were compiled and analyzed. Results: Approximately 50 ADCs are currently under development and two ADCs are approved (Adcetris, Kadcyla). The most common payloads are auristatins (~60%) and maytansinoids (~20%), and the most common linkers are cleavable (~90%). Three components (i.e., conjugate, total antibody, and payload) were characterized to describe the pharmacokinetics of Adcetris and Kadcyla. While both the Adcetris and Kadcyla labeling describes the potential for drug interactions, dedicated drug interaction studies were only conducted for Adcetris. Organ impairment studies for both Adcetris and Kadcyla suggest decreased tolerability in patients with varying degrees of hepatic or renal impairment. Conclusions: As most ADCs are in early clinical development, FDA recommendations for clinical pharmacology studies are still evolving. Currently available data suggest that the pharmacokinetics of at least two components (e.g., conjugate and payload) should be described and incorporated into product labeling. The potential for drug interactions should be addressed. Organ impairment studies should be conducted with a specific focus on the assessment of safety, as well as on pharmacokinetics.

Identification of candidates for sorafenib dose-escalation using sorafenib plasmatic concentration monitoring: Proof of concept. First Author: Jennifer Arroueado, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France

Background: Sorafenib is approved in various advanced cancers, including hepatocellular carcinoma (HCC), differentiated iodo-resistant thyroid cancer (DTC), and renal cell carcinoma (RCC). We previously described that sorafenib plasmatic concentrations may decrease over months. We examined the inter-individual variability of sorafenib exposure at the time of disease progression to identify a subset of patients likely to benefit from dose increase. Methods: Patients treated with sorafenib from October 2008 to December 2014 were included in the analysis. adverse events were prospectively collected and graded using the National Cancer Institute Common Terminology Criteria. The sorafenib plasma concentrations were prospectively determined by liquid chromatography, 30 days after treatment initiation (Cm1) and at disease progression (Cp). Variations of sorafenib concentrations were analyzed using the Wilcoxon test. Results: A total of 124 patients (85 males and 39 females) were studied, 68 having a sorafenib concentration measurement at the time of dose progression. The primary study objective was to assess the tolerability, pharmacokinetics and preliminary efficacy of HuMax-tissue factor-ADC (TF-ADC) in patients with solid tumors. First Author: Ulrik Niels Lassen, Rigshospitalet, Copenhagen, Denmark

Background: TF-ADC is an antibody drug conjugate composed of a TF-specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E (MMAE). TF-ADC is presently being tested in an ongoing Phase I dose-escalation study (NCT02001623) in patients (pts) with locally advanced and/or metastatic solid tumors known to express TF. Methods: The primary study objective is to assess the tolerability of TF-ADC. In addition, maximum tolerated dose (MTD), pharmacokinetics and preliminary efficacy will be evaluated. Pts with cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophageal, SCCHN and lung (NSCLC) will be included. This is a classical 3+3 dose escalation study followed by cohort expansion. Responses are evaluated according to RECIST 1.1. Results: Eighteen pts have been enrolled across the first 6 dose cohorts (0.3-1.8 mg/kg). Mean number of prior lines of therapy is 3.7 (range 1-14). The most common AEs seen in ≥ 4 pts are fatigue, anemia, epistaxis, nasal congestion, pyrexia, and diarrhea. Elevation in liver enzymes was seen in 9 pts mainly grade (Gr) 1 including 2 pts with Gr 3 single events. One event of fatal pharyngeal hemorrhage in the 0.6 mg/kg cohort has been reported in a SCCHN pt with normal coagulation values previously treated with 3 lines of therapy including radical radiotherapy. Relationship with trial drug could not be excluded. Five pts experienced related AEs Gr ≥ 3. Seven SAEs were observed in 5 pts (transaminisits Gr 3, pharyngeal hemorrhage Gr 5, fever Gr 1, maligia pain Gr 2, dyspnea Gr 2, hypotension Gr 3, gastritis Gr 3). No significant changes in coagulation parameters and no DLTs have been observed. Preliminary evidence of activity includes prolonged disease stabilizations in 1 ovary (10 weeks) and 1 cervix (23 weeks) and a confirmed PR in an ongoing pt with cervical cancer.

Conclusions: Preliminary data demonstrated manageable toxicity, with no DLTs observed and no changes in coagulation values up to 1.8 mg/kg. Preliminary evidence of anti-tumor efficacy is encouraging and study design allows for increased exposure to establish therapeutic window. Clinical trial information: NCT02001623.
Population pharmacokinetics and dosing implications for cobimetinib in patients with solid tumors. First Author: Kelong Han, Genentech, Inc., South San Francisco, CA.

Background: Cobimetinib (COBI), an inhibitor of mitogen-activated protein kinases, when combined with vemurafenib (VEM) has been shown to significantly improve PFS (p < 0.001) over VEM alone in patients with BRAF V600 mutated melanoma in the Phase 3 study, coBRIM. This analysis aimed to characterize COBI PK and evaluate impact of clinically relevant covariates on COBI PK and exposure to inform dosing. Methods: Plasma samples (n = 460) were collected from 221 patients enrolled in various solid tumors (mainly melanoma) in 3 clinical studies (MEK4592q, NO25395Q, G028141Q). COBI was administered orally, once daily on a 21-day-on/7-day-off, 14-day-on/14-day-off or 28-day-on schedule in a 28-day dosing cycle as a single agent or in combination with VEM. COBI doses ranged from 2.1 to 125 mg. Nonlinear mixed effect modeling was used for PK analysis. Results: A linear two-compartment model with first-order absorption, lag time and first-order elimination described COBI PK. The typical estimates (inter-individual variability) of apparent clearance (CL/F), central volume of distribution (V/F) and terminal half-life were 322 L/day (58%), 511 L (49%) and 2.2 days, respectively. Inter-occasion variability on relative bioavailability (F) significantly improved the fitting and was estimated at 46%. CL/F decreased with age. V/F increased with body weight (BWT). However, the impact of age and BWT on COBI steady-state exposure (peak and trough concentrations and AUC following 60 mg 21-day-on/7-day-off) was limited (< 20% changes across the distribution of age and BWT in the population studied). No significant difference in COBI PK parameters or steady-state exposure was observed between patient subgroups by gender, renal function, ECOG score, hepatic function tests, race, region, cancer types, V600 mutation subtype and co-administration of moderate and weak CYP3A inducers or inhibitors and VEM. Conclusions: A population PK model was developed for COBI in cancer patients. Age and BWT were the only statistically significant variables influencing COBI PK, but showed minimal impact on steady-state exposure, suggesting no need for dose adjustment and supporting the recommended daily dose of 60 mg 21-day-on/7-day-off for all patients.

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Results of OAK: A phase 1, open-label, multicentre study to compare two dosage forms of AZD5363 and to explore the effect of food on the pharmacokinetic (PK) profile of ramucirumab in patients with advanced solid malignancies. First Author: Emma Jane Dean, The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: AZD5363 is a potent pan-Akt inhibitor and acts on cancers by blocking a cell survival pathway. AZD5363, administered to patients in the fasted state, was originally formulated as a capsule (C). For patient convenience and ease of manufacturing, a tablet formulation was developed. In vitro work has indicated that T and C perform similarly; PK comparability needed to be verified to introduce T to the clinical programme. The effect of food on PK, safety and tolerability was unknown.

Methods: Part A assessed whether PK of T was comparable to C when both were given as a 480 mg bd dose in a 4 days on / 3 days off schedule; patients received T (Week 1) followed by C (Week 2). Part B examined the effect of a standardised meal on PK of T; patients received T in the fasted state (Week 1) and 30 minutes after a meal (Week 2). PK was assessed on the last day of weekly dosing in each of the cross-overs. Results: Part A data are available in 13 evaluable patients. AUC\textsubscript{tau,inf} and C\textsubscript{max} observations for T and C were comparable with GLS mean ratios (90% CIs) of 0.9 (0.79 to 1.03) and 1.01 (0.88 to 1.16), respectively. CIs of the ratios lay within the 0.75 to 1.33 pre-specified limits. Median t\textsubscript{1/2,inf} was shorter for T than C (1.03 vs 2.03 h respectively), consistent with the in vitro dissolution data. T and C safety data were comparable and consistent with the known safety profile for AZD5363. Part B data are available from 10 patients. PK profiles for T(fasted) versus T(fed) indicated a later t\textsubscript{max} and lower exposure in the fed state. GLS mean ratios of C\textsubscript{max} and AUC\textsubscript{inf} were 0.86 (0.74 to 1.01) and 0.68 (0.57 to 0.81) respectively. No significant differences in safety profiles were noted between the fasted and fed states. Conclusions: PK, safety and tolerability of the tablet and capsule formulations of AZD5363 are comparable. Tablets are being introduced across the ongoing clinical trials. Food has been shown to reduce the rate and extent of absorption of AZD5363 without a discernible effect on safety and tolerability; the existing food restrictions in ongoing clinical trials will be maintained. Clinical trial information: NCT01899546.

2578 Poster Session (Board #294), Sat, 8:00 AM-11:30 AM Exposure-response (E-R) and case-control analyses of ramucirumab leading to recommendation for dosing optimization in patients with gastric cancer.

First Author: Runyan Jin, U.S. Food and Drug Administration, Silver Spring, MD

Background: Ramucirumab was approved for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma in combination with paclitaxel based on an efficacy and safety trial that demonstrated 2.2 months (median) of overall survival (OS) benefit with a hazard ratio of 0.81 (p = 0.02) for patients treated with ramucirumab plus paclitaxel as compared to patients treated with placebo plus paclitaxel. In exploratory Kaplan-Meier survival analyses stratified by model predicted ramucirumab minimum concentration after first dose (C\textsubscript{min,1}), the OS effect was only shown for the patients with C\textsubscript{min,1} greater than the median value. Further exploratory E-R analyses were conducted. Methods: Data for E-R analyses were obtained from a randomized (1:1), double-blind, placebo-controlled, efficacy and safety trial that randomized 665 patients. Case-control analysis was conducted to match patients in the placebo arm to patients in each C\textsubscript{min}, quartile subgroup (Q1-Q4) based on key baseline prognostic factors, which could potentially confound assessment of therapeutic benefit from ramucirumab. The relationship between C\textsubscript{min}, and OS based on exposure subgroups and matched placebo controls was re-evaluated by Kaplan-Meier analyses. Results: Four baseline prognostic factors were identified: ECOG performance status (0 vs. 1), tumor differentiation (well, moderately, poorly or unknown), Asian (yes vs. no), and the total number of target and non-target tumor lesions (< 4, 4-8 or > 9). These were used for selection of case-controls. Kaplan-Meier curves showed no apparent difference in OS throughout the treatment period for the Q1 and Q2 subgroups and > 4-month difference in estimated median OS for the Q3 and Q4 subgroups as compared to their corresponding controls. Conclusions: These results should be considered in combination with results from the current Phase III trials of ramucirumab after case control, suggesting that patients with higher ramucirumab exposure may derive more benefit from the addition of ramucirumab to paclitaxel. These analyses led FDA to recommend a post-marketing clinical trial to explore the benefits and safety of a higher dosing regimen of ramucirumab.
Comparison of adult oncology phase 1 trials to pediatric oncology phase 1 trials of targeted therapies. First Author: Vivek Subbiah, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Intractable aggressive cancers continue to take the lives of children, adolescents and young adults at the prime of their lives. The prior era of drug development wherein pediatric cancer becomes the last cancer to be tested with novel agents, ‘if the agent seems promising in adult cancers may need to be re-visited. Phase 1 trials are the first critical step in drug development. Data based on compassionate chemotherapy phase 1 trials demonstrated a strong correlation between adult and pediatric maximum tolerated dose (MTD)s. We sought to compare pharmacokinetic (PK) parameters and dosing of small molecule inhibitors and monoclonal antibodies (MAbs) studied in adult vs. pediatric phase 1 trials. Methods: We conducted an extensive review of all published pediatric phase 1 trials of small molecule inhibitors and MAbs, and their corresponding adult phase 1 trials. Multiple data elements including MTD, recommended phase 2 dose (RP2D), and dose-limiting toxicity (DLT) were collected from pediatric and adult phase 1 trials. PK parameters for the small molecules including drug clearance (CL), area under the concentration curve (AUC), and half-life were analyzed. Results: We identified 25 targeted agents (21 small molecules, 4 MAbs) and compared data from the pediatric and adult trials. The MTD was not reached for 14 of the 25 (56%) agents in adults (3/25), pediatric patients (7/25), and both (4/25). Excluding the agents for which the MTD was not reached, the median ratio of pediatric to adult MTD was 1.0. PK data was available for 13 small molecules and 2 MAbs. The median ratio of pediatric to adult PK parameters for small molecules was: 0.9 for drug CL, 1 for AUC, and 0.8 for half-life. There was substantial heterogeneity in the PK parameters investigated across the studies. Conclusions: The PK and MTD of small molecule targeted agents in pediatric trials and adults patients are comparable. Initial pediatric dosing close to the adult MTD or RP2D and extrapolation of PK data from adults may help expedite drug development of these agents in children. Standardized strategies to study and report PKs are needed.

Phase 1 study of the mTOR inhibitor sirolimus and the HDAC inhibitor vorinostat in patients with advanced malignancies. First Author: Haeseong Park, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Preclinical models suggest synergistic antitumor activity of histone deacetylase (HDAC) and mTOR inhibitors by reducing activity of TSC2 and PIK3CA. PD studies and PK analysis are pending. The combination of sirolimus and vorinostat is well-tolerated at RP2D and approval. To evaluate the association of relative survival benefit (additional benefit / historic control) as a modality to predict for oncology drug approval. Methods: Data was extracted from transcripts of drug license application sessions of the FDA's Oncology Drug Advisory Committee (ODAC). Relative survival benefit (RB) is defined as the percent survival improvement associated with new therapy over standard therapy. SAS was used to conduct statical analyses. Researchers may need to consider using relative survival benefit to improve the success of FDA approval of novel drug agents.
Phase I study of pemetrexed and sorafenib in advanced solid tumors.

First Author: Andrew Stewart Poklepovic, Virginia Commonwealth Univ Health System, Richmond, VA

Background: Pemetrexed (Pem) blocks thymidylate synthase, activates AMPK, and inactivates mTOR, increasing autophagy. Sorafenib (Sor) also stimulates autophagy through down-regulation of GRP78/BIP and ER stress signaling. Preclinical data demonstrated the combination of Pem and Sor caused synergistic cell death through a form of toxic autophagy. A phase I trial evaluating the combination of Pem and Sor in advanced solid tumors was initiated. The initial 3-week phase was followed by a dose-escalation phase. The current study was conducted in patients (pts) with advanced malignancies. Standard 3+3 dose escalation design was used, with escalating doses of Pem (500 mg/m²-1,000 mg/m² IV) every 2 weeks with Sor (200-400 mg PO BID) continuously (cohort A). The initial 4-week period (Cycle 1) was used for dose-limiting toxicity (DLT) assessment. After treatment of 24 pts on cohort A, it was determined that continuous dosing of Sor with any dose of Pem was associated with unacceptable cumulative constitutional symptoms beyond Cycle 1. The protocol was amended to evaluate intermittent Sor (BID dosing days 1-5 of each Pem dose) (cohort B). Radiographic assessments were conducted every 8 weeks using RECIST 1.1. Results: Thirty-seven pts were enrolled and 36 treated, 24 on cohort A and 12 on cohort B. The MTD in cohort A was defined as Pem 500 mg/m² and Sor 200 mg PO BID on a continuous schedule. Dose reductions for cumulative toxicity became necessary in the majority of patients in cohort A. Intermittent dosing was more tolerable, with D12 cohort B pts experiencing DLTs treated at both 500 mg/m² and 750 mg/m² of Pem every 2 weeks with intermittent Sor at 200-400 mg. Of the 36 treated pts, best responses to date are 1 CR, 4 PR, 10 SD, 15 PD, 2 NE, and 4 TETE. Five pts with progressive breast cancer were identified as responders. One PR and the CR had duration of responses approximating 1 year. All responding pts were heavily pretreated, with a median of 6 prior lines of therapy. Cutaneous, nodal, and visceral metastases were all observed to respond to treatment. Conclusion: The RP2D for the combination is Pem 750 mg/m² IV every 2 weeks with Sor 400 mg PO BID days 1-5 with each dose of Pem. A phase II study in breast cancer is planned. Clinical trial information: NCT01450384.

Clinical trial information: NCT01450384.
Phase I study of receptor tyrosine kinase (RTK) inhibitor, MGD2625, in patients (pts) with advanced solid tumors. First Author: Christian K. Konstantinberger, BC Cancer Agency, Vancouver Cancer Centre, Vancouver, BC, Canada

Background: MGD2625 is a spectrum-selective and ATP-competitive inhibitor with MET and Axl as clinically relevant RTK targets. In nonclinical studies, MGD2625 demonstrated anti-tumor activity in cancer models exhibiting dysregulation of MET or Axl RTKs. Methods: Phase I objectives were to evaluate the maximum tolerated dose (MTD), safety, pharmacodynamics (PK), pharmacokinetics (PK) and tumor inhibition activity of MGD2625. Eligible pts with advanced solid tumors received MGD2625 on Cycle 1 Day 1, then continuous dosing starting on Cycle 1 Day 3 for 21-day cycles. PK/PD were evaluated after single dose and repeated administration. Results: 12 pts (6 males; median age 57 years; range 48-75) with advanced malignancies were treated with 6000 mg BID or 10,000 mg BID of MGD2625 in non-aqueous suspension capsules. At 1200 mg BID, 2 out of 6 evaluable pts experienced DLT (G3 fatigue; G3 diarrhea). 1050 mg BID was defined as the MTD with no DLTs in 3 pts. Treatment-related AEs (> 20% all grades) included diarrhea, nausea, vomiting, fatigue, AST increase, ALT increase and lipase increase. Stable disease of at least 6 weeks was observed (n = 2). At MTD, preliminary data show that steady state average and maximum concentrations were 501 and 562 ng/mL respectively; the area under the concentration-time curve for the dosing interval was 6010 ng.hour/mL. Preliminary data show that plasma concentrations exceeded levels projected for near complete inhibition of both MET and Axl for the full dosing interval. Maximal increase of plasma soluble MET ectodomain (sMET) was observed at each dose level including those associated with sustained steady state plasma concentrations (Cmax) as low as 200 ng/mL, suggesting that the MET pathway was inhibited at all 3 dose levels and concentrations achieved in this study are likely to result in tumor inhibition. MGD2625 is well tolerated at the MTD of 1050 mg BID. Based on safety, PK data and PD data suggesting robust inhibition of MET and Axl, the expansion phase of the study began recruitment in December 2014. Patients with NSCLC and other solid tumors with specific genetic alterations for MET and AXL will be enrolled. Clinical trial information: NCT00697632.

Efficacy, safety, biomarkers, and phase II dose modeling in a phase I trial of the oral selective c-Met inhibitor tepotinib (MSC21561191). First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO

Background: Tumor c-Met overexpression is associated with tumor aggression and poor prognosis, making it a target for therapy. This phase I study (NCT01014936) in patients (pts) with advanced solid tumors provided data that allowed determination of a recommended phase II dose (RP2D) for the selective oral c-Met inhibitor tepotinib (MSC21561191). Methods: Primary objectives were to determine the MTD and RP2D. Secondary endpoints included antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics. Pts received tepotinib according to one of three dose schedules. Eligible pts were treated at 600, 1200, or 1500 mg BID or 10,000 mg BID of MGD2625 in non-aqueous suspension capsules. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase I/II dose-escalation study of GSK2256098 (FAKi) plus trametinib (MEKi) in patients with selected advanced solid tumors. First Author: Hendrik-Tobias Arkenau, Sarah Cannon Research United Kingdom, London, United Kingdom

Background: The focal adhesion kinase (FAK) and MAPK pathways share conditions (ASCO 2014). In this abstract, we report a companion Phase I/IIa study of entrectinib in selected patients with advanced solid tumors.

Methods: This phase I/II study was conducted at 325 sites worldwide (NTD01358463, funded by GSK) evaluated GSK2256098 twice daily combined with trametinib once daily in pts with advanced solid malignancies enriching for mesothelioma. The objectives were to determine the maximum-tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics (PD).

Results: As of 25 Nov 2014, 24 pts were enrolled (11 M, 10 F; median age 66 yr (range 30–78)). GSK2256098 at 250 or 500 mg twice-daily (BID) was orally co-administered with trametinib at 0.25, 0.375, 0.5 or 1 mg once-daily (QD) in 28-day cycles. Systemic exposure to trametinib was 2-4 X that predicted for monotherapy causing DLTs (skin rash) and dose de-escalation. GSK2256098 PK was unchanged in the presence of trametinib. The MTD was determined to be GSK2256098 250 mg BID plus trametinib 0.5 mg QD and exposure for both agents are at concentrations predicted for monotherapy causing DLTs (skin rash) and dose de-escalation. The MTD for combined GSK2256098 and trametinib was reached, and the preliminary safety and PK/PD profile justifies further exploration. Clinical trial information: NCT01938443.

Lung Colon Gastric Ovary Cholangiocarcinoma Other (arachnoid) 
Rel 7 1 3 2 1 0
Ct N 10 N 1 7 2 2 2

PR 4 2 1 1 1 0
SD 4 2 1 2 0 1
PD 6 8 1 2 0 0

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Lung Colon Gastric Ovary Cholangiocarcinoma Other (arachnoid) PR 4 SD 4 PD 6

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Phase 1 study of combination of crizotinib (C) and dasatinib (D) in patients (pts) with advanced cancer. First Author: Shumei Kato, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Although C and D both demonstrate activity resistance can develop. Preclinical studies demonstrated that activation of MET requires c-SRC. We hypothesized that a c-SRC inhibitor (D), in combination with a MET inhibitor (C), may overcome resistance and demonstrate activity. This study was not in-human attempt to combine C and D. Methods: This is a 2 arm concurrent phase I study (3–5) to determine the safety of C and D (Table). Arm A: C fixed at 250mg BID with escalation of D. Arm B: D was fixed at 140mg QD with escalation of C. Endpoints included MTD, DLT, RP2D at least 10 evaluable pts at MTD of each arm and response (RECIST 1.1). Results: 47 pts were enrolled. Median age was 59 yrs (16–76). 3 median prior therapies (1–12). Screening with C (19%) and D (7%) were the most common cancers were prostate (21%) and sarcoma (19%). 27 pts in Arm A were enrolled. 10 pts were not evaluable; consent withdrawal (n-3) primarily for G2 AE, most common AE (n=15) (7 pts only) for early DLT (exopharyngeal pain). 2 pts had PR with 2/10 pts with DLT (G3 fatigue [n=0] vs DLT [n=1]). 6 pts were evaluable for DLT/AE (dose level [DL] 1 [n=2], DL2 [n=4]), 5 pts (36%) had at least one G3 drug-related AE with grade 3-4 (DL 1 [n=1], DL2 [n=4]). Based on number of DLTs in the MTDs of each arm, our preliminary RP2D is DL1 on Arm A. 2 pts had DLT (prostate [34%] and uterine carcinosarcoma [27%]) and 2 pts had SD MTD with 2/10 pts with DLT (G3 fatigue [n=0] vs DLT [n=1]). 6 pts were evaluable for DL/TAE (dose level [DL] 1 [n=3], DL2 [n=4]), 7 pts (41%) had at least one G3 drug-related AE with diarrhea (n=9) the most common AE, 2/4 pts had DL/TAE at DL2 (all G3; dehydration, infection, nausea, vomiting [n=1 each]). We expanded Arm A DL1 to determine the MTD with 1/13 pts with DLG (3 esophageal pain). Arm B, 20 pts were enrolled. 6 pts were not evaluable; consent withdrawal (n=1), missed doses (n=5). Among 14 pts evaluable for DLT/TAE (DL1 [n=10], DL2 [n=4]), 5 pts (36%) had at least one G3 drug-related AE with fatigue (n=9) being the most common. 2/4 pts had DL at DL2 (G3 renal failure, G3 fatigue, G3 anorexia [n=1 each]). We expanded Arm B DL1 to determine the MTD with 2/10 pts with DLG (G3 fatigue [n=2]). Based on number of DLTs in the MTDs of each arm, our preliminary RP2D is DL1 on Arm A. 2 pts had DLT (prostate [34%] and uterine carcinosarcoma [27%]) and 2 pts had SD ≥ 6 months (NSCLC [10.1] and melanoma [11.4]). Conclusions: Preliminary RP2D for the combination is C (250mg PO BID) and D (50 mg QD). Responses have been observed and specific tumor and molecular expansions are ongoing. Clinical trial information: NCT01746452.

Phase I study of temsirolimus in combination with cetuximab in patients with advanced solid tumors. First Author: Antoine Hulbecque, Drug Development Department, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France.

Background: Preclinical studies suggest that temsirolimus (T), an inhibitor of mammalian target of rapamycin (mTOR) combined with cetuximab (C), an anti-EGFR monoclonal antibody, may have synergistic antitumor effects. Methods: A dose escalation study was conducted to define the MTD and to characterize the pharmacokinetics and safety profile of T (30 min infusion) given 1 hour later after C (1 hour infusion) on a weekly schedule of a 28-day cycle. Five dose-levels were evaluated with dose range of T from 15 to 25 mg weekly and C from 150 to 250 mg/m²weekly. Sequential biopsies were mandatory during the expansion cohort. Results: 39 patients (15M/24F), median age 57 years (range 39-76), previous number of lines 3 (range: 2-15) received the combination. 3/14 pts had PR (12.5%). The most common tumor types were colorectal (N = 6), breast (N = 5), uterine cervix SCC (N = 4) and NSCLC (N = 4). Three patients experienced dose limiting toxicities; grade 3 pulmonary embolism (at C 200 + T 20 level), grade 3 stomatitis (at C 250 + T 20 level) and grade 3 acniform rash (at C 250 + T 25 level). The C 250 mg/m² and T 25mg weekly dose level was selected as the recommended dose. The most common treatment-related adverse events were (All grade / grade 3–4): rash acneiform (97%/15%), mucositis (92%/23%), fatigue (59%/13%), nausea (41%/0%) diarrhea (36%/0%), hypomagnesemia (7%/5%), and hyperglycemia (66%/10%). The median progression-free survival and overall survival were respectively 2.0 months 95%Ci (1.8-3.5) and 7.5 months 95%Ci (5.5-11.9). Among all patients partial responses (PR) and stable diseases were observed in 2 (5.1%) and 18 pts (46.2%). Fifteen pts (38.5%) were treated because of a molecular alteration involving the EGFR and/or PIK3 pathways. Among molecularly selected patients (PR = 14%, SD = 51% was observed (cervix scc with an EGFR amplification and head and neck cancer with a PIK3CA amplification) and 7 pts (44%) had a PFS upper 5.5 months. Conclusions: Tolerance of T + C was acceptable. Clinical activity was modest among all patients. Molecular selection increased the objective response rate. Pre and post-exposure biopsies are available in 20 patients, and are currently been analyzed for pathway modulation and DNA structural changes. Clinical trial information: NCT02215720.

Phase 1 study of temsirolimus plus erlotinib in patients with refractory solid tumors. First Author: Andrea Wang-Gillam, Division of Oncology, Washington University in St. Louis, St. Louis, MO.

Background: Resistance to treatment with inhibitors of mammalian Target of Rapamycin (mTOR) is partially mediated by activation of epidermal growth factor receptor (EGFR). Based on pre-clinical evidence of synergy, we conducted a phase I study to determine the recommended phase II dose (RP2D) and dose-limiting toxicities (DLT) of temsirolimus (mTOR inhibitor) combined with erlotinib (EGFR inhibitor) in patients with refractory solid tumors. Methods: A classic 3+3 design was used for the dose escalation portion of the study. An expansion cohort at RP2D included only those mutations that may contribute to PI3K or EGFR pathway activation or squamous histology. A cycle was defined as 28 days. Patients started daily erlotinib 7 days prior to starting temsirolimus on cycle 1. Intravenous temsirolimus at a 250 mg weekly dose and 100 mg of daily erlotinib. The best tumor response to date has been stable disease. Conclusions: Doses of 10-20 mg/kg exceed target blood concentrations. KTN3379 doses of 20 mg/kg with other targeted agents are safe and PK supports 3-week dosing. KTN3379 has the potential to benefit patients in combination with other targeted agents against ErbB family members, and NRG may be a predictive biomarker of response to KTN3379 in future studies. Clinical trial information: NCT02014909.

2600 Poster Session (Board #316), Sat, 8:00 AM-11:30 AM

Phase 1 study of temsirolimus plus erlotinib in patients with refractory solid tumors. First Author: Andrea Wang-Gillam, Division of Oncology, Washington University in St. Louis, St. Louis, MO.

A phase 1, open-label study to evaluate the safety and pharmacokinetics of the anti ErbB3 antibody, KTN3379, alone or in combination with targeted therapies in patients with advanced cancer. First Author: Todd Michael Bauer, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN.

Background: KTN3379 is a human monoclonal antibody against a unique epitope of human epidermal growth factor receptor-3 (ErbB3) blocking ligand (neuregulin (NRG)) dependent and independent activation. This trial assessed safety and pharmacokinetics (PK) of KTN3379 alone or with each of four targeted minimally invasive breast cancers and evaluated potential biomarkers of KTN3379 activity. Methods: Part I evaluated KTN3379 in a single agent dose escalation design. Part II evaluated KTN3379 with each of cetuximab, erlotinib, vemurafenib and trastuzumab in patients with refractory SCCN, CRC, NSCLC, melanoma and HER2+ breast cancer (n = 6 each). Dose limiting toxicities (DLT) were evaluated in the first treatment cycle, RECIST tumor measurements every 3rd treatment cycle and PK and blood pharmacodynamic (PD) assessments each treatment cycle. Archival tumor tissue was evaluated for biomarkers and correlated with KTN3379 activity. Results: In Part I, no DLTs were observed in the 16 patients treated with KTN3379 at doses of 5 up to its maximally administered dose of 20 mg/kg IV every 3 weeks. PK parameters were linear, supported every 3-week dosing, and trough blood levels following dosing of KTN3379 at 10-20 mg/kg were consistent with maximum antitumor activity in preclinical models. Grade 3 or higher treatment related AE was reported in 1 patient (diarrhea). Other treatment related AEs were low grade diarrhea (n = 5), mucositis (n = 3), rash (n = 3), anemia (n = 2), and fatigue (n = 2). Patients in Part II to date had a similar profile, with low grade diarrhea, mucositis and rash being the most common AEs. In both Parts, elevations of soluble ErbB3 were noted after treatment. Other biomarkers and PK were not evaluated. The best tumor response to date has been stable disease. Conclusions: Doses of 10-20 mg/kg exceed target blood concentrations. KTN3379 doses of 20 mg/kg with other targeted agents are safe and PK supports 3-week dosing. KTN3379 has the potential to benefit patients in combination with other targeted agents against ErbB family members, and NRG may be a predictive biomarker of response to KTN3379 in future studies. Clinical trial information: NCT02014909.
TPS2601 Poster Session (Board #317a), Sat, 8:00 AM-11:30 AM
Pharmacodynamic study using FLT PET/CT in advanced solid malignancies treated with a sequential combination of X-82 and docetaxel. First Author: Martha M. Rampulla, University of Wisconsin, Madison, WI

Background: Clinical experience has shown that despite resolution of tumor pain while on vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKI), pain not only returns, but increases during treatment break. We believe this is due to a withdrawal flare i.e. increased tumor proliferation after VEGFR TKI cessation driven by VEGF. We have previously demonstrated this flare using 18-Fluorotymidine (FLT) PET/CT. (Liu G et al, Clin Cancer Res 2011;17:7634-44) A sequential approach synchronizing cell-cycle specific chemotherapeutic with this withdrawal flare may maximize therapeutic index of chemotherapuy. Here we propose a novel sequential study using X-82, a VEGFR TKI with docetaxel using FLT PET/CT to measure change in vascular parameters and proliferation. We plan comparing low and high doses of X-82 to explore if low dose is preferable with chemotherapuy. Methods: A phase 1 pharmacodynamic study in advanced solid malignancies is planned. Inclusion criteria include at least one lesion amenable to FLT PET/CT, ECOG performance status of $\leq 1$ with normal organ and marrow function. 30 patients will be randomized 1:1 to low dose X-82 (200 mg) or high dose X-82 (400 mg) arm. In Cycle 1, X-82 is administered daily on days 2-15. FLT PET/CT (FLT 1) is obtained on day 1, once on day 12-15 (FLT 2) and day 19-21 (FLT 3). Comparison between FLT 1 and 2 will characterize response to X-82 and FLT 2 and 3 will characterize withdrawal flare. In Cycle 2, docetaxel (75 mg/m²) is administered on day 1, followed by X-82 on days 2-15. FLT PET/CT (FLT 4) is obtained on day 12-15 will characterize response to X-82 and docetaxel. Sequential treatment is continued until progression or unacceptable toxicity. Correlative studies include VEGF levels and X-82 pharmacokinetics. Primary objectives are to evaluate safety, tolerability and FLT PET/CT changes with X-82 alone and with docetaxel. Secondary objectives include evaluating objective response rate to the combination. Toxicities will be monitored based on Pocock stopping boundaries with overall type I error of 0.10. At this time, 2 patients are enrolled on study. After establishing safety, we plan dose expansion cohorts in multiple disease sub-types. Clinical trial information: NCT02146222.

TPS2602 Poster Session (Board #317b), Sat, 8:00 AM-11:30 AM
A phase I study of a novel inhibitor of protein phosphatase 2A alone and with docetaxel. First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN

Background: Protein phosphatase (PP2A) is a multifunctional protein involved in regulation of cell cycle, DNA-damage response, and apoptosis. In pre-clinical studies, LB-100, a novel small molecule inhibitor of PP2A, inhibits the growth of a broad spectrum of leukemic and solid tumor cell lines. In cancer xenografts, LB100 potentiates the effectiveness of cytotoxic drugs (temozolomide, docetaxel, doxorubicin, cisplatin) and radiation without significant increases in toxicity. The predominant mechanisms responsible for potentiation are inhibition of mitotic exit and homologous recombination repair. PP2A inhibition also results in synthetic lethality of cancer cells overexpressing Mad2 (mitotic arrest deficiency protein 2) as a result of mutations in Rb and/or p53 pathways, suggesting that Mad2-overexpression may be a biomarker for LB100 responsiveness. In addition, cancers deficient in PP2A by somatic mutation such as (del)5q MDS are vulnerable to further PP2A inhibition, raising the possibility that other cancers with decreased PP2A resulting from increased endogenous PP2A inhibitors, CIP2A and SET, which include blast crisis CML, NSCLC (40%) and prostate cancers (60%), may also be vulnerable. PP2A has not been considered a practical target for anti-cancer therapy for concern of off-target effects. This trial seeks to determine appropriate doses of LB100 alone and LB100 plus docetaxel for phase II studies in (del)5q MDS and in cancers for which docetaxel is appropriate 2nd line treatment. Methods: This two-part phase I study aims to determine the MTD of LB100 alone given intravenously over 15 minutes daily for 3 days q3w and when given on the same schedule with docetaxel on day 2. In part 2, the starting dose of LB-100 is two levels lower than its single agent MTD combined with docetaxel at 60mg/m². LB100 is escalated to its MTD, and if tolerated, docetaxel is increased to 75mg/m² and LB-100 re-escalated. Eligible patients are $\geq 18$ y with progressive or metastatic tumors having failed standard treatment. In part 2, patients are also docetaxel-naive. Enrollment through the 5th dose level of LB100 alone was completed in January 2015. Clinical trial: NCT01837667.

TPS2603 Poster Session (Board #318a), Sat, 8:00 AM-11:30 AM
First-in-human, dose-escalation, safety, and PK study of a novel 5T4-ADC in patients with advanced solid tumors. First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA

Background: PF-06263507 is an anti-5T4 antibody drug conjugate (ADC) comprised of a humanized anti-5T4 IgG1 antibody conjugated via cysteine residue to the microtuble disrupting agent monomethylauristatin F (MMAF) and a 1522 disintegrating unit. (Liu G et al, Clin Cancer Res 2011;17:7634-44) A sequential approach synchronizing cell-cycle specific chemotherapeutic with this withdrawal flare may maximize therapeutic index of chemotherapy. Here we propose a novel sequential study using X-82, a VEGFR TKI with docetaxel using FLT PET/CT to measure change in vascular parameters and proliferation. We plan comparing low and high doses of X-82 to explore if low dose is preferable with chemotherapuy. Methods: A phase 1 pharmacodynamic study in advanced solid malignancies is planned. Inclusion criteria include at least one lesion amenable to FLT PET/CT, ECOG performance status of $\leq 1$ with normal organ and marrow function. 30 patients will be randomized 1:1 to low dose X-82 (200 mg) or high dose X-82 (400 mg) arm. In Cycle 1, X-82 is administered daily on days 2-15. FLT PET/CT (FLT 1) is obtained on day 1, once on day 12-15 (FLT 2) and day 19-21 (FLT 3). Comparison between FLT 1 and 2 will characterize response to X-82 and FLT 2 and 3 will characterize withdrawal flare. In Cycle 2, docetaxel (75 mg/m²) is administered on day 1, followed by X-82 on days 2-15. FLT PET/CT (FLT 4) is obtained on day 12-15 will characterize response to X-82 and docetaxel. Sequential treatment is continued until progression or unacceptable toxicity. Correlative studies include VEGF levels and X-82 pharmacokinetics. Primary objectives are to evaluate safety, tolerability and FLT PET/CT changes with X-82 alone and with docetaxel. Secondary objectives include evaluating objective response rate to the combination. Toxicities will be monitored based on Pocock stopping boundaries with overall type I error of 0.10. At this time, 2 patients are enrolled on study. After establishing safety, we plan dose expansion cohorts in multiple disease sub-types. Clinical trial information: NCT02146222.

TPS2604 Poster Session (Board #318b), Sat, 8:00 AM-11:30 AM
A multicenter phase II basket clinical trial of lurbinectedin (PM01183) in selected advanced solid tumors. First Author: Mariano Provencio Pulla, Hospital Puerta de Hierro, Madrid, Spain

Background: PM01183 (lurbincetin) is a new anticancer drug that binds to the DNA minor groove and blocks trans-activated transcription, inducing formation of double-strand DNA breaks leading to cell apoptosis. COM-PARE analysis revealed that lurbinectedin’s mechanism of action differs from the other 98 chemotherapy agents tested Advanced small cell lung cancer (SCLC), neuroendocrine tumors (NET), head and neck (H&N), bladder tract and endometrial carcinoma, BRCA1/2-associated metastatic breast cancer, carcinoma of unknown primary site, germinal cell tumors and Ewing family of tumors represent unmet medical needs. Cytotoxic chemotherapy remains a major component of their therapeutic armamentarium but new anticancer agents are needed to broaden clinical benefit. PM01183 has already shown clinical activity in BRCA1/2 breast cancer, SCLC, endometrial carcinoma, NET, H&N and in tumors with high proliferation index. This exploratory phase 2 trial has been designed to confirm the PM01183 anticancer activity, as a single agent, in several difficult-to-treat tumors. Methods: Primary objective: antitumor activity of PM01183 in terms of response rate by RECIST v.1.1, in the aforesmen-tioned indications. Secondary objectives: duration of response, clinical benefit, progression-free survival and 1-year overall survival in each tumor type. Pharmacokinetics, pharmacogenomic analyses of potential prognostic/predictive factors. Safety profile. Patients with each tumor type will be enrolled in nine cohorts, 25 evaluable patients will be recruited in each of them. To consider PM01183 active in the tumors analyzed, at least two confirmed responses in the 25 patients of each cohort are expected. If no responses are observed in the first 15 evaluable patients, recruitment of patients in each cohort will be stopped. If one confirmed response is observed in the first 15 evaluable patients, recruitment of this cohort will continue to 25 patients. Patients will receive PM01183 i.v. as a 1 hour infusion, every three weeks at a dose of 4 mg/m². In patients with ECOG PS = 2 or > 70-years-old, dose will be 3 mg/m². Twenty six centers in 8 countries participate in this trial.

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A phase I study of RX-3117, an oral agent activated by uridine cytidine kinase 2, to treat subjects with advanced solid tumors. First Author: Drew Watson, ASCO, STAT, Willard, CA

Background: RX-3117 is an oral small-molecule antimitabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117’s efficacy in xenograft models (Colo-205, H460, H69 and CaSkii), which are moderately sensitive or resistant to gemcitabine, indicates that RX-3117 may have the potential to treat tumors that do not respond to gemcitabine or have become gemcitabine resistant. Methods: This phase 1, open-label, multicenter study evaluates the efficacy and safety of RX-3117 in subjects with solid tumors. RX-3117 is administered 3 times a week for 3 weeks with 1 week off during each 4 week cycle. Dose escalation starts with an accelerated design treating 1 subject per dose followed by a standard 3+3 design using a modified Fibonacci sequence after the occurrence of a single Grade 2 or greater adverse event. The primary endpoint is the overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms, any dose limiting toxicities that occur during Cycle 1, serious adverse events, or adverse events leading to study treatment discontinuation. Secondary endpoints include pharmacokinetic parameters (e.g., time to maximum observed concentration \(C_{\text{max}}\)), maximum observed plasma concentration \(C_{\text{max}}\), trough concentration \(C_{\text{trough}}\), area under the concentration-time curve (AUC)) and Indices of anti-tumor activity (e.g., overall response rate, time to response, duration of response, progression-free survival). Exploratory endpoints are baseline biomarker-expression/concentration, including (but not limited to) concentration-nucleoside transporter 2; equilibrate nucleoside transporter 1; uridine-cytidine kinase 1; and ribonucleotide reductases 1 and 2. Target recruitment is approximately 30 subjects. Eligible subjects must have confirmed histologic or cytologic diagnoses of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. Clinical trial information: NCT02030067

Phase I study of procaspase activating compound-1 (PAC-1) in the treatment of advanced malignancies. First Author: Dana C. Danciu, University of Illinois at Chicago, Chicago, IL

Background: Members of the caspase family of cysteine proteases are key players in both the initiation and execution of apoptosis; the activation of procaspase-3 to caspase-3 is a critical event in the apoptotic cascade. Procaspase-3 levels are elevated in: glioblastoma, breast cancer, colon cancer, lung cancer, lymphoma, neuroblastoma, melanoma, and liver cancer. As a consequence, caspase-3 levels are abnormally low in these cancers. As a consequence, caspase-3 levels are abnormally low in these cancers. PAC-1 is a small molecule that activates procaspase-3 and induces apoptosis of cancer cells in culture. PAC-1 showed efficacy across a wide range of cancer cell lines, as well as in animal models of cancer, including brain cancer. This novel compound potently synergizes with chemotherapy agents (e.g., doxorubicin, tamoxolomide, etoposide, carboplatin). Methods: This is a Phase I dose escalation study with a modified Fibonacci 3+3 design, consisting of 2 parts: to determine the maximum tolerated dose (MTD) of PAC-1 in advanced malignancies, and to determine the MTD of PAC-1 when combined with temozolomide in patients with primary brain tumors. For both parts the MTD dose level will expand to a total of 9 patients to ensure safety. Primary objectives: establish MTD, tolerability and toxicity. Secondary and correlative objectives: pharmacokinetics, pharmacodynamics, preliminary antitumor activity correlation with procaspase-3 expression in tumor, clinical response and adverse effects, Neurological symptoms of CNS toxicity will be assessed throughout the trial. Imaging. This trial is currently enrolling at four US sites; Cohort 3 (96 mg/m2) has been completed without dose-limiting toxicity and Cohort 4 (168 mg/m2) has been enrolled as of February 2015. In conclusion, PAC-1 showed efficacy across a wide range of cancer cell lines, as well as in animal models of cancer, including brain cancer. Clinical trial information: NCT020244861

A phase I, dose-escalation, multi-center study of PFK-158 in patients with advanced solid malignancies explores a first-in-man inhibitor of glycolysis. First Author: Rebecca A. Redman, James Graham Brown Cancer Center, University of Louisville, Louisville, KY

Background: In human cancers, activation of the MAP kinase and PI3K/PTEN/AKT pathways converge to increase the expression and activity of a potent regulator of glycolysis, 6-phosphofructo-kine/fructose 2,6-bisphosphatase (PFKFB3). This enzyme synthesizes fructose 2,6-bisphosphate (F2,6BP), which is an activator of FPK-1, a key enzyme of glycolysis that is tightly controlled by multiple metabolic feedback mechanisms and dictates the overall rate of glycolytic flux to lactate and the TCA cycle. PFKFB3 is a potent small molecule inhibitor of PFKFB3 that selectively cytotoxic to cancer cells and displays broad anti-tumor activity causing significant growth inhibition in preclinical models of breast, lung, glioblastoma, ovarian, pancreatic, melanoma and colon cancer. In addition, because resistance mechanisms frequently activate pathways that result in up-regulation of glycolysis, combination treatments with cytotoxic and targeted agents result in increased efficacy and tumor regressions. Importantly, IND-enabling safety and toxicity studies have demonstrated that PFK158 is well tolerated in rats and dogs resulting in an acceptable pre-clinical therapeutic index. Methods: The primary objective of this phase I clinical trial is to describe the dose limiting toxicity of PFK158 and to determine either the maximum tolerated dose or biological effective dose of PFK-158 in a “3+3” cohort-based dose escalation design that follows a modified Fibonacci scheme. Multiple secondary endpoints have been incorporated to assess the effects of PFK-158 on peripheral blood mononuclear cell F2,6BP activity, and on glucose uptake using FDG-PET imaging. This trial is currently enrolling at four US sites; Cohort 3 (96 mg/m2) has been completed without dose-limiting toxicity and Cohort 4 (168 mg/m2) has been enrolled as of February 2015. In conclusion, PFK-158 is a first-in-human and first-in-class PFKFB3 inhibitor that is currently under evaluation in a phase I trial and is expected to have significant clinical utility either as a monotherapy or when combined with other targeted agents. Clinical trial information: NCT02003092

A phase I study of RX-5902, an oral agent targeting phosphorylated p68, to treat subjects with advanced solid tumors. First Author: S. Gail Eckhardt, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO

Background: RX-5902 is a novel compound that targets phosphorylated p68 RNA helicase (also known as DDX5), a member of the DEAD box family of RNA helicases. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. As a single agent, RX-5902 inhibits tumor growth and enhances survival in a variety of in vivo xenograft tumor models (e.g., renal, ovarian, pancreatic, melanoma). Methods: This Phase 1, open-label, multicenter study evaluates the efficacy and safety of RX-5902 in subjects with solid tumors. RX-5902 is administered orally once weekly for 3 weeks with 1 week of rest in each 4 week cycle. Dose escalation starts with an accelerated design treating 1 subject per dose followed by a standard 3+3 design using a modified Fibonacci sequence after the occurrence of a single Grade 2 or greater adverse event that is considered at related to RX-5902. The primary endpoint is the overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms as well as the description of any dose limiting toxicities that occur during Cycle 1, serious adverse events, or adverse events leading to discontinuation of study therapy. Secondary endpoints include pharmacokinetic parameters (e.g., time to maximum observed concentration \(C_{\text{max}}\)); maximum observed plasma concentration \(C_{\text{max}}\), trough concentration \(C_{\text{trough}}\); area under the concentration-time curve (AUC)) and Indices of anti-tumor activity (e.g., overall response rate, time to response, duration of response, and progression-free survival during treatment. Exploratory endpoints are biochemical levels of drug targets in blood and tumor samples. Eligible subjects must have confirmed histologic or cytologic diagnoses of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens. Clinical trial information: NCT02003092

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Background: Signaling hyperactivation secondary to MAPK pathway aberrations are common. RAF kinases play key roles in the RAS/RAF/MEK/ERK signaling cascade, representing potentially valid therapeutic targets. In a phase 1 study, single-agent MLN2480 had an acceptable safety profile, expected pharmacodynamic effects, and preliminary antitumor activity (Middleton et al, ENA 2014, Abstract 364). Preclinically, MLN2480 has shown synergistic/additive effects in xenograft models and cell lines when combined with MLN1208, alisertib or the taxane, docetaxel. Potential overlapping toxicities of each combination are expected to be manageable, with no apparent risks for clinically meaningful pharmacokinetic (PK) drug–drug interactions based on in vitro ADME data and exposures achieved clinically. Methods: This three-arm, open-label study (NCT02327169) is the first-in-human study for MLN2480 + MLN1208/ alisertib/docetaxel. Primary objective is to evaluate the safety, tolerability, and MTD of each combination. Secondary objectives are to characterize PK profiles and preliminary antitumor activity. An exploratory objective is to assess tumor samples and circulating tumor DNA for biomarkers of response/resistance. Pts aged ≥ 18 yrs with radiographically/clinically evaluable advanced solid tumors who failed standard therapies are eligible. Pts in the expansion phase require tumors measurable by RECIST v1.1. MAPK pathway aberrations are not required. Pts will receive MLN2480 100–200 mg (d 1, 3, 5 per week) in 28-d cycles plus: (A) MLN1208 2–9 mg (d 2, 3, 4 per week), (B) alisertib 30–50 mg twice daily (d 1–3, 8–10, 15–17) or (C) paclitaxel 80 mg/m2 (d 1, 8, 15) for up to 12 cycles. Serial blood samples will be taken in cycle 1 for PK evaluation. A 3+3 dose escalation algorithm, based on cycle 1 DLTs, will be used, with up to 20/20/15 pts in groups A/B/C. Enrolment is ongoing. Once MTDs are established, ≥ 1 combination regimens will be selected for the expansion phase (~16 pts per group) based on safety, exposure and preliminary antitumor activity data. Clinical trial information: NCT02327169.

Methods:

This phase I study of ADI−PEG 20 in combination with pemetrexed and cisplatin (TRAP) in patients with ASS1−deficient mesothelioma and non−squamous lung cancer.

Phase 1 study of ADI-PEG 20 in combination with pemetrexed and cisplatin (TRAP) in patients with ASS1−deficient mesothelioma and non−squamous lung cancer.

Background:

Loss of the metabolic tumor suppressor, argininosuccinate synthetase (ASS1), a rate−limiting enzyme in arginine biosynthesis, sensitizes mesothelioma and lung carcinoma cells to apoptosis following arginine withdrawal. Recently, we showed potentiation of the cytotoxic effect of pemetrexed by the arginine depletor pegylated arginine deiminase (ADI−PEG 20) in ASS1−negative tumor cells, which was accompanied by suppression of de novo pyrimidine synthesis and the pyrimidine salvage pathway (Allen et al, Cancer Res 2014). Consequently, we have initiated a phase I study (NCT02029690) to assess the maximum tolerated dose (MTD), safety and toxicity, and preliminary efficacy of ADI−PEG 20 combined with first−line pemetrexed and cisplatin chemotherapy in patients with ASS1−deficient mesothelioma or non−squamous non−small cell lung cancer (NSCLC).

Methods:

Up to 47 good performance (ECOG 0−1) patients are being enrolled in a 3+3+3 phase 1 design using tumoral ASS1 loss as a selection biomarker. Weekly ADI−PEG 20 is being dose escalated (18, 27 and 36 mg/m2 IM), with pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 both given every 3 weeks, for a maximum of 18 weeks of treatment. Cohorts 1 and 2 have been completed without dose−limiting toxicity and enrollment to cohort 3 began in January 2015 at the maximum ADI−PEG 20 dose of 36mg/m2. A further 10 patients with mesothelioma and 10 patients with NSCLC will be recruited at the MTD with pharmacodynamic monitoring of response using plasma arginine and citrulline, and assessment of tumor proliferation with (18F)−fluoro−L−thymidine (FLT)−positron emission tomography (PET). In summary, TRAP is the first triplet chemotherapy combination study to assess the role of arginine deprivation with ADI−PEG 20 in solid cancers using ASS1 as a selection biomarker. Patient accrual at the MTD cohort is nearing completion and ADI−PEG 20 in combination with cisplatin and pemetrexed will be evaluated further in the planned expansion cohorts. Clinical trial information: NCT02029690.
A phase 1, dose-escalation, safety, pharmacokinetic, pharmacodynamic study of thioiredoibutryonitrile, a novel p53 targeted therapy, in patients with advanced solid tumors. 

First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA

Background: Thioredoibutryonitrile, Kevetrin, induced apoptosis in wild type p53, mutant p53 and p53 null cell lines. In A549 lung carcinoma cells, wild type p53 was stabilized by Kevetrin. Kevetrin induced nongenotoxic activation of the p53 signaling pathway. Kevetrin also induced p21 and PUMA, known transcriptional targets of p53. Kevetrin caused accumulation of monoubiquitinated p53 and induced transcriptionally independent apoptosis. In p53 mutant breast carcinoma cells (MDA-MB-231), Kevetrin induced degradation of hyperstable oncogenic mutant p53 and induced apoptotic cell death. Apoptotic cell death was also induced in K-562, a p53 null CML cell line. Consistent with in vitro data, Kevetrin induced potent antitumor activity in wild type p53 (A549), mutant p53 (MDA-MB-231), and p53 null (K-562) human tumor xenograft models. Kevetrin has the unique ability to target both wild type and mutant p53 tumors controlling tumor growth in various preclinical tumor models (ASCO 2013). Based on the pre-clinical data, a Phase I study was initiated at Dana-Farber/ Harvard Cancer Center in 2012. Methods: Adults with refractory locally advanced or metastatic solid tumors, acceptable liver, kidney function, and hematologic status were eligible. Objectives include determination of DLT, MTD, pharmacokinetics, pharmacodynamics, and evaluating preliminary evidence of antitumor activity. Kevetrin is given as an intravenous infusion once weekly for 3 weeks in 28-day cycles. The starting dose was 10 mg/m². In a 3+3 design, groups of 3-6 patients are evaluated for toxicity at each dose level. Dose escalation is based upon the number and intensity of adverse events in cycle 1. Kevetrin PK is characterized for the first and last doses given in cycle 1. Kevetrin induced p21 in lymphocytes preclinically; therefore p21 expression in peripheral blood mononuclear cells is measured as a PD biomarker. Antitumor activity by RECIST 1.1 criteria and serum tumor markers is assessed. The p53 status of tumors of selected patients will be determined. The first nine cohorts were completed in December 2014. Enrollment in the tenth cohort at 450 mg/m² began January 2015. Clinical trial information: NCT01164000.
TPS2617 Poster Session (Board #325a), Sat, 8:00 AM-11:30 AM
Phase II study of the PARP inhibitor talazoparib (BMN-673) in advanced cancer patients with somatic alterations in BRCA1/2, mutations/deletions in PTEN or PTEN loss, a homologous recombination deficiency (HRD) or germline BRCA1/2 mutations. There is, however, a great need to define the spectrum of patients who may benefit. Methods: This is an investigator-initiated, single-center, non-randomized, multi-cohort trial of subjects enrolling at veliparib 300 mg PO twice daily and topotecan 3 mg/m2/dose. The trial is currently recruiting. Secondary endpoints include baseline molecular and pharmacodynamics markers, concordance of BRCA1/2 alterations and HRD status, concordance of genomic alterations in tumor and circulating free DNA, progression free survival, duration of response, and overall survival. Statistical plan includes descriptive statistics, Kaplan Meier techniques and Cox proportional hazard modeling. Enrollment has already commenced. Clinical trial information: NCT02286687.

TPS2618 Poster Session (Board #325b), Sat, 8:00 AM-11:30 AM
A phase I trial of veliparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), and topotecan (TPT) in patients with solid tumors. Background: PARPs are a highly conserved family of enzymes whose predominant function is to preserve genomic integrity following DNA damage. Preclinical studies demonstrated that PARP inhibitors enhance the cytotoxicity of DNA damaging agents. Specifically, PARP inhibition sensitizes tumor cells to topotecan in vitro and in vivo by trapping PARP1 on damaged DNA and preventing repair of DNA-induced DNA damage (Patel et al., J. Biol. Chem. 287:4198, 2012). Veliparib has been combined with daily topotecan but found to be quite myelosuppressive, requiring reduction in doses of both agents (Kummar et al., Cancer Res. 71:5626, 2011). Based on these data, we sought to determine the maximum tolerated dose (MTD) of veliparib in combination with less myelosuppressive weekly administration of topotecan in patients with solid tumors. Correlative studies were included to assess the impact of topotecan and veliparib on poly(ADP-ribose) levels in peripheral blood mononuclear cells as well as the pharmacokinetics of both agents. Methods: Eligible patients include any histologically confirmed solid tumor malignancy that is metastatic or unresectable with measurable disease (longest diameter > 2 cm with conventional CT) in patients 18 or older who have received < 2 chemotheraphy regimens, ECOG PS < 2 and adequate bone marrow, renal and hepatic function. Using a standard 3+3 design, patients have been treated with veliparib PO twice daily on days 1-3, 8-10 and 15-17 and topotecan IV on days 2, 9 and 16 every 28 days. The trial is currently enrolling at veliparib 300 mg PO twice daily and topotecan 3 mg/m2/dose. Once MTD is established, a phase II clinical trial in platinum resistant ovarian, peritoneal and fallopian tube malignancies is planned. Supported in part by U1UCA186686 and P50CA136393. Clinical trial information: NCT01012817 Clinical trial information: NCT01012817.
TPS2621 Poster Session (Board #327a), Sat, 8:00 AM-11:30 AM

Background: MGCD516, is an orally-available, potent small molecule inhibitor of a closely related family of RTKs including RET, TRK family, DDR2, MET, Axl family, Kit, as well as VEGFR and PDGFR family members. RTKs inhibited by MGCD516 are genetically altered in a variety of cancers, including non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC), functioning as oncogenic drivers promoting cancer development and progression. Mutations in the TRKs have also been implicated in tumor resistance mechanisms. MGCD516 has demonstrated broad antitumor activity including demonstration of tumor regression in preclinical models harboring genetic disruption of MGCD516 targets including MET amplification, MET-ex14del, RET rearrangement and CHRq12 amplification. Methods: This first-in-human, open label Phase I/1b study is designed to evaluate the safety, pharmacokinetics, metabolism, pharmacodynamics and clinical activity of MGCD516 in patients with advanced solid tumors. Phase 1 is the dose escalation phase and uses the modified toxicity probability interval (mTPi) method to determine the MTD (Recommended Phase 1 Dose). Phase 1b is the expansion phase in which MGCD516 will be evaluated in patients with NSCLC, HNSCC, or any other solid tumor type harboring specific MGCD516 RTK target mutations of interest. Phase 1 and 1b are each anticipated to enroll 60 patients. Phase 1 enrollment started in September 2014, with patients receiving continuous daily dosing (QD) of 10mg MGCD516 in cycles of 21 days. Cohort 1 and Cohort 2 (QD 20mg) have been completed without DLTs and enrollment to Cohort 3 (QD 40mg) started in January 2015. Pharmacokinetics is evaluated after single and repeated administration. Pharmacodynamic biomarkers, including soluble (s)MET, sVEGFR2 and sVEGFR1 will be explored in plasma samples for prognostic potential and possible relationship with clinical outcome. Clinical trial information: NCT02219711.

TPS2623 Poster Session (Board #328a), Sat, 8:00 AM-11:30 AM
First-in-human dose escalation study of oral ONC201 in advanced solid tumors. First Author: Mark N. Stein, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: ONC201 is an orally active first-in-class small molecule with strong antitumor activity in preclinical models of advanced cancers. In cancer cell lines and patient samples ONC201 induces an integrated stress response (Ishizawa et al, 2014), late-stage inactivation of Akt and ERK, and downstream activation of the apoptotic TRAIL pathway as part of innate immune surveillance (Allen J et al, Sci Trans Med, 2013). Activity is independent of p53 status. ONC201 is well tolerated at efficacious doses in animal models, crosses the blood brain barrier, is particularly effective in refractory tumors, depletes cancer stem cells (Ishizawa et al, ASCO 2014; Prabhni et al, Blood 2014; Zhao et al, ASCO 2014), and is effective with infrequent dosing preclinically. Based on the compelling efficacy and safety profile of ONC201 as well as the engagement of signature pathways critical for many cancers, the clinical introduction ONC201 in advanced cancer patients is warranted. Methods: The first-in-human study of ONC201 (NCT02250781) began in January 2015 as an open-label single-site phase I trial enrolling adult patients with refractory advanced solid tumors and glioblastoma (GBM). Patients with symptomatic brain metastases or glioblastoma are excluded. The primary endpoint is progression-free survival. Secondary endpoints include toxicity, objective response rate (RECIST1.1) and overall survival. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

TPS2624 Poster Session (Board #328b), Sat, 8:00 AM-11:30 AM
A first-in-human study of LOXO-101, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family. First Author: Howard A. Burris, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN

Background: The TRK family of neurotrophin receptors, TRKA, TRKB, and TRKC (encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) and their neurotrophin ligands regulate growth, differentiation and survival of neurons. Translocations involving the NTRK1/2/3 kinase domain, mutations involving the TRK ligand-binding site, amplifications of NTRK, TRK splice variants, and autocrine/paracrine signaling have been described in a diverse number of tumor types and may contribute to tumorigenesis. Recently NTRK1 fusions were described in a subset of adenocarcinoma lung cancer patients (Vaishnavi, 2013) and NTRK2 and NTRK3 fusions have been described in multiple tumor types (Skalova, 2014; Ricarte-Filho, 2013; Vaishnavi, 2014). LOXO-101 is a potent, oral, ATP- competitive pan-TRK inhibitor with IC_{50} values in the low nanomolar range for inhibition of TRK family members in binding and cellular assays, with 100X selectivity over other kinases. LOXO-101 has demonstrated tumor inhibition in preclinical models. Methods: This study (NCT01229313) is an ongoing phase Ia/Ib dose escalation plus expansion trial in adults with advanced solid tumors. The phase Ia component is an open-label, multicenter, dose escalation trial. Patients with solid tumors refractory to standard therapy, with normal hematopoietic and major organ function are eligible for study. LOXO-101 is administered orally QD or BID for continuous or intermittent cycles. The phase Ib component is an open-label, phase I/Ib trial plus expansion to a standard 3+3 randomization for efficacy. The study employs an accelerated, single patient per cohort, dose escalation design with expansion to a standard 3+3 design if a subject has grade > i = grade 2 toxicity or dose limiting toxicity within cycle 1. The maximum tolerated dose is the highest dose level in which 6 patients have been treated with < i = 1 instance of DLT. A subject in Cohort 1 (125mg) has completed the first cycle of treatment without any > i = grade 2 toxicity. Cohort 2 (250mg) is currently enrolling. This phase I study will identify the RP2D to enable evaluation of the antitumor efficacy of ONC201 in select advanced cancer indications. Clinical trial information: NCT02250781.

TPS2622 Poster Session (Board #327b), Sat, 8:00 AM-11:30 AM
A randomized, open-label, Phase II trial evaluating the clinical benefit of a maintenance treatment targeting tumor molecular alterations in patients with advanced solid tumors. First Author: Prabhu M. Anjaria, University of Minnesota, Minneapolis, MN

Background: Therapeutic decision for most cancers is mainly based on primary disease site, histological type and/or tumor burden. However, genotype-driven clinical trials where treatments are adapted to the molecular alteration supposed to drive tumor progression have recently emerged with promising early results e.g. (Battle, SAPHIR01/02, SHIVA, ...). MOST (My Own Specific Therapy) is a randomized, open-label, adaptive phase II trial conducted in patients (pts) with progressive solid tumors (any subtype) after at least one prior therapy in the advanced setting. This trial aims to evaluate the clinical benefit of maintenance therapy targeting molecular alterations identified in the patient's tumor. Primary endpoint is progression-free survival. Secondary endpoints include toxicity, objective response rate (RECIST1.1) and overall survival. Based on the presence of molecular alterations detected by a previous tumor molecular profiling, pts are treated with one of the following targeted therapies: nilotinib (400 mg BID for ABL1, KIT, PDGFRB/A, DDR1/2, CSF1R mut/ampl/ transloc.), everolimus (10 mg QD for PI3KCA, PI3K3, AKT1/2, mTOR mut/ampl or TSC1/2 or PTEN loss); sorafenib (400 mg BID for VEGFR1-3, PDGFRB, FLT3, RAF, CRAF, KRAS or RET mut/ampl/transloc); lapatinib (1500 mg QD for HER2 mut/ampl or pazopanib (800 mg QD for VEGFR1-3, PDGFRB/A or Kit mut/ampl). After 12 weeks of treatment, pts with objective response are proposed to continue the targeted therapy, while pts with stable disease are randomly assigned (1:1) to continuation (arm A) or interruption of treatment (arm B); reintroduction is allowed at disease progression. Statistical analysis will be carried out in each of the 5 treatment groups using a sequential Bayesian approach. Three interim analyses are planned after randomization of 10, 15 and 20 pts per arm. The trial will continue until the maintenance arm is shown with high posterior probability to be superior to the interruption arm according to a pre-defined stopping rule, or until the maximum sample size (i.e. 50 pts) is reached. To date, 66 of 400 planned patients have been enrolled. Clinical trial information: NCT02029001.

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3000 Oral Abstract Session, Mon, 1:15 PM–4:15 PM

Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001. First Author: Jed D. Wolchok, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Immune-related response criteria (irRC) were developed to better characterize the atypical response patterns observed with ipilimumab. Previously, we showed that 7.2% of melanoma pts treated with the anti–PD-1 monoclonal antibody pembrolizumab also demonstrated atypical response patterns and that irRC may better represent the clinical benefit of pembrolizumab than conventional RECIST. This updated analysis includes all 655 melanoma pts enrolled in KEYNOTE-001 (NCT01295827).

Methods: Pts received pembrolizumab 2 mg/kg every 3 wk (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W. Imaging was performed every 12 wk. Response was assessed centrally by irRC and RECIST v1.1. Investigator-assessed irRC was used for pt management. Early pseudoprogression was defined as ≥25% increase in tumor burden at first assessment that was not confirmed as progressive disease (PD) per irRC at the next assessment performed ~4 wk later. Delayed pseudoprogression was defined as ≥25% increase in tumor burden at any time point after the first assessment, followed by no-PD at the next assessment. Results: Of the 655 pts enrolled, 327 had ≥28 wk of follow-up by imaging at the time of analysis and were assessed for atypical responses. Overall, 29 pts (8.9%) experienced atypical response. Early pseudoprogression was observed in 15 (4.6%) pts. Late pseudoprogression was observed in 14 (4.3%) pts. In the 592 pts who survived ≥12 wk, 331 (56%) had best overall response of non-PD per RECIST and irRC, 177 (30%) had PD per both criteria, and 84 (14%) had PD per RECIST v1.1 but non-PD per irRC. OS was longer in pts with PD per RECIST but non-PD per irRC compared with those who had PD by both criteria (Table). Conclusions: Results of this expanded analysis are consistent with previous reports suggesting that pembrolizumab may result in atypical response patterns and that conventional response criteria may underestimate the therapeutic benefit of pembrolizumab in advanced melanoma. New standards such as irRC or irRECIST should be considered for assessing response to immunotherapy. Clinical trial information: NCT01295827.

3001 Oral Abstract Session, Mon, 1:15 PM–4:15 PM

Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon- inflammatory immune gene signature. First Author: Antoni Ribas, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA

Background: Immunotherapy with anti–PD-1 monoclonal antibodies such as pembrolizumab shows robust, durable antitumor activity in patients with advanced melanoma. Examining gene expression related to the immune response within the tumor may provide new insights into the molecular features associated with clinical response to these agents. We evaluated immune-related gene expression patterns in patients with melanoma enrolled in the phase Ib KEYNOTE-001 study. Methods: Baseline tumor biopsy samples from 19 patients with melanoma enrolled in KEYNOTE-001 were used as a discovery set. Results were validated using samples from 62 additional patients from KEYNOTE-001, of whom 51 were evaluable for response per RECIST v1.1 by central review. RNA was extracted from formalin-fixed paraffin-embedded tissue sections and analyzed using the NanoString nCounter. Two signatures, the “Interferon-gamma (IFNγ) 10-gene” and the “Expanded-immune 28-gene,” were pre-specified prior to linking NanoString data to clinical outcomes. Results: The overall response rate (ORR) was 47% in the validation cohort. Both the IFNγ and the expanded-immune signatures showed statistically significant associations with ORR (P = 0.047 and 0.027, respectively) and progression-free survival (P = 0.016 and 0.015). Analysis of top-ranked genes on the platform led to the discovery of two new signatures, “TCR-signaling” and “Denovo,” that were enriched in T-cell-infiltrated and MHC Class I gene signatures. Conclusions: Measuring immune-related biomarkers, including T-cell specific, antigen presentation–related, and IFNγ signaling–related genes, may allow for improved selection of patients likely to respond to anti–PD-1 therapy with pembrolizumab. Results are consistent with the hypothesis that clinical responses to PD-1 blockade are influenced by a preexisting interferon-mediated adaptive immune response. Further confirmation of these new signatures in melanoma is required. Clinical trial information: NCT01295827.

3002 Oral Abstract Session, Mon, 1:15 PM–4:15 PM

Density of immunogenic antigens and presence or absence of the T cell-inflamed tumor microenvironment in metastatic melanoma. First Author: Thomas Gajewski, The University of Chicago, Chicago, IL

Background: Patients with melanoma can be categorized based on the presence or absence of a T cell-inflamed tumor microenvironment. The presence of baseline CD8+ T cells is associated with clinical benefit to immunotherapies, including anti–PD1 and anti–CTLA4. The molecular mechanism explaining lack of a T-cell infiltrate in a major subset are poorly understood, but differential expression of immunogenic antigens has been proposed as one explanation.

Methods: Using the TCGA data set for melanoma show comparable expression of CT, differentiation, and mutational antigens. Spontaneous T-cell infiltration into tumors therefore could, in principle, render these patients response to immunotherapies once these antigens are recognized. But the density of immunogenic antigens and presence or absence of the T cell-inflamed tumor microenvironment in metastatic melanoma is unlikely to be due to lack of antigens. Strategies that improve density of immunogenic antigens and presence or absence of the T cell-inflamed tumor microenvironment in metastatic melanoma may result in atypical response patterns and that conventional response criteria may underestimate the therapeutic benefit of pembrolizumab in advanced melanoma. New standards such as irRC or irRECIST should be considered for assessing response to immunotherapy. Clinical trial information: NCT01295827.

3003 Oral Abstract Session, Mon, 1:15 PM–4:15 PM

Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma. First Author: Antoni Ribas, UCLA, Los Angeles, CA

Background: Inhibition of the MAPK pathway with dabrafenib (D) and trametinib (T) is efficacious in BRAF-mutant melanoma. MEK inhibitors have also shown activity in BRAF WT melanoma, particularly in NRAS-mutant tumors. However, melanoma (pts) developing D and T (D+T) resistance while on D represents a major challenge. This study combined dabrafenib (150 mg twice daily) with trametinib (2 mg daily), or D+T at full doses with a manageable safety profile, and demonstrated antitumor activity in a patient with BRAF WT and NRAS–mutant melanoma who had a viable disease burden after multiple prior regimens. Objective response rate (ORR) was 45% in the D+T arm. Conclusions: The combination of D+T is efficacious in patients with BRAF WT and NRAS–mutant melanomas.
A phase I study of PF-05082566 (anti-4-1BB) + rituximab in patients with CD20+ NHL. First Author: Ajay K. Gopal, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: 4-1BB agonists enhance cytotoxic T-cell and NK cell responses, including antibody-dependent cellular cytotoxicity, resulting in anti-tumor activity in preclinical models. PF-05082566 (PF-566), a fully humanized IgG2 monoclonal antibody, activates 4-1BB while blocking its negative regulation by endogenous soluble 4-1BB ligand (s4-1BBL). Methods: This Phase I study evaluated PF-566 in doses ranging from 0.03-10 mg/kg in combination with 375 mg/m2 rituximab (R) in patients (pts) with relapsed or refractory (R/R) NHL. Patients were treated using a Time-To-Event Continuous-Reassessment-Method design. Pts received PF-566 from D1 Q4 weeks up to 24 mo, and R from D-7 Q1W X4. The 1st endpoint was first 2-cycle DLT with PK/PD, safety, and anti-tumor activity as 2nd endpoints. Results: 35 pts with CD20 + NHL were treated with PF-566 combined with R. Folicular (FL) (n = 22), mantle cell (MCL) (n = 5), diffuse large B cell (n = 3), marginal zone (n = 2), small lymphocytic (n = 2) and nodular lymphocyte predominant Hodgkin’s (n = 1), 34 (97%) with prior R, and 20 (57%) with R-refractory disease. The median number of prior regimens was 3 (range of 1 - 9). No DLTs were observed and no pts discontinued treatment due to treatment-related AEs. The MTD was estimated as ≥ 10 mg/kg. No severe immune-related AEs were observed. PK data show a dose proportional increase in exposure and a half-life of ~10 days. Increases in soluble 4-1BB, memory T cell, and activated NK cells were observed. For pts up to 2.4 mg/kg (higher doses under evaluation for efficacy), the ORR was 21% (29/114), and in R-refractory pts the ORR was 29% (4/14), with 2 CR (0.03 and 0.12 %), 3 PR, and 3 MR. Safety and tolerability were observed, with AEs of grade 3 or 4 occurring in 21% of patients (21/114). Most frequent AEs (any grade) were asthenia (70%), peripheral edema (44%) and nausea (27%). Conclusions: PF-566 in combination with rituximab was well tolerated, with anti-tumor activity in R-refractory NHL patients, along with biomarker modulation consistent with 4-1BB agonist activity. In these R-refractory patients, the durability of anti-tumor activity appeared greater than their previous therapy. Further clinical studies of this combination in R-refractory indolent NHL patients are warranted. Clinical trial information: NCT01307267.

Immunotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells of defined subset composition. First Author: Cameron John Turtle, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Genetically modified T cells derived from distinct T cell subsets differ in the capacity to persist after adoptive transfer. We are conducting the first phase I/II clinical trial in which patients (pts) with CD19+ B cell malignancies receive T cells comprised of a defined composition of CD8+ TCM and CD4+ T cells engineered to express a CD19 CAR. Methods: CD8+ TCM and CD4+ T cells were separately enriched from each pts peripheral blood mononuclear cell (PBMC) and were generated into CAR T cells. The cell product for infusion was formulated in a 1:1 ratio of CD8+CAR T cells and infused at one of three dose levels (2x105 – 2x107 CAR-T cells/kg) after lymphodepleting chemotherapy. Results: Thirty-seven pts with ALL (n = 20), NHL (n = 14) or CLL (n = 3) have been treated and 33/37 received a product that conformed to a prescribed CD8+CAR T composition. There was no serious acute infusion toxicity. Severe cytokine release syndrome (sCRS) consisting of fever, hypotension, coagulopathy and neurotoxicity associated with elevated serum IFN-γ and IL-6 was only observed in ALL pts with high tumor burden. One ALL patient treated with the highest dose level developed complications associated with a CRS. No NHL or CLL pts had sCRS. Eighteen of 20 ALL pts were evaluated for response, with 15 (83%) achieving complete marrow remission by high resolution flow cytometry. Clinical responses in NHL included complete (n = 1) or partial (n = 6) remission in 7/13 pts. Two of 3 CLL pts achieved minimal residual disease by flow cytometry. Twenty-three of 34 pts had clinical persistence of both CD4+ CAR T cells and CD8+ CAR T cells were associated with clinical response. We are investigating the impact of distinct lymphodepletion regimens on CAR-T cell proliferation and persistence in vivo. A T cell immune response to the murine CD19-specific scFv component of the CAR transgene was detected in a subset of pts with limited CAR-T cell persistence. Conclusions: Adoptive immunotherapy with CD19 CAR-T cells of defined subset composition is feasible and safe in a majority of heavily pretreated pts with refractory B cell malignancies and has potent anti-tumor activity at low cell doses. CAR-T cell doses for phase II studies in ALL and NHL cohorts have been determined. Clinical trial information: NCT01865617.

Safety and antitumor activity of chimeric antigen receptor modified T cells in patients with chemotherapy refractory metastatic pancreatic cancer. First Author: Gregory Lawrence Beatty, Hosp of the Univ of Pennsylvania, Philadelphia, PA

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by an immunosuppressive microenvironment with a scarcity of effector T cells. Adoptive T cell therapy to restore anti-tumor immunity has demonstrated promise in several advanced malignancies. However, its role in PDAC remains to be established. This Phase I study was performed to determine the safety and feasibility of administering autologous T cells genetically modified with a chimeric antigen receptor (CAR) that recognizes mesothelin (MSTN) overexpressed on PDAC. Methods: Patients (ECOG 0-1; adequate organ function) with chemotherapy refractory metastatic PDAC (> 1 prior chemotherapy) were treated with autologous T cells engineered using a retroviro transcribed mRNA to transiently express a mesothelin-specific CAR that includes both CD3-zeta and 4-IBB co-stimulatory domains. CAR T cells were infused 3 times per week for 3 weeks. The primary endpoint was to determine safety and manufacturing feasibility. Secondary endpoints were to measure clinical and immune responses. Results: 10 patients were evaluated (6 treated, 2 withdrew due to progressive disease prior to treatment, 1 manufacturing failure, 1 did not complete apheresis necessary for manufacturing). 53 of 54 (98%) planned CAR T cell infusions were administered without dose limiting toxicity. Infusions were well tolerated without evidence of cytokine release syndrome, pleuroperticiditis or peritonitis. Treatment related adverse events > grade 3 included; 2 hematological (1) and 1 back pain (1). CAR T cells were transiently detected in the peripheral blood after infusion. Two of six patients experienced stable disease by RECIST 1.1 with disease control off therapy seen in one patient for > 4 months. The change in SUVmax of all lesions for each patient detected on 18FDG-PET/CT imaging performed before and 1 month after beginning treatment was -1.9% (95% CI: -25.5% to 21.7%). In one patient, abnormal 18FDG avidity seen in liver metastases at baseline was no longer detected at 1 month after therapy. Conclusions: Mesothelin-redirected CAR T cell therapy is well tolerated and shows preliminary evidence of antitumor efficacy in PDAC. Clinical trial information: NCT01897415.
**Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): Data from the KEYNOTE-029 phase 1 study.**

**First Author:** Michael B. Atkins, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC

**Background:** Pembrolizumab is a potent, highly selective, humanized monoclonal antibody against PD-1 that has shown robust antitumor activity against several advanced malignancies. In phase 1 testing, combination therapy with the anti–PD-L1 monoclonal antibody nivolumab (NIVO) was being studied. Pembrolizumab and low-dose IPI (3 mg/kg) was being studied. Pembrolizumab plus IPI was being studied. Pembrolizumab was being studied. Pembrolizumab plus IPI was being studied. Pembrolizumab plus IPI was being studied. Pembrolizumab was being studied. Pembrolizumab and low-dose IPI were being studied. Pembrolizumab and low-dose IPI were being studied. Pembrolizumab and low-dose IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied. Pembrolizumab and low-dose IPI plus IPI were being studied.
Efficacy based on tumor PD-L1 expression in KEYNOTE-002, a randomized comparison of pembrolizumab (pembro; MK-3475) versus chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) advanced melanoma (MEL). First Author: Igor Puzanov, Vanderbilt University Medical Center, Nashville, TN

**Background:** Pembrol is an anti-PD-1 antibody approved for treating advanced MEL that progressed following IPI and, if BRAF(V600) mutant, a BRAF inhibitor. In KEYNOTE-002 (NCT01704287), pembrol dosages of 2 mg/kg and 10 mg/kg every 3 wk (Q3W) significantly improved PFS compared with investigator-choice chemotherapy in IPI-R MEL (ORR 26% vs. 13%; P = .0001). We also observed a trend toward improved OS with pembrol (HR = 0.75; 95% CI: 0.59–0.96), with no difference between pembrol doses (P = .44). Data from KEYNOTE-001 showed that PD-L1 positivity was correlated with a higher ORR and longer PFS in MEL pts. We evaluated efficacy of pembrol and PD-L1 in KEYNOTE-002, with PD-L1 expression evaluated centrally by immunohistochemistry (IHC) using the SP142 assay. In KEYNOTE-002, pembrol-treated pts had higher ORR, PFS, and OS compared with the chemotherapy arm. Pembrol’s safety profile was consistent with previous trials. Pembrol saw a lower rate of infusion-related reactions and a lower incidence of grade 3 and 4 laboratory abnormalities compared with chemotherapy.

**Methods:** Pts were randomized 1:1:1 to pembrol 2 or 10 mg/kg every 3 wk (Q3W) or chemotherapy. PD-L1 expression was assessed centrally by IHC using the SP142 assay. The cut point for positivity was staining in ≥1% of tumor cells. Response was assessed at wk 12 and every 6 wk thereafter (RECIST v1.1, central review). Primary end points were PFS and OS (final analysis at 1.3 years). pembrol 2 mg/kg and 10 mg/kg every 3 wk (Q3W) or chemotherapy. PD-L1 expression was assessed centrally by IHC using the SP142 assay. Pembrol’s safety profile was consistent with previous trials. Pembrol saw a lower rate of infusion-related reactions and a lower incidence of grade 3 and 4 laboratory abnormalities compared with chemotherapy.

**Conclusions:** Pembrol improved efficacy over chemotherapy in both PD-L1 and PD-L1 IPI-R advanced MEL. These data indicate that in IPI-R MEL pts, pembrol therapy should not be limited to pts with PD-L1 positive tumors. Clinical trial information: NCT01704287.

### Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimunab, a cytotoxic T lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. First Author: Scott Joseph Antonia, Moffitt Cancer Center, Tampa, FL

**Background:** The inhibitory PD-L1 and CTLA-4 pathways control T-cell activation. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to programmed cell death 1 and CD80 with high affinity and selectivity. Tremelimunab (T) is a selective human IgG2 mAb inhibitor of CTLA-4. M and T have demonstrated acceptable tolerability and safety as single agents and T and M block distinct interactions contributing to immunosuppression and the combination may provide greater antitumor activity versus either agent alone.

**Methods:** A Phase I, open-label dose escalation and expansion study (NCT02000947) is assessing the safety/tolerability and antitumor activity of M + T combinations in pts with advanced NSCLC. Results: As of 4/2016, 1,341 pts had been treated during the dose escalation phase (table). An MTD has not yet been defined; the Cohort 5a dose exceeded the MTD in ≥2 dose-limiting toxicities; Grade 3/4 increased AST/ALT, Grade 4 increased hypotension. DNA dose-limiting AE was the most frequent; fatigue (26%), diarrhea (21%), and increased amylase (13%). 31% of pts had ≥1 G3/4 AE. The most frequent = 5% were diarrhea (8%) and colitis (7%). Increasing doses of T with pembrol resulted in no difference in duration of response (DOR) based on PD-L1 expression. There was no prognostic effect in the control arm. Conclusion: MEDI4736 and pembrol improved efficacy over chemotherapy in both PD-L1 and PD-L1 IPI-R advanced MEL. These data indicate that in IPI-R MEL pts, pembrol therapy should not be limited to pts with PD-L1 positive tumors. Clinical trial information: NCT01704287.

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**Background:** The inhibitory PD-L1 and CTLA-4 pathways control T-cell activation. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to programmed cell death 1 and CD80 with high affinity and selectivity. Tremelimunab (T) is a selective human IgG2 mAb inhibitor of CTLA-4. M and T have demonstrated acceptable tolerability and safety as single agents and T and M block distinct interactions contributing to immunosuppression and the combination may provide greater antitumor activity versus either agent alone.

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### Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimunab, a cytotoxic T lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. First Author: Scott Joseph Antonia, Moffitt Cancer Center, Tampa, FL

**Background:** The inhibitory PD-L1 and CTLA-4 pathways control T-cell activation. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to programmed cell death 1 and CD80 with high affinity and selectivity. Tremelimunab (T) is a selective human IgG2 mAb inhibitor of CTLA-4. M and T have demonstrated acceptable tolerability and safety as single agents and T and M block distinct interactions contributing to immunosuppression and the combination may provide greater antitumor activity versus either agent alone.

**Methods:** A Phase I, open-label dose escalation and expansion study (NCT02000947) is assessing the safety/tolerability and antitumor activity of M + T combinations in pts with advanced NSCLC. Results: As of 4/2016, 1,341 pts had been treated during the dose escalation phase (table). An MTD has not yet been defined; the Cohort 5a dose exceeded the MTD in ≥2 dose-limiting toxicities; Grade 3/4 increased AST/ALT, Grade 4 increased hypotension. DNA dose-limiting AE was the most frequent; fatigue (26%), diarrhea (21%), and increased amylase (13%). 31% of pts had ≥1 G3/4 AE. The most frequent = 5% were diarrhea (8%) and colitis (7%). Increasing doses of T with a constant dose of M were associated with greater severity and frequency of AEs. 18% of pts had drug-related AEs leading to discontinuation; the most frequent was colitis (7%). All AEs were manageable with standard therapy, including steroids, except G4 myasthenia gravis in 1 pt in Cohort 5. Of 31 pts with ≥18-week scan, 8 (26%) had partial response (PR) and 11 pts (35%) had stable disease. PRs occurred in 3 of 10 pts with PD-L1-targeted negative conclusions. The combination has a manageable safety profile with evidence of clinical activity, including in PD-L1-negative disease. These data support continued study of the combination; recruitment is ongoing. Clinical trial information: NCT00200094.
In a sub-study, biodistribution was analyzed using PET imaging of $^{89}$Zr-CEA-IL2 at doses of 6 and 30 mg. Results: Of the 11 pts treated at 30 mg, 4 had sequential tumor biopsies evaluable both by IHC and FC. An increase in the median density (IHC) of CD8+ T cells from 62.5 (7–90) [median (range)] to 104.2 (7–255) cells/mm² was observed in 3/4 subjects after the 1st dose. No relevant change in the density of CD4+ T cells was detected. FC analysis confirmed the increase in CD8:CD4 ratio in the same 3/4 patients: from 0.88 (0.57 – 1.24) to 4.54 (0.36 – 7.47). Effects in peripheral blood included strong lymphocyte expansion that was mostly driven by Natural Killer (NK) and CD8+ T cells. Medians and ranges for the 11 pts before and 4 days after dosing were: NK: 168 (range: 52 – 337) vs. 655 (206 – 1569) cells/μL; CD8+: 340 (19 – 464) vs. 831 (78 – 3754) cells/μL. While there was no clear evidence of CEA-mediated tumor accumulation at 6 mg in the first 6 pts, intra-tumoral accumulation of IL-2 was observed in one RCC patient at doses up to 75 mg IL-2/pts at 30 mg. Additional studies are ongoing. Conclusions: Collectively, these data support the concept that reduced affinity of CEA-IL2 for IL2R-alpha together with high-affinity binding to CEA enables tumor targeting. These findings suggest that CEA-IL2 is the first tumor-targeted cytokine, which increases immune infiltration and activates NK and T cells both in the periphery and within tumors. Clinical trial information: NCT02004165.

A phase I study of intratumoral injection of ipilimumab and interleukin-2 in patients with unresectable stage III-IV melanoma. First Author: Randy Christopher Bowen, University of Utah, Salt Lake City, UT

Background: Intratumoral (IT) IL-2 is highly effective and well tolerated, but does not generate systemic immunity or response in untreated lesions. Intravenous (IV) ipilimumab (Ipi) lowers the threshold for T cell activation leading to a durable clinical response in a minority of melanoma patients, but is associated with potentially severe toxicities. Since IL-2 is not tissue distribution, circulating anti-tumor T cells activated by this drug may differ greatly from tumor-infiltrating lymphocytes (TILs) activated by IT Ipi in terms of quantity and quality. Therefore, we hypothesized that a combination of IT IL-2 and IT Ipi would effectively hyperactivate and expand TILs to engender systemic immunity with minimal toxicity. Methods: This was a phase I dose escalation study for Ipi with fixed dose IL-2 in patients with unresectable stage III/IV melanoma and at least one injectable lesion. A single dose (0.5-2.0 mg) in each patient was treated with IL-2 (3 ml) IT TWH x 2 weeks, then BIW x 6 weeks, with escalating doses of Ipi (0.5-6 mg/kg) over 8 weeks for cycles (C)1-8 and 9. Results: No dose limiting toxicity was observed in 11 of 12 evaluable patients. Most common grade 1 toxicities were fatigue, rash, and pruritis. One grade 2 toxicities were grade 2 fatigue. All grade 1 and 2 toxicities resolved after treatment was discontinued. Two patients were evaluable for response by immune-related response criteria: 1 PR (40%) and 6 PD. 1 PD was found to be a CR by PS. All 2 evaluable patients had progression of multiple skin lesions. An increase in the frequency of peripheral total IFN-γ-producing CD8+ T cells was detected in 5/8 absopal responders. Tbet+ and granzyme-B + CD8+ T cells were observed in 4/5 and 3/5 responders tested, respectively. Conclusions: IT injection with the combination of Ipi/IL-2 is well tolerated and generates responses in both injected and non-injected lesions in the majority of patients. We plan to conduct a phase II trial using IT Ipi/IL-2 in conjunction with systemic immunotherapy. Clinical trial information: NCT01672450.

A first-in-human dose escalation study of PEGylated recombinant human IL-10 (AM0010) in advanced solid tumors. First Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Background: PEGylated IL-10 induces the expansion of tumor reactive CD8 T cells both in the periphery and within the tumor. In mice, PEG-IL-10 but not non-PEG-IL-10 induces the rejection of tumors and establishes immunological memory. Primary objectives of this FIH study were to establish safety, tolerability and the MTD of AM0010. Secondary objectives were to assess anti-tumor-activity, pharmacokinetics, immunogenicity and induced immune activation. Methods: Patients with advanced melanoma (4), non-small cell lung cancer (1), renal cell cancer (6), colorectal cancer (16), prostate cancer (1), ovarian cancer (1) and pancreatic cancer (1) were included in each cohort of 6 patients each followed by expansion cohorts. AM0010 was self-administered daily subcutaneously at doses of 1 to 40 μg/kg. PK, anti-drug antibodies and immune responses were monitored. Results: Since November 2013, 33 patients were enrolled in cohorts of 1, 2, 5, 10, 20, and 40 μg/kg. An MTD was not defined through the planned maximally administered dose. Common treatment related adverse events included injection site reaction, rash, fatigue, thrombocytopenia and anemia. Most adverse events were low grade. Eight G3 adverse events were observed including anemia (3), thrombocytopenia (1), rash (1), increased lipase (1), dyslipidemia (1), transaminitis (1). The half-life of AM0010 half-life was observed to be 8 hours. Additional studies are ongoing. Conclusions: AM0010 has a manageable safety profile and leads to sustained systemic immune stimulation. The pharmacodynamic and clinical activity observed support the ongoing monotherapy expansions and future combination development in a variety of advanced malignancies. Clinical trial information: NCT02009449.

Immunogenomics-based development of personalized immunotherapy for lung cancers. First Author: Yataro Daigo, Research Institute, Hospital of Medical Science, The University of Tokyo, Tokyo, Japan

Background: Oncoantigens are oncogenic and high immunogenicity proteins specifically expressed in cancers, and are promising targets for personalized immunotherapy. Methods: We have established a strategy to identify new oncoantigens; i) screening of genes expressed in the majority of 120 lung cancers with DNA microarray covering 27,266 genes, ii) verification of no expression of these genes in normal tissues, iii) validation of the clinicopathological significance of their expression with tissue microarray covering 400 lung cancers, iv) characterization of their role in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, v) screening of the epoR peptide recognized by HLA-A*0201 or A*2402 restricted cytotoxic T lymphocyte (CTL) for clinical trials. Results: We identified dozens of 10-amino-acid peptides from 45 oncoantigens, each of which was a candidate to be presented on the surface of HLA-A*0201 or HLA-A*2402 that induced CTL response. We conducted a phase I study for HLA-A*0201 restricted, advanced non-small cell lung cancer patients who failed to standard therapy, using the combination of three peptides from NYG6, CDDA1, and KF20A mixed with adjuvant once a week. 20 evaluable patients have been enrolled, and this cancer vaccine therapy demonstrated tolerability and had very high immunogenicity to induce antitumor-activity. Conclusions: Our current data of the cancer vaccine therapy with screening of companion diagnostic in immunogenomics approach by analyzing pattern of CTL response, genomic/proteomic profiles of CTLs, cancer tissues and serum, as well as genetic variation of patients and identified various candidate biomarkers detectable in cancer tissues and/or serum. Current data of the cancer vaccine therapy combined with screening of companion diagnostic promises further clinical studies to develop more personalized and effective immunotherapy. Clinical trial information: NCT01069575.
Vaccination of MSI-H colorectal cancer patients with frameshifft peptide antigens: A phase I/IIa clinical trial. 

First Author: Matthias Kloor, University of Heidelberg, Heidelberg, Germany

Background: High level microsatellite instability (MSI-H) occurs in 15% of colorectal cancers as a consequence of DNA mismatch repair deficiency. MSI-H colorectal cancers are characterized by a dense immune cell infiltration. They are characteristic of the inherited HNPCC (hereditary non-polyposis colorectal cancer) or Lynch syndrome, but can also develop sporadically. DNA mismatch repair deficiency causes insertions or deletions of DNA sequence (frameshift) mutations at the microsatellite loci. This leads to the generation of frameshift peptide (FSP) antigens. FSP antigens are attractive targets for vaccination, because they are highly immunogenic shared antigens, which directly result from driver mutations in MSI-H cancers. To evaluate safety and immunological efficacy of FSP vaccination, we have initiated a clinical phase I/IIa vaccination trial (Micoryx). Methods: The protocol comprised 3 cycles of 4 subcutaneous applications of FSP antigens (frameshift variants of the coding microsatellite-containing genes AIM2, HT001, TAF1B) mixed with Montanide ISA-51 VG over a 6 month period. Inclusion criteria were history of colorectal cancer (UICC stage IIC or III) or who received standard chemotherapy. Phase I of the trial evaluated safety and toxicity as the primary endpoint (6 patients), phase Ia addressed the induction of cellular and humoral immune responses (16 patients). Results: No FSP antigen-induced severe adverse events have been reported. Induction of FSP-specific immune responses against one or more FSP antigens was observed in all patients vaccinated per protocol. Few patients had stage IV disease and were evaluable according to RECIST. One heavily pretreated patient with bulky metastases showed a stable disease and stable CEA levels over 7 months under the phase I/IIa vaccination (Micoryx) induction of tumor regressions in two patients (one complete and one partial). The development of immune responses against FSPs is well tolerated and leads to the induction of humoral and cellular immune responses. FSP vaccination represents a promising novel approach for treatment of MSI-H colorectal cancer patients and for tumor prevention in Lynch syndrome, allowing the evaluation of the concept of preventive cancer vaccines in an ideal model scenario of a defined high-risk patient population. Clinical trial information: NCT01461148.

Utility of FDG-PET/CT in lymphoma patients undergoing immunotherapy with autologous CTL019 T-cells. First Author: Nirav Niranjan Shah, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: Molecular imaging with FDG-PET/CT (PET/CT) is an established modality for response assessment in lymphoma patients (pts) undergoing treatment (Tx). However, pts treated with novel immunotherapies may have false positive PET/CT findings due to tumor site inflammation and/or drug side effects. In particular, Tx with CTL019 cells (autologous chimeric antigen receptor modified T-cells redirected at CD90) can be complicated by ‘cytokine release syndrome’ (CRS) due to a severe systemic inflammatory reaction. Infiltration of tumors by activated CTL019 cells may impact radiographic and functional imaging findings. The role of PET/CT in pts treated with CTL019 has not previously been described. Methods: We performed a pilot, single arm, prospective study to explore the utility of early PET/CT in pts with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) undergoing Tx with CTL019 T-cells. Pts had PET/CT prior to CTL019infusion and then early PET/CT (at 1 month [mo] post-Tx). The primary outcome was the amount/change in metabolically active tumor volume (MTV) and FDG uptake. Secondary outcomes included the association of early PET/CT findings with radiographic and clinical outcomes. Pre-Tx and post-Tx images were evaluated with a change in MTV of ≥50% as significant. Results: We enrolled 6 pts (DLBCL 4, FL 2). 5 of 6 had baseline PET/CT with active disease. 4 of 6 pts developed CRS but all resolved symptoms prior to the 1 scan. On the 1 mo PET/CT, 3 had response (CR or PR) and 2 had disease progression (PD). There was 100% correlation of early PET/CT result with 3 month CT response assessment (Table). Development of CRS did not confound PET/CT findings. Conclusions: In DLBCL and FL pts on Tx with CTL019, early PET/CT may predict response to this novel immunotherapy. The development of CRS did not influence image assessment at 1 mo. We plan to include early PET/CT in future CTL019 lymphoma studies to better define its role in this setting.

Phase I, first-in-human trial of LV305 in patients with advanced or metastatic cancer expressing NY-ESO-1. First Author: Neeta Somaiah, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Generation of tumor-specific cytotoxic T cells (CTLs) in vivo is a major goal of cancer immunotherapy. LV305 is a replication-incompetent, integration-deficient, hybrid viral vector based on the ZVex platform designed to target dendritic cells (DC) in vivo via CD209 (DC-SIGN) and induce the full-length expression of the cancer tests antigen, NY-ESO-1, in order to generate and expand anti-cancer CTLs. In preclinical models, LV305 is a potent inducer of CTLs and anti-tumor immunity. In this first-in-human study, the safety, immunogenicity and efficacy of LV305 are being examined in patients (pts) with cancer. Methods: Adults with previously treated, advanced or metastatic melanoma, breast, lung or ovarian cancers expressing the NY-ESO-1 protein by IHC were eligible. Following a 3–3 dose escalation design, 3 pts were enrolled into 4 cohorts to receive 3 or 4 intradermal injections every 3 weeks of 109, 1010 or 1011 vector genomes (vg) per dose. Expansion of up to 53 pts at the 1011 dose is underway. Results: During dose escalation, 12 pts with NY-ESO-1 positive sarcomas were treated. No DLT or SAEs were observed and all related AEs were CTCAE grade 1 or 2. Common AEs were fatigue (58%), injection site reaction (33%), and myalgia (33%). After review by an independent DSMB, the highest dose, 1011 vg, was determined to be safe. Immunogenicity data from the initial 6 pts at the low dose (109 vg) demonstrated increased NY-ESO-1-specific CD8+ and/or CD4 T cells in 3 pts by ELISPOT, tetramer assay of unstimulated blood, and/or TCR sequencing of blood and TILs. Data indicate the induction of T cells to new epitopes and boosting of TIL TCR sequences in blood. Of these initial 6 pts, 4 had a best response of SD (range 12–54 weeks) with 1 pt achieving regression of 13.8%, and 2 had PD. The 6 pts dosed at 1010 and 1011 vg are completing therapy. Conclusions: LV305 demonstrated acceptable safety and was well tolerated in all doses tested. At the lower dose of 1010 vg, 4 of 5 pts showed T cell responses and preliminary evidence of anti-tumor effect. Data from the mid and high dose are pending. These encouraging results will be followed by studies with LV305 (1011 vg) in patients with NY-ESO-1 negative melanoma (protein-TLR4 agonist) and with anti-PD-1 therapy. Clinical trial information: NCT02122861.
3024 Poster Session (Board #350), Sat, 8:00 AM-11:30 AM

Phase I study of MEDI0639 in patients with advanced solid tumors. First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HEDNOONE, Denver, CO

Background: MEDI0639 is an investigational monoclonal antibody that selectively binds to Delta-like ligand 4 (DLL4) and blocks its ability to bind to and activate signaling through the Notch receptors, potentially inhibiting tumor growth by multiple mechanisms. Methods: This study (NCT01577745) included patients (pts) with advanced solid tumors who had ECOG performance status 0–1 and adequate organ function. MEDI0639 10–200 mg was given every 21 days with a 3–3 dose-escalation design. Primary objective was to determine maximum tolerated dose (MTD) and safety. Other objectives included pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity (IG), and antitumor activity. Results: As of Jan 7, 2015, 20 pts were enrolled (median age 61 y [range 40–83 y], median number of prior therapies: 5). The most common tumors were colorectal (n = 5), small cell lung cancer (n = 4), and melanoma (n = 4). No dose-limiting toxicities were identified through the 150 mg dose; the 200 mg dose is currently being evaluated. Of 20 safety-evaluable pts, the most common treatment-related adverse events (trAEs) were increased aspartate aminotransferase, increased brain natriuretic peptide (BNP), and fatigue (n = 3 each). Grade 3/4 trAEs were observed in 3 pts (acute myocardial infarction [AMI], atrial fibrillation [AF], ventricular dilatation [VD], and ventricular hypokinesia [VH] in 1 pt; lower abdominal pain in 1 pt, and hypertension in 1 pt), and 3 pts had serious trAEs (AMI, AF, VD, VH in 1 pt; diplopia in 1 pt; hemorhagic diarrhea (HD), HD fist, and back pain in 1 pt). One pt discontinued due to a trAE (AMI). The trAEs of interest consistent with the mechanism of action included AMI (n = 1), hypertension (n = 2), increased BNP (n = 3), and HD (n = 1). No treatment-related deaths occurred. Of 19 efficacy evaluable pts, partial response was observed in 1 pt having progressive disease treated for 12 weeks. Preliminary PK was nonlinear at doses <100 mg, and PD showed target engagement at the doses tested. IG has not been observed. Conclusions: MEDI0639 150 mg did not exceed the MTD. Enrollment at the 200 mg dose level is ongoing. The safety profile is consistent with the mechanism of action and appears to be manageable. Preliminary evidence of antitumor activity was observed. Clinical trial information: NCT01577745.

3025 Poster Session (Board #351), Sat, 8:00 AM-11:30 AM

Baseline serum predictors of clinical response to CTLA4 inhibitor therapy in melanoma patients. First Author: Kristian Homsics, University Hospi- tal Zürich, Zürich, Switzerland

Background: A CTLA4 specific antibody (Ipilimumab, Yervoy) has been approved as first line therapy for metastatic melanoma. Despite long-term benefit for a subpopulation (~20%) of patients, the majority will unfortunately not benefit. To date, only VEGFA levels have been suggested as a potential predictive marker in serum. In the current study we set out to identify serum protein marker(s) that could identify patients benefiting from ipilimumab. Methods: We performed a retrospective discovery analysis of serum samples obtained before melanoma patients started Ipilimumab treatment. We selected 5 responder and 5 non-responder patients. Response was evaluated based on the first CT scan (W12) after the first course of Ipilimumab therapy. The protocol was approved by the local IRB. Samples were analyzed for 440 proteins using the RayBio Quantibody Multiplex ELISA platform. Results are being verified in a validation cohort of 12 patients. Results: Out of 440 proteins, 29 showed a statistically significant difference (p < 0.05, two-tailed Student t-test), with 7 proteins upregulated and 22 downregulated in responders. VEGFA levels were not predictive (p = 0.4246). One protein showed the most significant difference and was undetectable in 5 out of 5 responders, while 4 out of 5 non-responders in the discovery cohort had the protein expressed. In this cohort, this protein showed a positive predictive value (PPV) of 83% and also a negative predictive value of 100%. We will also present the ongoing analyzes of 12 additional pretreatment samples as a validation cohort. We generated a 10-protein signature, which we are comparing with the single protein predictor. Multivariate analyzes of markers and clinical parameters are ongoing to confirm that protein B alone or the 10-protein signature is a better predictor of response and survival. Recruitment of additional patients in this transitional protocol is ongoing. Conclusions: The finding that a serum protein or a protein signature predicts clinical response to ipilimumab warrants further validation in larger prospective studies. (The use of protein B and/or the 10-protein signature as predictors to response to anti-CTLA4 therapy is pending patent application).

3026 Poster Session (Board #352), Sat, 8:00 AM-11:30 AM

Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475). First Author: Veena Shankaran, University of Washington, Seattle, WA

Background: Pembrolizumab, an anti-PD-1 monoclonal antibody, has shown antitumor activity in advanced gastric cancers. Hypothesis testing of 4 prespecified multigene immune expression signatures enriched for T-cell mediated interferon signaling and antigen presentation genes was used to evaluate associations with clinical outcomes in patients with gastric cancer enrolled in KEYNOTE-012, a multicohort, phase 1 study of pembrolizumab in patients with PD-L1 melanoma; 7 pts had of 39 disease lasting treated on advanced gastric cancer patients had RNA expression profiling data of immune response (13 gene) and immune response (13 gene). Nominal One-Sided p*

<table>
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*From logistic or Cox regression for ORR and PFS, respectively.

Conclusions: Greater diversity of post-treatment peripheral T-cell repertoire favorably correlates with response to PD-1 inhibition, and differs from the non-specific increase observed with CTLA4 blockade. Of 38 circulating cytokines analyzed, 8 showed treatment induced changes, of which a decrease in FGF-2, MCP1, and IL-8 correlated with response.
3028 Poster Session (Board #354), Sat, 8:00 AM-11:30 AM
Biomarker analysis of patients treated with anti-CD19 chimeric antigen receptor (CAR) T cells. First Author: Adrian Bot, Kite Pharma Inc, Santa Monica, CA

Background: CAR engineered autologous T cell therapy has shown promising efficacy in B cell malignancies in an ongoing phase 1 study (Kochenderfer et al. J Clin Oncol 2014, ASH 2014). Anti-CD19 CAR T cell product characteristics and pharmacodynamic markers from patients in this study were correlated with clinical results. Methods: Patients with relapsed/refractory B cell malignancies received conditioning with fludarabine and cyclophosphamide, then Anti-CD19 CAR T cells engineered with a CAR comprising CD28 and CD3-zeta signaling domains. Product T cells were characterized as such, or upon co-culture with CD19+ tumor cells, by flow cytometry and multiplex cytokine analysis. Pre- and post-CAR T cell infusion peripheral blood mononuclear cells (PBMCs) and sera were also evaluated. Results: To date, 11 anti-CD19 CAR T cell products, and PBMCs and serum samples from 7 patients have been evaluated. Five had an objective response to anti-CD19 CAR T cell treatment. Product T cells comprised central memory, peripheral memory and effector T cells. Upon co-culture with CD19+ tumor cells, these CAR T cells produced 

3029 Poster Session (Board #355), Sat, 8:00 AM-11:30 AM
Immunological long-term follow-up of neuroblastoma stage IV patients after anti-GD2 ch14.18 antibody treatment. First Author: Simone Kayser, University Children’s Hospital, Tübingen, Germany

Background: Neuroblastoma stage IV is associated with low cure rates. Treatment with the GD2 antibody ch14.18 could improve the long-term overall survival. Apart from GD2 other tumor antigens (TA) are expressed in neuroblastoma and studies implicated that T-cell responses to TA are associated with a better outcome. For the present study we analyzed the immune response in long term neuroblastoma survivors treated with anti-GD2 ch14.18. Methods: Blood and serum of 17 neuroblastoma long-term survivors after GD2 therapy with > 5 years follow up (patients group) and 17 age and gender matched healthy donors (control group) were analyzed. Serum was analyzed for antibodies binding to neuroblastoma cell lines and antibodies to a nominal antigen GD2. T cells were stimulated with overlapping peptides of the tumor antigens (TA) NY-ESO-1, WT-1, Survivin, MAGE-A1 and two mimotope peptides to GD2 for 10 days and analyzed for IFN-γ secretion in flow cytometry. Results: T-cell responses to at least one TA could be found in 82% of healthy and in 93% of patients with no significant difference in the number of TA responders between the two groups to any of these TA (Fisher’s exact test). In contrast, T-cell responses to at least one of the GD2 mimotopes were found in 53% of neuroblastoma survivors but in 0% of healthy donors. Moreover, even priming with GD2 mimotope loaded dendritic cells did not induce a T-cell response in healthy donor cells. No differences between patient and control group could be detected in binding of antibodies to neuroblastoma cell lines and no GD2-specific antibodies were detected in patients and controls. Conclusions: Survivors of neuroblastoma treated with anti-GD2 ch14.18 demonstrated robust T-cell responses to neuroblastoma associated TA that was comparable to healthy donors. This could enable patients to attack minimal residual disease efficiently. Moreover more than half of the patients had T-cell responses to GD2 which could be an effect of the GD2 antibody therapy. Our results show that involvement of the cellular immune system might have an impact on the better outcome of this treatment in stage IV neuroblastoma patients.

3030 Poster Session (Board #356), Sat, 8:00 AM-11:30 AM
Association of epithelial-mesenchymal transition with an immunosuppressive, inflammatory tumor microenvironment with elevated levels of checkpoint inhibitors in lung adenocarcinoma. First Author: Yanyan Lou, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Promising results in the treatment of NSCLC have been seen in vivo mouse models were analyzed. Methods: Detailed biomarker analysis from patients treated with anti-CD19 CAR T cells, may provide insight to clinical outcomes and guide the design of T-cell therapies.

3031 Poster Session (Board #357), Sat, 8:00 AM-11:30 AM
Exploratory analysis of clinical and translational factors associated with the inflamed phenotype in HNSCC. First Author: Narendiran Rajasekaran, Center for Clinical Sciences Research Stanford, Stanford, CA

Background: Immunotherapy with PD-1/PD-L1 axis blockade shows encouraging activity in head and neck squamous cell carcinoma (HNSCC). T-cell inflammation and gamma interferon driven gene expression patterns delineate a group of tumors that are most likely to benefit from anti-PD-1 therapy (Seiwert ASCO 2015, Keck CCR 2015). We examined two large, genetically annotated cohorts (TCGA & CHGC) in order to identify putative clinical and translational biomarkers that may predict benefit from anti-PD-1/anti-PD-L1 therapy in patients with HNSCC. Methods: 424 HNSCC tumors from the TCGA cohort were used to calculate a continuous score for tumor inflammation/inflamed mesenchymal phenotype (Keck CCR 2015). Respective scores were then correlated with available clinical, and translational characteristics. We used a second cohort, the Chicago Head and Neck Cancer Genomics cohort (CHGC) N = 132 for validation. In particular we focused on HPV status, tobacco use, anatomic site, stage, gender, race, and mutational burden for discovery of novel biomarkers/associations for HNSCC immunotherapy. Results: HPV status was moderately associated with inflamed phenotype in both cohorts (58/65) of HPV-positive tumors showed a high degree of inflammation, which only 30%/34% of HPV-negative tumors showed this. Smoking status, race, gender, anatomic site (controlling for HPV status), and stage did not correlate with the inflamed phenotype. The highest mutational burdens were seen in inflamed tumors, however correlation was weak. Conclusions: "Inflamed phenotype" is a candidate predictive biomarker of clinical benefit from anti-PD-1 treatment and HPV status correlates with inflamed phenotype. In this study none of the other examined clinical or pathologic features including mutational burden demonstrated predictive characteristics of a therapeutic biomarker to PD-1/PD-L1 blockade.
Background: Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer. Most patients exhibit clinically detectable metastases at diagnosis and have an extremely poor prognosis despite combined modality therapy. HuD-antigen is a neuronal RNA-binding protein that is expressed in 100% of SCLC tumor cells. High levels of circulating anti-HuD antibodies in patients appear to be linked to spontaneous remission of their SCLC. This suggests that the HuD-antigen might be a potential molecular target for SCLC immunotherapeutic treatment. Methods: We constructed a new antibody-toxin compound (BW-2) comprised of mouse-anti-human-HuD mAb bound to saporin and tested the compound in vivo in the NCI-H69 SCLC cell line. In vivo SCLC experiments utilized male athymic nude mice (NC/Nim) xenografted with NCI-H69 cells. Tumor xenografted mice received a single intravenous or intratumoral injection of BW-2, while control tumor xenografted mice were treated with either anti-HuD antibody or saporin alone. Normal C57BL/6 mice were used to test for potential neurological side effects from BW-2. Results: In vitro experiments showed a high level of HuD+ tumor cell specific cytotoxicity in the presence of BW-2 immunotoxin and minimal HuD- cell cytotoxicity only at much higher concentrations of BW-2. Immunotoxin therapy in a nude mouse model of human SCLC demonstrated clear tumor shrinking while control tumor xenografted mice demonstrated rapid tumor volume expansion. Tumor volume in immunotoxin treated mice regressed for several weeks. Neurological testing revealed no manifestations of neurological disease in normal C57BL/6 mice even at doses of BW-2 as high as 10mg/kg. Conclusions: Our findings demonstrate in vitro and in vivo effectiveness of anti-HuD immunotoxin therapy for HuD+ SCLC. This approach to tumor antigen specific immunotherapeutic targeting may one day provide an additional treatment for SCLC.
Antibody dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody, avelumab (MSB0010718C), on human tumor cells. First Author: Kweong-Yok Tsang, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MD

**Background:** The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. In addition to disruption of immune suppressive signaling induced by the binding of PD-L1 on tumor cells with PD-1 on tumor infiltrating immune cells, avelumab was designed to mediate antibody dependent cellular cytotoxicity (ADCC). Other anti-PD-1/anti-PD-L1 monoclonal antibodies (mAbs) undergoing clinical evaluation are either of the IgG1 isotype and modified to remove ADCC activity or of the IgG4 isotype, which does not mediate ADCC. We present data from preclinical studies examining the ability of avelumab to induce ADCC and factors affecting tumor cell sensitivity to this mechanism. **Methods:** The ability of avelumab to induce lysis of human carcinoma cells was assessed using whole peripheral blood mononuclear cells (PBMCs) or purified natural killer (NK) cells as effectors. PD-L1 expression was reweighed as % positive tumor cells and mean fluorescence intensity (MFI) as determined by flow cytometry. **Results:** Using PBMCs as effectors, avelumab induced ADCC in 8/18 human carcinoma cell lines; tumor cell lysis positively correlated with the percentage of PD-L1 positive tumor cells and PD-L1 MFI. Lysis was induced in 14/18 when NK cells were used as effectors. Eight of these lines with IFN-γ increased PD-L1 expression, but augmented lysis in only 4/10 cell lines. Reactivating NK cells with IL-12, however, increased lysis, suggesting a potential for synergy by combining avelumab with IL-12-based therapy. Little or no lysis was observed in NK-mediated ADCC assays vs whole PBMCs or dendritic cells isolated from PBMCs. A tumor cell line insensitive to lysis by CD8+ T cells was lysed by ADCC using NK cells and avelumab. **Conclusions:** Avelumab induced lysis of many human tumor cell lines via ADCC. Further clinical trials are necessary to determine whether the additional mechanism of inducing tumor lysis by ADCC will result in enhanced clinical activity compared with similar agents without ADCC activity.

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3040 Poster Session (Board #366), Sat, 8:00 AM-11:30 AM

Strategies for clinical development of monoclonal antibodies beyond first-in-man trials: Tested doses and rationale for dose selection.

First Author: Marie Vinches, Institut Régional du Cancer de Montpellier - Val d’Aurelie, Montpellier, France

Background: We conducted a comprehensive survey (J. Clin. Oncol., in press) on the design, implementation and outcome of first-in-human trials (FIHT) of monoclonal antibodies (mAbs) over the last decade. We showed that, due to the limited observed toxicity, the maximum tolerated dose was often unclear in published papers, a fact that represents a weakness in the description of these studies.

Methods: We searched the literature for first-in-human trials (FIHT) of mAbs whose FIHT was published between April 1, 2003 and April 1, 2013. For each mAb, we examined the tested doses in these non-FIHT trials (NFIHT) with respect to the choice of the FIHT dosing regimen and the rationale for dose selection in NFIHT.

Results: Sixty-nine NFIHT of 36 mAbs were selected for analysis, of which 30 were phase I, 37 phase II and 2 phase III trials. For each mAb, the number of trials ranged from 1 to 8. In phase I NFIHT, the maximum administered dose (MAD) coincided with the FIHT MAD for the tested mAb in 12 cases (40%), and the ratio between the NFIHT and FIHT MAD ranged from 0.28 to 2. An RP2D was indicated in only 14 phase I NFIHT (47%) and coincided with the FIHT RP2D or MAD for the tested mAb in 2 and 8 trials, respectively. The ratio between the phase I NFIHT RP2D and the FIHT RP2D or MAD ranged from 0.33 to 2 and from 0.28 to 2, respectively. While a FIHT RP2D was available for the tested mAB in 22 phase II-III NFIHT (56%), the dose actually administered was the FIHT RP2D in only 11 trials (28%) and the FIHT MAD in 12 other trials (31%). In the 16 phase II-III NFIHT (41%) in which the tested dose was different from FIHT RP2D or MAD, a rationale for dose selection was indicated in few cases, reporting former pharmacokinetics data (4 trials) for safety issues (1 trial).

Conclusions: The RP2D and the MAD determined in FIHT is infrequently used in the subsequent clinical development of mAbs. The rationale beyond dose selection in phase II and III trials of mAbs is often unclear in published papers, a fact that represents a weakness in the description of these studies.

3041 Poster Session (Board #367), Sat, 8:00 AM-11:30 AM

Adoptive immunotherapy of acute myeloid leukemia (AML) with allogeneic CAR T-cells targeting CD123.

First Author: Roman Galetto, University Medical Center, Maywood, IL

Background: Studies in adoptive T-cell transfer have suggested that persistence of the transduced T-cells is central to the viability of this therapeutic option. The objectives of this phase I clinical trial using TCR TIL 1383I transduced T-cells in stage IV melanoma patients include measuring of persistence and monitoring the behavior of tumor-reactive T-cells in vivo.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from three melanoma patients, activated with anti-CD3 with rHIL2 and rHLI5, transduced with lentivirus encoding the TIL 1383I TCR, and expanded to treatment numbers. The transduced cells were suspended in 5% human albumin and infused over 30 minutes. The infusion was preceded by lymphodepletion with fludarabine and cyclophosphamide and followed with low dose IL-2 for one week. A modified CD34 cassette in the vector enabled monitoring of the transduced T-cells in the patient’s PBMC post-infusion. PBMCs were collected from patients on days 1, 3, 5, 7, 14, 25 and monthly up to 3 months and then every 1-3 months as clinically indicated. The presence of transduced T-cells at each time point was measured by staining with anti-CD34 mAb and analyzed using a BD LSRForteza flow cytometer. Results: Transduced T-cells were detected in the blood of all three patients post-infusion. Clinical activity was demonstrated in two patients – one in the form of tumor shrinkage and another with development of progressive vitiilgo.

Conclusions: Previous studies with TIL suggest better T-cell engraftment, persistence, and therapeutic efficacy with homeostatic proliferation after lymphodepletion. Out results confirm that the infused TIL 1383I TCR transduced T-cells could be detected up to 6 months after infusion and demonstrate activity. Clinical trial information: NCT01586403.
3044 Poster Session (Board #370), Sat, 8:00 AM-11:30 AM
Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with metastatic or locally advanced solid tumors: assessment of safety and tolerability in a phase I expansion study. First author: Kenji Kikutani, University of Chicago, Chicago, IL
Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. The primary objective of this phase I, open-label, parallel-group expansion study (NCT01772004) was to assess the safety and tolerability of avelumab in patients (pts) with metastatic or locally advanced solid tumors. Methods: Pts with advanced or metastatic disease (including NSCLC, gastric, ovarian, breast, and melanoma; ECOG PS 0-3) were treated with avelumab at 10 mg/kg Q2W until confirmed complete response (CR), progression, unacceptable toxicity, or withdrawal. Adverse events (AEs) were evaluated by CTCAE v4.0. Results: In total, 480 pts treated with avelumab were followed-up for at least 4 weeks (wks) by Nov 5, 2014 and assessed in this interim analysis (median age, 60 years [range 29-85]; ECOG PS 0 [40.6%], 1 [59.0%], 3 [0.2%], or unknown [0.2%]; median of 2 prior treatments [range 1–4]). Drug-related treatment-emergent AEs (TEAEs; all grades) occurred in 68.8% of pts, with the most frequent being fatigue (20.2%), nausea (12.9%), infusion-related reaction (IRR) (9.8%), diarrhea (6.9%), chills (6.9%), decreased appetite (6.3%), pyrexia (5.6%), influenza-like illness (5.2%), and arthralgia (5.0%). Drug-related TEAEs that resulted in treatment discontinuation in 34 pts; of these, 8 were due to an IRR. Drug-related grade ≥ 3 TEAEs were reported in 12.3% (n = 59); the most common of these were anemia (5%), fatigue (5%), increased GGT (4), IRR (4), increased lipase (4), and decreased lymphocytes (3). AEs that were potentially immune-related were observed in 11.7% of pts, with the most common being hypothyroidism (4.0%) and pneumonitis (1.5%). Conclusions: Avelumab demonstrated an acceptable safety profile in a heavily pretreated population across a range of tumor types. Development of avelumab as a monootherapy and in combination is ongoing.*Proposed INN. Clinical trial information: NCT01772004.

3046 Poster Session (Board #372), Sat, 8:00 AM-11:30 AM
Effect of denileukin diftitox (DD) on vaccine-induced T-cell responses and depletion of Tregs in melanoma. First Author: Jason John Luke, University of Chicago, Chicago, IL
Background: Depletion of CD25+ Tregs improves anti-tumor immunity in preclinical models. DD is a recombinant fusion protein of hIL-2 and dipheria toxin fragment that also kills CD25+ T cells. Prior clinical trials of DD suggested reduction of FoxP3+ Tregs, improved immune responses, and some clinical responses. We evaluated the effect of DD prior to vaccination in patients (pts) with metastatic melanoma. Methods: Pts were randomized to 4-epitope vaccine (250 mcg of Melan-A gp100, MAGE3 and NY-ESO-1) or GM-CSF 125 mcg emulsified in Montanide alone or after single dose of DD (18 mcg/kg). Vaccine was given every 2 weeks for 3 doses and absent progression continued every 2 weeks. Toxicity was evaluated by CTCAE and response by RECIST. Pts were HLA-A2+ with stage III/IV melanoma. Any prior therapy, standard biochemical parameters and no history of autoimmunity were allowed. Blood and tissue biopsy (when possible) were obtained pretreatment and after 3 vaccinations for immunologic assessments. Results: 17 pts were enrolled (7 receiving DD, 41%). Characteristics included (median) age:63, M:14; ECOG:1; cutaneous: mucusosal (15:2), M status A:B:C% (6:29:65), pretreated 83%. There were no drug-related G3-4 adverse events. 9 pts (4 DD: 5 vaccine only) showed clinical benefit (1 PR, 8 SD). Time to progression was 4.9 months for DD and 4.4 mo for non-DD. Flow cytometry showed that DD did not affect total Tregs in peripheral blood (p = 0.76). ELISPOT assays revealed that in some pts peptide vaccination augments the number of Ag-specific CD8 T cells in the blood but DD did not increase Ag-specific CD8 T cell response. On-treatment biopsy from DD and non-DD treated pts showed no depletion of intratumoral FoxP3+ T cells by RT-PCR. ELISA for IL2R-alpha demonstrated that outcomes were not impacted by soluble CD25 level (p = 0.13). Conclusions: In contrast with previous studies DD did not effectively deplete Tregs, augment T cell responses or improve clinical activity in pts with melanoma. Clinical trial information: NCT00515528.

3047 Poster Session (Board #373), Sat, 8:00 AM-11:30 AM
Safety and tolerability results from a phase I study of MEDI4736, a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib in patients (pts) with non-small-cell lung cancer (NSCLC). First Author: Ben C. Creel, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Background: MEDI4736 is a human IgG1 monoclonal antibody which blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. A Phase I open-label multicenter study was initiated to evaluate MEDI4736 combined with the EGFR tyrosine kinase inhibitor (TKI) gefitinib in NSCLC (NCT012088112). Dose escalation phase data are reported here. Key eligibility criteria included: locally advanced/metastatic NSCLC of any EGFR mutation status, relapsed/refractory/intolerant of standard treatment; ≤ 4 prior therapies. Cohort A received MEDI4736 3 mg/kg (starting dose) every 2 weeks plus gefitinib 250 mg once-daily (QD). If no dose-limiting toxicities were observed, Cohort B received MEDI4736 at a higher dose of 10 mg/kg every two weeks plus gefitinib 250 mg QD. Primary endpoint: safety/tolerability and recommended dose of the MEDI4736 plus gefitinib combination. Secondary endpoints included: tumor response (RECIST 1.1); pharmacokinetics (PK); immunogenicity. Results: Of 10 pts (Cohort A = 3; Cohort B = 7): 4 male; 4 Asian; median age 58.5 years. Maximum tolerated dose was not reached, and no dose limiting toxicities were observed. Adverse events (AEs) were observed in all pts; treatment-related CTC Grade 3-4 AEs in 3 pts led to study discontinuation: dyspepsia/hypoxia (Cohort A; 1 pt), myalgia/fatigue and elevated ALT (Cohort B; 1 pt each). These did not result in any significant change in management guidelines. Two unrelated deaths occurred in Cohort B. No PK interactions were observed nor anti-drug antibodies detected with the drug combination. Of 7 pts with ≥ 1 8-week tumor assessment, 3 pts had reduction in tumor size (Cohort A = 2; Cohort B = 1). Conclusions: MEDI4736 (3 and 10 mg/kg) plus gefitinib was generally well tolerated in pts with NSCLC in the escalation phase, with early clinical activity observed in these heavily pre-treated pts. Preliminary data support continued evaluation of MEDI4736 10 mg/kg with gefitinib 250 mg as the recommended expansion phase dose in pts with EGFR sensitized mutation-positive/TKI naïve NSCLC. Sponsored by MedImmune, global biologics R&D arm of AstraZeneca Clinical trial information: NCT02088112.
2.1-2.5 m) and 21% in arm B (p = 0.4 m PFR in arm A was 2.7 m (95% CI 2.3-3.2 m) and 15% vs 2.3 m (95% CI 0.4-0.8). OS data were not mature at time of final study analysis, since only 35% of MGN1703 patients and 50% of placebo patients had an event. The HR for OS of the whole study population was 0.63 (median 22.6 vs. 15.1 months). The subgroup of patients randomized into the study with confirmed RECIST response had a HR of 0.40 (median 24.5 vs. 15.1 months), suggesting this may be the population with greater benefit. HR for patients with normalized CEA or with activated NKT cells were 0.69 and 0.43, respectively. Based on this evidence, patients with mCRC and objective response after standard induction therapy are randomized in the phase 3 IMPALA study to standard treatment or switch maintenance with MGN1703. CEA and activated NKT cells are stratification factors for the study and will be prospectively assessed.

Conclusions: The pretreatment characteristics predictive of a PFS benefit in the IMPACT study seem to retain their value also in exploratory analyses for OS. This information has been used to design the phase 3 IMPALA study, currently recruiting patients. Clinical trial information: NCT01208194.

**Background:** Immunotherapy may produce durable responses in some patients. IMM-101, a systemic immunomodulator containing heat-killed Mycobacterium bovis (NCI T313665), can be combined with various forms of chemotherapy and has shown survival benefits in cancer patients. Methods: IMM-101, a systemic immunomodulator containing heat-killed M. bovis (Gem) (1000 mg/m² q7d3) (n = 92) benefited most with a significant increase in median OS from 4.4 months in the Gem group (n = 75) to 11.5 months in the IMM-101 group (n = 18). The times corresponding to 25% probability of survival were 7.2 and 11.5 months for the Gem and IMM-101 respective groups. The times corresponding to 25% probability of survival were 7.2 and 11.5 months for the Gem and IMM-101 groups, respectively.

Conclusions: First line IMM-101 with adjunctive chemotheraphy produced significant survival benefits in patients with metastatic cancer. The durable responses seen in a follow-up study to the phase 3 trial were not predicted in advanced pancreatic cancer. Clinical trial information: NCT01303172.
**Effect of human OX40 ligand fusion protein (MEDI6383) on immune cells in the setting of human cancer.**

First Author: Michael D Oberst, MedImmune, Gaithersburg, MD

**Background:** MEDI6383 is a human OX40 ligand fusion protein currently in clinical development for the treatment of advanced solid malignancies. In vitro, this OX40 agonist binds and activates the human OX40 receptor to potently induce activation and proliferation of OX40-expressing human T cells. Given that MEDI6383 binds and signals through human OX40, we hypothesized that the fusion protein would mediate T cell activation in vivo in a non-human primate model.

**Methods:** To test this hypothesis, a PK/PD study was conducted wherein non-human primates were administered MEDI6383, a vehicle control, or an agonist mouse anti-human OX40 monoclonal antibody (mAb). Pharmacodynamic changes in the peripheral blood were measured using flow cytometry-based immunophenotyping.

**Results:** Peripheral CD4 and CD8 memory T cell activation and proliferation were observed after administration of MEDI6383, and differed quantitatively and qualitatively from that following treatment with the OX40 mAb. Likewise, MEDI6383 also induced the proliferation of peripheral B cells, suggesting an effect on T cell-to-B cell crosstalk in vivo. Other pharmacodynamic changes observed with OX40 agonism will also be presented.

**Conclusions:** These findings suggest that MEDI6383 activates both humoral and cellular immune responses, activities that have the potential to boost anti-tumor immunity in the setting of human cancer.

**Targeting the Wnt5a-β-catenin pathway in the melanoma microenvironment to augment checkpoint inhibitor immunotherapy.**

First Author: Brent Allen Hanks, Duke University Medical Center, Durham, NC

**Background:** While checkpoint inhibitor immunotherapy has demonstrated recent success in patients with advanced melanoma, a significant fraction of these patients continue to fail therapy. The β-catenin signaling pathway plays a role in dendritic cell (DC) tolerization and regulatory T cell (Treg) differentiation however the factors responsible for inducing this pathway are unknown.

**Methods:** We utilized a BRAF+/−PTEN+ autochthonous model of melanoma to identify melanoma-derived factors capable of driving local Treg development and the generation of an immunotolerant microenvironment. Primary human melanoma specimens were examined for expression of these candidate factors by immunohistochemistry while sentinel lymph node-derived DCs were analyzed for expression of downstream mediators of the identified signaling pathway. Based on these observations, a small molecule inhibitor of the candidate signaling pathway was tested to augment the anti-tumor immune response of checkpoint inhibitors in a murine melanoma model.

**Results:** We identified the Wnt5a ligand as a critical mediator β-catenin signaling in DCs and of Treg generation in the BRAF+/−PTEN+ model. We further determined Wnt5a to be associated with expression of the Treg marker, FoxP3, in human melanoma tissues and for Wnt5a expression by primary melanomas to be associated with an improved objective response to anti-CTLA-4 antibody therapy. In addition, our work suggests that activation of the β-catenin signaling pathway in sentinel lymph node derived DCs correlates with higher tumor burden and inferior clinical outcome. Finally, we show that suppressing Wnt ligand secretion and downstream signaling by targeting the Porcn acyl transferase enzyme functions to enhance the anti-melanoma immune response and suppress melanoma growth when administered in combination with anti-CTLA-4 antibody therapy.

**Conclusions:** The Wnt5a-β-catenin signaling pathway represents a novel pharmacological target within the melanoma microenvironment that is worthy of further investigation in combination immunotherapy clinical trials.

**Pharmacokinetic profile and receptor occupancy of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in a phase I, open-label, dose escalation trial in patients with advanced solid tumors.**

First Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD

**Background:** The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Reported here is the pharmacokinetic (PK) profile of avelumab and receptor occupancy (RO) from a phase I dose escalation trial (NCT01772004). Previous in vitro experiments spiking anti-PD-L1 into human whole blood samples from healthy donors confirmed that 1 mcg/mL was sufficient for >95% RO. Methods: In this study, dose escalation (3+3 design) was performed for 4 dose levels (DL 1, 3, 10, and 20 mg/kg). PK and RO data was reported. Exploration through prospective studies is needed to determine the optimal sequence of these immunotherapies. Clinical trial information: NCT00869599.

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### 3056 Poster Session (Board #382), Sat, 8:00 AM-11:30 AM

**Human OX40 ligand fusion protein (MEDI6383) as a potent OX40 agonist and immune-modulator in vitro and in vivo.**

**First Author:** Scott A Hammer, MedImmune, Gaithersburg, MD

**Background:** OX40 is a tumor necrosis factor receptor found primarily on activated T effector (Teff) cells and regulatory T (Treg) cells including lymphocytes infiltrating mouse and human tumors. Costimulation of OX40 by agonist molecules is hypothesized to improve antitumor immunity by enhancing Teff cell activity and inhibiting Treg cell suppression. MEDI6383 is a novel, agonist, human OX40 ligand fusion protein currently undergoing early clinical testing for the treatment of advanced solid malignancies. 

**Methods:** Preclinical pharmacological properties of MEDI6383 were assessed using in vitro and in vivo models. Results: MEDI6383 bound specifically and with high affinity to human and monkey OX40 expressed on the cell surface of T cells, and did not bind to OX40 expressed on the cell surface of either rat or mouse T cells. The OX40 signaling pathway was activated by MEDI6383, as measured by NFkB signaling in human OX40-expressing Jurkat T reporter cells. Co-culture of reporter cells with cells that express Fcγ receptors enhanced OX40 signaling, demonstrating that clustering of MEDI6383 by Fcg receptors increased the OX40 intracellular signaling strength and magnitude of response. MEDI6383 enhanced T cell receptor mediated (co-stimulatory) activation of primary human CD4 + T cells as demonstrated by the induction of cell proliferation and cytokine release, and reduced Treg cell suppression in T cell co-cultures. MEDI6383 showed no such activity in the absence of concomitant CD3/CD28 T cell receptor complex signaling. MEDI6383 demonstrated potent in vivo antitumor activity that was dependent on the addition of alloreactive human T cells in a xenograft mouse model of human cancer. Intravenous administration of MEDI6383 to rhesus monkeys in the absence of a defined antigen challenge resulted in the proliferation of both CD4+ and CD8+ T cells in TCR co-selected memory T-cell populations as measured by induction of the cell-proliferation marker Ki67, and by an increase in absolute numbers of these T cell populations. Conclusions: These results demonstrate that MEDI6383 is a potent, soluble agonist of the OX40 pathway that may be utilized to boost anti-tumor immunity in patients with cancer.

### 3057 Poster Session (Board #383), Sat, 8:00 AM-11:30 AM

**Phosphatidylinerine targeting antibody in combination with anti-PD-1 antibody treatment activates infiltrating T lymphocytes of the spleen and tumor microenvironment in pre-clinical models of melanoma and breast cancer.**

**First Author:** Xianming Huang, The University of Texas Southwest, Dallas, TX

**Background:** Despite substantial progress, only a select subset of patients benefit from anti-PD-1/PD-L1 therapies. The underlying cause for these failures of immune checkpoint blockade therapy is the overwhelming, persistent and multifocal immune suppression within the tumor microenvironment. Anti-PD-1/PD-L1 treatement activates infiltrating T lymphocytes of the spleen and tumor microenvironment in pre-clinical models of melanoma and breast cancer. However, despite impressive antitumor responses, immune checkpoint inhibitors are associated with high rates of immune-related adverse events and high rates of resistance. One mechanism of resistance to anti-PD-1/PD-L1 therapy is the overwhelming, persistent and multifocal immune suppression within the tumor microenvironment. Blocking phosphatidylserine is a potential novel immunotherapeutic strategy. Tumor associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells can suppress antitumor immunity. Evidence suggests that phosphatidylserine (PS) is presented on many immune cell subsets including MDSCs and TAMs. The PS-anti-PS interaction involves immune checkpoint receptors and the PS-anti-PS interaction may be a novel target for anti-cancer therapy. Blocking PS-anti-PS interactions might lead to immune reconstitution and immune reactivation. These results suggest anti-PS therapy might be a viable approach to achieve immune reconstitution in patients with metastatic cancer.

**Methods:** A 2-compartment model with linear clearance from the central compartment adequately describes the clinical pharmacokinetics of pembrolizumab (pembro) over the 1-10 mg/kg dose range (Table). No significant differences in efficacy have been observed for pembro 2 and 10 mg/kg Q2W and 10 mg/kg Q2W and Q3W. The PK profile is similar to other monoclonal antibodies, with a low clearance (0.2 L/day), limited central volume of distribution (3.8 L), and to modeled relative variability (22-41%). The effect of age, sex, geographic location, baseline EOCO PS, eGFR, AST, bilirubin, albumin, glucocorticoid coadministration, tumor type and burden, and prior ipilimumab on pembro exposure is limited, as alterations of 20% or less are predicted by the popPK model. Of 268 pts evaluable for ADA, 1 (<1%) developed confirmed treatment-emergent ADA with no impact on efficacy or safety. Conclusions: The pembrolizumab PK model was developed and validated in the NOVA study. The model may be useful for clinical simulations and for dosing and optimized volume distribution, consistent with other monoclonal antibodies. There was no clinically meaningful effect of baseline clinical factors on pembro exposure. Pembro has limited potential to elicit the formation of ADA. Clinical trial information: NCT01295827 and NCT01704287.

**Median (90% prediction interval) PK parameters of pembrol at steady state based on popPK model.**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>2 mg/kg Q2W</th>
<th>10 mg/kg Q2W</th>
<th>10 mg/kg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{adm} (mg/L)</td>
<td>0.03 (3.4; 22.2)</td>
<td>0.10 (5.5; 0.50)</td>
<td>0.10 (4.2; 5.0)</td>
</tr>
<tr>
<td>C_{ss} (mg/L)</td>
<td>1.25 (3.4; 22.2)</td>
<td>3.00 (5.5; 0.50)</td>
<td>3.00 (4.2; 5.0)</td>
</tr>
<tr>
<td>AUC_{ss} (wk)</td>
<td>158.3 (73.3; 273.0)</td>
<td>3685 (943.0; 1373)</td>
<td>10353 (5038; 20137)</td>
</tr>
<tr>
<td>(pg/mL)</td>
<td>10 mg/kg Q2W</td>
<td>10 mg/kg Q2W</td>
<td></td>
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Activation of CD8+ tumor infiltrating lymphocytes by bavituximab in a 3D ex vivo system of lung cancer patients. First Author: Soner Altiok, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Bavituximab is a chimeric monoclonal antibody that targets the membrane phospholipid phosphatidylserine (PS) exposed on endothelial cells and cancer cells in solid tumors. Bavituximab blocks PS-mediated immune suppression in the tumor microenvironment. Methods: Fresh tumor tissues from consented patients with adenocarcinoma of the lung extracted at the time of surgical resection were utilized in a proprietary 3D ex vivo tumor microsphere assay to assess the immunomodulatory effects of bavituximab and potential immunosuppressive mechanisms such as expression of PD-1, CTLA-4, LAG3, TIM3, BTLA, and adenosine A2A receptor on the CD4+ and CD8+ tumor infiltrating T-cells. 3D tumor microspheres were prepared and cells were treated ex vivo with (f(ab')2) version of bavituximab, bavituximab, docetaxel, and a combination of bavituximab and docetaxel for 36 hours within an intact tumor microenvironment. Flow cytometry analysis evaluated treatment-mediated activation of TILs and changes in CD4, CD8, and Treg (CD25+CD127-) subpopulations. A multiplex human cytokine assay was used to simultaneously analyze the differential secretion of cytokines. Additionally, a NanoString platform containing probes to quantitate 770 immune function genes was used to determine potential positive or negative associations between expression of immune function genes and TIL activation by bavituximab. Results: Bavituximab induces activation of TILs in 3D ex vivo tumor microsphere model of lung cancer, as evaluated by a significant increase in IFNγ, TNF-a, and GM-CSF secretion. Flow cytometry analysis revealed that this effect was associated with low PD-1 expression on CD8 cells, but did not correlate with expression of other immune inhibitory molecules. Conclusions: Our preliminary data support the use of bavituximab as an immunomodulatory treatment in non-small cell lung cancer by enhancing the activation of CD8+ TIL that correlates with increased cytokine production by lymphoid and myeloid cells. We identified PD-1 expression as a potential biomarker of response to bavituximab treatment, suggesting that the interruption of the PD-1/PD-L1 axis may enhance the bavituximab effect in lung cancer.

A phase I/Ii study of ipilimumab in women with metastatic or recurrent cervical carcinoma: A study of the Princess Margaret and Chicago N01 Cervix. First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Response to second-line therapy in cervical cancer (CC) is infrequent. Based on evidence of HPV-induced immune evasion, immunotherapy is an attractive strategy in CC. Ipiilimumab (Ipi) is a fully humanized monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4, a molecule that acts to downregulate the T cell immune response. Methods: A multi-center phase I/Ii trial was designed to evaluate Ipi IV in metastatic/recurrent cervical cancer (NCT01693783). Eligibility requirements included measurable disease progression and prior exposure to platinum therapy. A run-in phase I safety cohort was scheduled using Ipi 3mg/kg every 21 days for four cycles in 6 patients (pts). The phase II was planned in 32 pts with Ipi 10mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks for pts demonstrating radiologic response/stabilization. Primary objectives were safety and response rate at the end of cycle 4. Immune correlative studies were performed on peripheral blood pre- and post-Ipi therapy, on archival tissue, on fresh tumor obtained prior to registration and 7 days post cycle 2. Results: From Dec/12 to Sept/14, a total of 42 pts with a median age of 49 (23-78) were enrolled; 29 pts had squamous CC and 13 pts had adenocarcinoma. Thirty five pts had prior radiation completed > 3 months prior to enrolment and 21 pts had received ≥2/3 prior regimens. Toxicities were manageable and Grade 3 toxicities included diarrhea (4 pts) and colitis (3 pts). Best response (RECIST 1.1) for the 34 evaluable pts (2 pts awaiting results) included: 3 PR (1 PR and 2 uPR), 8 SD and 23 PD. The median PFS was 2.5 months (95% CI: 2.3-3.2). HPV testing was positive in 33 tumors. Intratumoral CD3, CD4, CD8, FoxP3, iDO and PD-1 expression pre and post treatment were performed. Phosphatidylserine (PS) exposure on peripheral lymphocytes revealed a treatment dependent increase of ICOS, HLA-DR, CCR4, and PD-1 during initial treatment which returned to baseline during maintenance. Conclusions: Ipi was well tolerated in cervical cancer pts. There is a signal of activity of immunotherapy in cervical cancer. Following Ipi treatment, an immune activation has been observed. Clinical trial information: NCT01693783.
Background: Treatment of B cell malignancies with CAR-modified T cells has shown remarkable efficacy, but clinical responses in solid tumors have been limited due to poor T cell persistence and expansion. We examined whether incorporation of unconventional signaling elements, derived from the “universal” toll-like receptor adaptor molecule, MyD88, and the TNF family member, CD40, into CARs could improve T cell survival, proliferation, and antitumor efficacy. Methods: Bicistronic vectors encoding inducible Caspase-9 (iCasp9) and CD19- or Her2-targeted CARs incorporating various costimulatory domains (e.g., CD28, 4-1BB, MyD88/CD40) were generated and used to transduce T cells. CAR-T cells were assessed for antitumor function in tumor coculture assays using CD19+ (Raji and Daudi) cells or Her2+ (SK-BR-3) tumor cells. Efficacy was monitored in immunodeficient (NSG) mice engrafted with tumor cell lines followed by i.v. CAR-T cell injection. In vivo T cell proliferation, as well as elimination via iCasp9 after i.p. injection of rimiducid, was measured using bioluminescent imaging (BLI). Tumor burden was also assessed by BLI or caliper measurements. Results: All CAR constructs could be stably expressed in T cells (30-90% CAR expression). MC costimulation resulted in greatly increased IL-2 production compared to CARs with alternative costimulation (~2500 pg/mL and ~200 pg/mL for MC and CD28/41BB, respectively). This correlated with enhanced T cell proliferation and corresponded to better tumor elimination in coculture assays (99% elimination at a 1:1 E:T ratio within 14 days). MC costimulation also enhanced the efficacy of tumor elimination in coculture assays (99% elimination at a 1:1 E:T ratio within 14 days). Consequently, MC costimulation resulted in greatly enhanced T cell proliferation and corresponded to better tumor elimination in coculture assays (99% elimination at a 1:1 E:T ratio within 14 days). MC costimulation also enhanced the efficacy of tumor elimination in coculture assays (99% elimination at a 1:1 E:T ratio within 14 days).

Conclusions: MC costimulation increased the efficacy of CAR-T therapy in CD19+ and Her2+ tumor models, respectively, compared to control CARs. Furthermore, T cells transduced with MC-encoding CARs could be rapidly eliminated in vivo (within 1 day) via iCasp9 following rimiducid administration. Conclusions: MyD88/CD40 represents a potent, new T cell costimulatory molecule for CAR-T cells, resulting in robust IL-2 production, improved survival and proliferation, increased antitumor activity against CD19+ and Her2+ tumors in vitro and in vivo, while retaining a high safety profile through the iCasp9 suicide gene.

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Model-based analysis of the relationship between pembrolizumab (MK-3475) exposure and efficacy in patients with advanced or metastatic melanoma. First Author: Richard Wayne Joseph, Mayo Clinic Cancer Center, Jacksonville, FL

Background: Optimization of antibody dosing in oncology drug development is an area of growing interest. We have previously demonstrated that the dose and schedule of pembrolizumab does not correlate with clinical outcomes in melanoma. Here, we assess the relationship between steady state plasma exposure and tumor growth dynamics in patients enrolled in the KEYNOTE-001 and KEYNOTE-002 studies. Methods: Patients received pembrolizumab 2 mg/kg every 3 weeks (Q3W) to 10 mg/kg Q2W or Q3W. Exposure was defined as the area under the serum concentration curve (AUC) over 6 weeks. Results: Response was defined as the change in tumor size per standard rules for measuring target lesions (ie, sum of the longest diameters [LD]). Tumor size was monitored using dynamic tumor size modeling demonstrates a framework for identifying an optimal efficacious dose in oncology. Clinical trial information: NCT01295827 and NCT01704287.

Conclusions: In this initial analysis, we found that reduction in tumor growth was best characterized by an exponential decline, with an estimated halving time of approximately 4 months. The 90th percentile of pembrolizumab exposures ranged from 0.8 to 14 g/L/day. In agreement with the flat dose-efficacy relationship observed per objective response criteria, the observed individual pembrolizumab exposures do not significantly correlate with extent of tumor reduction or overall growth patterns over time. Conclusions: The significant and prolonged reductions in tumor size under pembrolizumab treatment were well characterized by the tumor size dynamics model. Tumor size reductions were independent of a wide (15-fold) range of exposure to pembrolizumab, supporting 2 mg/kg Q3W as an effective dosage that achieves a level of exposure sufficient to saturate tumor response. This examination of a wide exposure range for pembrolizumab treatment using nonlinear mixed effects modeling; specifically, we tested whether individual exposures predict patterns of tumor response. Results: Conclusions: This valuable dataset supports the development of allogeneic CAR T-cells, and UCART19 will be investigated in an exploratory, first-in-human, clinical trial where refractory/refractory CD19+ B-cell leukemia patients are to be enrolled.

3070 Poster Session (Board #396), Sat, 8:00 AM-11:30 AM

Durability and characteristics of objective tumor responses with the innate immune cell modulator Imprime PGG in combination with standard of care frontline treatment for patients (pts) with metastatic non-squamous NSCLC. First Author: Walburga Engel-Riedel, Hospital Cologne-Merheim, Lung clinic, University Witten/Herdecke, Cologne, Germany

Background: Recently, we reported numeric improvements in objective tumor response (OR) and overall survival (16.1 vs 11.6 months median; HR = 0.66) with Imprime PGG (PGG) in a randomized (2:1) phase 2 study in 92 patients (pts) with stage IV non-squamous NSCLC receiving standard of care chemotherapy and bevacizumab (bev) or cetuximab (cet), respectively, was published. Methods: Pts were randomized to bev (n = 59) or cet (n = 33). Following completion of C/P chemotherapy, there was continued reduction of lesions on maintenance treatment with PGG+B but not B alone: 6 pts (20%) in the PGG group vs 0 in the ctrl group had further > 1 cm reductions in target lesions’ sum of longest diameters (SLD) during the study (AE). Imaging assessments (CT of chest and abdomen every 6 wks) were reviewed centrally in an independent blinded manner. Pts were removed from treatment upon disease progression. Results: PGG (vs ctrl) in combination with C/P/B achieved a 60.4% (vs 43.5%) OR rate. Time to OTR was short (12 wks vs > 18 wks) and responses were durable: median duration of response was 10.3 mos vs 5.6 mos (KM), with OTR lasting 12 mos in 7% of pts in the PGG vs ctrl groups. Following completion of C/P chemotherapy, there was continued reduction of lesions on maintenance treatment with PGG+B but not B alone: 6 pts (20%) in the PGG group vs 0 in the ctrl group had further > 1 cm reductions in target lesions’ sum of longest diameters (SLD), incl. 1 CR at 47 wks; this pt remained on treatment 2 yrs post randomization. In the PGG group, OTR were observed regardless of baseline tumor burden (up to > 30cm SLD) or lesion location (incl. lung, lymph nodes, adenals, liver). Change from baseline in target lesions (SLD) over time will be presented for each pt. 1-yr survival was 62.8% vs 42.7% with PGG vs ctrl, and 13 (vs 1) pts remained in survival follow-up at primary analysis. Safety results have been reported previously and were favorable overall. Conclusions: Combined use of chemotherapy, B and PGG mediated rapid and durable responses of metastatic NSCLC regardless of baseline tumor burden or lesion location. There was further regression of lesions on maintenance PGG+B. Innate immune cell modulation with PGG holds promise for pts with metastatic non-squamous NSCLC. Clinical trial information: NCT00874410.

Conclusions: Conclusions: Imprime PGG, a novel innate immune cell modulator, in adults with stage IV non-small cell lung cancer: an integrated analysis of two randomized phase 2 studies. First Author: Folker Schnellner, Polyclinic of the Klinikum rechts der Isar, Technical University Munich, Munich, Germany

Background: Imprime PGG (IPG; beta-1,3/1,6 glucan), a yeast-derived pathogen-associated molecular pattern (PAMP), can prime innate immune effector cells to kill cancer cells opsonized by therapeutic antibodies. In two recent, identically designed phase 2 trials in patients (pts) with stage IV NSCLC, IPG in combination with frontline carboplatin/paclitaxel (C/P) chemotherapy and bevacizumab (bev) or cetuximab (cet), respectively, was associated with numeric increases in objective tumor response rates and survival. This analysis evaluates the safety of IPGG across these studies. Methods: Patient-level data from two identically designed, randomized phase 2 trials of patients (pts) with stage IV NSCLC were combined for safety analyses. Results: A total of 177 pts were enrolled (118 IPGG, 59 Control [Ctrl]) and evaluable for safety. Overall (IPGG vs Ctrl), 99.2% (vs 100%) of pts experienced at least 1 treatment-emergent adverse event (AE) over the course of the study. Grade (Gr) III/IV AEs occurred in 85.6% vs 76.3% of pts in the IPGG vs Ctrl groups, respectively. Most common Gr III/IV AEs (occurring in at least 10% of pts in either arm) included neutropenia (35.6%, 37.3%), leukopenia (10.2%, 16.9%) and thrombocytopenia (11%, 11.9%). Gr III/IV AEs occurring at a ≥ 2% higher frequency in the IPGG arm included nausea (4.2%, 1.7%), abdominal pain (3.4%, 2.0%), fatigue (2.6%, 1.7%), hypotension (2.5%, 0%), polyneuropathy (5.9%, 3.4%) and pleural effusion (2.5%, 0%). Most common Gr III/IV AEs were experienced by 11% vs 3.4% of pts; no event occurred in > 1 pt in either arm, except general physical health deterioration (2.5%, 0%); all fatal AEs were deemed unrelated or unlikely related to IPGG. In the IPGG arm, 72% of pts experienced AEs reported as related to IPGG; of these, 10.2% were considered unlikely related and 61.9% were considered possibly or probably related to IPGG. AEs of specific interest (e.g. infusion-related reactions; immune-mediated AEs) as well as subset analyses by histology will be presented. Conclusions: IPGG was generally well tolerated in pts with stage IV NSCLC receiving C/P chemotherapy and cet or bev therapy frontline. Clinical trial information: NCT00874117 and NCT00874848.
Likewise, SEA-CD40 also stimulated T-cell proliferation and IFN-γ immune checkpoint inhibitors.

Enhanced immune stimulatory activity alone and in combination with a sugar engineered non-fucosylated anti-CD40 antibody, SEA-CD40, with binding to Fc receptor-mediated activity and humanized IgG1 previously developed for B-lineage malignancies. Anti-non-fucosylated SEA-CD40 has a higher affinity for both low (158F) and high expression has been linked to progression and drug resistance. DPX-Survivac vaccine (DPX) contains a mix of survivin HLA class I peptides designed to evoke a cytotoxic T cell response against survivin. This trial reported tumor antigen-specific CD8 cytotoxic T cells that was impaired by Ibrutinib. Similar results were obtained when autologous peripheral blood mononuclear cells were cultured with Ibrutinib and GA101 with anti-CD137 mAb was evaluated in a xenotransplant model of DHL4 lymphoma. Following tumor inoculation, athymic mice received GA101 on day 14 and oral dose of Ibrutinib twice daily and CD137 stimulation that warrants clinical investigation.

Conclusions: DPX-Survivac is well tolerated with proven immunogenicity and preliminary evidence of clinical activity. The Phase II dose phase 2 dose is based on tolerance for localized ISR and immune responses to the primed phase in one indication/maintaining open and open trials in recurrent DBLBCL and OC are planned. Clinical trial information: NCT01416038.

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Background: In a recent phase I immunotherapy (IT) study in 23 women with metastatic breast cancer (MBC), 8 infusions of activated T cells (ATC) armed with anti-CD3 x anti-HER2Bi bispecific antibody (HER2Bi) given in combination with IL-2 and GM-CSF induced specific anti-SK-BR-3 breast cancer (BrCa) cytotoxicity and increased Th1 cytokines and in IL-12 in the serum. This study investigated whether specific cellular and humoral anti-BraCa immunity is induced by infusions of HER2Bi armed T cells (BATs) could be transferred after high dose chemotherapy (HDC) and SCT. This study investigated whether specific cellular and humoral anti-BraCa immunity is induced by infusions of HER2Bi armed T cells (BATs) could be transferred after high dose chemotherapy (HDC) and stem cell transplant (SCT). Methods: BATs were cryopreserved in 8 doses for multiple infusions after the HDC and SCT. Transfer of anti-breast cancer immunity induced by infusions of BATs could be observed in 2 to 4 weeks after vaccination with BATs and cryopreserved for multiple infusions after the HDC and SCT. Results: Six of 8 MBC patients enrolled in the protocol completed the protocol were evaluable for transfer of cellular and humoral immunity. Five of 6 evaluable patients exhibited 2 to 40% CTL activity after vaccination with BATs and 2.5-45% up to 12 months post SCT. Of one of 6 evaluable patients showed poor immune responses and no evidence of transfer. Serum anti-SK-BR-3 IgG levels increased from 1 to 11µg/ml post IT and 1 and 8 µg/ml after SCT. In vitro antibody synthesis showed gradual increases in antibody levels after SCT. Serum cytokine profile changes showed important increases in Th1 cytokines after SCT. IL-2, IL-12, IFN-γ, MIP-1β and IP-10. No dose-limiting events for the infusions, delays in engraftment, and life-threatening infections were observed. In the one patient who rapidly progressed after SCT, CTCL and IFN-γ ELISpot were absent and the serum had high levels of Th1 cytokines. Conclusions: This pilot study suggests that optimal adoptive transfer of cellular and humoral immunity, induced by BAT infusions, by immune anti-breast cancer T cells after SCT accelerates not only immune reconstitution but, more importantly, enhances reconstruction of anti-tumor cellular and humoral immunity after HDC and SCT. Clinical trial information: NCT0002780 and NCT0002722.

An analysis of phase II and III therapeutic cancer vaccine trials and review of the successes and failures behind 10 different vaccine modalities. First Author: Holbrook Edwin Kohrt, Stanford University, Stanford, CA

Background: Between 1996-2014, the FDA approved 175 drugs for the treatment of various indications of oncology and despite the progress that has been made in other forms of cancer therapy, Provenge (sipuleucel-T) is the only therapeutic vaccine that has received FDA approval for the treatment of cancer. To understand the current landscape of therapeutic oncology vaccines, an analysis of cancer vaccines under phase 2 and phase 3 trials was performed. Methods: A search of the terms “vaccine” and “cancer” or “oncology was performed on the clinicaltrials.gov. registry and medtrack. A literature review was also performed to identify factors that have impacted the perceived success or failure of 10 different vaccines. Results: Database analysis of 451 phase 2 and phase 3 therapeutic cancer vaccine trials identified the most targeted indications, vaccine modalities, adjuvant and vaccine-treatment combinations and highlighted the shift in trends between studies completed prior to 2014 and those with completion scheduled after 2014. Despite the lower number of phase 3 compared to phase 2 trials, the registration of phase 3 trials between 2010 and 2014 appeared stable indicating continued investment in the development of immunotherapeutic vaccines at this stage. The review of vaccine trials revealed that patient characteristics (disease stage, HLA-type, MGMT status, antigen signature) and combination treatments had an impact on on vaccine success while the detection of immune responses was found to be important, provided parameters such as tumour antigen expression, breadth and magnitude of the response and correspondence to intra-tumour responses were considered. Conclusions: Identification of factors that can impact on vaccine success and their implementation into study design could ensure vaccine trials are best matched to patients most likely to benefit from the selected mode of vaccination, improving the outlook for both the patient and the development of therapeutic cancer vaccines.

Anti-tumor efficacy and PD-L1 expression in the tumor microenvironment after poxvirus-based active immunotherapy and PD-1 blockade. First Author: Stefanie J Mandl, Bavarian Nordic Inc., Mountain View, CA

Background: Treatment with poxvirus-based active immunotherapies shows evidence of robust immune responses against a variety of tumor-associated antigens in preclinical and clinical studies. These active immunotherapies are in clinical trials to treat tumors expressing PSA (PROSTVAC/Phase 3), CEA and MUC-1 (CV-301/Phase 2), HER-2 (MVA-BN-HER2), and Brachyury (MVA-BN-Brachyury). Because these immunotherapies drive IFN-γ-producing T cells to the tumor, we hypothesized that the tumors would upregulate PD-L1 in an attempt to evade the immune response. Thus, combination treatment of poxvirus-based immunotherapy with PD-1 axis blockade has the potential to yield therapeutic synergy against tumors in preclinical and clinical regimens. Methods: In therapeutic MC38-CEA and CT26-HER2 tumor models, mice were treated with CV-301 or MVA-BN-HER2, respectively, in combination with anti-PD-1 antibody. PD-L1 expression was evaluated in the tumor microenvironment by immunofluorescence and FACS. Results: Poxvirus-based immunotherapies induced activation and trafficking of antigen specific T cells that produce high levels of IFNγ in the tumor microenvironment. TumorPD-L1 expression was upregulated following CV-301 and MVA-BN-HER2 immunization in vivo as measured by immunofluorescence. The PD-L1 expression was significantly elevated on tumor cells (p < 0.01) and infiltrating immune cells (p < 0.05) as measured by FACS. Combining poxvirus-based immunotherapy with PD-1 axis blockade in therapeutic mouse tumor models demonstrated synergistic anti-tumor efficacy. Conclusions: In preclinical studies, CV-301 and MVA-BN-HER2 poxvirus-based immunotherapies drive a robust, tumor-infiltrating T cell response that provokes tumor PD-L1 expression. Synergistic anti-tumor efficacy in mice resulted from combining active immunotherapy with PD-1 immune checkpoint inhibition. The potentiation of active immunotherapy to drive productive antigen specific T cell immunity could provide patients with PD-L1<sub>high</sub> tumors an opportunity to benefit from PD-1/PD-L1 axis blockade when given in combination with poxvirus-based immunotherapies.
Background: Advanced HER2-overexpressing breast cancer eventually develops resistance to standard therapies; however, the HER2 receptor persists and may serve as a target for immunotherapy. We tested an immunization strategy with a novel alphaviral based vaccine encoding the extracellular and transmembrane domains of HER2 (VRP-HER2), alone and in conjunction with standard anti-HER2 agents, in patients with predominantly metastatic treatment refractory HER2-overexpressing breast cancer to determine safety, immunogenicity, and clinical activity. Methods: Cohort 1 (n = 4) enrolled patients not receiving any other anticancer therapy. Cohort 2 (n = 10) enrolled patients receiving either concurrent trastuzumab +/- pertuzumab, TDM-1, or Lapatinib. VRP-HER2 was given at OS x 10^5 viral particles and fludarabine on days 1, +7, and +14 with 75 mg/m^2 fludarabine. Primary endpoints included adverse event rates and tumor response. Secondary endpoints included immune monitoring. Results: VRP-HER2 immunizations were well tolerated in these heavily pre-treated cohorts (median 4.5 prior therapies). There were no dose limiting toxicities or significant decreases in cardiac ejection fraction. Adverse events were predominantly grade 1 and 2, with one grade 3 AE, hypotension, felt not attributable to the VRP-HER2 vaccine. T cell responses specific for HER2 were detected by ELISPOT in patients from cohort 1. The magnitude of the immune response was not altered by prior anti-HER2 therapy. In cohort 1, median PFS was 57 days, median overall survival (OS) was not reached, and median follow-up for OS was 26 months. In cohort 2, median PFS was 58 days, with one partial response and stable disease in two patients, median OS was not reached, and median follow-up for OS was 7 months. Conclusions: VRP-HER2 was safe and immunogenic alone or with concurrent anti-HER2 therapy. Future studies will combine the vaccine in prime boost strategies alone and in combination with other therapies. Clinical trial information: NCT01526473.

Background: Merkel cell polyomavirus (MCPyV) proteins in ~80% of cases, these tumors are able to evade host immunity. MCC is an aggressive skin cancer with suboptimal therapeutic options. Despite persistent expression of Merkel cell polyomavirus (MCPyV) proteins in ~80% of cases, these tumors are able to evade host immunity. G100 is a potent TLR4 agonist, and is capable of directly activating dendritic cells (DCs), T cells, and NK cells. G100 IT studies in other cancers and in combination with anti-PD-1 therapy are planned. Clinical trial information: NCT02035657.

Conclusions: This first-in-human clinical trial found that localized administration of the vaccine in prime boost strategies alone and in combination with other therapies. Clinical trial information: NCT01349569.

Conclusions: This first-in-human clinical trial found that localized administration of the vaccine in prime boost strategies alone and in combination with other therapies. Clinical trial information: NCT01349569.
Background: Clinical studies consistently show how adenosine, unlike other viral agents, can both prime and boost immune responses. Consequently, adenosine is used to develop vaccines against various human diseases, such as cancer. Adenosine can be armed with transgenes for further enhancement of a tumor-specific immune reaction. We present results from a phase I study describing both locoregional immune activation following administration of ONCOS-102, a chimeric oncolytic adenosine, in patients with refractory solid tumors. Methods: A total of 12 patients were treated with up to 9 intratumoral injections of ONCOS-102. Biopsies were collected at baseline, 1 and 2 months after treatment initiation to analyze tumors for the presence of tumor infiltrating lymphocytes (TILs), expression of PD-L1, and gene expression profiles. Peripheral blood mononuclear cells (PBMCs) were collected to assess antigen specificity of CD8+ T cells by IFN-gamma ELISPOT. Results: No dose limiting toxicity was identified. An immediate short-term increase in systemic pro-inflammatory cytokines and an infiltration of innate immune cells into tumors was seen following ONCOS-102. Furthermore, increase in tumor infiltrating CD8+ T cells was seen in 11 out of 12 patients. 10 out of 12 patients showed an increase in PD-L1+ tumor and/or lymphoid cells. Two patients showing the most striking post-treatment increase in TILs showed a systemic induction of tumor-specific CD8+ T cells (MAGE-A3, NY-ESO-1, mesothelin) while none of these tumor-recognizing T cell populations were detected at baseline. These two patients showed high expression levels for genes associated with activated Th1 cells (perforin, granzyme B, granulysin, IFN-gamma) and Th1 type immunoprofiles (IRF-1, X3CL1, CXCL9, OX40L, CCL5, CCL2) in post-treatment biopsies.

Conclusions: Concomitant increase in CD8+ TILs and PD-L1 expressing cells in tumors suggests that local ONCOS-102 treatment is able to break the immunological ignorance towards tumors by activating the immune system in advanced refractory tumours which were immunologically silent before treatment. Clinical trial information: NCT01598129.

TPS3087
Phase I, open-label study of MEDI0680, an anti-programmed cell death-1 (PD-1) antibody, in combination with MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody, in patients with advanced malignancies.

First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA

Background: The PD-1/PD-L1 pathway plays a key role in controlling T-cell activation and may be utilized by tumor cells to evade antitumor responses. The PD-1/PD-L1 pathway inhibition and may be more specific for different tumor groups in ongoing, with a target enrollment of approximately 150 patients across 3 centers in the United States. Clinical trial information: NCT02118337.
First-in-human study assessing safety and tolerability of REGN1979, a novel CD20xCD3 bispecific antibody, in patients with CD20+ B-cell malignancies previously treated with anti-CD20 therapy. REGN1979 has been shown to specifically kill CD20+ B-cells in vitro and has shown potent in vivo anti-tumor activity in several mouse models (established Raji tumors and B16_NCD20XVargahe B et al. ASH 2014. Abstract 4501). In cynomolgus monkeys, REGN1979 at doses > 0.1 mg/kg depleted peripheral and tissue CD20+ B-cells to similar levels achieved with significantly higher doses of rituximab (30 mg/kg). At > 0.1 mg/kg, REGN1979 depleted B-cells in spleen, mesenteric lymph nodes, and thymus to undetectable levels.

Methods: This open label, multicenter, Phase 1, FIH study (NCT02290951) uses a 3+3 dose-escalation design with a 28-day DLT observation period to assess both acute and late toxicity. Each dose level (DL) has an initial dose followed by a second and subsequent higher dose, if the initial dose was tolerated. Patients receive REGN1979 IV weekly during a 4-week induction period at their assigned DL, then monthly for 5 additional doses. There will be parallel independent dose escalation cohorts for patients with NHL and CLL at each DL. After determining the recommended dose for further study, there will be an expansion phase with independent cohorts for patients with indolent NHL, aggressive NHL, and CLL. The primary objective is to assess the safety, tolerability, and DLTs of REGN1979. Secondary objectives include characterization of the PK profile, immunogenicity, and preliminary anti-tumor activity of REGN1979. Enrollment is ongoing. Clinical trial information: NCT02290951.

A phase 1b/2, open-label study to evaluate the safety and tolerability of MEDI6469 in combination with immune therapeutic agents or therapeutic mAbs in patients with selected advanced solid tumors or aggressive B-cell lymphomas. First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC

Background: Anti-CTLA-4 and anti-PD-1/PD-L1 have shown antitumor activity in 10–30% of patients (pts) with select tumors. Combinations of co-stimulatory agonists, such as OX40, and antagonist Abs against the T-cell checkpoints CTLA-4 or PD-L1 could synergize to yield higher response rates. Additionally, nonclinical models show OX40 cell surface expression is induced following activation of NK cells. OX40 ligation promotes enhanced NK cell activity, suggesting greater antitumor activity could be achieved with an OX40 agonist in combination with an anti-CD20 antibody engaging NK cells for antitumor activity. Depleting B cells with rituximab could decrease immunogenicity of murine MEDI6469 by decreasing anti-drug Ab production. MEDI6469, an agonist human OX40 receptor murine mAb, showed clinical activity in a Phase 1 study and is being evaluated as monotherapy and in combination with tremelimumab (anti-CTLA-4) or MEDI4736 (anti-PD-L1) in pts with select advanced solid tumors or DLBCL. MEDI6469 has been shown to specifically kill B-cells in vitro and has shown potent in vivo anti-tumor activity in several mouse models (established Raji tumors and B16_NCD20XVargahe B et al. ASH 2014. Abstract 4501). In cynomolgus monkeys, REGN1979 at doses > 0.1 mg/kg depleted peripheral and tissue CD20+ B-cells to similar levels achieved with significantly higher doses of rituximab (30 mg/kg). At > 0.1 mg/kg, REGN1979 depleted B-cells in spleen, mesenteric lymph nodes, and thymus to undetectable levels.

Methods: This open label, multicenter, Phase 1, FIH study (NCT02290951) uses a 3+3 dose-escalation design with a 28-day DLT observation period to assess both acute and late toxicity. Each dose level (DL) has an initial dose followed by a second and subsequent higher dose, if the initial dose was tolerated. Patients receive REGN1979 IV weekly during a 4-week induction period at their assigned DL, then monthly for 5 additional doses. There will be parallel independent dose escalation cohorts for patients with NHL and CLL at each DL. After determining the recommended dose for further study, there will be an expansion phase with independent cohorts for patients with indolent NHL, aggressive NHL, and CLL. The primary objective is to assess the safety, tolerability, and DLTs of REGN1979. Secondary objectives include characterization of the PK profile, immunogenicity, and preliminary anti-tumor activity of REGN1979. Enrollment is ongoing. Clinical trial information: NCT02290951.
A Phase I study of MEDI6383, an OX40 agonist, in adult patients with select advanced solid tumors. First Author: Todd Michael Bauer, Sarah Cannon Research Institute / Tennessee Oncology, PLLC., Nashville, TN

Background: Enhancing T-cell function in cancer patients (pts) through T-cell co-stimulatory pathways such as OX40 has the potential to overcome cancer-induced immune suppression. MEDI6469, a human OX40 agonist murine antibody, administered for a single cycle in a phase I clinical study showed both an acceptable toxicity profile and regression of ≥1 metastatic lesion in 12 of 30 treated pts(Curti B, et al. Cancer Res 2013;73:7189–98). Humanized OX40 agonists are expected to have reduced immunogenicity relative to murine antibody, which may allow for repeat-dose administration, potentially enhancing biologic and antitumor activity. MEDI6383 is a human OX40 ligand fusion protein that in preclinical models initiates an intracellular signaling cascade to enhance T-cell survival, proliferation of T cells and macrophage lineage cells, and cytokine production. Methods: This is a phase I, multicenter, open-label study of MEDI6383 (NCT02221960) in adult pts with select recurrent or metastatic solid tumors. In the dose-escalation phase, sequential cohorts of pts will receive 1 of 6 dose levels (3+3 design) of MEDI6383 IV every 2 weeks for up to 48 weeks or until PD. Pts who achieve a response and then have PD in follow-up may have 1 round of MEDI6383 retreatment. All pts will be followed for survival through end of study. The primary endpoint is safety and determination of the maximum tolerated dose; secondary endpoints are antitumor activity (objective response and disease control by immune-related RECIST, duration of response, progression-free survival, overall survival, survival, overall survival), pharmacokinetics, immunogenicity, and pharmacodynamics. Enrollment of up to 122 pts (42 pts, dose escalation; 80 pts, dose expansion) is ongoing. Clinical trial information: NCT02221960.

A Phase II multicenter trial to evaluate combination ipilimumab and high-dose IL-2 in patients with unresectable stage III and IV melanoma. First Author: Howard Kaufman, Rush University Medical Center, Chicago, IL

Background: High-dose (HD) IL-2 (600,000 IU/kg) and ipilimumab (3 mg/kg) are approved immunotherapy agents for selected patients with advanced melanoma and both are associated with durable responses in a small number of patients. Previous studies in a pre-clinical melanoma tumor models and in a small phase III dose escalation clinical trial suggested that concurrent combination treatment was associated with improved response rates, including a 17% complete response rate in the clinical trial, without an increase in toxicity. Data has also suggested that higher doses of ipilimumab may improve response rates as shown in clinical trials comparing 3 to 10 mg/kg dosing. To better define the potential benefit of this combination in patients with melanoma, this phase II multicenter, open-label, single arm trial, is being conducted (NCT02203604). Methods: The primary goal of this trial is to determine the clinical OR rate within the first 24 weeks. Secondary end points include safety, feasibility, overall survival, one- and two-year survival, progression-free survival, best overall response, and frequency of effector CD8+ T cells and CD4+FoxP3+ regulatory T cells in peripheral blood, and when possible in the tumor microenvironment. Adults with advanced unresectable stage III and IV melanoma and who meet criteria for high-dose IL-2 therapy are eligible. Main exclusion criteria are active brain metastases, active autoimmune disease, concurrent systemic immunosuppressive therapy as well as prior immunotherapy with IL-2 or ipilimumab. Up to 82 patients will be enrolled and receive ipilimumab (10 mg/kg) for 4 cycles (Days 1, 22, 43, 64) and high-dose IL-2 (600,000 IU/kg) for 2 cycles (Days 22-26, 43-47) followed by maintenance ipilimumab. Preliminary safety assessment will be performed on the first 6 patients, and other patients are not allowed to enter the study. If significant toxicity occurs in the first 6 patients, ipilimumab will be dose reduced to 3 mg/kg. As of Feb 4, 2015 3 patients have been enrolled. Clinical trial information: NCT02203604.

A Phase I study evaluating high dose ADXS11-001 treatment in women with carcinoma of the cervix. First Author: Sharad Ghamande, Georgia Regents Univ, Augusta, GA

Background: This is a phase I, dose-escalation, open-label, single-center study, in subjects with carcinoma of the cervix who have failed conventional therapy. ADXS11-001 is a live attenuated Listeria monocytogenes (Lim)-LLO immunotherapeutics engineered to secrete an antigen-adjuvant fusion protein (fused to HPV16 E7). The primary objective of the study is to evaluate the tolerability and safety of ADXS11-001. Secondary objectives are tumor response, progression-free survival and correlative immunologic studies. Methods: Subject eligibility: Women ≥ 18 years of age with histologically-confirmed, measurable and/or evaluable (defined by RECIST 1.1) persistent, metastatic, or recurrent squamous or adenocarcinoma of the cervix with documented disease progression that is not amenable to surgery or standard radiotherapy. Subjects must have received ≥ 2 prior regimens for treatment of their metastatic disease. Planned sample size is approximately 6-12 subjects. Subjects will receive ADXS11-001 every 3 weeks during a 12-week treatment cycle. Doses will be escalated in the standard 3+3 fashion, in two doses, starting with 5 x 10^9 colony forming units (cfu) to a maximum dose level of 1 x 10^10 cfu. If DLT is seen in one of 3 subjects, another 3 subjects will be treated at that same dose. If DLT is seen in 2 of 6 subjects, then that dose level will be considered maximum tolerated dose (MTD) and the previous dose level will be selected as the recommended phase II dose (RP2D). Blood samples will be evaluated for immunologic effects in cycle 1 only. Treatment cycles can be repeated at the RP2D (or less) for an individual subject until a discontinuation criterion is met, including documented disease progression, intolerable side effects. The end of study will be defined as 1 year after the last subject’s first treatment or until that subject has met a discontinuation criterion. Assessment of the RP2D level may be further explored in an expansion cohort of 15 subjects. Clinical trial information: NCT02164461.
Phase I study of AMG 211/MEDI-565 administered as continuous intravenous infusion for relapsed/refractory gastrointestinal (GI) adenocarcinoma. First Author: Elisabeth de Vries, University Medical Center Groningen, Groningen, Netherlands

Background: The bispecific CD19-directed CD3 T-cell engager (BiTE™) blinatumomab was recently approved by FDA as single-agent immuno-therapy for patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. The clinical activity of blinatumomab seen in 4-week infusion regimen provides rationale for BiTE administration as continuous intravenous infusion (cIV). Experience with an EpCAM-directed BiTE first-in-human study (FIH) suggests that in solid tumor indications dose levels achieving exposure comparable to 50% or even 90% of the maximal effective concentration in in vitro might be needed to observe substantial anti-tumor activity translating into objective response (Fiedler et al. J Clin Oncol 30, 2012, abstr 2504). The CEA-directed BiTE (MEDI-565, AMG 211) inhibited the growth of CEA-expressing cancer cells in various cancer models in the presence of CD3+ T-cells and has been explored as an intermittent 3-hour infusion for 5 subsequent days in a FIH study (NCT01284231). The present study aims at cIV AMG 211 administra- tion that will result in lower Cmax concentrations compared to intermit-tent infusions. The steady state levels with potential effective exposure should range above a threshold level required for anti-tumor activity for a prolonged period of time. The therapeutic index may be improved by reduction of adverse events attributable to a higher Cmax of discontinuous administration but other adverse events due to prolonged exposure will need to be assessed. Methods: Approximately 34 patients with relapsed/ refractory GI adenocarcinomas will be treated with AMG 211 for 7, 14 or 28 days at 200-6,400 µg/day cIV infusion in repeated cycles with 2-week breaks until confirmed disease progression, occurrence of a dose-limiting toxicity (DLT) or discontinuation for other reasons. A two-stage Bayesian interval Bayesian model will guide dose escalation after a first DLT. Study objectives include evaluation of safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy. Cohort 1 has been completed without DLT and cohort 2 started enrollment in January 2015. ClinicalTrials.gov Identifier: NCT02291614 Clinical trial information: NCT02291614.

A phase I study to evaluate the safety and tolerability of MEDI4736, an anti- programmed cell death-ligand-1 (PD-L1) antibody, in combination with temelimumab in patients with advanced solid tumors. First Author: Patrick Alexander Ott, Dana-Farber Cancer Institute, Boston, MA

Background: Programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are regulators or checkpoints of T cell activation, utilized by tumor cells to evade antitumor immune responses. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to PD-1, permitting immune cells to attack tumor cells. MEDI4736 is a non-aggregated td1 mAb inhibitor of CTLA-4. Blocking both of these checkpoints is associated with antitumor effects. The mechanisms for activating PD-1 and CTLA-4 are non-redundant, suggesting the potential for additive or synergistic effects; clinical studies have shown synergistic antitumor activity of anti-PD-1/anti-PD-L1 and anti-CTLA-4 as combination therapy. Methods: An ongoing, phase 1, multicenter, open-label study (NCT01975831) is evaluating the safety/tolerability, pharmacokinetics (PK), immunogenicity and antitumor activity of M in combination with T in patients with advanced solid tumors. The study comprises a dose-escalation phase (3+3 design) and a subsequent dose-expansion phase. Patients with non-small cell lung, cervical, head and neck, colorectal, ovarian cancers, or renal cell carcinoma are eligible. M is administered at escalating doses starting at 0.3 mg/kg (up to 10 mg/kg) every 2 weeks and T is administered at escalating doses starting at 3 mg/kg (up to 10 mg/kg) every 4 weeks for the first 6 cycles, then every 12 weeks. Treatment may continue for up to 1 year if the patient remains progression free and there are no days off treatment in the prior 28 days. If there is progression while on therapy, the patient will be taken to the operative room for planned surgery (within 2 weeks of imaging). Postoperatively, patients will receive off-study standard of care adjuvant gemcitabine (1000mg/kg IV weekly for 3 out of 4 weeks for 6 months). Post operatively resected patients will be followed for up for PFS and OS for up to 2 years. Clinical trial information: NCT02305186.

A randomized multicenter phase Ib/I study to assess the safety and the immunological effect of chemoradiation therapy (CRT) in combination with pembrolizumab (anti-PD-1) alone or in combination with chemotherapy in patients with non-small cell lung cancer or borderline resectable pancreatic cancer. First Author: Matthew H. G. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tumor-infiltrating lymphocytes (TILs) play a major role in anti-tumor immune responses, and their presence is correlated with survival in a variety of tumors. These TILs do not reach the pancreatic cancer (PC) cells in significant numbers due to the presence of stroma and a suppressive microenvironment. One of the leading causes for immune suppression is elevated expression of PD-L1 either by the tumor cells or the surrounding regulatory cells, resulting in dysfunction of TILs. There is recent evidence to suggest that CRT can increase the presence of TILs in the PC microenvironment (PCMe), leading to production of interferon-γ (IFN-γ), which could increase the expression of PD-L1 through a negative feedback loop. Methods: This is a prospective multicenter randomized trial that will accrue subjects with resectable or borderline resectable PC who had not received prior treatment. The primary objectives of the study are: (1) to determine the safety of neoadjuvant CRT in combination with pembrolizumab. (2) To estimate the difference in the number of TILs in PC subjects receiving neoadjuvant CRT in combination with pembrolizumab to the number of TILs in subjects receiving neoadjuvant CRT alone. This study will also investigate the effect of CRT +/- anti-PD-1 on the other effector and suppressive immune cells. Eligible subjects will be randomized 2:1 to CRT (radiotherapy and systemic chemotherapy) or CRT alone. Tumor biopsies will be collected to confirm the diagnosis and to measure TILs. Biopsies will be obtained pre- and post-radiotherapy. The primary endpoint is the number of TILs over time. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and safety. The ACCC-031R trial compared CRT alone to CRT with pembrolizumab in the same population of patients, and showed similar results. We expect to recruit about 320 patients between June 2016 and December 2018. Clinical trial information: NCT02353143 Clinical trial information: NCT02353143.

"ARMY": First-in-human study of the humanized, defucosylated monoclonal antibody (mAb) MEN1112/BOBT357 targeting CD157 antigen, in relapsed or refractory (R/R) acute myeloid leukemia (AML). First Author: Adriano Venditti, Fondazione Policlinico Tor Vergata, Rome, Italy

Background: Defucosylated mAbs enhance antibody dependent cell-mediated cytotoxicity (ADCC) through an improved affinity for Fc receptors. MEN1112/BOBT357 is a humanized, defucosylated mAb targeting Bist1/ CD157, a GPI-anchored transmembrane protein highly expressed on blasts of AML patients either at primary diagnosis or relapse. Preclinical findings show that MEN1112/BOBT357 has the potential to exert powerful ADCC against AML (Aud et al ASH 2014; Venditti et al ASH 2014). Methods: Multi-center, non-randomized, 3 + 3 dose escalation/expansion cohort trial of MEN1112/BOBT357 intended to recruit approximately 50 adult patients (pts) with R/R AML. Refractory pts must have failed ≥ 1 cycle of cytotoxic chemotherapy or hypomethylating agents. A baseline WBC count < 10 x 10^9/L is required (pre-treatment with hydroxyurea is permitted). Main exclusion criteria are acute promyelocytic leukemia, hematopoietic stem cell transplant within 3 months prior to screening and active central nervous system involvement. MEN1112/BOBT357 is given intravenously at 5 incremental doses on Days 1, 8, and 15 in a 21-day cycle for a total of 2 cycles; monthly maintenance is allowed in pts achieving clinical benefit. Primary objective is to identify dose limiting toxicities and maximum tolerated dose of MEN1112/BOBT357 in pts with R/R AML; secondary objectives include (1) clinical pharmacokinetics, (2) potential immunoge- necity, (3) correlation with target expression/saturation, natural killer cells status, ex vivo activity at baseline and clinical/biological AML features. AEs will be graded according to NCI CTCAE v. 4.0 guidelines. Study variables will be presented by dose-cohort and overall using appropriate descriptive statis-tics. Efficacy will be evaluated in each cohort in pts completing the first cycle and with ≥ 1 post-cycle assessment using modified IWG 2003 criteria. The individual study duration is 6 months. The enrollment began on December 2014. Clinical trial information: NCT02353143 Clinical trial information: NCT02353143.

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Phase I expansion cohort trial to investigate the safety and clinical activity of avelumab (MSB0010718C) in patients with metastatic or locally advanced solid tumours. First Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Methods: This is a parallel group expansion trial of avelumab in patients (pts) with selected tumor indications following the determination of dose and regimen in a phase I, open label, dose escalation study. The dose escalation cohort has been completed (n=53). Pts in 11 separate cohorts of advanced solid tumors will receive avelumab at 10 mg/kg, as a 1h infusion, Q2W. Treatment will continue until disease progression, unacceptable toxicity, or if any criterion for withdrawal of investigational medicinal product occurs. In addition to evaluating tolerability, specific objectives for the expansion cohorts include: assessment of best overall response (BOR) and progression-free survival (PFS) according to RECIST 1.1; assessment of immune-related BOR and immune-related PFS using the modified Immune-Related Response Criteria; and assessment of overall survival. Association between tumor PD-L1 expression and efficacy will be evaluated and the PK/PD profile of avelumab characterized. This trial is in progress: recruitment for 2nd-line non-small cell lung cancer (n=184), metastatic breast cancer (n=168), colorectal cancer (n=21), and ovarian cancer (n=75) is complete. Recruitment for gastric/gastroesophageal junction cancer (n=150), melanoma (n=50), castration-resistant prostate cancer (n=20), adrenocortical carcinoma (n=50), mesothelioma (n=50), urothelial carcinoma (n=50), and 1st-line NSCLC (n=150) is ongoing (target enrollment provided for each tumor type). Overall, >700 pts have received avelumab (in current and current expansion cohorts) (start Jan 2013, estimate end Oct 2016). NCT01772004. *Proposed INN. Clinical trial information: NCT01772004.

Phase I/II study of stereotactic body radiation therapy (SBRT) to metastatic lesions in the liver or lung in combination with monoclonal antibody to OX40 in patients with progressive metastatic breast cancer (mBC) after systemic therapy. First Author: Marke Crittenden, Earle A. Chiles Research Institute, Portland, OR

Background: Focal radiation mediates tumor regression not only through direct cell killing, but also by influencing adaptive immune responses. We and others have investigated pre-clinical murine tumor models using the combination of high dose per fraction radiation (SBRT) given in conjunction with T-cell checkpoint and co-stimulatory molecules. For instance, in combination of high dose per fraction radiation (SBRT) given in conjunction with monoclonal antibody to OX40. Secondary objectives include response of circulating CD4+ and CD8+ T cells and proliferation and high risk features. A human-derived affinity-optimized TERT DNA delivered with hTERT significantly enhanced immune responses in preclinical studies. Those achieved by viral vectors; (2) non infectiousness of the immunogen; DNA-based immunotherapy include (1) strong immunogenicity exceeding those achieved by viral vectors; (2) non infectiousness of the immunogen; (3) ability for repeated dosing; and (4) relatively low cost. EP can be used to optimally and safely deliver DNA in vivo by creating a transient electric field to enhance the cellular uptake of large molecules such as DNA. Additional of IL-12 to hTERT significantly enhanced immune responses in preclinical models. We hypothesized that generation of robust T-cell immunity by immunotherapy with hTERT + IL-12 can be clinically used to reduce the risk of relapse in high-risk cancer patients in the adjuvant setting. Methods: This hypothesis is being tested in a phase I clinical trial (NCT01327468) sponsored by Inovio and opened at Abramson Cancer Center of the University of Pennsylvania.INO-1400 is a plasmid encoding hTERT. INO-9012 is a dual promoter plasmid encoding human IL-12 subunits p35 and p40. INO-1400 and INO-9012 are delivered IM followed by EP with the CELLECTRA device. INO-1400 open label dosing study in patients with lung, pancreas, or breast carcinomas at high risk of relapse. Eligible patients must have early stage ER+ or HER2+, or any stage triple negative breast cancer; or Stage IB-IIIA NSCLC; or Stage I-IIIB pancreatic cancer. Patients will enroll ≥ 4 and ≤ 16 weeks from completion of definitive surgery and adjuvant therapy into 1 of 6 cohorts (total N = 54); dose INO-1400 at 2 or 8 mg = INO-9012 at 0.5 or 2 mg, with EP, once every 4 weeks for 4 total treatments. Primary Endpoints: Safety and tolerability. Secondary Endpoints: (1) Time to progression; (2) Antigen-specific T cell response by IFN-γ ELISPOT and flow cytometry; (3) antigen-specific humoral responses by ELISA. Clinical trial information: NCT02327468.

TPS3101 Poster Session (Board #420a), Sat, 8:00 AM-11:30 AM

Genetically engineered NY-ESO-1 specific T cells in HLA-A201+ patients with advanced cancers. First Author: Melinda S. Merchant, Natl Cancer Inst, Bethesda, MD

Background: NY-ESO-1 (CTAG-1B) is a cancer testis antigen associated with spontaneous and vaccine-induced immunity that can lead to improved clinical outcomes. NY-ESO-1 is not expressed in vital tissues, and is expressed in approximately 40% of ovarian, 60% of advanced myeloma, and 70% of synovial sarcoma tumors. Expression is correlated with tumor proliferation and high risk features. A human-derived affinity-optimized TERT DNA delivered with INO-9012 at 0.5 or 2 mg, with EP, once every 4 weeks for 4 total treatments. Primary Endpoints: Safety and tolerability. Secondary Endpoints: (1) Time to progression; (2) Antigen-specific T cell response by IFN-γ ELISPOT and flow cytometry; (3) antigen-specific humoral responses by ELISA. Clinical trial information: NCT02327468.

TPS3102 Poster Session (Board #420b), Sat, 8:00 AM-11:30 AM

Study of hTERT and IL-12 DNA immunotherapy using electroporation in patients with solid tumors after definitive surgery and adjuvant therapy. First Author: Robert H. Vonderheide, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Background: hTERT, the human catalytic reverse transcriptase subunit of telomerase, is highly expressed in breast, lung, and pancreatic cancers. Peptides derived from hTERT can be recognized on MHC by cytotoxic T cells and mediate tumor death. In preclinical studies, TERT DNA delivered with electroporation (EP) triggered an immune response in vivo that slowed tumor growth in HPV16-associated tumor-bearing mice. The advantages of DNA-based immunotherapy include (1) strong immunogenicity exceeding those achieved by viral vectors; (2) non infectiousness of the immunogen; (3) ability for repeated dosing; and (4) relatively low cost. EP can be used to optimally and safely deliver DNA in vivo by creating a transient electric field to enhance the cellular uptake of large molecules such as DNA. Additional of IL-12 to hTERT significantly enhanced immune responses in preclinical models. We hypothesized that generation of robust T-cell immunity by immunotherapy with hTERT + IL-12 can be clinically used to reduce the risk of relapse in high-risk cancer patients in the adjuvant setting. Methods: This hypothesis is being tested in a phase I clinical trial (NCT01327468) sponsored by Inovio and opened at Abramson Cancer Center of the University of Pennsylvania.INO-1400 is a plasmid encoding hTERT. INO-9012 is a dual promoter plasmid encoding human IL-12 subunits p35 and p40. INO-1400 and INO-9012 are delivered IM followed by EP with the CELLECTRA device. INO-1400 open label dosing study in patients with lung, pancreas, or breast carcinomas at high risk of relapse. Eligible patients must have early stage ER+ or HER2+, or any stage triple negative breast cancer; or Stage IB-IIIA NSCLC; or Stage I-IIIB pancreatic cancer. Patients will enroll ≥ 4 and ≤ 16 weeks from completion of definitive surgery and adjuvant therapy into 1 of 6 cohorts (total N = 54); dose INO-1400 at 2 or 8 mg = INO-9012 at 0.5 or 2 mg, with EP, once every 4 weeks for 4 total treatments. Primary Endpoints: Safety and tolerability. Secondary Endpoints: (1) Time to progression; (2) Antigen-specific T cell response by IFN-γ ELISPOT and flow cytometry; (3) antigen-specific humoral responses by ELISA. Clinical trial information: NCT02327468.

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TPS3105
Poster Session (Board #422a), Sat, 8:00 AM-11:30 AM

**In situ vaccine for low-grade lymphoma: Combination of intratumoral Flt3L and poly-ICLC with low-Dose radiotherapy.** First Author: Thomas Urban Marron, Mount Sinai Hospital, New York, NY

**Background:** Lymphomas are the 5th most incident cancer in the U.S. and indolent non-Hodgkin’s lymphoma (iNHL) are incurable with standard therapy. We previously completed three trials of ‘in situ vaccination’ - combining low-dose radiotherapy (XRT) with intratumoral administration of a TLR9 agonist (CpG). We demonstrated induction of tumor-specific CD8 T cell responses and clinical remissions of patients’ untreated sites of disease, lasting up to > 4 years. One limitation may have been the scarcity of intratumoral dendritic cells (DC). DC are uniquely able to endocytose dying (e.g. irradiated) tumor cells for cross-presentation to anti-tumor CD8 T cells. **Methods:** Flt3L– the predominant DC differentiation factor – induces tumor leukocyte infiltration and regression of lymphoma tumors pre-clinically and a new formulation of this cytokine -CDX-301- was shown to mobilize BDCA-1 and BDCA-3 DC subsets in an early phase trial. These DC subsets respond to several TLR agonists and cross-present antigens more effectively than plasmacytoid DC (the CpG-responsive DC subset). We initiated a phase I/I study of a new iteration of the in situ vaccine, adding Flt3L-priming and replacing the prior TLR9 agonist with the TLR3 agonist poly-ICLC (Fig 1A). The vaccine consists of: -intratumoral Flt3L administration to increase DC within the tumor -low-dose XRT to induce immunogenic tumor cell death and release tumor-associated antigens, and -intratumoral poly-ICLC administration to activate tumor antigen-loaded DC. The current study will assess two cohorts of patients (n = 15, each) with either previously untreated or relapsed/refractory INHL to test the hypothesis that in situ vaccination will induce clinical remissions at distant (untreated) tumor sites. Eligibility: INHL, either previously untreated or relapsed/refractory INHL. Treatment: Intratumoral CDX-301 25ug/kg x 9 days. Local radiotherapy 2Gy x 2. Intratumoral poly-ICLC 2mg weekly x 8 weeks. Patients will have tumor (FNA) and blood collected for immune monitoring at weeks 0, 2, 4, 6, 8, 12 as well as pre treatment biopsy. Restaging CT scans will be done pretreatment and at week 12. Clinical trial information: NCT01976585. Clinical trial information: NCT01976585.

TPS3106
Poster Session (Board #422b), Sat, 8:00 AM-11:30 AM

**Phase I study of safety and immunogenicity of ADU-623, a live-attenuated *Listeria monocytogenes* vaccine (LactA/aInIB) expressing EGFRvIII and NY-ESO-1, in patients with WHO grade III/IV astrocytomas.** First Author: Marka Crittenden, Earle A. Chiles Research Institute, Portland, OR

**Background:** The neo-antigen EGFRvIII is expressed in multiple tumor types, including high-grade astrocytomas. It is associated with a poor prognosis and resistance to conventional therapies such as chemotherapy and radiation that are part of the standard treatment. We propose that immunization with a live-attenuated *Listeria*-based vaccine, ADU-623, expressing EGFRvIII and NY-ESO-1 will elicit robust tumor-specific immune responses capable of killing EGFRvIII and/or NY-ESO-1-expressing tumor cells and improve survival of the patients. In addition, ADU-623 induces a potent innate immune response that can kill transformed cells even in the absence of neo-antigens. We designed a translational vaccine study to evaluate the safety and immunogenicity of this vaccine in patients with high-grade astrocytomas after standard of care therapy or at progression. **Methods:** Patients with a pathologic diagnosis of WHO Grade III/IV astrocytic tumors that have completed standard of care external beam radiation therapy and concurrent temozolomide followed by adjuvant temozolomide or with radiographic evidence of progression following standard of care radiation and chemotherapy treatment, including those who have gone on to a second surgical resection are eligible. Patients are enrolled and assigned consecutively to one of the following ADU-623 dose level cohorts: Cohort 1 3x10^7 cfu, Cohort 2 3x10^8 cfu, or Cohort 3 3x10^9 cfu, each administered IV on Days 0, 21, 42 and 63. Adverse events are monitored throughout the treatment and patients are followed for up to 24 months. Patients are currently accruing to Cohort 3. The primary objective is to determine the maximum tolerated dose and characterize the safety profile of ADU-623 in patients with treated and recurrent WHO Grade III/IV astrocytomas. Secondary objectives include progression free survival, time to progression and overall survival rates in patients vaccinated with ADU-623. Exploratory studies of EGFRvIII-, NY-ESO-1-, vector-specific and innate immune responses will be performed. Clinical trial information: NCT01967758.
**Background:** The FOWARC study investigates whether peri-operative mFOLFOX6 chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer. 

**Methods:** Between 01/2011-02/2015, patients with rectal cancer within 12 cm from the anal verge, clinical stage II-III were randomized assigned to receive 5-FU with radiation (RT) (control arm), or receive mFOLFOX6 with RT (FOFOX-RT arm), or receive 4-6 cycles of mFOLFOX6 alone (mFOLFOX arm), post-operative is administered. Clinical staging (ypTNM U-I) was achieved in 34.7%, 57.8%, and 37.9% of patients respectively. Higher toxicity and post-op complications were observed in patients received RT. Similar results were seen in subgroup of patients with lesions located within 5cm from the anal verge. Conclusions: mFOLFOX6 concurrent with RT resulted in higher pCR rate, neoadjuvant mFOLFOX6 alone achieved similar down staging rate with less toxicity and post-op complications, compared to preoperative 5-FU with RT. Clinical trial information: NCT01211210.

**Comparison of Toxicities and Complications**

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicities</th>
<th>Control</th>
<th>FOFOX-RT</th>
<th>FOFOX</th>
<th>mFOLFOX6 alone</th>
<th>mFOLFOX6 plus SIRT</th>
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<tbody>
<tr>
<td>Anastomotic leakage</td>
<td>24.3</td>
<td>18.8</td>
<td>6.3</td>
<td>20</td>
<td>18.4</td>
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<tr>
<td>Leucopenia</td>
<td>34.7</td>
<td>57.8</td>
<td>37.9</td>
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<tr>
<td>Radiation proctitis</td>
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<td>41.3</td>
<td>34.4</td>
<td>20.9</td>
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<tr>
<td>Leucopenia</td>
<td>90.1</td>
<td>88.2</td>
<td>72.2</td>
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<td>74</td>
</tr>
<tr>
<td>Sepsis/Infection</td>
<td>76.5</td>
<td>82.8</td>
<td>86.0</td>
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<tr>
<td>Grade 3/4 Leucopenia</td>
<td>14.8</td>
<td>20.9</td>
<td>7.9</td>
<td>15.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Grade 3/4 Leucopenia</td>
<td>13.6</td>
<td>20.0</td>
<td>17.0</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Grade 3/4 Leukopenia</td>
<td>9.8</td>
<td>13.2</td>
<td>13.1</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Grade 3/4 Infection</td>
<td>24.3</td>
<td>26.6</td>
<td>18.8</td>
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<td>18.8</td>
</tr>
<tr>
<td>Grade 3/4 Infection</td>
<td>25.7</td>
<td>29.9</td>
<td>9.5</td>
<td>30.8</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**Conclusions:** This is the first study that prospectively investigates the efficacy of RFA with systemic treatment in patients with unresectable CRC, and confirms the efficacy of RFA plus systemic treatment in patients with unresectable CRC in the phase II trial, RFA+CT was associated with improved long-term OS compared to CT alone. Clinical trial information: NCT0043004.
Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study. First Author: Simon Baines, The Biotechnology and Centre for Molecular Medicine Norway, Nordic EMBL Partnership, University of Oslo, Oslo, Norway, Oslo, Norway

Background: Regular use of aspirin (acetylsalicylic acid) has been associated with reduced incidence and mortality of colorectal cancer (CRC). However, the use of aspirin as primary prevention in the general population is still being debated due to the risk of serious hemorrhagic side effects. In contrast, the use of aspirin as secondary prevention in patients with CRC may be more justified from a risk-benefit prospective, and also as we have observed that aspirin reverses tumor immune evasion mechanisms in established colorectal cancer. This study was conducted to examine the association between aspirin use after diagnosis of CRC with CRC-specific survival (CSS) and overall survival (OS) in the largest cohort ever reported.

Methods: An observational population-based retrospective cohort study was undertaken by linking patients diagnosed with CRC from 2004 through 2011 (Cancer Registry of Norway) with the use of aspirin in the same patients (The Norwegian Prescription Database). The registries used cover more than 95% of the Norwegian population, and include all cases in an unselected manner. Exposure was defined as having received prescription for more than 6 months of aspirin after diagnosis of CRC. Multivariate Cox proportional hazard and competing risk analyses were used to model survival. The main outcome measures of the study were CSS and OS.

Results: In total, 25,644 patients were diagnosed with CRC in the study period and 6,109 of them were defined as exposed to aspirin after the diagnosis of CRC. The median follow-up was 2.2 years. Among aspirin exposed cases (n = 6,109), a total of 2,088 (34.2%) deaths were recorded of which 1,172 (19.2%) were CRC-specific. Among non-exposed aspirin cases (n = 19,535), a total of 7,595 (38.9%) deaths were recorded of which 6,356 (33.5%) were CRC-specific. In multivariate analysis, aspirin exposure after the diagnosis of CRC was independently associated with improved CSS (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.50-0.57; p<0.001) and OS (HR, 0.71; 95% CI, 0.68-0.75; p<0.001). Conclusions: Exposure to aspirin after the diagnosis of CRC is independently associated with improved CSS and OS.

Analysis of DNA mismatch repair (MMR) and clinical outcome in stage III colon cancers from patients (pts) treated with adjuvant FOLFOX +/- cetuximab. First Author: Aziz Zaanan, Mayo Clinic and Mayo Cancer Center, Rochester, MN

Background: The prognostic impact of deficient (d) MMR, including sporadic and familial types, in stage III colon cancer pts receiving standard adjuvant FOLFOX therapy remains unknown. We examined the association of dMMR status with outcome in a large phase III clinical trial of adjuvant FOLFOX +/- cetuximab. Methods: Prospectively collected tumors from both studies were separately analyzed for MMR protein (MLH1, MSH2, MSH6) expression and mutations in BRAF (V600E). Loss of any MMR protein indicates dMMR. Methylation status of the promoter region of MSH2 was studied in tumors with loss of MLH1 and wild-type (WT) BRAF. Associations of MMR status with time-to-recurrence (TTR), disease-free survival (DFS) and overall survival (OS) were analyzed using a stratified Cox proportional hazards model. Multivariate models were adjusted for treatment and covariates (age, sex, tumor grade, T/N stage, tumor location, EGCG PS, BRAF/KRAS). Results: The frequency of dMMR in the overall colon cohort was 0.7% (499/67,647). 3-year DFS for dMMR vs proficient (p) MMR pts was 75% vs 74% (HR = 0.87; 95% CI, 0.71-1.07; padjusted = 0.19). Among pts with complete biomarker data (N = 4339), there were 405 dMMR tumors of which 265 (65.4%) were categorized as sporadic (BRAF mutation or WT with MLH1 methylation) and 140 (34.6%) as familial (BRAF WT and unmethylated MLH1 or loss of MSH2 or MSH6). DFS rates with clinical and factorial dMMR tumors were in the larger cohort examined was only significantly associated with the CD45RO subset (p = 0.0003). Higher tumor neoantigen load predicted significantly improved CSS-specific and overall survival (p = 0.014 and p = 0.048, respectively).

Conclusions: In the large prospective study of molecularly characterized CRCs, tumor neoantigen load predicts greater tumor-infiltrating lymphocytes and memory T-cell infiltration and represents a novel genomic predictor of CRC survival. Our findings link tumor genomics to specific immune response elements and have implications for the therapeutic manipulation of the latter in CRC.

Analysis of DNA mismatch repair (MMR) and clinical outcome in stage III colon cancers from patients (pts) treated with adjuvant FOLFOX +/- cetuximab: A pooled analysis of 3934 pts from the PETACC8 and NO147 trials. First Author: Julien Taieb, Paris Descartes University, Georges Pompidou European Hospital, Paris, France

Background: The prognostic value of BRAF and KRAS mutations in resected CC pts remains controversial due to published studies that include stage II & III, microsatellite instability (MSI) and MSS, colon and rectal tumors, and variable treatments. We examined the question prospectively using a large and heterogenous prospectively collected biospecimens from MSS stage III CC pts receiving adjuvant FOLFOX +/- cetuximab. Methods: Tumors were analyzed for BRAF V600E and KRAS exon 2 mutations in microsatellite-stable (MSS), stage III colon cancers (CC) from patients (pts) treated with adjuvant FOLFOX +/- cetuximab: A pooled analysis of 3934 pts from the PETACC8 and NO147 trials. First Author: Marios Gianna-Katsarelis, Dana-Farber Cancer Institute and Boston Children’s Hospital, Boston, MA

Table 1: Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>3-yr DFS %</th>
<th>HR (95% CI)</th>
<th>Adjusted P value</th>
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<tr>
<td>WT</td>
<td></td>
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<tr>
<td>KRAS WT</td>
<td>2205</td>
<td>78.1</td>
<td>Ref</td>
<td>---</td>
</tr>
<tr>
<td>dMMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Survival dMMR</td>
<td>265</td>
<td>77.3</td>
<td>0.99 (0.73,1.32)</td>
<td>0.9263</td>
</tr>
<tr>
<td>Familial dMMR</td>
<td>140</td>
<td>77.6</td>
<td>0.86 (0.58,1.26)</td>
<td>0.4342</td>
</tr>
</tbody>
</table>

Conclusions: Comprehensive molecular characterization of colorectal cancer reveals genomic predictors of immune cell infiltrates. First Author: Marios Gianna-Katsarelis, Dana-Farber Cancer Institute and Boston Children’s Hospital, Boston, MA

Background: Colorectal cancer (CRC) is a molecularly heterogeneous disease that arises and progresses in the context of a complex microenvironment. Tumor immune infiltrates have been shown to be associated with an improved CRC-specific and overall survival. However, the genomic features of CRC that determine the number and types of immune infiltrates remain largely uncharacterized. Methods: We performed Whole Exome Sequencing and microsatellite instability (MSI) analysis on primary CRCs from 689 patients (pts) identified from two large prospective cohorts, the Nurses’ Health Study and the Health Professionals Follow-Up Study. We also immunohistochemically characterized the immune infiltrate (peri-tumoral, intratumoral periglandular, Crohn’s-like, tumor-infiltrating, and total lymphocyte score) and conducted tissue microarray imaging analysis for T-cell subsets (CD3+, CD8+, CD45RO+, FoxP3+). We utilized a novel computational pipeline to calculate tumor neoantigen load (peptides resulting from somatic mutations and recognized by the immune system as foreign) and subsequently correlated the tumor neoantigen load with the aforementioned immune variables and with pt survival. Results: When compared to microsatellite-stable cancers, MSI-high tumors expressed significantly more neoantigens (p < 2e-16). Tumor neoantigen load significantly correlated with total lymphocytic score in the primary CRCs (P = 4.9e-9) and was most significantly associated with tumor infiltrating lymphocytes (P = 1.6e-15). Among T-cell subsets, tumor neoantigen load was only significantly associated with the CD45RO+ T-cell subset (p = 0.0003). Higher tumor neoantigen load predicted significantly improved CSS-specific and overall survival (P = 0.014 and P = 0.048, respectively).

Conclusions: In the large prospective study of molecularly characterized CRCs, tumor neoantigen load predicts greater tumor-infiltrating lymphocytes and memory T-cell infiltration and represents a novel genomic predictor of CRC survival. Our findings link tumor genomics to specific immune response elements and have implications for the therapeutic manipulation of the latter in CRC.
Background: We conducted a phase II of trastuzumab (T) and lapatinib (L) in HER2-amplified, KRAS exon 2 wild-type, mCRC pts resistant to standard therapies (HERACLES Trial EudraCT 2012-002128-33). Methods: Pts progressing after fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab were eligible if tumor was HER2+ (IHC3+ or 2+ and FISH positive (HER2:CEP17 > 2) > n > 50% cells). L was given po qd, T qw at standard doses. Response was assessed q5 wks. The primary end-point was objective response (OR, RECIST v1.1). To consider the study positive 6/27 ORs had to be observed (α = 0.05; β = 85%; H1 = 30%). Serial liquid biopsies for HER2 ctDNA (ddPCR/NGS) and ectodomain (ECD) plasma levels (ELISA) were collected until progression. Results: Of 123 pts enrolled, 913 pts were screened, 44 found HER2+ (4.8%), and 23 eligible and evaluable: 21F/21M, median age 63 yrs (r = 40-86), ECOG PS ≤ 1, median prior regimens 5 (r = 3-8). Primary endpoint was met with 8/23 ORs (7 PR, 1 PRunc (too early); ORR = 35% (95% CL 20-55%); 7/8 ORs were observed in HER2 IHC3+ pts. Responses lasted: 8 > 12, > 14, > 24, > 24, > 32, > 54 + > 55 + weeks. Median time to progression was 5.5 months (95% CL 3.7-9.8). Toxicity was limited to G2 diarrhea, fatigue, and rash (1 G3). HER2+ ctDNA and ECD levels decreased in 2/3 ORs and 0/2 non responders and in 2/2 ORs 0/6 with SD or PD, respectively. Exploratory correlative analyses of HER2 gene dosage will be presented together with non responders and in 2/2 ORs 0/6 with SD or PD, respectively. Exploratory correlative analyses of HER2 gene dosage will be presented together with non responders and in 2/2 ORs 0/6 with SD or PD, respectively.

CONCLUSIONS: HERACLES is a phase II trial of treatment of HER2+ mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients. HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with exon 2 KRAS mCRC patients.
Randomized phase III study of adjuvant chemotherapy with S-1 versus capecitabine (cape) in patients with stage III colon cancer (CC): Results of Japan Clinical Oncology Group study (JCOG0910). First Author: Tetsuya Hamaguchi, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

**Background:** We previously reported the results of the JCOG0205 study, which indicated that D2/D3 lymph node dissection followed by adjuvant fluoropyrimidine (F) monotherapy resulted in better disease-free survival (DFS) and overall survival (OS) in Japan than in Western countries (JAC 2014). Cape is one of standard adjuvant chemotherapy for stage III CC (NEJM 2005). Recently, S-1 was demonstrated to be non-inferior to uracil and tegafur plus leucovorin in DFS (Ann Oncol 2014). This is the first result of JCOG0910, which compared S-1 with cape. **Methods:** Key eligibility criteria were: stage III, colorectal adenocarcinoma except for lower rectal cancer, RO with D2/D3 lymph node dissection, 20-80 years old. Patients were randomized to 8 courses of cape (2,500 mg/m2/day, days 1–4, q3w) or 4 courses of S-1 (80 mg/m2/day, days 1–28, q4w). Primary endpoint was DFS. Planned sample size was 1,950 to provide 80% power with a non-inferiority margin of hazard ratio (HR) of 1.24 and 1-sided α = 0.05; with interim analyses after 50% of the planned accrual and 1 year after completion of accrual. **Results:** Between Mar 2010 and Aug 2013, 1,564 pts were randomized to cape (n = 782) or S-1 (n = 782). Median age was 66; male/female: 52%/48%, colon/rectum: 68%/32%, number of positive nodes ≤ 3/≥ 4: 84%/16%. At the second interim analysis on Sep 2014, 48% of required events (258/535) were observed, and JCOG Data Safety Monitoring Committee recommended early publication because S-1 was apparently inferior to cape in DFS. With median follow-up of 23.7 months (range 2.1–60.0), the 3-year DFS rate was 82.0% in cape and 77.9% in S-1. The HR of DFS was 1.23 (99.05% CI, 0.887–1.70) and the non-inferiority of S-1 was not demonstrated (P = 0.111). The incidence of grade 3/4 adverse events was 21.2% in cape and 12.1% in S-1. Hand-foot syndrome was common in cape, whereas diarrhea and anorexia were common in S-1. **Conclusions:** This study failed to demonstrate the non-inferiority of adjuvant S-1 to cape in DFS. Adjuvant cape remains the standard treatment and S-1 should not be used for stage III CC. Clinical trial information: UMIN0000039722.

Toxicity and quality of life data from SCOT: An international phase III randomized (1:1) noninferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy. First Author: Timothy Iveson, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

**Background:** Oxaliplatin/Fluoropyrimidine combination chemotherapy is an established adjuvant treatment for colorectal cancer (CRC). Neutropenia and mucositis from Oxaliplatin is cumulative, dose limiting, and potentially irreversible. **Methods:** SCOT is designed to determine whether 3 months of adjuvant chemotherapy with OxMdG or XelOx (physician/patient choice) in Stage III CRC is as effective as 6 months, with less toxicity. In the initial 867 patients toxicity was graded during treatment using NCI-CTCAE. Quality of life was assessed using EORTC QLQ-C30/EQ-5D (n = 1776) and neuropathy using GOG-Ntx4 (n = 1776). **Results:** From May 2008 to Nov 2013, 6087 patients were randomized from 237 centers/6 countries. Median age was 65 years. 4972 (82%) were Stage III, 4983 (82%) had colon cancer and 4105 (67%) received XelOx. There were 31 toxic deaths (0.5%) equally distributed between the randomized arms. Toxicity profiles depended on the FU backbone with more grade 3/4 neutropenia on OxoMdG (23% v 5%) and more grade 3/4 diarrhea (9% v 15%) on XelOx. 16% overall did not complete 3 months of treatment mainly due to toxicity (56%). Peripheral neuropathy was cumulative, (24% grade 2/3 toxicity by 3 months; 56% by 6 months) and as measured by GOG-Ntx4 persisted and was much higher at 1 year on the 6 month group compared to the 3 months randomized arm (mean difference = 19 [se = 1.3]). QLQ-C30 global health status worsened during treatment and stayed more depressed in months 4-6 in the 6 month arm. By 12 months the mean difference between the arms was small (2.20±3.1); a similar pattern was seen with the QLQ-C30 functional scales. The pattern for the EQ-5D health score were also similar with small differences at 12 months (0.3 [0.2] respectively). **Conclusions:** Both OxMdG and XelOx were safe and well tolerated. In months 4-6 expected, the main toxicities did vary according to FU backbone (but this was not randomized). Quality of life worsened while patients were on treatment but recovered by 1 year despite persistent peripheral neuropathy, suggesting that current schedules of life tools may not adequately capture the morbidity associated with this toxicity. Clinical trial information: IS-RCTRNS95757862.

A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC). First Author: Akihiko Murata, Department of Gastrointestinal Surgery, Hiroaki University Graduate School of Medicine, Hiroaki, Japan

**Background:** The ACTS-RC trial is a phase III trial designed to superiority of S-1 (tegafur, 5-chloro-2,4-dihydroxypyrimidine, and potassium oxonate) to UFT (uracil and tegafur), a standard treatment in Japan as adjuvant chemotherapy for curatively resected stage II/III rectal cancer. **Methods:** 20-80 aged patients (pts) with stage II/III rectal cancer who underwent curative surgery without preoperative therapy randomly assigned to receive UFT (500, or 650mg/day according to BSA on days 1 to 5 days, followed by 2 days rest) for 1 year or S-1 (80, 100, or 120mg/day according to BSA on days 1 to 28, followed by 14 days rest) for 1 year. The primary endpoint was Relapse-free survival (RFS). The 5-year RFS rate in the UFT group was assumed to be 70%. We calculated that a total enrollment of 800 pts was needed for a hazard ratio (HR) of 0.70 in the S-1 group as compared with the UFT group, with the use of the log-rank test, two-sided alpha of 0.05, and power of 0.80. **Results:** A total of 959 pts were enrolled (959 pts in S-1 group). Of these, 490 pts were randomized between April 2006 and March 2009 (480 pts in UFT group, 479 pts in S-1 group). Median age: 63 years, upper/lower rectum: 52%/48%. The groups were balanced. At a median follow-up of 5.02 years, 5-year RFS rate was 61.7% (95%CI: 57.1-66.5%) in the UFT group and 66.4% (95%CI: 61.9-70.5%) in the S-1 group. The 3-year RFS was 0.773 (95%CI: 0.625-0.955) and superiority of S-1 was demonstrated (p = 0.0165). The complete rate of the protocol treatment was 61.8% in UFT group and 61.3% in S-1 group. 5-year overall survival rate was 80.2% (95%CI: 76.3-83.5%) in the UFT group and 82.0% (95%CI: 78.3-85.2%) in the S-1 group. The overall incidence of grade ≥ 3 adverse events in UFT group and S-1 group were 11.7% and 13.4%; anemia(1.3% v 1.3%), diarrhea(2.3% v 2.6%), anorexia(1.0% v 2.6%), nausea(0.4% v 1.3%), hyperbilirubinemia (1.0% v 1.3%), AST(1.5% v 0.9%) and ALT(2.3% v 0.9%), respectively. **Conclusions:** Adjuvant chemotherapy using S-1 demonstrated improvement in 5-year RFS in pts with curatively resected stage II/III rectal cancer. S-1 is an adjuvant chemotherapy treatment option for these pts. Clinical trial information: C000000385.
safety and tolerability of veliparib combined with capecitabine plus radiotherapy in patients with locally advanced rectal cancer (LARC). Final results of a phase Ib study. First Author: Michael Michael, Peter MacCallum Cancer Centre, East Melbourne, Australia.

Background: Standard treatment for patients (pts) with LARC consists of chemoradiation followed by surgery. To achieve higher response rates and reduce risk of recurrence, further optimization is needed. Veliparib (ABT-888), a potent and orally bioavailable PARP1/2 inhibitor, has been shown to enhance antitumor activity of chemotherapy and radiotherapy (RT) in preclinical models. Herein, we present the final results from a phase Ib dose-escalation study (NCT01589419) of veliparib plus capecitabine (C) and RT (C/RT) in pts with LARC. Methods: Stage II/III rectal cancer pts (≥ 18 years) received 40–400 mg veliparib p.o. BID and 540 cGy boost x 3 (stage II; 5.5 weeks (5 days/week). Veliparib (p.o. 20–400 mg BID) was administered from day 2 until 2 days after RT (7 days/week). Pts underwent surgery 5–10 days after RT. Primary objectives were to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of veliparib plus C/RT, using an exposure-adjusted continual reassessment method. Safety, pharmacokinetics (PK), and antitumor activity were also assessed.

Results: As of 23 Nov 2014, 32 pts (81% male, median age 57 years) received study treatment (veliparib < 400 mg, n = 16; 400 mg, n = 16).

Most common adverse events possibly or probably related to treatment were fatigue (41%), nausea (41%), diarrhea (25%), and vomiting (22%); grade 3/4 events were diarrhea (n = 2), anemia, lymphopenia, and pulmonary embolism (n = 1 each). Dose-limiting toxicities (grade 2) occurred in 2 pts: radiation skin injury, and nausea and vomiting, at 70 and 400 mg veliparib, respectively. The MTD was not reached. The RP2D for veliparib was 400 mg p.o. BID and C at 540 mg BID PFS was dose proportional, with no clear impact on the PK of C. Post-surgery tumor downstaging was observed in 72% of evaluable pts; 28% achieved a pathologic complete response. Sphincter-sparing surgery was performed in 70% of evaluable pts.

Conclusions: Veliparib plus C/RT had an acceptable safety profile in LARC pts with C at 540 mg BID. Veliparib has a dose-dependent PK profile and no effect on the PK of C. The combination treatment showed promising preliminary antitumor activity. Clinical trial information: NCT01589419.

Comprehensive multplatform biomarker analysis of 212 anal squamous cell carcinomas. First Author: Patrick McKay Boland, Roswell Park Cancer Institute, Buffalo, NY.

Background: Squamous cell anal carcinoma is a rare, HPV-associated malignancy accounting for 2% of digestive system cancers. Usually these malignancies are detected early and successfully managed with chemoradiation. Uncommonly, these cancers recur or present with metastases. In this setting, cisplatin and 5-fluorouracil represent the only approved regimens. Beyond standard therapy, few therapeutic options exist. The purpose of this study is to identify other novel, potential targets and therapeutic options for this disease, utilizing a multplatform approach.

Methods: 212 squamous cell anal carcinoma specimens were tested via a multplatform profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (CISH or FISH). Tissue from a metastatic site was submitted in 80.2% of the cases. Documentation of positive HPV or HIV status was provided in six cases. Results: IHC data set analysis was not available for 30 cases. EGFR (89.7%, 35/39), TOP01 (68.3%, 123/180), MGMT (67.2%, 125/186), and PTEN (46.9%, 90/192). EGFR and HER2 were amplified in 7.4% (5/68) and 1.8% (2/111) of cases. High mutation rates were seen in biomarkers associated with the PIK3CA/Akt pathway: PIK3CA (26.8%, 28/104), FBXW7 (3.1%, 2/64), and Akt1 (1.5%, 1/68). PIK3CA exon 9 mutations were detected in 75% of all PIK3CA mutations. KRAS mutations were rare (1.8%, 2/111). Point mutations in other genes were identified, including a few co-occurring mutations.

Conclusions: Multitumor platform profiling identified several potential targets. Protein expression aberrations identified potential treatment options not routinely considered. Mutations in PIK3CA, Akt1, and FBX7/W7 and PTEN loss indicate potential for targeting the PI3 kinase pathway. Targeting the ErbB-family receptors, namely with anti-EGFR agents or newer generation pan-HER inhibitors, may represent another option, given EGFR and HER2 amplification as well as EGFR overexpression. Differences in anal carcinomas whose etiology is of viral origin may present different treatment options based on the driver mutations.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Checkpoint kinase (CHK) 1/2 inhibitor LY2606368 in a phase I, dose-expansion study in patients (pts) with metastatic squamous cell carcinoma (mSCC) of the anus. First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Nashville, TN

Background: LY2606368 is a CHK 1/2 inhibitor. CHK is a multifunctional kinase essential for checkpoint control, DNA repair, cell cycle replication, and proliferation. Potent inhibition of CHK1 is predicted to generate DNA damage and mitotic catastrophe. LY2606368 was evaluated as a single agent in an expansion cohort of pts with mSCC of the anus. Methods: This was a phase I study in pts with advanced cancer (NCT01115790). Preliminary signs of activity in the dose-escalation phase warranted a dose-expansion cohort of pts with mSCC of the anus given LY2606368 at the maximum tolerated dose (MTD) of 100 mg/m2 IV on day 1 of a 14-day schedule. Radiographic assessment every 6 weeks and pretreatment biopsies were obtained. Safety, tolerability, preliminary efficacy, and pharmacogenetic results are reported. Results: Of 26 pts enrolled, 62% had ≥ 2 prior regimens (median = 2 regimens; range: 1-13) and 92% of pts had prior radiotherapy. The most frequently reported adverse event (AE) was neutropenia, which occurred in 92% of pts (grade 4: 7%), but was of relatively brief duration; 1 pt experienced febrile neutropenia. Other drug-related AEs occurring in > 20% of pts were thrombocytopenia (58%), anemia (38%), and fatigue (31%). Nonhematologic AEs included nausea (15%), diarrhea (15%), anorexia and headache (12% each), which were mostly grade 1 or 2. One pt (4%) had a CR, 3 pts (12%) had a PR, and 11 pts (42%) had SD, for an overall response rate of 15% (95% CI: 5, 32) and a disease control rate of 58% (95% CI: 40, 74). Of the 4 pts with response, 3 pts (including the pt with a CR) remain on treatment, and 1 pt has had a prolonged duration of response (10.1 mos) before discontinuing therapy. Tissue samples were available from 14 pts with evaluable response data. Alterations of genes in the PI3K pathway occurred in 5/8 (63%) pts with clinical benefit vs 1/6 (17%) pts without (p = 0.12). Conclusions: The CHK 1/2 inhibitor LY2606368 demonstrated an acceptable safety profile despite relatively high rates of transient grade 1-2 neutropenia. Single-agent activity was observed in pretreated mSCC of the anus, a disease with a high unmet medical need. The MTD of 105 mg/m2 is confirmed as the recommended phase II dose. Clinical trial information: NCT01115790.

Comprehensive genomic profiling of anal squamous cell carcinoma to reveal frequency of clinically relevant genomic alterations in the PI3K/mTOR pathway. First Author: Eric M. Sanford, Foundation Medicine, Inc., Cambridge, MA

Background: Anal squamous cell carcinoma (ASCc) is an HPV-associated rare tumor that has newly doubled in incidence since 1973, with cisplatin-based chemotherapy as the only treatment shown to be effective for patients with metastatic disease. We performed comprehensive genomic profiling (CGP) on 70 patients with ASCc to identify the spectrum of clinically relevant and genomically altered oncogenic drivers in ASCc. We confirmed 82 of 86 mutations (96%) in 149 genes, by hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 692X for the entire coding regions of 236 cancer-related genes plus 47 introns from 19 genes frequently rearranged in cancer. CGPa were defined as GA linked to FDA-approved agents or investigational agents in clinical trials. Results: There were 48 female and 22 male patients with a median age of 59.5 years (range 31-88). Three tumors (4%) were grade 1, 33 (47%) were grade 2, and 34 (49%) were grade 3. At the time of sequencing, 5 (7%) cases were stage II, 13 (19%) were stage III, and 47 (67%) were stage IV, with staging information unavailable for 5 (7%) patients. HPV-16 or HPV-18 was detected in 61 (87%) tumors: 59 were positive for HPV-16 and 2 were positive for HPV-18. CGP revealed 238 GA (3.4 per tumor), 111 of which were CRGA (1.6 per tumor). At least one CRGA was detected in 53 (76%) cases. The most common CRGA were in PIK3C2A (9 cases; 10% cases; 14%), and FBXW7 (8 cases; 11%). For the 9 (13%) tumors where HPV DNA was not detected, a significant enrichment of LOF mutations was observed in TP53 (6 of 8 altered cases; p < 0.0001) and CDKN2A/5 of 5 altered cases; p < 0.0001). Clinical outcomes for PI3K/mTOR-pathway-altered patients are being investigated. Conclusions: ASCc features a high rate of potentially targetable PIK3C/mTOR pathway alterations, with 37 (53%) tumors harboring alterations in PIK3CA, PTEN, or FBXW7—a mutational profile similar to HPV positive head and neck and cervical SCC. The enrichment of TP53 and CDKN2A alterations in tumors where HPV DNA was not detected was similarly found in head and neck squamous cell carcinoma, suggesting a distinct route to carcinogenesis for HPV negative ASCc.
Masitinib (MAS) is a selective inhibitor of c-Kit and mast cell function. Increased mast cell activity in the tumor microenvironment is an established therapeutic strategy. However, controversies exist when mast cells are found concomitantly in both the organs or when the patients, who have undergone either liver or lung resection, have a recurrence in the other organ. Methods: All consecutive patients operated for CRC liver and lung metastasis (LLM) at our institution from January 1990 to December 2012 were reviewed. Our policy was to propose sequential surgery of both sites with perioperative chemotherapy, provided that the strategy was potentially curative. We aimed to evaluate Overall Survival (OS) of these patients, to develop a clinical usable prognostic score and to find out if cure is possible. Results: A total of 150 patients (89 men - 61 women; median age - 56 years) were included in the study. Median number of LLM resected was 3 and 1 respectively. Median Follow-up was 5 years (Range 0.6 - 22.8 years). Median OS, 5-year OS and 10-year OS from first metastasis resection were 6 years, 93% and 35% respectively. Multivariate analysis identified metastatic CRC at initial diagnosis (P = 0.027), Pre-Lung resection CEA level > 100 ng/ml (P = 0.007), Pre-Lung resection CA19-9 level > normal (P = 0.029), Interval between 1st liver and 1st lung resection < 24 months (P = 0.004), > 2 lung metastases resected (P = 0.049) and Non-curative lung resection (P = 0.012) were independent predictors of OS. Simultaneous presentation of LLM and perioperative chemotherapy was not associated with OS. Prognostic model was developed using 5 preoperative factors. LLM score > 3 was associated with good 5-year survival (AUROC 0.7, Sensitivity 90%, Specificity 67%). Fifteen patients were considered as cured with > 5 years disease-free survival from the last surgery (median LLM score 7). Conclusions: Good long-term survival can be achieved in patients who undergo sequential resection of the liver and lung metastases from CRC with 10% being cured. LLM score is an effective way to select patients for sequential resection. Higher the score better is the survival after sequential surgery and better is the chance of cure. Conversely, the role of surgery should be questioned in patients with LLM score < 3.

Masitinib plus FOLFIRI for second line treatment of metastatic colorectal cancer: An open label phase Ib/II trial.

Descartes University, Georges Pompidou European Hospital, Paris, France

Masitinib plus FOLFIRI for second line treatment of metastatic colorectal cancer (CRC). In vitro, MAS acts as a chemosensitizer of 5-fluorouracil and irinotecan in CRC cell lines. This trial evaluated MAS in combination with FOLFIRI. Methods: Patients (pts) with metastatic CRC refractory to 1st line chemotherapy received MAS 400 mg/m² until progression, refusal or unacceptable toxicity. Patients previously treated with irinotecan were excluded. Phase 1 evaluated safety of the combination with Dose Limiting Toxicity (DLT) determining subsequent dose and recruitment. DLT was defined as grade 3 non hematological adverse event (AE) or any grade 4 AE related to MAS. Phase 2 evaluated efficacy. Results: Eighteen pts (50% with mutated KRAS) from 6 centers in France were treated. MAS dose was reduced from 9 to 6 mg/kg/day for the first 2 pts. The safety profile of MAS based on new mechanistic understanding and to minimize risk of toxicity. No DLT was reported for the phase 1 (3 pts) at 9 mg/kg/day. After a median follow-up of 22.8 months, median OS was 17.6 months (95%CI [9.3-25.9]) and median PFS was 9.2 months (95%CI [4.3-14.1]). The 1 year PFS rate was 39%, and 2 year PFS rate was 28%, including 1 pt with a confirmed complete response. Efficacy was still evident in the 3 pts treated at 6 mg/kg/day with PFS of 9.1 months. After grade 3-4 AE in this cohort, Overall, 6/18 pts (33%) reported grade 3-4 AE and 4/18 pts (22%) experienced serious AE. No treatment related deaths were reported. Conclusions: The safety profile of MAS + FOLFIRI was acceptable. Efficacy findings seem to compare favorably against historic benchmarks (see table). MAS may therefore offer patients a new active compound for mCRC. A confirmatory phase 3 trial evaluating FOLFIRI + MAS 6 mg/kg/day as second line for mCRC is ongoing.

Impact of UGT1A1 genotype on prognosis in Japanese advanced colorectal cancer patients treated by irinotecan-based regimens. First Author: Wataru Ikawara, Division of Medical Oncology, Showa University, School of Medicine, Tokyo, Japan

Background: The influence of UGT1A1*6 and UGT1A1*28 on prognosis of irinotecan (IRI)-based regimens has been controversial, although UGT1A1 genotypes are risk factors for IRI-related toxicities in Asians. We conducted a prospective analysis to examine the correlation between UGT1A1 genotypes and safety/efficacy of IRI-based regimens in Japanese patients (pts) treated for advanced colorectal cancer (aCRC) (NCT01035506). The validated nomogram for predicting the probability of severe neutropenia induced by IRI-based regimens was proposed based on safety analysis (ASCO 2014, Abst No. 3543). We analyzed the efficacy in terms of UGT1A1 genotypes. Methods: 1,376 pts who had histologically confirmed aCRC and received IRI-based regimens were enrolled. UGT1A1 genotypes were categorized into three groups: wild (*1/*1), hetero (*1/*6, *1/*28), and homo (*6/*6, *6/*28, *28/*28). The primary objective was to investigate the non-inferiority of hetero or homo to wild in progression-free survival (PFS) under the non-inferiority margin of hazard ratio (HR) of 1.25, using propensity score weighting to adjust for baseline characteristics. Progression was evaluated by investigators according to the RECIST 1.1 criteria. The association of prognosis with IRI exposure was also examined. Results: The efficacy analysis was performed using 1,339 pts. The prevalence of UGT1A1 genotypes were 47% wild, 42% hetero, and 11% homo. The median PFSs according to UGT1A1 genotypes were 6.0 (95% CI, 5.6 – 6.7) months (mo) in wild, 6.0 mo (5.4 – 6.6) in hetero, 5.6 mo (4.4 – 6.1) in homo. The HR of hetero to wild was 0.988 (0.864 – 1.130; non-inferiority p = 0.0006) and that of homo to wild was 1.202 (0.988 – 1.463, non-inferiority p = 0.6977). The HRs in the homo group with a starting dose not less than 80% to wild and with a dose less than 80% of the standard IRI dose were 1.037 (0.779 – 1.379, p = 0.8052) and 1.393 (1.106 – 1.754, p = 0.0049). Conclusions: This analysis revealed that PFS in the UGT1A1 hetero group were non-inferior to the wild group. However, the homo group had worse PFS as compared with the wild group. The excessive dose reduction of the starting IRI dose might account for the unfavorable results in the homo group.

A phase II study of NK012, a polymeric micelle formulation of SN-38, in colorectal cancer patients who had received prior oxaliplatin-based regimens. First Author: Akihito Tsujii, Department of Medical Oncology, Kochi Health Sciences Center, Kochi, Japan

Background: NK012 is a micelle-forming macromolecular produrg of SN-38, an active metabolite of irinotecan. In the completed phase I study, the recommended dose was decided to be 28 mg/m², with a DLT of myelosuppression. This phase II study was conducted to evaluate an efficacy and safety of NK012 in patients with recurrent or metastatic colorectal cancer. Methods: This was a multicenter, open-label, single-arm phase 2 study. Patients with a history of oxaliplatin-based treatment against metastatic colorectal cancer, or recurrence within 6 months after the last dose of adjuvant oxaliplatin had been enrolled. NK012 (28 mg/m²) was administered intravenously every 3 weeks. Administrations continued until disease progression. Objective clinical response was evaluated according to the RECIST 1.1. The primary endpoint was overall response rate (ORR). Results: In the 58 patients registered, 53 patients received NK012. Median number of previous oxaliplatin-based therapy was 11.0 courses. 4.2% of patients had a history of previous irinotecan. Median treatment period was 3 courses. ORR was 3.8 %, and DCR (CR + PR + SD) was 56.0%. Median PFS and OS were 99.0 and 451 days, respectively. Major adverse drug reactions were absolute neutrophil count (ANC) decreased, of which grade 4 or more manifested in 81% of patients. Ratio of Grade 4 ANC decreased was higher in patients who had received previous oxaliplatin for more than 6 courses. After Grade 3 diarrhea, the ratio of Grade 4 manifestation was 7.5% and 8.9%, respectively. The ratio of Grade 4 manifested was 2.0% (0.1%-2.2%) and 5.0% (2.0%-8.0%) in patients with and without wild-type KRAS, respectively. Conclusions: Efficacy of NK012 against recurrent or metastatic colorectal cancer was comparable with that of irinotecan monotherapy previously reported, and disease control by NK012 was suggested. Unlike irinotecan, the major ADR was myelosuppression, with mild gastrointestinal toxicity. These safety profiles implicate a possibility of combination with less-myelotoxic anticaner agent(s) like 5-FU/LV and of being preferable to FOLFIRI. Further optimization of dosage and schedule of NK012 administration and its combination strategy would be worthwhile.
Multivariable analysis.

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<th></th>
<th>OS</th>
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<th>DFS</th>
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<tr>
<td>HR (95%CI)</td>
<td>p-value</td>
<td>HR (95%CI)</td>
<td>p-value</td>
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<tr>
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<td>0.93 (0.95, 0.94)</td>
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<td>1.02 (1.10, 1.35)</td>
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<td>Male vs Female</td>
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<td>0.98 (0.78, 1.22)</td>
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<td>T stage (I/III vs IVa</td>
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<td>1.34 (0.53, 3.28)</td>
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<td>0.001</td>
<td>0.48 (0.29, 0.79)</td>
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Multivariable analysis results: Median age was 74 years, 47% of patients were female. BM were found in 55 patients (38%). Median follow-up was 74 months (87 months for patients who survived) with no loss to follow-up. Overall, 30 patients (21%) had a recurrence and 56 patients (39%) died. In univariate analyses, BM-positive patients had a significantly worse OS (hazard ratio [HR] 0.61; 95% confidence interval [95%CI] 0.50,0.74; p < 0.001) and DFS (HR 0.61; 95%CI 0.57,0.65; p < 0.001). Time to in situ recurrence (TTISR) was significantly shorter in group 2A than in group 1 (HR: 2.89; 95%CI [1.04-8,01; p = 0.004). The shortest TTISR was observed in group 2B. In multivariate analyses, this group was the only independent indicator for IRS after RFA (p < 0.001). Conclusions: Initially oversized CRLM do remain beyond the optimal indications for RFA despite downsizing and should be considered as contraindication to RFA procedure. The rate of IRS remains in this situation doubled to that of upfront small liver metastases reaching 32%.

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3532 Poster Session (Board #24), Mon, 8:00 AM-11:30 AM

**DPYD c.1905+1G>A and c.2846A>T and UGT1A1*28 allelic variants as predictors of toxicity: Pharmacogenetic translational analysis from the phase III TRIBE study in metastatic colorectal cancer.**

**First Author:** Del Re, University of Pisa Department of Clinical and Experimental Medicine, Ghezzano, Italy

**Background:** Adverse drug reactions (ADRs) caused by fluoropyrimidines depend, at least in part, from DPD deficiency resulting from the loss-of-function mutations c.1905+1G>A and c.2846A>T. Moreover, irinotecan ADRs appear frequently in patients bearing the UGT1A1*28 variant, associated with reduced UGT1A1 expression. In this study, we analyze the association between DPYD and UGT variants with ADRs by 5-fluorouracil and irinotecan in subjects enrolled within the phase III TRIBE study, whose final results have been recently reported. **Methods:** Out of 508 randomized patients, blood samples for pharmacogenetic analyses were available for 440 patients. DNA was extracted from 200μl of blood and analyses of DPYD c.1905+1G>A, c.2846AT and UGT1A1*28 was performed by a Pyrosequencing platform (Qiagen, USA). The study was approved by the local Ethics Committee. **Results:** Each of the DPYD c.1905+1GA and c.2846AT genotypes were found in 5 out of 440 subjects, with a combined frequency of 2.2%. c.1905+1GA and c.2846AT had the same impact on ADRs and, taken together, patients bearing these variants (N=10) had an increased risk of G3/4 neutropenia (OR: 4.14, p=0.043) and stomatitis (OR: 10.36, p=0.003) as compared to wild-type patients. Five out of 10 DPYD mutant patients experienced a G4 ADR after the first cycle of therapy, UGT1A1*28 was found in 39/436 patients (8.9%); these patients had an increased risk of G3/4 neutropenia as compared to both *1*1*1*1 (OR: 3.81, p<0.001) and *1*2*2*2 (OR: 2.28, p=0.022) genotypes. Patients bearing DPYD c.1905+1GA, c.2846AT and UGT1A1*28 (N=49) had an increased risk of G3/4 neutropenia (OR: 2.98, p<0.001), febrile neutropenia (OR: 2.78, p=0.003) and stomatitis (OR: 6.83, p<0.001). No significant correlation with G3/4 diarrhea was found. **Conclusions:** DPYD c.1905+1GA, c.2846AT and UGT1A1*28 are associated with a higher risk of G3/4 ADRs also in the TRIBE trial, underscoring the predictive role of DPYD and UGT1A1 variants across fluoropyrimidine and irinotecan-containing schedules, and therefore their potential usefulness in treatment tailoring.

3533 Poster Session (Board #25), Mon, 8:00 AM-11:30 AM

**Dual targeting of vascular endothelial growth factor-A (VEGF-A) and angiopoietins (Ang) without chemotherapy in metastatic colorectal cancer (mCRC): Results of the VENGEANCE study.**

**First Author:** Jennifer Mooi, Austin Health, Melbourne, Australia

**Background:** VEGF-A and Ang play complementary roles in regulation of blood vessel growth, maturation and function. However, we postulate that combined blockade of VEGF-A and Ang would have clinical activity in mCRC. Trebananib/AMG386 (Treb) is a peptibody that inhibits binding of Ang 1/2 to the Tie2 receptor. Previous studies have established the safety of Treb with various VEGF inhibitors including bevacizumab (Bev). **Methods:** VENGEANCE is an open label Phase II study evaluating the combination of Bev and Treb without chemotherapy as 1st line treatment of mCRC. Key eligibility criteria: patients (pts) with unresectable mCRC, no prior therapy, PS 0-2, adequate organ function, and who investigator considers not requiring immediate anti-angiogenic chemotherapy. **Treatment:** Bev 7.5mg/kg q3w and Treb 15 mg/kg qw. Primary endpoint: disease control rate (pts without disease progression, i.e. RECIST CR+PR+SD) at 6 mths (DC6m). Stage II Simon design required stage I: DC6m >5/17 pts, stage II: DC6m >13 pts, for a positive study. Secondary endpoints: response rate (RR), toxicity, progression-free survival (PFS) and overall survival (OS). **Results:** 45 pts were enrolled from 4 Australian sites from Sep 2010 to Aug 2013. Med follow up is 33.7 mths. At time of analysis, 7 pts remain on study treatment (3 PR, 4 SD; duration on study 19–32 mths). Key AE of interest were GI hemorrhage, TIA, cardiac ischemia, PE, GI perforation and CNS hemorrhage (2% each) and g3 hypertension (4%). **Conclusions:** Treb plus Bev showed promising activity that merits evaluation in further randomized studies, including combinations with chemotherapy. RR of the combination is greater than previously reported for Bev monotherapy (3%). The toxicity profile is manageable and the combination does not appear to increase toxicities in excess of those expected with Bev + chemotherapy. Clinical trial information: NCT01249521.

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A phase II, randomized, double-blinded, placebo-controlled study of simtuzumab or placebo in combination with FOLFIRI for the second line treatment of metastatic KRAS mutant colorectal adenocarcinoma. First Author: J. Randolph Hecht, David Geffen School of Medicine at UCLA, Los Angeles, CA

A phase II study of AUY922 and cetuximab in patients with KRAS wild-type (WT) metastatic colorectal cancer (mCRC). First Author: So- massundaram Subramaniam, Swedish Cancer Inst, Seattle, WA

Expansion
70 250 4 1 (SD)

AUY922 Dose (mg/m²)

Cetuximab Dose (mg/m²)

Number of patients

Patients with Disease Control (PR/SD)

Cohort

1

2

3

Expansion

70 250 4 1 (SD)

AUY922 Dose (mg/m²)

Cetuximab Dose (mg/m²)

Number of patients

Patients with Disease Control (PR/SD)

A strong association between 3Y DFS and 5Y OS was observed in this population-based cohort, which did not differ between CCA and RCa. Correlations remained significant when stratified by tumor stage and treatment era. 3Y LR DFS was a strong surrogate of 5Y OS in RCa.

Pearson’s r.

<table>
<thead>
<tr>
<th>DFS vs OS</th>
<th>3Y DFS vs 5Y OS</th>
<th>3Y LR DFS vs 5Y OS</th>
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<tr>
<td>All</td>
<td>0.93 (p &lt; 0.01)</td>
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<td>RCa</td>
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<td>0.84 (p &lt; 0.01)</td>
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<td>Stage I</td>
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<td>II</td>
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<tr>
<td>III</td>
<td>0.94 (p &lt; 0.01)</td>
<td>0.84 (p &lt; 0.01)</td>
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<td>Era ≤ 200</td>
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<td>&gt; 200</td>
<td>0.90 (p &lt; 0.01)</td>
<td>0.82 (p &lt; 0.01)</td>
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Background: Heat shock protein-90 (HSP90) is a molecular chaperone which has an important role in EGFR stability. AUY922 inhibits ATPase activity of HSP90. Combined HSP90/EGFR inhibition is effective in pre-clinical models. In this phase Ib study, we examined safety, tolerability, and maximum tolerated dose of AUY922 in combination with cetuximab in patients with KRAS WT mCRC.

Methods: This was a single-center open-label dose escalation study. Patients who had disease progression on ≥ 2 prior chemotherapy regimens were eligible. Treatment with prior cetuximab was allowed. Inclusion criteria: ECOG 0-1, measurable lesion and adequate organ function. All patients received weekly AUY922 dose-limiting toxicities. Grade 3 toxicities were seen in 62.5% of patients. Median age 54.5 (range 25 – 77), M/F: 5/11. Patients had a median of 3 prior chemotherapy regimens (range 2-6) and 15 patients (94%) had progressed on prior cetuximab. Median time to progression was 7.9 weeks (range 5.9 – 29.9) and median overall survival was 45.7 weeks (range 37.6 – 115.1). One patient (6%) had a partial response (PR) and 4 patients (25%) had stable disease (SD), for a disease control rate of 31.3%. For patients with disease control, median survival was 45.7 weeks (range 37.6 – 115.1). Treatment was well-tolerated without dose-limiting toxicities. Grade 3 toxicities were seen in 62.5% of patients treated including anemia(2 patients), nausea/vomiting(2), dehydration(2), fever(1), fatigue(1), anorexia(1), abdominal pain(1), headache (1), diarrhea(1) and prolonged QT interval(1). There were no grade 4 toxicities. Pharmacoki netic studies showed AUY922 half-life of approximately 50 hours, and no interaction with co-administration of cetuximab. Conclusions: AUY922 can be safely administered with cetuximab in patients with mCRC. Median survival of ≥ 3C Cancer is suggestive of clinical activity in this heavily pretreated patient population. Further studies of this combination are warranted. Recommended Phase II dose is weekly cetuximab 250mg/m² and AUY922 70mg/m².
PRODIGE 20: Bevacizumab + chemotherapy (BEV-CT) versus chemotherapy alone (CT) in elderly patients (pts) with untreated metastatic colorectal cancer (mCRC): A randomized phase II trial. First Author: Thomas Aparicio, Hôpital Avicenne, Assistance Publique Hôpitaux de Paris, Bobigny, France

Background: AVE study has demonstrated increased progression-free survival (PFS) with capecitabine + bevacizumab compared to capecitabine alone in pts aged 70 with mCRC. The treatment with bevacizumab has so far been evaluated in combination with other standard chemotherapy regimens for elderly pts. Methods: Pts aged 75 and over were randomly assigned in a 1:1 ratio to BEV-CT versus CT. Treatment regimens were: LV5FU2, FOLFOX and FOLFIRI, chosen by the investigators. The primary endpoint, assessed 4 months after randomization was composite, based on efficacy: tumor control (stable disease or objective tumor response) and absence of decrease of the Spitzer QoL index and safety; absence of severe cardiovascular toxicities and unexpected hospitalization. The decision rules for the experimental arm were: if <15 pts met the efficacy criterion and >25 pts met the safety criterion, the BEV-CT treatment is considered efficient and well tolerated. Results: 102 pts were randomized (51 BEV-CT and 51 CT arm), median age was 80 (range 75-91), men (55%), ECOG 0: 27%, 1: 53% and 2: 20%. CT was LV5FU2 in 53 pts (27 BEV-CT and 26 CT) and a doublet regimen in 49 pts (24 BEV-CT and 25 CT) including 23 FOLFOX and 26 FOLFIRI. Primary tumor was resected in 31 pts in BEV-CT and 30 pts in CT. Of the 46 pts evaluable in the BEV-CT arm, 23 pts (50% [90% CI: 37.1-62.9]) responded to the efficacy criterion and 28 pts (61% [90% CI: 47.7-73.0]) to the safety criterion. Multivariate analysis show that primary tumor resected and normal independent activity of daily living are predictive for the composite criterion. Conclusions: BEV-CT arm responded to the efficacy and safety criterion. Addition of bevacizumab to 1st line chemotherapy in pts aged over 75 with a mCRC is efficient and well tolerated. Clinical trial information: NCT01417494.

Preliminary follow-up results.

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<th>CT</th>
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<td>Grade 3-5 toxicities</td>
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<td>Median time to serious failure in months (m)</td>
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<td>Median time to QoL deterioration (m)</td>
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<td>Median overall survival (m)</td>
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Grade 3-5 toxicities: 55% | BEV + CT: 80% | CT: 55% (p < 0.001)
Median time to serious failure in months (m): 16.3 (95% CI: 11.6-11.6) | Not achieved | BEV + CT: 10.7 (95% CI: 8.2-13.8)
Median time to QoL deterioration (m): 7.8 (95% CI: 6.6-10.6) | 17.9 (95% CI: 13.4-21.9) | BEV + CT: 21.7 (95% CI: 14.6-24.6)
Median overall survival (m): 25.6 (95% CI: 24.0-27.2) | Not achieved | BEV + CT: 33.8 (95% CI: 31.4-36.2)

First Author: Jianmin Wang, RTI Health Solutions, Durham, NC

The PRIME trial: Quality-adjusted survival in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC) receiving first-line therapy with panitumumab plus FOLFOX versus FOLFOX alone. First Author: Jianmin Wang, RTI Health Solutions, Durham, NC

Background: The pivotal phase III PRIME trial demonstrated that, compared with FOLFOX alone, panitumumab plus FOLFOX prolongs overall survival (OS) and progression-free survival (PFS) in patients with RAS WT mCRC without having a detrimental effect on overall quality of life. The objective of this analysis was to use the quality-adjusted time without symptoms of disease or toxicity or treatment (Q-TWiST) method to compare quality-adjusted survival between the treatment arms of PRIME. Methods: Patients with RAS WT mCRC from each treatment arm of PRIME were included in this analysis, and the area under the survival curve (AUSC) was estimated using the nonparametric Kaplan-Meier method (48 months follow-up). The AUSC was partitioned into three health states: toxicity (TOX), time without symptoms of disease progression or toxicity (TWiST, i.e., PFS minus TOX), and relapse (REL, i.e., OS minus PFS). The durations of the health states were then adjusted using utility weights derived from patient-reported EuroQol 5 measures. The null hypothesis of no difference between treatment arms was tested based on the normal approximation, with standard errors (SE) calculated by the bootstrap method. In the primary analysis, TOX consisted of grade 3 and 4 adverse events. A sensitivity analysis, with grade 2, 3, and 4 adverse events classified as TOX, was performed. Results: Of 1,183 patients with mCRC who were randomized, 571 patients had RAS WT tumors (panitumumab arm: n = 259; FOLFOX arm, n = 252) and were included in this analysis. Patients receiving panitumumab plus FOLFOX had a significantly longer Q-TWiST (20.5 months) than patients receiving FOLFOX alone (18.2 months) resulting in 2.3 ± 1.0 SE additional quality-adjusted months (P < 0.03). The secondary analysis of RAS WT pts and patients with KRAS WT tumors (panitumumab arm: n = 259; FOLFOX arm, n = 252) was included in this analysis. Patients receiving panitumumab plus FOLFOX had a significantly improved duration of quality-adjusted survival compared with patients treated with FOLFOX alone. Clinical trial information: NCT00364013.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Association between c-Met expression, miR-31-3p expression and progression free survival in the New EPOC study. First Author: Sian Alexandra Poulakis, University Surgery, University of Southampton, Southampton, United Kingdom

Background: Cetuximab in combination with chemotherapy resulted in a shorter progression free survival (PFS) when given before and after resection for colorectal liver metastases (CRLM) in the New EPOC study. MIr-31-3p expression in the primary tumor of these patients was shown to be predictive of the effect of cetuximab and other studies implyc c-Met in resistance to anti-EGFR therapy. We evaluated if c-Met expression in CRLM, in parallel with miR-31-3p, was associated with the earlier progression seen with cetuximab. Methods: MIr-31-3p expression was determined by qPCR and c-Met protein expression by immunohistochemistry in primary tumor and CRLM tissue for 94 New EPOC patients (Chronos (CT) n = 48, ChemoCetux (CTC) n = 46). c-Met expression was scored dependent on staining intensity; 0, negative; 1, weak; 2, moderate; 3, strong. Consequences of elevation or lowering of c-MET and miR-31-3p were analyzed using Spearman rank correlation (median time to progression (TTP) confirmed, duration 6 mo, 1 continuing; 13% ORR), and 7 (46%) SD (median time to progression (TTP) = 5.0 mo). All 3 GC pts had SD (one continuing for 11 mo). Of 14 PC pts (median 2 prior therapies), 7 (50%) had SD with a median TTP of 3.4 mo. In 26 CRC pts (median 4 prior therapies), there was 1 PR (confirmed, duration 10 mo), 14 SD (54%), and a median TTP of 5.1 mo. Conclusions: Repeated cycles of IMMU-132 monotherapy are well tolerated, leading to more favorable neutropenia and diarrhea rates compared to irinotecan. Objective responses in esophageal cancer and extended stabilization in colorectal cancers are encouraging for this monotherapy. The manageable toxicity and promising disease control in these pts warrant further study in combination with other appropriate agents for GI malignancies. Clinical trial information: NCT01631552.

Evaluation of miR 31 3p as a biomarker of prognosis and panitumumab benefit in RAS-wt advanced colorectal cancer (aCRC): Analysis of patients (pts) from the PICCOLO trial. First Author: Pierre Laurent-Puig, UMR-S1147, INSERM, Paris Descartes University, Paris, France

Background: miR 31 3p expression has previously shown correlation with outcomes in KRAS wild-type (wt) aCRC patients receiving EGFR-targeted therapy. We have therefore evaluated miR 31 3p in a large randomized trial of panitumumab. The a priori hypothesis was that pts with the lowest miR 31 3p expression would have better outcomes and increased benefit from panitumumab. Methods: miR 31 3p was measured in tumor from 213 pts randomized to irinotecan (ir, n = 111) or irinotecan/panitumumab (irPan, n = 102) in a trial of second line therapy for aCRC (PICCOLO). The analysis population comprised RAS wt (KRAS and NRAS wt) pts (n = 188: ir = 101, irPan-B7). End-points were progression-free survival (PFS), overall survival (OS), complete/partial response rate (RR) and disease control rate (DCR). The predefined model divided pts into 3 tertiles with high, intermediate (int) and low miR 31 3p expression, and compared outcomes and treatment effects across these groups. Multivariate analysis was performed, adjusting for Kôhne score. Results: In the prognostic analysis, compared with low expression pts and after adjustment for treatment, int and high pts had worse OS (HR 1.58, 2.03 respectively; p = 0.0012) and worse PFS (HR 1.60, 1.60 respectively; p = 0.018). In multivariate analysis, miR 31 3p and Kôhne score were independently associated with OS (p = 0.0006 and p = 0.002 respectively). miR 31 3p was also significantly independently associated with PFS (p = 0.016, 0.015) and OS (p = 0.074). In the predictive analysis, panitumumab produced marked PFS benefit in pts with low and int miR 31 3p expression (HR = 0.50 [p = 0.019] and HR = 0.57 [p = 0.031] respectively), but not in pts with high expression (HR 0.72, p = 0.23); however, a statistically significant treatment expression interaction was not seen. Conclusions: Pts with low miR 31 3p have significantly better OS, PFS, RR and DCR, independent of treatment. Pts with low int miR 31 3p had significant PFS benefit from panitumumab whilst pts with high miR 31 3p did not; however this study was not powered to demonstrate a statistically significant treatment/ expression interaction. miR-31-3p is a highly promising biomarker in aCRC.

Sacituzumab govitecan (IMMU-132) is a conjugate of a humanized anti-Trop-2 (trophoblast cell-surface antigen) coupled site-specifically to SN-38 (7.6 moles SN-38/IgG), an active metabolite of irinotecan, using a proprietary linker. Trop-2 is widely expressed in most epithelial cancers, including gastrointestinal (GI) tumors, and therefore the safety and efficacy of this new ADC is being examined in esophageal (EAC), gastric (GC), pancreatic (PC), and colorectal cancers (CRC). Methods: A Phase II clinical trial (ClinicalTrials.gov, NCT01631552) was initiated in patients with diverse epithelial cancers, administering IMMU-132 i.v. on days 1 and 8 of 21-day treatment cycles. Treatment was continued based on tolerance or until progression. Results: In Phase I, 23 assessable pts were given 8, 10, 12, or 18 mg/kg. Dose-limiting neutropenia occurred at 18 mg/kg. For Phase II, enrollment was expanded to multiple cycles of 8 and 10 mg/kg. Safety data from 123 patients given 8-10 mg/kg showed neutropenia (G3, 18%; G4, 6%), febrile neutropenia (G3, 2%; G4, 2%), but only 3% G3 diarrhea (no G4). Other G3 toxicities included anemia (6%), fatigue (5%), leukopenia (2%), vomiting (2%), and asthenia (1%). No pt developed antibodies to the ADC. Among assessable patients by RECIST 1.1, of 15 EAC pts (median 3 prior therapies), 2 had PR (confirmed, duration 6 mo, 1 continuing; 13% ORR), and 7 (46%) SD (median time to progression (TTP) = 5.0 mo). All 3 GC pts had SD (one continuing for 11 mo). Of 14 PC pts (median 2 prior therapies), 7 (50%) had SD with a median TTP of 3.4 mo. In 26 CRC pts (median 4 prior therapies), there was 1 PR (confirmed, duration 10 mo), 14 SD (54%), and a median TTP of 5.1 mo. Conclusions: Repeated cycles of IMMU-132 monotherapy are well tolerated leading to more favorable neutropenia and diarrhea rates compared to irinotecan. Objective responses in esophageal cancer and extended stabilization in colorectal cancers are encouraging for this monotherapy. The manageable toxicity and promising disease control in these pts warrant further study in combination with other appropriate agents for GI malignancies. Clinical trial information: NCT01631552.

C-reactive protein and interleukin-6 as markers of systemic inflammatory response and as prognostic factors for metastatic colorectal cancer. Data from the randomized phase III NORDIC-VII study. First Author: Maria Thomsen, Oslo University Hospital, Oslo, Norway

Background: A systemic inflammatory response (SIR) affects prognosis and treatment outcome in metastatic colorectal cancer (mCRC). The aim of the study was to explore the prognostic significance of several SIR-derived markers and the correlation between the best marker of SIR and plasma interleukin-6 (IL-6). Methods: The study was based on data from the randomized phase III NORDIC-VII study (NORDIC FLOX +/- cetuximab as first line treatment of mCRC). The effect of different markers of SIR, including modified Glasgow Prognostic Score (mGPS), derived Neutrophil Lymphocyte Ratio (dNLR), levels of platelets and levels of C-reactive protein (CRP) on survival were analyzed by Kaplan-Meier plots, log-rank test, and Cox Proportional Hazards model. Further, the relationship between CRP, IL-6 and RAS and BRAF mutation status was examined.

Results: 374 patients were eligible for the comparison of markers of SIR and 393 were eligible for the final analysis related to CRP, IL-6 and RAS and BRAF mutation status. The prognostic significance of CRP was at least as strong as the other markers of SIR. CRP together with 23's were selected for further investigation. Log-transformed CRP and IL 6 were highly correlated (r = 0.661, p < 0.0001) and an increasing level of pretreatment CRP was associated with impaired survival. Stratified by CRP level ≥ 10, 11-30, 31-60, and > 60 mg/L, the different groups showed a median overall survival (OS) of 6.17, 3.15, 1.96, and 1.61 months respectively (HR = 1.34, 95% CI 1.22-1.48, p < 0.001), and had a median progression-free survival (PFS) of 8.9, 7.6, 8.2, and 6.6 months, respectively (HR = 1.21, 95% CI 1.10-1.33, p < 0.001). Furthermore, CRP levels had a similar influence on prognosis in subgroups of patients based on RAS and BRAF mutation status. Conclusions: This is the largest study analyzing markers of SIR in a population of homogenously treated mCRC patients. Increasing CRP values were associated with impaired prognosis and the prognostic significance of CRP is at least equal to that of other markers of SIR. CRP values were highly correlated with IL-6 levels and may be used as a marker for plasma levels of IL-6. Clinical trial information: NCT00145314.
Epidermal growth factor receptor mutations confer resistance or cross-resistance to cetuximab and panitumumab and can be detected in circulating tumor DNA. First Author: Katsunori Imai, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France

Background: Acquired resistance to epidermal growth factor receptor (EGFR) targeted antibodies represents a clinical challenge in the treatment of gastrointestinal tumors such as metastatic colorectal cancer, but its molecular mechanisms are incompletely understood. Methods: We scanned KRAS exon 2/3/4, NRAS exon 2/3/4 and the overlapping epitopes of the EGFR antibodies cetuximab and panitumumab for mutations in pre- and post-treatment tumor tissue of 21 patients with gastrointestinal cancer treated with chemotherapy +/- EGFR antibodies by targeted next-generation sequencing (“tumor tissue” cohort). Binding, signaling and drug sensitivity studies were performed in Ba/F3 cells stably transduced with wt and mutant EGFR. Results were validated in circulating tumor DNA (ctDNA) of an independent “liquid biopsy” cohort of 27 patients. Results: We describe a novel EGFR exon 12 mutation acquired in tumors of 1 out of 3 patients treated with panitumumab in the “tumor tissue” cohort. This mutation introduces a positive charge within the overlap of the panitumumab and cetuximab epitopes. It abrogates antibody binding and mediates cross-resistance to both antibodies in EGFR-mutant transfected Ba/F3 cells. In ctDNA from the “liquid biopsy” cohort, we found this novel mutation in 1 out of 6 panitumumab-treated patients while about one third of patients show acquired RAS mutations. Conclusions: We show that acquired resistance by epitope-changing mutations also emerges during panitumumab treatment and may follow similar biochemical principles as in cetuximab resistance. Such mutations can be easily detected by next-generation sequencing of ctDNA and may perspectively help in tailoring EGFR-targeted therapies.

A simplified nomogram to predict long-term survival after conversion chemotherapy followed by hepatectomy for initially unresectable colorectal liver metastases. First Author: Yu Sunakawa, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Although the recent advances in surgery and chemotherapy have enabled hepatectomy in patient with initially unresectable colorectal liver metastases (CRLM), limited number of patients could actually benefit from this strategy. The aim of this study was to develop a simplified nomogram to predict long-term survival for initially unresectable CRLM treated with conversion chemotherapy followed by hepatectomy. Methods: From a cohort of 1275 patients who underwent hepatectomy between 1990 and 2012, 439 patients (34.4%) with initially unresectable colorectal liver metastases (CRLM) were enrolled in this study. A nomogram to predict overall survival was developed based on the result of multivariate cox model. The predictive performance of the model was assessed by C-index, Harrell's concordance index, calibration plots. Results: The median number of liver metastases was 5 both at diagnosis and at hepatectomy, and median tumor size was 50 mm at diagnosis and 35 mm at hepatectomy, respectively. Median number of preoperative chemotherapy courses was 10 with 136 patients (31.0%) receiving more than 3. Concomitant extrahepatic disease was observed in 148 patients (33.7%). Liver curative and globally curative surgery were achieved in 380 (86.6%) and 335 patients (76.3%), respectively. The 5-year overall and disease-free survival was 39.9% and 10.0%, respectively. Based on the multivariate cox model, 5 independent prognostic factors were selected in the nomogram: Tumor sub-group: Lynch syndrome, microsatellite stable (MSS), MSS with MSIR, MSS with PIK3CA mutations, and MSS with PIK3CA and MSI neo-mutations. KRAS mutation was not included in the nomogram. We developed logistic regression model. The predictive performance of the model was assessed by C-index, Harrell's concordance index, calibration plots. Conclusions: The proposed nomogram could easily stratify individual patients with initially unresectable CRLM into prognostic groups. Patients with nomogram-predicted score > 15 should be contraindicated to surgery.
Comprehensive genomic profiling of clinically advanced colorectal carcinoma (CRC) can reveal frequent opportunities for targeted therapies. First Author: Jennifer S. Ross, Albany Medical College.

Background: For patients presenting with advanced and metastatic colorectal cancer (mCRC), to influence and personalize therapy selection. Given the limited treatment options, the number of patients harbored CRC which have the potential to benefit from personalized therapy. These tools have the potential to aid prognostication and externally validate. These tools have the potential to aid prognostication and externally validate.

Conclusions:

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Impact of primary tumor stage on survival following resection of metachronous liver and/or lung metastases in colorectal cancer. First Author: Hui-Li Wong, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Background: Resection of isolated liver and/or lung metastases in patients (pts) with metastatic colorectal cancer (mCRC) offers a chance at long-term survival. Multiple prognostic models have been developed to predict outcomes following resection, but the role of primary tumor stage remains controversial. Contributing to a recent debate regarding the impact of stage on the value of routine pt follow-up.

Methods: Consecutive pts with resected liver and/or lung metastases following prior therapy for an early stage CRC, entered into a retrospective database between 2000 and 2014 were identified. Cox regression analysis was performed to examine the impact of primary tumor stage on overall survival.

Results: 867 pts with mCRC were identified; median follow-up was 40.1 months. 215 (25%) had undergone liver and/or lung resection. Among the 125 patients who were planned to perform TSH and were enrolled in this study. Based on the result of univariate analysis, initial stage was predictive of OS, where best outcomes were seen in pts with stage I or II disease (Table). Conclusions: Pts with a previous stage I primary cancer contribute only a small proportion of those undergoing resection of metachronous disease but have excellent outcomes, suggesting routine follow-up of stage I pts is worthwhile. With increasing primary tumor stage, survival outcomes deteriorate. However, the majority of 5-year survivors are pts with high-risk primaries, justifying follow-up in this pt group. Better markers of recurrence risk and of benefit from metastasectomy would be beneficial.

**Table**

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<th>Stage</th>
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<td>I</td>
<td>12.1 (8.0 to 16.2)</td>
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<tr>
<td>II</td>
<td>3.5 (2.4 to 4.6)</td>
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<tr>
<td>III</td>
<td>0.9 (0.6 to 1.2)</td>
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<td>IV</td>
<td>0.5 (0.3 to 0.7)</td>
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**Conclusion:** The results indicate that primary tumor stage is an important predictor of survival following resection of liver and lung metastases in mCRC, with stage I pts having the best outcomes.

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Moving forward and beyond the standard through a non-operative management in rectal cancer? Our watch and wait approach experience in Co-Recto. First Author: Ilma Soledad Sais, Clinical Oncology Unit, Hospital Bonorino Udaondo, Buenos Aires, Argentina

Background: Controversies exist about the proper management of pts with clinical complete tumor regression after preoperative therapy. A non-operative management (NOM) of selected patients has achieved promising long-term outcomes in some Watch and Wait (W&W) series. Regardless of encouraging results, and in spite of being a readily accepted strategy by patients, reluctance to recommend this strategy is still an affordable option that still exists in rectal cancer guidelines. Our aim is to evaluate the NOM for pts with clinical complete response discussed in Co-Recto interdisciplinary and cooperative team for the Management of Rectal cancer阿根廷 Methods: Pts with resectable rectal cancer (stage I-III) selected for neoadjuvant therapy in Co-Recto between 2008-2014 were retrospectively reviewed to determine pts with clinical complete response(CR) selected for Non operative management. cCR was defined between digital exam, endoscopic criteria, MRI and CEA. F-up for W&W policy was performed during the first two years with MRI and EUS three-monthly and CT six-monthly. Results: 32pts with cCR were included. Initial staging was performed by MR (30/32, 94%) and EUS(6/32, 19%). 40.5% (12/32) were T2-T3ab N0; 59.5% (19/32 were T3c/d-T4, N+ and 49% (16/32) had CRM+. Median distance from anal verge was 30mm . Involvement into/below the elevator muscle: 34%/11/32 . CRT consisted of long-course RT (50.4 Gy) with capecitabine (825mg/m² for 7 (8)w). Induction chemotherapy (CAPOX) was administered in 37.5% followed by CRT. Response assessment was done at 7 (5-12)w. Adjuvant therapy was administered in 18%. LR was observed in 3/32 pts (9%) within the rectal wall, 2/3 a mesorectal nodal recurrence without endoluminal recurrence, 1/3 had endoluminal component. All pts had free of salvage resection, PFS= 36 m(25-49m) Distant metastases and extrarectal pelvic recurrence weren’t observed in any case. After fup of 40 m (8-66m), no deaths occurred. Conclusions: A NOM with a close follow was a feasible approach, had optimal outcome avoiding surgical functional sequelae. To mitigate the remaining skepticism about W&W, collaborative randomized trials should be implemented.

3563 Poster Session (Board #55), Mon, 8:00 AM–11:30 AM

Improvement in long-term survival in patients with metastatic colorectal cancer (CRC) after liver resection with modern chemotherapy and hepatic arterial infusion (HAI). First Author: Nancy E. Kemeny, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Hepatic resection of metastases from CRC is associated with 5-year (y) and 10-year overall survival (OS) of 30-50% and 20%. The aim of this study was to update OS of 5 consecutive adjuvant (adj) studies using HAI + systemic (sys) after liver resection and to determine effects of clinical factors on long-term OS. Methods: Patients (pts) treated on protocols with HAI FUDR/doxorubicin + sys from 1991 to 2015 with the following inclusion criteria: completely resected hepatic metastases, no extrahepatic disease, bilirubin <1.5mg/dL, platelet count >100,000/uL, and no concurrent infection. Pts on studies before 2003 were treated with HAI + sys FUDR or irinotecan (CPT) and pts on studies after 2003 were treated with HAI + sys oxaliplatin/LV or CPT/FU/LV = molecular targeted therapies. OS was calculated from the time of liver resection until death and was estimated using the Kaplan-Meier method. Using Greenwood’s formula, 95% CI at fixed time points for outcomes were calculated and compared between treatment years (before 2003 vs after 2003). Results: 329 pts were included with a median follow-up of 9.6 y. 5 y for those treated before and after 2003 was 56% (95% CI: 49%-63%) and 80% (95% CI: 71%-85%), respectively (p < 0.01). 10 y OS for pts treated before 2003 was 40%, while 10-y OS is not yet obtainable for pts treated after 2003. Various clinical factors and significant p-values (p) known to influence survival are shown in the table below. Conclusions: Survival for pts undergoing hepatic resection and adj HAI is improving. Pts treated before 2003 with liver resection and adj HAI = sys have a 5-y OS of 56%, while pts treated after 2003 with HAI + mod sys chemotherapy have a 5-y OS of 80%.

3564 Poster Session (Board #56), Mon, 8:00 AM–11:30 AM

Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups. First Author: Atsushi Ohtsu, National Cancer Center Hospital East, Kawasaki, Japan

Background: TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analog trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). The efficacy and safety of TAS-102 in patients (pts) with metastatic colorectal cancer refractory/irrelevant to standard therapies were evaluated in the RECOURSE trial; enrollment criteria included ≥2 prior lines of standard chemotherapy. Primary results of RECOURSE demonstrated a significant improvement in overall survival (OS) and progression-free survival (PFS) with TAS-102 vs placebo (PBO) (hazard ratio [HR] = 0.68 and 0.48 for OS and PFS, respectively; both P < 0.0001). Methods: RECOURSE data were evaluated for efficacy and safety, including rate of hospitalizations, of TAS-102 vs PBO by each geographic subgroup of US, EU, and Japan (JP). Results: Of 768 pts, 99 US (mean age, 60 y), 403 EU (mean age, 65 y), and 266 JP (mean age, 62 y) pts were randomized to receive TAS-102 or PBO. Median OS with TAS-102 vs PBO was 6.6 mo vs 4.3 mo in US pts, 6.8 mo vs 4.9 mo in EU pts, and 7.8 mo vs 6.7 mo in JP pts. HRs for OS and PFS for US, EU, and JP vs PBO are shown in the Table. No statistically significant subgroup interactions were observed in each geographic subgroup randomized to TAS-102 vs PBO, with an acceptable safety profile. Clinical trial information: NCT01607957.
3565  Poster Session (Board #57), Mon, 8:00 AM-11:30 AM
Using mutational load in next generation sequencing (NGS) to identify mismatch repair (MMR) deficiency in colorectal cancer (CRC). First Author: Francesca Battaglin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NCCN guidelines recommend screening all CRC patients diagnosed at age ≤ 70 years and those > 70 who meet Bethesda Criteria with either immunohistochemistry (IHC) for MMR protein expression or PCR for microsatellite instability (MSI), and also recommend tumor sequencing for RAS/BRCA mutations in all CRC patients with metastatic disease. MMR status is also needed for management of patients with stage III colon cancer patients, and BRAF mutational status is useful in work up of MMR-deficient (dMMR) tumors. We hypothesized that the higher mutational burden of dMMR tumors would permit their identification on the basis of the mutation count in an NGS panel, thus allowing a single multi-gene NGS assay to replace those currently used for only RAS/RAF detection, and also MMR deficiency. Methods: Under an IRB waiver, an institutional electronic database was queried to identify all CRC analyzed with MSK-IMPACT, our custom 341-gene NGS assay. Tumor mutational load, defined as the raw number of somatic mutations identified, was determined for each case and compared between MMR-proficient and MMR-deficient cases. Results: We identified 149 unique CRC patients tested with MSK-IMPACT. Of these, 93 had MMR status available, including 8 dMMR cases. 83 of 85 (98%) of MMR-proficient cases had 16 or fewer mutations, while two outliers with 158 and 250 mutations each were found to be POLE-mutant. MMR-deficient tumors had a higher mutational load with a significantly higher median number of somatic mutations (45, range 23-67) than MMR-proficient tumors (6, range 0-16), p = 0.0024. Conclusions: This preliminary analysis suggests that using a cut-off for mutational load, such as 20 mutations for MSK-IMPACT, may provide a highly sensitive and specific means of identifying dMMR cases, and may serve as the same assay used for tumor genotyping. If validated, the use of a single multi-gene sequencing assay to screen for both dMMR and RAS/BRCA mutations could be cost effective, particularly in metastatic CRC, but also in early stage disease, while providing additional genetic information that may be useful for research purposes. Larger numbers of dMMR tumors are currently being analyzed with MSK-IMPACT to validate this hypothesis.

3566  Poster Session (Board #58), Mon, 8:00 AM-11:30 AM
Genomic analysis of colitis-associated cancers. First Author: Rona D. Yaeger, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients (pts) with inflammatory bowel disease (IBD) (Crohn’s disease (CD) and ulcerative colitis (UC)) are at increased risk for small bowel or colorectal cancers (Colitis Associated Cancers, CAC). The genomic alterations (GA) associated with CAC have not been well-described. We hypothesized that GA associated with CAC are different than those seen with sporadic colorectal cancer (CRC). Identification of these alterations may lead to improved early detection and therapeutic options. Methods: We defined GA in 15 CAC cases confirmed as being associated with IBD (MSKCC including 11 UC and 4 CD, 14 primary and 1 metastasis (median age 55, range 29-77; 73% male). Primary tumor sites were ileum (2), right colon (5), and left colon (8). Histologic subtypes were moderately differentiated adenocarcinoma (4), mucinous (7), and signet ring/diffuse (4). Hybridization capture of the entire coding sequence of 405 cancer-related genes, including those associated with early onset IBD, was applied to DNA extracted from FFPE tumor specimens and sequenced to high, uniform coverage (> 500x). All classes of GA including substitution, indel, copy number alteration and rearrangement were determined. Results: Potentially clinically relevant GA were identified in 8/15 CAC, including ERBB2 amplification (amp), ERBB2S310F, EML4-ALK, FGFR2 amp, FGFR2 amp + FGFR2-TACC2 (same patient), PDGFA T1345, and Braf V600E + TSC2 truncation (same patient). IDH1 R132H/C were found in 2/4 CAC cases (one concurrent with FGFR2 amp/fusion). Overall, 5.7 GA per tumor were detected (range 1-12), GA in TPS3 (the most commonly altered gene), occurred in 14/15 cases (93%; 10 known hot spot mutations), compared to 52% in CRC TCGA. KRAS and APC mutations occurred in 33% and 20%, respectively, compared to 43% and 76% in CRC TCGA. Other recurrently altered genes included SMAD4 (20%) and RNF43 (13%). Key GA analyses with early onset IBD were identified. Conclusions: Comprehensive genomic profiling identified a high frequency of potentially clinically relevant GA in CAC. GA seen in CAC suggest substantial differences from those of sporadic CRC; APC activation is infrequent and TP53 mutations are nearly universal including frequent possibly gain of function. Study of additional cases is ongoing.

3567  Poster Session (Board #59), Mon, 8:00 AM-11:30 AM
FOLFOX-afibercept followed by maintenance therapy with fluoropyrimidine-afibercept as first-line therapy in patients with metastatic colorectal cancer: A GERCOR single-arm phase II study (VELVET). First Author: Benoist Chibaudel, Institut Hospitalier Franco-Britannique, Levallois-Perret, France

Background: VEGF inhibition with (ziv-)afibercept, a recombinant human fusion protein, in combination with FU/irinotecan improves patient outcomes (overall survival (OS), progression-free survival (PFS), overall response rate (ORR)) in second-line therapy of patients with metastatic colorectal cancer (mCRC) (2016). In a recent screen (2018) with the same assay used for tumor genotyping, if validated, the use of a single multi-gene sequencing assay to screen for both dMMR and RAS/BRCA mutations could be cost effective, particularly in metastatic CRC, but also in early stage disease, while providing additional genetic information that may be useful for research purposes. Larger numbers of dMMR tumors are currently being analyzed with MSK-IMPACT to validate this hypothesis.

Methods: From May 2013 to May 2014, 49 patients were included. One patient did not receive study treatment. Thirty-seven (84.1%, se 5.5) patients were alive at 6 months without documented RECIST progression. Conclusions: The preliminary analysis suggests that using a cut-off for mutational load, such as 20 mutations for MSK-IMPACT, may provide a highly sensitive and specific means of identifying dMMR cases, and may serve as the same assay used for tumor genotyping. If validated, the use of a single multi-gene sequencing assay to screen for both dMMR and RAS/BRCA mutations could be cost effective, particularly in metastatic CRC, but also in early stage disease, while providing additional genetic information that may be useful for research purposes. Larger numbers of dMMR tumors are currently being analyzed with MSK-IMPACT to validate this hypothesis.

3568  Poster Session (Board #60), Mon, 8:00 AM-11:30 AM
Cetuximab biweekly plus mFOLFOX6 as first-line therapy in patients (pts) with KRAS wild-type (wt) (exon 2) metastatic colorectal cancer (mCRC): Primary endpoint and subgroup analysis of the CEBIFOX trial. First Author: Stefan Kasper, Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany

Background: The multicenter, single-arm, phase II CEBIFOX trial (Simon’s two stage minimax design) evaluated the efficacy of mFOLFOX6 + biweekly cetuximab (500 mg/m²) as 1st line therapy in KRAS wt (exon 2) mCRC. Final efficacy data as well as extended molecular and clinical subgroup analyses were presented at ASCO (2022) and this abstract will present an update. Methods: Primary endpoint was objective response rate (ORR) per RECIST 1.0, secondary endpoints were safety, metastasectomy rate, quality of life, progression-free (PFS) and overall survival (OS). Extended molecular profiling was performed using NGS-based panel sequencing including NRAS (exon 2-4), KRAS (exon 2-4), BRAF (exon 15) and PIK3CA (exon 10 and 21). Clinical parameters included: tumor localisation (right sided vs. left sided-LCRC), liver-limited disease (LLD), early tumor-shrinkage (ETS), depth of response (DPR), metastasectomy rate, quality of life, progression-free (PFS) and overall survival (OS). Conclusions: This study warrants further investigation to confirm efficacy and safety of the combination in a randomized controlled trial. Clinical trial information: EudraCT 2012-003521-25.
3569 Poster Session (Board #61), Mon, 8:00 AM-11:30 AM
Phase I study of preoperative chemoradiation with temozolomide and capecitabine in patients with locally advanced rectal cancer. First Author: Yong Sang Hong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

**Background:** Preoperative chemoradiation (CRT) with capecitabine is one of the standard treatment strategies in patients with locally advanced rectal cancer (LARC). Temozolomide improved survival of patients with glioblastoma when administered with radiotherapy (RT), especially in those with hypermethylated MGMT (O'-methylguanine DNA methyltransferase). MGMT hypermethylation has been suggested as one of the colorectal carcinogenesis pathways. **Methods:** RT was delivered with 45 Gy/25 daily fractions with coned-down boost of 5.4 Gy/3 fractions. Concurrent chemotherapy consisted of fixed dose of capecitabine (825 mg/m² twice daily) and escalating dose of temozolomide (45 [level 1], 60 [level 2], and 75 mg/m²/day [level 3]). MGMT hypermethylation was examined by methyl-specific PCR in the pre-treatment tumor samples. **Results:** Between May 2013 and Apr 2014, a total of 22 patients with LARC of CT3-4NO or cT3,cN1-2 were accrued. Dose-limiting toxicity did not occur among 10 patients up to dose level 3, and the dose level 3 was chosen as the recommended dose (RD). Additional 12 patients were accrued in the RD. There was no grade 4 adverse event (AE), and grade 3 AEs included leucopenia (9.1%), nausea (4.5%), and vomiting (4.5%). Pathologic complete responses (pCR) were observed in 7 patients (7/22, 31.8%). MGMT hypermethylation was found in 16 patients (16/22, 72.7%). The pCR rate was 37.5% (G1/6) in the hypermethylated MGMT group and 16.7% (1/6) in the unmethylated MGMT group (p = 0.62). **Conclusions:** The RD of temozolomide was determined to 75 mg/m²/day when added in the preoperative CRT with capecitabine. Preoperative CRT with temozolomide plus capecitabine was tolerable. There was a tendency of higher pCR rates in those with hypermethylated MGMT; therefore, further randomized study will be warranted. Clinical trial information: NCT01781403.

3571 Poster Session (Board #63), Mon, 8:00 AM-11:30 AM
Immunohistochemistry to initiate a complex screening cascade in the detection of Lynch syndrome. First Author: Graine O’Kane, St. James’s Hospital, Dublin, Ireland

**Background:** Lynch Syndrome (LS) accounts for 2-4% of all colorectal cancers (CRC) and is caused by germline mutations in DNA mismatch repair (MMR) genes. Increasing literature supports routine screening for LS using immunohistochemistry (IHC) to detect deficiencies of MMR proteins in tumor tissues. We reviewed practices at 3 Irish cancer centres. The number of MMR deficient (dMMR) tumours detected was evaluated, and the subsequent number of genetic referrals and LS diagnoses determined. **Methods:** Colorimetric database of 3 Irish academic centres were reviewed from January 2005 - 2013. Centre 1 performs IHC upon physician request, centre 2 implemented reflex IHC (IHC in November 2008, and Centre 3 implemented IHC since 2012. All cases were diagnosed of colorectal adenocarcinoma with available histology were included. Pathology reports were reviewed and genetic referrals analysed. **Results:** A total of 4,021 new CRC were diagnosed in 3,929 patients across 3 centres. The results are presented in the table below. The implementation of universal screening using IHC in cancer centre 3 detected an increased number of dMMR tumours (p = 0.01), however this did not result in a similar increase in cancer genetics referrals or Lynch syndrome diagnoses. A high proportion of patients underwent germline testing once referred.

<table>
<thead>
<tr>
<th>Centre</th>
<th>IHC when requested</th>
<th>IHC since 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre 1</td>
<td>964</td>
<td>1246</td>
</tr>
<tr>
<td>Centre 2</td>
<td>70 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
| Centre 3 | 1706 | 153 (15%)
| No. (%) patients with dMMR | 536 (64%) | 1760 (100%) | p < 0.01 |
| No. (%) patients with IHC | 69 (27.6%) | 201 (11%) | p < 0.01 |
| 31 (3%) | 40 (7%) | 56 (28%) |
| 14 (5%) | 17 (11%) |
| 14 (5%) | 16 (9%) | 36 (25%) |
| 7 (2.7%) | 7 (2.8%) | 191 (11.5%) |

* First author does not account for IHC if patients who may not have been referred. ** 2 results pending. *** 7 results are pending.

3570 Poster Session (Board #62), Mon, 8:00 AM-11:30 AM
S-1 as adjuvant chemotherapy for stage III colon cancer: Updated outcomes of ACTS-CC trial. First Author: Yusuke Kinugasa, Division of Cancer and Rectal Surgery, Shizuoka Cancer Center Hospital, Shizuoka, Japan

**Background:** The ACTS-CC trial, a randomized phase III trial, demonstrated that adjuvant therapy with S-1 for stage III colon cancer was non-inferior in 3-year disease-free survival (DFS) to that of tegafur-uracil plus leucovorin (UFT/LV). We updated DFS and overall survival (OS), and performed some clinically relevant subgroup analyses. **Methods:** A total of 1,535 patients with stage III colon cancer were randomly assigned to receive S-1 (80-120 mg/day on days 1-28 every 2 days, 4 courses) or UFT/LV (UFT: 300-600 mg/day and LV: 75 mg/day on days 1-28 every 35 days, 5 courses). Primary endpoint was DFS. Secondary endpoints were OS and safety. **Results:** A total of 1,518 patients (758 in the S-1 group and 760 in the UFT/LV group) were included in the efficacy analysis. Median follow-up was 63.5 months, the mean age at enrollment was 64.5 years, wide lymph node dissection (D3) was done in 79.8%, the median number of dissected lymph nodes was 17, and stage II/III/IV IIIC were 15%/71%/14%. The hazard ratio (HR) for DFS was 0.88 (95% CI, 0.74-1.06; p = 0.177). The 5-year DFS rate was 70.2% in the S-1 group and 66.9% in the UFT/LV group. In the subgroup analysis, no significant interactions were identified between the major baseline characteristics and the DFS in S-1 and UFT/LV, except for histological type; favors S-1 in patients with poorly-differentiated adenocarcinoma. Approximately 5% of patients in the both groups experienced second cancers. Among the patients with recurrences in each group, 46.3% and 44.7% underwent surgical resection as an initial treatment for recurrence. The HR for OS was 0.92 (95% CI, 0.72-1.17; p = 0.488). The 5-year OS rates were 86.0% and 84.4% in the S-1 and UFT/LV groups, respectively. **Conclusions:** Adjuvant therapy of S-1 for stage III colon cancer was confirmed to be non-inferior in DFS and OS to those of UFT/LV after long follow-up. Favorable OS might be brought by the high recurrence rate of recurrent lesions. Clinical trial information: NCT00660894.

3572 Poster Session (Board #64), Mon, 8:00 AM-11:30 AM
Cost-effectiveness for extended RAS/RAF testing in metastatic colorectal cancer. First Author: Marwan R. Al-hajeili, Karmanos Cancer Ctr, Grosse Pointe Farms, MI

**Background:** Epithelial growth factor receptors (EGFR) inhibitors (Cetuximab and panitumumab) are monoclonal antibodies directed against EGFR and promote apoptosis. Douillard et al demonstrated the benefit of using EGFR inhibitors agents in wild type (WT) KRAS metastatic colorectal cancer (mCRC) and lack of benefit in mutated KRAS mCRC patients. Only WT KRAS mCRC are candidate for EGFR inhibitors, they constitute 57.6% of all mCRC patients, 27.3% of them carry other RAS/RAF mutations that preclude them from EGFR inhibitors benefits. Insurance companies are willing to pay the cost of KRAS testing and EGFR inhibitors treatment for all WT KRAS mCRC. We conducted this analysis to assess the cost-effectiveness of the extended testing for other RAS/RAF mutations for WT KRAS mCRC patients. **Methods:** A decision analysis model using TreeAge pro Software, Williamstown, MA was developed to assess and compare treatment costs and disease outcomes associated with presence or absence of additional mutations (RAS/RAF) in a WT KRAS mCRC. For utility estimate, Quality of life (Qol) assessment based on Skindex-16 for EGFR inhibitors side effects. The difference in median survival time was used to calculate incremental effectiveness of using EGFR inhibitors based on the extended testing or not. Costs were determined through Medicare records and direct hospital charges for extended testing, and treatment with EGFR inhibitors. For sensitivity analysis, we modify mutations probability and the extended testing cost, in both 1-way and combined 2-way sensitivity analyses. **Results:** The total expected cost was $56,306.06 vs. $42,683.75 favoring additional testing. The median overall survival was 15.8 vs. 14.5 months favoring additional testing. In order to conclude extended testing is not worth it, mutation probability has to be less than 1.8%, or extended testing cost, in both 1-way and combined 2-way sensitivity analyses. Our analysis shows that extended testing for other RAS/RAF mutations is cost-effective in WT KRAS mCRC patients before treating with EGFR inhibitors.
Molecular classification of the invasive front in colorectal cancer. 

**First Author:** Darragh McArt, CCRCB, Queen’s University, Belfast, United Kingdom

**Background:** Despite the use of 5-FU-based adjuvant therapies, a large proportion of stage III (locally advanced) colorectal cancer (CRC) patients will relapse and die of metastatic disease. Recent data from phase III trials using the anti-VEGF or the anti-EGFR mAbs have shown that, in contrast to the metastatic setting, these agents do not prolong survival in stage III CRC. Therefore, novel drugs are needed that result in further increases in overall survival in stage III CRC patients. The aim of this study was to investigate the invasive front of stage III CRC at the molecular level and correlate with clinical and pathological variables. 

**Methods:** mRNA was extracted from macrodissected FFPE CRC, central tumour and invasive front from 25 patients. Transcriptional analysis was performed using the CRC DSA microarray platform. Samples were analysed using limma for lists of differential expressed genes and using a supervised learning approach, pamr, to extract succinct gene lists between contrasts and visualised with bootstrap clustering and heatmaps. 

**Results:** The pre-treatment status of E-cadherin was measured using IHC. E-cadherin expression was examined in both the centre of the tumour and the invasive front. Prominent classifiers evidenced included genes with a role in inflammation and immune signalling (eg. CXCL5, C7, IL8), EMT (eg. SFRP2, WNT5A) and growth factor receptor signalling (eg. IGF1). Comparison of this expression list with the recent published gene lists, characterizing the poorest prognostic EMT/stem-cell like subgroup, showed that there is a high degree of overlap between these two signatures. 

**Conclusions:** Taken together, our study is the first to indicate that, in order to disseminate and metastasize, tumour cells at the invasive front develop an EMT phenotype with a molecular signature, similar to the poor prognostic stem-like molecular CRC subgroup. This data could aid in the identification of novel treatment strategies to prevent tumour recurrence/metastasis in stage III CRC.

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**Poster Session (Board #65), Mon, 8:00 AM-11:30 AM**

**Zonal differences in PD-1 expression in centre of tumour versus periphery in microsatellite stable and unstable colorectal cancer.** 

**First Author:** Simon O’Kane, The Mater Misericordiae University Hospital, Dublin, Ireland

**Background:** Colorectal cancers that show evidence of microsatellite instability (MSI-H) are marked by a high tumour infiltrating lymphocyte population (TIL) which is thought to be prognostic. Programmed Death-1 (PD-1) is a negative regulator of the immune system and targeting the interaction with its ligand PD-L1 offers a potential therapeutic target in many malignancies. We aimed to characterize CD8 and PD-1 expression in both the tumour centre and tumour periphery of microsatellite stable (MSS) and unstable colorectal cancers. 

**Methods:** Paraffin-embedded tumour blocks were cut at 4um, prepared and stained using specific antibodies for CD8 and PD-1. The tumour periphery was defined as the area within a 400x high power field (HPF) from the outline of the tumour. The tumour centre was defined as the area at least one 400x HPF apart from the tumour outline toward the centre of the tumour. Images were taken at 40x, 100x, 200x and 400x. Positive cells were averaged across 3 high power fields and classified as high or low positivity. 

**Results:** Forty-two specimens have been analysed to date including 28 MSI-H and 13 MSS tumours. Sixty-eight percent of MSI-H specimens were stage II and 69% of MSS were stage III. In the MSI-H group, a high CD8 count in the tumour centre and tumour periphery correlated with earlier tumour size and stage. PD-1 positivity was seen in 61% of MSI-H tumour centres compared to no positivity in the tumour centres of MSS specimens. The periphery of both MSS and MSI-H specimens showed significant PD1 expression with 71% and 85% of samples showing positivity respectively. There was no association between high or low densities of staining and stage. 

**Conclusions:** Zonal differences exist in the expression of CD8 and PD-1 in microsatellite stable and unstable tumours. A high proportion of MSI-H tumours show PD-1 activity in the centre of the tumour despite an improved prognosis. Further profiling of other T cell populations may help to further understand this expression which may act as a biomarker or provide a therapeutic target.

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**Poster Session (Board #66), Mon, 8:00 AM-11:30 AM**

**Placebo-controlled, double-blinded multi-center phase III trial of XELIRI/FOLFIRI plus simvastatin in metastatic colorectal cancer.** 

**First Author:** Sung Hee Lim, Samsung Medical Center, Seoul, Korea South

**Background:** The purpose of this randomized phase III trial was to evaluate the addition of synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin to XELIRI/FOLFIRI in patients with previously treated metastatic colorectal cancer. 

**Methods:** We undertook a double-blind, placebo-controlled phase III trial of 269 patients with previously treated metastatic colorectal cancer, enrolled to 5 centers in South Korea. 

**Results:** Patients were randomly assigned (1:1) to receive irinotecan 180 mg/m² as a 90-min infusion following by leucovorin 200mg/m² in a 2-h infusion, and then 5-FU 400mg/m² bolus injection followed by 2400mg/m² as a 46-h continuous infusion (FOLFIRI) or irinotecan 250mg/m² as a 90-min infusion with capcitabine 1000mg/m² twice daily for 14days (XELIRI) plus simvastatin (1.34 patients) or XELIRI/FOLFIRI plus placebo (135 patients). The primary end point was progression-free survival (PFS) and secondary end points included response rate, duration of response, overall survival (OS), time to progression (TTP) and toxicity. 

**Conclusions:** Between April 2010 and July 2013, 269 patients were enrolled and assigned to treatment groups (134 simvastatin, 135 placebo). The median progression-free survival (PFS) was 5.9 months (95% CI, 4.5-7.3) in XELIRI/FOLFIRI plus simvastatin group and 7.0 months (95% CI, 5.4-8.6) for XELIRI/FOLFIRI plus placebo group (P = 0.937). There was no significant difference in overall survival (median, 15.9 months (simvastatin vs. 19.9 months (placebo), P = 0.826). Grade 3 or higher grade nausea and anorexia were noted slightly more in patients with simvastatin arm compared to placebo arm (4.5 vs 0.7%, 3.0 vs 0% respectively). 

**Conclusions:** These results show that the addition of 40mg simvastatin to XELIRI/FOLFIRI did not improve PFS in previously treated metastatic colorectal cancer although it does not increase toxicity. Clinical trial information: NCT01238094. 

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**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
A randomized controlled trial to evaluate laparoscopic versus open with Japanese D3 dissection for stage II,III colorectal cancer (CRC). First objective response following preoperative chemotherapy. Therefore, we plan to initiate the first randomized study to can serve as a testing platform for treatment optimization of targeted therapy addressing secondary resistance. Conclusions: Background: Colorectal cancer (CRC) is one of the most common malignant tumors. All advanced CRC will progress after first-line treatment. Therefore, it is emergent to seek an efficient and low-toxic maintaining regimen to prolong progression free survival (PFS). Some clinical researches demonstrated that maintaining treatment followed first-line treating could extend PFS. Our previous non-randomized small sample study indicated that patients receiving first-line treatment of XELOX followed by capecitabine as maintenance therapy had significantly prolonged median time to progression (TTP). Therefore, we plan to initiate the first randomized study to evaluate the efficacy and safety of maintenance therapy with capecitabine following induction of XELOX (or FOLFIRI) versus observation until progression in first-line therapy in metastatic colorectal cancer. Methods: Samples of 100 CRC patients undergoing surgery were implanted subcutaneously in nude mice. Treatment cohorts of 10 wildtype (WT for KRAS, BRAF, NRAS, PI3K) tumors and 3 tumors with either KRAS, BRAF or PI3K mutation respectively were generated for i.p. treatment with Sym004, c-mab (25mg/kg b.i.w.) or control. Primary observational period was 29 days. In case of response, treatment was continued until acquired resistance – defined as tumor doubling after primary observational period – arose. Conclusions: Here, we present the first preclinical patient derived xenograft model of acquired resistance to anti-EGFR targeted therapy in CRC. We show that Sym004 is able to generate a deeper and prolonged response in 5 of 10 tested WT CRC patient derived tumors. This superior response rate of Sym004 suggests that clinical trials of Sym004 in CRC are warranted. Lastly, our successful proof of principle experiments for in vivo modeling of secondary resistance in CRC indicate that this strategy can serve as a testing platform for treatment optimization of targeted therapy addressing secondary resistance.
Baseline carcinoembryonic antigen (CEA) serum levels to predict bevacizumab-based treatment response in patients with KRAS exon wild-type metastatic colorectal cancer (mCRC). First Author: Michael Michi, Department of Hematology and Medical Oncology Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany

Background: Recently, Prager et al. proposed the hypothesis that carcinoembryonic antigen (CEA) is involved in tumor angiogenesis and therefore might predict bevacizumab-based treatment response in metastatic colorectal cancer (mCRC). Cancer Research, 2013; Cancer Science, 2014. The present study aimed to evaluate this hypothesis in the FIRE-3 trial where patients (pts) with KRAS exon 2 wild-type mCRC were randomized to receive first-line chemotherapy with either FOLFIRI + cetuximab (cet) or FOLFIRI + bevacizumab (bev). Methods: Baseline CEA levels were analyzed either as continuous variable (ln) or categorized in two groups (< 1.75% quartile; ≤ 6.2ng/ml with regard to their predictive impact on PFS and OS in the two different treatment arms. Correlations relied on Cox regression analysis. Survival was estimated by Kaplan-Meier. Results: For analysis of CEA, 529/592 pts (cet: 257 pts; bev: 265 pts) were eligible. When CEA baseline level was evaluated as a continuous variable, CEA (ln) was inversely correlated with PFS (p = 0.02) and OS (p = 0.001) in the bev arm, but not in the cet arm. Using the 25% quartile of CEA as a cut-off, only in the bev arm an effect on OS (24.2 mo vs. 33.3 mo; HR 0.60; 95% CI: 0.41-0.88; p = 0.009) and PFS (10.4 mo vs. 11.7 mo; HR 0.67; 95% CI: 0.48-0.94; p = 0.02) was observed, but not in the cet arm. Pts with high CEA baseline levels (> 6.2ng/ml) showed a shorter OS in the bev arm compared to the cet arm (bev: 24.2 mo vs. cet: 30.0 mo; HR 1.52; 95% CI: 1.16-2.00; p = 0.002). In pts with low CEA baseline level (≤ 6.2ng/ml) no significant survival difference was observed between arms (HR 0.92; 95% CI: 0.58-1.44; p = 0.70). Univariate analysis identified CEA as an independent predictor of OS in the bev arm, but not in the cet arm. Conclusions: The present analysis supports the hypothesis that CEA acts as a predictor of bev activity, while outcome parameters in the cet arm are not affected by baseline CEA. Patients with elevated CEA baseline levels appeared to benefit from anti-EGFR directed therapy, while anti-VEGF based treatment was inferior.
Background: mCRC or cmab had higher ORR, PFS, and OS compared with those pts who the pmab vs the cmab arm. Pts who developed any grade hypomag with dis- continued treatment and 5% of pts had dose modifications due to a priori intention, oxaliplatin, and fluorouracil treatment, and no prior anti-EGFR therapy. Pts were stratified by geographic region (North/Australia vs rest of world) and ECOG PS (0-1 vs 2) and randomized 1:1 to receive pmab 6 mg/kg qw or cmab 400 mg/m² followed by 250 mg/m² qw. The primary endpoint was OS assessed for non-inferiority (retention of ≥50% of the cmab effect vs best supportive care [BSC]; HR ≤ 0.55 [95% CI: 0.41 - 0.74] based on NCIC CTG C0.17). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. All pts were frozen for survival for up to 2 years after the last pt was randomized and a final analysis of efficacy and safety was conducted. No formal hypothesis testing was performed. Results: 999 pts were randomized and treated. 499 pmab and 500 cmab. 90% of pts had died at the time of this analysis (78% in the previously reported primary analysis). Baseline demographics and disease characteristics were similar between arms. Non-inferiority results for OS are shown (Table). Overall, any grade and grade 3-4 adverse events (AEs) were similar between arms. AEs of interest were (pmab vs cmab): grade 3-4 skin toxicity 13% vs 10%, grade 3-4 infusion reactions 0.5% vs 2%, and grade 3-4 hypomagnesemia 7% vs 3%. Conclusions: Consistent with the primary analysis, the final analysis of ASPECT showed that pmab was non-inferior to cmab for OS in chemorefractory WT mCRC. Safety profiles were as expected for pmab and cmab. Clinical trial information: NCT01001377.

Conclusions: In ASPECT, rates of hypomag were higher in the pmab vs the cmab arm. Pts who developed any grade hypomag with pmab or cmab had higher ORR, PFS, and OS compared with those pts who did not. Clinical trial information: NCT01001377.

Background: ASPECT met its primary endpoint of non-inferiority of overall survival (OS) of pmab vs cmab. We evaluate outcomes by hypomag, an on-treatment, anti-EGFR related adverse event that develops due to the inhibition of EGFR function. Conflicting reports have suggested hypomag is associated with improved overall survival (OS). Progression-free survival (PFS) and objective response rate (ORR) were secondary endpoints. Pts were categorized as any grade hypomag during the study and data from the primary analysis was evaluation by treatment. Analysis of Mg supplementation during hypomag was not conducted. Results: 999 pts with random- ized and treated: 499 pmab, 500 cmab. Any grade hypomag was 28.8% and grade ≥3 was 7.3% in the pmab arm and 18.9% and 2.6% in the cmab arm, respectively. Median time to first hypomag onset was 82 days in the pmab arm and 57 days in the cmab arm. In the pmab arm, 1.0% of pts discontinued treatment and 5% of pts had dose modifications due to hypomag vs <0.5% and 3% in the cmab arm, respectively. Results are shown (Table). Conclusions: In ASPECT, rates of hypomag were higher in the pmab vs the cmab arm. Pts who developed any grade hypomag with pmab or cmab had higher ORR, PFS, and OS compared with those pts who did not. Clinical trial information: NCT01001377.

Background: The primary analysis of ASPECT demonstrated that pmab was non-inferior to cmab for overall survival (OS) in chemorefractory WT KRASmCRC. Here, we report the final analysis of ASPECT. Methods: In ASPECT, pts (N = 999) pts had WT KRASmCRC, ECOG performance status (PS) ≤ 2, prior irinotecan, oxaliplatin, and fluorouracil treatment, and no prior anti-EGFR therapy. Pts were stratified by geographic region (North/Australia vs rest of world) and ECOG PS (0-1 vs 2) and randomized 1:1 to receive pmab 6 mg/kg qw or cmab 400 mg/m² followed by 250 mg/m² qw. The primary endpoint was OS assessed for non-inferiority (retention of ≥50% of the cmab effect vs best supportive care [BSC]; HR < 0.55 [95% CI: 0.41 - 0.74] based on NCIC CTG C0.17). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. All pts were frozen for survival for up to 2 years after the last pt was randomized and a final analysis of efficacy and safety was conducted. No formal hypothesis testing was performed. Results: 999 pts were randomized and treated. 499 pmab and 500 cmab. 90% of pts had died at the time of this analysis (78% in the previously reported primary analysis). Baseline demographics and disease characteristics were similar between arms. Non-inferiority results for OS are shown (Table). Overall, any grade and grade 3-4 adverse events (AEs) were similar between arms. AEs of interest were (pmab vs cmab): grade 3-4 skin toxicity 13% vs 10%, grade 3-4 infusion reactions 0.5% vs 2%, and grade 3-4 hypomagnesemia 7% vs 3%. Conclusions: Consistent with the primary analysis, the final analysis of ASPECT showed that pmab was non-inferior to cmab for OS in chemorefractory WT KRASmCRC. Safety profiles were as expected for pmab and cmab. Clinical trial information: NCT01001377.

Conclusions: In ASPECT, rates of hypomag were higher in the pmab vs the cmab arm. Pts who developed any grade hypomag with pmab or cmab had higher ORR, PFS, and OS compared with those pts who did not. Clinical trial information: NCT01001377.
Treatment until progression: Data of the “on-treatment” population of the FIRE-3 (AIO KRK-0306) study. First Author: Sebastian Stintzing, Department of Hematology and Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany

Background: The FIRE-3 study (AIO KRK-0306) was designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab (cet) to FOLFIRI plus bevacizumab (bev) as first-line treatment in KRAS WT mCRC patients. FOLFIRI plus cet as first-line treatment of KRAS WT mCRC patients resulted in comparable overall response rates (ORR) and progression free survival (PFS) with FOLFIRI plus bev. Overall survival (OS) was significantly longer in the FOLFIRI plus cet arm. Methods: In this exploratory analysis outcome parameters were calculated in dependence of progression during antibody treatment. As reported by Saltz et al. (ASCO GI 2007) an “on study treatment” population was defined using all RAS wild-type pts that were treated until progression or death occurred. To exclude early progressing patients the analysis was also performed in patients with a PFS >6 months. Results: See Table. Conclusions: In general, patients progressing during 1st-line treatment had a shorter PFS and OS than patients that had progressed after stop of treatment for any cause. Patients that discontinued treatment for other reasons than progression had a significantly longer median OS when treated with FOLFIRI plus cetuximab in first-line when compared to FOLFIRI plus bevacizumab. This effect was also seen after exclusion of early progressors (PFS <6 mo).

<table>
<thead>
<tr>
<th>All patients</th>
<th>Medium PFS (95% CI)</th>
<th>P</th>
<th>Medium OS (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event during treatment</td>
<td>FOLFIRI + Cet (n = 72)</td>
<td>7.6 (6.3-9.7)</td>
<td>0.94</td>
<td>22.6 (17.5-27.9)</td>
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<td>PFS event during treatment</td>
<td>FOLFIRI + Bev (n = 74)</td>
<td>7.4 (6.0-9.0)</td>
<td>0.9</td>
<td>21.2 (15.2-27.3)</td>
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<tr>
<td>PFS event after treatment</td>
<td>FOLFIRI + Cet (n = 106)</td>
<td>10.8 (10.0-13.3)</td>
<td>0.59</td>
<td>27.1 (24.8-30.3)</td>
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<td>PFS event after treatment</td>
<td>FOLFIRI + Bev (n = 111)</td>
<td>10.5 (10.3-13.1)</td>
<td>0.17</td>
<td>28.3 (24.8-33.3)</td>
</tr>
</tbody>
</table>

Patients PFS >6 months | Medium PFS (95% CI) | P | Medium OS (95% CI) | P |
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>PFS event during treatment</td>
<td>FOLFIRI + Cet (n = 46)</td>
<td>11.0 (8.6-13.9)</td>
<td>0.85</td>
<td>27.0 (21.2-32.8)</td>
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<td>PFS event during treatment</td>
<td>FOLFIRI + Bev (n = 46)</td>
<td>10.4 (8.4-12.7)</td>
<td>0.45</td>
<td>26.1 (22.1-30.5)</td>
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<tr>
<td>PFS event after treatment</td>
<td>FOLFIRI + Cet (n = 91)</td>
<td>12.4 (12.0-14.1)</td>
<td>0.35</td>
<td>38.7 (36.4-40.9)</td>
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<td>PFS event after treatment</td>
<td>FOLFIRI + Bev (n = 100)</td>
<td>12.4 (11.1-13.4)</td>
<td>0.26</td>
<td>29.4 (26.5-32.3)</td>
</tr>
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</table>

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Phase II trial of preoperative radiation with concurrent cetaplatin, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes of a trial of the ECOG-ACRIN Cancer Research Group (E3204). First Author: Jerome Carl Landry, Emory University, Winship Cancer Institute, Atlanta, GA

Background: As previously reported, the regimen of preoperative cepatbine, oxaliplatin, and bevacizumab with radiation therapy (RT) followed by surgery and postoperative 5-FU, leucovorin, oxaliplatin (FOLFOX) and bevacizumab for locally advanced rectal cancer did not improve overall pathologic complete response (path CR) rates. However, the effect of an intensified adjuvant regimen is not reflected in path CR. The purpose of this report is to describe the 5-year oncologic outcomes of this regimen. Methods: Fifty-seven patients (pts) with resectable T3/T4 rectal adenocarcinoma were enrolled. Preoperative treatment: cepatbine (825 mg/m² b.i.d.), oxaliplatin (50 mg/m² weekly), bevacizumab (5 mg/kg D1, 15, 29), and RT (50.4 Gy). Surgery was performed by 8 weeks after neoadjuvant therapy. Beginning 8 – 12 weeks after surgery, patients received FOLFOX plus bevacizumab (5 mg/kg) Q2 weeks for 12 cycles. Results: Fifty-three of 57 enrolled pts were eligible and included in the analysis. Most patients were clinical (c)T3 (92%) and cN positive (64%). Of the 48 patients who underwent curative surgery, 26 (54%) began adjuvant chemotherapy. After a median follow-up period of 41 months, the 5-year overall survival (OS) rate for all patients was 80% (90% confidence interval (CI) [67%, 92%]). Only patients experiencing pathologic complete response (path CR) were included. The 5-year recurrence free survival rate (RFS) was 81% (90% CI [68%, 94%]). Conclusions: Despite the path CR endpoint of this trial not being reached, the 5-year OS and RFS rates were excellent. However, as previously reported, the neoadjuvant and surgical toxicity of this regimen was significant and was the primary reason for the low compliance with adjuvant systemic therapy. Due to the lack of an improvement in the path CR rate, the substantial associated toxicity, and negative phase III trials of adjuvant bevacizumab in colon cancer, this regimen cannot be recommended for further study. Clinical trial information: NCT00321685.
3593 Poster Session (Board #86), Mon, 8:00 AM-11:30 AM
Time-dependent patterns of recurrence and death in resected colon cancer (CC): Pooled analysis of 12,223 patients from modern trials in the ACCENT database containing oxaliplatin. First Author: Lindsay A. Renfreo, Mayo Clinic, Rochester, MN

Background: A 2009 analysis of 20,898 CC patients from 18 randomized studies of adjuvant therapy (AT) in the ACCENT database showed that treatment with AT (versus surgery alone) lowers the risk of recurrence and death at all time points, especially in stage III (versus stage II) disease. However, this analysis evaluated only FU/LV therapies and excluded modern oxaliplatin-based (Ox) therapies. Methods: With mature follow-up now available (median 6 years), 12,223 patients from ACCENT enrolled to C-07, C-08, N0147, MOSAIC, and XELOXA (18% stage II, 82% stage III) were pooled to examine the impact of Ox and tumor specific factors (tumor stage, nodal stage, tumor location, and tumor grade) on the time course of recurrence and death from all causes. For each endpoint, continuous time risk was modeled over 8 years post-treatment in (1) Ox-treated patients from all trials and (2) patients concurrently randomized to Ox versus 5FU/LV, where the latter set of analyses supported time-dependent treatment comparisons. Results: Addition of Ox reduced the risk of recurrence and death at all time points and in all disease subgroups, with no differences in the timing of outcomes between treatment groups (i.e., Ox did not simply postpone recurrence or death compared to 5FU/LV alone; see Table). Ox significantly reduced recurrence risk during the first 4 years, and significantly reduced risk of death from 2 to 6 years post-treatment. Recurrence risk peaked near 14 months for both treatment groups, with 83% of patients treated with Ox (80% of patients treated with 5FU/LV) who recurred within 8 years doing so by 3 years post-treatment. Risk of recurrence and death increased with increased tumor and nodal burden. Conclusions: These analyses support the addition of oxaliplatin to fluoropyrimidines as a curative therapy in the adjuvant setting and underscore the need for adequate surveillance of CC patients, especially during the first 3 years after adjuvant therapy.

<table>
<thead>
<tr>
<th>Year</th>
<th>Recur 5FU</th>
<th>Ox</th>
<th>Death 5FU</th>
<th>Ox</th>
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<tr>
<td>1</td>
<td>11.0%</td>
<td>8.6%</td>
<td>2.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>2</td>
<td>10.5%</td>
<td>8.8%</td>
<td>5.4%</td>
<td>5.3%</td>
</tr>
<tr>
<td>3</td>
<td>5.2%</td>
<td>4.7%</td>
<td>5.4%</td>
<td>4.3%</td>
</tr>
<tr>
<td>4</td>
<td>3.4%</td>
<td>2.2%</td>
<td>4.9%</td>
<td>4.5%</td>
</tr>
<tr>
<td>5</td>
<td>2.0%</td>
<td>1.9%</td>
<td>3.8%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

3595 Poster Session (Board #88), Mon, 8:00 AM-11:30 AM
TAS-102 vs placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the RECOREC trial. First Author: Eric Van Cutsem, University Hospitals Leuven, Leuven, Belgium

Background: TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). Efficacy and safety of TAS-102 vs PBO in pts with mCRC refractory to standard therapies were evaluated in the RECOREC trial; enrollment criteria included ≥ 2 prior lines of standard chemotherapy. Primary results of RECOREC demonstrated a significant improvement in overall survival (OS) (TAS-102 vs PBO, 6 mos vs PBO, P = 0.0001) and progression-free survival (PFS) (HR = 0.48; P < 0.0001). Methods: This prespecified analysis compared the efficacy and safety of TAS-102 vs PBO in pts ≥ 65 y and <65 y with mCRC. A retrospective analysis of pts ≥ 75 y was also performed. Results: Of 800 randomized pts, 352 (44.0%) were ≥ 65 y and 60 (7.5%) were ≥ 75 y; Median OS in pts ≥ 65 y was 7.0 mo with TAS-102 vs 4.6 mo with PBO (HR = 0.62, 95% CI: 0.48-0.80, P = 0.0002). PFS HR was 0.41 (95% CI: 0.32-0.52, P < 0.0001) for pts ≥ 65 y, also favoring TAS-102. In pts ≥ 65 y, disease control rate (complete or partial response or stable disease) was 48.7% with TAS-102 vs 15.5% with PBO. An age-related difference in overall incidence of adverse events (AEs) was not observed in either treatment arm. Treatment-related AEs ≥ Grade 3 AEs, and severe AEs were generally more common in pts ≥ 65 y than in pts < 65 y (Table), Mean drug exposure was similar among pts ≥ 65 y and ≥ 75 y, as was overall safety profile. Conclusions: TAS-102 improved OS and PFS in OS and PFS was observed in pts ≥ 65 y who received TAS-102 vs PBO, with a mild increase in toxicity. Pts ≥ 65 y and < 65 y showed a generally favorable safety profile. A significant increase in toxicity in pts ≥ 75 y was not apparent vs the overall ≥ 65 y population. Clinical trial information: NCT01607957.

3596 Poster Session (Board #89), Mon, 8:00 AM-11:30 AM
Phase I study of ganetesib (G), capstacibine (C), and radiation (RT) in rectal cancer. First Author: Bassel F. El-Rayes, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Ganetesib (G) is a heat shock protein 90 inhibitor . Preclinical data show that G is a potent radiosensitizer for rectal cancer. The aim of this study is to determine the recommended phase II dose of G when combined with capstacibine (C) and radiation (RT) in resectable rectal cancer. Methods: Patients (pts) with stage II or III rectal adenocarcinoma with distal border within 12 cm of anal verge, no prior therapy, and adequate organ functions were eligible. A +3 dose escalation design was used. Pts received 2 weeks of G at 150 mg/m² I.V. on days -14, -11, -7, and -4, Pre and post-treatment tumor biopsies were obtained. C (825 mg/m²) and RT (50.4Gy) were administered 5 days per week for 5.5 to 6 weeks starting day 1. G was administered on days 1, 8, 15, 29 and 36. G dose levels were 60, 80, 100, and 120 mg/m². Pharmacokinetic sampling for C and G were performed on days 1, 2, 5, and 16. Dose limiting toxicities (DLT) were defined as the occurrence of any treatment related: grade 4 hematologic or gr 3 or higher non-hematologic toxicities, gr 3 nausea, vomiting or diarrhea lasting ≥ 4 days, any interruption of RT > 10 days, plasma level interruptions of RT, noncompliance of RT for ≥ 1 hr, or inability to deliver more than 85% of planned RT dose. Results: 16 pts were enrolled in the study; 1 pt received only day-14 and was not evaluable for toxicity. Evaluable pts had a median age of 61 yrs, 7 females, and endoscopic stage: T3N0 (6 pts), T3N1 (6), T3N2 (1), T4N1 (1); 3 pts were treated with each dose level, except with dose level 1, so we enrolled 3 additional pts on level 3 (100 mg/m²). One DLT was observed (gr 3 diarrhea for more than 4 days). Other toxicities on the study were: diarrhea gr 3 (5 pts), gr 2 (6), gr 1, 2 (2), radiation dermatitis gr 2 (9), gr 1 (3), fatigue gr 2 (5), gr 1 (4), hand foot syndrome gr 2 (1), mucositis gr 1 (2), and nausea/vomiting gr 2 (2), gr 1 (8). 12 pts have completed surgical resection (2 APR and 10 LAR). Pathologic complete response (pCR) rate was 25% (3/12) and 2 pts had residual tumors less than 1 cm (pT1NO). Histology of 9 (67%) pts had clearing of lymph nodes disease on pathologic specimen. Conclusions: G can be safely combined with standard C and RT in the neoadjuvant setting in rectal cancer. Preliminary data on activity appear promising. Clinical trial information: O1554969.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
3597 Poster Session (Board #80), Mon, 8:00 AM-11:30 AM
Therapeutic biomarker differences between MSI-H and MSS colorectal cancers. First Author: Zoran Gatalica, Caris Life Sciences, Phoenix, AZ

Background: Approximately 15% of colorectal cancers (CRC) display high levels of microsatellite instability (MSI), often associated with hereditary non-polyposis colorectal cancer (Lynch syndrome, LS) or somatic hypermethylation of MLH1. They carry a significantly different prognosis and responses to treatments compared with microsatellite stable (MSS) or low microsatellite instability (MSI-L) CRC. We investigated therapeutically important biomarkers, which may underlie different treatment options for CRC. Methods: Sixty-four MSI-H (including 20 confirmed LS cases), 9 MSI-L and 558 MSS cases were profiled at Caris Life Sciences (Phoenix, AZ) using immunohistochemistry and sequencing (NextGen and Sanger). Results: Compared with non-MSI-H, MSI-H tumors had significantly higher expression of Thymidylate Synthase (TS) (85% vs. 31%), PTEN (71% vs. 48%) expressions and significantly higher mutation rates of BRAF (35% vs. 5%), CTNNB1 (10% vs. 0.7%), HNF1A (32% vs. 0.2%), BRCA1 (19% vs. 5%) and BRCA2 (50% vs. 14%). MSI-H cancers were also significantly more infiltrated with PD-1+ lymphocytes (71% vs. 43%). Features found specific to sporadic MSI-H tumors (defined as MSI-H and BRAF V600E) in comparison with non-MSI-H tumors included higher mutation rates on select genes within the PI3K/AKT/mTOR pathway, including FBXW7 (31% vs. 7%), PTEN (19% vs. 3%) and STK11 (18% vs. 1%). 20 confirmed LS cases also exhibited significantly higher TS (100%) expression, CTNNB1 (10%) and HNF1A (40%) mutations than non-MSI-H and lower FBXW7 (10% vs. 31%), PTEN (10% vs. 19%) and STK11 (0%) vs. 18%) mutation rates than sporadic MSI-H tumors (all p < 0.02). Conclusions: Significantly higher TS expression is a characteristic of both sporadic MSI-H and Lynch tumors, potentially explaining the observed reduced clinical benefit from 5-FU. Higher PD-1+ TIL, BRCA1/2 and CTNNB1 mutations suggest MSI-H as a more promising group for targeted immunotherapeutic and Wnt pathway inhibitors. Different molecular features of sporadic MSI-H and Lynch subgroups including PI3K/AKT/mTOR offer insight into targeted therapies for these subgroups of CRC.

3598 Poster Session (Board #91), Mon, 8:00 AM-11:30 AM
Measuring the impact of Next Generation Sequencing (NGS) technique implementation in metastatic colorectal cancer (mCRC) drug development programs. First Author: Carolina Ortiz, Vall d’Hebron University Hospital, Barcelona, Spain

Background: Molecular screening and biomarker enrichment strategies in mCRC trials may impact patient (pt)’s outcome. The introduction of NGS technologies in clinical investigation may enhance pt inclusion through the discovery of a wider set of mutations (mt) in oncogenes and tumor suppressor genes. Methods: From March/2012 to December/2014 411 pts with metastatic mCRC underwent genetic tumor testing as part of the molecular enhancement strategy in our early drug development program. Base extension chemistry followed by mass detection (MassARRAY, Sequenom) (SQ) was used including 268 frequent hotspots in 25 oncogenes with a sensitivity of 10% of mutant alleles. Since June/2014, Amplion sequencing (NGS) was implemented assessing mt in 59 onco- genes and tumor suppressors with a sensitivity of 3% mutant alleles. Results: From March/2012 to June/2014 324 pts were screened using SQ, 261 mt were detected: 0.80 mt per patient. A total of 117 pts (36%) resulted wild-type (wt) after the test. Frequency of mt of were: 48.77% KRAS, 16.67% PI3KCA, 7.41% NRAS, 7.41% BRAF along with a tumor ever 2.7% BRAF, along with a tumor ever 2.03x10-6), and 2.03x10-6). Among these genes, the most compelling evidence for a link to the biology of CRC is for AXIN1 (32.9-41.1) months, respectively. Testing of arm and extended RAS by MALDI-TOF mass spectrometry, showed a correlation of mt found in CRC compared to prior generation genomics tests, although this has been failed to be translated yet into higher inclusion rates in clinical trials with targeted agents. An enhanced discovery of mutations in tumor suppressor genes, thus far out of therapeutic reach and other factors like recent implementation of NGS and the increasing search for more specific molecular populations can contribute to this fact.

3599 Poster Session (Board #92), Mon, 8:00 AM-11:30 AM
A genome-wide association study (GWAS) of overall survival (OS) in 609 metastatic colorectal cancer (mCRC) patients treated with chemotherapy and biologics in CALGB 80405. First Author: Pedroco Innocenti, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Support: U10CA180821, U10CA180882, CA31946, Bristol-Myers Squibb, Genentech, Pfizer Background: Ingnirecan-5-FU (FOLFIRI) or oxaliplatin-5-FU (FOLFOX), combined with bevacizumab or cetuximab, are first-line treatments for mCRC. We aimed to identify germline variants associated with survival in mCRC patients treated with these regimens. Methods: In CALGB 80405, patients with wild-type KRAS (codons 12 and 13) mCRC received either FOLFOX (> 80% of patients) or FOLFIRI and were randomized to either cetuximab or bevacizumab. The primary endpoint of the study was OS. DNA was extracted from peripheral blood and genotyped for ~700,000 single-nucleotide polymorphisms (SNPs). The association between SNPs and OS in 609 patients (both arms) was evaluated with Cox proportional hazards model. Results: Median OS in genotyped patients was 29.6 months, and was comparable to that of the parent study (Venook et al., ASCO 2014). The three most significant SNPs associated with OS were in the genes RHD14 (hazard ratio, HR 1.63, 95% CI 1.42-1.87; TS = 2.0x10-6, 32.6x10-6, 1.3x10-5), and AXIN1 (HR 1.40, p < 0.63x10-6). Among these genes, the most compelling evidence for a link to the biology of CRC is for AXIN1. The AXIN1 protein functions as a negative regulator of WNT signaling by interacting with APC in CRC (Li et al., Cell 2012). In the present GWAS, rs11644916 was associated with OS (p = 0.989 (0.986-0.99) and 0.983 (0.981-0.985), 1.134) and OS (HR 0.925 (0.742-1.155), 1.031 (0.899-1.184). However, when initial dose was compared, HR favored 180 mg/m2 over 150 mg/m2 after adjusting for UGT1A1 genotypes, sex and dose intensity of irinotecan for PFS (HR 0.640 (0.559-0.733)) and OS (HR 0.619 (0.522-0.741)). In a subset analysis, colorectal cancer patients who received 1st line FOLFIRI showed a significant benefit for initial usage of 180 mg/m2 over 150 mg/m2 in PFS (P < 0.001) and OS (P < 0.001).

Conclusions: Our findings indicate that lowering the starting dose of FOLFIRI may have an effect on the PFS (HR 0.988 [0.831-1.174], 1.013 [0.905-1.134]) and OS (HR 0.925 [0.742-1.155], 1.031 [0.899-1.184]).
3601 Poster Session (Board #94), Mon, 8:00 AM-11:30 AM
Clinical utility of a circulating cell-free DNA assay for clinical trial enrollment in refractory metastatic colorectal cancer patients. First Author: Valen Darling Morris, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Circulating cell-free DNA (cfDNA) isolated from the plasma of cancer patients has been shown to accurately reflect the genomic mutation profile of the tumor, and assays are now available for clinical use. However, physician and patient assessment of clinical utility of these assays in patients has not been previously evaluated. Methods: Patients (pts) were prospectively consented as part of the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) protocol, with collection of 20mL of blood cfDNA extraction and sequencing on a 54-gene panel in a CLIA-certified lab (Guardant360, Guardant Health). FFPE tissue from prior resections or biopsies underwent 50-gene sequencing (Ion Torrent, Life Technologies). Results: Results were shared with the treating physicians for patient care and clinical trial selection. Follow up surveys and chart reviews assessed clinical utility. Results: 120 mCRC pts were enrolled between 6/2014 and 1/2015, with a median of 3 prior lines of therapy. With cfDNA sequencing, 83% (99/120) of samples had a detectable genomic alteration (including 29% with detectable amplifications in EGFR, MET, or ERBB2), with an average of 4.2 mutations/pt. Sequencing of tissue provided detectable mutations in 88% of cases (106/120), with an average of 2.9 mutations/pt. cfDNA testing provided results within a median of 11 days, 14-days faster than tissue testing. 54% of cfDNA cases had potentially actionable alterations, and 66% of cases could be genomically matched to at least one clinical trial in the institution. 52% of these pts were able to be identified in the identified trial, with the remainder limited by eligibility criteria (9%), lack of patient interest (22%), or no current trial openings (17%). Physicians felt that the cfDNA testing improved the quality of care, as they were able to provide care to 75% of the targeted patients and improved patient satisfaction with the efforts to personalize treatment options in 92% of cases. Conclusions: cfDNA sequencing can provide timely information on potentially actionable mutations and amplifications, thereby facilitating clinical trial enrollment and improving the perceived quality of care.

3602 Poster Session (Board #95), Mon, 8:00 AM-11:30 AM
Outcome evaluation of matched molecular targeted agents (MTAs) in metastatic colorectal cancer (CRC) patients (pts): WHO experience. First Author: Quilim Arghids, Vall d’Hebron Institute of Oncology, VHI, Barcelona, Spain

Background: Biomarker-driven selection of new MTAs has not been widely successful in CRC as we reported in 2012. New screening platforms and drugs have reached early drug development. We aimed to evaluate outcome evaluation between 2012 and 2014. Methods: MTAs given to CRC pts based on circulating tumor profiling (MTP) from Jan/2012 to Dec/2014 were compared to the reported in 2012. MTP included mutations (mt) detected by Sequenom (Sq), Guardant360, Eurofins, mitogen-activated protein, cMET amplifications (amp), PTEN and PDL1 expression. Benefit was calculated comparing treatment failure of prior line (TF1) to the MTAs’ one (TF2). TF2/TF1<1.3 supposed MTAs benefit. Relevant MTAs-biomarker pairs were analyzed. Results: A total of 174 MTAs were given. Pairs biomarker-MTAs were: KRASmt; MEK inhibitors (i) + PI3Ki or MET + anti-receptor tyrosine kinase (RTK), and anti-RTK mAbs; PIK3/mTOR inhibition; PIK3/mTORi + anti-RTK mAbs; cMET path activation; METi (mAbs or RTKs); BRAF V600mt; BRAFi, BRAFi + MEK i + CDK4i, BRAFi + anti-EGFR mAbs + PI3Ki; RAS wild-type (wt); 2nd generation anti-EGFR mAbs. Median (m) TF1 was 21.9 weeks (w) (18.9-24.8), mTF2 8.3w (7.7-8.9), with 17.2% of pts benefiting from MTA (i.e. TF2/TF1<1.3). Derived benefit was not higher in the reported in 2012 mTF2/TF1 16.3w (14.8-18.5), mTF2 7.9w (7.2-8.5) with 14.3% pts benefiting from MTAs (p=0.47). BRAF V600E mt pts receiving BRAFi combos was the group with more benefit from MTAs (30%). Conclusions: Recent evolution with MTAs in CRC does not widely correlate with better outcome in overall population. However, significant benefit is observed when there is a mechanistic rationale for MTA (BRAF V600E). Future CRC molecular subtypeing is needed to improve outcomes.

3603 Poster Session (Board #96), Mon, 8:00 AM-11:30 AM
Retrospective study of patients (pts) who were managed with Watch and Wait strategy (W&W) after neoadjuvant chemoradiation (NCRT) for Locally Advanced Rectal Cancer (LARC). First Author: Sina Vatandoust, Flinders Medical Centre and Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, Australia

Background: The management of LARC involves NCRT followed by resection +/- adjuvant chemotherapy. Rectal resection has associated short and long-term morbidity and functional compromise. Complete Response (CR) is observed in ~20% of cases after NCRT and resection may be achievable in these pts. We retrospectively report a cohort of pts who received NCRT and have been followed up with ‘W&W’. Methods: All patients with LARC who had CR to NCRT, and did not proceed to surgery but instead were managed by a surveillance strategy, were identified from clinical records. All pts had received long course NCRT as suggested by multidisciplinary team meeting. CR was defined as the absence of any residual viable cancer, managed by a surveillance strategy, were identified from clinical records. All pts had received long course NCRT as suggested by multidisciplinary team meeting. CR was defined as the absence of any residual viable cancer, thereby facilitating clinical trial enrollment and improving the perceived quality of care.

3604 Poster Session (Board #97), Mon, 8:00 AM-11:30 AM
Predictors of clonal evolution in metastatic colorectal cancer patients. First Author: M. Pia Morelli, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Concordance of somatic mutations between primary and metastatic colorectal tumors is high in colorectal cancer (CRC), circulating cell-free DNA (cfDNA) accurately reflects the mutation status of metastatic disease. Intervening treatment and metastatic dissemination may result in clonal evolution from pre-existing intratumoral heterogeneity, with the resulting discordance in minor clones. Methods: Patients (pts) were prospectively enrolled for clinical trials from DNA microarray samples collected from 2012 to 2014. Mutations were sequenced on a 54-gene panel optimized for very low allele frequencies (Guardant360), with concurrent sequencing of clinically available and macrodissected historic FFPE tissue (50-gene Ion-Torrent panel), both performed in CLIA-compliant labs. Eligible cases had plasma and tissue sequencing. Tissue mutation status was considered the gold standard. We used a 1% threshold, 5% was used for low confidence alleles. Mutations were deemed discordant if present in plasma but not tissue or if present in tissue but not plasma.

Methods: cfDNA cases had potentially actionable alterations, and 66% of cases could be genomically matched to at least one clinical trial in the institution. 52% of these pts were able to be identified in the identified trial, with the remainder limited by eligibility criteria (9%), lack of patient interest (22%), or no current trial openings (17%). Physicians felt that the cfDNA testing improved the quality of care, as they were able to provide care to 75% of the targeted patients and improved patient satisfaction with the efforts to personalize treatment options in 92% of cases. Conclusions: cfDNA sequencing can provide timely information on potentially actionable mutations and amplifications, thereby facilitating clinical trial enrollment and improving the perceived quality of care.

Conclusions: Intervening chemotherapy and microsatellite instability results in the appearance of new minor clones in potentially clinically relevant genes in more than half of metastatic CRC pts. Based on this small data set, development of minor clones may be dependent on exposure to specific cytotoxic or molecular drugs.
Prognostic and predictive value of tumour budding in stage II colorectal carcinoma. First Author: Bojana Mitrović, Mount Sinai Hospital, Department of Pathology and Laboratory Medicine, Toronto, ON, Canada

Background: High-grade tumor budding (HTGB) is reported to be an independent adverse prognostic factor in colorectal cancer (CRC). Its presence is not routinely assessed by pathologists due to uncertainties about its clinical value, risk group thresholds, and the reproducibility of its assessment. Moreover, the benefit of chemotherapy in stage II CRC with HTGB remains to be demonstrated. This study aimed to (1) confirm the prognostic significance of HTGB in stage II CRC (2) determine an optimum threshold for HTGB reporting and (3) determine the responsiveness of stage II CRC with HTGB to chemotherapy.

Methods: Whole slide images from CRC resections of 979 QUASAR trial patients (majority stage II) were evaluated for tumor budding as per the method of Ueno (2002). A tumor bud was defined as a single cell or a cluster of < 5 cells on a hematoyxin and eosin stained section. The highest tumor bud count per 1.23 mm²-field was recorded. The optimal cutoff for HTGB was determined by maximal likelihood methods. Influence of risk group on recurrence and all-cause mortality was investigated in stratified logrank analyses in ‘training’ (n = 501) and ‘test’ (n = 478) data sets. Results: The optimal cut-off for HTGB was determined to be 10+ buds/1.23 mm²-field. Defined as such, HTGB was associated with significantly worse outcome: 10-year recurrence 35% vs 22% (risk ratio [RR] = 1.93 [95%CI 1.48–2.51], 2p < 0.00001) and mortality 51% vs 36% (RR = 1.73 [1.38–2.16], 2p < 0.00001), which was largely independent of other factors, including N and T-stage, grade, MMR, KRAS and BRAF status. There was a non-significant trend towards increasing chemotherapy efficacy with increasing bud counts (p = 0.12).

Conclusions: HTGB is a strong independent predictor of disease recurrence and survival in stage II CRC. The proportional reductions in recurrence with chemotherapy in patients with higher bud counts appear at least equivalent to those with low counts, hence the absolute reductions in recurrence with chemotherapy should be about twice as large in patients with 10+ than < 10 tumor bud counts.

A phase II study of 5-fluorouracil (5-FU), ziv-aflibercept, and radiation for the preoperative and adjuvant treatment of patients (pts) with stage II/III rectal cancer. First Author: Peter Acs, Florida Cancer Specialists/SCRI, Ft. Myers, FL

Background: Radiation exposure upregulates VEGF expression which protects endothelial cells from the effects of radiation therapy. Combining an angiogenesis inhibitor with radiation therapy may help to suppress VEGF expression and enhance antitumor activity. Aflibercept is an antiangiogenic agent that binds to VEGF-A, VEGF-B and placental growth factor. This phase II, non-randomized study combined ziv-aflibercept (aflibercept outside the US) with chemoradiation as preoperative treatment for pts with stage II/III rectal cancer, followed by 4 months of mFOLFOX6 plus ziv-aflibercept. Methods: Pts with stage II/III adenocarcinoma of the rectum received preoperative 5-FU (225 mg/m² IVCI, days 1-42), radiation (50.4 Gy, Mon.-Fri., weeks 1-6), and ziv-aflibercept (4 mg/kg IV weekly from 1-15) for a 28 day cycle for 6 weeks. Six weeks from last dose of ziv-aflibercept, pts underwent surgical resection. Treatment with mFOLFOX6 plus ziv-aflibercept began 8 weeks after surgery for 4 cycles. The primary objective was to evaluate the pathologic complete response (pCR) rate. Secondary objectives included overall survival (OS), disease-free survival (DFS), sphincter preservation (SP), and safety. Results: Thirty-nine pts were treated: median age 60 yrs (range, 36-89), 64% male, 82% ECOG 0, 69% stage III. Ninety-five percent of pts received preoperative treatment, 82% underwent resection, and 54% received postoperative treatment. The most common treatment-related toxicities (% G1/2) included diarrhea (51%; 21%), fatigue (59%; 5%), mucositis (38%; 15%), nausea (46%; 0), and hypertension (13%; 21%). Three postoperative complications of G3 pelvic abscess (2) and GI fistula (1) were seen. Of the 32 pts resected, 8 pts (25%) achieved pCR, and pathologic partial response was seen in 24 pts (75%; 9 macroscopic, 15 microscopic). The SP rate was 72%; 31 pts (97%) had R0 resection. Median OS/DFS have not yet been reached. Conclusions: The 5-FU-based chemoradiation therapy combined with ziv-aflibercept in localized rectal cancer pts was well tolerated and showed a pCR rate in range with historical data. Median DFS is pending. Clinical trial information: NCT01749596.

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A phase I/II single arm feasibility trial of neoadjuvant chemotherapy (NAC) with oxaliplatin/fluorouracil (OxMDx) then short-course preoperative radiotherapy (SCPRT) then curative rectal cancer surgery COPERNICUS (NCT01263171). First Author: Simon Gollins, North Wales Cancer Treatment Centre, Bodelwyddan, United Kingdom

Background: Feasibility was assessed of giving NAC prior to SCPRT then immediate surgery in CRC at high risk of metastatic relapse. Methods: Patients (pts) had non-metastatic rectal adenocarcinoma. Pre-treatment pelvic MRI showed resection margin was not at risk (distance > 1 mm from mesorectal fascia), but adverse risk factors were present (e.g. node positive or extramural vascular invasion). Pts received 4x2-weekly cycles of oxaliplatin 85mg/m² + levofolinic acid 175 mg, fluorouracil (FU) 400 mg/m² (bolus), then FU 2400 mg/m² (continuous IV in 46 hr). Within 14 days pts had pelvic SCPRT to 25 Gy in 5 daily fractions. Definitive surgery then occurred within a week. Post surgery pts received 16 weeks of OxMDx or oxaliplatin/capecitabine. The primary endpoint was the proportion of pts completing protocol treatment including surgery. Results: 60 UK pts were recruited May 2012-June 2014. At baseline: male 44 (73%), median age 63 (IQR: 56.5-70), WHO PS 0/1 55/5. On pre-treatment MRI tumour was T2/3a/3b/3c/3d/4a in 2/2/16/24/12/13 and NO/1/2 in 7/40/13 pts. All pts commenced OxMDx with 57(95%) receiving all 4 cycles, 20 pts (33%) needed a dose reduction and 22 (37%) a dose delay. 58 pts commenced SCPRT (all received full dose) and 57 underwent surgery. anterior resection in 43 (75%), abdominopelvic resection in 11 (19%), Hartmann's in 2 (3%). Three pts withdrew prior to surgery; one lost to follow up after SCPRT, one pt choice and one due to cardiacoemia during NAC. Median gap between OxMDx and starting SCPRT was 10 days (IQR: 5-15) and between completing SCPRT and surgery 10 days (IQR: 5-13). Postoperative histology was TO/1/2a/3b/3c/3d/4a in 7/3/19/8/9/10/1 pts, NO/1/2 in 39/13/5 pts and ypTO/pypNO/pypT4 in 7/67/12 pts (12%). All 57 resected pts had a clear (R0) resection margin with no 30 day postoperative mortality. Conclusions: This is the first trial to report on giving NAC prior to SCPRT then surgery within a short time interval in CRC, which proved feasible with good compliance and promising efficacy. The UK NCRI intend to include a similar regimen in a future phase III trial. Clinical trial information: NCT01263171.

Proteomic signatures of colorectal cancer to identify distinct and reproducible subgroups and to reflect prognosis. First Author: Michael Sangmin Lee, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: While colorectal cancer (CRC) has classically been categorized into gene expression, proteomic analysis directly elucidates the functional state of protein signaling, which may better reflect cellular behavior. We performed an antibody-based proteomic analysis (reverse-phase protein array; RPPA) of a large cohort of MD Anderson (MDACC) and The Cancer Genome Atlas (TCGA) samples to determine patterns of protein expression in CRC. Methods: Proteins were extracted from formalin-fixed paraffin-embedded tumor tissue of 360 CRC samples (23 available) after surgery alone (S), chemotherapy (Cht) alone, Cht + anti-VEGF and Cht + anti-EGFR. The density of CD3 (T cells), CD8 (cytotoxic), CD45RO (memory), CD20 (B cells) and FoxP3 (regulatory) in the core (CT) and invasive margin (IM) of all synchronous LCM and PCT was quantified on immunostained slides. The mean density value (CT, IM) was calculated for each marker with a dedicated image analysis software on whole-slide imaging. Comparisons were made using the Wilcoxon-Mann-Whitney test. Results: Global analysis of immune cell density in LCM and corresponding PCT showed no significant correlation even when further subcategorizing by treatment (preoperative or S), metastatic burden or subdividing by the mean, or the highest infiltrated LCM for patients with multiple LCM.Compared to PCT, LCM were more frequently associated with a high immune infiltrate for CD3 and CD45RO in the IM (p < 0.001) and CD8 in CT and IM (p < 0.001). Conversely, high CD20 and FoxP3 were more likely to be high in the CT of PCT (p < 0.001). We assessed the effect of preoperative treatment to S, only Cht+anti-EGFR significantly increases CD3 and CD8 in CT of LCM but not PCT (p < 0.001). Conclusions: Cytotoxic/memory T cells and B/Regulatory T cell densities were significantly higher in LCM and PCT, respectively. Only anti-EGFR treatment increases T cells densities in the CT of the LCM but not in the PCT, suggesting a specific treatment effect in this tumor region.

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3613 Poster Session (Board #106), Mon, 8:00 AM-11:30 AM

Genetic variants of kinases suppressors of Ras (KSR) to predict tumor response to first-line cetuximab in patients with mCRC. Prospective analysis in the FIRE 3 trial. First Author: Arturo Loaiza-Bonilla, University of Pennsylvania, Philadelphia, PA

Background: Activation of EGFR pathway in RAS-BRAF wild-type models can be modulated by scaffold proteins kinase suppressor of ras (KSRs) that binds RAS promoting ERK activation. We previously showed in patients with KRAS-BRAF wild-type tumor treated with FOLFIRI-cetuximab that KSR2 rs11068551 TT was associated to significantly longer PFS. On the other hand, among female patients treated with FOLFIRI-cetuximab the KSR1 rs2241906 CC genotype was associated to significantly shorter PFS. We aimed at validate our finding by investigating the correlation between KSR variants and clinical outcomes in patients enrolled in the FIRE 3 trial.

Methods: Genomic DNA was isolated from tissue samples of 592 patients with KRAS exon 2 wild-type enrolled in the randomized phase III, FIRE 3 trial that was designed to compared the efficacy of two targeted agents when associated to FOLFIRI regimen. Patients were randomly assigned to first-line FOLFIRI associated with either bevacizumab (n = 295) or cetuximab (n = 297) (NCT00439327). In both arms, DNA was amplified by PCR and KSR variants were detected by direct sequencing. Results: We confirmed prospectively that KSR2 rs11068551 could predict outcomes in patients receiving cetuximab. 1/Patients with the TT genotype (n = 40) demonstrated a significantly lower response rate than patients carrying C (n = 133) in the cetuximab arm (55% vs. 77%, p = 0.008). 2/Patients with left-sided tumors and TT genotype (n = 32) showed a significantly longer PFS (12.9 vs. 10.2 months, log rank p = 0.049) than patients harboring any of the C allele (n = 128) in the cetuximab arm. 3/ No association between KSR2 rs11068551 and outcomes was seen in the bevacizumab arm. We did not confirm the relation between KSR1 rs2241906 and outcome response rate, PFS or OS even when adjusted with gender and location. Conclusions: We prospectively validated the predictive value of KSR2 rs11068551 mCRC pts treated with first-line cetuximab-containing treatment. This predictive value may depend on tumor location. We could not confirm the predictive value of KSR1 rs2241906 in patients receiving bevacizumab-containing treatment.

3614 Poster Session (Board #107), Mon, 8:00 AM-11:30 AM

Phase II trial of autophagy inhibition using hydroxchloroquine (HCQ) with FOLFIRX/bevacizumab in the first-line treatment of advanced colorectal cancer. First Author: Arturo Loaiza-Bonilla, University of Pennsylvania, Philadelphia, PA

Background: We have shown that autophagy, the regulated dissolution of cellular elements to maintain survival in adverse environmental conditions, is a determinant of resistance to chemotherapy in colorectal cancer models, and is reversed by chloroquine (Selvakumaran M, et al Clin Cancer Res, 2013). A Phase I run-in demonstrated that full doses of mFOLFOX6/bevacizumab were tolerated with HCQ 600mg PO twice daily. Methods: We report a Phase II trial in previously-untreated patients with metastatic colorectal cancer. Patients were treated every two weeks with 5-FU (400mg/m² bolus, then 2400 mg/m² over 46h) together with leucovorin 200mg/m², oxaliplatin 85mg/m², bevacizumab 5mg/kg, all IV, repeated every two weeks, with HCQ as above. After 12 cycles, oxaliplatin was omitted and patients were continued on 5-FU, bevacizumab, and HCQ. Imaging was performed every 8 weeks. Results: Twenty-four patients (pts) have been accrued, of whom 23 are eligible: 10 female/13 Male; 19 Caucasian/3 Black/1 East-Asian. Toxicity has been generally tolerable. Grade 3 effects included neutropenia 9/23, diarrhea (1/23), and anorexia (1/23). There were two episodes of myocardial infarction, one fatal, one of atrial arrhythmia, and two of pulmonary embolism in the course of the trial. 20/23 patients were able to maintain full dose of HCQ. Patients evaluable for response include 19 (4 pts too early). There were 1 complete response (5%), 9 partial responses (47%), and 7 stable disease (37%). Four patients went off study for resection of metastatic disease after 3-25 months. Median progression-free and overall survival have not been reached. Autophagy biomarkers in peripheral mononuclear cells show autophagy inhibition in the majority of patients. Six of thirteen patients with genomic testing available had a TP53 mutation. Four of these six patients had a major response (1CR, 3 PR). Conclusions: The combination of FOLFIRX/bevacizumab with HCQ is an active regimen in unselected patients with colorectal cancer. A randomized Phase II trial of the combination is in development. Clinical trial information: NCT01206530.

3615 Poster Session (Board #108), Mon, 8:00 AM-11:30 AM

Phase 1 extension study of BB1503, a first-in-class cancer stemness kinase inhibitor, in patients with advanced colorectal cancer. First Author: Derek J. Jonker, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Targeting cancer stem cells (CSC) has shown pre-clinical efficacy and holds therapeutic promise. BB1503 is a first-in-class cancer stemness kinase inhibitor with potent in vitro and in vivo activity against CSC. BB1503 works through inhibition of stemness pathways, including Nanog. High Nanog expression in patients with colorectal cancer (CRC) predicts poor prognosis. Patients with advanced CRC who had failed all standard treatment regimens were enrolled in a phase I and disease-specific cohort expansion study. Methods: BB1503 was given orally and continuously in 28-day cycles until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Eligible patients with CRC received BB1503 monotherapy at 20 mg to 500 mg total daily. Archival tissue was evaluated by IHC for Nanog expression. Results: 47 patients with heavily pre-treated CRC were enrolled (median 4 prior lines standard therapy). Bevacizumab was used in 80%, anti-EGFR AB in 60%, and regorafenib in 23%. Most (N = 35, 75%) received BB1503 at RP2D, 300 mg once daily. Median duration was 8 weeks (range < 1 to 46+). Common adverse events (AE) considered related to therapy were grade 1 to 2 diarrhea, abdominal pain, fatigue, and nausea/vomiting/anorexia. At RP2D, Grade 3 AE were diarrhea (N = 3), fatigue (N = 3), nausea (N = 2), and weight loss (N = 1). Archival tissue was available from 39 patients (83%). DCR (CR + PR + SD) in evaluated patients with high Nanog expression (biomarker positive) was 44%, while DCR in biomarker negative patients (ITT) was 13% (p = 0.040). Median overall survival (mOS) in biomarker positive patients (ITT) was 38 weeks, while mOS in biomarker negative patients (ITT) was 16 weeks (p = 0.089 Log-Rank). Conclusions: BB1503, a first-in-class cancer stemness kinase inhibitor, demonstrated tolerability at the RP2D administered to patients with pre-treated mCRC. Disease control and prolonged overall survival were observed in CRC patients with positive Nanog expression in tumor tissues. Further clinical evaluation of BB1503 alone or in combination with standard chemotherapeutic agents in CRC is warranted. Clinical trial information: NCT01781455.

3616 Poster Session (Board #109), Mon, 8:00 AM-11:30 AM

A phase IIb study of BB1608 in combination with FOLFIRI with and without bevacizumab in patients (pts) with advanced colorectal cancer (CRC). First Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN

Background: BB1608 is an oral first-in-class cancer stemness inhibitor of Stat3. Potent anti-tumor activity was observed in vitro and in vivo in mono- and combination therapy. In a phase I study, BB1608 monotherapy was generally well tolerated at 500 mg BID with encouraging signs of anti-tumor activity. Methods: A phase IB label open, multi-center study in pts with advanced CRC was performed to determine RP2D, safety, tolerability, and preliminary anti-cancer activity of BB1608 in combination with FOLFIRI with or without bevacizumab. BB1608 was administered at 240 mg BID in combination with FOLFIRI (5-FU 400 mg/m² bolus with 2400 mg/m², irinotecan 180 mg/m², and leucovorin 400 mg/m²) with or without bevacizumab 5 mg/kg, administered bi-weekly until progression of disease, unacceptable toxicity, or other discontinuation criterion was met. Results: 9 pts were enrolled with 4 pts receiving FOLFIRI and 5 pts receiving FOLFIRI with bevacizumab in combination with BB1608. All pts were pretreated with ≥ 1 line and 67% (6/9) of pts with ≥ 4 prior lines of therapy. Combination treatment was well tolerated with no dose-limiting toxicity and safety profile similar to that of each regimen individually, with no difference in safety observed with addition of bevacizumab. Most common adverse events included grade 1 and 2 diarrhea, abdominal cramps, nausea, vomiting and anorexia. Grade 3 diarrhea was observed in 2 pts, and resolved with a brief BB1608 dose holiday or dose reduction to 160 mg once daily. BB1608 was generally well tolerated at 240 mg BID in combination with FOLFIRI, with or without bevacizumab. BB1608 was administered at 240 mg BID in combination with FOLFIRI (5-FU 400 mg/m² bolus with 2400 mg/m², irinotecan 180 mg/m², and leucovorin 400 mg/m²) with or without bevacizumab 5 mg/kg, administered bi-weekly until progression of disease, unacceptable toxicity, or other discontinuation criterion was met. Conclusions: BB1608 at 240 mg BID can be safely combined with FOLFIRI with and without bevacizumab. Encouraging anti-tumor activity was observed in pts with advanced and heavily pretreated CRC. Clinical trial information: NCT02024607.
3617 Poster Session (Board #110), Mon, 8:00 AM-11:30 AM
A phase Ib/II study of cancer stem cell inhibitor BI66058 administered with panitumumab in KRAS wild-type (wt) patients (pts) with metastatic colorectal cancer (mCRC) as second line therapy. First Author: Katrina Pedersen, Mayo School of Graduate Medicine, Rochester, MN
Background: BI66058 is an oral first-in-class cancer stemness inhibitor that works by targeting Stat3. Potent preclinical anti-tumor activity was observed in vitro and in vivo, in mono- and combination therapy. In a Phase I study, BI66058 was well tolerated with encouraging signs of activity and a RP2D of 500 mg BID with additional ongoing studies showing it can be safely combined with multiple chemotherapeutics. Methods: A phase Ib/II open-label, multi-center study in pts with advanced K-Raswt mCRC was performed to determine safety and preliminary activity of BI66058 administered orally at 480-500 mg BID with panitumumab (6 mg/kg bi-weekly) until disease progression, unacceptable toxicity, or other discontinuation criterion was met. Following clearance of the DLT period in 6 pts, 18 more pts were enrolled. Results: All of the 24 pts enrolled were pre-treated with ≥2 lines of therapy and 12/24 with ≥3 lines of therapy. An MTD was not determined and BI66058 could be given in combination with full dose panitumumab. The safety profile was consistent with that of each agent as monotherapy and most common adverse events included grade 1-2 diarrhea, abdominal cramps, nausea and vomiting. Grade 3 hypokalemia and dehydration occurred in 2 pts. No significant pharmacokinetic interactions were observed. Disease control (SD+PR) was observed in 4 of 9 (44.4%) anti-EGFR naive pts of those, 2 of 9 (22%) had PR (33.3% and 33.3% regressions), and 2 had SD. Disease control (only SD) was observed in 8/15 (53.3%) pts who had failed anti-EGFR (ceftuximab) therapy, 2 of which had SD with regression (12.9% and 6.8%). The median progression free survival was 9 and 16.4 weeks in anti-EGFR naive and previously exposed pts, respectively. Conclusions: This phase Ib/II study demonstrated that BI66058 and bi-weekly panitumumab can be safely combined at full dose. The response rate in anti-EGFR naive pts was notably greater than that of anti-EGFR monotherapy. Moreover, encouraging preliminary activity was observed in K-Ras wt mCRC regardless of prior anti-EGFR exposure, suggesting that BI66058 may sensitize pts to repeat anti-EGFR therapy. Clinical trial information: NCT01776307.

3619 Poster Session (Board #112), Mon, 8:00 AM-11:30 AM
Programmed death-ligand 1 (PD-L1) expression in small bowel adenocarcinomas (SBA): A randomized controlled trial. First Author: Katrina Pedersen, Mayo School of Graduate Medicine, Rochester, MN
Background: SBAs are rare, resulting in a paucity of data on effective treatments. Highly active immune surveillance within all parts of the intestine may explain the rarity. In such an environment, tumor cells may express PD-L1 intracellularly may have worse outcomes. Further studies to address prognostic and therapeutic implications PD-L1 expression are indicated.

3618 Poster Session (Board #111), Mon, 8:00 AM-11:30 AM
Phase II/II study of everolimus (E) with irinotecan (Iri) and cetuximab (C) in 2nd line metastatic colorectal cancer (mCRC): Hoosier Cancer Research Network (HCRN) 6005-102. First Author: E. Gabriela Chiorean, University of Washington, Seattle, WA
Background: Preclinically, mTOR and EGFR inhibitors are synergistic. We hypothesized that the mTOR inhibitor E would enhance clinical efficacy when added to C. The Phase I portion determined the safety, and maximum tolerated dose (MTD), and the Phase II evaluated the response and survival rates with this combination. Preliminary results of the Phase I study (ASCO 2016, Landra et al) determined the MTD as E 6 mg qd daily (qd) combined with Iri and C. Here we report overall safety and efficacy results of the Phase II/II study. Methods: Patients (pts) were treated with Iri 125 mg/m² weekly (qw) x 2 every 3 wks, C 400 mg/m² loading, then 250 mg/m² qw, and escalating doses of E: 5 mg qd, 5 mg qd and 10 mg qd in 21-day cycles (Phase I), and 8 mg qd (Phase II). Eligibility allowed KRAS mutated (MUT) mCRC. During Phase II, KRAS wild-type (WT) pts were randomized to Iri+C vs Iri+C+E, and all KRAS MUT pts received Iri+C+E. Archival tumors were analyzed for biomarkers of EGFR and mTOR pathways activation. The study was discontinued early due to funding termination by Novartis. Results: 43 pts were enrolled, median age 65 y (25-77), 24 male, 30 pts enrolled in phase I (KRAS wt n = 15, KRAS MUT n = 13, KRAS unknown n = 2), and 13 pts in phase II (KRAS WT: n = 5 + 3 Iri+C+E, n = 2 Iri+C; KRAS MUT n = 6 Iri+C+E). The most common 3/4 AEs were diarrhea (35%), neutropenia (23%), fatigue (21%), mucositis (21%), and rash (19%). Among KRAS WT pts (n = 22) there were 1 CR, 3 PR (RR 18%), 12 SD (54%), and among KRAS MUT pts (n = 19) there were 1 PR (5%) and 11SD (52%). Median progression-free survival (PFS) and overall survival (OS) rates were 6 and 16 mos, respectively for all KRAS WT pts treated with Iri+C+E (n = 20), and 8.3 and 21.6 mos, respectively for KRAS WT pts treated with Iri+C (n = 11). Median PFS for KRAS WT pts were 8.0 and 12.3 mos, respectively for KRAS MUT pts. Only 2 KRAS WT pts were randomized to Iri+C before study closure. PD markers will be presented. Conclusions: The combination of Iri+C+E has an expected toxicity profile, and was clinically active as second-line treatment for KRAS WT mCRC pts. Further studies should delineate the CRC pts most likely to benefit from mTOR inhibitors in addition to EGFR blockade. (NCT00522665) Clinical trial information: NCT000752665.
**TPS3621** Poster Session (Board #113b), Mon, 8:00 AM-11:30 AM

**Gastrointestinal (Colorectal) Cancer**

**Genotype-directed phase II study of irinotecan dosing in metastatic colorectal cancer (mCRC) patients receiving FOLFIRI-bev for mCRC**

**First Author:** Richard Richard Williams, UNC Chapel Hill, Chapel Hill, NC

**Background:** Infusional fluorouracil/leucovorin plus irinotecan with bevacizumab (FOLFIRI-bev) is a standard first-line option for mCRC. The active metabolite of irinotecan, SN-38, is inactivated via glucuronidation by UGT1A1. Common germline variants of UGT1A1 are well known to alter the rate of glucuronidation and exposure to SN-38. UGT1A1*28 decreases UGT1A1 expression such that *28/*28 homozygotes have increased SN-38 exposure and increased risk of neutropenia. Despite the well-described association of genotype and SN-38 exposure, irinotecan doses have been established independent of genotype. Dose-limiting toxicity in the ~10% of patients homozygous for *28/*28 may have led to under-dosing of patients with other genotypes. In phase I genotype-directed dose-finding studies of FOLFIRI + bev, *1/*1 and *1/*28 patients were able to tolerate significantly higher doses of irinotecan—will increase the overall benefit of FOLFIRI-bev for patients with mCRC with tolerable toxicity. GENIC is a phase II multicenter, single arm trial designed to estimate the progression-free survival (PFS) of genotype-guided irinotecan dosing in patients receiving first-line FOLFIRI-bev for mCRC (NCT02361671). Methods: Patients with unresectable mCRC eligible for FOLFIRI-bev will be assigned irinotecan dose based on UGT1A1 genotype: *1/*1 = 310mg/m2; *1/*28 = 260mg/m2; or *28/*28 = 180mg/m2. Fluorouracil, leucovorin, and bevacizumab are given at standard doses. The primary objective is to estimate PFS compared with recently reported PFS from FIRE-3 and BO20041. 100 patients are planned to ensure 86% power to detect a 3.5 month improvement in PFS. Secondary objectives will evaluate toxicity, response rate, and overall survival. Efficacy by genotype will be explored. The Patient Reported Outcomes (PRO) version of the CTCAE will evaluate patient reported tolerance and the concordance between patient and clinician assessment. Clinical trial information: NCT02138617.

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**TPS3622** Poster Session (Board #114a), Mon, 8:00 AM-11:30 AM

**Gastrointestinal (Colorectal) Cancer**

**Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases: The randomized phase III CAIROS study of the Dutch Colorectal Cancer Group**

**First Author:** Joost Huiksen, Academic Medical Centre, Amsterdam, Netherlands

**Background:** Colorectal cancer patients with unresectable liver-only metastases may be cured after downsizing of metastases by neoadjuvant systemic therapy. However, the optimal neoadjuvant induction regimen has not been defined, and the lack of consensus on criteria for (un)resectability complicates the interpretation of published results. Methods: CAIROS is a multicenter, randomized, phase III clinical study. Colorectal cancer patients with initially unresectable liver-only metastases are eligible, and will not be selected for potential resectability to avoid selection bias. The unresectability status is prospectively assessed by a central panel consisting of at least one radiologist and three liver surgeons, and defined as no radical resection possible in one session with resection only. Tumors of included patients will be tested for RAS and BRAF (for stratification purpose) mutation status. Patients with RAS wild type tumors are treated with doublet chemotherapy (FOLFOX/FOLFIRI, choice of investigator) and randomized between the addition of either bevacizumab or panitumumab, patients with RAS mutant tumors are randomized between doublet chemo-therapy (FOLFOX/FOLFIRI) or triple chemotherapy (FOLFIRI/BEV), both with bevacizumab. Resectability status will be re-evaluated every two months. The primary study endpoint is median progression-free survival. Secondary endpoints include the R0/1 resection rate, and median overall survival. Conclusion: CAIROS is a prospective multicenter trial that investigates the optimal systemic therapy for patients with initially unresectable, liver-only colorectal cancer metastases. Discussion: The unique aspects of CAIROS concern the prospective phase III randomized comparison of neoadjuvant treatment regimens in this population with the use of uniform and transparent criteria for unresectability by an expert panel. This CAIROS panel may contribute to a consensus on criteria for unresectability and to awareness of secondary resections in these patients. Clinical trial information: NCT02162563.

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Background: Clinical studies with anti-VEGF agents, such as regorafenib, demonstrate that angiogenesis is critical to CRC tumor growth and metastasis. Roshanvand et al. (2022) have reported that bevacizumab plus placebo for 3-years resulted in a significant reduction in clinical benefit in trials for several tumor types. In a phase I study of N in CRC, a clinically relevant anti-angiogenic effect was observed in 67% of patients. The combination of Nintedanib (N) with placebo resulted in a 76% reduction in risk of HRAs and 2nd primary CRCs. Polyamines, in excess, are considered a new treatment alternative for patients with locally advanced rectal (LAR) cancer. Willet et al. (Nat Rev 2004) demonstrated that Induction treatment with anti VEGF therapy bevacizumab (BEV) before CRT, decreased tumor interstitial fluid pressure and blood flow, suggesting normalization of the tumor vasculature. The AVACROSS phase II trial (Nogue, The Oncologist 2011) showed that BEV combined with induction CT followed by BEV combined with CRT and surgery produced high pCR rates (36%) but with an unacceptable rate of surgical reoperations. Aflibercept (Aflibercept (Afli) is a novel antiangiogenic agent that acts as a soluble receptor that binds to human VEGF-A, VEGF-B, PI GF. We hypothesized that administering induction Afli/FOLFOX followed by CRT will improve pCR rate without compromise wound healing.

Methods: We will conduct a multicenter phase II randomized trial, stratified by m7 stage and institution, with 2:1 allocation, comparing preoperative induction mFOLFOX6 with or without Afli prior to standard CRT (capcitabine with 50.4 Gy) and surgery. Primary endpoint: pathological complete response (pCR). 180 patients (p) will be recruited (120 p for mFOLFOX6 + Aflibercept group and 60 p for mFOLFOX6). Assumptions: 10% of dropouts, 0.10% one-sided type-I error, 80% power to detect a 15% difference in pCR. 2 interim analyses for safety, efficacy/futility (Lan de Mets, O’Brien-Fleming). Major eligibility criteria: High-risk rectal cancer with 1 of the following criteria on high resolution MRI: Extramural vascular invasion or extramural extension > 5 mm into perirectal fat or mesorectal fascia threatened or involved in middle T3 tumors, mT4 or N2 middle or distal tumors. Enrollment began in January 2015. ClinicalTrials.gov Identifier: NCT02340949 Clinical trial information: 02340949.
TPS3629  Poster Session  (Board #117b), Mon, 8:00 AM-11:30 AM  
Phase II/II study of neoadjuvant chemoradiation therapy with CRLX101 and capecitabine for locally advanced rectal cancer.  
First Author: Andrew Worsecke, MD  
NC Chapel Hill, NC  

Background: There is strong interest in the development of novel agents and strategies to further improve the therapeutic ratio of neoadjuvant chemoradiation therapy for rectal cancer. One innovative approach is to incorporate nanoparticle (NP) therapeutics, which are designed to preferentially accumulate in tumors. CRLX101 is an investigational nanoparticle-drug conjugate with a camptothecin payload. Preclinically, CRLX101 has been shown to be a potent radiosensitizer in colorectal cancer. The purpose of this Phase II/II study is to assess tolerability and to evaluate whether the addition of CRLX101 to capecitabine and radiotherapy can improve pathologic complete response (pCR) and clinical outcomes for rectal cancer.  
Methods: This ongoing open label, single-arm multicenter Phase II/II study is designed to evaluate the addition of CRLX101 to a standard 5FU-based chemoradiotherapy regimen in patients with locally advanced rectal carcinoma (stage cT3-4N0 or cT4N+). Phase IIb employed a 3 + 3 dose escalation design with starting dose of 12 mg/m². Dose level 1 was 15 mg/m², the MTD for single agent CRLX101. 8 patients have completed treatment without DLT (3 in cohort 1 and 5 in cohort 2) and 1 patient is undergoing treatment at the 15 mg/m² dose level. We have identified 15 mg/m² as the MTD/RPD2. The Phase II portion of the study is ongoing and will evaluate the efficacy of this MTD/RPD2 and further characterize the safety of CRLX101 combined with CRT. Patients in the Phase IIb portion with resectable disease and who were treated at the RPD2 will be included in the Phase II study population for efficacy analysis. Target accrual is 53 evaluable patients in the Phase II trial and a primary endpoint of pCR rate will be evaluated using a Simon two-stage design. Secondary objectives include evaluation of pathological response, disease free survival (DFS) and overall survival (OS). We hypothesize that our programmed regimen will improve the rate of pCR compared to 15-20% historical benchmarks. If results are consistent with a pCR rate of at least 35%, the treatment regimen will be considered worthy of further investigation. Clinical trial information: NCT02010567. Clinical trial information: NCT02010567.  

TPS3630  Poster Session  (Board #118a), Mon, 8:00 AM-11:30 AM  
The CAIRO4 study: The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous resectable metastatic colorectal cancer.  
First Author: Andrew Worsecke, MD  
NC Chapel Hill, NC  

Background: There is no consensus regarding resection of the primary tumour with few or absent symptoms in patients with synchronous resectable metastatic colorectal cancer. A potential benefit of resection of the primary tumour is to prevent complications of the primary tumour in later stages of the disease. Retrospective studies also show a potential survival benefit for patients undergoing resection. However, surgery can cause severe morbidity and mortality in this patient group. We hereby propose a randomized trial in order to demonstrate that resection of the primary tumour improves overall survival.  
Methods: The CAIRO4 study is a multi-center, randomized, phase III trial. The CAIRO4 Study is sponsored by the Dutch Colorectal Cancer Group (DCCG). Patients with synchronous resectable metastases of colorectal cancer and few or absent symptoms of the primary tumour are randomized 1:1 between systemic therapy only, and resection of the primary tumour followed by systemic therapy. Patients will be stratified according to location of the primary tumour (colon versus rectum), WHO performance status (0-1 versus 2), hospital of inclusion, serum LDH (normal versus abnormal) and number of metastatic sites (single versus multiple). To demonstrate a survival benefit of 6 months in the experimental arm, a total of 218 events are needed (80% power, significance level 0.05). Accounting for accrual time and follow-up, we need a total of 360 patients (180 patients per arm). Systemic therapy will consist of fluoropyrimidine-based chemotherapy in combination with bevacizumab. The primary objective of this study is to determine the clinical benefit in terms of overall survival of initial resection of the primary tumour. Secondary endpoints include progression-free survival, overall survival, disease-free survival, quality of life and the number of patients requiring resection of the primary tumour in the control arm. Accrual has started in September 2012. As of January 2015, 64 centres in the Netherlands and Denmark are participating in the CAIRO4 study. Clinical trial information: NCT01606098.  

TPS3631  Poster Session  (Board #118b), Mon, 8:00 AM-11:30 AM  
The ORCHESTRA trial: A phase III trial of adding tumor debulking to systemic therapy versus systemic therapy alone in (mCRC) multi-organ metastatic colorectal cancer.  
First Author: Elske C. Gootjes, Department of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands  

Background: In the current multidisciplinary approach of mCRC, local treatment of oligometastases is common practice. Results of large case series of selected patients treated with complete surgical resection of metastatic lesions suggest that this approach substantially improves survival rates to around 30-60%. Other techniques such as radiofrequency or microwave ablation (RFA, MWA), transarterial chemoembolization (TACE) or stereotactic ablative radiotherapy (SABR) can also be applied in local treatment. Curative treatment options are generally not available for patients with extensive hepatic and/or extrahepatic mCRC. These patients primarily receive palliative systemic treatment consisting of combination chemotherapy as well as targeted agents. So far, reports on the benefit of local treatment for metastases in multi-organ mCRC have major limitations, including being small, non-randomized, single-center and prospective. The benefit from local treatment of metastases for these patients should be established to allow for interruption of the standard systemic therapy and exposure to possible adverse events from local treatment.  
Methods: The ‘ORCHESTRA’ trial is a randomized multicenter clinical trial for patients with multi-organ mCRC, comparing the combination of chemotherapy and maximal tumor debulking versuschemoradiotherapy alone (NCT01792934). We will examine the interplay of both efficacy and toxicity for the combination of surgery and CRT. We hypothesize that our programmed regimen will improve the rate of pCR compared to 15-20% historical benchmarks. If results are consistent with a pCR rate of at least 35%, the treatment regimen will be considered worthy of further investigation. Clinical trial information: NCT02010567. Clinical trial information: NCT02010567.  

TPS3632  Poster Session  (Board #119a), Mon, 8:00 AM-11:30 AM  
MErCuRIC1: A Phase I study of MEK1/2 inhibitor PD-0325901 with cMET inhibitor crizotinib in RAS(T wild-type) mCRC and RAS(T with aberrant c-MET) metastatic colorectal cancer (mCRC) patients.  
First Author: Sandra Van Schaybroeck, Queen’s University Belfast Centre for Cancer Research and Cell Biology, Belfast, United Kingdom  

Background: RAS is mutated (RAS(T)) in ~55% of mCRC, and phase III studies have shown that patients harbouring RAS mutations do not benefit from anti-EGFR MoAbs. In addition, ~50% of RAS Wild Type (RAS(T)) will not benefit from the addition of an EGFR MoAb to standard chemotherapy. Hence, novel treatment strategies are urgently needed for RAS(T) and >50% of RAS(T) mCRC patients. c-MET is overexpressed in ~50-60%, amplified in ~2-3% and mutated in ~3-5% of mCRC. Recent preclinical studies have shown that c-MET is an important mediator of resistance to MEK inhibitors (i) in RAS(T) mCRC, and that combined MEK1/2/c-MET inhibition is synergistic in tumour growth in RAS(T) and c-MET xenograft models (1). A number of recent studies have highlighted the role of c-MET in mediating primary/secondary resistance to anti-EGFR MoAbs in mCRC, suggesting that patients with RAS(T) tumours with aberrant c-MET (RAS(T)/c-MET+) may benefit from anti-c-MET targeted therapies (2). These preclinical data support phase I/II clinical trial of the combination MEK1/2/c-METi treatment in RAS(T) and RAS(T) CRC patients with aberrant c-MET signalling (overexpression, amplification or mutation; RAS(T)/c-MET+).  
Methods: MErCuRIC1 is a phase I combination study of MEKi (PD-0325901) and c-METi (crizotinib) in RAS(T) and RAS(T)/c-MET+ mCRC patients with biopsies available. The dose escalation phase, utilizing a 3 + 3 dose escalation design with starting dose of 12 mg/m². Dose level escalation phase began in December 2014 with cohort 1 still ongoing. The dose escalation phase utilized a 3 + 3 dose escalation design with starting dose of 12 mg/m². Dose level 1 was 15 mg/m², the MTD for single agent PD-0325901. The Phase II portion of the study is ongoing (NCT01792934). We will examine the interplay of both efficacy and toxicity for the combination of surgery and CRT. We hypothesize that our programmed regimen will improve the rate of pCR compared to 15-20% historical benchmarks. If results are consistent with a pCR rate of at least 35%, the treatment regimen will be considered worthy of further investigation. Clinical trial information: NCT02010567. Clinical trial information: NCT02010567.
**TPS3633**  
**Poster Session (Board #119b), Mon, 8:00 AM-11:30 AM**

Development of a phase Ib/IIa proof-of-concept study of imalumab (BAX69), a first-in-class anti-macrophage migration inhibitory factor (MIF) antibody, as a 3rd or 4th line treatment in metastatic colorectal cancer (mCRC).  
First Author: Xiaochun Liu, Baxter Healthcare Corporation, Deerfield, IL  

**Background:** Patients with mCRC who fail 2 or 3 lines of treatment have few effective treatment options. MIF is dramatically upregulated in CRC tissue and its serum concentration positively correlates with increased tumor aggressiveness and risk of hepatic metastasis in CRC pts. MIF appears to contribute to cancer progression in tumor-associated anti-apoptosis, angiogenic growth factor expression, neovascularization and hypoxic adaptation. I malumab is a novel recombinant, fully-human, monoclonal antibody specific for the pathogenic form of MIF (oxMIF). I malumab showed preliminary antitumor activity with acceptable tolerability in a phase I study (NCT01765790) in patients with cancers, including mCRC. I malumab has synergistic effects with chemotherapeutic agents in mCRC preclinical models independent of KRAS or p53 mutational status, leading us to evaluate imalumab-based combination regimens. **Methods:** We adopted a two-step approach for this trial. A safety run-in dose escalation phase will be conducted first with imalumab at 7.5mg/kg weekly in combination with 5-FU/LV or panitumumab in mCRC patients with or without KRAS/NRAS mutation, respectively. In the absence of dose limiting toxicities (DLTs), imalumab will be escalated to 10mg/kg weekly to evaluate DLT (primary endpoint) and determine the recommended phase II dose of imalumab combined with 5-FU/LV or panitumumab. Then, a randomized (2:1) phase II portion will investigate whether imalumab plus 5-FU/LV (KRAS/NRAS mut) or panitumumab (KRAS/NRAS wild type) is superior to standard of care at the 3rd or 4th line treatment setting in prolonging progression-free survival (primary endpoint) in mCRC patients. Secondary endpoints include safety and tolerability, overall survival and response rate, the pharmacokinetic (PK) profile of imalumab in combination with 5-FU/LV or panitumumab, quality of life, and biomarker association with treatment response. An accrual of 12-24 pts for the safety run-in phase and 66 pts for the randomized phase is planned. Eligibility includes diagnosis of mCRC and failure of 2-3 lines of therapies. Clinical trial information: pending.

**TPS3635**  
**Poster Session (Board #120b), Mon, 8:00 AM-11:30 AM**

A phase 3 open-label, randomized, multicenter study of imprime PGG in combination with cetuximab in patients with KRAS wild type metastatic colorectal cancer.  
First Author: Richard Dale Huhns, Biothera, Eagan, MN  

**Background:** Imprime PGG (Imprime) is a beta-1,3/1,6 glucan complex carbohydrate biologic, which harnesses innate immune effector cells to enhance killing of antibody-targeted, complement-opsonized tumor cells. In a phase 2 single-arm clinical trial in metastatic colorectal cancer (mCRC), the combination of Imprime with cetuximab resulted in 24% objective response rate (ORR), 62% disease control rate (DCR), and median time to progression (TPP) of 12 wks (Tamayo ME, Ann Onc 2010), representing approximate 100% increases vs historical control (Cunningham, NEJM 2004). ORR was 45%, DCR, 82% and TPP of 24 wks in patients (pts) with KRAS wild-type (WT) tumors (post hoc analysis). Single-agent cetuximab has been shown to improve ORR, progression-free survival (PFS) and overall survival (OS) in pts with epidermal growth factor receptor (EGFR) expressing, KRAS WT mCRC who failed oxaliplatin- and irinotecan-based therapy or are intolerant to irinotecan. The mechanism of action of cetuximab is thought to rely on competitive blockade of endogenous ligand binding and downstream signaling, internalization and down regulation of EGFR, as well as antibody-dependent cellular cytotoxicity (ADCC) (Erbutz USPI). The current trial, sponsored by Biothera and registered with ClinicalTrials.gov (NCT01309126) is to confirm these findings in phase 3. **Methods:** Eligible pts have received prior oxaliplatin- and irinotecan-based therapy or are intolerant to irinotecan, have measurable or evaluable disease and ECOG performance status of 0 or 1. Approximately 795 pts will be randomized 2:1, stratified by geographic region, prior chemotherapy and site, to receive weekly open-label Imprime plus cetuximab or cetuximab alone. The primary endpoint of the study is OS and the primary analysis will occur when ~709 deaths have occurred. Secondary endpoints include PFS, ORR (based on RECIST 1.1), quality of life, safety and pharmacokinetics. Exploratory endpoints include biomarker analyses. Pt screening and enrollment is underway in the United States and Europe. Clinical trial information: NCT01309126.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
In this phase III trial, the efficacy and safety of neoadjuvant chemotherapy with regorafenib (REG) in patients with resectable oesophagogastric cancer (OESG) following failure of 1st or 2nd line chemotherapy (CT) where few options exist. Final overall and subgroup results. First Author: Nick Pavlakis, Department of Medical Oncology, Royal North Shore Hospital, The University of Sydney, Sydney, Australia

Background: REG is an oral multi-kinase inhibitor warranting evaluation in AOGC following failure of 1st line chemotherapy (CT) where few options exist. Methods: INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC). A study by the Australasian Gastrointestinal Trials Group (AGITG)—A study of regorafenib in refractory advanced oesophagogastric cancer (AOGC). Final overall and subgroup results. First Author: Nick Pavlakis, Department of Medical Oncology, Royal North Shore Hospital, The University of Sydney, Sydney, Australia
SWOG S0518: Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis pancreatic neuroendocrine tumors (NCT00569127). First Author: James C. Yao, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment options for advanced carcinoid tumors (NETs) are limited. Somatostatin analogues (SSA) prolong progression-free survival (PFS) among patients (pts) who are treatment naive or have stable disease. Interferon (INF) added to SSA has also demonstrated antitumor activity. Bevacizumab (BEV), added to SSA, octreotide (OCT), was associated with tumor regression and encouraging antitumor activity in a phase II study. The current study compares BEV + OCT to INF-a+2b + OCT. Method: Pts with metastatic or unresectable, well-differentiated, G1/2 NETs with progressive disease or other poor prognostic features were randomly assigned (1:1) to receive OCT LAR 20 mg q 21 days with either BEV 15 mg/kg every 21 days or INF-a 2b 5 million units three times per week. PFS by central review was the primary endpoint. Results: 427 pts were enrolled, of whom 402 were eligible, between December 2007 and September 2012. Median PFS by central review was 16.6 (95% CI: 12.9 – 19.6) months in BEV arm and 15.4 (95% CI: 9.6 – 18.6) months in the INF arm (HR 0.93; 95% CI 0.73-1.18, P = 0.55). By investigator review, median PFS was 15.4 (95% CI: 12.6 – 17.2) months in BEV arm and 10.6 (95% CI: 8.5 – 14.4) months in the INF arm (HR 0.90; 95% CI: 0.72 – 1.12, P = 0.33). TTF was significantly longer with BEV compared to INF (HR 0.72; 95% CI 0.58 - 0.89; P = 0.003). Median TTF was 9.9 (95% CI: 7.3 – 11.1) months in the BEV arm and 5.6 (95% CI 4.3 – 6.4) months in the INF arm. Confirmed radiologic response rates were 12% (95% CI: 8% – 18%) in the BEV arm and 4% (95% CI: 2% - 8%) in the INF arm. Common AEs with BEV + OCT included HTN (32%), proteinuria (8%), and fatigue (7%); and with INF-a TTF included fatigue (27%), neutropenia (12%), and nausea (6%). Conclusion: BEV + OCT was associated with a significantly higher RR (31%) compared to E alone (12%; p = 0.005) Conclusions: Treatment with E + BEV led to superior PFS compared to E but with more adverse events in this randomized phase II study. The RR was significantly higher in pts pts treated with E + BEV. The combination of E + BEV warrants further investigation in pts with advanced pNET. Clinical trial information: NCT01229943.

High response rate and PFS with PEGPH20 added to nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study. First Author: Sunil R. Hingorani, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Poor outcomes in pancreatic cancer (PDA) are associated in part by high-HA tumors. HA status was tested retrospectively. Primary endpoint is PFS, secondary endpoints include: ORR, OS and Safety. Due to a temporary clinical hold, ORR is from data through April 2014; and PFS is data through December 2014. Results: 146 pts were enrolled and 135 pts received at least one dose of study drug. The mean age was 65.1 yrs. (Range 29-83 yrs), 93% had a KPS of ≥ 80. The most common AEs related to study drugs (PAG vs. AG): fatigue (68% vs. 69%), nausea (55% vs. 44%), anemia (42% vs. 36%), peripheral edema (56% vs. 31%) and muscle spasms (2% vs. 2%). There was an imbalance of thromboembolic (TE) events with 42% vs. 25% of subjects having at least one TE event. Overall RR and PFS are shown in the table below. Conclusions: PEGPH20 was well tolerated in advanced PDA. Patients with HAhigh tumors receiving PAG had greater ORR and longer PFS than HAlow patients receiving AG. Overall survival will be presented at the time of the meeting. ClinicalTrials.gov identifier NCT01839487. Clinical trial information: NCT01839487.

Endpoint/Population PAG AG P-value

<table>
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<tr>
<th>ORR</th>
<th>N = 135</th>
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<tr>
<td>HAlow N = 34</td>
<td>10/19 (71%)</td>
<td>16/15 (67%)</td>
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<td>HAhigh N = 28</td>
<td>9/18 (50%)</td>
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<tr>
<th>PFS</th>
<th>N = 135</th>
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<tr>
<td>HAlow N = 48</td>
<td>42/74; 5.7 months</td>
<td>39/61; 5.2 months</td>
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<tr>
<td>HAhigh N = 58</td>
<td>22/36; 9.5 months</td>
<td>22/36; 4.8 months</td>
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CONKO-005: Adjuvant therapy in RO resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study. First Author: Marianne Sinn, Chantel - Universitätssmedizin Berlin, Medical Oncology, Berlin, Germany

Background: Adjuvant chemotherapy with gemcitabine (Gem) for 6 months significantly improves survival of pancreatic cancer patients. CONKO-005 was designed to evaluate an additional effect of the EGFR-tyrosinkinase-inhibitor erlotinib (Eriko 100 mg p.o. daily) in combination with Gem (1000 mg/m2 i.v. day 1,18,29) for 24 weeks in pts after R0 resection. Methods: Randomized multicenter, open-label phase III trial of Gem plus concurrent standard dose octreotide. The primary endpoint was PFS. The potential superiority of Gem+Eriko (GemErlo) versus Gem alone (Gem) was evaluated with a stratified log-rank test with 90% power (1-sided α = 0.05) to detect a HR of 0.8. Secondary endpoints included overall survival (OS), response rate, RR, and safety. Results: 150 pts were randomized; 75 per arm. Pt characteristics were similar between treatment arms and included: median age 59 years (range 21-86), 56% male, ECOG PS 0 (57%) and 1 (43%), prior cytotoxic chemotherapy 24%. The median number of 28-day treatment cycles was 13 (E + B) and 12 (E), with a range of 1-4 cycles. Median follow up was 25.9 months. Pts on E + B experienced a higher frequency of grade 3 AEs, including diarrhea (14% vs. 3%; p = 0.01), hyponatraemia (12% vs. 3%; p = 0.02), hypophosphatemia (11% vs. 3%; p = 0.04), proteinuria (16% vs. 1%; p = 0.001), and hypertension (41% vs. 12%; p < 0.001). The frequency of grade 4 AEs was 11% in both arms; a single grade 5 event occurred on E. The median PFS was 16.7 mos (E+B) vs. 14 mos (E); HR = 0.80 (95% CI: 0.55, 1.17; 116 PFS events), 1-sided p = 0.12. The median OS was 36.7 mos (E+B) vs. 35.0 mos (E); HR = 0.75 (95% CI: 0.42-1.33; 49 OS events), 1-sided p = 0.16. Treatment with E + B was associated with a significantly higher RR (31%) compared to E alone (12%; p = 0.005). Conclusions: Treatment with E + B led to superior PFS compared to E but with more adverse events in this randomized phase II study. The RR was significantly higher in pts pts treated with E + B. The combination of E + B warrants further investigation in pts with advanced pNET. Clinical trial information: NCT01229943.
Preoperative modified FOLFIRINOX (mFOLFIRINOX) followed by chemoradiation (CRT) for borderline resectable (BLR) pancreatic cancer (PDAC): Initial results from Alliance Trial A022101. First Author: J. Shunk, Second Author: N. K. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Infusional 5-FU, oxaliplatin, leucovorin and irinotecan (FOLFIRINOX) is effective for metastatic PDAC. The tolerability and efficacy of neoadjuvant FOLFIRINOX and CRT for BLR PDAC is unknown. Methods: Patients (pts) with ECOG PS 0/1 and PDAC meeting any of the following centrally-reviewed radiographic criteria: 1) tumor-vessel interface (TVI) with superior mesenteric/portal vein (SMA > 180°, 2) TVI with mesenteric artery (SMA < 180°), 3) TVI with hepatic artery of any degree, received mFOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m² on day 1 followed by 5-FU 2400 mg/m² x 48 hours for 4 cycles) and CRT (50.4 Gy in 28 fractions) with capecitabine (2250 mg/m² P0D 1-3 and 3333 mg/m² P0D 4-17) followed by planned resection. Results: 22 of 23 enrolled pts started therapy (median age 64 years, 64% ECOG PS 0). All pts completed mFOLFIRINOX and 21 (95%) completed CRT. The best RECIST responses during pre-op treatment were 2 CR, 4 PR, 15 SD and 1 PD. 7 patients did not undergo planned resection due either to progression (6) or refusal (1). Among the 15 (68%) patients who did undergo pancreatectomy, 14 (93%) operations were RO; 80% and 27% of operations required vein or hepatic artery resection, respectively; 7 (47%) specimens had < 5% residual tumor cells following therapy. Among all pts, 68% (95% CI (45.1 – 86.4)) underwent RO/R1 resections and 2 (9%) achieved pathologic CR. Related grade III and IV adverse events were observed in 46% (10 of 22) and 5% (1 of 22) of pts during chemotherapy, 38% (8 of 21) and 0% during CRT, and 15% (2 of 13) and 31% (5 of 13) following pancreatectomy; 1 pt died within 90 days of surgery. 18 pts are alive with an immature median follow-up of 10 months. Conclusions: mFOLFIRINOX and CRT are associated with manageable toxicity that did not preclude subsequent resection. Although a RECIST response was uncommon, the efficacy of this preoperative regimen is suggested by high rates of RO resection and pathologic response. Clinical trial information: NCT01821612.

Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028. First Author: Toshihiko Doi, National Cancer Center Hospital East, Chiba, Japan

Background: Pembrolizumab is a programmed death-ligand 1 (PD-L1) or programmed death receptor 1 (PD-1) based therapy. Six pts (26%) experienced drug-related adverse events (DRAEs) that did not have response assessed at the time of analysis. Six pts, including all ARID1A alterations, were compared using the log rank test. Results: 63% of patients were Texas residents with male to female ratio = 3:1. Patients with HBV were more likely to develop HCC at younger age than HCV patients, with poorly differentiated tumor (PDT), portal thrombosis (PT), larger tumor size (> 5 cm), extensive liver involvement (> 50%), high alpha-fetoprotein, and advanced CLIP stage (3-6). On the other hand, patients with HCV were more likely to exhibit underlying cirrhosis, have a history of greater alcohol and cigarette use, and had higher co-occurrence of diabetes mellitus (DM). One-year survival rates were similar between both groups (43.3%) and median survivals were 10.9 and 9.3 mos. for HCV and HCV, respectively (P = 0.9). Conclusions: Significant clinicopathologic variations exist in HCC patients associated with HCV vs HBV, which may impact patients’ eligibility for treatment, but not prognosis.

Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Hepatitis B- and C-associated hepatocellular carcinoma in a large U.S. cancer center: Do clinicopathologic features or patient outcomes differ by the potentially causative viruses? First Author: Marc I. Uemura, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Hep B virus (HBV) and hep C virus (HCV) are the main viral causes of hepatocellular carcinoma (HCC) development and are responsible for ~50% of USA cases. Because HBV is a DNA virus (Hepadna family) and HCV is an RNA virus (flavivirus family), it is unclear whether such virologic differences influence clinicopathologic features of HCC or patient outcomes. We analyzed clinicopathologic features of HCC patients associated with HBV vs HCV. Methods: Between 1992 to 2011, 815 HCC patients (HCV = 472, HBV = 343) were referred for treatment at the Univ. of Texas MD Anderson Cancer Center. Under IRB approval, detailed patient characteristics at time of diagnosis were documented. Chi-square tests were used to assess the significance of differences in the distributions of categorical variables between HBV and HCV groups. Median survival (mos.) was calculated using Kaplan Meier product-limit method and survival rates were compared using the log rank test. Results: 63% of patients were Texas residents with male to female ratio = 3:1. Patients with HBV were more likely to develop HCC at younger age than HCV patients, with poorly differentiated tumor (PDT), portal thrombosis (PT), larger tumor size (> 5 cm), extensive liver involvement (> 50%), high alpha-fetoprotein, and advanced CLIP stage (3-6). On the other hand, patients with HCV were more likely to exhibit underlying cirrhosis, have a history of greater alcohol and cigarette use, and had higher co-occurrence of diabetes mellitus (DM). One-year survival rates were similar between both groups (43.3%) and median survivals were 10.9 and 9.3 mos. for HCV and HCV, respectively (P = 0.9). Conclusions: Significant clinicopathologic variations exist in HCC patients associated with HBV vs HCV, which may impact patients’ eligibility for treatment, but not prognosis.
METGastric: A phase III study of onartuzumab plus mFOLFx in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). First Author: Manish A. Shah, Well Cornell Medical College, New York, NY

Background: Dysregulation of the MET/HGF pathway is associated with poor prognosis in GEC. Onartuzumab (O), a monovalent anti-MET antibody, inhibits the MET/HGF pathway. We investigated first-line mFOLFx + O in metastatic HER2-, MET + GEC. Methods: This double-blind, placebo-controlled phase 3 study randomized patients (pts) 1:1 to mFOLFx/placebo (P) or O (10 mg/kg) for up to 24 months. Eligibility criteria included no prior treatment for metastatic disease, age ≥ 18 yrs, ECOG PS 0–1, received organ function, HER2-, MET+ (IHC 1+, 2+ or 3+ GEC). Co-primary endpoints: overall survival (OS) in ITT and MET + pts. Secondary endpoints: progression-free survival (PFS), overall response rate (ORR) and safety. The study was designed to enroll ~800 pts and powered to demonstrate improvement in OS from 9 to 12.3 mo (ITT pts) (HR 0.73) and 9 to 18 mo (MET 2+/3+ pts; HR 0.49). Enrollment stopped early due to negative final results from a phase 2 trial assessing mFOLFx + O. Results: The ITT population comprised 562 pts (enrolled 19 Nov 2012–7 Mar 2014). The treatment arms were well balanced; median age (59 yrs O, 58 yrs P), male (67% O, 65% P), and MET 2+/3+ (38% O, 39% P). Serious adverse events (AEs) were slightly more frequent with O vs P (35.8% v 32.5%). Grade ≥ 3 AEs more commonly seen with O included neutropenia (35.1% v 29.3%), thrombocytopenia (4.3% v 1.1%), peripheral edema (4.7% v 0.4%), and pulmonary embolism (6.1% v 3.6%). At data cutoff (25 Apr 2014), 26% of ITT pts in each arm had OS events. In the MET 2+/3+ subgroup, 38% of P and 33% of O pts had OS events. See Table for efficacy data. Exploratory subgroup analyses showed improved OS for the O arm in non-Asian pts vs P (0.90, 0.429; 0.79, 0.223). There was no prior treatment effect regardless of MET status. Conclusions: The addition of onartuzumab to mFOLFx was ineffective in ITT or MET 2+/3+ pts. Subgroup analysis suggests non-Os (7%) and age >60 gastric. Further analysis will explore whether FGFR2 may delineate the role of the MET pathway in GEC. NCT01662869. Clinical trial information: NCT01662869.

4012 Poster Discussion Session; Displayed in Poster Session (Board #121), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 3:00 PM-4:15 PM

FOLFOX alone or combined to rituximab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (AGEA): An open-label, randomized phase II trial (PRODIGE 17 ACCORD 20 MEGA). First Author: David Malika, Gustave Roussy, Villejuif, France

Background: EGFR and HER2-Met pathways are often deregulated in AGEA. We assessed whether EGFR or HER2 inhibition with panitumumab or rituximab is beneficial in the first-line treatment of pts with AGEA. Methods: Pts ≥18 yrs with non-HER2+, measurable AGEA and ECOG performance status (PS) 0–1 were randomized (minimization; stratification factors: Lauren classification, disease stage, center) to mFOLF6 (oxaliplatin 85 mg/m², folinic acid 400 mg/m², fluorouracil: 400 mg/m² bolus then 2400 mg/m² over 46 h) alone (O) or combined to panitumumab (6 mg/kg, arm B) or rituximab (10 mg/kg; arm C), every 2 weeks until toxicity or disease progression. The primary endpoint was 4-month progression-free survival rate (4-PFS) (Ferriini’s one-step design, one-sided α = 5%, β = 10%; H0: 60%; H1: 65%). A clinical trial was presented. Results: 162 pts (median age, 64 years, range, 23-87, ECOG PS 0, 33/67%) were enrolled from 2011/10/14 to 2013/08/19 in 29 French centers. Most had metastatic (97%), intestinal (69%) adenocarcinoma of the stomach (50%) or GE junction (30%). Main results were (median follow-up, 23.6 months; 95%CI, 19.7-27.3). Conclusions: All combination regimens reached the primary study endpoint. Adding panitumumab or rituximab seemed more toxic and not more effective than mFOLF6 alone. Subgroup analyses according to tumor biomarker status (e.g., RAS/BRaf and MET) will be presented later. Clinical trial information: 2009-01212-12.

4013 Poster Discussion Session; Displayed in Poster Session (Board #122), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 3:00 PM-4:15 PM

Untreated metastatic diffuse gastric adenocarcinoma (DGAC): Randomized phase III study of S-1 and cisplatin vs. S-FU and cisplatin (the DIGEST trial). First Author: Jaffer A. Ajani, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The prognosis for metastatic DGAC is poor but the first line therapy for patients (pts) with DGAC is the same as that of without DGAC. Analyses of the FLAGS study suggested that S-1/Cisplatin might be better than 5-FU/Cisplatin in DIGEST. Therefore another phase III study was executed. Methods: Pts with metastatic DGAC (histology confirmed by central pathology review) with PS 0–1, adequate organ function, measurable/ evaluable disease were consented and randomized to S-1 (25 mg/m² po BIO on days 1-21 q 4 weeks)/cisplatin (75 mg/m² q 4 wk s)/CS or 5-FU (800 mg/m² continuous infusion for 5 days q 3 wks)/cisplatin (80 mg/m² q 3 wks); CF). Randomization was 2:1 in favor of CS, stratified by histologic subtype, extent of metastasis, ECOG PS and geographical region. The primary endpoint was overall survival (OS). The study was stopped after 361 pts were randomized versus a target 500 pts, and 264 events (deaths) were observed versus an analysis target of 472/244. OS of pts with metastatic DGAC compared to CF. Both arms were well balanced with respective pts characteristics. For ITT pts, the median OS was 7.5 months (95%CI); 6.7-9.3 for CS and 6.6 months (5.7-8.1) for CF (HR 0.99, 95%CI; 0.97-1.01, p = 0.9312). There was no statistical difference in progression-free survival. Overall response rate was 34.7% for CS compared to 19.8% for CF (p = 0.012). The number of cycles was 4 in both arms. The dose intensity was >90% in both arms. The rate at least one Gr. ≥ 3 AE related to study medication was 45.2% in CS and 55.9% in CF. The most frequent (≥ 5%) Gr. ≥ 3 AEs for CS were neutropenia (27.3%), neutropenic fever (16.3%), febrile neutropenia (15.5%), anaemia (7.7%), abdominal pain (5.7%), and asthenia (5.7%) and for CF were neutropenia (28.3%), anemia (8%), asthenia (10.2%), hyponatremia (10%), hypophosphatemia (7.9%), hyperkalemia (7%), anorexia (5.9%), and hyperkalemia (5%). One drug related death occurred in both CS (OS) and CF (0.8%). Conclusions: In the DIGEST study, CS did not prolong OS of pts with metastatic DGAC compared to CF. However, efficacy and safety were similar for CS and CF. (Supported by Taiho Oncology Inc, NJ, USA). Clinical trial information: NCT01285557.
4016 Poster Discussion Session; Displayed in Poster Session (Board #125), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO. First Author: Claudia Faulzig, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany

Background: Pathological response can be a potent surrogate factor for efficacy of neoadjuvant chemotherapy. Data from our phase III/I trial comparing perioperative FLOT with ECF(FX) in resectable stages were analyzed for pathological response upon request of the German Cancer Aid in order to further sponsor the trial. Methods: In the FLOT4, 714 patients (pts) are stratified and randomized to either 3 + 3 perioperative cycles of ECF/ECX (epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m², p.o.) d1-d21, q2d1) or 4 + 4 perioperative cycles of FLOT (docetaxel 50mg/m², d1; d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1; q14). Central pathology (by AT) is performed according to Becker classification. Results: Samples of 157 pts of the phase-II part of the study were analyzed. Median age was 63 yrs; 79.6% of pts were male. The primaries were gastric in 43.3%, EGJ in 56.1%, and not evaluable in 0.6% of pts. In the most relevant categories complete (CR) and subtotal (SR) histopathological response, FLOT was superior to ECF with CR 12.8% vs. 5.1% and SR 16.7% vs. 10.1%, respectively, with statistical significance for CR + SR (FLOT, 29.5% vs. ECF, 15.2%, p < 0.036). Also, significantly more pts in the ECF-arm had no pathological regression or even did not reach surgery (ECF, 41.8% vs. FLOT, 24.4%; p < 0.027). See also Table. Conclusions: Perioperative FLOT shows more pathological remissions (CR + SR) than ECF/ECX in patients with resectable gastric cancer. Clinical trial information: NCT01216644.

4018 Poster Discussion Session; Displayed in Poster Session (Board #127), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A randomized, double-blind, placebo-controlled phase III study of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE). First Author: Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan

Background: An unmet medical need persists for patients (pts) with sorafenib-refractory advanced hepatocellular carcinoma (HCC). This study was conducted to evaluate the efficacy and safety of S-1 in pts with sorafenib-refractory advanced HCC. Methods: Japanese men and women (aged ≥ 20 years) with Child-Pugh (C-P) A or B liver function and disease progression with or intolerance to sorafenib were randomized in a 2:1 ratio. S-1 (80, 100, or 120 mg/day) or a placebo was administered orally, according to the body surface area on days 1–28 of a 42-day cycle until disease progression or unacceptable toxicities were observed. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. For a statistical consideration of the heterogeneous population with advanced HCC, we conducted the subgroup analysis. Results: A total of 334 pts were enrolled (S-1 = 223, placebo = 111). Patient characteristics were well balanced; median age, 70.0 years; C-P A liver function, 81.0%; vascular invasion, 17.7%; and extrahepatic metastasis, 53.8%. The median OS was 337.5 days with S-1 and 340.0 days with the placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.67–1.09; P = 0.220). The median PFS were 80 and 42 days, respectively (HR, 0.60; 95% CI, 0.46–0.77; P < 0.001). ORRs were 5.4% and 0.9%, respectively (P = 0.068). In the subgroup analysis showed the efficacy of S-1 on OS was different depending on patient characteristics; C-P liver function, HR was 0.79 (C-P A) and 1.19 (C-P B); Tumor stage, HR was 2.08 (Stage III/IV) and 0.79 (Stage I/II). The main adverse events (AEs) with S-1 were anorexia, fatigue, elevated total bilirubin, and diarrhea. Most AEs were mild to moderate, and the study discontinuation rate due to AEs was 19.2% in S-1 pts. Conclusions: Although S-1 did not statistically extend OS compared to the placebo in pts with sorafenib-refractory advanced HCC, the subgroup analysis showed S-1 has potential to improve OS in the clinically-important heterogeneous population. The observed benefit in the outcomes of PFS and subgroup analysis warrant further investigation. Clinical trial information: JapicCTI-090920.

4019 Poster Discussion Session; Displayed in Poster Session (Board #128), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

The protective effect of hormonal intake on risk of hepatocellular carcinoma in the United States. First Author: Gehan Butrus, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In the United States, the incidence of hepatocellular carcinoma (HCC) has been tripled over the last two decades. Despite the overwhelming effect of several environmental risk factors of this cancer, the association between oral contraceptive (OC) and hormone replacement therapy with HCC has been poorly investigated. We aimed to investigate the association between OC and HCC in the largest study in USA showing protective effect of hormonal use on HCC.

Methods: We conducted a hospital-based case-control study where cases are pathological or radiological diagnosed patients with HCC. Controls are spouses of patients at MD Anderson who had cancers other than GI cancers. Between 2005 and 2014 total of 235 female cases and 257 female controls were enrolled. Cases and controls were interviewed for lifetime intake of OC, hormonal replacement, type of hormone, method of hormonal use, and duration of exposure. We performed multivariate logistic regression analyses by using all variables that were significant on the bivariate analyses to estimate odds ratio (OR) and 95% confidence interval (CI). The estimated ORs were adjusted for age, race, diabetes, hepatitis C virus, hepatitis B virus, cigarette smoking, alcohol drinking, and family history of cancer. Results: Ever use of OC was reported by 75.1% of the controls and 61.3% of cases (P = 0.007). The hazard ratio leading to 43% reduction in OR where the estimated OR (95% CI) was 0.57 (.35–.91). Ever intake of estrogen hormone during lifetime was recalled by 49.8% controls and 30.6% cases (P = 0.001) yielding 62% reduction in HCC risk, (95% CI) = .38 (.24–.59). Combined hormonal use from OC and estrogen hormonal replacement was reported by 89% of the controls and 75% of cases. The estimated OR (95% CI) was .47 (.27–.84), P = .01. A dose response relationship was observed with duration of exposure where the estimated OR (95% CI) were .53 (28-1), .37 (16-.83), and .35 (19–.64) for lifetime years of exposure of < 5, 5-10, and > 10 years respectively. Conclusions: This is the largest study in USA showing protective effect of hormonal use on HCC. Experimental investigations are necessary for thorough assessment of the relationship between hormonal exposure and risk of HCC in females.
Multi-institutional phase II study of high dose, hypofractionated proton beam therapy (HP-PBT) for unresectable primary liver cancers: Long term outcomes in patients (pts) with intrahepatic cholangiocarcinoma (ICC).

First Author: Theodore S. Hong, Massachusetts General Hospital, Boston, MA

Background: Modern radiotherapy (RT) techniques such as protons permit delivery of ablative doses of RT to the liver. Prior reports of PBT in hepatocellular carcinoma (HCC) demonstrate loco-regional control exceeding 85% but outcomes with high dose RT in pts with ICC remain lacking. We report on clinical outcomes of high dose, HP-PBT in pts with unresectable ICC.

Methods: Pts enrolled on an NCI sponsored, multi-institutional, phase II study (NCT00976899). Key eligibility were HCC or ICC, unresectable by multidisciplinary review and failing systemic therapy. Baseline characteristics included: 41 pts had ICC, 2 pts had mixed HCC/ICC, and 47 pts had HCC (reported separately). In this ICC specific-analysis (n = 41), median age was 67 (range 29-87), 16 (37%) were male. 36 (88%) had cirrhosis, 25 (58%) pts had prior systemic therapy. 29 (68%) pts had prior symptomatic IA, 2 (4.7%) pts had IA, 2 (4.7%) pts had 3 . Median tumor size was 6.0 cm (range 2.2-10.9). Median RT dose received was 58 GyE (range 15-167.5). 6 (14%) pts developed Gr 3 RT-related toxicity, including thrombocytopenia (2), hyperbilirubinemia (2), gastric ulcer (1), pain (1), elevated LFTs (1), and liver failure/ascites (1). With a median follow up of 13 months (range 5d-51 mo) among 22 pts still alive, the 2 year LC was 96%, mOS was 21 months (95% CI 13-29) and mPFS was 9 months (95% CI 6-24). When excluding Child’s B (n = 38), mOS was 23 months (95% CI 15-49) and mPFS was 10 months (95% CI 5-24); 2 yr OS rate was 48% and 2 yr PFS rate was 38%. High dose PBT for ICC resulted in high rates of LC and OS. This data forms the basis for the ongoing NRG GI-001 study, a randomized trial of gem/cis +/- hypofractionated RT. Support: NCI # P01CA2123 Clinical trial information: NCT00976899.

4022 Poster Discussion Session; Displayed in Poster Discussion Session (Board #131), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Prognostic value of plasma circulating tumor (ct) DNA KRAS mutations and serum CA19-9 in unresectable pancreatic cancer (PC) patients. First Author: Julia S. Johansen, Department of Oncology, Herlev Hospital, Herlev, Denmark

Background: Median overall survival (OS) time of patients with unresectable PC varies widely. Diagnostic tools are presently lacking to predict outcomes. The majority of pancreatic tumors have KRAS mutations. The study aim was to evaluate the utility of baseline and serial analyses of ctDNA KRAS mutation load, alone or in combination with serum CA 19-9, as an outcome prognostic biomarker in patients with unresectable PC undergoing palliative chemotherapy.

Methods: In the Danish BIOPAC prospective biomarker study, plasma was collected from 182 unresectable PC patients (85 females, 97 males, median age 68, range 45-89 years; locally advanced disease n = 48; metastatic n = 134) undergoing treatment with gemcitabine (n = 151) or FOLFIRINOX (n = 31). ctDNA KRAS G12/13 mutation levels in archival (≤ 6 years) plasma was assessed with enrichment PCR followed by next generation sequencing and standardized reporting of copies per 10⁷ genome equivalents (GE). Results: In a prospective preliminary review of study samples, we explored whether PDAC with KRAS mutation load, alone or in combination with serum CA 19-9, is a strong prognostic factor in patients with unresectable PC receiving palliative treatment with gemcitabine or FOLFIRINOX.

4023 Poster Discussion Session; Displayed in Poster Discussion Session (Board #132), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Allelic ratio of KRAS mutations in pancreatic ductal adenocarcinoma. First Author: Jochen K Lennerz, Massachusetts General Hospital, Boston, MA

Background: Traditional sequencing studies of KRAS in pancreatic ductal adenocarcinoma (PDAC) delineated a mutation frequency of ~75% and that KRAS mutant tumors are associated with shorter overall survival. Recently highly-sensitive next-generation sequencing technologies have delineated that the KRAS mutation frequency in PDAC is ~93% indicative of a large number of cases missed by traditional sequencing approaches. Here, we explored whether PDAC with KRAS mutations at low-allelic ratios carry prognostic differences. Methods: We employed the PDAC dataset (n = 142) from the International genome consortium (IGCG) initially reported by Biankin et al., 2012. We accounted for tumor purity by calculating the corrected allelic ratio ( = allelic ratio/cellularity). Overall survival differences using a corrected allelic ratio cutoff of 10% were calculated employing Kaplan-Meier, log-rank, and Cox proportional hazard regression analysis (HR). Results: Accounting for tumor purity, we identified 115 cases (80.9%) with allelic ratios of mutant KRAS ≥ 10% while the remainder (n = 27 cases, 19.1%) harbored either mutant alleles at low-allelic ratios (< 10%) or wild-type KRAS (n = 10). Allelic ratios span the full range from wild-type to > 100% mutant KRAS. The lower as well as the upper end of this spectrum suggest heterogeneity within the cancer cell population (clonality) or variations in DNA content (ploidy), respectively. The subset with low-allelic ratios (~ 10%) of mutant KRAS exhibited slightly inferior OS compared to PDAC cases when compared to those with high-allelic ratios (20.3 months; HR 1.68 CI 0.9-3.13). While this difference did not reach statistical significance (P = 0.10), several prior studies employing thresholds around 10% (cutoff determined by sensitivity of the sequencing technology) have shown that the presence of a KRAS mutation is a marker of poor prognosis. Conclusions: KRAS is not simply mutated or wild-type in PDAC – it has actually never been. While over 90% of PDAC carry mutated KRAS alleles, the impact on PDAC biology may vary with the tumor-specific allelic ratio and dosage of mutated KRAS. Therefore, we propose that the tumor-specific allelic ratio of somatically mutated genes should become part of a comprehensive molecular diagnostic report.
A phase II study of sequential capecitabine plus oxaliplatin (XELOX) followed by docetaxel plus capecitabine (TX) in patients with unresectable gastric adenocarcinoma: The TCOG T3211 trial. First Author: Sung-Hwan Chen, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Background: Fluorouracil and platinum can be considered a standard option for advanced gastric cancer (AGC). Docetaxel is also an effective agent with no cross-resistance with fluorouracil and platinum. Concomitant combination of docetaxel with fluorouracil and platinum had been explored, but demonstrated intolerable toxicities. A different way to include all active agents in first-line treatment of gastric adenocarcinoma may be to use them sequentially. We aimed to evaluate the activity and the safety profile of sequential chemotherapy with capectabine plus oxaliplatin followed by docetaxel plus capectabine in the first-line treatment of AGC. Methods: We conducted a phase II study of sequential chemotherapy in AGC. Treatment consisted of 6 cycles of capecitabine plus oxaliplatin (XELOX), Capecitabine 1000 mg/m^2 bid on day 1-10 and Oxaliplatin 85 mg/m^2 on day 1, Q2W followed by 4 cycles of docetaxel plus capectabine (TX, Docetaxel 30 mg/m^2 on D1 and D8, Capecitabine 825 mg/m^2 bid on day 1-14, Q3W). Primary end-point was the objective response rate. Results: Fifty-one patients were enrolled: median age 63 years; Male/Female: 37/14. Main grade 3-4 toxicities were ANC decreased (25.5%), diarrhea (11.8%), hand-foot syndrome (15.7%) and anemia (11.8%). The objective response rate was 56.5%. Median PFS and OS were 6.6 and 10.8 months, respectively. Five patients (9.8%) received surgery after chemotherapy and four were still on disease-free status. Conclusions: This sequential treatment demonstrated feasibility with a favorable safety profile and produced encouraging results in terms of activity and efficacy. Clinical trial information: NCT01558011.

Masitinib plus irinotecan for second line treatment of esophagogastric adenocarcinoma: An open label phase IIb/III trial. First Author: Aziz Zaanan, Department of Gastroenterology, HEGP, Paris, France

Background: Masitinib (MAS) is a selective c-KIT inhibitor that efficiently inhibits mast cell function. In vitro studies have shown that MAS could enhance efficacy of 5-fluorouracil (5-FU) and irinotecan (IRI) for treatment of gastric cancer cell lines. Methods: Patients (pts) with measurable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction were eligible to receive MAS (6 mg/kg/day) in combination with 5-FU (400 mg/m^2 bolus then 2400 mg/m^2, iv, q2w) or IRI (350 mg/m^3/3w), or FOLFIRI, after progression to platinum based first line chemotherapy. The phase I study evaluated safety with “Dose Limiting Toxicity” (DLT) defined as grade 3 for non-hematological adverse event (AE), or any grade 4 AE related to MAS. The phase II study evaluated efficacy. Results: Thirty-six pts from 6 centers in France were included. MAS + 5-FU arm was closed after 6 pts were included due to lack of efficacy on PFS (1.7 months). Reduction of dose (-25%) was performed for IRI and FOLFIRI regimens due to occurrence of DLT. In the MAS + IRI arm (n = 15), median OS and PFS was 13.4 and 3.9 months, respectively. Pts did not experience (PR) and stable disease (SD) were reported in 15/15 pts and 10/15 pts respectively, leading to a disease control rate (DCR) of 80%. In the MAS + FOLFIRI arm (n = 15), median OS and PFS was 10.9 and 2.4 months, respectively. SD was reported for 4 pts with 31% of DCR. No treatment related deaths occurred. In the MAS + IRI arm, 9/15 pts (60%) reported grade 3-4 AE (neutropenia 40%, anemia 8%, diarrhea 26%, nausea 22%, vomiting 13%, febrile neutropenia 7%, asthenia 13%, constipation 10%). In the MAS + FOLFIRI arm, 10/15 pts (67%) reported grade 3-4 AE (neutropenia, 47%; and 2/15 pts (13%) reported serious AE (1 pt with neutropenia). Conclusions: MAS + IRI seems to be active in advanced gastric cancer pts (c.f. median OS ~ 7.5 months; average from 7 studies: reporting second-line IRI*) with an acceptable safety profile. A confirmatory phase III trial evaluating MAS at 6 mg/kg/day in combination with IRI in second line has been initiated.
4028 Poster Session (Board #137), Mon, 8:00 AM-11:30 AM

Prognostic factor analysis of overall survival (OS) in gastric cancer from two phase III studies of second-line ramucirumab (RAM) (REGARD and RAINBOW) using pooled individual patient (pt) data. First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA

Background: From 2009-2012, 1020 pts were enrolled in two phase III, randomized, double-blind studies of RAM in metastatic gastroesophageal junction and gastric adenocarcinoma following progressive disease (PD) on first-line platinum- and fluoropyrimidine-containing therapy: REGARD (N = 355, RAM + best supportive care [BSC] vs placebo [PL] + BSC) and RAINBOW (N = 665, RAM + paclitaxel [PTX] vs PL + PTX). Methods: Individual pt data were pooled, and 41 key baseline covariates were examined (19 clinical characteristics; 22 lab parameters). Lab tests were parameterized in two ways based on local lab abnormality assessments (high/normal/low: high vs normal or low; low vs normal or high). To identify prognostic factors for OS, univariate Cox models were first used to select covariates with p < 0.05. For these covariates, a multivariate Cox model was used to make stepwise regression within with both entry and exit p = 0.01. All models were stratified by treatment and geographic region. Results: Of 1,020 pts, 953 (93%) were included in the stepwise COX regression, after excluding pts with missing covariate values. We identified 12 independent prognostic factors (5 clinical; 7 lab). Conclusions: We identified 12 independent prognostic factors for pts with second-line gastric cancer from the largest randomized, controlled, global trial dataset. A simple prognostic index using these factors to divide pts into risk groups will be constructed and presented. This information may help clinical decision-making, pt risk stratification, and planning future clinical studies. Clinical trial information: NCT00917384 and NCT007107663 and NCT00917384.

4029 Poster Session (Board #138), Mon, 8:00 AM-11:30 AM

Candidate biomarker analyses in gastric or gastro-esophageal junction carcinoma: REGARD trial of single-agent ramucirumab (RAM) vs. placebo (PL). First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA

Background: Vascular endothelial growth factor (VEGFs) are key regulators of tumor angiogenesis. RAM, a recombinant human IgG1 monoclonal antibody specific for VEGF receptor 2 (VEGFR2), inhibits VEGF-A, -C, and -D binding to VEGFR2 and ligands of the VEGF family in vitro and in vivo. In REGARD, we evaluated candidate tumor (HER2, VEGFR2) and serum (VEGFC-D, -E, and -F) biomarkers for correlation with overall survival (OS) and progression-free survival (PFS) in patients from the randomized phase III REGARD trial (NCT00917384) that demonstrated survival benefits for RAM vs. PL. Methods: Of 355 patients randomized to RAM or PL in REGARD, there was at least one evaluable biomarker result for 193 (54.4%). Serum samples using VEGF-A, VEGF-C, VEGF-D, VEGF-E, and VEGF-F immunoassays were available to explore survival benefit for RAM vs. PL. Analyses were blinded. Results: The table provides the results of the HER2 analyses in tumor tissue (N = 147) and VEGFR2 analyses in tumor blood vessels (N = 143). The small number of patients with serum samples limited interpretation of the role of VEGF2 pathway biomarkers is warranted in ongoing RAM trials. Clinical trial information: NCT00917384.

4030 Poster Session (Board #139), Mon, 8:00 AM-11:30 AM

Phase I study of GS-5745 alone and in combination with chemotherapy in patients with advanced solid tumors. First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Nashville, TN

Background: GS-5745 is a monoclonal antibody that inhibits matrix metalloproteinase 9 (MMP9), an extracellular enzyme involved in matrix remodeling, tumor growth, and metastasis. Inhibiting MMP9 is expected to block paracrine signaling and metastasis and to alter the immune environment within the tumor. Methods: The safety, pharmacokinetics (PK), and efficacy of GS-5745 alone and in combination with chemotherapy are being evaluated in a phase I dose escalation and expansion study in patients (pts) with advanced solid tumors. Dose escalation occurred at doses up to 1800 mg of GS-5745 IV every 2 weeks followed by a dose expansion at 800 mg IV every 2 weeks in pts with pancreatic adenocarcinoma combined with mFOLFOX6. All pts continued until disease progression or unacceptable toxicity. Results: As of January 13, 2015, 88 pts were treated. Treatment-emergent AEs (TEAEs) in > 30% of pts included nausea (38%), dyspnea (31%), and fatigue (31%). No DLTs were observed after monotherapy treatment. Non-linear PK, suggestive of target-mediated disposition, was observed with a mean half-life of ~8 days at doses of 600 and 1800 mg. When combined with chemotherapy, the most common TEAEs were diarrhea (59%), fatigue (47%), and nausea (38%). There were no observed responses in the monotherapy escalation phase. In the expansion phase, objective response rates in pts with measurable target lesions were 64% (7/11 esophageal) and 41% (7/17 pancreatic) based on investigator evaluation. Two complete responses in the esophageogastic cohort were noted based on central radiology review. Conclusions: Preliminary safety data demonstrate a manageable toxicity profile for GS-5745 alone and in combination with chemotherapy. The study has been expanded to enroll additional subjects with pancreatic and esophageogastic cancer to identify potential pharmacodynamic and predictive biomarkers of response.

4031 Poster Session (Board #140), Mon, 8:00 AM-11:30 AM

Adaptive immune resistance in gastro-esophageal cancer: Correlating tumoral/stromal PDL1 expression with CDB cell count. First Author: Ronan Joseph Kelly, The Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins, Baltimore, MD

Background: In adaptive resistance, tumors use PDL1 induction as a protective mechanism against an antitumor immune response implying underlying immuno-surveillance. By upregulating the expression of ligands for inhibitory receptors on tumor specific lymphocytes in the tumor microenvironment a growing malignancy can avoid immune elimination. Here we report the interaction between PDL1 expression and PDL1 in the tumoral and stromal microenvironment. Phase II and Phase III clinical trials investigating CTLA-4 inhibitors are currently ongoing in patients with advanced G/GEJ. Method: We identified 12 independent prognostic factors for pts with gastroesophageal cancer to identify potential pharmacodynamic and predictive biomarkers. First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA

4032 Poster Session (Board #137), Mon, 8:00 AM-11:30 AM

Candidate biomarker analyses in gastric or gastro-esophageal junction carcinoma: REGARD trial of single-agent ramucirumab (RAM) vs. placebo (PL). First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA

Background: Vascular endothelial growth factor (VEGFs) are key regulators of tumor angiogenesis. RAM, a recombinant human IgG1 monoclonal antibody specific for VEGF receptor 2 (VEGFR2), inhibits VEGF-A, -C, and -D binding to VEGFR2 and ligands of the VEGF family in vitro and in vivo. In REGARD, we evaluated candidate tumor (HER2, VEGFR2) and serum (VEGFC-D, -E, and -F) biomarkers for correlation with overall survival (OS) and progression-free survival (PFS) in patients from the randomized phase III REGARD trial (NCT00917384) that demonstrated survival benefits for RAM vs. PL. Methods: Of 355 patients randomized to RAM or PL in REGARD, there was at least one evaluable biomarker result for 193 (54.4%). Serum samples using VEGF-A, VEGF-C, VEGF-D, VEGF-E, and VEGF-F immunoassays were available to explore survival benefit for RAM vs. PL. Analyses were blinded. Results: The table provides the results of the HER2 analyses in tumor tissue (N = 147) and VEGFR2 analyses in tumor blood vessels (N = 143). The small number of patients with serum samples limited interpretation of the role of VEGF2 pathway biomarkers is warranted in ongoing RAM trials. Clinical trial information: NCT00917384.
Background: The safety and efficacy of laparoscopic D2 distal gastrectomy for the treatment of advanced gastric cancer (AGC) with curative intent is still controversial. Thus, the Chinese Laparoscopic Gastrintestinal Surgery Study (CLASS) group conducted a multicenter prospective randomized controlled trial, aiming to evaluate the surgical safety and long-term outcomes of laparoscopic D2 gastrectomy compared with conventional open surgery for AGC. (NCT01609309)

Methods: The patients with tumor located at distal stomach at clinical T2-4a, N0-3, M0 stage were eligible. Thus, our multicenter prospective study on long-term outcomes justifies continued exploration. Clinical trial information: NCT01609309.

Results: A total of 607 consecutive patients were recruited and randomly assigned into either LG group (n = 308) or OG group (n = 299) between September 2012 and January 2014. The LG group and OG group were similar in the compliance rates of D2 lymphadectomy (97.4% vs. 98.3%; P = 0.591). The rate of conversion to open surgery was 4.5%. There was no significant differences between the LG group and OG group in the incidence of intraoperative complication (5.8% vs. 4.3%; P = 0.402), morbidity (18.8% vs. 14.7%; P = 0.175), and mortality (0.6% vs. 0; P = 0.499). The patterns of severity grading were also comparable between the two groups. (P = 0.372).

Conclusions: Laparoscopic D2 distal gastrectomy for AGC could be safely performed by experienced surgeons. Thus, our multicenter prospective study on long-term outcomes justifies continued exploration. Clinical trial information: NCT01609309.

4034 Poster Session (Board #143), Mon, 8:00 AM-11:30 AM
MET as a prognostic biomarker of survival in a large cohort of patients with gastroesophageal cancer (GEC). First Author: Daniel Vigil Thomas Cal- enacci, University of Chicago, Chicago, IL

Background: Estimates of the frequency of genomic/protome alterations in MET in solid tumors vary widely, but a growing body of evidence suggests that MET amplification and/or Met expression are biomarkers for poor prognosis. We examined both MET gene copy number and Met protein expression as potential prognostic biomarkers for survival in a large set of GEC samples with full clinical annotations (staging, HER2 status, treatment, and overall survival). Methods: Formalin-fixed, paraffin-embedded (FFPE) GEC samples (N = 394) primarily from early-stage tumors were collected in the United States and Italy. Samples were analyzed by fluorescence in situ hybridization (FISH) for MET gene amplification (Dako MET IQFISH probe mix, research use only) and by immunohistochemistry (IHC) for Met protein expression (Dako Met IHC assay, research and investigational use only). All assays were performed according to the manufacturer's instructions. Samples with a MET/CEP 7 ratio ≥ 2.0 were considered amplified, whereas samples with ≥ 25% Met tumor membrane staining by IHC (≥ 1+ intensity) were considered Met positive. Spearman's rank correlation coefficient was used to assess correlations between parameters. Cox proportional hazards models and Kaplan-Meier estimates were applied to explore relationships between MET, overall survival, and other clinical characteristics. Results: MET gene copy number variation (≥ 5 copies) was observed in 18 of 344 samples (5.2%), and MET gene amplification (MET/CEP 7 ratio ≥ 2.0) was observed in 41 (12.0%) of 344 samples. Among the 344 samples, 37 (10.8%) were positive for Met protein expression. There was considerable overlap between MET amplification and Met expression; 12 of 15 MET-amplified samples (80.0%) were positive for Met expression. Survival analyses showed that both MET gene amplification and Met IHC positivity were prognostic of poor outcomes. Conclusions: MET amplification was observed in ~5% of this large set of GEC samples. Prevalence of MET amplification and Met expression were similar to those found in previously published studies. Our results indicate that MET gene amplification and Met protein expression are prognostic of poor outcomes in GEC.

4035 Poster Session (Board #144), Mon, 8:00 AM-11:30 AM
Randomized phase II study of recombinant human endothostatin combined with definitive chemoradiotherapy in locally advanced esophageal squamous cell carcinoma. First Author: Jiahua Lv, Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Chengdu, China

Background: Recombinant human endothostatin (endostar) has been documented to be an inhibitor of tumor angiogenesis. The short- and long-term effects of endostar on angiogenesis, progression-free survival (PFS) and objective response rate (ORR) were assessed before and after the treatment of endostar. The primary end point was overall survival (OS). The secondary end points were the effect of endostar on angiogenesis, progression-free survival (PFS) and object response rate (ORR). Results: Between Oct. 2012 and Sep. 2014, 63 patients were enrolled and divided into endostar group (n = 32) or the control group (n = 31). The endostar group resulted in a slight improvement in ORR (62.3% vs 55.1% in the control group), and a significant increase in the 1-year and 2-year overall survival rates (78.1% vs 67.7% and 56.2% vs 45.1%, respectively). The median PFS was extended to 16.5 months in the endostar group versus 9.3 months in the control group (P < 0.05). Endostar combined with CRT led to a marked decrease in tumor blood flow (BF) and blood volume (BV) with correction of MVD, compared to CRT alone (P < 0.05). There was no significant difference in toxicities in two arms. No new or unexpected endostar-related toxicities were observed. Conclusions: Recombinant human endothostatin combined with CRT can reduce tumor angiogenesis. The short- and long-term effects of endostar combined with CRT were an improvement over that of CRT alone in this study. Clinical trial information: ChiCTR-TRC-13003908.
Estrogen receptor beta (ERβ) gene polymorphisms as a predictor of overall survival in patients with gastric cancer (GC) from Japan and Los Angeles County (LAC). First Author: P. Paredes, Farber Cancer Institute, Boston, MA

Background: Use of menopausal hormones has correlated with a lower risk of colon cancer in women. Prostate cancer patients (pts) treated with estrogen have a reduced risk of developing GC as a secondary primary. Several ERβ gene (ESR2) polymorphisms have been associated with colorectal cancer survival (Cancer Res 2013;73:767). To better understand the role of ERβ in GC to QO outcome, we tested whether ESR2 polymorphisms will be associated with overall survival (OS) in GC pts from 2 different regions. Methods: We analyzed genomic DNA extracted from blood or tumor tissues of 169 pts from Japan (64% men, stage IB-IV of AJCC-6th, median age 67, median follow-up 3.6 years, median survival 5.7 years) and 214 pts from LAC (68% men, stage 0-IV of AJCC-6th, median age 62, median follow-up 8.2 years, median survival 2.6 years), using PCR-based direct sequencing. ESR2 polymorphisms, which were shown to be of biological significance (rs2978381, rs3020443 and rs1271572), were analyzed for association with OS in both cohorts. Multivariate Cox proportional hazard regression was conducted to test the association after adjustment for age, sex, primary tumor site, stage and other covariates. Results: ESR2 rs1271572 and rs3020443 had uni- and multivariate associations with OS in the Japanese but not LAC cohort. Any C allele of ESR2rs2978381 (T > C) was associated with longer OS than T/T genotype in the Japanese cohort (5-year survival 63 vs 41 %, p = 0.021) but shorter OS in the LAC cohort (5-year survival 30 % vs 51 %, p = 0.049) although these findings did not remain significant in multivariate analysis. In analysis restricted to distal GC, the ESR2rs1271572 (C > A) correlated with OS but the effect of A allele was in the opposite direction between the Japanese (n=121, adjusted HR 2.19, p = 0.019) and LAC cohort (n=116, unadjusted HR 0.62, p = 0.031). Conclusions: ESR2 polymorphisms have prognostic value in pts with GC. These data also suggest that ERβ pathway may play a key role in tumor progression of GC and its prognostic impact may differ depending on histopathologic, ethnic or epidemiologic differences. Further studies to evaluate the association among different races are warranted.

Prognostic impact of Forkhead box-F1 (FOXF1) polymorphisms on the clinical outcome in gastric cancer patients. First Author: Satoshi Matsui, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: A recent genome-wide association study reported associations between risk of Barrett’s esophagal and esophageal adenocarcinoma and seven single-nucleotide polymorphisms (SNPs) in region 16q24 on chromosome 16 near the Forkhead box-F1 (FOXF1) gene. The FOXF1 gene is known to regulate mesenchymal-epithelial interactions of the lung and gut morphogenesis and to regulate cancer-associated fibroblasts to stimulate cancer cell migration. We tested whether these SNPs are associated with clinical outcome of gastric cancer (GC) patients from Japan and Los Angeles County (LAC). Methods: We isolated genomic DNA from blood or tissue of GC patients from two independent cohorts. A total of 150 patients with advanced GC from Japan [107 male/43 female; median age 61 year-old; median follow-up time, 3.1 years; median overall survival (OS), 13.8 months; median progression-free survival (PFS), 6.6 months] who overexpress high levels of HER2, but those with low HER2 expression as chemotherapy will be effective not just in oesophago-gastric cancer (OGC) but also in patients with high HER2 (XEOX) in patients with oesophago-gastric cancer (OGC). Methods: Chemonaive patients with metastatic OGC were recruited into this rolling 6 dose escalating study to determine MTD, safety (NCI-CTC version 4.0) and pharmacokinetics of the combination. Patients received oxaliplatin (130 mg/m²/day(1) every 21 days (q21) and capcitabine (X) (1250mg/m²/d) q3, for a maximum of 8 cycles. AZD9391 dosing was planned at 3 cohorts (20mg bd, 40 mg bd, 60 mg bd continuously). With emerging toxicity at 20mg bd, AZD9391 was also investigated at 2 intermittent schedules (14d on and 7d off, 4d on and 3d off, from d1, q21). Results: 24 pts (median age 60 years) were enrolled in 4 cohorts and 4 DLTs within cycle 1 were observed: diarrhoea, vomiting and skin rash (Table 1). 58% (14/24) patients showed SAE grade ≥ 3 (mostly GI disorders and infections). 95% (18/19) patients had at least stabilisation of disease as best tumour response from cycle 3 (stable disease, 9 partial and 1 complete response). PK data, full demographic data including HER2 status and justification of RP2D dose will be presented. Conclusions: In this pt group the RP2D of AZD9391 in combination with XELOX is 20mg bd 4d on and 3d off q21. We are now recruiting pts with operable disease into the randomised phase of the study with XELOX versus XELOX and AZD9391. Translational studies are ongoing. Clinical trial information: 2011-003169-13.

No of Pts enrolled (evaluable for dose escalation) DLTs
20 mg continuous 6 (6) 2 GI2 diarrhea*
20 mg 14d on and 7d off q21 7 (6) 2 GI1 diarrhea*
20 mg 4d on and 3d off q21 7 (6) 2 GI1 diarrhea*
40 mg 4d on and 3d off q21 4 (4) 1 GI3 vomiting & 1 GI3 skin rash

*Dose of AZD9391 bd
50% toxicity
0.027
0.031
0.022
0.023

Conclusions:
1 G3 skin rash
1 G3 diarrhea*
1 G3 Diarrhea
1 G3 vomiting
0.030
0.019
0.022
0.028

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**Background:** Perioperative chemotherapy (pCT) significantly improved survival of patients (pts) with locally advanced esophagogastric adenocarcinoma (la EGC). However, ~60% of pts will later die from their disease. Thus, targeted drugs are worthwhile to be investigated further to improve survival (P).

**Methods:** To evaluate the role of the EGFR-antibody panitumumab with pCT, we performed an open randomized phase II study in 22 German centres. Untreated pts with la EGC (cT3-4 N0-3 M0) were eligible and treated with standard ECX therapy with (arm 1) or without (arm 2) panitumumab (9 mg/kg body weight iv, q 3 weeks). Three cycles were given prior to and after surgery, 163 from 171 pts (83 arm 1, 80 arm 2) were eligible from 11/2010 to 7/2013. Results: Compliance and dose intensity of pCT was equal in both arms, however 49% started and only 31% completed postop. CT in arm 1 versus 50% and 40% in arm 2, respectively. The cumulative capectabine dose was lower in arm 1 (58% vs. 70% of planned dose). No death was observed until 30 days after postop. CT. Local efficacy was slightly increased with panitumumab (75% vs. 68% without progression/death or with downstaging, p = 0.24). PFS (HR 1.21, 0.78-1.89) and OS (HR 1.30; 0.79-2.13) was not significantly lower in arm 1. Molecular analyses were possible in 76/163 (47%); c-MET overexpression was high (53%); however c-MET amplification (4%), EGFR-amplication or overexpression (7%), HER2-positivity (8%) or Ras-mutations (3%) were rarely observed. 117 plasma samples were analyzed for 25 EGFR signaling markers and ligands. At baseline, patients had slightly higher levels vs. healthy controls for BDNF, EGF, HGF, PDGF, PIGF, VEGF-A. Conclusion: Adding EGFR-antibody panitumumab to ECX did not improve the results in unselected locally advanced EGC pts. The rare pt numbers with possible predictive molecular alterations made it unlikely to define subgroups who may have benefited from the addition of panitumumab to perioperative CT.


**Results:**

**4040**

**Prognostic significance of tumor infiltrating immune cells and PD-L1 expression in gastric carcinoma in Chinese patients.**

First Author: Ruixuan Geng, Fudan University Shanghai Cancer Center, Shanghai, China

**Background:** Programmed death-1 receptor (PD-1) and its ligand (PD-L1) play an integral role in the immune response against cancer. This study in Chinese patients (pts) with gastric carcinoma (GC) investigated the prognostic significance of PD-L1 expression on tumor cells and its association with tumor-infiltrating lymphocytes (TILs). Methods: 398 archived, formalin-fixed, paraffin-embedded GC samples were collected Oct 2001-Feb 2010 from a single institution. TILs were evaluated using fluorescence in-situ hybridization (FISH), with a gene to control ratio >2.2 as defined as positive. Clinical characteristics, treatment factors, and survival were recorded. A cohort of pts diagnosed between 8/2002 and 10/2012 with metastatic non-MET-amplified EGCs was evaluated as a comparison group. Results: We identified 23 pts with MET-amplified EGCs, 15 of whom were identified between 2012-2014. Compared to 37 non-MET-amplified tumor, MET-amplified tumors were more typically poorly differentiated and located in the distal esophagus or gastrointestinal junction rather than distal stomach. Patterns of metastases did not differ between MET-amplified and non-MET-amplified pts. In the 17 pts for whom HER2 status was obtained, 4/17 EGCs showed co-amplification of MET and HER2. One EGC had concurrent MET and EGFR amplification. Additionally, 1/17 genotyped tumors harbored a MET-PI3KCA mutation. Conclusions: The data suggest that MET amplification is a biomarker for drug responses to single-agent MET inhibitors in esophagogastric cancer (J Clin Oncol 33, 2015, suppl 3; abstr 1). Clinical characteristics and outcomes were evaluated in patients (pts) with MET-amplified esophagogastric cancers (ECC) to facilitate identification of pts and establishment of treatment paradigms. Methods: Pts with metastatic MET-amplified ECC were identified between 2007 and 2014. MET amplification was determined in paraffin-embedded tissue using fluorescence in-situ hybridization (FISH), with a gene to control ratio of >2.2 as defined as positive. Clinical characteristics, treatment factors, and survival were recorded. A cohort of pts diagnosed between 8/2002 and 10/2012 with metastatic non-MET-amplified EGCs was evaluated as a comparison group. Results: We identified 23 pts with MET-amplified EGCs, 15 of whom were identified between 2012-2014. Compared to 37 non-MET-amplified tumors, MET-amplified tumors were more typically poorly differentiated and located in the distal esophagus or gastrointestinal junction rather than distal stomach. Patterns of metastases did not differ between MET-amplified and non-MET-amplified pts. In the 17 pts for whom HER2 status was obtained, 4/17 EGCs showed co-amplification of MET and HER2. One EGC had concurrent MET and EGFR amplification. Additionally, 1/17 genotyped tumors harbored a MET-PI3KCA mutation. Conclusion: This series represents the largest cohort of clinically annotated MET-amplified ECCs and highlights this subgroup as a distinct clinical entity characterized by rapid progression. Patients should be identified early and directed to appropriate MET-targeted clinical trials.

**Conclusions:**
A phase II single-arm pilot study of second-line icotinib treatment in advanced esophageal cancer with EGFR over-expression or amplification. First Author: Jing Han, National Cancer Center Hospital and Institute, Chinese Academy of Medical Sciences, Beijing, China

**Background:** Epidermal growth factor receptor (EGFR) has been reported to be overexpressed in esophageal cancer, suggesting EGFR-directed treatment is a potential option. Here we report the antitumor activities of icotinib, a selective EGFR tyrosine kinase inhibitor (TKI), as second-line treatment for advanced esophageal cancer with EGFR over-expression or amplification. **Methods:** In this phase II, single-arm study, elderly patients who were adults with advanced esophageal cancer confirmed by histology, who received at least first-line chemotherapy, with EGFR over-expression (immunohistochemistry (IHC), 3+ or amplification (positive fluorescence in situ hybridisation (FISH))). Participants were treated with oral icotinib (250 mg twice daily). The primary endpoint was objective response rate (ORR).

**Results:** Between December, 2013 and January, 2015, 38 patients were enrolled (37 with squamous cell carcinoma, 1 with adenocarcinoma) with a median age of 60, in which 36 were IHC 3+ (94.7%) and 2 were IHC 2+ with positive FISH. And as of the December 31, 2014 cutoff, 33 patients were evaluable for response. The ORR was 15.2% (9/53), consisting of 1 CR and 4 PRs, and the disease control rate was 54.5% (18/33). The median duration of treatment in 18 patients (CR + PR + SD) is 12.3 weeks with the longest being 28+ weeks. Twenty-three out of 33 patients (69.7%) experienced at least one adverse event (AE) with rash (42.4%), diarrhea (24.2%), pain (21.2%), fatigue (15.2%) and vomiting (12.1%) as the most common ones. Most AEs were mild and reversible and no grade 3 or 4 AEs were reported. **Conclusions:** Second-line icotinib treatment in advanced esophageal cancer with EGFR over-expression or amplification demonstrated favorable outcome along with a high safety profile. However, the role of EGFR over-expression or amplification as predictive biomarker still needs further exploration.

Clinical trial information: NCT01855854.

Poster Session (Board #153), Mon, 8:00 AM-11:30 AM

**Patterns of local-regional relapse after complete response by definitive chemoradiotherapy for stage II/III (non-T4) esophageal squamous cell carcinoma.** First Author: Kazuki Sudo, National Cancer Center Hospital, Tokyo, Japan

**Background:** Definitive chemoradiotherapy (dCRT) has been recognized as one of treatment options for esophageal squamous cell carcinoma (ESCC) patients who are not fit for surgery. Recent studies revealed that surveillance after dCRT was important in an adenocarcinoma dominant population. However, clinical utility of surveillance for ESCC is not clear. **Methods:** The subjects of this retrospective study were patients who underwent dCRT for stage II/III (excluding T4 disease) ESCC from 2000 to 2011 at National Cancer Center Hospital in Tokyo, Japan. We reviewed the patterns of relapse after clinical complete response (cCR). Each patient was generally surveyed with computed tomography (CT) and esophagogastroduodenoscopy (EGD) every 3-6 months. We also recorded new cancers (NC) diagnosed by EGD during surveillance after cCR. Local-regional relapse (LRR) without distant metastasis was classified into luminal-only relapse (LR) and other type of regional relapse (RR) with or without luminal relapse. Overall survival (OS) was estimated using the Kaplan-Meier method.

**Results:** Among 351 patients treated with dCRT, 233 (66%) achieved cCR. The median follow-up time was 64.0 months. A total of 94 (40% of 233) patients had relapse after cCR: 45 (19%) with distant metastasis and 49 (21%) with LRR including 33 with LR and 16 with RR. Of the remaining 139 patients without relapse, 20 (14%) had NC: 17 with new esophageal cancer, 2 with hypopharynx cancer and 1 with esophagogastric junction cancer. Of 49 LRR, 31 (63%) were diagnosed within 1 year of dCRT and 46 (94%) within 3 years. Fifty-three of 69 patients (77%) with LRR or NC underwent local treatment (surgery, endoscopic treatment or radiation). For these 53 patients with local treatment, the median OS from diagnosis of LRR or NC was 57.1 months (95% CI, 20.3-88.9). **Conclusions:** Our data suggest that 94% of LRR occurred within 3 years of dCRT. Of patients without relapse after cCR, 14% were diagnosed with NC by EGD. Outcome of local treatment for LRR or NC was excellent.

Poster Session (Board #154), Mon, 8:00 AM-11:30 AM

**Multicenter retrospective analysis for elderly patients with advanced gastric cancer (AGC) received first-line chemotherapy in clinical practice.** First Author: Kenji Kunieda, Department of GI Oncology, Shizuoka Cancer Center, Shizuoka, Japan

**Background:** Indication of elderly patients (pts) to intensive chemotherapy has not been established. We hypothesized that a survival benefit of doublet chemotherapy with fluoropyrimidine plus platinum, standard treatment might be attenuated in elderly AGC pts with decreased physiological function due to their low tolerability. **Methods:** We retrospectively investigated clinical outcomes of the elderly AGC pts, 70 years or older, who were treated with S-1 or S-1 +DDP (SP) as the first-line chemotherapy between 2009 and 2011 at 29 medical centers participating West Japan Oncology Group. Among these pts we selected the pts considered to be fit for SP, and the efficacy and toxicity of S-1 with SP therapy was compared, calculating the propensity scores for receiving each treatment and conducted survival analyses by inverse probability of treatment weighting.

**Results:** Among 464 pts enrolled this study, 446 pts were eligible for the criteria. Patient characteristics were: median age 75 years old (range 70-86); PS 0/1/2 38%/54%/8%; male/female 71%/29%; some co-morbidities (1+8%); CCR < 50 ml/min/1.73m2 = 50 ml/min/1.73m2; received S-1/SP 47%/53%. Between the S-1 and SP groups, there was a large imbalance in PS, better in the SP group (p < 0.001). Limited to the 170 pts with PS 0, 56 pts (33%) and 114 pts (67%) received S-1 and SP, respectively. Between the two groups in this subset of PS 0 showed no significant differences in gender and co-morbidity rate and CCR. The S-1 group showed better background such as age, (p < 0.001), CCR (p < 0.05). The median PFS in the S-1 and SP group, were 8.0 months and 7.9 months (HR = 0.999, 95% CI 0.698-1.429, p = 0.999), and median OS were 15.0 months and 17.2 months (HR = 1.116, 95% CI 0.760-1.640, p = 0.574). The results were consistent after background factors were statistically adjusted by propensity score. Hematologic toxicities (p < 0.001), G3/4 adverse event (p < 0.001) and hospitalization due to AE (p < 0.001) were more frequent in the SP group. **Conclusions:** It is suggested optimal treatment strategy for elderly AGC patients should be established separately from younger patients, we are now planning the clinical trial for elderly AGC patients.

Poster Session (Board #155), Mon, 8:00 AM-11:30 AM

**A phase I dose expansion trial of avelumab (MSB0010718C), an anti-PD-L1 antibody, in Japanese patients with advanced gastric cancer.** First Author: Yasuhide Yamada, National Cancer Center Hospital, Tokyo, Japan

**Background:** The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Here we present preliminary results from a phase Ib dose expansion study (NCT01943461) evaluating safety and clinical activity in a cohort of Japanese patients (pts) with advanced gastric cancer (GC). **Methods:** Pts with previously treated progressive GC, ECOG PS 0-1, received avelumab at 10 mg/kg, Q2W. Responses were assessed according to RECIST 1.1 and modified immune-related RECIST (irRECIST). Adverse events (AEs) were evaluated by CTCAE v4.0. Initial data from a prespecified analysis are reported here. A total of 20 pts in this expansion cohort were enrolled.

**Results:** As of Oct 8, 2014, 11 pts were treated with avelumab. Pts were followed-up for at least 3 weeks (wks) and the median treatment duration was 9.9 wks (range 4-12). Median age was 69 years (range 38-76) and all pts had an ECOG-PS of 0 or 1, with a median of 3 prior lines (range 1–4) of therapy. Drug-related treatment-emergent AEs (TEAEs; all grades) occurred in 10/11 pts (90.9%). The most frequently observed treatment-related TEAEs (> 1 case; all grade 1 or 2) were infusion-related reactions (IRRs) (3 pts, 27.3%), hyperthyroidism, and pruritus (2 pts each, 18.2%). There were no treatment discontinuations from AEs. One pt had grade 3 acute kidney injury was assessed as not drug-related. At data cutoff, 2 pts (18.2%) had come off study due to disease progression. Nine patients were still on treatment. To date, partial responses according to RECIST have been observed in 3 pts. **Conclusions:** Avelumab at 10 mg/kg Q2W can be safely administered in Japanese pts with heavily pretreated, metastatic GC. Additional studies to evaluate the efficacy of avelumab in Japanese pts with GC are planned and biomarkers from tumor tissue and blood samples including PD-L1 expression and soluble factors related to immune response will be evaluated. *Proposed INN. Clinical trial information: NCT01943461.
Evaluation of tumor MET protein expression, MET gene amplification, and HER2 expression in Chinese patients with advanced gastric or gastroesophageal junction (G/GEJ) cancer. First Author: Rui-hua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Gastric cancer is a disease with high unmet medical needs in China. MET and its ligand, hepatocyte growth factor, are potential targets in G/GEJ cancer. This study evaluated overall survival (OS) according to tumor MET expression, HER2 gene amplification, and the association between MET and HER2 status in Chinese patients with advanced G/GEJ cancer.

Methods: Baseline tumor biopsy samples (formalin-fixed, paraffin-embedded primary tumor and metastatic tissue) from patients with stage IV unresectable G/GEJ cancer, archived at Sun Yat-Sen University Cancer Center, were assessed for MET and HER2 protein levels and MET and HER2 gene amplification by IHC and FISH, respectively. MET-positive: membrane protein staining in ≥ 25% or ≥ 50% of tumor cells. HER2-positive: IHC 2+ and a confirmatory HER2 FISH-positive result (HER2: centromere 17 ratio ≥ 2.0, or IHC 3+ and MET-amplified). MET:centromere 7 ratio > 2.0. We evaluated associations between Kaplan-Meier OS and MET status (log-rank test), MET expression and HER2 gene amplification, and MET and HER2 status (Fisher exact test).

Results: Of 289 eligible patients, 271 had evaluable IHC samples, and MET-positive rates were 42.1% and 25.1% by 25% and 50% cutoffs, respectively. Median OS by different levels of MET-positive expression is shown in the Table. Of 183 patients with evaluable FISH samples, 8 (4.4%) were MET-amplified. In 171 patients with IHC and FISH data, MET-positive expression by 25% and 50% cutoffs was associated with MET amplification (P < 0.009, both cutoffs). In 145 patients with MET IHC, FISH, and HER2 data, the HER2-positive rate was 13.8%. Of patients who were MET-positive by 25% and 50% cutoffs, 8/48 (16.7%) and 4/29 (13.8%), respectively, were also HER2-positive. Additionally, 1/6 (16.7%) MET-amplified patients were HER2-negative.

Conclusions: MET-positive status was associated with shorter OS in this population of Chinese patients with advanced G/GEJ cancer. MET high expression or MET amplification was not associated with HER2 expression.

Quantitative measurement of HER2 levels by multiplexed mass spectrometry to predict survival in gastric cancer patients treated with trastuzumab. First Author: Chan-Young Ohc, Seoul National University Hospital, Seoul, South Korea

Background: Trastuzumab-based chemotherapy is standard treatment for HER2-positive advanced gastric cancer (AGC). Although increased HER2 gene amplification by fluorescent in situ hybridization (FISH) has been correlated with sensitivity to trastuzumab, the predictive value of HER2 protein expression levels for trastuzumab sensitivity has not been reported. In this study, we quantitated levels of HER2 using high mass spectrometry-based assay and identify a cutoff for HER2 protein levels that is predictive of enhanced response to trastuzumab.

Methods: A multiplexed, selected reaction monitoring (SRM) mass spectrometry assay was used to determine the absolute level of the HER2 protein in patient tumors. HER2 immunohistochemistry (IHC) status, HER2:CEP17 ratio, HER2/FISH ratio, and HER2 protein levels were compared in 249 AGC tumors, 95 of which were treated with trastuzumab. Overall survival (OS) in the trastuzumab cohort was correlated with HER2 protein levels and a predictive cutoff was determined by the lowest p value of log rank test. Results: While HER2 protein quantitation by mass spectrometry positively correlated with both FISH and IHC, a wide range of HER2 protein levels was observed in tumors classified as HER2-positive by conventional methods. Ninety five trastuzumab treated patients were stratified into two groups based on HER2 protein level: HER2 high expressers and HER2 moderate expressers. Patients classified as HER2 high expressers (n = 48), with HER2 levels above 2383 amol/ug, had twice the overall survival (OS) of patients (n = 47) classified as moderate expressers (OS: 35.0 vs. 17.5 months, HR 0.5, p = 0.007). Conclusions: We used a non-antibody based assay to quantify absolute levels of HER2 protein in samples from AGC patients. We found high variability in HER2 expression within a patient population that had been classified as 3+ by IHC. High levels of HER2 correlated with increased overall survival following trastuzumab. This study demonstrates the HER2 measurement by SRM could guide physicians in their patient’s selection for trastuzumab-based chemotherapy.

First-line capcitabine (X) monotherapy versus capcitabine plus oxaplatin (XELOX) in elderly patients with advanced gastric cancer (AGC): results from the first interim analysis. First Author: In Gyu Hwang, Division of Hematology/Oncology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea

Background: While doublet combination with fluoropyrimidines and platinum is currently considered standard first-line chemotherapy in AGC, there has been a price to pay in terms of toxicity. Since the main goal of AGC treatment remains palliation, this multi-center randomized phase III trial compared efficacy and safety of X monotherapy with those of XELOX combination in elderly patients with AGC. Methods: Patients with chemotherapy-naive, measurable AGC, aged 70 years or older were randomized 1:1 to receive X (capcitabine 1,000 mg/m2 bid po on D1-D14) or XELOX (capcitabine 1,000 mg/m2 po on D1; oxaplatin 110 mg/m2 on D1). Treatment was repeated every 21 days until disease progression, unacceptable toxicity, or withdrawal. Primary end point was overall survival (OS). The present report contains the results from the first interim analysis conducted at Dec 2014. Results: As of Oct 2014, 50 patients with a median age of 77 years (range, 70 to 84) were enrolled (X, n = 26; XELOX, n = 24). The two treatment arms were well balanced with respect to baseline characteristics. No treatment-related serious adverse events or unexpected toxicities were observed. The most frequently observed toxicities were nausea and hand-foot syndrome, with fatigue and peripheral neuropathy more common in XELOX than in X patients. Median PFS was significantly longer in XELOX arm than in X arm (7 v 3 months, respectively; HR 0.33, 95% CI 0.17-0.64). OS was also longer with XELOX (14 v 6 months; HR 0.60; 95% CI 0.29-1.23).

Conclusions: XELOX combination chemotherapy results in improved efficacy but does not increase toxicities compared with X monotherapy in elderly patients with AGC. Although HR for OS did not achieve predefined margin, an independent data monitoring committee recommended early stopping of the trial based on the evidence of superiority with XELOX. Clinical trial information: NCT01470742.
Comparison of open esophagectomy with minimally invasive esophagectomy: An observational nationwide study in Japan. First Author: HIROYA TAKEUCHI, Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: To date, there has been a very limited number of prospective multicenter trials to verify the benefits of minimally invasive esophagectomy (MIE) such as thoracoscopic esophagectomy for esophageal cancer. In this study, we focused on the comparison of MIE and open esophagectomy (OE) using a Japanese nationwide database.

Methods: Patient registration for the National Clinical Database (NCD) commenced in January 2011. It is a nationwide project that is linked to the surgical board certification system in Japan. Propensity score matching was performed to compare the MIE with the OE by use of the 2011-2012 NCD database.

Results: Esophagectomy for 9584 patients with thoracic esophageal cancer were categorized into MIE (n = 3589) with OE (n = 5995) in the NCI 2011-2012 database. Propensity score matching created a matched cohort of 3515 pairs of patients with MIE and with OE. The operative time was significantly longer in the MIE group than in the OE group (P < 0.001), whereas blood loss was markedly lesser in the MIE group than in the OE group (P < 0.001). There was no significant differences in overall morbidity between the MIE (42.0%) and OE groups (43.1%). In particular, the incidence of the patients who needed prolonged respiratory ventilation more than 48 hours after surgery was significantly less in the MIE group than the OE group (8.9% vs 10.9%, P = 0.006). Moreover, the incidence of superficial surgical site infection was significantly less in the MIE group compared with the OE group (6.7% vs 8.1%, P = 0.037). However, the operation rate within 30 days was significantly higher in the MIE group than in the OE group (7.0% vs 5.3%, P = 0.004). There were no significant differences in 30-day or operative mortality rates between the MIE and OE groups (0.9% vs 1.1%, P = 0.73). The 3-yr OS rates were 48% vs 38% (95% CI: 67%-94%). 17 of 36 pts are progression-free at 6 mos, with 3 pts still on study for < 6 mos. NGS of 15 tumors completed to date. 94% of tumors harbored at least one genomic alteration, TP53 mutations (73%); amplifications of KRAS (13%), EGFR (13%), CDK12 (7%), MET (7%) and FGFR2 (7%). Conclusions: Our results suggest that MIE is comparable with conventional OE in terms of short-term outcome after surgery and is regarded as a desirable surgical option for patients with esophageal cancer although MIE was associated with higher reoperation rates and there were no marked benefits in operative mortality.

Changing chemotherapy (C) with concurrent radiation (RT) followed by surgery after sub-optimal FDG-PET response to induction chemotherapy improves outcomes in locally advanced (LA) esophageal adenocarcinoma (EA). First Author: Anuja Kripiani, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pre-operative CRT is a standard-of-care for LA EA. We showed that PET scan after induction C prior to CRT and surgery predicts outcomes (Cancer 118:2820; 2012). PET responders (PET +) defined as > 35% decrease in mSUV of tumor) had superior pathologic complete response (pCR) rates and progression-free survival (PFS) vs non-responders (PET, < 35% decrease). Some Pts with progression (PD) on PET after induction C had long-term overall survival (OS) when changed to alternative C during RT. Methods: We retrospectively reviewed all Pts with LA EA who received induction C and chemRT prior to planned surgery. All Pts had PET scan before and after induction C. Results: 201 Pts were treated between 2002 to 2013, median age 62, 76% with uN+ disease. Induction C regimens included cisplatin/irinotecan (= bevacizumab on study) in 63% and carboplatin/paclitaxel in 29%. 113 Pts (56%) were PET + and 88 (44%) were PET -. All PET + received same C during RT. Of PET -, 49 (56%) continued with same C during RT (PET-no change) and 39 (44%) received different C with RT (PET-change). 49 Pts (24%) did not undergo surgery because of PD (16%), medical inoperability (6%), or refusal given clinical decision (4%). Of PET-, 49 (56%) were PET-. All PET - patients (50.44%) still alive, and a median disease-free survival (DFS) of 22.5 mos and a median OS of 27.1 mos were seen. Conclusions: We present outcomes and survivorship data following induction C and chemRT in patients with LA EA and PET + who received alternative C during CRT.

Phase II study of FOLFOX plus regorafenib (REGO) in patients with unresectable or metastatic esophageagastrectic (EG) cancer. First Author: Yumie Yanjigian, Memorial Sloan Kettering Cancer Center, New York, NY

Background: REGO is a VEGFR2, FGFR2 and PDGFR small-molecule inhibitor with survival benefit in metastatic colorectal cancer. We performed a phase II trial of first-line FOLFOX + REGO in metastatic EG cancer.

Methods: Patients (pts) with previously untreated metastatic EG adenocarcinoma with measurable or evaluable disease received mFOLFOX 6 (FOLFOX, 80 mg/m² q21d and oral REGO 150 mg daily on days 4 to 10 and 18 to 24 q28d). The primary objective was to improve historical 6-month progression-free survival (PFS) from 40% to 61% with REGO. With target accrual of 36 pts and 5% type I error rate, FOLFOX + REGO would be considered promising if ≥ 20 pts are progression-free at 6 months. Tumor biomarker analysis was performed on samples using an on-site next generation sequencing (NGS) assay. Secondary endpoints included safety, partial response (PR) rate, disease control rate (DCR, PR+ stable disease), exploratory biomarker analysis and overall survival.

Results: Between 8/2013 - 11/2014, 36 pts (10 esophageal/16 gastric/10 GEJ) were accrued to this single-center study. Median age 59 and KPS 80%. Common adverse events included: Gr 2/3 hypertension (52%), Gr 2 neuropathy (39%), Gr 3/4 neutropenia (36%), Gr 2 fatigue (28%), Gr 2/3 diabetes (17%), Gr 2 hand-foot syndrome (14%). 11 pts (31%) had one REGO dose reduction to 120mg; 5 pts (14%) were further reduced to REGO 80mg. In 27 pts with RECIST 1.1 measurable disease, the PR rate 56% (95% CI: 38%-73%). Overall DCR rate in pts with RECIST measurable and evaluable disease was 81% (95% CI: 67%-94%). 17 of 36 pts are progression-free at 6 mos, with 3 pts still on study for < 6 mos. NGS of 15 tumors completed to date. 94% of tumors harbored at least one genomic alteration, TP53 mutations (73%); amplifications of KRAS (13%), EGFR (13%), CDK12 (7%), MET (7%) and FGFR2 (7%). Conclusions: mFOLFOX in combination with one-week-on-one-week-off REGO dosing is well tolerated. NGS is ongoing on additional samples. Updated survival, response and correlative molecular analysis data will be presented. Clinical trial information: NCT01913639.
Comprehensive characterization of PDL-1 and CTLA-4 in gastric cancer. First Author: Hans Anton Schloesser, Department of General, Visceral and Cancer Surgery, University of Cologne, Cologne, Germany

Background: Recently remarkable efficacy of immune checkpoint inhibition has been reported for several kinds of solid cancers. This study is the first comprehensive analysis of cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 ligand 1 (PD-L1) in gastric cancer and the first study integrating oncogenic analyses. Methods: PD-L1 and CTLA-4 were stained on paraffin embedded tumor sections of 127 patients with gastric cancer by immunohistochemistry. Genetic driver mutations were identified by next-generation Sequencing and FISH analysis. Expression of PD-1, PD-L1 and CTLA-4 on lymphocytes in tumor sections, lymph nodes and peripheral blood were studied by 10-colour flow cytometry and 4-colour immune-fluorescence microscopy in an additional cohort. Results: PD-L1 and CTLA-4 were expressed on primary tumor cells by 44.9% (57/127) and 86.6% (110/127) of the analyzed gastric cancer samples, respectively. Correlation to clinical and pathological parameters revealed no correlation for PD-L1, whereas CTLA-4 negativity was correlated to higher grading and diffuse type according to Lauren. Positivity of PD-L1 or CTLA-4 on tumor cells was associated with inferior overall survival. Expression of PD-1 (52.2%), PD-L1 (42.2%) and CTLA-4 (1.6%) on tumor-infiltrating T cells was significantly elevated compared to peripheral blood lymphocytes. We could identify distinct genotypic profiles comparing the subgroups of checkpoint molecule expression. Conclusions: Our analysis revealed a great impact of PD-1/PD-L1 and CTLA-4 on the biology of gastric cancer. Hence corresponding checkpoint-inhibitors should be evaluated in this disease and approaches combining molecular targeted therapy and checkpoint inhibition could be of additional benefit. An extensive immune monitoring should be included in these studies.

The prognostic impact of extracapsular lymph node involvement after neoadjuvant therapy and esophagectomy. First Author: Sjoerd M Lagarde, Academic Medical Center, Amsterdam, Netherlands

Background: In patients with esophageal cancer, little attention has been paid to the biological significance of extracapsular lymph node involvement (LNI) in patients who underwent neoadjuvant treatment followed by esophagectomy. Therefore, the aim of the present study was to assess the incidence, extent of extracapsular LNI and prognostic significance in a consecutive multicenter series of patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant chemoradiotherapy (radiotherapy followed by surgery). Methods: From a prospectively collected database, a consecutive series of patients in two high volume centers in Europe was analyzed. All patients with potentially curable adenocarcinoma of the oesophagus or gastroesophageal junction were treated with neoadjuvant chemoradiotherapy or chemoradiation therapy followed by transthoracic esophagectomy and two-field lymphadenectomy. Results: Between January 2000 and September 2013 a consecutive series of 707 patients underwent an esophagectomy after neoadjuvant therapy. A mean number of 29 (5-77) nodes were resected and identified. 347 (49%) patients had no evidence of lymph node metastases (NO). There were 360 (51%) with positive nodes. Extracapsular LNI was identified in 197 (27%) patients. Five-year overall survival rates were 63% for NO patients, 45% for patients with intracapsular LNI and 14% for patients with extracapsular LNI (p < 0.001). On multivariate analyses ypT, ypN and the presence of extracapsular LNI were independent factors. Conclusions: The presence of extracapsular LNI after neoadjuvant chemo(radiation) therapy identifies a subgroup of patients with a significantly worse long-term survival. Extracapsular LNI reflects a particularly aggressive biologic behavior and has significant prognostic potential and should be considered for the future edition of the TNM staging system for esophageal cancer.

Comparison of HER2 gene amplification (AMP) in primary esophageal and gastroesophageal junction adenocarcinomas (EAC) and their metastatic regional lymph nodes (MLNs). First Author: Harry H. Yoon, Mayo Clinic, Rochester, MN

Background: The status of HER2 AMP in primary EACs compared to their MLNs is unknown. This is clinically important since selection of patients for HER2-targeted therapy is usually based on HER2 analysis in primary tumors. Here, we report the largest HER2 AMP evaluation of MLNs in EACs to date. Methods: Resected primary tumors and MLNs (209 patients) were tested for HER2 AMP (fluorescence in situ hybridization) and protein expression (immunohistochemistry; IHC); HER2/CEP17 ratio ≥ 2 in ≥ 5% tumor cells). HER2/CEP17 ratio ≥ 2 and protein expression ≥ 3+ (IHC) were considered HER2 positive (IHC). Results: Among the 25 EACs without AMP positivity in the primary tumor, the median was 2.5 months (95% CI, 1.9-3.4), and 2-month PFS was 25.6%. The median overall survival was 5.8 months (95% CI, 5.1-6.6). Grade 3 or 4 drug-related toxicities in 15% of patients included neutropenia (13.3%), anemia (13.3%), stomatitis (8.9%), and pneumonia (6.7%). Conclusions: Everolimus was safe, and it showed better activity in the current study which included biomarker-selected patients, compared with our previous study in biomarker-unselected population. Currently, further biomarker analysis is ongoing. Clinical trial information: NCT01482299.

Phase II study of everolimus as a salvage treatment after failure of fluoropyrimidine and platinum in patients with metastatic gastric cancer positive for pS6Ser240/4 expression. First Author: Hyun Young Park, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Everolimus is a macrolide derivative of rapamycin which inhibits mTOR. Our previous phase II study in 2nd line setting showed that everolimus had no significant activity with 1.7 months of median progression-free survival (PFS) in unselected population with gastric cancer (GC) and we speculated that pS6 could be a potential predictive biomarker of everolimus (Yoon et al, Br J Cancer. 2012;106:1039). In this study, we aimed to evaluate the efficacy and safety of everolimus in 2nd line GC patients selected by pS6 expression. Methods: The primary endpoint was 2-month PFS rate. Patients with metastatic or recurrent GC positive for pS6Ser240/4 were enrolled after failure of fluoropyrimidine and platinum. pS6Ser240/4 positivity was defined as immunostain of 10% or more cancer cells with moderate or strong intensity. Patients received everolimus 10 mg p.o. once daily until disease progression or unacceptable toxicity. Results: Between December 2011 and May 2013, a total of 45 patients were enrolled. Median age was 58 years (range 34-78). Thirty-nine (86.7%) patients had ECOG performance status 0-1, and 6 (13.3%) had 2. In addition to fluoropyrimidine and platinum, 14 (31.1%) and 5 (11.1%) patients received docetaxel and irinotecan, respectively. One (2.2%) patient achieved a partial response and 26 (57.8%) showed stable disease. With a median follow-up of 13.3 months (range, 9.9-31.1) in surviving patients, the median PFS was 2.6 months (95% CI, 1.9-3.2), and 4-month PFS was 25.6%. The median overall survival was 5.8 months (95% CI, 5.1-6.6). Grade 3 or 4 drug-related toxicities in > 5% of patients included neutropenia (13.3%), anemia (13.3%), stomatitis (8.9%), and pneumonia (6.7%). Conclusions: Everolimus was safe, and it showed better activity in this subgroup may identify new candidates for HER2-targeted therapy. Comparison of HER2 gene amplification (AMP) in primary esophageal and gastroesophageal junction adenocarcinomas (EAC) and their metastatic regional lymph nodes (MLNs). First Author: Sjoerd M Lagarde, Academic Medical Center, Amsterdam, Netherlands

The presence of extracapsular lymph node involvement (LNI) in patients who underwent neoadjuvant treatment followed by esophagectomy. First Author: Sjoerd M Lagarde, Academic Medical Center, Amsterdam, Netherlands

Background: In patients with esophageal cancer, little attention has been paid to the biological significance of extracapsular lymph node involvement (LNI) in patients who underwent neoadjuvant treatment followed by esophagectomy. Therefore, the aim of the present study was to assess the incidence, extent of extracapsular LNI and prognostic significance in a consecutive multicenter series of patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant chemoradiotherapy (radiotherapy followed by surgery). Methods: From a prospectively collected database, a consecutive series of patients in two high volume centers in Europe was analyzed. All patients with potentially curable adenocarcinoma of the oesophagus or gastroesophageal junction were treated with neoadjuvant chemoradiotherapy or chemoradiation therapy followed by transthoracic esophagectomy and two-field lymphadenectomy. Results: Between January 2000 and September 2013 a consecutive series of 707 patients underwent an esophagectomy after neoadjuvant therapy. A mean number of 29 (5-77) nodes were resected and identified. 347 (49%) patients had no evidence of lymph node metastases (NO). There were 360 (51%) with positive nodes. Extracapsular LNI was identified in 197 (27%) patients. Five-year overall survival rates were 63% for NO patients, 45% for patients with intracapsular LNI and 14% for patients with extracapsular LNI (p < 0.001). On multivariate analyses ypT, ypN and the presence of extracapsular LNI were independent factors. Conclusions: The presence of extracapsular LNI after neoadjuvant chemo(radiation) therapy identifies a subgroup of patients with a significantly worse long-term survival. Extracapsular LNI reflects a particularly aggressive biologic behavior and has significant prognostic potential and should be considered for the future edition of the TNM staging system for esophageal cancer.
Background: Gastric cancer is the 2nd most common cause of cancer deaths worldwide. Currently, endoscopy is the only reliable method for early diagnosis. However, the invasiveness and cost limit its usage as a screening test. MicroRNAs (miRNAs) have been shown to be important in the diagnosis. However, the invasiveness and cost limit its usage as a screening test. MicroRNAs (miRNAs) have been shown to be important in the diagnosis. However, the invasiveness and cost limit its usage as a screening test. MicroRNAs (miRNAs) have been shown to be important in the diagnosis. However, the invasiveness and cost limit its usage as a screening test.

Methods: We screened 600 miRNAs using our MiReX qPCR technology in the sera of 236 gastric cancer subjects and 236 matched high risk subjects, serving as the discovery set. 191 miRNAs were reliably detected in all the serum samples, out of which 75 informative ones were identified to be significantly (false discovered corrected P value below 0.001) altered between gastric cancer and high risk controls. Multivariate miRNA biomarker panels were then formulated by sequence forward floating search and support vector machine using all the quantitative data obtained for the expression of 191 miRNAs. Results: Multiple iterations of two-fold cross-validation were performed in silico where the panels with 8 or more miRNAs consistently achieved high accuracy (areas under the curve (AUC) > 0.87 in the receiver operating characteristic (ROC) curve). A 24-miRNA model was optimized based on the discovery set (AUC = 0.92 (95% Confidence Interval [CI]: 0.88-0.95)) and validated in two blinded studies with fixed algorithm and threshold definition; Korean case-control cohort (n = 129, 74 cancer cases) and Singaporean Chinese case-control cohort (n = 89, 20 cancer cases). The 24-miRNA panel showed 90% sensitivity and 81% specificity in the Korean cohort (AUC = 0.91 (95% CI: 0.86-0.96)) and had 90% sensitivity and 76% specificity in the Singaporean Chinese cohort [AUC = 0.89 (95% CI: 0.79-0.99)]. Importantly, the 24-miRNA panel was able to distinguish between gastric cancer and both Korean gastric cancer cases (n = 86, 95% CI: 0.88 (95% CI: 0.81-0.96)) and Singaporean Chinese [AUC = 0.91 (95% CI: 0.80-1.00)) cohorts. Conclusions: We have identified a serum miRNA panel which can confirm that gastric cancer including the early-stage cancers from controls. This may be able to serve as a non-invasive screening test for gastric cancer which warrants study in larger cohorts.

Results: A total of 49 pts. with a median age of 64 years were enrolled in 5 centers. 46 pts. completed stNACT, 1 patient had only 1 cycle and 2 pts. had 3 cycles. 47 patients underwent surgery. R0 resection rate was 91.5% (43/47). We saw no pathological complete response (pCR) and 19 partial responses (pPR 45%, 3/49 pts. developed progressive disease (6,1%). Grade 3-4 toxicities included neutropenia (42,9%), febrile neutropenia (8,2%) and diarrhea in 22%. 4,2% died after resection (4/98). Conclusions: stNACT with 4 cycles of FLOT is effective and tolerable in resectable GEC. R0-resection rate was very high. Clinical trial information: EudraCT-Nr. 2009-1260820 Neoflot.
The aim of this study was to determine whether inclusion of the postoperative pathological nodal status could improve the prognostic value of TRG. We analyzed 278 EC patients who had baseline EUS-FNA between 2010 and 2013. A subgroup of 85 patients with Squamous cell type I or II EC had FNAs of the paratracheal or subcarinal nodes (far away from the primary EC) were carefully reviewed. The accuracy of EUS, PET, EUS + PET, and FNA were compared using FNA as the gold standard. McNemar's test was used to determine whether EUS + PET or FNA performed differently in identifying positive nodes. Results: In the subgroup of 85 patients, FNA was positive for malignancy in 27 (32%) leading to modifications of the radiation field in upper thorax. Moreover, EUS, PET, and EUS + PET had an accuracy of 83.0% (EUS), 87.1% (PET), and 93.0% (EUS + PET), respectively. Comparing FNA to EUS + PET, FNA was positive whenever EUS or PET was positive. In 6 patients, PET-negative nodes were malignant by EUS-FNA (p = 0.03). Of 58 cases with negative initial FNA, only one was malignant, on follow-up, when surgically removed. Conclusions: Our data show that in distal ECs with suspicious paratracheal or subcarinal lymph node(s), EUS-FNA is a highly effective tool to help with appropriate treatment decisions. An extremely low false negative rate (1/58) suggests that EUS-FNA is highly complimentary to PET and can also identify malignant nodes that are not FDG-avid. From U. T. M. D. Anderson Cancer Center (UTMDACC), Houston, Texas, USA. (Supported in part by UTM-DACC, and CA 138671 and CA172741 from the NCI).

The prognostic value of a modified tumor regression grade after neoadjuvant chemoradiotherapy and resection of esophageal carcinoma. First Author: Maarten CJ Anderegg, Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: The tumor regression grade (TRG) is used to define the response to preoperative chemoradiotherapy for esophageal carcinoma. The aim of this study was to determine whether inclusion of the postoperative pathological nodal status could improve the prognostic value of TRG. Methods: All patients who underwent an esophagectomy after chemoradiotherapy between 2003 and 2013 were included in this retrospective study. Patients were classified according to a modified TRG consisting of the TRG by Mandard and this modified TRG Kaplan-Meier survival analyses were performed and compared. Results: 411 patients underwent neoadjuvant chemoradiotherapy followed by esophagectomy. After exclusion due to non-specific histology (n = 2), unknown TRG (n = 3), intraoperative detection of distant metastases (n = 3), salvage procedures (n = 17) and in-hospital mortality (n = 15) 371 patients were analysed (289 adenocarcinoma, 82 squamous cell carcinoma). A significantly improved median disease free survival was observed in patients with TRG 1 compared to patients with TRG > 1 (90.3 vs. 30.8 months, P = 0.004). After implementation of the modified TRG significant differences in median disease free survival were found between the four categories: TRG 1-N0 (n = 76) 90.3 months; TRG 1-N+ (n = 10) 20.8 months; TRG > 1-N0 (n = 146) 81.3 months; TRG > 1-N+ (n = 139) 18.1 months (P < 0.001).

Conclusions: The TRG, determined in the primary tumor, provides sufficient information about the prognosis after chemoradiotherapy followed by resection of esophageal cancer. It is advisable to use a modified classification in which the postoperative pathological nodal status is considered.
4068 Poster Session (Board #178), Mon, 8:00 AM-11:30 AM
Association of high tumor infiltrating cytotoxic T cells with absence of lymph node involvement in resected colorectal and gastric cancer: Implications for immunosurveillance. First Author: Tong Dai, Weill Cornell Medical College, New York, NY

Background: Adaptive immune response can play an important role in restricting tumor growth, and the presence of tumor infiltrating lymphocytes (TIL) is associated with lower cancer stage and improved survival. However, the characterization of TILs with gastrointestinal malignancies, and their clinical implication, remains poorly understood. Methods: To characterize TIL subpopulations in different gastrointestinal cancer types, we performed immunohistochemistry (IHC) staining of CD3, CD8, CD45RO, and CD4/FOXP3 markers for all T cells, cytotoxic, memory, and regulatory T cells, respectively. Tissue microarrays (TMA) from 122 colorectal, 37 gastric, and 59 esophageal cancer patients were included in the study, and IHC staining for each immune marker was scored as low (<5 cells/hpf), intermediate (5-50 cells/hpf), and high (>50 cells/hpf). Results: LN- colorectal and gastric cancer was associated with higher CD3+ and CD8+ cell infiltration, when compared with LN+ disease (Table 1). This was not observed in esophageal cancer. Increased memory T cell infiltration is also associated with LN- disease in gastric cancer. In addition, increased high- and regulatory T cells are associated with LN- disease in colorectal cancer.

Conclusions: Across a panel of gastrointestinal malignancies, we found that for both gastric and colorectal cancer, increased infiltration of cytotoxic T cells (CD3+/CD8+) was associated with LN- disease. These findings suggest high cytotoxic T cells may protect from LN metastasis in colorectal and gastric cancer. Regulatory FOXP3+ regulatory T cells may have similar function in colorectal cancer. Understanding the spatial distribution of proteins that regulate the immune response in the tumor microenvironment will have implications for subsequent immunomodulatory treatments.

4069 Poster Session (Board #179), Mon, 8:00 AM-11:30 AM
Phase Ib/II study of cancer stem cell (CSC) inhibitor BBIB068 combined with paclitaxel in advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma. First Author: Carlos Becerra, Texas Oncology-Baylor Sammons Cancer Center, Dallas, TX

Background: BBIB068, a first-in-class CSC inhibitor that works through inhibiting Stat3, has shown potent synergistic anti-tumor and anti-metastatic activity with paclitaxel in vivo. In a phase Ib dose escalation study in patients with advanced solid tumors, BBIB068 + weekly paclitaxel was well tolerated and a RP2D of BBIB068 500 mg BID was determined. Moreover, patients with advanced, pre-treated gastric and GEJ adenocarcinoma were enrolled in a phase Ib/II extension study to assess safety, tolerability, and preliminary anti-cancer activity in patients with advanced gastric/GEJ adenocarcinoma. Eligible patients received ≥ 1 line of prior treatment in the metastatic setting with a platinum/fluoropyrimidine/TS inhibitor. BBIB068 was administered orally at 480 mg or 500 mg twice daily with paclitaxel 80 mg/m² IV weekly 3 of every 4 weeks. A sample size of 40 set the bounds of the 90% CI at ±10% to 14%, assuming a DCR of 60% to 80%. Results: 46 patients (87% Caucasian, 7% Black, 6% Asian) were enrolled in US and Canada; 10 (22%) had 1 line of prior therapy, 16 (35%) had 2 prior lines, and 20 (43%) had 3 or more prior lines. Common adverse events (AE) were grade ≥ 1 diarrhea, abdominal cramps, nausea, and vomiting. Grade 3 AEs included vomiting (10%), diarrhea of days 5 or longer (7%), fatigue (7%), and abdominal cramps, nausea, dehydration (2%) each. In 20 patients who had not received a taxane in the metastatic setting, the per-protocol ORR was 31% (5/16) and DCR was 70% (12/16), median PFS was 23.4 weeks (95% CI: 10.8–53.7) with a 4-mth PFS of 56% (p = 0.02), and median OS was 13.3 months (95% CI: 4.0–57.6) with a 4-mth OS of 50% (p = 0.02). Conclusion: Signals of clinical benefit with respect to toxicity and efficacy were observed. A phase 3 study of BBIB068 in combination with weekly paclitaxel in patients with gastric/GEJ cancer who had failed first line therapy is underway. Clinical trial information: NCT01325441.

4071 Poster Session (Board #181), Mon, 8:00 AM-11:30 AM
Randomized phase II crossover trial exploring the clinical benefit from targeting EGFR or VEGF with combination chemotherapy in patients with non-resectable bile duct adenocarcinoma. First Author: Lars Henrik Jensen, Vejle Hospital and University of Southern Denmark, Vejle, Denmark

Background: Non-resectable biliary tract cancer (BTC) is chemosensitive but there are no clear signals of effect from inhibiting any specific molecular target. The most promising targets are EGFR and VEGF. This trial evaluated the effect of adding panitumumab or bevacizumab to chemotherapy in a crossover design. Methods: Eligible patients with biopsy proven non-resectable BTC (o你好 years). KRAS wild-type and performance status (PS) 0-2 were randomized 1:1. Patients in arm A received panitumumab 6 mg/kg + gemcitabine 1,000 mg/m² + oxaliplatin 60 mg/m² on day 1 and capecitabine 1,000 mg/m² b.i.d. on days 1-7 of a 2-week cycle. In arm B the chemotherapy was similar but added bevacizumab 10 mg/kg on day 1. At progression patients crossed over to bevacizumab in arm A or to panitumumab in arm B with the same chemotherapy backbone. The primary endpoint was the fraction of patients with PFS at six months (PFS6m). Secondary endpoints were PFS and overall response rate (ORR) both before/after crossover, overall survival (OS), toxicity, translational analysis and of second line treatment. Results: Three centres recruited 88 patients with a median age of 66 y (range 35-84). Selected base line characteristic were PS 0 (n = 23), 1 (n = 47), 2 (n = 18) and 73 metastatic/15 locally-advanced disease. Cases of grade ≥ 2 toxicity were equal with more skin toxicity in arm A and more hypertension and infection in arm B. PFS6m in arm A/panitumumab was 43% (95%CI 29-58) and in arm B/bevacizumab 55% (95%CI 40-70). ORR was 46% (95%CI 30-62) in arm A and 18% (95%CI 6-31) in arm B. Median PFS was 6.1 m (95%CI 5.8-8.1) vs 8.2 m (95%CI 5.3-10.6) and OS 9.5 m (95%CI 8.3-13.3) vs 12.3 m (95%CI 8.8-16.3) in arm A vs B. OS was 17.7, 9.5 and 5.6 m in P0, 1 and 2, respectively. As a phase II study, comparison between treatment arms were exploratory and revealed no differences in PFS6m (p = 0.39), median PFS (p = 0.13) or OS (p = 0.47), but ORR was superior in arm A (p = 0.01). Conclusion: Signals of clinical benefit with respect to PFS and OS were equal for targeting EGFR and VEGF, but ORR was higher with bevacizumab. This might be due to implications for potentially resectable disease in the neoadjuvant setting. Clinical trial information: NCT01206049.

4072 Poster Session (Board #182), Mon, 8:00 AM-11:30 AM
Pazopanib (P) and trametinib (T) in advanced cholangiocarcinoma (CC): A phase Ib study. First Author: Rachna T. Shroff, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CC is an aggressive disease with a dismal prognosis and no clear therapy in the refractory setting. Mek inhibition and anti-angiogenic therapies have shown modest activity in advanced CC, while dual inhibition of these pathways has not been evaluated. We investigated the safety of combining of P+T in a phase I trial (previously reported). 2 patients (pts) with CC were enrolled during dose escalation with 1 prolonged partial response (PR) and the other with stable disease (SD). Based on this possible signal, we evaluated the safety and efficacy of this combination in an expansion cohort of 25 advanced, pre-treated CC pts. Methods: P+T were administered daily for a 28-day cycle with radiographic imaging performed every two cycles. Patients were monitored for toxicity throughout the study. The primary endpoint was progression-free survival (PFS) with secondary endpoints including overall survival (OS), response rate (RR) and disease control rate (DCR, partial response + stable disease). Results: 25 patients were enrolled (median age = 62, 20 evaluable for response). The median follow-up was 8.9 months with pts having received a median number of 2 prior therapies (range 1-9). The most common grade ≥ 3 toxicities attributable to study drugs included: rash, thrombocytopenia, hypertension, fatigue (all n = 3), and elevated LFT’s (n = 2). ORR was 5% with a DCR of 75% (15/20 pts). Median PFS was 4.3 mths (95% CI: 3.5-7.6) with a 4-mth PFS of 56% (p < 0.002 compared with a previously reported null hypothesis rate of 25%). Median OS was 6.7 mths. Conclusion: P+T was well tolerated with evidence of activity in refractory CC. Further studies are needed to assess the benefit of combining anti-angiogenic therapy with Mek inhibition and to explore a potential molecular phenotype in which this combination may provide a clinically meaningful benefit. This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by GlaxoSmithKline. Clinical trial information: NCT01438554.
A phase II clinical trial on combined axitinib and transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC): Final results and evaluation of clinicopathological factors for survival.

Methods: This is a investigator-initiated, single-arm, phase II study. Patient eligibility criteria includes: diagnosis of inoperable HCC; Child’s A function; without portal vein thrombosis/distant metastases. Patients were stratified with a cut-off value of 2 cm with the minimal p-value to these cohort can be defined as T1. Multivariate analysis of prognostic factors 

Background: Axitinib is a potent and specific inhibitor of VEGFRs. Elevation of VEGF level in plasma and tumor is frequently observed after TACE treatment for HCC. We hypothesize that combining axitinib and TACE has synergistic inhibitory effect with the VEGF surge after TACE. TACE is conducted every 2 months (m). TACE is give if is viable HCC and pts are suitable for TACE. Axitinib is withheld 24 hours before and resumed 24 hours after TACE. CT Imaging is arranged every 8 weeks (mRECIST). The primary endpoint is 2-year survival rate. Secondary endpoints include determination of response, toxicity and clinical predictors of outcome. The sample size is 50. Results: From May 11 to Apr 14, 50 pts have been recruited. Data cut-off date was 31 Dec 14. The median follow-up is 21.6m. Median age: 61.8 years; median tumor diameter: 6.8cm. BCLC Stage B/C: 38/12. Median cycle of TACE given is 2. The median OS is 15.9m (95% CI 13.7-21.3m) with 2-year OS rate of 41.9%. The median time-to-progression is 10.4m. Amongst 45 evaluable pts, 30 (68.2%) have partial or complete response. Total 6 pts underwent surgical resection after downsizing of HCC with 5 of the specimens showing complete tumor necrosis. Common ≤ grade 3 toxicities include: ALT elevation (40%), AST elevation (24%) and liver function test (13%). The median dose density of axitinib is 90.6%. Development of hypertension (any grade) during the treatment course is associated with better OS (25.0 vs. 13.7m; p = 0.03).

Conclusions: The combination of axitinib and TACE is efficacious with high response rate. The regimen is well tolerated without significant safety concern. Selection criteria should be modified to operable state after downsizing. Further clinical development is indicated. (NCT01352728) Clinical trial information: NCT01352728.
REACH did not demonstrate a significant improvement in overall survival (OS) in the ITT population, but pts in the RAM group with an elevated baseline alpha-fetoprotein (AFP) (>400 nmol/L) showed an improvement in OS (HR 0.67, p < 0.05). Here we present PFS (pt-reported FACT Hepatobiliary Symptom Indexes [FHSI-B] and clinician-reported Eastern Cooperative Oncology Group [ECOG] performance status [PS]) from the RAM vs. PBO arm of the REACH study. Methods: Eligible pts had advanced HCC, Child-Pugh A, ECOG PS 0-1, and prior sorafenib. Pts were randomized 1:1 to receive RAM (8 mg/kg) or placebo (PBO) on day 1 of an every 2 week cycle. The FHSI-B was completed at baseline, cycles 4, 10, 16, and end of treatment. PS was assessed at baseline, each cycle, and end of treatment. Time to deterioration (TtD) in FHSI-B was defined as the time from the randomization date to the first date with a ≥3-point decrease (based on 32-point scale) from baseline. TtD in PS was defined as the time from the randomization date to the first date a change to PS ≥2 was observed. Kaplan-Meier method and Cox regression were used to assess TtD. Results: Compliance with FHSI-B was balanced between treatment arms. In the ITT population, TtD in FHSI-B and PS were similar between RAM and PBO. In the elevated AFP population, there was a strong trend toward a delay in the deterioration of symptoms in FHSI-B (p = 0.054) and PS (p = 0.057) for RAM treated pts compared to PBO. Conclusions: In the ITT population, symptom score and TtD were comparable between treatment arms; RAM did not result in the detriment in symptoms or pt functioning. Delay in symptom and PS deterioration coupled with survival benefit was observed in pts treated with RAM in the elevated AFP population. Clinical trial information: NCT01143457.

FHSI-B Compliance Baseline, %
RAM 96.5 94.7 99.2 94.7
PBO 97.3 94.7 99.2 94.7
FHSI-B Compliance End of Treatment, %
RAM 92.8 92.8 93.7 93.7
PBO 91.7 92.8 94.4 92.6
FHSI-B Score Change from Baseline, mean
PTD-HF101, mo
RAM -2.4 -2.86 -2.21 -3.73
PBO 96% (0.801-3.4) 0.69 (0.471-1.01)
TtD-HF11021, mo
0.78 0.054
FHSI-B Score Change from Baseline, mean
PTD-HF11021, mo
RAM 0.89 (0.651-2.2) 0.64 (0.411-2.0)
PBO 0.47 0.057

GlycoCirrhoTest may help to stratify cirrhotic patients according to the risk of HCC and optimize screening.

Glycated (G), capectabine (C) and bevacizumab (B) in patients with advanced biliary cancers (ABC): final results of a multicenter phase II study. First Author: Renuka V. Iyer, Roswell Park Cancer Institute, Buffalo, NY

Background: Role of antiangiogenic therapy is still undefined in ABC. We examined BV combined with G + C, a standard chemotherapy for ABC when the study began. Methods: Pts with ABC (inoperable stage III or IV), ECOG PS 0-1, normal organ and marrow function. Schema: BV 15 mg/kg q 21 days; C 650 mg/m2 bid x 14 days, both starting day 1; G 1000 mg/m2 days 1 and 8. Cycles repeated q 21 days. Primary objective was progression free survival (PFS), secondary objectives were overall survival (OS) quality, life of QOL using the FACT HEP tool and circulating tumor cell (CTC) number. Results: Fifty pts enrolled at 2 sites; 11(22%) fail bladder (GB), 29(58%) intrahepatic cholangiocarcinoma (iHC) and 10(20%) extrahepatic cholangiocarcinoma (eHC). Median age 63 (range 25-84 years), 52% male, inoperable 16% and metastatic 84%. Cycles: median 8 cycles/patient (range 1-33), median time on treatment was 5.8 months. Responses (RECIST): PR 12(24%), SD 24(48%), PD 6(12%) and 8(16%) 2 too early/6 clinical progression (nonscalable). Clinical benefit rate (PR + SD) = 72 %. Median PFS: 8.1 months (95% CI: 5.3, 9.9). Median OS: 11.3 months (95% CI: 8.1, 13.1). One year survival rate was 0.47 (95%CIS: 0.32-0.60). Grade 3/4 toxicities (>5%): hematologic 28(58%), GI 18 (36%), infections 14 (28%) and thromboembolic events 6 (12%). Treatment discontinuation for toxicity (10%), progression (64%), death (4%), or other reasons (22%). Median OS in 21 (46%) pts with detectable CTCs was 9.4 months compared to 13.7 months in the 25(54%) pts without detectable CTCs at baseline. Patients with QOL scores after one and two cycles of therapy that were above median score at baseline for the whole group had higher OS of 13 months compared to 11.3 months. Conclusions: PFS and OS in ABC with combination of G, C and BV is relatively comparable to that reported with gemcitabine and cisplatin with acceptable toxicity. Lack of detectable CTCs and higher than median QOL score after one/two cycles of therapy may serve as biomarkers to predict improved outcome. Acknowledgement: Study is supported by a grant from Genentech. Clinical trial information: NCT01007552.

Evaluation of the value of serum glycomics (GlycoCirrhoTest) for risk prediction of hepatocellular carcinoma in compensated cirrhosis. First Author: Xavier Verhelst, Department of Hepatology and Gastroenterology, Ghent University Hospital, Ghent, Belgium

Background: Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC) with a yearly incidence ranging from 1 to 8%. EASL and AASLD guidelines recommend systematic screening with liver ultrasound at 6 months interval in cirrhotic patients. A glycemic based test, called GlycoCirrhoTest, based on the respective abundance of bisecting GlcNAc residues and triantenarry glycans on serum proteins, has shown a 79% sensitivity and 86% specificity for the diagnosis of cirrhosis among patients with chronic liver diseases. The aim of the present study was to determine whether serum glycomics are predictive for the development of HCC in compensated cirrhosis. Methods: Blood samples of 132 cirrhotic (Child A or B) patients collected between 1995 and 2005 were analysed. Seventy percent suffered of Hepatitis C. In the remaining patients, the cause of cirrhosis was HBV infection, alcohol and autoimmune diseases. Cirrhosis was confirmed by liver biopsy. The patients were followed until the appearance of a HCC, death or liver transplantation. At the moment of serum sampling there was no evidence of HCC. GlycoCirrhoTest was performed using capillary electrophoresis as previously described by Callewaert et al. (Nature Medicine 2004). Results: After a median follow up of 4 years (IQR: 3.5–8.0), 35 (26.5%) of the patients developed a HCC. Mean follow up in the patients who did not develop HCC was 3.7 years (IQR: 2.5–9.9). There was a significant increase of the baseline GlycoCirrhoTest value in the patients who developed a HCC during follow up (p < 0.001) as compared to those who did not. ROC Curve analysis showed an AUC of 0.716 (95% CI: 0.611-0.820) for the prediction of HCC in the patients with a follow up of at least 1 year. An 0.1 increase in the value of GlycoCirrhoTest was associated with a 36% increased risk for developing HCC (OR 1.37, 95%CI: 1.098-1.475). Conclusions: This study suggests that an analysis of the serum protein glycome could generate a useful biomarker for the identification of cirrhotic patients at high risk for the development of HCC. GlycoCirrhoTest may help to stratify cirrhotic patients according to the risk of HCC and optimize screening.

A multicenter cohort study on transarterial chemoembolization with or without sorafenib for intermediate-stage hepatocellular carcinoma: Reconsidering combination-therapy trial design. First Author: Yan Zhao, Department of Liver Disease and Digestive Intervventional Radiology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi’an, China

Background: The proof of the superiority of combination therapy with sorafenib and transarterial chemoembolization (TACE) over TACE alone for hepatocellular carcinoma (HCC) in term of survival is lacking. We conducted a multicenter retrospective study to evaluate the efficacy of combination therapy over TACE alone, and to compare the overall survival (OS) between patients with ≥ grade 2 sorafenib-related dermatologic adverse events (AEs) in the combination therapy group and patients treated with TACE alone. Methods: From January 2009 to December 2012, 606 consecutive patients with intermediate stage HCC, Eastern Cooperative Oncology Group performance status 0-1, and Child-Pugh class A-B (<7) were included. Of them 202 received combination therapy and 404 received TACE alone therapy, respectively. Results: There was no significant difference between the two groups in median OS although a trend toward longer survival was observed (7.7 vs. 6.9 months, P=0.281). After propensity score matching the difference in OS was still not different (22.3 vs. 19.7 months, P=0.343). Of note, in the combination therapy group, 119 patients with ≥ grade 1 dermatologic AEs within the first two months of sorafenib initiation, which were defined as “high risk of death” and “hard stop” patients, had grade 2 or grade 3 dermatologic AEs which were defined as responders (HR = 1.85; 95%CI: 1.27-2.68; P=0.001). By using the second propensity score matching to balance the baseline differences between responders subgroup and TACE alone group, a significantly prolonged median OS was observed in the responders subgroup (27.9 vs. 18.3 months, P=0.046). Conclusions: Combination therapy, not in all, but in responders to sorafenib, results in longer overall survival than TACE alone. Sorafenib-related dermatologic AEs may be considered a possible clinical marker to stratify responders from all patients. Before the appearance of any assured biomarkers, the design of prospective comparative studies needs to focus on the responders to treatment who are evaluated by clinical markers.
A pilot study of tremelimumab—a monoclonal antibody against CTLA-4—in combination with either trans catheter arterial chemooembolization (TACE) or radiofrequency ablation (RFA) has been shown to induce a peripheral immune response which may enhance the effect of anti-CTLA4 treatment in patients with advanced HCC. **Methods:** Patients with HCC (Childs Pugh A/B7; Barcelona Clinic Liver Cancer Stage B/C; ECOG O/1; sorafenib refractory/intolerant (BCLC stage C only)) were enrolled in a pilot study of Tremelimumab at 2 dose levels (DL1 and DL2) until PD (mRECIST). Subtotal TACE or RFA was performed during study week 6 with DLT evaluation period encompassing first 8 weeks of study. Tumor biopsy at baseline and at time of R/F/TACE. Results: 20 pts were enrolled with N=18 evaluable for primary endpoint. Baseline characteristics: M:F 15:3; Median age = 54(range 42-76); Cirrhosis present in 13 pts; BCLC Stage B/C: 4/14; Hepatitis B/C/neg: 4/10/4. 8 pts received TACE, 10 underwent RFA during week 6 of tremelimumab therapy. No DLT encountered. Most common toxicity was pruritus. One patient developed pulmonitis and was taken off study but remains disease-free at 16months. Of N=10 pts evaluable for response outside of TACE/RFA-treated lesion 4 (40%) achieved confirmed partial responses. 5 of 7 pts with quantifiable HCV experienced a marked reduction in viral load. 6-week tumor biopsies showed immune cell infiltration on all evaluable patients. Median PFS for the study population (N=17) was 7.4months. **Conclusions:** Tremelimumab in combination with subtotal TACE or RFA in patients with advanced HCC is safe and feasible. Obtaining tumor biopsies at baseline and at the time of RFA/TACE is safe. Evidence of immune cell infiltration was seen on evaluable patients. Encouraging clinical activity has been seen with objective confirmed responses, TTP 7.4m and possibly surrogate reductions in HCV viral load. Clinical trial information: NCT01853618.

**Background:** Endoglin (CD105) is an endothelial cell membrane receptor highly expressed on proliferating tumor vasculature, including in HCC. CD105 is essential for angiogenesis and its expression is upregulated by hypoxia and VEGF inhibition. **Methods:** In a phase I study of TRC105 at 3, 6, 10, 15mg/kg q 2wks plus best supportive care (BSC) or placebo plus BSC. Tumor assessments were performed every 6 weeks by contrast-enhanced computed tomography plus best supportive care (BSC) or placebo plus BSC. Tumor assessments were performed every 6 weeks by contrast-enhanced computed tomography or magnetic resonance imaging. Assessment of response was done by central radiological review using mRECIST. Multivariate models using time-dependent covariate analysis defined variables with independent prognostic value (SFSS 18 and SAS 9.2). **Results:** 210/226 (93%) patients in the brivanib arm and 101/108 (94%) in the placebo arm, who had baseline and on-study scans available for central blinded review, were evaluable according to mRECIST. 26/210 patients on brivanib and 2/101 on placebo achieved partial response (p < 0.01). At the end of follow up, 284 patients had died, the median OS for the brivanib arm being 9.4 months (95% CI, 7.6 – 11.2) vs. 6.7 months (95% CI, 5.3 – 7.9) for placebo. **Conclusions:** ORR by mRECIST is an independent predictor of OS in HCC patients receiving a systemic multi kinase inhibitor, brivanib. mRECIST response is a marker of antitumor activity and warrants further evaluation in prospective clinical trials exploring novel agents in HCC patients. Clinical trial information: NCT09019901.

**Background:** Biliary tract cancer encompasses a group of genetically heterogeneous tumors. Panitumumab is a human EGFR inhibitor and has shown anti-tumor activity in RAS WT colorectal cancer. **Methods:** Pts with advanced KRAS wild type biliary tract or gallbladder adenocarcinoma were 2:1 randomized to receive Cis (25mg/m2) followed by Gem (1000mg/m2) on days 1 and 8 of a 21-day cycle, plus Panitumumab (6mg/kg) in arm A until disease progression. Primary endpoint was the progression-free survival rate at 6 months. For genetic profiling, massive parallel multigene sequencing was done by using a custom designed cholangiocarcinoma multigene panel on an IonTorrent Proton. Mutations (21 genes) as well as amplifications and deletions (13 genes) were identified by panel tailored bioinformatic algorithms. **Results:** 93 pts were enrolled (63 per arm A and 30 arm B). Pts characteristics (panitumumab vs. control): median age 61.5 vs. 58.5 years; 59% vs. 50% male; intrahepatic, extrahaepatic, gall bladder (%): 63, 16, 17 vs. 71, 11, 11; ECOG PS 0, 1, 2 (%): 64, 3, 2 vs. 45, 55; prior resection (%): 46 both arms. The most common grade 3-4 non-haematological adverse event (AE) was skin toxicity (39% vs 0%). Distribution of other grade 3-4 haematological and non-haematological AEs were not significantly different between both arms. 6-months PFS rate was not significantly different (55% vs 73%); mPFS was 6.7 vs. 8.2 mo, HR (95% CI, Gem/Cis ref.): 0.73 (0.43 – 1.24), p = 0.24; mDSS was 12.8 vs. 21.4 mo, HR (95% CI, Gem/Cis ref.): 0.74 (0.39 – 1.4), p = 0.35; response (in evaluable pts): panitumumab (28/63 [45%] vs. control 11/28 [39%]). The most frequent genetic variations were detectable in p33 (34%), IDH1/2 (19%) and SMAD4 (11%) (with up to 9 events per patient). The prognostic and predictive role of the variants is currently under investigation and will be presented. **Conclusions:** Panitumumab in combination with chemotherapy does not improve response rate, PFS and OS in patients with advanced biliary tract cancer. Further investigations of chemotherapy in combination with anti-EGFR antibodies are not warranted. Clinical trial information: NCT01320254.
Changes in VEGFA correlated with OS for pts on P but not C. These findings with increased and decreased risk of death, respectively, in C-treated pts. ABC. Increasing levels of CA19-9 and PDGFbb from BL were associated CK18 and tumor markers are associated with a poor outcome in pts with high expression of PD-L1 on cholangiocarcinoma cells represents a killing of tumor cells. This LN like structures need to be further characterized associated with significant better outcome reflecting the immune-mediated regression analyses.

Positive. The association between PDL1, CD45R0, OS and PFS was not feasible due to high expression of PD-L1 in HCC samples. The analysis was performed in a subset of patients treated based on biomarker-therapy associations is ongoing. In 1 patient an EGFR mutation (predictive of response to erlotinib in NSCLC) was identified, and the patient has begun treatment with erlotinib. Conclusions: The molecular profile in HCC suggests potential targeted therapies, such as tyrosine kinase inhibitors, anti-PD1 agents, or PI3 kinase pathway inhibitors. Immu-no-modulatory agents may be an option, particularly in metastatic HCC, based on levels of PD-1. Concurrent protein changes in CTNNB1-mutated tumors suggest potential benefit of combination therapies when targeting the WNT pathway. Review of responses to targeted therapies, such as being tried with erlotinib in the patient with EGFR mutation may provide additional insight into efficacious therapies.

% of samples with change, by IHC.

High expression levels Low expression levels
EGFR TOP01 PD-1 TOP2A SPARC cMET RRM1 TS PTEN MGMT
83 52 60 38 36 25 82 80 72 31

A phase II trial of bevacizumab and erlotinib as second line therapy for advanced hepatocellular carcinoma. First Author: Ahmed Omar Kaseb, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The objective of the study was to evaluate the efficacy and tolerability of bevacizumab (B) and erlotinib (E) combination as second line therapy for advanced hepatocellular carcinoma (HCC). Methods: Patients who had advanced HCC that was not amenable to surgical or regional therapies, had shown progression with sorafenib therapy: Childs-Pugh score A or B liver function; Eastern Cooperative Oncology Group performance status 0, 1, or 2 received bevacizumab 10 mg/kg every 14 days and erlotinib 150 mg orally daily, continuously, for 28-day cycles. The tumor response was evaluated every 2 cycles by using Response Evaluation Criteria in Solid Tumors Group criteria. The primary objective will be to assess progression-free survival (PFS) measured at 16 weeks following initiation of therapy. The secondary objective will be to assess time to progression (TTP) and overall survival (OS). Results: A total of 44 patients were included. PFS at 16 weeks was 43% (95% CI 28%-59%), the Median TTP was 3.9 months (95% CI 2.0-8.3) and median overall survival (OS) was 9.9 months (95% CI, 8.3-15.5). Grade 3-4 adverse events included fatigue (13.3%), acne (11.1%), diarrhea (8.8%), anemia (6.6%), upper gastrointestinal hemorrhage (6.6%). Conclusions: Bevacizumab and Erlotinib combination showed promising activity in this first US study in the second line setting. Validation studies are warranted. Clinical trial information: NCT03180959.
Prognostic score in high-grade gastrointestinal neuroendocrine tumours (pNETs). First Author: Angelia Lambar, Department of Medical Oncology, The Christie NHS Foundation Trust, Mancun. UK.

Background: Outcomes of patients with high-grade GI-NETs are poor; prognostic markers for risk-stratification are needed. Methods: Consecutive patients, diagnosed with high-grade GI-NETs between 1997-2014, were included. Prognostic factors were identified by the Log-rank test, Cox regression and logistic regression and ROC curve comparisons performed for prediction accuracy. Internal validation of the score by Bootstrap- corrected Harrell Concordance Index (C-index) and Resampling Model Calibration were performed. Results: One-hundred and nine patients were eligible for analysis. Median follow-up time was 9.7 months (1.3-102.9). Median age: 67.7 years (16.3-84.1); 62% male, 84% metastatic; 19% unforeg, 5% midgut, 19% pancreas, 28% hindgut and 29% unknown primary. Median ki67: 70% (20-120); EGCG OS: 0.26%; 1%: 70% received chemotherapy. Baseline median alkaline phosphatase (ALK) and LDH were 109 IU/l (45-2035) and 70 IU/l (258-11069), respectively. The maximum model included stage, PS, LDH, Na, ALK, ki67, number of metastatic sites, presence of liver and presence of lung metastases. The score, selected by the lowest Akaike Index Criterion, included liver metastases, PS, ki67, LDH and ALK with 0-6 points assigned to each, resulting in 4 risk groups (A-D) with predicted risk of death, detailed in Table. There was no difference in the survival prediction accuracy between the maximum model and the score. On multivariable analysis, the score was prognostic for overall survival (HR 1.95, 95%CI 1.55-2.47; p=0.001) and had good discrimination (C-index, 0.76) and calibration (mean error, 0.021; percentile 90, 0.037). Conclusions: This simple score identified high-grade GI-NET patients with meaningful differences in survival and may inform clinical decision-making and trial design.

4091 Poster Session (Board #201), Mon, 8:00 AM-11:30 AM

Everolimus in patients with advanced, progressive pancreatic neuroendocrine tumors: Overall survival results from the phase III RADIANT-3 study after adjusting for crossover bias. First Author: Marianne E. Pavel, Charité Berlin Campus Virchow-Klinikum, Berlin, Germany.

Background: In the RADIANT-3 study, everolimus (EVE) improved progression-free survival (PFS) by 6.4 mo versus placebo (PBO; HR, 0.35; 95% CI, 0.27-0.45; P < 0.001) in patients (pts) with advanced, progressive pancreatic neuroendocrine tumors (pNET). Here we present final overall survival (OS) results of the RADIANT-3 study with updated safety and also report OS adjusted for confounding due to crossover. Methods: A total of 410 pts with advanced, progressive, low-/intermediate-grade pNET were randomized to EVE 10 mg/d (n = 207) or PBO (n = 203), both with best supportive care. Upon disease progression in double-blind phase, crossover from PBO to open-label EVE was allowed at investigator's discretion. At the end of core phase, ongoing pts from both arms were unblinded and switched to open-label EVE. OS was analyzed by one-sided stratified log-rank test. Rank-preserving structural failure time (RPSFT) analysis was performed to estimate treatment effect corrected for crossover bias. Results: A total of 225 pts received open-label EVE; including 85% (172 of the 203) pts randomized to PBO arm. Median OS (95% CI) was 44.0 mo for those randomized to EVE versus 14.7 mo for those randomized to PBO (HR, 0.94; 95% CI, 0.73-1.20; P = 0.3). Dose limiting toxicities (DLT) were defined as the occurrence of any treatment-related grade 4 hematologic or grade 3 non-hematologic toxicity for EVE or any grade 3-4 non-hematologic toxicity for PBO. In the first cycle, most frequently reported drug-related adverse events included stomatitis (45%), rash (37%), and diarrhea (26%) in open-label EVE arm. Conclusions: The randomized, placebo-controlled, phase III RADIANT-3 study reports unprecedented median OS of 44 mo with EVE in advanced, progressive pNET. Although statistically not significant, a survival benefit of 6.3 mo with EVE was observed, consistent with previous studies. A stronger OS advantage with EVE after a correction for crossover effect confirms that crossover of majority of PBO pts (85%) likely confounded the survival results. The safety profile of EVE remained consistent with earlier experience. Clinical trial information: NCT00510068.

4090 Poster Session (Board #200), Mon, 8:00 AM-11:30 AM

Association of progression-free survival with overall survival (OS) in patients (pts) with neuroendocrine tumor (NET) treated with somatostatin analogs. First Author: Monica Ter-Minassian, Dana-Farber Cancer Institute, Boston, MA.

Background: Progression-free survival (PFS) is commonly used as a primary endpoint in NET clinical trials. Whether PFS is associated with OS is uncertain. We assessed the association between PFS and OS in a large observational cohort of pts with NETs treated with somatostatin analogs (SSA). Methods: We enrolled 1330 pts to a prospective observational study, beginning in 2003. Of these pts, we identified 440 with metastatic NETs who had received single-agent SSA and were evaluated for tumor progression, based on medical record review. We performed a landmark analysis to assess OS in pts with progression (PD) or without PD at 6 month intervals, from 6 to 24 months after treatment initiation. Adjusted hazard ratios were assessed with Cox proportional hazards models. Kaplan-Meier estimates were used to calculate median OS for pts with PD vs. those without PD at each landmark time. PFS was defined as time of treatment initiation to time of first progression or death. OS was defined as time of treatment initiation plus the landmark time to time of death. Results: Of the 440 pts, 224 had small bowel NETs; 93 had pancreatic NETs and 123 other NETs. 311 pts progressed and 215 died. Median follow-up was 7.6 yrs, PFS was associated with OS at the 6, 12, 18, and 24 month landmarks; those who progressed by each landmark time had shorter median OS times than those who did not progress (see table). A trend suggesting association of PFS with OS was seen across tumor subgroups. Conclusions: In this observational cohort of pts with metastatic NETs treated with SSA, PFS was associated with OS. Our findings support the use of PFS as an endpoint in NET clinical trials.

PFS and OS in NET patients treated with SSA (N = 440).

<table>
<thead>
<tr>
<th>Landmark time</th>
<th>No PD</th>
<th>PD</th>
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<tr>
<td>(N (Median OS))</td>
<td>(N (Median OS))</td>
<td>Adjusted HR* (95%CI)</td>
</tr>
<tr>
<td>6 mo</td>
<td>327</td>
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<td>12 mo</td>
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<tr>
<td>24 mo</td>
<td>147</td>
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*Adjusted for age, gender, tumor grade, tumor origin, and post-progression treatment.
**4093** Poster Session (Board #204), Mon, 8:00 AM-11:30 AM

Novel score to predict outcome in resected pancreatic neuroendocrine tumors (pNET). First Author: Antonio Viudez, Department of Medical Oncology, Complejo Hospitalario de Navarra-Fundacion Navarrabiomed, Pamplona, Spain

**Background:** MGMT expression can predict response to temozolomide-based treatment. In pNET PHLD-3a silencing is a common event while the expression of NDRG-1 and its functional role is unknown. We conducted a retrospective review of immunohistochemistry (IHC) expression of MGMT, NDRG-1 and PHLD-3a in pNET and investigated their potential as prognostic biomarkers. Methods: IHC staining for MGMT and PHLD-3a was scored as 0, 1-5%, 6-50% and ≥ 51%. For NDRG-1, we used a cytoplasmic score from 0 to 3 based on staining intensity. Based on the long-rank test result between 2 clusters for each IHC staining, we designed an IHC score (IHC-S, score from 0 to 3). Finally a Global Score (GS) was designed with those variables that showed most significant differences in the univariate analysis (IHC-S and margin). Results: 92 samples from patients (pts) with resected pNET and follow-up > 24 moths were analyzed. Median follow-up was 55.5 months (mo). Pts had a median age of 56.5 y (16-88) and RO resection occurred in 84.8%. Median DFS was 7 mo while median DS has not been reached yet. Significant statistical differences were observed in DFS based on surgical margin status (RO: 118 mo vs R1: 34 mo; p = .005), ypNO vs ypN1 (p = .004) and ki67 < 2% ( < 2% vs ≥ 2-20% p = .015). DFS was significantly poorer in pts without any expression of MGMT (p = .045), in pts with low-expression of NDRG-1 (or 1, p = .03), and in pts with high-expression of PHLD-3a (≥ 51%, p = .01). Significant differences were observed between pts with IHC-S = 0 vs IHC-S = 1 (p = .009), IHC-S = 2 (p = .012) or IHC-S = 3 (p = .0001). Pts with IHC-S = 0 never recurred while up to 70% of pts with IHC-S = 3 progressed during follow up. Using the Cox proportional hazards regression, GS was found as independent prognostic factor for DFS (HR: 5.043; 95%CI: 1.278-19.901). Conclusions: Our results suggest the potential use of MGMT, NDRG-1 and PHLD-3a IHC expression as predictor of outcome in pNET. Our Global Score may be able to discriminate between pts that will be cured after surgery from those with high risk of relapse.

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**4094** Poster Session (Board #205), Mon, 8:00 AM-11:30 AM

Study of the therapeutic management of gastric carcinoid tumors from data of the French national cohort of neuroendocrine tumors: CAGRS study. First Author: Sylvain Manfredi, CHU Pontchaillau, Rennes, France

**Background:** 4 types of gastric NETs are described: type 1 developed on atrophic gastritis (70-80% of cases), type 2 (5-6% of cases) as part of MEN 1, sporadic type 3 (14-25% of cases), and type 4 corresponding to poorly differentiated NETs (6-8%) (1). The natural history of types 1 and 2 is usually benign, while type 3 and 4 are more aggressive. Treatments of these four types are different and based on European guidelines (2). Those recommendations are based on data of small series. Methods: The objective of this study was to study of the treatment and monitoring of gastric NETs registered prospectively in a national cohort. Secondary objectives: epidemiology, overall survival. The National Register of GTE records all TNE via e-crf. Results: At the end-point of the study 197 gastric NETs were recorded (2.5% of all the NETs registered, 11th frequency tumor). A study of each case, on site, was conducted. 181 (91.9%) complete records were analyzed. The characteristics of these tumors are presented in the table below. Gastrin was measured in 31% of patients and chromoggin A in 36.9%. A somatostatin analogue was administered to 16 patients (8.8%).

**Conclusions:** This cohort represents the largest cohort known to date. It provides us important data on epidemiology of these tumors and their management. There are very likely over-reporting of type 3 and 4 in this register.

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**4095** Poster Session (Board #206), Mon, 8:00 AM-11:30 AM

Characteristics, prognosis and treatments of 294 patients with poorly differentiated neuroendocrine carcinoma: The FFCD-GTE national cohort. First Author: Thomas Walter, Hopital Edouard Herriot, St Didier Au Mont D’or, France

**Background:** Data on poorly differentiated neuroendocrine carcinoma (NEC) are limited or retrospective. We designed a French cohort to describe characteristics, prognosis and treatments of NEC. Methods: All patients with a diagnosis of NEC (WHO 2010) performed between 01/2010 and 31/12/2013 could be included in this national prospective cohort. Patients with small-cell NEC from lung, mixed tumors, and well-differentiated neuroendocrine tumors (NET) were not included. Results: 294 patients from 49 centers were included: median age was 66 (range: 23-92) years, 6 (2%) were female, 64% (187) had metastases at diagnosis, 22% (67) had local tumor recurrences, and 88% (261) had distant metastases. 70% (206) patients were graded as R1 resections (R0: 118 m vs R1: 34 m; p < .0001). Age at diagnosis 53.3 ± 17.8. GEP-NEC had similar characteristics and survival than other NEC. Metastatic disease (75%). At that time, 85 (29%) pathological specimens have follow-up on study (20/22). 15 out of 22 pts have follow-up on study > 12 months. The Kaplan-Meier 12 month PFS was 54% (95% CI: 34-85%). Median PFS is 13.6 months (95% CI 10.6-NA). Therapy was well tolerated with no grade 3-4 AE’s except 36% grade 3 hypertension. Conclusions: This cohort represents the largest cohort known to date. It provides us important data on epidemiology of these tumors and their management. There are very likely over-reporting of type 3 and 4 in this register.

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**4096** Poster Session (Board #207), Mon, 8:00 AM-11:30 AM

Multicenter prospective phase II trial of bevacizumab (bev) for progressive pancreatic neuroendocrine tumor (PNET). First Author: Timothy J. Hobday, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN

**Background:** Single agent trials of mTOR inhibitors and VEGF receptor TKIs in PNET yield response rates < 10%. We previously demonstrated a 39% PR rate in PNET with the combination of temsirolimus and bev in patients with progressive PNET. There are no data regarding the efficacy of single agent bev in PNET. Methods: We conducted a multicenter phase II trial of bev at a dose of 10 mg/kg IV q 2 weeks in patients (pts) with well or moderately well-differentiated NET, and different organ functions and ECOG PS of 0-1. Important eligibility criteria included requirement for progression of disease by RECIST within 7 months of study entry. No prior anti-VEGF pathway inhibitor therapy was allowed. Ongoing octreotide was allowed at stable dose if required for symptom control. Primary endpoint was response with null hypothesis of 10% and promising rate was defined as 30%. Planned enrollment was 21 pts. Results: 22 pts enrolled from 10/2012 through 6/2014 were eligible for the primary endpoint of response assessment. 9 patients remain on therapy. Conformed PR rate is 9% (2/22). 6 month progression free survival (PFS) was 95% (20/22). 15 out of 22 pts have follow-up on study > 12 months. The Kaplan-Meier 12 month PFS was 54% (95% CI: 34-85%). Median PFS is 13.6 months (95% CI 10.6-NA). Therapy was well tolerated with no grade 3-4 AE’s except 36% grade 3 hypertension. Conclusions: Bev therapy for PNET is associated with a 9% PR rate in PNET with the combination of temsirolimus and bev in patients with progressive PNET. There are no data regarding the efficacy of single agent bev in PNET. Mammography was not performed. Ongoing octreotide was allowed at stable dose if required for symptom control. Primary endpoint was response with null hypothesis of 10% and promising rate was defined as 30%. Planned enrollment was 21 pts. Results: 22 pts enrolled from 10/2012 through 6/2014 were eligible for the primary endpoint of response assessment. 9 patients remain on therapy. Conformed PR rate is 9% (2/22). 6 month progression free survival (PFS) was 95% (20/22). 15 out of 22 pts have follow-up on study > 12 months. The Kaplan-Meier 12 month PFS was 54% (95% CI: 34-85%). Median PFS is 13.6 months (95% CI 10.6-NA). Therapy was well tolerated with no grade 3-4 AE’s except 36% grade 3 hypertension. Conclusions: Bev therapy for PNET is associated with a 9% PR rate in PNET. For a population required to have RECIST criteria progression within 7 months prior to study enrollment, the 6 and 12 month PFS rates of 95% and 54% are promising with minimal systemic toxicity. Clinical trial information: NCT01010126.

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Background: Bronchial neuroendocrine neoplasms (NENs) are a biologically heterogeneous group of malignancies whose differences are incompletely understood. We aimed to study the demographics and survival of patients with these neoplasms by reviewing the SEER database. Methods: We identified 945,331 cases in the SEER database with malignancies of the lung and extracted 187,991 bronchial NENs to examine patient characteristics & clinical outcomes by histology and stage. Results: By histology and grade, there were 130,092 cases of small cell carcinoma, 44,520 cases of large cell carcinoma, 3,349 cases of neuroendocrine carcinoma (grade 3/4), 9,135 cases of typical bronchial carcinoid (grade 1), and 895 cases of atypical bronchial carcinoid (grade 2). The ethnic predilection was Caucasian (87%), with 9% black and 4% other. Overall there were more cases in men (55% of the entire cohort), but women accounted for 66% of the carcinoid cases. Mean age at diagnosis for all NENs was 66, with typical carcinoids having the youngest mean age (60) than any other type. By SEER stage, 13% of NENs were localized, 24% were regional, and 63% were metastatic, with median survivals of 39.7, 14.4, and 4.3 months, respectively. Survival by histology is summarized in the table below.

**Conclusions:** Bronchial NENs vary widely in their clinical behavior. By histology, large cell carcinomas carry the worst prognosis, whereas typical carcinoids are associated with the longest survival, as well as lowest age at diagnosis & female sex. Atypical carcinoids bear more semblance to typical carcinoids than to small cell, large cell, or neuroendocrine carcinomas in their biology.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Median survival (months) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large cell carcinoma</td>
<td>6.0 (5.9-6.1)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>7.0 (6.9-7.1)</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>9.0 (8.5-9.5)</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>101.0 (80.8-121.2)</td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>201.0 (191.7-210.3)</td>
</tr>
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</table>

Bronchial neuroendocrine neoplasms: A Surveillance Epidemiology and End Results (SEER) database review of demographics and survival in 187,991 cases. First Author: Mark Andrew Lewis, MD Anderson Cancer Center, Sugar Land, TX

**Background:** Atypical carcinoid, neuroendocrine carcinoma, small cell carcinoma, and large cell carcinoma are a heterogeneous group of malignancies whose differences are incompletely understood. In this study, we aimed to understand the demographics and survival of patients with these neoplasms by reviewing the SEER database. Methods: We identified 945,331 cases in the SEER database with malignancies of the lung and extracted 187,991 bronchial NENs to examine patient characteristics & clinical outcomes by histology and stage. Results: By histology and grade, there were 130,092 cases of small cell carcinoma, 44,520 cases of large cell carcinoma, 3,349 cases of neuroendocrine carcinoma (grade 3/4), 9,135 cases of typical bronchial carcinoid (grade 1), and 895 cases of atypical bronchial carcinoid (grade 2). The ethnic predilection was Caucasian (87%), with 9% black and 4% other. Overall there were more cases in men (55% of the entire cohort), but women accounted for 66% of the carcinoid cases. Mean age at diagnosis for all NENs was 66, with typical carcinoids having the youngest mean age (60) than any other type. By SEER stage, 13% of NENs were localized, 24% were regional, and 63% were metastatic, with median survivals of 39.7, 14.4, and 4.3 months, respectively. Survival by histology is summarized in the table below.

**Conclusions:** Bronchial NENs vary widely in their clinical behavior. By histology, large cell carcinomas carry the worst prognosis, whereas typical carcinoids are associated with the longest survival, as well as lowest age at diagnosis & female sex. Atypical carcinoids bear more semblance to typical carcinoids than to small cell, large cell, or neuroendocrine carcinomas in their biology.

Gene expression profiling of neuroendocrine neoplasms: a comprehensive approach to classification. First Author: Jonathan R. Strosberg, Moffitt Cancer Center, Tampa, FL

**Background:** Neuroendocrine tumors (NETs) are highly vascular neoplasms overexpressing VEGF as well as VEGFR. Axitinib is an inhibitor of receptor tyrosine kinases with picomolar potency against VEGFR-1, -2, and -3 and nanomolar potency against PDGFR-β. Methods: We performed a phase II trial of axitinib 5 mg twice daily in patients with unresectable or metastatic low to intermediate grade carcinoid tumors. Prior antiangiogenic therapy with a dedicated VEGF pathway inhibitor was not permitted. The primary endpoints were PFS and 12-month PFS rate. H0 = 12 mo PFS rate of 36% (corresponding to median PFS of 8.1 months); H1 = 12 mo PFS rate of 56.5% (corresponding to median PFS of 14.6 months). Preliminary findings are reported. Results: 30 patients were enrolled and assessable for toxicity; 29 were assessable for response. Primary sites included small intestine (19 patients), lung (3), unknown (3), colon (2), rectum (2), and thymus (1). 21 patients had low-grade and 9 patients had intermediate-grade tumors. Carcinoid syndrome was diagnosed in 16/30 patients. Median TTF was 8.99 months (SD ± 7.18) and the 12 mo PFS rate was 65% (SD ± 13%). Median PFS not yet determined due to small number of events. The 1-year OS rate was 93% (SD:±6.4%). Best radiographic response was PR in 1/30 (3.3%) and stable disease in 21/30 (70%); 8/30 patients (27%) objective radiographic response higher than 50% of the tumors and 5% of patients experienced hypertension (any grade). Grade 3 and 4 hypertension were seen in 18 (60%) and 2 (7%) patients respectively. Hypertension appeared to be tolerated well in the majority of cases. Conclusion: The 12 mo PFS rate associated with axitinib in advanced carcinoid disease appears promising when compared to results observed in phase II studies of other antiangiogenic TKIs such as sunitinib or pazopanib. Although associated hypertension is common, axitinib treatment was overall well tolerated. Clinical trial information: NCT01435122.
**Poster Session (Board #212), Mon, 8:00 AM-11:30 AM**

Randomized, phase III trial of adjuvant adefovir vs. therapeutic laminuvida in post-operative BCLC stage 0 or A HBV-related HCC: The Taipei Cooperative Oncology Group 2006 study. First Author: Dr. James Lee, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

**Background:** To investigate the role of adjuvant anti-viral nucleoside in the treatment of HBV-related HCC. Results: Between April 2007 and August 2010, a total of 95 patients were enrolled. The median age was 58 years, and 58% were male. The primary endpoint was late RFS. Results: The late RFS in those with RFS > 2 years was also similar between the two study arms. Conclusions: Despite the two adjuvant anti-HBV nucleoside vs. no treatment, no significant differences were observed in the OS and PFS rates between the two groups. Therefore, adjuvant anti-HBV nucleoside therapy is not recommended for patients with HBV-related HCC.

**Poster Session (Board #213), Mon, 8:00 AM-11:30 AM**

Phase II studies of BEZ235 in patients with advanced pancreatic neuroendocrine tumors (pNET). First Author: Dr. Ramon Salazar, Instituto Català d'Oncologia-

**Background:** The phase II studies of BEZ235 in patients with advanced pancreatic neuroendocrine tumors (pNET) were designed to evaluate the antitumor activity of BEZ235 as a single agent or in combination with other therapies in pNET patients. Results: In the phase II study, BEZ235 demonstrated a favorable safety/tolerability profile that support LAN as a first-line midgut NET treatment. These data indicate antitumor effects and a significant improvement in OS and PFS rates in the midgut NET subgroup. Conclusions: Beneficial effects of LAN for CS symptom control in NET patients are consistent regardless of baseline characteristics. Clinical trial information: NCT00455091.

**Poster Session (Board #219), Mon, 8:00 AM-11:30 AM**

Lanreotide depot/autogel (LAN) or placebo (PBO) for carcinoid syndrome (CS) in patients with neuroendocrine tumors (NETs): Subgroup analysis of the ELET study. First Author: Dr. Aaron Vinik, Eastern Virginia Medical School, Norfolk, VA

**Background:** ELET, a large phase 3 study of the long-acting somatostatin analog (SSA) LAN for symptomatic control of CS in NET patients showed significant improvement over PBO in % days with short-acting octreotide as rescue medication. Here, we report the reduction in rescue medication use for LAN and PBO in subgroups defined by baseline characteristics. Methods: Patients with histologically confirmed NETs and history of CS received double-blind LAN 120 mg (n = 59) or PBO (n = 50) every 4 weeks for 16 weeks with access to short-acting octreotide for breakthrough symptoms (NCT00774930). Results: Mean doses of rescue medication used for LAN vs PBO were calculated by ANCOVA within subgroups. Results: The significant reduction for LAN vs PBO in rescue medication use in the overall population (Table; approximately one-third lower for LAN group relative to PBO group) was generally consistent with reductions favoring LAN over PBO across subgroups, except small subgroups in which CS symptoms were wide (e.g., BMI > 30). Conclusions: Beneficial effects of LAN for CS symptom control in NET patients are consistent regardless of baseline characteristics. Clinical trial information: NCT00774930.

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4105 Poster Session (Board #216), Mon, 8:00 AM-11:30 AM
Low objective response and high toxicity to single-agent mitotane in patients with metastatic adrenocortical carcinoma (ACC): A 25 year experience at MSKCC. First Author: Betty Y Lung, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ACC is a rare but devastating disease, with short life expectancy in the setting of metastatic, unresectable disease. Mitotane, an oral adrenocorticolytic agent, is often used as a systemic treatment though its therapeutic window is narrow. We retrospectively assessed outcomes of patients (pts) with metastatic ACC who received single-agent mitotane therapy to determine treatment toxicities and effectiveness. Methods: In this retrospective IRB-approved study, we identified 35 pts with metastatic ACC treated with single-agent mitotane at MSKCC from 3/1989-9/2014. All pts had follow-up at MSKCC and all imaging was reviewed according to RECIST 1.1 by reference radiologists. We reviewed pt demographics, clinical symptoms, toxicity (based on CTCAE Version 4), and treatment outcomes. Results: 35 pts were identified with mean age of 53 years (range, 23-87), 60% female. 18/35 tumors (51%) were functional; estradiol (n = 1), cortisol (n = 12), testosterone and cortisol (n = 2). Grade 3 toxicities were observed in 15 of the 35 pts (45%). Severe toxicities included anorexia (9%), depression (6%), fatigue (20%), rash (6%), nausea (11%), vomiting (11%), and abdominal pain (6%). Radiographic progression of disease occurred in 30 of 35 pts (86%) and 1 pt (3%) experienced clinical progression. 2 pts (6%) had a complete response, 1 pt (3%) had partial response, and 1 pt (3%) had stable disease. The 3 pt (9%) with response (CR+PR) were asymptomatic prior to initiating mitotane; all had low volume indolent disease limited to one site (1 pt lung only; 1 pt retroperitoneal LN; 1 pt liver). All 3 pts experienced grade 3 toxicities on mitotane requiring treatment interruption and/or discontinuation. Conclusions: Among pts with ACC treated with mitotane-based therapy, 43% experienced grade 3 toxicities and 89% experienced POD. Response was noted in only 9% of pts and came with significant toxicity. The tumors in these responders are currently undergoing next generation sequencing analysis and results will be reported at the annual meeting. More effective and less toxic therapies are desperately needed in this rare disease.

4106 Poster Session (Board #217), Mon, 8:00 AM-11:30 AM
Clinical diagnostic utility of a blood-based multi-transcriptome assay for gastroenteropancreatic disease. First Author: Irvin Mark Modlin, Yale School of Medicine, New Haven, CT

Background: Current blood-based biomarkers for the diagnosis and follow-up of neuroendocrine tumors (NETs) do not achieve acceptable metrics of sensitivity and specificity. We report the sensitivity and selectivity of the PCR-based test, the NETest, to detect tumors with reference to other benign and malignant gastrointestinal diseases. We report the utility of a 51 transcript peripheral blood signature, the NETest, in comparison to Composognatin A (Cga) measurement in pancreatic NETs. Methods: One hundred and seventy nine cases (Set 1: gastrointestinal tumors: n= 81 including NETs (n= 41) and gastrointestinal carcinomas (n= 40); Set 2: pancreatic disease: n= 98 including NETs (n= 45), pancreatitis (n= 4), cysts (n= 31) and adenocarcinoma (n= 14)) were prospectively collected and analyzed by the NETest (disease activity index >20% (0-100 score)) or by chromogranin A (Cga) ELISA to determine metrics for detecting small intestinal and pancreatic NETs. Marker gene expression (qPcr) and Cga (DAKO) were compared (x², non-parametric) in Set 1. For Set 2, selectivity was assessed; sensitivity and specificity metrics were calculated for the entire cohort (n= 179). Results: Set 1: For intestinal disease, the accuracy of the NETest was 93% (all NETs positive, Cga was positive in 80% but 29% (n= 7) of colorectal cancers were Cga positive and 3 (7.5%) colorectal tumors were NETest positive). Set 2: For pancreatic disease, the NETest accuracy was 92% (96% NETs positive, 2% intraductal papillary mucinous neoplasms (IPMN) positive) while for Cga it was 56% (29% of pancreatic NETs were Cga positive). Overall, the NETest was significantly more sensitive than Cga for the detection of small intestinal (AUC 0.98±0.01 versus 0.75±0.06 p= 0.0001) and pancreatic NETs (0.95±0.02 vs. 0.5±0.06, p< 0.0001). When Cga was normal, The NETest was elevated (93%). Conclusions: This “real-world” study comparing NETs to unknown gastroenteropancreatic diseases demonstrates the sensitivity and specificity of a blood-based multiplex assay NET gene transcript measurement for identifying small intestinal and pancreatic neuroendocrine tumor disease.

4107 Poster Session (Board #218), Mon, 8:00 AM-11:30 AM
Recurrence following surgical resection of gastroenteropancreatic neuroendocrine tumors (NETs): An analysis from the NCCN oncology outcomes database. First Author: Katherine Van Loon, University of California, San Francisco, San Francisco, CA

Background: Recurrence of gastroenteropancreatic NETs is known to prolong survival. Current NCCN guidelines recommend that complete surgical resection of the primary tumor and metastases should be performed if possible. However, large multicenter studies of recurrence patterns following resection have not been performed. Methods: Patients ≥18 years who presented to 7 participating NCCN institutions after 2004 with a new diagnosis of a small bowel, pancreas, or colorectal NET were included. All underwent complete (R0) resection of the database, 301 patients underwent R0 resection. 50% of patients included in the database, 301 patients underwent R0 resection. 50% of patients included in the study. The overall survival (OS) HR for the RAM population was presented at ESMO 2014. The overall survival (OS) HR for the ITT population (RAM 283; placebo [PBO] 282) was 0.866 (95% CI 0.717, 1.045, p= 0.1391). In pts with baseline alpha-fetoprotein (AFP) >400 ng/mL (RAM 119; PBO 153), OS HR was 0.67 (95% CI 0.51–0.96, p= 0.0359). Methods: Efficacy and safety of RAM based on CP score are presented for all pts enrolled in REACH inclusive of ITT (n = 565) and CP (n = 78) population. Results: In REACH, pts with CP5 (n = 177) and CP6 (n = 38), RAM, N = 100 PBO, and CP7 and 8 (CPB) (N = 39 RAM, N = 39 PBO) were enrolled. Baseline pt characteristics were generally balanced between treatment arms by CP score. The table below shows OS, DFS, ORR and DCR according to CP score. The safety profile of RAM in pts with CP5 and CP6 was similar, and consistent with that observed in the ITT analysis of CP A pts. In pts with CP7 and 8 (CP B), an increase in liver events grade ≥ 3 was observed on the RAM vs PBO arm (56% vs 41%), including an increase in hepatic encephalopathy grade ≥ 3 (10% vs 0%). This observation led to exclusion of CP B pts from enrollment after 441 total pts were randomized during the study. Conclusions: A greater RAM treatment benefit was observed in pts with lower CP scores. In the CP B pt population, an increase in liver events was observed for RAM, specifically hepatic encephalopathy. A consistent and clinically meaningful improvement in OS, regardless of CP score, was observed in pts with elevated baseline AFP levels (> 400 ng/mL). Clinical trial registration: NCT01140347.

4108 Poster Session (Board #219), Mon, 8:00 AM-11:30 AM
Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Analysis of REACH pts by Child-Pugh (CP) score. First Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center, Boston, MA

Background: REACH was a global, randomized, double-blind, phase III study evaluating the efficacy and safety of RAM as a single-agent treatment of pts with advanced HCC after prior sorafenib therapy. The primary outcome for the ITT population was OS at 24 weeks. Treatment groups were generally balanced. Methods: Patients ≥18 years who presented to 7 participating NCCN institutions after 2004 with a new diagnosis of a small bowel, pancreas, or colorectal NET were included. All underwent complete (R0) resection of the database, 301 patients underwent R0 resection. 50% of patients included in the analysis were male, 98% were Caucasian, and 99% had an ECOG PS 0-1. The median age was 55 years (range 20-90); however, patients with a colorectal NET were younger (p<0.001). Median follow-up time from R0 resection was 62.1 months. Among patients with small bowel NET (n=110), 18% recurred. Among patients with pancreatic NET (n=141), 26% recurred. Among patients with colorectal NET (n=50), 10% recurred. The proportion of patients without recurrence and the proportion alive at 12, 24, 36, 48, and 60-month follow-up are below. Stratification according to stage will be presented. Conclusions: RAM resection was associated with a favorable risk of recurrence across subtypes by 5 years of follow-up. Greater than 90% of patients who underwent an R0 resection were alive at 5-year follow-up; similarly, the majority of patients were disease-free. Further inquiry into appropriate surveillance strategies following R0 resection is needed.

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A phase I/II study of bavitalumab and sorafenib in advanced hepatocellular carcinoma (HCC). First Author: Adam Charles Yopp, The University of Texas Southwestern Medical Center Columbia College of Physicians and Surgeons New York-Presbyterian Hospital, New York, NY

Background: Bavitalumab, a first-in-class immunomodulator targeting phosphatidylserine (PS), a membrane lipid externalized on tumor and endothelial cells. In preclinical HCC models, sorafenib upregulated PS externalization providing more bavitalumab targets altering the tumor environment from immunosuppressive to immunoreactive. Methods: In the 3+3 phase I trial, adults with advanced HCC, ECOG PS ≤ 2, and Child-Pugh class A or B7 received escalating doses of bavitalumab (0.3, 1, and 3 mg/kg) and sorafenib 400 mg bid for one 4-week cycle to determine the MTD of bavitalumab. In the phase II trial with the same eligibility, patients received 3 mg/kg bavitalumab and sorafenib until progression or toxicity. The primary endpoint was radiologic time to progression (TTP). Secondary endpoints included safety, 4-month progression-free survival (PFS), overall survival (OS), and response rates. Correlative studies from pre- and post-treatment tumor biopsies included IHC analysis of immune infiltrates. Results: Ten patients were enrolled in the phase I trial without DLTs, demonstrating a MTD of 3 mg/kg of bavitalumab and 400 mg PO of sorafenib. In the phase II trial, 38 patients were accrued, with 4 remaining on treatment at the time of this submission. Median follow-up is 6.1 months. Patient characteristics: median age: 60.5 years, male: 74%, HCC: 79%, macrovascular invasion: 84%, previous treatment: 40%, and metastases: 24%. Median TTP is 6.7 months (95% CI 4.14). Median OS is 6.2 months (95% CI 5.7). Four month PFS is 61% and two patients achieved partial response. Treatment related AEs include seven grade 3 but no grade 4 or 5 events. Most common all grade events were diarrhea (32%), fatigue (26%), and anorexia (24%). Six patients had tissue analyzed pre- and post-treatment, two of the six had significant increase in tumor infiltration of CD4+, CD8+, and macrophages with a corresponding decrease in T regulatory cells. Conclusions: Bavitalumab and sorafenib were well tolerated in advanced HCC. When compared with historical controls, combination therapy in a patient population with more unfavorable disease biology demonstrated an improvement in TTP and 4-month PFS. Combination therapy increased immune tumor infiltrates. Clinical trial information: NCT01264705.

Long-term outcomes of cytoreduction and HIPEC for malignant peritoneal mesothelioma. First Author: Gineara Elizabeth Bates, Mesothelioma Center Columbia College of Physicians and Surgeons New York-Presbyterian Hospital, New York, NY

Background: The prognosis of malignant peritoneal mesothelioma (MPM) has improved over the past decade in patients undergoing operative extirpation and intraperitoneal chemotherapy (IC). This study investigates the largest reported cohort of patients operated on for MPM. Methods: Kaplan-Meier curves and univariate cox proportional hazards model was used to estimate tumor infiltration of CD4+, CD8+, and macrophages with a corresponding decrease in T regulatory cells. In preclinical HCC models, sorafenib upregulated PS externalization providing more bavitalumab targets altering the tumor environment from immunosuppressive to immunoreactive. Results: Median survival time was 3.21 years with (95% CI: 2.39-5.53), with median follow-up of 3.44 years (SD = 3.4, minimum = 0.034 and maximum = 16.75). First operation. The mean age at diagnosis was 54.8 years (HR: 1.027 (95% CI: 1.012-1.042)) with 111 men (57%) and 84 women (43.1), with female gender having favorable survival (HR: 0.442 95% CI: 0.296-0.659). Asbestos exposure was reported in 77 patients (39.5%) with n = 80 (41.0%) having no known asbestos exposure and in 38 patients (19.5%) asbestos exposure was not documented. The majority of patients had epithelioid histology (n = 161(82.6%), with the remainder biphasic/ carcinosarcoma (n = 34, 17.4%), with increased risk of death with non-epithelioid histology (HR: 2.46(95%CI 1.59-3.82)), (P = 0.001). Of the 195 patients who underwent cytoreductive surgery and or HIPEC treatment between 1995-2014; patients were not excluded for bicavity progression (TTP). Secondary endpoints included safety, 4-month progression-free survival (PFS), overall survival (OS), and response rates. Correlative studies from pre- and post-treatment tumor biopsies included IHC analysis of immune infiltrates. Results: Ten patients were enrolled in the phase I trial without DLTs, demonstrating a MTD of 3 mg/kg of bavitalumab and 400 mg PO of sorafenib. In the phase II trial, 38 patients were accrued, with 4 remaining on treatment at the time of this submission. Median follow-up is 6.1 months. Patient characteristics: median age: 60.5 years, male: 74%, HCC: 79%, macrovascular invasion: 84%, previous treatment: 40%, and metastases: 24%. Median TTP is 6.7 months (95% CI 4.14). Median OS is 6.2 months (95% CI 5.7). Four month PFS is 61% and two patients achieved partial response. Treatment related AEs include seven grade 3 but no grade 4 or 5 events. Most common all grade events were diarrhea (32%), fatigue (26%), and anorexia (24%). Six patients had tissue analyzed pre- and post-treatment, two of the six had significant increase in tumor infiltration of CD4+, CD8+, and macrophages with a corresponding decrease in T regulatory cells. Conclusions: Bavitalumab and sorafenib were well tolerated in advanced HCC. When compared with historical controls, combination therapy in a patient population with more unfavorable disease biology demonstrated an improvement in TTP and 4-month PFS. Combination therapy increased immune tumor infiltrates. Clinical trial information: NCT01264705.

Importance of tumor grade in stage III mucinous appendiceal carcinoma: An analysis of the SEER Database. First Author: Olivia Fukui, Carolinas Healthcare System, Charlotte, NC

Background: Appendiceal cancers are rare tumors with prognostic heterogeneity and treatment-responses dependent upon histologic characteristics. In the 7th edition AJCC manual, mucinous tumors were separated from non-mucinous. Histologic grade was used to distinguish stage IVA from IVb in mucinous tumors. We examined SEER data to investigate the impact of cancer grade on all stages of appendiceal cancer. Methods: We identified patients (pts) with primary appendiceal cancer from the SEER data, Disease-specific survival (DSS) was analyzed based on histologic subtype, stage, and grade. Hazards ratios were calculated using Cox models. Tumor grades were grouped according to AJCC criteria (Grade 1 vs. Grade 2 and above). Results: From 1998-2011 a total of 4491 appendiceal adenocarcinomas were identified in the SEER database; 2026 (45%) pts had mucinous histology and 1578 (35%) had non-mucinous histology. Tumor grade had no impact on DSS in stage I and II tumors. However, in Stage III and IV mucinous tumors higher tumor grade was significantly correlated with worse survival. In pts with Stage III mucinous disease, those with grade 1 tumors had significantly longer DSS than those with tumors ≥ grade 2, with 5-year survival of 75% vs. 44%, respectively (p = 0.02, HR 3.15, 95% CI 1.11 - 8.96). Survival for mucinous stage III grade 1 tumors was similar to stage II tumors. Conclusions: Tumor grade is a strong prognostic indicator in pts with stage III mucinous appendiceal carcinoma. We propose that tumor grade should be included in AJCC staging for stage III mucinous appendiceal cancers, and should not be limited to Stage IV disease as in the AJCC 7th staging manual. Continued investigation into the clinical implications of the observed difference in survival in patients with Stage III appendiceal mucinous adenocarcinoma is warranted, and may potentially alter adjuvant treatment recommendations in selected pts.
Background: This study aims to investigate the role of preoperative FDG-PET/CT as a prognostic factor in advanced gastric cancer (AGC).

Methods: A total of 953 AGC patients who underwent FDG-PET/CT and subsequent curative surgical resection were enrolled from 2003. Afterward, 548 patients with pathologically proven T stage 3 or 4 were visually reassessed and, in patients with positive FDG-PET/CT findings, SUVmax were evaluated as prognostic factors according to histologic subtype for cancer recurrence and death. Results: Of 548 patients, 497 (90.1%) showed positive FDG-cancer uptake. In terms of WHO classification, well or moderately differentiated adenocarcinoma (WMD) demonstrated the highest Suvmax (WMD: 9.3; PD: 6.4; SRC: 4.8; P < 0.001). Based on Lauren’s classification, intestinal type displayed significantly higher mean SUVmax than diffuse type (Intestinal: 8.5; Diffuse: 5.3; P < 0.001). While mean SUVmax of WMD or intestinal type GC were well correlated with primary tumor size (both P < 0.001), those of SRC or diffuse type GC were not well correlated. TNM stage was not associated with SUVmax regardless of histologic subtype. When patients were divided into two groups (low vs. high SUVmax patients with diffuse type GC had a significantly increased risk of histologic subtype. FDG PET/CT could provide prognostic information on cancer recurrence and death.

Conclusions: FDG uptake of gastric cancer is different according to histology in advanced gastric cancer. Prognostic impact of different FDG-PET uptake according to histology in gastric cancer: Phase II results.

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A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer.

First Author: Aaron James Scott, University of Colorado Denver, Aurora, CO

Background: Rigosertib (ON 01910.Na), a first-in-class Ras mimetic and small molecule inhibitor of multiple signaling pathways including polo-like kinase 1 (PLK1) and phosphoinositide 3-kinase (PI3K), has shown efficacy in preclinical pancreatic cancer models. In this study, rigosertib was assessed in combination with gemcitabine in patients with treatment-naïve metastatic pancreatic adenocarcinoma. Methods: Patients with metastatic adenocarcinoma of the pancreas were randomized in a 2:1 fashion to gemcitabine 1000 mg/m² weekly for 3 weeks of a 4-week cycle plus rigosertib 1800mg/m² via 2-hr continuous IV (CIV) infusions given twice weekly for 3 weeks of a 4-week cycle (RIG+GEM) versus gemcitabine 1000mg/m² weekly for 3 weeks in a 4-week cycle (GEM). Results: A total of 160 patients were enrolled globally and randomly assigned to RIG+GEM (106 patients) or GEM (54). The most common grade 3 or higher adverse events were neutropenia (8% in the RIG+GEM group vs. 6% in the GEM group), hypotension (17% vs. 4%), and anemia (8% vs. 4%). The primary outcome of the study, median overall survival (OS), was 6.1 months for RIG+GEM versus 6.4 months for GEM (hazard ratio (HR), 1.24; 95% confidence interval [CI], 0.85-1.81). The median progression-free survival (PFS) was 3.4 months for both groups (HR = 0.96; 95% CI, 0.68-1.36). The partial response rate by Response Evaluation Criteria in Solid Tumors (RECIST v.1) was 19% versus 13% for RIG+GEM versus GEM, respectively. Of 64 tumor samples sent for molecular analysis, 47 were adequate for multiplex genetic testing and 41 were positive for mutations. The majority of cases had KRAS gene mutations (40/47, 85%). Other mutations detected included TP53 (13 cases) and PIK3CA (11 case). No correlation between mutational status and PFS or OS was detected. Conclusions: The combination of RIG+GEM failed to demonstrate an improvement in survival or response compared to GEM in metastatic pancreatic adenocarcinoma. Rigosertib had a similar safety profile to that observed in other trials of the IV formulation.

Clinical trial information: NCT01360853.

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Background: TG01 targets oncocogenic mutations in RAS genes that are present in 80-90% of pancreatic cancers. TG01 is a mixture of 7 RAS peptides and previously, as monotherapy in patients with pancreatic cancer, induced specific cellular immune responses in 100% of patients. This study evaluated safety and whether induced immune responses are maintained with standard adjuvant chemotherapy. Methods: Patients were eligible after an R0 or R1 pancreatic adenocarcinoma resection and expected to receive gemcitabine (1000 mg/m² for 3/4 weeks x 6 cycles) started within 12 weeks of surgery. For gemcitabine toxicity 5-FU/leucovorin could be substituted. TG01 0.7 mg id was given on days 1, 3, 5, 8, 15, 22 and 2-weekly until end of chemotherapy, 4-weekly up to 1 year and 12-weekly thereafter. GM-CSF 0.03 mg id was given 15 minutes prior to TG01. TG01 was used for the DTH test. Results: 18 patients were included from 3 sites (Norway and UK). 6 patients are ongoing 3 to 50 weeks from the start of vaccinations. 5 patients were withdrawn due to recurrent disease, 1 for an unrelated death, 3 for related AEs and 2 for other reasons. 10 SAEs in 6 patients occurred; 3 related to gemcitabine (pulmonary infection and fever) and 2 related to TG01 (anaphylaxis) the others were unrelated to gemcitabine or GM-CSF/TG01. The main AEs related to GM-CSF/TG01 were local reactions in 4/18 patients (8 events), allergic reactions in 4/18 patients (6 events); one occurring before gemcitabine (Grade 1). Anaphylaxis only occurred after gemcitabine completion. Other adverse events were flu-like symptoms and single cases of fatigue, arthralgia, fever, nausea and vomiting. 14/16 patients (87.5%) had a positive DTH by week 11 persisting after gemcitabine and to date 7/8 patients (87.5%) generated positive T cell responses. Conclusions: TG01/ GM-CSF generated immune responses in 87.5% of patients with resected pancreatic cancer, these responses were maintained with chemotherapy and persisted with booster injections. The regimen was generally well tolerated although some late allergic reactions were seen. Clinical trial information: NCT02261714.

Nab paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after failure of folfirinox: Results of an AGEO multicenter prospective cohort. First Author: Alix Portal, Hopital Européen Georges Pompidou, Paris, France

Background: Both Folfirinox and Nab-paclitaxel plus Gemcitabine showed a benefit in terms of survival in first-line treatment of metastatic pancreatic adenocarcinoma (MPA) when compared to gemcitabine. It could be of interest to use them consecutively, knowing that there is currently no standard for 2nd line treatments for MPA and that median Progression free survival (PFS) is consistently less than 4 months in this setting. The aim of this study was to evaluate the efficacy and tolerability of gemcitabine plus Nab-paclitaxel after Folfirinox failure in MPA. Methods: From February 2013 to July 2014, all consecutive patients (pts) from 12 French centers treated by Nab-paclitaxel plus Gemcitabine for a historically proven MPA after failure of Folfirinox were prospectively recorded. Nab-paclitaxel plus Gemcitabine was delivered on days 1, 8, and 15 every 4 weeks, as previously reported, until disease progression, patient refusal or unacceptable toxicity. Results: Nab-paclitaxel plus Gemcitabine was administered to 57 pts. They received a median number of 4 cycles (1–12). Disease control rate was 58% (n = 33) with a 18.5 % (n = 18) objective response rate (RECIST). Within the whole cohort, median overall survival (OS) was 8.8 months (95% CI: 6.2-9.7) and median PFS was 5.1 months (95% CI : 3.2-6.2). Since the start date of first line chemotherapy with Folfirinox, median OS was 18 months (95% CI: 16-21). No toxic death occurred. Grade 3-4 toxicities were reported in 40% of patients and were neutropenia (12%), neurotoxicity (12%), asthenia (8%) and thrombocytopenia (8%). Conclusions: With median PFS and OS of respectively 5.1 and 8.8 months Nab-paclitaxel plus Gemcitabine seems promising with a manageable toxicity profile after folfirinox failure, in selected patients able to receive second line treatment for a MPA. These promising results have now to be confirmed in a phase III randomized trial.
A retrospective single institution review of 90 pancreatic adenocarcinoma (PASC) patients (pts), First Author: Jennifer Brooke Goldberg, The University of Texas MD Anderson Cancer Center, Medical Oncology Fellowship, Houston, TX

Background: PASC is a rare and aggressive subset of pancreatic cancer. PASCs are more likely to have poorly differentiated histology and positive lymph nodes. No separate treatment guidelines exist for PASC, however platinum-based therapy (tx) is commonly used based on a few published case series. The molecular signature of PASC has been reported in small studies and mirrors that of pancreatic adenocarcinoma. Most mutations commonly involving TP53, CDKN2A, KRAS and loss of SMAD4 and the recently reported UFP1. These genomic analyses have been limited to genes known to be important in PA. Methods: We retrospectively reviewed the medical records of pts with PASC that were seen at M.D. Anderson Cancer Center from 1993 to 2014. Pts were chosen based on a pathological diagnosis of PASC either in the primary tumor or metastasis. Descriptive statistics and survival analysis were performed using Stata 13.1. Results: A total of 90 pts were identified as having PASC, 75 diagnosed from the primary tumor and 15 from a metastatic site. Median age was 65 years (40-86), 62% were male, and 67% had locally advanced or metastatic disease at presentation. The median overall survival (OS) was 8.8 mths (95%CI (6.8-10.3)). Of 29 pts who underwent surgical resection, the median time to recurrence was 6.7 mths (95%CI (3.4-Not Estimable)). First line platinum-based tx did not impact OS (HR 1.07, 95% CI 0.66-1.75, P=0.786). 6 pts had genomic testing performed. All 6 had mutations in codon 12 of KRAS (three G12D, two G12R, and one G12V), 4 carried mutations in PIK3CA and 2 had mutations in FGFR2 and 4 had mutations in PTEN. 2 pts had KRAS mutations with a different codon (G12S and G13D). Of 6 pts tested for EGFR mutations, 1 pt had a point mutation in the gene. Additionally, 2 of 6 pts showed alterations in KRAS and TP53 mutations seen in PA, but a potentially novel amplification of FGF 3 and 19, which could play a role in tumorigenesis. Further molecular profiling may demonstrate potential targets for tx not traditionally seen in PA.

Conclusions: Our results demonstrate that PASC has a poor prognosis and is undertreated compared with other pancreatic tumors. Our results provide novel insights into PASCs target therapy.

Dendritic cells generated with PDL-1 checkpoint blockade for treatment of advanced pancreatic cancer, First Author: Jan Nesselhut, Institut Fuer Tumorthherapie, Duderstadt, Germany

Background: The efficacy of immunotherapy with monocyte derived dendritic cells (MoDC) is controlled via immune checkpoints, among them the PD-1/PDL-1 pathway. PDL-1 expressed on DC delivers an inhibitory signal to T-cells upon binding to PD-1 expressed on activated T-cells. Blocking of PDL-1 on DC may lead to improved efficacy of DC therapy for pancreatic cancer. Methods: After isolating monocytes from peripheral blood of n=44 patients, we induced monocyte derived dendritic cells with IL-4 and TNF-alpha. We transduced these dendritic cells with PDL-1 checkpoint blockade. Cytokine release and T-cell activity were measured exemplary using a mixed lymphocyte culture (MLC). Results: Median survival after onset of DC-therapy was 8 months with MoDC alone (18 months after primary diagnosis) with longest follow up of 36 months (49 months after primary diagnosis). We could induce a secondary stabilisation (4 to 8 months) in 5 from 10 patients, who failed to respond to previous DC therapy by using MoDC modified by PDL-1 blockade. Cytokine release and T-cell activity were measured exemplary using a mixed lymphocyte culture (MLC). Conclusions: An effective immune response requires both the inhibition of inhibitory signals and the activation of an antigen specific T-cell response. The efficacy of dendritic-cell based therapy may be improved by blockade of PDL-1 on dendritic cells to avoid an inhibitory signal and thus improve the T-cell specific response. Further investigations are necessary to ascertain whether the combination of systemic anti PD1-therapy with DC therapy using MoDC modified with PDL-1 blockade may further enhance therapeutic efficacy in solid tumors.

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4129 Poster Session (Board #241), Mon, 8:00 AM-11:30 AM
Targeting Sema3D in pancreatic cancer: A novel therapeutic strategy. First Author: Adrian Murphy, The Sidney Kimmel Comprehensive Cancer Center John Hopkins, Baltimore, MD
Background: Pancreatic ductal adenocarcinoma (PDAC) is known for its chemotherapy resistance and dismal survival rates. Little is known about the mechanisms of metastasis in PDAC. We identified Annexin A2 (AnxA2), an essential mediator of metastasis using sera from patients with prolonged survival after GVAX treatment. AnxA2 regulates secretion of semaphorin 3D (Sema3D) promoting invasion and metastasis of PDAC cells. Sema3D and other axon guidance genes have been shown to be tempestuously most frequently altered in PDAC. Methods: KPC mice, which spontaneously developed PDAC, were generated from KRAS/P53 mice. KPCA-/- mice, which spontaneously developed PDAC, were generated with KRAS/P53 mutations. KPCA-/- mice were crossed with AnxA2 knockouts with KPC mice. Cell lines were measured from KPC and KPCA-/- cells by ELISA. Anti-AnxA2 antibodies were used to see the effect of AnxA2 inhibition on Sema3D secretion. Sema3D knockdown KPC cells were used in a semi-spleen model of liver metastasis to evaluate metastasis in vivo. Immunohistochemistry (IHC) was used to analyze Sema3D expression in resected human PDAC tissue. Results: While PDAC tumors spontaneously developed in both KPC and KPCA-/- mice, metastases were only seen in KPC (16/17) but not in KPCA-/- mice (0/23). Sema3D expression was down-regulated in KPCA-/- cells compared to KPC cells and Sema3D knockdown was significantly lower from KPCA-/- cells (0.25 ng/ml) than KPC cells (1.7 ng/ml) (p = 0.01). Antibody blockade of AnxA2 suppressed Sema3D secretion in KPC cells suggesting its role in Sema3D secretion. Animals injected with KPC cells transplanted with Sema3D-targeting shRNA had fewer metastases (5/13) and longer survival than mice injected with control (11/12) (p = 0.01). IHC on human PDAC tumors showed that 15/20 patients with DFS > 1 year abundantly expressed Sema3D. Sema3D knockdown can be used in 96 well plates after 24 hours of incubation and this platform is optimized for drug testing. Conclusions: Sema3D secretion, which is regulated by AnxA2, is crucial for PDAC metastasis. Targeting this pathway may lead to increased therapeutic options in PDAC. We have established a platform to detect drugs that reduce Sema3D secretion.

4132 Poster Session (Board #243b), Mon, 8:00 AM-11:30 AM
Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: A randomized phase III study (GASTREPIEC). First Author: Beate Rau, Charite Campus Mitte University of Berlin, Berlin, Germany
Background: Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) can improve prognosis of patients with peritoneal metastases (PM) in colorectal cancer. In gastric cancer (GC) patients with PM this concept is under debate. Perioperative chemotherapy has been shown to improve survival in gastric cancer. In patients with limited PM systemic chemotherapy, in a pulliative gastrectomy and CRS may prolong survival compared to chemotherapy alone (Sun) in selected patients. It is unclear whether HIPEC has an additional benefit in this setting. The GASTREPIEC trial (NCT02158988) will clarify the role of HIPEC. Methods: It is an open label, multicenter randomized phase III trial. 180 patients with histological proven GC or GE-Junction and PM will be included. All patients will receive 3 cycles of pre- and postoperative chemotherapy, dependent on the HER 2 status (Her 2 + ve: cisplatin, capecitabine, trastuzumab (CCT); HER 2 -ve: epirubicin, oxaliplatin, capecitabine (EOX)). All patients will receive gastrectomy and pancreatectomy. Patients randomized into group B will be treated with additional intraoperative HIPEC with Mitomycin C and Cisplatin for 60 minutes at 41-43°C. Main inclusion criteria: Histological proven PM in GC including adenocarcinoma of the GE-junction, no evidence of distant metastases in CT scan chest and abdomen other than PM (exclusion of Kreuzberg tumor metastasis), simultaneous lymph node and/or liver lesions. Exclusion criteria: Evidence of a new primary tumor or another primary disease, laparotomy, possibility of 80% tumor reduction at CRS, Karnofsky Index > 70%, written informed consent. We hypothesize a hazard ratio for overall survival to be 0.77. Other endpoint was R0-resection rate, secondary endpoints included overall survival, disease–free survival, safety. Up until January 2015, 638 subjects from 7 centers have been enrolled. Hematological toxicities included neutropenia, anaemia, and thrombocytopenia. Non-hematological toxicities included fatigue, abnormal hepatic/renal function, neurotoxicity, and skin pigmentation, most adverse events were tolerable. No treatment related death was observed. Updated safety data will be presented. This study was registered with Clinicaltrials.gov, NCT01516944. Clinical trial information: NCT01516944.

4133 Poster Session (Board #244a), Mon, 8:00 AM-11:30 AM
Perioperative chemotherapy vs. adjuvant chemotherapy for potentially resectable gastric cancer: A randomized and multicenter phase III study in locally advanced gastric cancer with D2 dissection. First Author: Qun Zhao, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China
Background: The MAGIC and ACTS-GC/CLASSIC trials demonstrated benefit in resectable gastric cancer from both perioperative and postoperative adjuvant chemotherapy, although such management remains controversial for locally advanced gastric cancer (LACG) after D2 lymph node dissection. Methods: A Phase III 1:1:1 randomized, open label, multicenter, trial comparing adjuvant (Arm A) or perioperative SOX (Arm B), and perioperative XELOX (Arm C) was initiated in February 2012, in T3/4, node+ gastric cancer patients after R0 resection. SOX included S-1 40 mg/m2 bid day 1-14, Oxaliplatin 130 mg/m2 on day 1, XELOX included Capecitabine 1000 mg/m2 bid day 1-14, plus Oxaliplatin 130 mg/m2 on day 1, each cycle was 3 weeks, each patient received 8 cycles. XELOX included Capecitabine 1000 mg/m2 bid day 1-14, plus Oxaliplatin 130 mg/m2 on day 1, each cycle was 3 weeks, each patient received 8 cycles. ARM B and C patients received 2 cycles prior to surgery, and 6 cycles post op. Patients were stratified by tumor stage, ECOG PS and institution. The study was powered to show superiority of perioperative over adjuvant SOX, and non-inferiority of SOX to XELOX. Eligibility included historically proven gastric cancer (including gastroesophageal junction), age 18-75, D2 or more extensive surgery with no residual disease, ECOG score < 2, and no distant metastasis. Primary endpoint was R0-resection rate, secondary endpoints included overall survival, disease–free survival, safety. Up until January 2015, 638 subjects from 7 centers have been enrolled. Hematological toxicities included neutropenia, anaemia, and thrombocytopenia. Non-hematological toxicities included fatigue, abnormal hepatic/renal function, neurotoxicity, and skin pigmentation, most adverse events were tolerable. No treatment related death was observed. Updated safety data will be presented. This study was registered with Clinicaltrials.gov, NCT01516944. Clinical trial information: NCT01516944.
Background: Several cancer genome alterations have been identified as important targets for treatment. Example of possible candidates in gastrointestinal (GI) cancer include BRAF mutations in colorectal cancer (CRC) or MET amplification in gastric cancer, for which corresponding targeting agents showed attractive activity in early phase clinical trials. Efficient screening systems for these relatively minor cancer genome alterations are necessary for the successful development of targeted therapies. We initiated a nationwide screening project in Japan (GI-SCREEN) in February 2014 to detect gastric cancer (GC) (GI-SCREEN 2013-01-CRC). The patient’s population will be expanded to non-CRC GI cancer (SCRUM-Japan GI-SCREEN 2015-01-Non CRC). The objective of these consecutive projects is to evaluate the frequency of oncogenic genome alterations in advanced GI cancers and to facilitate the enrollment of patients in IND registration trials for targeted therapies as well as optimal individualized treatment.

Methods: These prospective observational studies are designed to enroll patients with CRC or non-CRC GI cancer (gastric, esophageal, small-intestinal, appendiceal) cancers and neuroendocrine carcinoma) who are planned to receive systemic chemotherapy. Tumor samples from surgical or biopsy specimens have been examined by Luminex technology so far. Starting from February 2015, it will be redesigned to analyze more than 140 kinds of alterations in cancer genome, which included mutations, copy number variations, and gens fusions, using next generation sequencing of the Oncomine Cancer Research Panel (OCP) at a quality-controlled central laboratory. Patient characteristics and treatment outcomes are also planned to be collected. The targeted sample size is 2000 patients with CRC and 1000 patients with non-CRC. As of January 26, 2015, a total of 844 CRC patients were enrolled and non-CRC study will be opened in April 2015 with planned participation of 18 major cancer centers in Japan. Clinical trial information: UMIN000016344.

Results: Since Jan 2012, patients with newly diagnosed resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma at clinical stage T2,3,N(+) or T4/N(+) by AJCC 7th edition have been recruited. Key exclusion criteria are Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, history of any malignancy other than gastric or rectal cancer, or patients who had difficulties in oral ingestion/digestion/absorption. Patients are randomized 1:1 in open label to neoadjuvant DOS chemotherapy, surgery and then adjuvant chemotherapy (CSC) arm vs surgery and chemotherapy (SC) arm. Neoadjuvant DOS regimen consists of D 50mg/m² i.v. on day 1, O 100mg/m² i.v. on day 1 and S 50mg/m² i.v. once orally on days 1-14 every 3 weeks for 3 cycles. Surgical method is D2 dissection. Adjuvant chemotherapy is S 40mg/m² twice orally on days 1-28 every 6 weeks for 8 cycles. Primary endpoint is 3 year progression free survival (PFS). Secondary endpoints include overall survival (OS), pathologic stage, R0 resection rate and safety profiles compared in two arms. With power of 80% and two-sided α= level of 5%, 244 events are required to detect 70% of 3 year PFS in CSC arm compared to 60% in SC arm (HR = 0.698). Considering 10% of drop-out rate, target enrollment is 530 subjects from 17 sites in Korea until July 2016. The first Independent Data Monitoring Committee meeting was held in October 2014 and the committee recommended continuing the study as planned. NCT01515748 Clinical trial information: NCT01517478.

Background: In stage I (by AJCC 6th edition) gastric cancer (GC), recurrence rate is generally low, and long-term outcomes are considered very good after curative resection. For this reason, only limited number of stage I GC patients (pts) were included in most previous studies of adjuvant treatment. As a result, no stage I GC pts included in ACTS-GC and CLASSIC trials which compared adjuvant chemotherapy vs observation after D2 dissection. However, a large scale retrospective study (Park et al, Gastric Cancer. 2015 Jan 23 [Epub ahead]) demonstrated that pts with stage IB GC with high risk factors had high recurrence rate more than 20%. Considering more than 30% risk reduction of recurrence by adjuvant chemotherapy in stage II GC, stage I GC pts at high risk of recurrence may also get benefit from adjuvant chemotherapy. Moreover, in Korea, more than 50% of GC pts have stage I disease, which is increasing due to nationwide screening program. Based on this background, a phase III randomized study has been initiated. Methods: Since Jan 2012, patients with newly diagnosed resectable gastric or gastroesophageal junction(GEJ) adenocarcinoma at clinical stage T2,3,N(+) or T4/N(+) by AJCC 7th edition have been recruited. Key exclusion criteria are Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, history of any malignancy other than gastric or rectal cancer, or patients who had difficulties in oral ingestion/digestion/absorption. Patients are randomized 1:1 in open label to neoadjuvant DOS chemotherapy, surgery and then adjuvant chemotherapy (CSC) arm vs surgery and chemotherapy (SC) arm. Neoadjuvant DOS regimen consists of D 50mg/m² i.v. on day 1, O 100mg/m² i.v. on day 1 and S 50mg/m² i.v. once orally on days 1-14 every 3 weeks for 3 cycles. Surgical method is D2 dissection. Adjuvant chemotherapy is S 40mg/m² twice orally on days 1-28 every 6 weeks for 8 cycles. Primary endpoint is 3 year progression free survival (PFS). Secondary endpoints include overall survival (OS), pathologic stage, R0 resection rate and safety profiles compared in two arms. With power of 80% and two-sided α= level of 5%, 244 events are required to detect 70% of 3 year PFS in CSC arm compared to 60% in SC arm (HR = 0.698). Considering 10% of drop-out rate, target enrollment is 530 subjects from 17 sites in Korea until July 2016. The first Independent Data Monitoring Committee meeting was held in October 2014 and the committee recommended continuing the study as planned. NCT01515748 Clinical trial information: NCT01517478.

Gastrointestinal (Noncolorectal) Cancer

TPS4134 Poster Session (Board #244b), Mon, 8:00 AM-11:30 AM
The Nationwide Cancer Genome Screening Projects for Gastrointestinal Cancer in Japan (SCRUM-Japan GI-SCREEN): Efficient identification of actionable cancer genome alterations in advanced colorectal and non-CRC gastrointestinal cancer (GI Screen 2013-01-CRC and 2015-01-Non CRC), First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan

Multicohort phase II KEYNOTE-059 study of pembrolizumab (MK-3475) for recurrent or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA

Background: Many tumors suppress immune control via the programmed death receptor 1 (PD-1) pathway. Pembrolizumab is an anti–PD-1 monoclonal antibody designed to block the interaction of PD-1 with its ligands PD-L1 and PD-L2. In 39 patients (pts) with PD-L1–positive metastatic gastric cancer enrolled in the phase I KEYNOTE-012 trial, 67% of whom had ≤ 1 first-line of therapy, pembrolizumab 10 mg/kg every 2 wk (Q2W) provided a 22% confirmed ORR (RECIST v1.1, central review) and an acceptable safety profile. KEYNOTE-59 (NCT02335411) is an ongoing, international, 3-phase II study designed to further assess pembrolizumab in pts with gastric cancer. Methods: All cohorts of KEYNOTE-059 will enroll and treat 200 pts with recurrent or metastatic gastric cancer. Key endpoints are ORR and duration of response (DOR). ticking the table(s) with key points being presented in the text. Clinical trial information: NCT02335411.

TPS4136 Poster Session (Board #245b), Mon, 8:00 AM-11:30 AM
A randomized phase III study of adjuvant capecitabine vs observation in curatively resected stage IB (by AJCC 6th edition) gastric cancer (CAYTALYS; KCSG ST14-05). First Author: Min-Hee Ryu, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Although adjuvant chemotherapy with S-1 is now considered a standard after D2 resection in stage II or III locally advanced gastric cancer (LAGC) in Asia, many patients still experience recurrence of disease. Addition of neoadjuvant chemotherapy can be one method to further improve outcomes in LAGC. A previous phase II study of neoadjuvant DOS doublet and, if HER2 positive, trastuzumab, will receive pembrolizumab 200 mg Q3W. In cohort 2, approximately 20 non-Asian and 20 Asian treatment-naïve, HER2– pts with PD-L1–positive tumors will receive pembrolizumab 200 mg Q3W. In all cohorts, pembrolizumab will be given for 24 mo or until disease progression, intolerable toxicity, or investigator decision; treatment may be discontinued for complete response. Eligible pts may continue pembrolizumab beyond initial RECIST response. PD-L1 staining will be performed at wk 9 and every 6 wk thereafter per RECIST v1.1 and RECIST adapted to account for response patterns observed with immunotherapies. Primary end point is ORR per RECIST v1.1 by central review; secondary end points include PFS, OS, disease control rate, and duration of response. KEYNOTE-059 enrollment began in February 2015. Clinical trial information: NCT02335411.

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Adjuvant chemotherapy with gemcitabine and cisplatin compared to IV paclitaxel in PFS. With 10% of drop-out rate, target rate of 2.5%, 204 events are required to observe non-inferiority of DHP107 with a power of 80% and one-sided type I error of 0.025. The trial is ongoing and the progress is presenting here.

Methods: Since April 2013, patients with metastatic or recurrent gastric cancer in second-line setting have been enrolled. Patients are randomized as 1:1 in open label to Arm A (DHP107) vs Arm B (IV paclitaxel). Arm A regimen consists of 200mg/m² po bid on day 1, 8, 15, every 4 weeks. In arm B, paclitaxel 175mg/m² was infused on day 1, every 3 weeks. Key inclusion criteria are ECOG performance status ≤ 2, failure of first-line chemotherapy including fluoropyrimidine and/or platinum, at least 1 measurable lesion by RECIST version 1.1. Response evaluation is performed every 6 (±1) weeks. Primary endpoint is progression free survival (PFS). Secondary endpoints include overall response rate, overall survival and safety. With power of 80% and one-sided type I error rate of 0.025, 204 events are required to observe non-inferiority of DHP107 compared with IV paclitaxel in PFS. With 10% of drop-out rate, target enrolment is 238 subjects from 12 sites in Korea. For the efficacy analysis, test for non-inferiority will be performed sequentially, first with non-inferiority margin of 1.48, and then 1.25. Clinical trial information: NCT01839773.

**Conclusion:** The BRIGHTER trial is a phase III randomized double-blind study of BB1608 vs IV paclitaxel in pretreated advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma. First Author: Marish A. Shaha, Weill Cornell Medical College, New York, NY

Background: BB1608 is an orally administered first-in-class cancer stemness inhibitor. By targeting Stat3, β-catenin as well as immune checkpoint gene expression. Potent anti-tumor and anti-metastatic activity was observed in preclinical models, with marked synergy between BB1608 and paclitaxel. Moreover, cancer stemness genes, such as Stat3 and β-catenin, two poor prognostic biomarkers in many cancer types, predict sensitivity to BB1608. Encouraging anticancer activity in refractory gastric and GEJ adenocarcinoma was observed in a phase Ib (Stephenson et al, ASCO 2014 abstr) and a subsequent phase II study including 39 gastric or GEJ adenocarcinoma pts. On the basis of these data, a phase III trial is being conducted in North America, South America, Europe, Australia, and Asia. Methods: This study (ClinicalTrials.gov NCT02178956) will assess the efficacy of BB1608 vs paclitaxel vs PBO in pts with pre-treated, advanced gastric and GEJ adenocarcinoma (target n = 680). Pts must have failed one prior line of therapy containing a fluoropyrimidine/platinum doublet for unresectable disease. Pts are randomized in a 1:1 ratio to receive BB1608 480 mg or PBO twice daily continuously plus paclitaxel 80 mg/m² IV, weekly, for 3 of every 4 weeks. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is overall survival (OS) in the general study population; secondary endpoints include progression free survival (PFS), OS and PFS in a predefined biomarker (µ-ctatin)-positive sub-population, objective response rate, disease control rate, and safety. In addition, blood, plasma, and archival tissue will be assessed for pharmacokinetic and biomarker analyses and quality of life will be measured. As of January 2015, 28 pts were randomized and recruitment is ongoing. Clinical trial information: NCT02178956.
SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer

Background: No standard treatment options are available for patients with advanced biliary cancer (BC) who fail gemcitabine/platinum based regimens. The most commonly used second line regimens are 5-fluorouracil (5-FU) with leucovorin (LV), or capecitabine based on limited data. Trametinib is an orally bioavailable, potent, and specific allosteric inhibitor of MEK1/2. In cell lines, increased sensitivity to trametinib was observed especially in cells with mutations in the MAPK pathway. Aberrant activation of the Ras/Raf/MAPK pathway occurs in more than 60% of BC indicating the importance of these pathways. Furthermore other MEK inhibitors have been studied in advanced BC demonstrating promising results including complete responses (Bekkai-Saab et al. JCO 2012, Finn RS Gastro Oncology 2011). Methods: An open label phase II trial was designed to randomly assign patients to receive trametinib (2.0mg daily) versus 5-FU (400 mg/m² bolus and 2400 mg/m² infusion over 48 hours) with LV (400 mg/m²) every 2 weeks or capecitabine (1000 mg/m² BID 14 days on 7 days off) in refractory BC. Eligible patients must have histologically or cytologically documented BC (excluding ampullary cancer) following progression of first line chemotherapy. The primary endpoint is overall survival. Secondary endpoints include progression-free survival and overall response rate. Additional endpoints will assess a 16 gene expression signature as a biomarker of MEK efficacy and to measure inflammatory cytokines. MRI or CT scan will also be obtained for all patients at the time of study entry and at 6 weeks into treatment to estimate lean soft tissue and fat mass weight gain according to treatment with trametinib. Analysis will compare randomized groups, stratified by SFLU/LV versus capecitabine and cholangiocarcinoma versus gall bladder. Assuming a one-sided type 1 error of 10%, 80% power, and 2 years of accrual with an additional year of follow-up, approximately 80 eligible patients (40 per arm) are needed to detect an improvement in median OS from 5 months to 8.25 months (corresponding to a 1.65 hazard ratio). As of Jan 2015, 33 of the planned 89 patients have been randomized. Clinical trial information: NCT02044243.

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**JANUS 2: A phase III study of survival, tumor response, and symptom management in patients with advanced or metastatic pancreatic cancer (mPC) after failure or intolerance of first-line chemotherapy.**

**First Author:** Eileen Mary O’Reilly, David M. Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** The systemic inflammatory response characteristic of PC is mediated in part by JAK-STAT signaling and may contribute to local tumor growth and disease-related weight loss, decreased muscle mass, and poor performance status. In this phase II, randomized, double-blind RECAP study, the combination of the JAK1/JAK2 inhibitor ruxolitinib with capcitabine improved overall survival (OS) versus placebo + capcitabine in patients with mPC and elevated C-reactive protein (CRP) levels or a modified Glasgow Prognostic Score (mGPS) of 1 or 2 (Hurwitz et al. J Clin Oncol. 32:5s, 2014 [suppl; abstr 4000]). Methods: JANUS 2 is a phase III, randomized, double-blind, multicenter study. Eligible patients are ≥ 18 years of age and have histologically or cytologically confirmed pancreatic ductal adenocarcinoma, advanced or inoperable or metastatic disease; ECOG performance status of 0–2; only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy); no concurrent anticancer therapy; and an mGPS of 1 (CRP > 10 mg/L and albumin ≥ 35 g/L) or 2 (CRP > 10 mg/L and albumin < 35 g/L). Exclusion criteria are prior severe reaction to fluoropyrimidines, dihydroxy nimide dehydrogenase deficiency, or other sensitivity to 5-fluorouracil. Patients are randomized 1:1 to receive 21-day cycles of capcitabine 2000 mg/m²/d (days 1–14) + ruxolitinib 15 mg twice-daily or capcitabine 2000 mg/m²/d + placebo twice-daily. The primary endpoint is OS; secondary endpoints include progression-free survival, tumor response per RECIST 1.1, and duration of response. An exploratory endpoint is the assessment of change from baseline in PC symptoms using the Pancreatic Cancer Symptom Assessment Form electronic diary. Treatment will continue as long as it is tolerated and discontinuation criteria are not met. Patients who discontinue treatment will be followed for subsequent anticancer treatments and survival. Enrollment began in April 2014 and is ongoing. The planned enrollment is 270 patients. Clinical trial information: NCT02119663.

**JANUS 3: A phase III, placebo-controlled study of ruxolitinib plus capcitabine in patients with advanced or metastatic pancreatic cancer (mPC) after failure or intolerance of first-line chemotherapy.**

**First Author:** Herbert Hurwitz, Duke University Medical Center, Durham, NC

**Background:** The systemic inflammatory response observed in PC is a negative prognostic factor and is mediated in part by JAK-STAT signaling. Treatment with the JAK1/JAK2 inhibitor ruxolitinib in combination with capcitabine was previously investigated as second-line therapy for patients with mPC and evidence of a systemic inflammatory response (elevated C-reactive protein [CRP] levels or a modified Glasgow Prognostic Score [mGPS] of 1 or 2) in the phase 2, randomized, double-blind RECAP study. Results showed improved overall survival (OS) relative to placebo + capcitabine (Hurwitz et al. J Clin Oncol. 32:5s, 2014 [suppl; abstr 4000]). Ruxolitinib has US Food and Drug Administration orphan drug status for the treatment of PC. Methods: JANUS 3 is a phase 3, international, multicenter, randomized, double-blind study. Eligible patients are ≥ 18 years of age with histologically or cytologically confirmed pancreatic adenocarcinoma that is advanced and inoperable or metastatic; have an ECOG performance status of 0–2; have received 1 prior chemotherapy regimen for advanced or metastatic PC not including neoadjuvant and/or adjuvant therapy; and have an mGPS of 1 (CRP > 10 mg/L and albumin ≥ 35 g/L) or 2 (CRP > 10 mg/L and albumin < 35 g/L). Patients are excluded for > 1 prior chemotherapy regimen for advanced or metastatic disease; radiation therapy; concurrent anticancer therapy; or prior severe reaction to fluoropyrimidines, dihydroxy nimide dehydrogenase deficiency, or other sensitivity to 5-fluorouracil. Patients are randomized 1:1 to receive 21-day cycles of capcitabine 2000 mg/m²/d (days 1–14) + ruxolitinib 15 mg twice-daily or capcitabine 2000 mg/m²/d + placebo twice-daily. The primary endpoint is OS. Secondary endpoints include progression-free survival, tumor response per RECIST 1.1, and duration of response. Treatment will continue as long as it is tolerated and discontinuation criteria are not met. Patients who discontinue treatment will be followed for subsequent anticancer treatments and survival. Enrollment was initiated in March 2014 and is ongoing. The planned enrollment is 310 patients. Clinical trial information: NCT02119749.

**JANUS 1: A phase 3, placebo-controlled study of ruxolitinib plus capcitabine in patients with advanced or metastatic pancreatic cancer (mPC) after failure or intolerance of first-line chemotherapy.**

**First Author:** Hedy Lee Kindler, University of Chicago, Chicago, IL

**Background:** A heterologous prime-boost vaccination strategy using GVAX pancreatic vaccine and CRS-207 is showing promise in patients with mPC and elevated C-reactive protein (CRP) levels or a mGPS of 1 or 2 (Le, JCO 2015). Furthermore, blockade of the immune checkpoint programmed death-1 (PD-1) is active in some pancreatic cancers. Combimetric strategies aimed at priming tumor antigen-specific adaptive immunity by activating T cells and NK cells. Nivolumab is an engineered to express the tumor-associated antigen mesothelin and is unique in its capacity to stimulate both innate and adaptive immunity. CRS-207 boosts responses against attenuated Listeria monocytogenes engineered to express the tumor-associated antigen mesothelin. CRS-207 boosts responses against mesothelin and is unique in its capacity to stimulate both innate and adaptive immunity by activating T cells and NK cells. Nivolumab is an antibody against PD-1. Methods: This is a phase 2 study comparing CY/GVAX and CRS-207 with or without nivolumab in subjects with PDA who failed only one chemotherapy regimen for metastatic disease. Subjects are randomized in a 1:1 ratio to receive either 2 doses of CY/nivolumab/GVAX and 4 doses of nivolumab/CRS-207 (Arm A) or 2 doses of CY/GVAX and 4 doses of CRS-207 (Arm B). The primary objective is to compare OS between Arms A and B. Secondary/exploratory objectives include: assessment of safety and clinical responses (tumor assessments and CA19-9 levels) and correlation of Lm- and mesothelin-specific T cell and other immunological responses with OS, progression-free survival and best overall response. Clinical trial information: NCT02243371. Clinical trial information: NCT02243371.

**JANUS 2: A phase III study of survival, efficacy, and immune response of GVAX pancreatic vaccine (with cyclophosphamide) and CRS-207 with or without nivolumab in patients with previously treated metastatic pancreatic adenocarcinoma (STELLAR).**

**First Author:** Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

**Background:** A heterologous prime-boost vaccination strategy using GVAX pancreatic vaccine and CRS-207 is showing promise in patients with metastatic pancreatic cancer (mPC) and a germline BRCA1/2 mutation (gBRCAm) who have not progressed following first-line chemotherapy. Methods: Eligible mPC patients must have documented disease control after completing at least 16 weeks of a first-line platinum-based regimen and must have a known or suspected deleterious gBRCAm, which will be confirmed by Integrated BRACAnalysis (Myriad Genetic Laboratories) during the trial. Patients are randomized (3:2) to olaparib (300 mg orally bid) or placebo. The primary endpoint is PFS, determined by blinded independent central review using RECIST 1.1. Disease will be assessed by CT scans at baseline, every 8 weeks for 40 weeks and every 12 weeks thereafter. Patients will receive treatment until objective disease progression unless toxicity is unacceptable. The primary PFS analysis will be performed after ~89 PFS events (~60% maturity) using a log-rank test. Secondary endpoints include OS, time from randomization to second progression (PFS2), HRQoL, safety and tolerability. Enrollment began in Q4 2014. The target number for randomization is ~145 patients across ~80 centers worldwide. Clinical trial information: NCT02184195.

**JANUS 1: A phase III trial of olaparib tablets in patients with metastatic pancreatic cancer (mPC) and a germline BRCA1/2 mutation (gBRCAm) who have not progressed following first-line chemotherapy.**

**First Author:** Hedy Lee Kindler, University of Chicago, Chicago, IL

**Background:** Germline mutations in BRCA1/2 define a molecular subgroup of PC that in some populations has a prevalence as high as 15%. gBRCAm-defective tumors are intrinsically sensitive to platinum and PARP inhibitors. In a Phase II trial (NCT01078662), 23 previously-treated gBRCAm mPC patients received the PARP inhibitor olaparib (Lynparza) as monotherapy. The tumor response rate was 22%, progression-free survival (PFS) was 4.6 months and overall survival (OS) was 9.8 months (Kaufman, JCO 2014). These data led to a double-blind, placebo-controlled Phase III trial (NCT02184195; POLO) of olaparib ‘switch maintenance’ monotherapy in patients with gBRCAm-associated mPC who have not progressed on first-line platinum chemotherapy. Methods: Eligible mPC patients must have documented disease control after completing at least 16 weeks of a first-line platinum-based regimen and must have a known or suspected deleterious gBRCAm, which will be confirmed by Integrated BRACAnalysis (Myriad Genetic Laboratories) during the trial. Patients are randomized (3:2) to olaparib (300 mg orally bid) or placebo. The primary endpoint is PFS, determined by blinded independent central review using RECIST 1.1. Disease will be assessed by CT scans at baseline, every 8 weeks for 40 weeks and every 12 weeks thereafter. Patients will receive treatment until objective disease progression unless toxicity is unacceptable. The primary PFS analysis will be performed after ~89 PFS events (~60% maturity) using a log-rank test. Secondary endpoints include OS, time from randomization to second progression (PFS2), HRQoL, safety and tolerability. Enrollment began in Q4 2014. The target number for randomization is ~145 patients across ~80 centers worldwide. Clinical trial information: NCT02184195.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma (mRCC): Association of biomarkers with clinical outcomes. First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA

Background: This prospective biomarker study in patients (pts) with mRCC treated with the programmed death-1 (PD-1) inhibitor antibody nivolumab assessed baseline (BL) and changes in serum chemokines, tumor T cell infiltrates (TIL), gene expression, T cell repertoire (TCR), and other biomarkers potentially associated with clinical outcomes (NCT01358721). Methods: Pts treated with 1–3 prior therapies received nivolumab 0.3, 2, or 10 mg/kg IV Q3W; treatment-naïve pts received 10 mg/kg IV Q3W. Biopsies were obtained at BL and cycle 2 day 8. Overall survival (OS) parameters were assessed by Kaplan-Meier method. Tumor PD-L1 expression was measured by immunohistochemistry (28-8 antibody; Dako). PD-L1 positivity was defined as ≥1% tumor membrane staining in ≥1 biopsy; tumor burden response as ≥20% reduction. Gene expression data were obtained on Affymetrix U219. Results: 91 pts were treated. Of 56 evaluable BL biopsies, 32% were PD-L1+ Median OS (95% CI) was 16.4 mo (10.1–not reached) for NR; for 0.3 mg/kg, 25.2 mo (12.0–NR) for 10 mg/kg, and NR for treatment-naïve pts. 1-yr and 2-yr OS rates (95% CI) were 75% (64–83) and 58% (46–68), respectively. OS by PD-L1 status is summarized (table). Pts with tumor burden response (n = 13) had ≥ 1.3-fold differential BL expression of 311 genes (P < 0.01, false discovery rate < 16%). Cell-mediated immune transcripts were elevated, including effector cell markers GZMB, NKG7, and CD7, NK/CD8-activating ligand MICB, inflammasome component AIM2, and activated macrophage marker IL-1α. Analysis of association between OS and serum chemokine levels, TCR and TIL is ongoing. Conclusions: Association of immune markers at BL with subsequent tumor burden response suggests that infiltrating immune-activating cells may mediate response to nivolumab in mRCC pts. Consistent with the randomized phase II study of nivolumab in mRCC, OS appears longer in PD-L1+ pts but promising in both PD-L1+ and PD-L1- pts, especially when treatment-naïve. Clinical trial information: NCT01358721.

Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012. First Author: Elizabeth R. Plimack, Director, Genitourinary Clinical Research Fox Chase Cancer Center, Philadelphia, PA

Background: Pembrolizumab, an anti–PD-1 antibody, demonstrated antitumor activity and acceptable safety in patients with recurrent or metastatic PD-L1–positive urothelial cancer enrolled in the phase 1b KEYNOTE-012 study (NCT01848834). We present updated efficacy and safety data for these patients, as well as an analysis of the relationship between PD-L1 expression and efficacy of chemotherapy. This trial was designed to evaluate efficacy and safety of a combination of gemcitabine and cisplatin (GC) in patients (pts) with advanced BC. Methods: Chemotherapy naïve pts with advanced BC were randomized to GC+A 600 mg combined with pembrolizumab 100 mg every 3 weeks (GC+A). Pts with visceral mets had ORRs of ≥32% (GC+A). Prospective sub-groups were retrospectively evaluated using multiple variable modeling and hierarchical step down. A post hoc analysis was performed to explore the hypothesis that Hsp27 inhibition might be relevant to OS in poor prognosis treated with GC. Results: A total of 179 pts were randomized/treated. Median OS was 15.2 months (m). When compared to GC + placebo, GC+A was 65% efficacy-stratified survival (OS HR = 0.50; GC+A 1 PRs vs GC 0.50). Pts with poor prognosis treated with GC+A had a greater survival benefit (HR = 0.717) than pts with good prognosis (HR = 1.44). The most significant prognostic factor was PFS ≤ 80% (35% pts in GC+A 600 vs GC) resulting in HR = 0.50 in favor of GC+A 600. Overall survival was well tolerated. Most common Grade ≥ 3 adverse events (AEs) were neutropenia, anemia, thrombocytopenia and hypertension. Frequency of ≥ 3 Grade toxicities were: 89% (GC), 93% (GC+A 600) and 95% (GC+A 1000). GC+A 1000 had a higher treatment discontinuation rate due to AEs. Conclusions: Advanced BC pts with poor prognosis benefited from apoterson 600mg combined with first line GC. Apoterson may be impacting the intrinsic biology of patients with poor risk factors. Further evaluation is warranted in this pt population. Clinical trial information: NCT01454089.

A phase Ia study of MPDL3280A (anti-PD-L1): Updated response and survival data in urothelial bladder cancer (UBC). First Author: Daniel Peter Petri, Yale Cancer Center, New Haven, CT

Background: PD-L1 may contribute to immune escape in UBC, a disease of high mutational complexity and immunogenicity. MPDL3280A was designed to restore T cell-mediated antitumor activity by blocking PD-L1 binding to PD-1 and B7.1 receptors. Methods: Previously treated, metastatic UBC pts were enrolled in an expansion cohort and received 15 mg/kg or 1200 mg IV MPDL3280A qw3. Efficacy-evaluable pts had ≥ 12 wk of follow-up closed by Sep 9, 2014; Sep 2, 2014 cutoff. ORR was assessed by RECIST v1.1 (unconfirmed), and archival biopsies were centrally evaluated for PD-L1 tumor-infiltrating immune cell (IC) expression by IHC. In-tumor gene expression and peripheral biomarkers were assessed as exploratory analyses in a subset of pts. Results: Updated analyses include 81 efficacy-evaluable, 66 treatment-naïve pts treated with 10 mg/kg IV MPDL3280A qw3. Median age was 66 y (36–89 y), and 75% were male. Baseline visceral mets were present in 77% of pts; 98% received ≥1 prior therapy (eg platinum in 93%). The ORR for IHC 2/3 pts was 46% (95% CI 31–61%; 6 Cs, 15 PRs), and for IHC 0/1 pts was 16% (95% CI 6–31%; 6 Pts) with median response durations not yet reached (IHC 2/3 pts, 0+ to 54+ wk; IHC 0/1 pts, 4+ to 33+ wk). Median PFS was 24 wk (95% CI 12–NE) for IHC 2/3 pts and 8 wk (95% CI 6–12 wk) for IHC 0/1 pts. 24-wk OS rates for IHC 2/3 and 0/1 pts were 85% (95% CI 74–96%) and 71% (95% CI 54–88%), respectively, with the medians not yet reached (3 to 72+ wk and 2+ to 51+ wk, respectively). Pts with visceral mets had ORRs of 32% (IHC 2/3: 3 Cs, 7 Pts; n = 31) and 12% (IHC 0/1: 4 PRs; n = 33). Median safety follow-up was 16 wk (3–73 wk). Drug-related AEs occurred in 64% of 87 safety-evaluable pts (most often fatigue, asthenia, nausea); 8% had a related Grade 3–4 AE. 12% of pts had an immune-related AE. No related deaths occurred. Baseline mets were present in 60% of pts but promising in both PD-L1+ and IHC 0/1 UBC pts vs historical controls. Response also correlated with in-tumor and blood-based biomarkers. Clinical trial information: NCT01375842.
4504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Erribulin in advanced urothelial cancer (AUC) patients (pts): A California Cancer Consortium trial—NCI/CTEP 7435. First Author: David I. Quinn, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: There is an unmet need for new agents in AUC. We previously reported that eribulin, a microtubule modulator derived from black Pacific sea sponge toxin, is highly active against metastatic UC in frontline and previously treated settings (ASCO/ECO 2013). Here we report composite results of 150 AUC pts treated in a single phase II trial. Methods: Eligible pts with AUC, calculated CrCl > 20 mL/min were treated in 3 cohorts of first line, 2nd line or without tubulin exposure. Erribulin 1.4mg/m² IV on days 1, 8, q3 ws. In each cohort RR > 20% considered promising; 41 pts in a Simon 2-stage design, PFS & OS vs. second line endpoints. Results: Pts characteristics: Median age 68 yrs (range: 25-90); Males: 71%; KPS ≥ 90%; 57% transition cell histology; 90%; Lower tract 88%, Visceral mets 67%, Bajorin risk groups: 0: 30%, 1: 61%, 2: 2% Bajorin risk group, visceral mets - associated with OS & PFS (p < 0.01) while renal age, line of therapy & prior tubulin exposure did not. Toxicities included Gr3/4 neutropenia: 57%, FN; 4%; Gr3/4 Alt/Creat: 13%, 24%. Gr3/4 sensory neuropathy: 45%. Age > 70 associated with Gr3/4 neuropenia, no factors including tubulin exposure predicted neuropathy, developing any Gr3+ toxicity associated with age > 70 & KPS. Conclusions: Erribulin exceeded the prespecified benchmark in all strata with highly encouraging single agent activity in AUC. Phase III evaluation of eribulin in AUC is warranted. (NCT00365157; U11 CA186717; U01 CA062505; P30 CA014089; P30 CA033572). Clinical trial information: NCT00365157.

4505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

A phase II/III, double-blind, randomized trial comparing maintenance lapatinib versus placebo after first line chemotherapy in HER1/2 positive metastatic bladder cancer patients. First Author: Thomas Powies, Bates Cancer Institute, Bates Health and the Royal Free NHS Trust, London, United Kingdom

Background: First-line chemotherapy for metastatic transitional cell carcinoma (TCC) is associated with clinical benefit. Further therapies are largely ineffective. The purpose of this trial was to establish if maintenance lapatinib after first-line chemotherapy was associated with clinical benefit in HER1/HER2 positive patients. Methods: Patients with urothelial carcinoma, were screened for their HER1/HER2 status by centralised immunohistochemistry (IHC). HER1/2 positive patients with advanced/metastatic TCC who achieved clinical benefit after completing first-line chemotherapy (4-8 cycles) were potentially eligible for randomisation (1:1). The primary endpoint was to compare progression free survival (PFS). Secondary endpoints included adverse events (AE), overall survival (OS) and subset analysis for HER status. Results: Between 2007-2013, 455 patients were screened and 232 HER 1 or 2 positive patients were randomised to lapatinib (L) (n = 116) or placebo (P) (n = 116). 71.2% had visceral metastasis. 64.1% received cisplatin based chemotherapy. The median number of chemotherapy cycles was 6. The progression free survival for L and P was 4.6 months (95% CI: 2.8 - 5.4) and 5.3 months (95% CI: 3.0 - 5.9) respectively (HR: 1.04 (95% CI: 0.79 – 1.39) p = 0.77). The overall survival for L and P was 12.6 months (95% CI: 9.5 – 16.2) and 11.9 months (95% CI: 10.6 – 15.8) respectively (HR = 0.98 (95% CI: 0.71 – 1.35) p = 0.89). The best response rate for L and P was 13.8% vs 7.8% (p = 0.14). The rate of grade 3-4 AE’s for L and P was 24.3% vs. 15.5% (p = 0.09). Subset analysis of i) HER1/HER2 3+ positive patients on IHC ii) HER1 positive patients iii) HER2 positive patients showed no significant benefit in L (L: HR 0.94, p = 0.70; and L: 1.19 respectively; p > 0.05 for each) or OS (HR 0.76, 0.92 and 1.03 respectively; p > 0.05 for each) for lapatinib. A model predicting outcomes was constructed. Conclusion: This is the first personalised randomised trial in metastatic TCC. It shows maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals. Clinical trial information: NCT00949455.

4506 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN + EVE in patients (pts) with metastatic renal cell carcinoma (mRCC). First Author: Robert Motzer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lenvatinib (LEN), an oral tyrosine kinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, in combination with EVE had manageable toxicity and antitumor activity in a phase 1 mRCC trial (CCP2013;78:1). This phase 2 trial assessed the safety and antitumor activity of lenvatinib (LEN), everolimus (EVE), and LEN + EVE in pts with mRCC. Methods: Pts with progressive clear cell mRCC following 1 VEGF-targeted therapy were randomized 1:1:1 to LEN (24 mg/d), EVE (10 mg/d), or LEN + EVE. The primary endpoint was progression-free survival (PFS) of LEN + EVE or LEN vs EVE. Secondary objectives included overall survival (OS), objective response rate (ORR), and safety. Primary analysis was conducted at 1 year. One hundred and fifty-three pts were enrolled: 99% had one prior VEGF-targeted therapy, 1% had two, 18% had prior immunotherapy. LEN + EVE prolonged PFS vs EVE (Table; Table: Median OS (mo, 95% CI): 24, 40; HR (80% CI): 2.8, 6.4; P = 0.09). Subset analysis of i) HER1/HER2 3+ positive patients on IHC ii) HER1 positive patients iii) HER2 positive patients showed no significant benefit in PFS (HER1: HR 0.94, p = 0.70; and L: 1.19 respectively; p > 0.05 for each) or OS (HR 0.76, 0.92 and 1.03 respectively; p > 0.05 for each) for lapatinib. A model predicting outcomes was constructed. Conclusion: This is the first personalised randomised trial in metastatic TCC. It shows maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals. Clinical trial information: NCT00949455.

4507 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Final clinical results of a randomized phase II international trial of everolimus vs. sunitinib in patients with metastatic non-clear cell renal cell carcinoma (ASPEREN). First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC

Background: Limited evidence exists to guide therapeutic decisions in patients (pts) with metastatic non-clear cell RCC (NC-RCC). Methods: ASPEN was an international, randomized trial of pts with metastatic papillary, chromophobe, or unclassified histology who had exhausted all or no prior systemic therapy. Pts were randomized 1:1 to either everolimus (E) or sunitinib (S) until progression, stratified by histology and risk group. The primary endpoint was radiographic PFS by Independent Review Committee (IRC). Secondary endpoints included OS, incidence of AEs, and Subset Analysis of pts with metastatic transitional cell carcinoma (TCC) is associated with clinical benefit. Further therapies are largely ineffective. The purpose of this trial was to establish if maintenance lapatinib after first-line chemotherapy was associated with clinical benefit in HER1/HER2 positive patients. Methods: Patients with urothelial carcinoma, were screened for their HER1/HER2 status by centralised immunohistochemistry (IHC). HER1/2 positive patients with advanced/metastatic TCC who achieved clinical benefit after completing first-line chemotherapy (4-8 cycles) were potentially eligible for randomisation (1:1). The primary endpoint was to compare progression free survival (PFS). Secondary endpoints included adverse events (AE), overall survival (OS) and subset analysis for HER status. Results: Between 2007-2013, 455 patients were screened and 232 HER 1 or 2 positive patients were randomised to lapatinib (L) (n = 116) or placebo (P) (n = 116). 71.2% had visceral metastasis. 64.1% received cisplatin based chemotherapy. The median number of chemotherapy cycles was 6. The progression free survival for L and P was 4.6 months (95% CI: 2.8 - 5.4) and 5.3 months (95% CI: 3.0 - 5.9) respectively (HR: 1.04 (95% CI: 0.79 – 1.39) p = 0.77). The overall survival for L and P was 12.6 months (95% CI: 9.5 – 16.2) and 11.9 months (95% CI: 10.6 – 15.8) respectively (HR = 0.98 (95% CI: 0.71 – 1.35) p = 0.89). The best response rate for L and P was 13.8% vs 7.8% (p = 0.14). The rate of grade 3-4 AE’s for L and P was 24.3% vs. 15.5% (p = 0.09). Subset analysis of i) HER1/HER2 3+ positive patients on IHC ii) HER1 positive patients iii) HER2 positive patients showed no significant benefit in PFS (HER1: HR 0.94, p = 0.70; and L: 1.19 respectively; p > 0.05 for each) or OS (HR 0.76, 0.92 and 1.03 respectively; p > 0.05 for each) for lapatinib. A model predicting outcomes was constructed. Conclusion: This is the first personalised randomised trial in metastatic TCC. It shows maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals. Clinical trial information: NCT00949455.

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A total of 371 patients were enrolled. The median follow-up time was 16 months. The overall 2-year event-free survival rate was 52%. The median progression-free survival time was 6 months. The 2-year overall survival rate was 62%. The median overall survival time was 30 months. The 2-year disease-specific survival rate was 93%. The median disease-specific survival time was 36 months.

Methods: We used Cox proportional hazards regression analysis to determine the hazard ratio (HR) and 95% confidence interval (CI) for each factor. The multivariate analysis included the following clinicopathological factors: age, gender, tumor grade, tumor stage, and tumor size. The multivariate analysis was adjusted for age, gender, tumor grade, tumor stage, and tumor size.

Conclusions: The results of our study indicate that the presence of tumor-intrinsic PD-1/PD-L1 expression is an important factor in predicting survival in patients with NSCLC. Our findings suggest that targeting PD-1/PD-L1 inNSCLC may improve outcomes for these patients. Further studies are needed to confirm these results and to explore the potential clinical utility of PD-1/PD-L1-targeted therapies inNSCLC.

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Association of p53-ness with chemoresistance in urothelial cancers treated with neoadjuvant gemcitabine plus cisplatin. First Author: Roland Seiler, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

Background: Recent genomic analyses demonstrated that muscle-invasive bladder cancers can be grouped into intrinsic basal and luminal subtypes. Within the luminal subtype, tumors with "p53-like" gene expression were resistant to neoadjuvant chemotherapy (NAC) with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). We investigated the response of these subtypes to gemcitabine plus cisplatin (GC), the other major frontline NAC regimen in this disease setting. Methods: Fifty-two bladder cancer patients received neoadjuvant GC followed by cystectomy. At diagnosis 44 (85%) and 36 (62%) patients had extravesical disease and T1-3a, or T1-3b, or any T4 tumors and were clinically node-negative, respectively. At cystectomy, 37 (71%) patients did not respond to NAC (ypT ≥ 2 or any ypN1-3). RNA was isolated from pre-NAC transurethral resection (TUR) specimens and post-NAC cystectomy specimens using the RNeasy FFPE kit (Qiagen), amplified with the Ovation WTA FFPE system (NuGen) and hybridized to GeneChip Human Exon 1.0 ST microarrays (Affymetrix). A one nearest neighbor (oneNN) prediction model was used with the RNA normalized gene expression values to assign the tumors to intrinsic subtypes. Results: Unsupervised hierarchical clustering separated the tumors into clusters characterized by non-overlapping expression of basal and luminal markers. Assignment of pretreatment TUR tumors to subtypes yielded the expected ratios of basal, p53-like, and luminal tumors. Rates of pathologically down staging (< ypT2), disease specific survival (pH11005/H11350 0.007), with a trend towards improved OS (pH11005/H11349 0.013), were 82% male, had median age 62 y (47-74); 47% were ECOG PS 0. This test remained predictive for pT1N0M0 of the total number of mutations. Allele-specific SCNA analysis revealed significant inter and intra-patient heterogeneity in the 9p21 region. Conclusions: This study generates a detailed molecular profile of the genomic landscape of PRUC revealing extensive heterogeneity and clonal selection underlying evolution of platinum-resistance and metastatic spread.

Phase Ib/II study of an IL-2/T-cell receptor fusion protein in combination with gemcitabine and cisplatin in advanced or metastatic chemo-refractory urothelial cancer (UC). First Author: Mayer N. Fishman, Moffitt Cancer Center, Tampa, FL

Background: Although UC is sensitive to platinum-based chemotherapy such as gemcitabine (G) + cisplatin (C), patients who are refractory to G/C have limited therapeutic options. ALT-801 is an IL-2/7-Single-chain T-cell receptor fusion protein previously tested in various murine models. ALT-801 demonstrated potent activity against syngeneic and xenograft UC, suggesting sensitivity of this disease to IL-2 based immunotherapy. Methods: We report efficacy and safety results of co-administration of G (1000 mg/m²/dose, d 1 & 8) + C (70 mg/m²/dose, d 1) with ALT-801 (0.06 mg/kg ALT-801 G q2w EMA approved). G is the final dose of the 17; group 2, n = 17). They were 82% male, had median age 62 y (47-74); 47% were ECOG PS 1, and 76% had visceral metastases (primarily to the lung). Favorable response pathways including complete response (CR) were seen in both groups 1 and 2 with an overall response rate of 35% (95% CI: 20 - 54%) (3 CR, 9 PR, 6 SD, 12 PD, 4 non-evaluable). Median OS was 12.3 months for group 1; the group 2 median OS was 4.8 months (95% CI: 1.7 - 19.3). Conclusions: This study represents a detailed molecular profile of the genomic landscape of PRUC revealing extensive heterogeneity and clonal selection underlying evolution of platinum-resistance and metastatic spread.

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4516 Poster Discussion Session: Displayed in Poster Session (Board #186), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). First Author: Hans J. Hammers, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Nivolumab (N), a fully human IgG4 immune checkpoint inhibitor antibody, has shown durable response and overall survival (OS) in mRCC. Previously in CheckMate 016, N + ipilimumab (I) demonstrated manageable safety and promising antitumor activity in mRCC. Here, we report results from expansion cohorts in this study (NCCTN1472081).

Methods: Patients (pts) were randomized to N3 3 mg/kg (N3 I1) or N 1 mg/kg + I 1 mg/kg (N1 I3). N 1 mg/kg + I 3 mg/kg (N1 I3) or N 3 mg/kg + I 3 mg/kg (N3 I3) IV Q3W for 4 doses followed by N 3 mg/kg until progression; Primary endpoints: safety. Other endpoints: objective response rate (ORR), duration of response (DOR), OS, DOR and OS were assessed by Kaplan-Meier method. Results: Pts randomized to N3 + I1 and N1 + I3 cohorts were expanded to 473 pts per arm; N3 + I3 (n = 46) arm showed early toxicity and did not proceed to expansion. 53% and 47% of pts were treatment naive and previously treated in N3 + I3; 45% and 55% were in N3 + I3. Median (range) follow-up was 34.3 (15.4 - 80.1) wks in N3 + I3 and 31.3 (4.6 – 79.9) wks in N1 I3. Treatment-related AE’s were seen in 88% of pts. Discontinuations for any grade AE occurred in 16% of pts. Grade 3-4 treatment-related AEs occurred in 34% and 64% of pts in N3 + I1 and N1 + I3, respectively; most common: ↑ lipase (13% and 26%), ↑ ALT (4% and 19%), diarrhea (2% and 15%), colitis (0% and 1%), ↑ AST (4% and 9%), and ↑ amylase (4% and 9%). Most common grade 3-4 select AEs were GI and hepatic (N3 + I1; N1 + I3); GI: 2%; 23%; hepatic: 4%; 21%. Efficacy is summarized in the table below. Conclusions: Updated results from expanded cohorts in CheckMate 016 confirm initial safety findings and promising antitumor activity for N + I in pts with mRCC. OS results for N + I in mRCC appear encouraging and support further development of this combination in the first-line setting. Clinical trial information: NCCTN1472081.

<table>
<thead>
<tr>
<th>N3 + I3</th>
<th>n = 46</th>
<th>N1 + I3</th>
<th>n = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, mos (range)</td>
<td>13.5 (9.4 – 19.3)</td>
<td>17.2 (13.5 – 30.1)</td>
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<tr>
<td>Overall ORR, %</td>
<td>43 (95% CI: 31% - 56%)</td>
<td>34 (95% CI: 24% - 45%)</td>
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<tr>
<td>Stable disease, %</td>
<td>54 (95% CI: 43% - 65%)</td>
<td>42 (95% CI: 30% - 55%)</td>
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<tr>
<td>Median DOR, wks (range)</td>
<td>4.4 (2.4 – 13.3)</td>
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<tr>
<td>Median PFS, wks (range)</td>
<td>12.5 (7.5 – 18.6)</td>
<td>11.7 (7.5 – 16.4)</td>
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<tr>
<td>PFS, 24 wks, % (95% CI)</td>
<td>49 (95% CI: 36% - 62%)</td>
<td>52 (95% CI: 39% - 64%)</td>
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*Confirmed response + unconfirmed response; **Confirmed response. NR, not reached.

4518 Poster Discussion Session: Displayed in Poster Session (Board #188), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

RECORD-4: A multicenter, phase II trial of second-line everolimus (EVE) in patients (pts) with metastatic renal cell carcinoma (mRCC). First Author: Robert Motzer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In the pivotal RECORD-1 trial, EVE was superior to placebo in pts with mRCC previously treated with sunitinib, sorafenib, or both; prior treatment with cytotoxic chemotherapies, bevacizumab, and radiotherapy (Cancer 116:4258).

Methods: RECORD-4 study assessed EVE in pts with mRCC who progressed after 1 prior anti-VEGF or cytotoxic. Methods: RECORD-4 enrolled pts with clear cell mRCC into 3 cohorts based on prior first-line therapy: sunitinib, other anti-VEGF, or cytokines. Pts received EVE 10 mg/d until progression of disease or any grade 3/4 toxicity. Other endpoints: objectives response rate (ORR), duration of response (DOR), OS, DOR and OS were assessed by Kaplan-Meier method. Results: Pts randomized to N3 + I1 and N1 + I3 were expanded to 473 pts per arm; N3 + I3 (n = 46) arm showed early toxicity and did not proceed to expansion. 53% and 47% of pts were treatment naive and previously treated in N3 + I3; 45% and 55% were in N3 + I3. Median (range) follow-up was 34.3 (15.4 - 80.1) wks in N3 + I3 and 31.3 (4.6 – 79.9) wks in N1 I3. Treatment-related AE’s were seen in 88% of pts. Discontinuations for any grade AE occurred in 16% of pts. Grade 3-4 treatment-related AEs occurred in 34% and 64% of pts in N3 + I1 and N1 + I3, respectively; most common: ↑ lipase (13% and 26%), ↑ ALT (4% and 19%), diarrhea (2% and 15%), colitis (0% and 1%), ↑ AST (4% and 9%), and ↑ amylase (4% and 9%). Most common grade 3-4 select AEs were GI and hepatic (N3 + I1; N1 + I3); GI: 2%; 23%; hepatic: 4%; 21%. Efficacy is summarized in the table below. Conclusions: Updated results from expanded cohorts in CheckMate 016 confirm initial safety findings and promising antitumor activity for N + I in pts with mRCC. OS results for N + I in mRCC appear encouraging and support further development of this combination in the first-line setting. Clinical trial information: NCCTN1472081.

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4519 Poster Discussion Session: Displayed in Poster Session (Board #189), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Activating genomic mutations in the mTOR pathway to predict responses to everolimus and temsirolimus in patients with metastatic renal cell carcinoma (mRCC): Results from a large multi-institutional cohort. First Author: Andrea Papi Fay, Oncology Service and Oncology Research Unit, HSL/PUCRS, Porto Alegre, Brazil

Background: Mammalian target of rapamycin (mTOR) inhibitors are approved in mRCC but only a subset of patients derives clinical benefit. Recently, case reports have suggested that mutations in mTOR pathway genes might be associated with response to everolimus and temsirolimus in several malignancies, including mRCC. Methods: We amassed a large international cohort of mRCC patients with available tumor specimens who received mTOR inhibitors and had distinct clinical outcomes: responders were defined as complete response (CR), partial response (PR) or stable disease with any tumor shrinkage or no tumor growth for at least 6 months (R); non-responders were defined as disease progression within the first 3 months of therapy (NR). Tumor DNA from 94 patients was analyzed using a targeted next-generation sequencing panel covering 504 cancer genes. We performed a blinded analysis to investigate the correlation between mutations in mTOR pathway genes and response status. Results: Samples from 79 of 94 patients were successfully sequenced and were included in the analysis. Mutations are summarized in Table 1. Mutations in MTOR, TSC1 or TSC2 were more common in R (12/43) than NR (4/36) (OR: 3.05; p < 0.05; secondary hypothesis). Similarly, mutations in TSC1 or TSC2 were more common in NR (9/43) than NR (2/36) (OR: 4.42; p = 0.05; secondary hypothesis). In an exploratory analysis, 5/12 with PR/CNR had mutations in MTOR, TSC1 or TSC2 vs 4/35 NR (OR: 5.28; p = 0.04). Conclusions: In this large cohort of mRCC patients, mutations in MTOR, TSC1 or TSC2 were more common in patients with clinical benefit from everolimus or temsirolimus than in NR. Mutations in those 3 genes were associated with responses to mTOR inhibitors. In contrast, neither PTEN nor PIK3CA mutations showed any association with response. These findings suggest that a personalized medicine approach has value for selection of mTOR inhibitors in mRCC.

**Table 1.**

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>NR (n = 36)</th>
<th>R (n = 43)</th>
<th>Total (n = 79)</th>
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<tr>
<td>MTOR(activating)</td>
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<tr>
<td>PTEN(activating)</td>
<td>(5/14)</td>
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<td>(10/13)</td>
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<tr>
<td>TSC1(activating)</td>
<td>(2/6)</td>
<td>(3/7)</td>
<td>(5/6)</td>
</tr>
<tr>
<td>TSC2(activating)</td>
<td>0</td>
<td>(1/2)</td>
<td>(1)</td>
</tr>
<tr>
<td>PIK3CA(activating)</td>
<td>0</td>
<td>(1/2)</td>
<td>(1)</td>
</tr>
</tbody>
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4520 Poster Discussion Session; Displayed in Poster Session (Board #190), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Comprehensive genomic profiling of 443 patients with advanced renal cell carcinoma (RCC) to reveal clinically relevant genomic alterations and to aid in classification of rare subtypes. First Author: Sumanta Kumar Pal, City of Hope, Duarte, CA

Background: Large scale genomic sequencing studies in RCC (e.g., TCGA) have classically focused on localized disease, which is often curable. Advanced RCC represents a unique disease setting in which novel therapeutic targets may have a clinical impact. Methods: CGP for genomic alterations (GAs) was performed prospectively in 443 consecutive patients with advanced RCC (relapsed RCC or metastatic RCC at presentation). DNA was extracted from 40 microns of FFPE sections. CGP was performed on hybridization-captured, adapter ligated based libraries to a mean coverage depth of X48 for 3,230 exons of cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer (Frampton et al, Nat Biotechnol 2013). The CGP assay included base substitutions, INDELs, copy number alterations and fusions/rearrangements. Clinically relevant genomic alterations (CRGAs) were defined as alterations for which a selective inhibitor of the target or pathway is available. Results: There were 73% male and 27% female patients with a mean age of 56 years. 198 (44.6%) of the sequenced RCC cases were derived from metastatic sites. 400 patients (89%) had at least 1 GA with a mean 3.1 GAcase. Of the 400 RCC harboring GA, 396 (99%) had at least 1 CRGA involving 111 different genes with a mean of 1.32 CRGAs/RCC case. The most common CRGA in order of frequency were: ATM (11%), PTPN11 (5.8%), TSC1 (3.3%), PTEN (6.5%), AR (5.3%), DMRT14 (6.5%) and TSC2 (5%). Other GAs such the ones with prognostic value in RCC included (7%), the correlation: NCT01399918.

Conclusions: CGP can uncover a wide variety of CRGAs in advanced RCC with the criterion of SMARCB1 medullary carcinoma (RMC). Multiple CDC cases harbored BAP1 mutations: NCT01399918. Other GAs such the ones with prognostic value in RCC included (7%), the correlation: NCT01399918. Other GAs such the ones with prognostic value in RCC included (7%), the correlation: NCT01399918.

4522 Poster Discussion Session; Displayed in Poster Session (Board #192), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase II trial of everolimus (E) and bevacizumab (B) in advanced non-clear cell renal cell cancer (ncRCC) to show efficacy in patients (pts) with papillary renal cell carcinoma (pRCC). First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY

Background: VEGF- and mTOR-directed therapies achieve inferior outcomes in pts with advanced ncRCC compared to clear cell RCC. Limited benefit from monoclonal supports the need for combination regimens. The primary endpoint of a phase II trial of E + B in pts with metastatic ncRCC. Methods: Treatment-naive pts received concurrently E + B at standard doses until disease progression or intolerance to therapy. The primary endpoint was 6 month (mo) progression-free survival (PFS) with a planned sample size of 34 pts. Correlative analyses included targeted gene sequencing (NGS) from tumor and germline across 341 genes of interest. Results: 34 pts are evaluable (median follow-up 13.6 mo). The most common histologic subtype was unclassified RCC (URC, n=23), the majority of which had papillary growth as a major component (7 of 18 pts) or chromophobe (2 of 5 pts) elements. Presence of a major papillary component was associated with treatment benefit across the entire cohort (Table), particularly in pts with URC, where this feature correlated with ORR (43% vs. 11%), median progress-free survival (PFS) vs. 19.3 mo) (logrank p < 0.001). NGS, performed on 33 cases, provides insight into the molecular background of disease phenotypes (e.g. frequent loss of chromosome 7q/p53) or mutations, a splice variant or a kinase domain and predicted to be constitutively activated were also identified. We further defined MET alterations as either a MET mutation, a splice variant or a MET-fusion. These alterations were mutually exclusive but tended to co-occur with CNAs (p < 0.001), MET expression by RNA-seq was significantly elevated compared to the cohort (p < 0.001) when the alteration co-occurred with chromosome 7 gain. The MET-altered tumors exhibited a common phenotype associated with lower grade (p < 0.001), lower stage (p < 0.001), and better overall survival (log-rank p < 0.001) relative to all other pRCC. MET alterations were exclusive of all other pRCC, and their impact within the TCGA KIRP dataset. Conclusions: Overall, at least 17% of pRCC tumors included in the TCGA KIRP dataset present a MET alteration and display a common phenotype. A new splice variant is identified and may constitute a mechanism of ligand-independent MET activation. This report provides a survey of the diverse mechanisms of activation of the MET receptor. Ongoing preclinical and clinical exploration of pRCC will hopefully help characterize the functional relevance of each proposed mechanism of activation involving MET in pRCC. Funded in part by FNLCR Contract HHSN26120080001E.

4523 Poster Discussion Session; Displayed in Poster Session (Board #193), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

SWOG 1107: Parallel (randomized) phase II evaluation of tivantinib (ARQ-197) and tivantinib in combination with erlotinib in patients (Pts) with papillary renal cell carcinoma (pRCC). First Author: Przemyslaw Twardowski, City of Hope, Duarte, CA

Background: pRCC is associated with activation of MET signaling pathway and less favorable responses to VEGF inhibition than clear cell RCC. In SWOG 0317, the EGFR inhibitor erlotinib yielded a response rate (RR) of 11% and median overall survival (OS) of 27 months in pRCC pts. Tivantinib is an ATP-competitive inhibitor of MET. In a preclinical pRCC model, combination erlotinib and tivantinib showed synergistic activity. A randomized multicenter phase II trial of tivantinib alone or with erlotinib was conducted in pts with either type I or II pRCC. Methods: Pts with histologically-confirmed advanced or metastatic pRCC and 0-1 prior systemic therapy were randomly assigned to tivantinib 360 mg BID (Arm 1) or tivantinib 360 mg BID plus erlotinib 150 mg daily (Arm 2). A RR of 30% was to be considered a promising outcome. Target accrual was 70 pts (35 per arm) with interim analysis planned after enrolment of 40 pts. Robust accrual resulted in 56 pts registered by the time of interim closure. Results: Of 55 pts enrolled, 50 were eligible: 25 in each arm. Median age was 64 years; most pts were male (68%). 33 pts (66%) had no prior systemic therapy; 6% of pts had type I pRCC, 42% had type II, and 52% had no subtype assigned. The study was permanently closed at interim analysis where both Arm RR and OS were lower than planned. Median PFS was 2.0 and 5.4 months, and OS was 10.3 and 11.3 months in Arms 1 and 2 respectively. Most frequent adverse events: Arm 1-fatigue, nausea and anemia; Arm 2-rash, nausea, fatigue and diarrhea. Deep exome sequencing of archival tumor specimens is ongoing. Conclusions: Tivantinib - monotherapy or in combination with erlotinib has no clinical activity in pts with advanced pRCC. The addition of tivantinib to erlotinib may have reduced the latter’s previously reported efficacy (although wide confidence intervals preclude a definite conclusion); this was not predicted by preclinical modeling. Although MET remains a reasonable therapeutic target in pRCC, more careful credentialing of proposed MET inhibitors, biomarkers, and patient subsets most likely to benefit would be required. (NIH/NCI NCTN CA180887;CA180819;CA180820). Clinical trial information: NCT01688973.
4524 Poster Session (Board #194), Mon, 1:15 PM-4:45 PM

Adjuvant chemotherapy for residual disease after neoadjuvant chemotherapy for muscle invasive urothelial cancer (MIUC). First Author: Lauren Christine Hashim, Dana-Farber Cancer Institute, Boston, MA

Background: Neoadjuvant cisplatin-based chemotherapy (Neo) improves outcomes in MIUC. However, the benefit achieved with Neo correlates with pathologic downstaging and patients with residual disease (RD) remain at high risk for metastatic recurrence. The optimal management of such patients is unknown. We evaluated whether adjuvant chemotherapy (Adj) improves time to recurrence (TTR) in pts with RD after Neo. Methods: Data were captured from 23 sites participating in the Retrospective International Study of Cancers of the Urothelium (RISC). Pts with RD after Neo for UC were captured from 23 sites participating in the Retrospective International Study of Cancers of the Urothelium (RISC). Pts with RD after Neo for UC were identified. Median (med) TTR was estimated by Kaplan-Meier method from 2 mo post-surgery to minimize lead time bias in non-Adj pts. The association between Adj and TTR was assessed using a multivariate Cox regression model. Results: From 1/1999 to 4/2013, 185 pts were identified who had RD despite Neo and had adequate follow-up time for data on Adj. Med follow-up time was 30 mo. 25 pts received Adj while 160 proceeded with surveillance. Both groups had similar performance status and med age at time of Neo. Med time to Adj was 1.5 mo. The majority changed regimens between Neo and Adj. Gemcitabine/cisplatin and dose dense MVAC were the most common regimens used in either setting. Use of Adj significantly correlated with higher path stage (p < 0.002). Median TTR was 17 mo with 95/185 experiencing relapse. After adjusting for path stage, type of Neo and age, Adj pts had a significantly decreased risk of relapse (HR = 0.35, 95% CI: 0.17,0.74). A subset analysis (Adj = 19, surveillance = 50) of pts with residual pathologic T4 and/or N+ after Neo also revealed a significant improvement with Adj: median TTR of 20 mo versus 9 mo, p = 0.02 (HR = 0.43, 95% CI: 0.21,0.89). Conclusions: In this international series, the use of Adj chemo for RD after Neo was rare. While limited by small numbers and the potential selection bias inherent to retrospective analyses, Adj may delay recurrence in pts with residual ptT4 or N+ disease despite Neo. Overall survival analysis will be presented.

4525 Poster Session (Board #195), Mon, 1:15 PM-4:45 PM

JEVTC: Phase II trial of cabazitaxel (Cbz) in patients (pt) with advanced or metastatic transitional-cell carcinoma (mTCC), who progressed before 12 months after cisplatin-based chemotherapy—A Spanish Oncologic Genito-Urinary Group (SOUGU) study. First Author: Jose Angel Arranz Arija, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: Treatment of mTCC progressing to cisplatin is an unmet need. Prognostic factors (PF) for worse overall survival (OS) are ECOG >0, Hb <10 g/dL, and liver metastases (Bellmunt, JCO 2010). Taxane-resistant patients in mUC, Cbz, a semi-synthetic taxane, is a poor substrate for the multidrug resistance system. Methods: Phase II study of Cbz 25 mg/m2/w until progression, death or unacceptable toxicity, in each of 3 subgroups of mTCC. Very good, good or poor prognosis (VGP, GP, PP), defined by 0, 1 or > 1 of the above PF respectively. Primary endpoint of response rate ≥ 20% (RR, RECIST 1.1), required 35 pt in each group. Multinomial response and early progressions method (MREP, α = 0.05, β = 0.2), and 2-stage Simon’s optimal design (SOD, α0 = 10%, m0 = 30%, α0 = 0.05, β = 0.1), were used for early stopping rules in an interim analysis and a final analysis in each group, and follow-up of each pt respectively. Secondary endpoints: PFS, OS, and toxicity. Recruitment was not stopped until IA were available. Results: 71 pt were included (ITT population), 59 eligible and evaluable: 16/21 VGP, 28/34 GP, 15/16 PP. Mean age 65 ± 8, 85% male, 94% ECOG 0-1, 77% bladder mTCC. Metastatic sites: 69% lymph nodes, 41% lung, 32% bone, 24% liver, 30% others. Toxicity is described in a separate abstract. Response (R), stable disease (SD), progression (PD), % RR, PFS and OS (months, with CI 95%) are summarized in the table below. Conclusions: In the IA, a RR ≥20% of Cbz after cisplatin in mTCC could be excluded in all prognostic subgroups, and the study was stopped. However, PFS and OS seem to be similar to those obtained with other active drugs in 2nd-line mTCC. EUDRACT 20111003498-27. Funding: Sanofi. Clinical trial information: 20111003498-27.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Bladder cancer (BC) is one of the most common malignancies of the urinary tract and is 4th most common cancer among men. It is estimated that by the end of 2015, the US will have approximately 74,000 new BC cases, accounting for 16,000 cancer related deaths. Smoking is considered an important risk factor for BC; recent data demonstrate an increase in BC incidence in non-smokers as well. Molecular characterization of BC in non-smokers has not been well studied. To our knowledge, no retrospective or prospective study examining the correlation between smoking status (smokers vs non-smokers) and specific genetic alterations in BC has been published to date. Methods: 676 consecutive BC profiled at a CLIA certified laboratory were evaluated for differences in molecular characterization between smokers and non-smokers. Smoking status, patient characteristics, age, sex and survival data were collected on a subgroup; compilation of etiology is ongoing for additional patients. Results: 30 patients were confirmed lifetime nonsmokers (NS) and 39 were confirmed smokers or reformed smokers (R/S). Identified trends included differences in the PI3 kinase, WNT and EGFR pathways. Percentage of PIK3CA mutations was higher in NS (43%) vs. R/S (11%), whereas the WNT pathway aberration (CTNNB1 and APC mutations) occurred more frequently in R/S. EGFR amplification occurred in 22% NS and 11% in R/S, while HER2 was amplified only in R/S (23% vs. 0%, p = 0.05). Additionally, 3 of 8 R/S had an ALK 2p23 rearrangement, found in ~5% non-smoking lung malignancies. TP53 did not differ between the populations. Survival data for 31 patients (14 NS, 17 R/S) showed overall average survival in the NS cohort was 175 days longer than in the R/S cohort. Conclusions: The difference in molecular biology between R/S and NS with BC suggests a different oncogenesis with potentially different treatment options. Increased incidence of PIK3CA mutations in NS may inform therapeutic options in this select group of BC patients with no smoking history. The results will need further verification in a larger group of BC patients in a prospective clinical study; more studies also need to be conducted to identify other mutational abnormalities between smokers vs. lifetime non-smokers.

Role of miR-21, miR372, and E2F1 as biomarkers predicting outcome in cisplatin-treated bladder cancer patients. First Author: Chensheng Willa Zhou, Dana-Farber Cancer Institute, Boston, MA

Background: Cisplatin based chemotherapy is the gold standard for first line metastatic/localized advanced urothelial carcinoma (aUC). Variant expression of selected miRNAs and transcription factors (TF) are shown to correlate with and predict cisplatin efficacy in many types of cancers. In this study we aimed to confirm the role of selected miRNAs and TFs in patients receiving first line cisplatin combination therapy in aUC Methods: 82 clinically annotated patients with aUC (including N1 resected patients), with available tumor tissue, were identified, and total RNA was extracted from FFPE specimen. MicroRNA (miR21, miR106b, miR10b, miR142a, miR146b, miR371, miR372, miR373, miR1224, miR1248, miR200c, Let7i, miR27b, and miR262b) and TF panels (RELA, SMAD4, FOXO3, E2F1 and TWIST1) were identified using in silico data mining based on their roles in UC or in cisplatin response. Time to progression (TTP) was defined as time from chemotherapy start date to date of progression or censored on the last known without progression. For the TTP analysis, median miRNA expression levels were dichotomized and a cox regression model was used. For the extreme TTf phenotype, correlations were assessed by Wilcoxon’s test (P < 0.05). Multivariate analysis was performed for all miRNAs, adjusting for ECOG status and visceral disease. Results: The median TTP time was 12 mo, with 43 patients experiencing disease progression. In the TTP multivariate analysis, increased levels of E2F1 (p = 0.02, HR:0.49, (0.27, 0.90)), miR372 (p = 0.03, HR:0.53, (0.29, 0.97)) and miR21 (p = 0.02, HR:0.49, (0.26, 0.90), were associated with a shorter TTP. For the extreme phenotype, only miR21 and E2F1 were shown to be associated with TTP (p = 0.035). Conclusions: In this retrospective cohort of patients treated with cisplatin based therapy, higher levels of E2F1, miR21, and miR372 correlated with a shorter TTP. Biological validation of cisplatin effect on 6 bladder cancer cell lines that express different miR21 levels, from Cancer Cell Line Encyclopaedia, is ongoing and results will be presented.
4532 Poster Session (Board #204), Mon, 1:15 PM-4:45 PM
Association of somatic mutations in DNA damage repair (DDR) genes with efficacy of platinum-based chemotherapy in advanced urothelial carcinoma. First Author: Richard Martin Bambury, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Platinum-based chemotherapy (PBC) is standard of care in the neoadjuvant and metastatic UC settings. Recent work identified mutations in ERCC2, RB1, FANCC and ATM as potential predictive biomarkers of response. We assessed response to PBC among patients with locally advanced or metastatic UC who underwent pre-treatment tumor genomic sequencing. Methods: 72 patients treated with PBC had exon sequencing of >200 tumor suppressor/oncogenes using the MSK-IMPACT next generation sequencing (NGS) panel. Deletions, truncations, frameshift, splice-site and missense alterations were recorded among 33 genes involved in the nucleotide excision repair, homologous repair and Fanconi anemia pathways (Table). Inactivating alterations in RB1 and TP53 were also investigated as potential predictive biomarkers. Baseline clinical parameters, investigator-assessed radiologic response and PFS were recorded. Results: 31(43%) patients had alterations in DDR genes and these were associated with improved PFS (median 11.3 v 6.1 months, HR 0.51, p=0.01) Among 65 evaluable patients, radiologic response was observed in 81% of those with DDR gene alterations vs. 58% in those without (p=0.06). DDR alterations remained a significant predictor for PFS on multivariate analysis (HR 0.45, 0.004) after adjusting for ECOG performance status, visceral vs nodal metastases, chemotherapy type (cisplatin vs carboplatin) and prior perioperative cisplatin. Among 9 patients with deletion, truncation, frameshift or splice-site alterations of DDR genes, 8 achieved PFS >11 months. There was no association between FBS and TP53 (HR 1.37, p=0.32) or TP53 (HR 0.93, p=0.79) alterations. Conclusions: Alteration of DDR genes is associated with improved efficacy in patients receiving 1st line PBC for advanced UC. Further analysis and validation could lead to prospective identification of patients who will respond to PBC, as well as identify patients unlikely to benefit and for whom alternative approaches are warranted.

4533 Poster Session (Board #206), Mon, 1:15 PM-4:45 PM
Germ cell cancer and multiple relapses: Toxicity and survival. First Author: Jakob Lauritsen, Rigshospitalet, Copenhagen, Denmark

Background: A small fraction of patients with germ-cell cancer (GCC) receive more than one line of systemic treatment. The aim of this study was to evaluate late-toxicity and survival in an unselected cohort of patients who relapsed after initial systemic treatment for disseminated disease. Methods: Based on the Danish DaTeCa database we identified all patients who received two or more lines of systemic treatment. Information on late-effects and mortality in GCC-survivors was obtained through linkage to national registers. Prognostic factors for relapse and death were identified and compared to the International Prognostic Factors Study Group (IPFSG). Results: In total, 268 patients received two or more lines of systemic treatment for disseminated GCC. Approximately half of the patients died of their disease (n=136). The surviving patients (n=132) had highly increased risk of death of other causes hazard ratio (HR): 2.5 (95% CI: 1.6-4.1), second cancer HR: 3.4 (2.0-5.7), major cardiovascular disease HR: 1.9 (1.0-3.3), pulmonary disease HR: 2.4 (1.3-4.4), gastrointestinal disease HR: 7.1 (3.5-14.3), renal impairment HR: 9.2 (3.4-26.5), and neurological disorders HR: 5.4 (2.7-10.8) compared to patients treated with orchietomy only. We found a dose-response relationship with increasing number of treatment lines within most toxicities. The IPFSG-classification was confirmed in our population; however, we could not confirm primary site and nCG as independent factors. We identified increasing age as a possible new prognostic factor for treatment failure, hazard ratio (HR): 1.2 (1-2.5) per 10 years. Conclusions: GCC-survivors after second-line systemic treatment have a highly increased risk of severe late-toxicity and death, and should be candidates for life-long follow-up. The IPFSG-classification was confirmed in this unselected population.

4534 Poster Session (Board #207), Mon, 1:15 PM-4:45 PM
Wilms’ tumor gene 1 (WT1) aberrations in testicular germ cell tumors (TGCTs). First Author: Ludmila Bobulikova, Department of Pediatric Hematology and Oncology, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

Background: Wilms’ tumor gene 1 (WT1) is a transcription factor essential for normal development of the urogenital system and male gonadal formation. Its alterations have been found in Wilms’ tumor, other malignancies and testicular dysgenesis syndromes. We studied WT1 aberrations to address its role in the pathogenesis of testicular germ cell tumors (TGCT). Methods: In fresh-frozen samples of 95 TGCT (48 seminomas, 48 non-seminomas), 3 stromal tumors and 88 non-neoplastic controls, expression of total WT1 and its four main isoforms was quantified by qPCR. WT1 mutations were detected by direct and next-generation sequencing (NGS). The presence of WT1 protein was evaluated by standard immunohistochemistry. Results: The total WT1 expression was significantly lower (1 log) in TGCT than in the controls and stromal tumors (Kruskal-Wallis p < 0.0001), and was lower in seminomas than non-seminomas. Testicular tissue surrounding TGCT and containing in situ lesions expressed similar WT1 levels like other controls. WT1 isoforms lacking the exon S (EXS-I) isoforms A and C) were highly overexpressed in TGCT and stromal tumors in comparison with controls (Kruskal-Wallis, p < 0.0001). The isoform D, containing both main splice sites, was down-regulated in the tumors and this altered expression pattern was independent of total WT1 expression. Direct sequential of exon 7 and 9 (with clustered hot-spots) could identify only 2 types of SNPs – synonymous rs16754 (31% of TGCT) and intronic rs5030274 (2%). By NGS however, 1–3 mutations in WT1 newly occurring in TGCT cells. Staining for WT1 protein was positive in controls and was lower in seminomas than non-seminomas, and was undetectable in TGCT cells. The finding of total WT1 down-regulation in TGCT with the difference between seminomas and non-seminomas, the alteration of the isoform pattern with a pronounced shift to (EXS-) variants in TGCT independent of total WT1 levels, and the new occurrence of WT1 mutations in a high proportion of TGCT samples support the role of WT1 as a local tumor-suppressor gene in testicular tissue. Supported by grants IGA NT/12414-5, GAUK66413, UNCE204012 and CDO00064203FNM

4535 Poster Session (Board #208), Mon, 1:15 PM-4:45 PM
Impact of response to induction chemotherapy (CT) and prior paclitaxel (TXL)-based CT on the outcome of salvage high-dose chemotherapy (HDCT) for relapsed germ-cell tumors (GCT) in the modern era: An EBMT Solid Tumors Working Party study. First Author: Andrea Necchi, Istituto Nazionale Tumori di Milano, Milano, MI, Italy

Background: The prognostic impact of response to induction CT preceding salvage HDCT courses, and prior TXL-therapy for advanced GCT is unknown. This knowledge can inform trial design, stratification and eligibility criteria to HDCT. Methods: 23 European centers contributed data. Eligibility included adult male patients (pts) with GCT, and treatment with salvage HDCT between the years 2002 and 2012. Both TXL used in prior CT lines of therapy and in induction-mobilization regimens pre-HDCT were considered. Multivariable Cox analyses (MVA) evaluated the association of prespecified factors (prior TXL therapy, line of HDCT, primary site, pathology category, response to induction CT and chemosensitivity with progression-free (PFS) and overall survival (OS)). Results: Since 10/2013, 324 of 442 registered pts were suitable for present analysis. 165 pts (51%) received HDCT in second-line, 102 (31%) in third and 57 (18%) beyond the third-line. 76 (23%) HDCT regimens were taxane-containing. 192 pts (59.3%) have received prior TXL-regimens. 61 pts (19%) had a progression (PD) to induction CT, 234 (72%) a response (29 (9%) missing or GCSF only). Median follow up was 36 months (IQR: 19-70). PD to induction CT and prior TXL were significantly associated with shorter OS in the univariable model (p < 0.001 and p = 0.032). However, on MVA while PD to induction CT was a poor independent predictor, TXL use was associated with improved OS (HR: 0.95, 1.24-2.98, p = 0.003, and HR: 2.09, 95%CI: 1.27-4.42, p = 0.003), prior TXL-therapy was not: HR: 1.10 (95%CI, 0.70-1.73, p = 0.674) and HR: 1.09 (95%CI, 0.64-1.86, p = 0.739). Also, line of HDCT was not significant (p = 0.338 and p = 0.340 for PFS and OS). A separate model evaluated the interaction between prior TXL-therapy and taxane-containing HDCT: no significant interaction was found (p = 0.221 and p = 0.077 for PFS and OS). Conclusions: While PD to induction CT was independently prognostic for PFS and OS, prior TXL-regimens did not affect the outcome of HDCT. Stratification of trials for the latter factor did not appear to be required when accounting for the other clinical predictors.
4538 Poster Session (Board #211), Mon, 1:15 PM-4:45 PM
Perioperative morbidity and mortality with bleomycin in primary mediastinal non-seminomatous germ cell tumor (PMNSGCT).
First Author: Praveen Ranganath, Indiana University School of Medicine, Indianapolis, IN
Background: PMNSGCT represents one of the most challenging subsets of malignant germ cell tumors. PMNSGCT has a distinctly worse prognosis and is appropriately categorized as poor risk disease. A phase III intergroup study in patients with poor risk germ cell tumors, including PMNSGCT demonstrated equivalent survival in patients with Etoposide, Ifosfamide and Cisplatin (VIP) compared to standard Bleomycin, Etoposide and Cisplatin (BEP) regimen. For the mediastinal lesion (ATE) alone, the magnitude of post-chemotherapy surgery required for PMNSGCT is higher with potential for serious pulmonary complications including post operative pulmonary failure and death. This retrospective study from 1978-2013 compares perioperative morbidity and mortality associated with Bleomycin (BEP) vs. non-Bleomycin (VIP) containing regimens.
Methods: From 1978-2013, 221 PMNSGCT patients (mean age, 29 years; ranging from 12-50 years) who underwent post chemotherapy surgery were reviewed. Results: Of the 221 patients who underwent post chemotherapy surgery, 55 were treated with VIP and 166 with BEP chemotherapy. Among patients who received BEP, 83% had >3 cycles of Bleomycin. Both groups were well balanced in respect to the number of patients requiring pulmonary resection, extent of pulmonary resection and surgical approach. Post operative complications including acute respiratory failure and/or pneumonia (22 vs. 0, p value 0.004) and prolonged ventilator requirement > 48 hrs (30 vs. 2, p value 0.004) were significantly higher in patients who received BEP compared to VIP chemotherapy respectively. There were 11 post operative deaths reported- 10 patients with post operative respiratory failure and 1 death from pulmonary embolism. All deaths were in BEP chemotherapy group and 9 post operative deaths were reported in patients who received VIP chemotherapy (p value <0.005). The perioperative mortality associated chemotherapy regimens have traditionally been the standard of care for patients with poor-risk NSGCTs, including PMNSGCTs. Given the high rate of post-operative pulmonary failure after BEP, these results support our present policy of preferring VIP in PMNSGCT patients prior to major thoracic surgical procedures.

4539 Poster Session (Board #212), Mon, 1:15 PM-4:45 PM
A retrospective analysis of patients with metastatic germ cell tumor (GCT) treated at Indiana University (IU) from 2000 to 2012.
First Author: Kimberly Ku, Indiana University School of Medicine, Indianapolis, IN
Background: Metastatic GCT’s have been classified by the International Germ Cell Cancer Collaborative Group (IGCCCG) in 1997 into good, intermediate, and poor risk with 5-year progression-free survival (PFS) of 88, 75 and 41%, respectively. The comparison of 5-year PFS of 91% between the poor-risk and good-risk groups was similar, 93%. Among AS group, there was no significant difference between early and late relapse in 5-year PFS (91% vs 100%, p=0.1) or 10-year OS (96%, for both). Conclusions: In stage I seminoma, the extent and pattern of LR is similar to that for early relapse. For AS patients, selective use of RT/chemotherapy for relapse results in excellent outcomes regardless of time of relapse.

Explanatory covariates included in the Cox-Proportional Hazard Model for PFS and OS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>IGCCCG risk score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.41 1.40-4.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Poor</td>
<td>8.58 5.34-13.80</td>
<td>0.001</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-CT</td>
<td>3.13 1.42-6.89</td>
<td>0.006</td>
</tr>
<tr>
<td>On-CT</td>
<td>1.13 0.54-2.0</td>
<td>0.432</td>
</tr>
<tr>
<td>Post-CT</td>
<td>3.36 1.50-7.52</td>
<td>0.003</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>5.11 2.05-12.75</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Bleomycin-induced pulmonary changes on restaging CT scans: Frequency and correlation with fibrosis markers. First Author: Nico-Derk L. Westerink, University Medical Center Groningen, Groningen, Netherlands

Background: Bleomycin-induced pneumonitis (BIP) is a well-known, potentially fatal, side-effect in metastatic testicular cancer (mTC). We prospectively investigated I; prevalence of lesions suspect for bleomycin-induced pulmonary changes on restaging CT scans and II; which correlates of fibrosis markers. Transforming Growth Factor β1 (TGF-β1) and Growth Differentiation Factor 15 (GDF-15) were predictive for these radiological changes. Methods: mTC patients (pts), 18-50 years of age, treated with BEP (bleomycin, etoposide, cisplatin) chemotherapy were included from 2006 till 2012. Restaging CT scans were analyzed for bleomycin-induced pulmonary changes by 2 blinded radiologists and graded as minor, moderate or severe. Plasma samples were collected before, during and after chemotherapy and quantified for TGF-β1 and GDF-15. Results: 66 pts were included, 45 Pts (68%) showed signs of bleomycin-induced pulmonary changes. 37 pts were classified as minor and 8 as moderate. Treatment and disease characteristics did not differ between the groups. 3 Pts had clinical signs of BIP (for which bleomycin was halted). Although there was a vast induction of both TGF-β1 and GDF-15 plasma levels (table), this was not significant (p = 0.5) between pts with and without radiological signs of bleomycin-induced pulmonary changes. Conclusions: Bleomycin-induced pulmonary changes are very common after BEP chemotherapy for mTC. TGF-β1 and GDF-15 plasma levels before and during treatment were not different between pts with and without radiological signs of bleomycin-induced pulmonary changes and therefore not helpful as predictive markers.

Biomarker levels in relation to bleomycin-induced pulmonary changes on restaging CT scan.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Course</th>
<th>Day</th>
<th>Mean ± SEM</th>
<th>Median</th>
<th>Range</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β1</td>
<td>1</td>
<td>1</td>
<td>4788 ± 3499</td>
<td>5268</td>
<td>4002-13361</td>
<td>0.582</td>
</tr>
<tr>
<td>GDF-15</td>
<td>1</td>
<td>1</td>
<td>383 ± 1395</td>
<td>413</td>
<td>187-18767</td>
<td>0.397</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>5372 ± 1407</td>
<td>527</td>
<td>430-149407</td>
<td>0.878</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test. C = 4 weeks after last course.

Bevacizumab (Bev) alone or in combination with TRC101 for metastatic renal cell cancer (mRCC): A California Cancer Consortium clinical trial. First Author: Tanya B. Dorff, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Inhibition of vascular endothelial growth factor (VEGF) pathway is effective in mRCC, but resistance inevitably develops. CD105 (endoglin) is highly expressed on endothelial cells and has been shown in preclinical models to mediate resistance to VEGF pathway inhibitors, in part due to TGF-β signaling. TRC101 is a monoclonal antibody against CD105 which has shown to be tolerable in combination with Bev at full doses. Methods: Eligible mRCC patients (pts) with any histologic subtype may have received 1-4 prior systemic therapies including cytotoxines, VEGF, or mTOR agents. Bev was administered at 10 mg/kg IV on day 1 and 15 of 28-day cycles as a single agent (Arm A) or with TRC101 10 mg/kg IV on days 1, 8, 15, and 22 (Arm B). Primary end point was progression-free survival (PFS). A total of 88 pts were to be randomized to detect a halving of PFS with 80% power and 0.5) between arms, being 81% at 24 weeks for both arms. 44 patients had clear cell RCC and 15 had non-clear cell histology. One subject on each arm had a confirmed PR (3%) and 2 patients on each arm had stable disease lasting ≥ 9 cycles. For the 56 evaluable pts, the PFS (including early treatment termination as progression) at 12 weeks was 48% +/- 9% on Bev compared to 50% +/- 9% on Bev + TRC101. Survival did not differ significantly (p = 0.5) between arms, being 81% at 24 weeks for both arms. Grade > 3 toxicities were more common in Arm B and included anemia (8 vs 2 pts), electrolyte abnormalities (6 vs 2 pts), dyspnea (4 vs 2 pts), nausea/vomiting (4 vs 0 pts), hyperglycemia, hypotension, and infusion reaction (2 vs 0 pts); hemorrhage, hypertension, and proteinuria were more common in Arm A. Conclusions: TRC101 failed to prolong PFS when added to Bev. Further analysis will examine biomarkers of potential TRC101 benefit in this population, TRC101 is being studied in combination with VEGF receptor tyrosine kinase inhibitors in mRCC to determine whether there is an additive effect on PFS. Clinical trial: NCT01727089.
Cardiovascular toxicity following antiangiogenic therapy in persons over age 65 with advanced renal cell carcinoma. **First Author:** Sekwon Jang, **Institute:** Comprehensive Cancer Research Institute, Fairfax, VA

**Background:** Sunitinib and sorafenib are oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of patients with renal cell carcinoma (RCC) in 2005-2006. We conducted a population-based observational cohort study on the cardiovascular effects of VEGFR TKI therapy in elderly RCC patients. Methods: We analyzed patients with RCC diagnosed from 2000-2009 ages 66 and older using data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. We examined the incidence of cardiovascular adverse events through December 2010 including congestive heart failure and cardiomyopathy (CHF/CM), acute myocardial infarction (AMI), stroke, and cardiovascular deaths. We performed Cox-proportional hazard model to estimate the risk of these events associated with sunitinib or sorafenib adjusting for age, sex, comorbidity, and use of other systemic therapy.

**Results:** A total of 171 out of 670 patients who received either sunitinib or sorafenib had cardiovascular events. The incidence rates for CHF/CM, AMI, stroke, and cardiovascular death in those who received one of the two drugs were 0.87, 0.14, 0.14, and 0.05 per 1000 person-years, respectively. Sunitinib or sorafenib use was associated with an increased risk of stroke (adjusted HR = 2.72, 95% CI: 1.49-4.97) compared with those who initiated with sunitinib (62% vs 38%). Over half of treated mRCC patients in this study were found to be compliant compared with those who initiated with sunitinib (45% vs 30%) or sorafenib (46% vs nonrandomized arm); at least 75 censored patients were alive. Median OS (95% confidence interval (CI)) from first dose was 42.7 months (24.7-67.6) in the axitinib titration arm versus 30.4 months (23.7-45.0) in the placebo titration arm (HR 0.795; 95% CI 0.486-1.272; P = 0.161). Median OS (95% CI) in the nonrandomized arm was 41.6 months (33.0-NE). In all patients, median OS (95% CI) was 39.3 months (32.7-45.8). Safety data were consistent with previous reports. Follow-up treatment periods > 3.5 years, 9 (16%), 1 (2%), and 10 (1%) patients remain on treatment in axitinib titration, placebo titration, and nonrandomized arms, respectively.

**Conclusions:** Median OS exceeded 3 years in patients with mRCC treated with first-line axitinib. Median OS was numerically longer in patients receiving axitinib titration compared with placebo titration but did not reach statistical significance. A substantial percentage of patients remain on axitinib, and no new important safety signals were observed. Clinical trial information: NCT00835978.

**4546**

Analysis of real world treatment compliance in a cohort of 2,395 patients with metastatic renal cell carcinoma (mRCC). **First Author:** Jay Margolis, **Truven Health Analytics, Bala Cynwyd, PA**

**Background:** Given recent European data highlighting the importance of real world dose intensity, we sought to examine real world compliance in patients with mRCC from a US perspective (Cancer Med 2014; 3(6): 1517-26). Methods: In this retrospective cohort study, we used MarketScan Commercial and Medicare Supplemental administrative claims databases to select patients newly diagnosed with mRCC index event) during 1/1/2006 to 3/31/2014. First line therapy was defined by first prescription record post-index for any approved mRCC therapy and a change in line of therapy was defined by therapy switch. Compliance was measured using the medication possession ratio (MPR) during each and all lines of therapy. MPR was defined as total days of supply during the treatment period divided by the total treatment period until the start of the last treatment. Results: A total of 2,395 mRCC patients were identified as initiating 1L therapy. Across all treatments the mean MPR was 0.77 ± 0.20, which increased over time from 0.73 in 2006 to 0.81 in 2013. More than 50% of patients were noncompliant, defined as MPR < 80%. During 1L, patients treated with sunitinib had significantly lower mean MPR compared with most other treatments (table). Compliance was found to increase during 2L (0.85 ± 0.18) vs 1L (0.80 ± 0.19). A larger proportion of patients who initiated therapy with temsirolimus were compliant compared with those who initiated with sunitinib (62% vs 38%). Over half of treated mRCC patients in this study were found to be noncompliant with therapy. There were differences found between individual drugs. Compliance was significantly better with IV administered temsirolimus relative to the oral TKIs sunitinib and sorafenib. Real-world analysis of adherence behaviors provides information for clinicians in monitoring and optimizing targeted therapy.

**MPR in 1L and all lines.**

<table>
<thead>
<tr>
<th>Compliance</th>
<th>Sunitinib</th>
<th>Sorafenib</th>
<th>Pazopanib</th>
<th>Everolimus</th>
<th>Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L MPR, mean (SD)</td>
<td>0.76 (0.19)</td>
<td>0.84 (0.19)</td>
<td>0.86 (0.19)</td>
<td>0.89 (0.14)</td>
<td>0.83 (0.19)</td>
</tr>
<tr>
<td>All lines</td>
<td>0.74 (0.20)</td>
<td>0.78 (0.23)</td>
<td>0.84 (0.20)</td>
<td>0.76 (0.24)</td>
<td>0.81 (0.19)</td>
</tr>
</tbody>
</table>

* Reference group. In 1L, all differences were significant at P < 0.05.

**4547**

Randomized phase II study of sunitinib + CXCR4 inhibitor LY2510924 versus sunitinib alone in first-line treatment of patients with metastatic renal cell carcinoma. **First Author:** John D. Hainsworth, **Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN**

**Background:** Sunitinib is a standard first-line treatment for patients (pts) with metastatic renal cell carcinoma (RCC). CXCR4 and its only known ligand, SDF-1, are both overexpressed in tumor and vascular cells of clear cell RCC. LY2510924 is a selective peptide antagonist of CXCR4. We compared the results of open-label treatment with LY2510924 + sunitinib vs sunitinib alone. Methods: Previously untreated metastatic clear cell RCC pts were randomized (2:1) to receive standard-dose sunitinib (50 mg qd for 4 weeks [wk], then 2 wk off) + LY2510924 (20 mg sc, qd) (Arm A) or sunitinib alone (Arm B). Pts were evaluated (per RECIST v.1.1) every 8 wk. The primary analysis was done when all pts completed 72 wk of treatment, discontinued, progressed, or died and compared progression-free survival (PFS) between arms using a Bayesian time to event analysis incorporating prior information about sunitinib along with the trial data. PFS was also analyzed using the hazard ratio (HR) with only trial data. The Bayesian design was simulated to size the trial. The objective response rates (ORR) in each arm were compared using the chi-squared test. Results: 72 and 36 pts were treated in Arms A and B, respectively. Key pt characteristics (ECOG PS, Motzer risk score, prior nephrectomy) were similar in Arms A and B. Median number of cycles administered in each arm was 5. Median PFS was 8.1 and 12.3 months in Arms A and B, respectively (HR [95% CI]: 1.19 [0.69-2.00]) (Arm A). The ORR (95% CI) was 36% (95% CI 29.3-43.8) in Arm A and 38.9% (23.0-54.8) in Arm B. The most frequent (> 5% Arm A) grade 3/4 AEs (Arm A, Arm B) were hypertension (13.3%, 19.4%), fatigue (9.7%, 13.9%), diarrhea (6.9%, 16.7%), thrombocytopenia (8.3%, 5.6%), and anemia (8.3%, 2.8%). Of interest, there were more bleeding-related events (mostly grade 1 or 2) in Arm A than B (39%, 14%). More pts in Arm A discontinued treatment due to AE (18.1%, 8.3%). Two deaths in Arm A were due to adverse events (pulmonary edema/respiratory arrest and intracranial tumour hemorrhage). Conclusions: Adding the CXCR4 inhibitor LY2510924 to sunitinib as first-line treatment for metastatic RCC was tolerated but did not improve efficacy. Clinical trial information: NCT01391130.
**4548 Poster Session (Board #221), Mon, 1:15 PM-4:45 PM**

**CYP3A4 and ABCB1 polymorphisms as predictors for sunitinib outcome in metastatic renal cell carcinoma.**

*First Author: Meta Diekstra, Leiden University Medical Center, Department of Clinical Pharmacy and Toxicology, Leiden, Netherlands*

**Background:** In our exploratory studies we have associated single nucleotide polymorphisms (SNPs) in candidate genes with efficacy and toxicities of sunitinib in metastatic renal cell carcinoma (mRCC). The aim of the present study is to test these SNPs for association with sunitinib treatment outcome in the largest patient cohort to date. **Methods:** mRCC patients treated with sunitinib and a DNA sample available were pooled from 3 exploratory studies conducted in the US, Spain and the Netherlands. A total of 22 SNPs and 6 haplotypes in 10 candidate genes related to pharmacokinetics and pharmacodynamics of sunitinib were tested for associations with toxicity, dose reductions, progression-free survival (PFS), overall survival (OS) and best objective response. **Results:** Three-hundred and thirty-three patients were included. The presence of CYP3A4*1 I was associated with dose reductions (OR = 2.0, CI = 1.0-4.0, P = 0.039). Presence of C1G in the ABCB1 haplotype was associated with an increased PFS (HR = 1.9, CI = 1.3-2.6, P = 0.00027S) and remained significant after Bonferroni correction. These associations are consistent with prior observations. Similar size and direction of effect were observed for the association of VEGF rs1570360 with hypertension (OR = 1.9, CI = 0.8-4.5, P = 0.173) and FLT3 rs1933437 with leukenopia (OR = 3.6, CI = 0.8-16.7, P = 0.088). **Conclusions:** The confirmation of previously reported associations between polymorphisms in CYP3A4 and ABCB1 with sunitinib toxicity and efficacy respectively indicates that genotyping of these genetic variants may be useful for guiding sunitinib treatment.

**4549 Poster Session (Board #222), Mon, 1:15 PM-4:45 PM**

**Randomized phase II study of two different doses of AVE0005 (VEGF Trap, aflibercept) in patients (pts) with metastatic renal cell carcinoma (mRCC): An ECOG-ACＲIN study (E4805).**

*First Author: Roberto Pili, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** AVE0005 (VEGF Trap, aflibercept) is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human IgG1, that has potent anti-VEGF activity. We tested whether aflibercept has clinical activity in clear cell RCC. The randomized Phase 2 dose was 4 mg/kg but several pts treated at 1 mg/kg demonstrated prolonged progression-free survival (PFS). We therefore tested both doses in a parallel group randomized design. **Methods:** Eligible pts had metastatic clear cell RCC and previous treatments including prior exposure to a VEGF TKI. Pts were stratified on prior immunotherapy (IL2/IFN) and MSKCC Risk Category. Patients received aflibercept (either 1 mg/kg or 4 mg/kg) day 1 of a 14-day cycle until progression. Patients randomized to 1 mg/kg could crossover to 4 mg/kg at progression. The primary endpoint was proportion alive and progression-free at 8 weeks. A 2-stage design was used for each arm and 33 and 24 eligible pts/arm enrolled in stages 1 and 2. If 17 pts were alive and PF at 8 wks or an objective response was observed, an arm would continue to stage 2. If 34 of 57 eligible pts were PF at 8 wks, the arm would be considered for further study. This design had 91% power and 10% Type I error. **Results:** 94 pts were enrolled, 59 and 35 to 4 mg and 1 mg doses respectively. Median age was 61 with 72% male, 96% white, and 72% with 1 prior tx (most commonly sunitinib). 16 eligible pts crossed over at progression to the 4 mg dose. The most common adverse events were hypertension, proteinuria, and fatigue. Only 4 pts reported Grade 4 or higher toxicity. With 36/59 (61%) pts PF at 8 wks, the 4 mg/kg dose met protocol specified efficacy criteria. **Conclusions:** At a dose level of 4 mg/kg, 61% of patients were progression free at 8 weeks, meeting pre-specified criteria. Aflibercept at a dose of 4 mg/kg is active in previously treated ccRCC and may be worthy of further study. Clinical trial information: NCT00357760.

**4550 Poster Session (Board #223), Mon, 1:15 PM-4:45 PM**

**Pancreatic metastases from renal cell carcinoma: Prognostic relevance and outcome in patients treated with targeted agents.**

*First Author: Paolo Grassi, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

**Background:** Pancreatic metastases from renal cell carcinoma (PrmRCC) are uncommon and their prognostic role in the era of targeted therapies (TTs) is not well defined. We evaluated the outcome of a cohort of PrmRCC patients (pts) who were treated with either surgery and TTs Methods: PrmRCC pts treated between 1993 and 2014 were identified from the databases of 11 European centers. Clinical records were retrospectively reviewed and clinical outcome was analyzed. Kaplan-Meier methods and log-rank test were used to evaluate progression-free survival (PFS) and overall survival (OS). Cox proportional hazard models were used to analyze covariates associated to OS Results: A total of 276 pts were evaluated. PrmRCC were synchronous to the primary in 80 pts (29%). Pts treated with pancreatic local treatment (PLOT), including surgery, were 77 (28%). Pts receiving systemic treatment were 256 (93%). Pts with only PrmRCC were 42 (15%) whereas lung (47%), lymph nodes (28%) and liver (23%) were the most common metastatic sites in the remaining pts. Most of pts (95%) received nephrectomy (Nx). Median time from Nx to PrmRCC occurrence was 91 months (mo) (IQR 54-142). First-line TTs included: sunitinib (44%), sorafenib (12%), pazopanib (9%), temsirolimus (6%) and temsirolimus (1%); 37% of pts received cytokines and 53% received sorafenib (12%), pazopanib (9%), interferon (44%), sorafenib (12%), axitinib, aitinib (2%), pazopanib (12%), sorafenib (6%) and temsirolimus (2%). Objective tumor response was captured by protocol-defined tumor imaging according to RECIST. Targeting biomarker TPs was followed for TPs. Fs was assessed at first post-baseline scan and analyzed for sensitivity and specificity by receiver-operating characteristic (ROC) analyses to predict response measured by median progression free survival (PFS) or overall survival (OS). Patients were classified as responders if PFS (7 mo.) or OS (20 mo.) were above the median. Results: 4736 pts (71% male) with median age 59 years were identified within the database. Most patients were treatment naive (67%), had clear cell histology (89%), and favorable performance status (ECOG 0/1: 53/47%). Overall, an eTS of 7% or 8% was identified as the optimal cut-off for prediction of PFS or OS, respectively. Subgroups were analyzed and are depicted in table. **Conclusions:** Using a large clinical trials database in mRCC, we explored the predictive value of eTS in mRCC. Our analyses showed that the conventional 30% tumor shrinkage threshold is too high and that a cut-off at approximately 10% early TS predicts PFS and OS in mRCC. This finding is confirmed by a recent report on observer variability of eTS in mRCC, eTS should be further explored as a novel endpoint for clinical studies in mRCC.

**eTS as predictor in mRCC.**

<table>
<thead>
<tr>
<th>TTP</th>
<th>PFS sensitivity</th>
<th>PFS specificity</th>
<th>OS sensitivity</th>
<th>OS specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>7%</td>
<td>0.611/0.674</td>
<td>8%</td>
<td>0.602/0.632</td>
</tr>
<tr>
<td>1st line</td>
<td>11%</td>
<td>0.632/0.684</td>
<td>8%</td>
<td>0.596/0.621</td>
</tr>
<tr>
<td>2nd line</td>
<td>4%</td>
<td>0.530/0.724</td>
<td>5%</td>
<td>0.673/0.704</td>
</tr>
<tr>
<td>aitinib, sorafenib, sunitinib</td>
<td>10%</td>
<td>0.647/0.598</td>
<td>10%</td>
<td>0.653/0.659</td>
</tr>
<tr>
<td>temsirolimus</td>
<td>11%</td>
<td>0.652/0.621</td>
<td>12%</td>
<td>0.691/0.691</td>
</tr>
<tr>
<td>IFN</td>
<td>1%</td>
<td>0.728/0.621</td>
<td>1%</td>
<td>0.712/0.508</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Novel chromosome copy number changes to predict clinical response to sunitinib in patients with advanced renal cell carcinoma. First Author: Ching-Han Lee, Memorial Sloan Kettering Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: Sunitinib is a 1st-line therapy for clear cell Renal Cell Carcinoma (ccRCC); however, 20-30% of tumors show poor response to therapy (PRD) with progression as the best response. This study identifies the chromosomal copy number changes that are associated with sunitinib clinical response. Methods: Whole genome comparative genomic hybridization (aCGH) was performed on pretreatment tumor derived DNA from 76 sunitinib treated patients. Differential copy number alterations (CNAs) were identified using Fisher’s exact test with p-values < 0.05 and a 15% minimum threshold difference. Identified CNAs were univariately tested for association with PFS, and compared to two publically available ccRCC SNP datasets, TCGA-436 (N = 436, TCGA, Nature, 2013, 499; 43) and University of Tokyo-240 (N = 240, Nature Genetics, 2013, 45; 860).

Results: In patients with PRD gains of 22q and 6p were more common, and univariate PFS analysis for these CNAs showed a worse PFS (table). In patients with objective radiographic response (CR/PR), losses of 4q, 8p, and 10q were more common, and univariate PFS analysis identified loss of 4q and 8p tended toward improved PFS (table). Using databases comprising of largely sunitinib naïve patients (TCGA-436 and University of Tokyo-240), these CNAs were not correlated with overall survival, suggesting that these CNAs reflect sunitinib response, and not sunitinib-independent tumor biology. Conclusions: aCGH analysis of sunitinib treated ccRCC patients reveal multiple novel CNAs associated with clinical response. These CNAs warrant further investigation and may provide insight into mechanisms of sunitinib resistance.

Chromosome copy number changes.

<table>
<thead>
<tr>
<th>Worse Progression</th>
<th>Improved Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD as best response</td>
<td>CR/PR as best response</td>
</tr>
<tr>
<td>Gain 22q (P = 0.03)</td>
<td>Gain 22q (n = 0.06)</td>
</tr>
<tr>
<td>Gain 6p21.2 (P = 0.03)</td>
<td>Gain 6p21.2 (P = 0.03)</td>
</tr>
<tr>
<td>Gain 6q21.1 (P &lt; 0.03)</td>
<td>Gain 6q21.2 (P = 0.03)</td>
</tr>
</tbody>
</table>

Phase II study of individualized sunitinib as first-line therapy for metastatic renal cell cancer (mRCC). First Author: George A. Bjarnson, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Higher sunitinib drug exposure is associated with better response (RR), progression free (PFS) and overall survival (OS). Retrospective data show poorer PFS and OS in patients (pts) with minimum toxicity on the 28 day (d)/14 d schedule vs pts needing dose/schedule changes. We hypothesized that toxicity-driven dose/schedule changes would optimize drug exposure. Methods: In a prospective phase II study (eligibility identical to EFFECT trial, JCO 30(12):1371) with the primary endpoint of improving PFS from 8.5 (EFFECT 4/2) to 14 months (mo), pts start on 50 mg/d for 28 d with treatment (Rx) breaks reduced to 7 d. Pts with grade-2 toxicity before d 28 stay on 50 mg with the on Rx individually reduced aiming for ≤ grade-2 toxicity. Dose is reduced to 37.5 mg in pts that do not tolerate 50 mg for at least 7 d and to 25 mg in pts that do not tolerate 37.5 mg for 7 d with individualized duration of Rx. Pts with minimum toxicity on d 28 are dose escalated to 62.5 mg and then 75 mg on a 14/7 d schedule. Pts that develop grade-2 toxicity by d 28, stay on a 28/7d schedule. Results: With accrual completed and 116 pts entered at 12 centers, 83 pts are evaluable for RR (at least two CTs 2 mo apart) with median followup of 11.6 mo (Heng favorable 25%, intermediate 63%, poor 12%). Nine pts came off study early due to toxicity (5), non-compliance (2) or global deterioration (2). Of 61 pts still on therapy, 24 are too early for RR. Of 83 evaluable pts (37 still on Rx), 18 (21.2%) were dose reduced to 62.5 mg (11) and 75 mg (7). For 39 pts (47%), who would have been dose reduced by standard criteria, a 50 mg dose was continued for 7 - 24 d, while 7 pts (8.4%) stayed on a 28d schedule. Dose was reduced to 37.5 mg in 13 pts (15.7% vs 36 - 63% in 4 trials) and to 25 mg in 6 pts (7.2% vs 15 - 19% in 4 trials). Rx was stopped due to toxicity in 7116 pts (6% vs 15-19% in 4 trials). Best response was complete CR in 4 pts, partial PR in 36 pts, stable (SD, median 6.4 mo on Rx) in 32 pts and progression in 9 pts (10.8% vs 24.6% in EFFECT) for a CR + PR (median 14.3 mo on Rx) of 50.6% (vs 32% in EFFECT) and CR + PR + SD rate of 89.2% (vs 75% in EFFECT). Conclusions: Individualized dosing is safer in a multicenter setting and achieved improved drug exposure and the highest RR reported for mRCC. Clinical trial information: NCT01354431.
**4556 Poster Session (Board #230), Mon, 1:15 PM-4:45 PM**

Molecular analysis of sarcomatoid renal cell carcinoma (sRCC). First Author: Thai Huu Ho, Mayo Clinic, Scottsdale, AZ, Scottsdale, AZ

**Background:** Patients with sRCC have a worse prognosis and decreased likelihood of response to targeted therapy or IL-2. However, biomarkers of response are lacking in sRCC. We evaluated a cohort of RCC patients to identify potentially actionable recurrent molecular aberrations.

**Methods:** 112 renal cases referred to Caris Life Sciences over 2 years were evaluated for sarcomatoid components with central pathology review. 91 cases were clear cell (ccRCC) and 21 were sRCC. Testing included sequencing (next generation sequencing [NGS]), protein expression (immuno-histochemistry [IHC]), and gene amplification (CISH or FISH). For sequencing, DNA was isolated by microdissection of the sarcomatoid component. 20 RCC cases with sarcomatoid differentiation from Mayo Clinic Arizona were analyzed for external validation.

**Results:** The sRCC cohort showed 54% loss of PTEN, while sRCC had a 33% loss (p value 0.01). However, slightly more brain and bone metastases at baseline were observed in 19% of sRCC and 30% of ccRCC. Key differences are shown in the table below.

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Overexpression</th>
<th>TILs</th>
<th>% Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>ccRCC</td>
<td>25</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>sRCC</td>
<td>67</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>p value</td>
<td>0.0001</td>
<td>0.04</td>
<td>0.005</td>
</tr>
<tr>
<td>RM1</td>
<td>74</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>PBRM1</td>
<td>46</td>
<td>34</td>
<td>62</td>
</tr>
<tr>
<td>p value</td>
<td>0.0001</td>
<td>0.003</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusions:** Multiparameter molecular profiling of sRCC identifies numerous predictive biomarkers to targeted immunotherapies. In other solid tumors, overexpression of TOPO2A and loss of RRM1 are associated with sensitivity to anthracyclines and gemcitabine, respectively. sRCC have increased infiltration of PD-1+ TILs and may respond to PD1/PD-L1 targeted immunotherapies. Further evaluation of TOPO2A, RM1 and PD-1/PD-L1 as predictive biomarkers in sRCC is warranted.

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**4558 Poster Session (Board #232), Mon, 1:15 PM-4:45 PM**

Characteristics of metastatic renal cell carcinoma (mRCC) patients treated with delayed targeted therapy: Results from the International mRCC Consortium (IMoC). First Author: Haoran Li, Tom Baker Cancer Center, Calgary, AB, Canada

**Background:** A small proportion of patients with mRCC may not require immediate targeted therapy (TT). Their clinicopathological features and prognoses are not well characterized.

### Methods:

- A retrospective analysis was conducted in mRCC patients who did not start TT until at least 1 year after diagnosis of metastatic disease (delayed TT). Patients treated with traditional immunotherapy were excluded. For comparison, patients that received immediate TT within 1 month of metastatic diagnosis were used (immediate TT).
- **Results:** 467/3202 (14.6%) mRCC patients had delayed TT. The majority of patients (96.6%) in delayed group had prior nephrectomy. Compared to patients who received immediate TT (n = 800), patients with delayed TT were more likely to have clear cell histology (87.8% vs. 82.7%, p = 0.02), lower grade primary lesions (low/intermediate grade: 38.3% vs. 31.2%, p = 0.03), less likely to have sarcomatoid features (7.1% vs. 13.1%, p = 0.002), greater percentage of normal LDH (74.8% vs. 67.1%, p = 0.02) and less hyponatremia (11.9% vs. 19.3%, p < 0.05). However, slightly more patients with metastatic disease at baseline was seen in the delayed TT vs immediate TT groups (8.7% vs. 5.7%, p = 0.046 and 38.3% vs. 31.4%, p = 0.02, respectively) and it is unknown if these patients were delayed due to metastasectomy or radiotherapy. IMDC risk factors were more favorable in delayed TT group, with less anemia (43.2% vs. 54.3%, p = 0.02), lower weight loss (16% vs. 22%, p = 0.007), less thrombocytopenia (11.3% vs. 22.0%, p < 0.001), thrombophilia (8.6% vs. 18.4%, p = 0.001), KPS < 80 (20.9% vs. 26.6%, p = 0.03). The response rate of TT was similar between two groups (27.0% vs. 27.0%, p = 1.0). The median PFS was 9.3 months in delayed TT patients vs 5.6 months in immediate group (p = 0.001), and the median OS was 26.6 months in delayed group vs 17.2 months in immediate group (p = 0.001).

**Conclusions:** The differences in survival are due to patient selection.

### Summary of DLTs.

**Patient DLT Grade BMI DS**

<table>
<thead>
<tr>
<th>DLT</th>
<th>Grade</th>
<th>BMI Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>100 mg</td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>3</td>
<td>100 mg</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>2* 80 mg</td>
<td></td>
</tr>
</tbody>
</table>

*≥1 CTCAE grade level increase defined as DLT.*

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**4559 Poster Session (Board #233), Mon, 1:15 PM-4:45 PM**

A phase I study of buparlisib (BKM120) with bevacizumab (BEV) in patients (pts) with metastatic renal cell carcinoma (mRCC) progressing on prior vascular endothelial growth factor (VEGF) therapies. First Author: Rana R. McKay, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

**Background:** BKM120 is a pan-Pi3K inhibitor with demonstrated activity in VEGF-refractory mRCC. This was a 3+3 dose escalation study of BKM120 (60-100 mg/day (d)) + BEV (10 mg/kg every 2 weeks). After the MTD was defined, 14 pts were treated with sorafenib were crossed over to tivozanib per protocol. For the 260 pts originally receiving tivozanib was 14.6 and 29.8 mos, and for the 257 pts originally receiving sorafenib was 9.7 and 34.1 mos, respectively (PFS HR 0.77, OS HR 1.18). Long term safety assessment of pts who continued tivozanib indicated that incidence of the most common on target AEs (hypercalcemia and dysphoria) decreased over time. For the 163 pts who crossed over from sorafenib to second line tivozanib, median PFS was 21.6 mos and median OS was 26.6 mos, both calculated from the start of second line tivozanib. Conclusions: This long term analysis of PFS and OS underscores the positive impact of tivozanib treatment after sorafenib failure in mRCC. Lack of access to second line therapies in pts in the tivozanib arm due to geographical reasons most likely affected real survival.

**Clinical trial information:** NCT01030783, NCT01076010, NCT01369433.
Clinical effect of TKI dose-escalation after disease progression in patients with metastatic renal cell carcinoma. First Author: Moshe Chaim Ornstein, Cleveland Clinic Fdtn, Cleveland, OH

Background: Given the variability in drug levels with tyrosine kinase inhibitors (TKI) in patients (pts) with metastatic renal cell carcinoma (mRCC), escalation of dose at the time of progressive disease (PD) may have anti-tumor effect. Methods: Pts with mRCC who were treated at Cleveland Clinic with TKIs and were dose-escalated following PD per RECIST 1.1 were retrospectively reviewed. Patient and disease-related data were collected and summarized as frequency counts and percentages, or medians and ranges. The Kaplan-Meier method was used to summarize treatment duration on escalated doses. Results: Nineteen patients were identified. The majority of patients (84%) were male; median age was 58 (range, 40-71). The most common histology was clear cell (79%), 78% of pts were intermediate risk by IMDC criteria, and all but one patients had prior nephrectomy. Axitinib was the most frequently escalated agent following disease progression (89%); starting at 5mg BID and generally escalating by 1-2mg BID as tolerated. Sunitinib was the dose-escalated TKI in the remaining 2 patients; starting at 50 mg on a 4/2 schedule and escalating to 62.5mg on a 2/1 schedule. Prior to PD dose-escalation, best response was partial response (PR) in 7 (37%) pts, stable disease (SD) in 10 (53%), and PD in 2 (11%) pts with a median treatment duration of 6.7 months (range, 1.6-49.8). Of pts with evaluable tumor measurements during the escalation period (n = 15), 11 pts (73%) had a decrease in tumor burden. Median decrease in tumor burden after dose-escalation was 11% (range, 0-58%); 6 (40%) pts had decreases > 10%: 3 (20%) > 20%, and 1 (7%) > 30%. Most pts continue to be treated at escalated doses; median duration of escalated therapy is estimated to be 9.8 months (range 0.6+ to 21.1+ months). Conclusions: Dose-escalation of TKIs after PD in select mRCC can lead to reduction in tumor burden and extend the duration of therapy.

Clinical impact of loss of H3K36me3 expression in patients with clear cell renal cell carcinoma. First Author: Abhishek Swaika, Mayo Clinic, Jackson-ville, FL

Background: Mutations in chromatin modifying enzymes play a role in the pathogenesis of clear cell renal cell carcinoma (ccRCC). However, the clinical impact of histone methylation regulated by chromatin modifying enzymes remains unknown. Herein we analyze the clinical impact of loss of histone H3 lysine 36 trimethylation (H3K36me3) in a large cohort of ccRCC tumors and associate its expression with renal cell cancer-specific survival (RCC-SS) and pathologic features. Methods: We utilized the Mayo Clinic Renal Registry and identified 1454 patients who underwent nephrectomy to treat clinically localized ccRCC between 1/3/1990 and 4/14/2009 and who also had available tissue samples. We used immunohistochemistry (IHC) to detect H3K36me3 expression, and a central pathologist blinded to the outcomes scored tumors as either positive or negative. Tumors with heterogeneous or equivocal staining were not included in this analysis. For associations with pathologic features we employed Mann-Whitney U tests, and for associations with relapse free survival (RFS) and ccRCC-SS we generated Cox proportional hazard regression models. Results: Of the total 1454 samples, 1205 (83%) were scored as either positive or negative for H3K36me3 with 978 (81%) positive and 227 (19%) negative samples. H3K36me3 negative tumors strongly associated with male gender, older age, larger tumor size, higher grade (3-4), and positive tumor necrosis (p < 0.001 for all). After adjusting for age, H3K36me3 negative patients had decreased RFS (HR 2.8, p < 0.001). Median OS (MOD) was 10 (p < 0.001). After adjusting for age and the Mayo Clinic-Stage, Size, Grade, and Necrosis (SSIGN) score, H3K36me3 negative tumors continued to have decreased RFS (HR 1.3, p = 0.041) and trended towards decreased RCC-SS (HR 1.31, p = 0.064). Conclusions: This is the largest study evaluating the clinical significance of H3K36me3 expression in patients with ccRCC. Loss of H3K36me3 is a marker of poor prognosis and an independent predictor of decreased RFS. Efforts to elucidate the mechanisms of how loss of H3K36me3 contributes to worse tumor biology are underway.
4566  Poster Session (Board #240), Mon, 1:15 PM-4:45 PM

Efficacy and safety of endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors (TKI) after programmed cell death 1 (PD-1) inhibitor treatment in patients with metastatic clear cell renal cell carcinoma (mccRCC). First Author: Rosa Nadal, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Emerging agents blocking the PD-1 pathway may transform the current treatment landscape of mCRCC. The aim of this study was to evaluate the efficacy and safety of VEGF-TRK TKI therapy after PD-1 treatment. Methods: Patients (pts) with mccRCC treated with PD-1 monotherapy or in combination with immuno-oncology were included. Pts with a previous response to 4 (CTLA4)-inhibitor (PD-1/CTLA4) or TKI (PD-1/VEGFR-TKI) who subsequently received VEGFR-TKI, were retrospectively reviewed. The efficacy end points were objective response rate (ORR) and progression-free survival (PFS) stratified by type of prior PD-1 regimen. Safety by type and PD-1 exposure was also evaluated. Results: 63 patients were included and belonged to the following risk categories: 20% good, 251 (64%) intermediate, and 60 (15%) poor. A CR was identified in 35 (9%), PR in 39 (10%), SD in 125 (32%), progressive disease (PD) in 164 (42%), and not evaluable for response (NE) in 28 (7%) pts. Median OS for the favorable, intermediate and poor risk groups were 53.8 (p = 0.0015 vs intermediate), 26.4 (p < 0.0001 vs poor), and 12.2 (p < 0.0001 vs favorable) months, respectively. Table shows correlation of response to survival. Conclusions: Stable disease as best response to HD IL-2 was achieved in 32% of pts and survival outcomes were not statistically different in these pts from those achieving PR, however significantly greater than those with PD. Stable disease is an important response criterion for treatment with HD IL-2, and may be discussed with the pts.

Correlation of best responses with survival outcomes in mccRCC pts treated with HD IL-2: Landmark analysis at 2 months.  

<table>
<thead>
<tr>
<th>Response</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR vs SD</td>
<td>114.1 vs 8.9 (HR 0.13, CI 0.06-0.23)</td>
<td>156.7 vs 37.4 (HR 0.21, CI 0.10-0.42)</td>
</tr>
<tr>
<td>CR vs PR</td>
<td>13.8 vs 9.0 (HR 0.13, CI 0.06-0.23)</td>
<td>156.7 vs 38.4 (HR 0.13, CI 0.06-0.26)</td>
</tr>
<tr>
<td>CR vs PD</td>
<td>5.1 vs 3.2 (HR 0.23, CI 0.12-0.39)</td>
<td>101.2 vs 24.1 (HR 0.24, CI 0.13-0.37)</td>
</tr>
<tr>
<td>SD vs PD</td>
<td>13.8 vs 7.8 (HR 0.24, CI 0.13-0.37)</td>
<td>101.2 vs 24.1 (HR 0.24, CI 0.13-0.37)</td>
</tr>
</tbody>
</table>

Conclusions: Preferably: predominantly clear cell RCC, 1 prior VEGFR TKI, > 3 prior tx. Results: As of January 16, 2015, a total of 29 pts were enrolled. During dose escalation, 15 pts were enrolled in 3 cohorts (n = 6, 4, 5) at dose levels of 0.6, 0.9 and 1.2 mg/kg, respectively. There were no DLTs. The 1.2 mg/kg dose-level was expanded to include the 9 more pts and dosing events including peripheral edema (n = 8), fluid overload (n = 1), and ascites (n = 1) were reported. The 0.9 mg/kg dose level was then expanded to include 5 more pts. This dose level was well tolerated (4 pts with grade 1 edema, 1 pt with pleural effusion and no ascites), and selected for Part 2. AEs (> 30%) reported included fatigue, paronychia, increased creatinine, nausea, decreased appetite, chills, hypotension, arthralgia, creatinine rise, cough, and hand-foot rash. There were no grade 4/5 related adverse events. 28 pts were evaluable by RECIST v1.1. The ORR was 25% (n = 7). Disease control (PR + SD) at 6 months was 57% (n = 16). The median PFS of 8.3 months for all dose levels combined. The mPFS at the 0.9 mg/kg dose level has not been reached. Conclusions: The combination of dalantercept and axitinib is well tolerated and has shown encouraging activity in pts who have received prior VEGF, mTOR, and immune therapies. Part 2 of this study will randomize 130 pts to dalantercept + axitinib vs. placebo to axitinib and is actively accruing patients. Clinical trial information: NCT01727336.
Impact of salvage surgery and radiotherapy on overall survival in patients with recurrent primary urethral cancer. First Author: Georgios Gakis, Eberhard-Karls-University, Tübingen, Germany

**Background:** To evaluate the impact of salvage therapy (ST) on overall survival (OS) in recurrent primary urethral cancer (PUC). Methods: A series of 154 patients (109 men, 45 women; median age: 66, IQR: 58-76) were diagnosed with PUC at ten referral centers between 1993 and 2012. Kaplan-Meier analysis with log-rank was used to estimate the impact of ST on OS. The median follow-up was 21 months (mean: 32 months; IQR: 4-45). Results: The modality of primary treatment was cystectomy+urethrectomy in 43 (27.9%), total/partial urethrectomy in 39/6 (25.3/3.9%), transurethral resection in 39 (25.3%), chemoradiotherapy (CRT), radiotherapy (RT), chemotherapy (CT) and five in 9 (5.8%), 4 (2.6%), 3 (1.9%) and 9 (5.8%) patients, respectively. Neoadjuvant CT/CRT and adjuvant CT were administered to 16/9 (10.4/8.8%) and 23 (14.9%) patients, respectively. The locations of recurrences were: urethral in 28 (18.2%), lymph nodes (LN) in 18 (11.7%), LN+distant in 12 (7.8%), LN+distant+urethral in 9 (5.8%), LN+urethral in 6 (3.9%), distant in 5 (3.3%), distant+urethral in 4 (2.6%) and no recurrence in 72 (46.8%). In the 82 patients with recurrences, the modality of ST was surgery in 32 (39.0%), RT in 8 (9.8%), surgery+RT in 5 (6.1%) and none in 37 (45.1%). The 3-year OS for patients free of any recurrence (I), with solitary and/or concomitant urethral recurrence (II) and non-urethral recurrence (III) were 86.7%, 74.5% and 41.7% respectively (p < 0.001 for I vs. III, p = 0.001 for II vs. III, p = 0.53 for I vs. III). In patients with recurrences, those who underwent ST had similar 3-year OS: surgery: 84.9%, RT: 80%, surgery+RT: 80% compared to patients with no recurrence (86.7%, p = 0.79), and exhibited superior 3-year OS compared to patients who did not undergo ST (72.6%; p < 0.001 compared to surgery) or RT (p = 0.016 to RT-based ST; p = 0.53 for surgery vs. RT-based ST). Receipt of perioperative CT/CRT (N = 16) did not impact on 3-year OS after ST (79.3%) compared to no CT/CRT (N = 29, 85.5%, p = 0.95).

**Conclusions:** In this study, patients who underwent surgery or RT-based ST for recurrent PUC demonstrated improved OS compared to those who did not receive ST and exhibited similar survival to those who never developed recurrence after primary treatment.

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**KEYNOTE-045: Randomized phase 3 trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel, or vinflunine for previously treated metastatic urothelial cancer. First Author: Joaquin Bellmunt, Dana-Farber Cancer Institute, Boston, MA

**Background:** Paclitaxel, docetaxel, and vinflunine are commonly used as second-line therapy for advanced urothelial cancer, but median OS is only 7-9 months. The PD-1 pathway plays a key role in evading the tumor immune response. Pembrolizumab is a highly selective anti–PD-1 monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. In KEYNOTE-012, pembrolizumab 10 mg/kg every 2 weeks (Q2W) provided a 24% ORR (RECIST v1.1, central review) and an acceptable safety profile in 33 pts with PD-L1–positive advanced urothelial cancer, 76% of whom received ≥ 1 prior therapy. Methods: In the international, open-label, phase 3 KEYNOTE-045 trial (ClinicalTrials.gov, NCT02256436), pts with confirmed metastatic or locally advanced/unresectable urothelial cancer (transitional cell or predominantly transitional cell histology) of the bladder, renal pelvis, ureter, or urethra that has recurred or progressed following platinum-based chemotherapy are randomized 1:1 to pembrolizumab 200 mg Q3W or investigator’s choice of paclitaxel 175 mg/m2 Q3W, docetaxel 75 mg/m2 Q3W, or vinflunine 320 mg/m2 Q3W. Key eligibility criteria include ≥ 2 prior chemotherapy regimens and measurable disease per RECIST v1.1. Randomization is stratified by ECOG PS (0/1 vs 2), liver metastases (presence vs absence), hemoglobin level (< 10 vs ≥ 10 g/dL), and time from last chemotherapy discontinuation to first pembrolizumab treatment (≥ 3 mo). All pts must provide a recently obtained tissue sample for PD-L1 evaluation at a central laboratory. Pembrolizumab will be given for up to 24 mo or until disease progression, unacceptable toxicity, or investigator decision. Treatment may be discontinued beyond initial radiographic progression in select pts. Pts who achieve complete response may continue pembrolizumab. Response will be evaluated at wk 9 and every 12 wk thereafter. After discontinuation, pts will be followed for survival every 12 wk. Primary end points are OS and PFS assessed per RECIST v1.1 by independent central review. Secondary end points include ORR and duration of response. Enrollment began in Oct 2014 and will continue until approximately 470 pts are enrolled. Clinical trial information: NCT02256436.
Background: Standard first-line therapy for advanced urothelial cancer is cisplatin-based chemotherapy. Pts who are ineligible for cisplatin therapy, mainly due to renal dysfunction and/or poor performance status, have limited treatment options. The programmed death receptor 1 (PD-1) pathway is used by tumors to suppress immune control. Pembrolizumab is a highly selective, IgG4 anti-PD-1 humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. In the phase 1 KEYNOTE-012 trial, pembrolizumab 10 mg/kg once every 2 weeks (Q2W) demonstrated an ORR of 24% (RECIST v1.1, central review) in 33 pts with PD-L1-positive advanced urothelial cancer, 76% of whom received ≥ 1 prior therapy. Methods: KEYNOTE-005 (ClinicalTrials.gov, NCT02335424) is an international, open-label, phase 2 trial of pembrolizumab 200 mg Q3W as first-line therapy for adults with unresectable or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra who are ineligible to receive cisplatin. Pts are considered cisplatin ineligible if they have ≥ 1 of the following: ECOG PS 2, creatinine clearance (calculated or measured) < 60 but ≥ 30 mL/min, grade ≥ 2 (CTCAE v4) audiometric hearing loss or peripheral neuropathy, or NYHA class III heart failure. All pts must provide a recently obtained biopsy sample for PD-L1 evaluation at a central laboratory. Pembrolizumab will be given for up to 24 mo or until disease progression, unacceptable toxicity, or investigator decision; treatment may be discontinued following complete response. Select pts may continue pembrolizumab beyond initial evidence of radiographic progression. Response will be evaluated per RECIST v1.1 by independent central review at 9 wk and every 6 wk thereafter. Survival follow-up will continue every 3 mo. Primary end point is ORR in pts with PD-L1–dependent tumors. Secondary end points include ORR in all pts, PFS, OS, duration of response, and the association between PD-L1 positivity and ORR. Up to 350 pts will be enrolled. KEYNOTE-005 is currently enrolling pts. Clinical trial information: NCT02335424.

Phase II randomized placebo controlled neoadjuvant chemotherapy study of nintedanib with gemcitabine and cisplatin in locally advanced muscle invasive bladder cancer. First Author: Syed A. Hussain, University of Liverpool, Clatterbridge Cancer Centre, Liverpool, United Kingdom

Background: The triple angiokinase inhibitor nintedanib (nin) has shown activity as well as toxicity in patients with advanced UC, but no standard exists after first-line therapy. Mocetinostat (MGCD0103) is a spectrum selective inhibitor of HDAC 1, 2, 3 and 11. Site of drug action is mainly due to renal dysfunction and/or poor performance status, have limited treatment options. The programmed death receptor 1 (PD-1) pathway is used by tumors to suppress immune control. Pembrolizumab is a highly selective, IgG4 anti-PD-1 humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. In the phase 1 KEYNOTE-012 trial, pembrolizumab 10 mg/kg once every 2 weeks (Q2W) demonstrated an ORR of 24% (RECIST v1.1, central review) in 33 pts with PD-L1-positive advanced urothelial cancer, 76% of whom received ≥ 1 prior therapy. Methods: KEYNOTE-005 (ClinicalTrials.gov, NCT02335424) is an international, open-label, phase 2 trial of pembrolizumab 200 mg Q3W as first-line therapy for adults with unresectable or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra who are ineligible to receive cisplatin. Pts are considered cisplatin ineligible if they have ≥ 1 of the following: ECOG PS 2, creatinine clearance (calculated or measured) < 60 but ≥ 30 mL/min, grade ≥ 2 (CTCAE v4) audiometric hearing loss or peripheral neuropathy, or NYHA class III heart failure. All pts must provide a recently obtained biopsy sample for PD-L1 evaluation at a central laboratory. Pembrolizumab will be given for up to 24 mo or until disease progression, unacceptable toxicity, or investigator decision; treatment may be discontinued following complete response. Select pts may continue pembrolizumab beyond initial evidence of radiographic progression. Response will be evaluated per RECIST v1.1 by independent central review at 9 wk and every 6 wk thereafter. Survival follow-up will continue every 3 mo. Primary end point is ORR in pts with PD-L1–dependent tumors. Secondary end points include ORR in all pts, PFS, OS, duration of response, and the association between PD-L1 positivity and ORR. Up to 350 pts will be enrolled. KEYNOTE-005 is currently enrolling pts. Clinical trial information: NCT02335424.

Methods:
Statistical Design:
Planned accrual is 199 patients over 3 years with followup of 4 months.
Assuming median PFS of 4 months with paclitaxel, the target hazard ratio is 0.67 (PFS of 4 mo vs. 6 mo, 1-sided, 5% significance with 80% power). Estimated sample size accounts for loss to followup or withdrawal of consent.

Conduct to Date:

Background: Inactivation of p53 and PTEN mutations promotes progression in bladder cancer via deregulation of the mammalian target of rapamycin (mTOR) signaling pathway (mTOR). mTOR expression increases as a function of the disease stage as it progresses from superficial to invasive bladder cancer. Our group has proven the efficacy of intravesical rapamycin to treat bladder cancer in a mouse model. With the advent of the nanoparticle albumin bound (nab) version of rapamycin (ABI-009), this hydrophobic entity can now be tested intravesically. We sought to investigate the safety and efficacy in the management of Bacillus Calmette-Guerin (BCG) refractory non-muscle invasive urothelial carcinoma of the bladder (NMIBC).

Methods: Funded via the NIH small business innovation research program (grant 1R42CA171552 and 3R42CA171552), this combined phase I/I study is currently enrolling patients with BCG refractory NMIBC at Columbia University and Vanderbilt University. BCG refractory is defined as disease recurrence after BCG therapy (≥ 9 doses). This population was chosen given the dearth of effective, non-surgical second line options. Inclusion criteria include: histologically confirmed NMIBC including CIS and/or papillary lesions of high-grade Ta/T1, refractory to BCG; be eligible and refuse radical cystectomy; have all grossly visible disease fully resected. A maximum of 15 patients will be recruited in phase I with a dose-escalation scheme starting at 100 mg and escalating in the 3 remaining cohorts by 100 mg following a 3+1 rule. After the dose is determined, the phase 2 segment will enroll 29 patients. Success will be defined by a complete response in 20% of patients with negative biopsy 6 weeks post-treatment. This trial is enrolling with Cohorts 1 and 2 complete with no DLTs. Cohort 3 response in 20% of patients with negative biopsy 6 weeks post-treatment.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: RX-0201 is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). The specificity of RX-0201-mediated effect on AKT-1 mRNA levels was examined in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMR2 cells and resulted in a reduction of AKT-1 mRNA levels. Methods: The current study is a proof of concept phase 1b, multicenter, open label study, conducted in 2 stages. Stage 1 is an open-label, dose-escalation phase 1b study of RX-0201 administered in combination with everolimus. RX-0201 will be administered in a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest. It is expected that 250 mg/m2/day or a lower dose of RX-0201 will be identified as safe and well-tolerated when administered in combination with 10 mg of everolimus. The dose of RX-0201 identified in Stage 1 will be studied further in Stage 2 which is the randomized, open-label, 2-arm study of RX-0201 in combination with 10 mg of everolimus versus 10 mg of everolimus alone. Up to 8 cycles of study treatment will be permitted. Approximately 9 subjects are targeted to receive escalating doses of RX-0201 in combination with everolimus in Stage 1. The initial dose of RX-0201 is 125 mg/m2/day. In Stage 2 approximately 30 subjects are planned to be randomized in a 1:2 ratio (i.e., up to 10 subjects in the everolimus arm and up to 20 subjects in the everolimus/RX-0201 arm). Eligible subjects must have confirmed histologic or cytologic evidence of renal cancer with a clear cell component, measurable or evaluable disease as defined by RECIST, received at least 1 course of therapy with a VEGFR inhibitor and progressed within 6 months of planned first dose of on study treatment and received no more than 3 prior treatments of systemic renal cancer therapy. Radiological imaging for disease assessments will be according to RECIST ver. 1.1 Clinical trial information: NCT02089334.

TPS4581 Poster Session (Board #249b), Mon, 1:15 PM-4:45 PM A randomized, open label, multicenter phase 2 study to evaluate the safety and efficacy of sorafenib in patients (pts) with advanced Renal Cell Carcinoma (RCC) in the setting of a radical nephrectomy. First Author: Elena Verzoni, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Background: Complete response with targeted agents approved for meta- static renal cell carcinoma (mRCC) is rarely achieved. Retrospective findings seem to indicate that metastasectomy (Mtx) may improve survival in selected pts. The RESORT study was designed to evaluate whether Mtx followed by sorafenib may provide an additional clinical benefit. VEGF expression may represent a prognostic factor for survival Methods: Overall 132 mRCC pts undergoing complete Mtx will be randomized 1:1 (66 pts per arm) to receive either sorafenib or best supportive care (BSC) for 52 weeks or until disease recurrence. Prognostic factors including time from nephrectomy, site of disease and number of lesions will be used to stratify pts Key inclusion criteria: - Maximum 3 metastatic lesions. - Complete removal of all metastatic lesions. - Microscopic examination of margins showing no tumor cells (RO resection). - No more than three months from Mtx Pts will be recruited from 16 Italian centers. The primary endpoint is recurrence-free survival (RFS), defined as the time from randomization to diagnosis of disease relapse or death. Secondary endpoints are Overall survival (OS) and safety. Circulating levels of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) will be evaluated from consenting pts (optional) at baseline, every 3 months, and at the end of treatment. Sorafenib will be administered at the dose of 400 mg orally once daily for 21 days and then increased to 400 mg twice daily if the patient has not experienced grade 2 skin toxicity or any other grade 3 toxicities. Imaging assessments will be performed every 12 weeks Statistical plan Kaplan-Meier methods will be used for survival analyses and the log-rank test to compare sorafenib arm and BSC arm according to the stratification factors. The hazard ratio (HR) will be determined at the 95% confidence interval (CI). The hypothesis is to increase the RFS time from 12 months (BSC arm) to 18 months (sorafenib arm), corresponding to a 50% improvement. With a study power of 80% and a 1-sided error of 0.15, the estimated number of events required is 86. Twenty-six out of 132 pts have been enrolled Clinical trial information: NCT01444807.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase II study of pazopanib and weekly paclitaxel in metastatic or locally advanced squamous penile carcinoma patients previously treated with cisplatin-based chemotherapy: PAZOPEN study. First Author: Miguel Angel Climent, Fundación Instituto Valenciano de Oncología, Valencia, Spain

Background: Metastatic or locally advanced squamous penile carcinoma (MLASPC) is an infrequent disease, with extremely bad prognosis. Platinum-based chemotherapy is the most active treatment with a response rate (RR) of 30% and only 12 months of overall survival. New active agents are urgently needed. The combination of the antiangiogenic agent Pazopanib and paclitaxel have been tested in two tumor-cell models and in melanoma with high numbers of response and good tolerance profile. The aim of this study is to test the activity and safety of the combination in patients (pts) with MLASPC progressing to platinum based regimens. Methods: Phase II open label, single arm, multicentre study. Main inclusion criteria are: diagnosis of squamous penile carcinoma, measurable disease by RECIST criteria, progressive disease after previous platinum based treatment, either in neoadjuvant, adjuvant or metastatic setting, adequate hepatic, renal and haematological function. Patients will receive treatment with pazopanib 800 mg p.o daily and paclitaxel 65 mg/m2 weekly D1, 8 and 15 every four weeks cycle. Main objective is RR (complete CR) and partial response (PR) measured by RECIST criteria. Secondary objectives: Clinical benefit rate, (CR + PR + SD), progression-free survival, response duration, overall survival, toxicity and tolerance profile. Whole exome sequencing will be performed to describe most frequent alterations in penile cancer. This is a two stage Simon optimal design for phase II trials. Considering an estimated 30% RR with PO = 10%, (alpha error 5%, beta 20%), 10 patients will be included in first stage and if 2 or more responses are observed, then 19 additional patients will be included in second stage. If more than 5 responses are observed efficacy of treatment will be considered. The sample size, taking into account a 10% drop out rate will be 32 pts. Trial will be performed in 8 hospital centres of the SOGUG group. Study has been approved by ethic committees and health authorities. Funded by a grant from GlaxoSmithKline. NCT02279576. Clinical trial information: NCT02279576.

Impact of gemcitabine + cisplatin + ipilimumab on circulating immune cells in patients (pts) with metastatic urothelial cancer (mUC). First Author: Matt D. Galsky, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Immune checkpoint blockade may play a role in the treatment of mUC. However, the role of CTLA4 blockade, the impact of chemotherapy on immune cell populations, and the optimal approach to combination regimens in pts with mUC remains poorly defined. An increase in tumor infiltrating and circulating CD11b+ICOS+ cells after ipilimumab has been shown in pts with localized UC and correlated with improved outcomes in ipilimumab-treated melanoma pts (Carthon, Clin Can Res, 2010). Methods: Pts with mUC were enrolled on a phase 2 trial of chemotherapy + CTLA4 blockade. Patients received 2 cycles of gemcitabine + cisplatin (GC) followed by 4 cycles of GC + ipilimumab (GCI). Flow cytometry was performed on peripheral blood mononuclear cells after ipilimumab has been shown in pts with melanoma (Carthon, Clin Can Res, 2010). Comparisons between time-points were made using Wilcoxon's rank test. Results: The trial has completed enrollment (n = 36) and flow cytometry data are available for the complete treatment sequence on 17 pts as of 2/2025 (Table). Conclusions: GC alone generally had no significant impact on the median % of circulating immune cell subsets though the increase in CD4+ICOS+ cells warrants confirmation. GCI resulted in an increase in CD4+ and CD8+ T cells, including the subset of CD4+ICOS+ cells, with a lesser increase in Tregs. The impact of individual changes in immune cell subsets on pt outcomes, and the role of GCI in mUC, will be further defined as efficacy data matures. Clinical trial information: NCT01524991.

Impact of treatment on immune cell subsets (median % (IQR)).

<table>
<thead>
<tr>
<th>Baseline (BL)</th>
<th>Post-GC</th>
<th>Post-GCI</th>
<th>p (GC v. BL)</th>
<th>p (GC v. BL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+CD4+</td>
<td>4.9% (8.3%)</td>
<td>4.0% (5.0%)</td>
<td>6.8% (10.1%)</td>
<td>0.2 0.04</td>
</tr>
<tr>
<td>CD3+ICOS+</td>
<td>0.01% (0.4%)</td>
<td>0.05% (2.4%)</td>
<td>0.4% (3.7%)</td>
<td>0.2 0.9</td>
</tr>
<tr>
<td>CD4+PD1+</td>
<td>0.02% (0.3%)</td>
<td>0.02% (0.2%)</td>
<td>0.02% (0.2%)</td>
<td>0.7 0.7</td>
</tr>
<tr>
<td>CD4+PD1</td>
<td>9.0% (7.4%)</td>
<td>5.0% (6.8%)</td>
<td>15.9% (11.2%)</td>
<td>0.7 0.001</td>
</tr>
<tr>
<td>CD4+ICOS+</td>
<td>0.2% (0.7%)</td>
<td>0.5% (5.4%)</td>
<td>3.1% (8.9%)</td>
<td>0.03 0.04</td>
</tr>
<tr>
<td>CD4+MDSC</td>
<td>0.1% (0.2%)</td>
<td>0.1% (0.4%)</td>
<td>0.4% (0.4%)</td>
<td>0.08 0.03</td>
</tr>
<tr>
<td>TReg</td>
<td>0.4% (0.6%)</td>
<td>0.4% (1.4%)</td>
<td>1.0% (0.9%)</td>
<td>0.5 0.04</td>
</tr>
<tr>
<td>MDSC</td>
<td>0.7% (3.8%)</td>
<td>0.4% (2.1%)</td>
<td>0.6% (6.7%)</td>
<td>0.6 0.6</td>
</tr>
</tbody>
</table>
The full text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
Defining a molecular subclass of treatment resistant prostate cancer. First Author: Himisha Beltran, Weill Cornell Medical College, New York, NY

Background: A subset of advanced prostate cancers can progress from an androgen receptor (AR)-driven state to AR independent, often with low or absent AR expression and extensive neuroendocrine differentiation. Once neuroendocrine prostate cancer (NEPC) develops, patients often demonstrate an aggressive clinical course and poor overall survival. Diagnosis is important but remains challenging as the clinical and pathologic features associated with AR independence and NEPC are poorly defined.

Methods: We performed whole-exome sequencing (WES) of 61 advanced prostate cancers. Gene expression was assessed using the 12am 81 patients with measurable disease. Using Cox regression analysis, looking at survival and other covariates, we compared the NEPC group versus the AR+/AR- group. To define a molecular subclass of treatment resistant prostate cancer (CRPC), we used a combination of our WES data and the NEPC criteria to define a molecular profile of the disease.

Results: The molecular landscape of NEPC and castration-resistant prostate cancer (CRPC) failed to do significantly by rate of non-synonymous mutations or copy number burden (average > 40% of genome was aberrant), and polyplody was frequently detected together with common allelic imbalances. Comparative analysis at the DNA and mRNA level identified decreased AR signaling in NEPC and a range of AR signaling in CRPC, enrichment of copy number losses (including RB1 and multiple genes on 16q) in NEPC, and focal high level AR amplification in CRPC in contrast to NEPC (p = 0.0007). DNA allelic-specific analysis of multi-sample cases suggested diverse genomic state of key lesions including aberrations in MYCN and CDKN1B.

Conclusions: This is largest study to date focused on the molecular landscape of the NEPC resistance phenotype. NEPC is characterized by a molecular profile defined by distinct genomic alterations and decreased AR signaling. Patients with NEPC demonstrate lower AR signaling and molecular overlap with NEPC. This study supports clonal evolution of prostate adenocarcinoma to NEPC, provides new insight into NEPC biology and disease heterogeneity, and may aid in the detection of AR independence and emergence of the NEPC subclass of treatment resistance.

Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): Results of the GETUG-AFU 16 phase III randomized trial—NCT00423475. First Author: Christian Carrie, Department of Radiation Oncology, Centre Léon Bérard, Lyon, France

Background: RT is the standard as salvage treatment after RP. The role of HT is not demonstrated to date. This trial assessed the efficacy of RT alone or RT+HT on progression-free survival (DFS) (biological or/and clinical relapse) for patients with BR after RP. Secondary objectives were overall survival (OS), toxicity and quality of life (QoL). Patients (pts) were randomized (1:1; stratification on risk factors at RP and type of planned treatment)](1:1) to RT alone (66 Gy on prostate bed +/+ pelvic irradiation according to pN status and risk of initial node involvement) or RT+HT (goserelin, for 6 months). Assuming 5-year DFS of 45% for RT arm, the trial required 369 pts per arm to detect an improvement of 12% in DFS for RT+HT arm (90% power and 5% alpha risk). BR was evaluated according to Astro-consensus.

Results: From Oct. 2006 to Mar. 2010, 743 pts (RT: 374; RT+HT: 369) were randomized. Baseline characteristics were well balanced between the arms, median age: 67 y, pT2ac: 54%, pT3ac: 46%, Gleason > 6: 76%, positive margins: 51%, seminal vesicles’ involvement 13%. PSA doubling time at relapse was > 6 months in 74%. With a median follow-up of 63.1 months, 216 events were notified (138 in RT vs 78 in RT+HT). The intent to treat analysis showed an improved 5-year DFS of 62.1% (C95%: 59-65) vs 57.6% (C95%: 54-60) for RT and RT+HT, respectively (log-rank: p < 0.0001). The risk of disease progression (DPS) at 5 years was 50% in both arms (C95%: 47-54 vs 52-57). Cause of death was progressive disease in 2.1% pts on RT arm vs 0.8%. Acute toxicities occurred more frequently in RT+HT arm (89% vs 79%). No difference was found in grade 3 acute toxicities (1.9% vs 2.2%) and late toxicities (18.8% vs 21.5%). No toxic death was observed. Conclusions: GETUG-AFU 16 is the first randomized trial comparing RT vs RT+HT as salvage treatment for BR after RP with undetectable post-op PSA. RT+HT significantly improve the 5-year DFS without increasing acute or late grade 3 toxicities. A longer follow up is required to quantify the impact on OS but RT+HT could be considered as the standard in this situation. Clinical trial information: NCT00423475.
Long-term consequences of intermittent and continuous androgen deprivation in older patients with metastatic prostate cancer. First Author: Dawn L. Henderson. Columbia University Medical Center, New York, NY

Background: Although intermittent androgen deprivation therapy (ADT) has not been associated with better overall survival in prostate cancer (PC), it has the potential for lower side effects and potential for better quality of life (QOL). The incidence of long-term side effects has not been reported.

Methods: We analyzed a subset of patients from S9346, a randomized SWOG trial of intermittent vs. continuous ADT in patients with metastatic PC. To identify late effects by treatment arm, we estimated time to receiving therapy between those with and without ischemic or thrombotic events (47% vs 47%, p = 0.86). There were no statistically significant differences by arm in any other late effects.

Results: In total, n = 1134 eligible US-based patients with metastatic prostate cancer were randomized to continuous vs. intermittent ADT on S9346. A total of 636 (56%) of trial participants had > 1 year of continuous Medicare parts A & B coverage and no HMO participation. The mean age was 71.5 years. The most common late effects recorded in claims in the cohort were hypercholesterolemia (31%) and osteoporosis (21%).

The 10-year cumulative incidence of ischemic and thrombotic events were differing by arm; 23% for continuous therapy and 32% for intermittent ADT patients (Hazard Ratio = 0.68, p = 0.02). On IAD arm, there was no difference in the mean percentage of time receiving therapy between those with and without ischemic or thrombotic events (47% vs 47%, p = 0.86). There were no statistically significant differences by arm in any other late effects.

Conclusions: Despite beliefs that intermittent ADT could reduce long-term health-related effects compared to continuous ADT, we found that older men assigned to intermittent ADT had a slightly increased incidence of ischemic and thrombotic events and no apparent reduction in bone related, endocrine, or cognitive events.
Effects of radiium-223 dichloride (Ra-223) with docetaxel (D) vs D on prostate-specific antigen (PSA) and bone alkaline phosphatase (bALP) in patients (pts) with castration-resistant prostate cancer (CRPC) and bone metastases (mets): A phase 1/2a clinical trial. **First Author:** Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Ra-223 is an approved α-emitter that prolongs survival in CRPC with bone metastases. We presented data from a phase 1/2a study of safety and antitumor effects of Ra-223 + D vs D alone showing that Ra-223 + D is safe and well tolerated (ESMO 2014). Here we report the effect of Ra-223 + D vs D on bALP and PSA dynamics. **Methods:** D - eligible pts with progressive CRPC and ≥ 2 bone mets received (2:1) Ra-223 (50 kBq/kg × 6 wk × 5) + D (60 mg/m² q 3 wk × 10) or D (75 mg/m² q 3 wk with a step-down option to 60 mg/m²). bALP and PSA were recorded q 3 wk for 6 wk-cycle, then q wk and q 3 wk, respectively, and analyzed at a central laboratory. Changes in both markers are described by the % of pts whose best responses were > 50%, > 75%, > 90%, or >95%, with ≥ 80% declines from baseline (BL) and p = and bALP levels from baseline. No pt had a bALP increase. Pts continue in follow-up (to 12 mo after first injection) for safety and progression. **Conclusions:** Ra-223 + D appears to favorably impact post-treatment declines in PSA and bALP levels from baseline. Effective normalization of bALP levels was also recorded, regardless of % decline.

**Results:** 46 pts (33 Ra-223 + D vs 13 D alone) were enrolled. As of January 2015, 24 (Ra-223 + D) vs 5 (D) pts had all planned injections. Median (range) baseline PSA was 99 μg/L (3-1000) for Ra-223 + D pts and 43 μg/L (4-1042) for D pts. The table shows maximal changes in PSA and bALP levels from baseline. No pt had a bALP increase. Pts continue in follow-up (to 12 mo after first injection) for safety and progression. **Conclusions:** Ra-223 + D appears to favorably impact post-treatment declines in PSA and bALP levels from baseline. Effective normalization of bALP levels was also recorded, regardless of % decline.

**Methods:** Change from baseline, n (%)

<table>
<thead>
<tr>
<th>PSA</th>
<th>bALP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra-223 + D</td>
<td>D</td>
</tr>
<tr>
<td>N = 33</td>
<td>N = 13</td>
</tr>
<tr>
<td>Any increase</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Best responses, decreases</td>
<td></td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>4 (12)</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>26 (79)</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>21 (64)</td>
</tr>
<tr>
<td>&gt; 80%</td>
<td>10 (30)</td>
</tr>
</tbody>
</table>

*Pts with baseline bALP > ULN (> 21 μg/L). N/A = not applicable.
Validation of a genomic classifier for prediction of metastasis following postoperative salvage radiation therapy. First Author: Robert Den, The Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA

Background: Management of patients with a postoperative rising prostate-specific antigen (PSA) level is complex. Additional local treatment such as salvage radiation therapy (SRT) may be sufficient for many patients but some may require concurrent systemic therapy in order to delay or prevent metastatic disease. As PSA recurrence on its own is a poor surrogate for metastatic disease we hypothesized that the Decipher genomic classifier (GC), a validated predictor of metastasis may be able to better distinguish those patients where additional local therapy is beneficial from those where SRT on its own is likely insufficient. Methods: Genomic classifier (GC) scores were calculated from 166 prostate cancer patients, who received SRT at the Veteran Affairs Medical Center Durham, Thomas Jefferson University and Mayo Clinic, between 1990 and 2010. SRT was defined as administration of RT with Pre-RT PSA levels > 0.2 ng/ml. GC and CAPRA-S scores were compared using survival c-index, competing-risks and Cox regression analysis for the prediction of metastasis. Results: Survival c-index for predicting metastasis 5 years post SRT was 0.87 (95% CI: 0.73-0.90) for GC and 0.62 (95% CI: 0.48-0.77) for CAPRA-S. The cumulative incidence of metastasis at 5 years post-SRT was 2.8%, 5.8%, and 33.3% for low, average, and high GC scores (p < 0.001) for low, average and high CAPRA-S scores (p = 0.19). In univariable analysis only GC, extraprostatic extension and Pre-RT PSA were significant predictors of metastasis. In multivariable analyses with clinical risk factors or the CAPRA-S nomogram, GC was the only independent predictor of metastasis with a HR of 1.59 (1.17-2.16, p = 0.0017) for a 10% unit increase in risk score. Conclusions: In patients treated with postoperative SRT for PSA recurrence, GC is a powerful predictor of metastasis. Patients with low Decipher have excellent prognosis with SRT and may avoid concurrent hormone therapy. Patients with high Decipher risk are at higher risk for metastatic disease and SRT failure and may benefit from concurrent systemic therapy.

Combination statin/metformin and prostate cancer specific mortality: A population-based study. First Author: Grace L. Lu-Yao, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Obesity and metabolic syndromes (MetS) are associated with an increased risk of prostate cancer mortality. A recent pre-clinical study showed that combination statin/metformin (CSM) was more effective in inhibiting prostate cancer metastasis than standard chemotherapy (docetaxel) with less toxicity in an in vivo mouse model. As clinical data on this topic are limited, this population-based study is to examine the association between treatment with CSM and prostate cancer specific mortality (PCSM) by obesity/MetS status. Methods: SEER-Medicare linked data were used to identify patients with high-risk prostate cancer (stage T3/T4 or PSA >20 or Gleason 8-10) in 2007–2009. Prescription drug use was identified from Medicare Part D Event files. Obesity/MetS conditions were identified by the presence of ICD-9 diagnosis codes 278.00, 278.01, or 277.7. Cox proportional hazards models were used to test CSM with covariates including demographic characteristics, prognostic factors, and cancer treatment received. Results: This study cohort consisted of 22,110 high-risk prostate cancer patients, of which 1,365 died of prostate cancer by 12/31/2009. Use of CSM was associated with a 43% reduction in PCSM, more pronounced in men with obesity/MetS conditions (Table). The results were similar when we limited the analysis to patients with minimal morbidity. Conclusions: To our knowledge, this is the largest clinical study to assess the potential effect of CSM on PCSM. CSM or statin use was associated with a large reduction in PCSM, particularly in patients with obesity/MetS conditions. The potential benefits of metformin use may be secondary to concomitant statin use in this population. Further studies are needed to confirm these results.

Statin/metformin treatment and PCSM among high-risk prostate cancer patients.

<table>
<thead>
<tr>
<th>Medication used</th>
<th>Overall (HR (95% CI) ▶)</th>
<th>Non-Obese &amp; Non MetS (HR (95% CI) ▶)</th>
<th>Obese or MetS (HR (95% CI) ▶)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin + Metformin</td>
<td>0.30 (0.07 – 1.27)</td>
<td>0.60 (0.39 – 0.93)</td>
<td>0.57 (0.38 – 0.88)</td>
</tr>
<tr>
<td>Statin alone (N=4,075)</td>
<td>0.09 (0.01 – 0.64)</td>
<td>0.64 (0.50 – 0.82)</td>
<td>0.60 (0.47 – 0.76)</td>
</tr>
<tr>
<td>Metformin alone (N=4,115)</td>
<td>—</td>
<td>0.98 (0.57 – 1.68)</td>
<td>0.92 (0.54 – 1.57)</td>
</tr>
</tbody>
</table>

*HR = Hazard Ratios compared to non-users (N = 15,802) and 95% confidence intervals (CI).
HSDB1 and resistance to androgen deprivation therapy in prostate cancer. First Author: Jason W.D. Hearn, Cleveland Clinic, Cleveland, OH

Background: The somatic mutation HSDB1 (1245A > C) has been mechanistically linked to castration-resistant prostate cancer by encoding a mutant enzyme that augments intratumoral dihydrotestosterone (DHT) synthesis. Given the HSDB1 (1245C) allele is also frequently found in the germline, we hypothesized men inheriting this variant allele would exhibit resistance to androgen deprivation therapy (ADT), as manifested by earlier clinical outcomes. Methods: We used a large, prospectively maintained prostate cancer registry to identify men treated with ADT for biochemical failure in the post-prostatectomy setting who were without evidence of metastatic disease. We analyzed progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) according to HSDB1 genotype using Kaplan-Meier methods. Cox proportional hazards regression was performed to evaluate potential gene-dosage effects, with homozygous wild-type men serving as the reference group. Demographic and treatment characteristics were compared to assess for possible confounders using Fisher’s exact test and Kruskal-Wallis analysis of variance. Multivariable analysis (MVA) was performed to assess whether HSDB1 genotype independently predicted clinical outcomes. Results: Of 118 men genotyped, 37% were homozygous wild-type, 53% were heterozygous, and 10% were homozygous variant. Demographic and treatment characteristics did not differ across groups. Median PFS diminished as a function of the number of variant alleles inherited (6.6 years in homozygous wild-type men, 4.1 years in heterozygotes, and 2.5 years in homozygous variant men; P = 0.01). Median DMFS likewise decreased according to the number of variant alleles inherited (9.1 years vs. 6.8 years vs. 3.6 years, respectively; P = 0.01). Finally, OS similarly diminished (5-year OS: 82% and 55% vs. 74% and 58% and 0%, respectively; P = 0.006). On MVA, the associations between HSDB1 genotype and metastasis (hazard ratio (HR) 2.76; P = 0.001) and death (HR 3.33; P = 0.016) were maintained. Conclusions: Inheritance of the variant HSDB1 (1245C) allele that enhances DHT synthesis may be a powerful predictor of resistance to ADT for prostate cancer.

Project Data Sphere: A first look at prostate cancer including concomitant medication use, prognosis, and toxicity. First Author: Anthony M. Joshua, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: PDS (www.projectdatasphere.org) enables patient-level analyses of control arms of cancer trials. We aimed to include the use of concomitant medications (CM) to (i) validate and establish prognostic metastatic prostate cancer (mCRPC) models (ii) establish novel predictive factors of toxicity. Methods: Data was obtained for 2,747 control subjects with mCRPC from 7 Phase III clinical trials (1962 subjects were available for OS analysis) and 5 studies used to calibrate the Kaplan-Meier method. Cox-proportional hazards models, stratified by trial, were used to estimate hazard ratios. Results: Of 23 medication classes examined patients taking proton pump inhibitors (HR: 1.17, P = 0.017) and Erythropoetin (HR: 1.45, P < 0.001) had worse OS. Patients taking fish oil (HR: 0.67, P = 0.025) and non-hippocampal statins (HR: 0.67, P = 0.017) had improved OS. Initially, metastatic site was significant for OS (predicted median: Node 24,61m, Bone 22,77 m, Lung 21,39 m, Liver 15,18 m; P = 0.001). After adjusting for metastatic site, these medication classes remained significant (HR 1.15, P = 0.017; HR 1.493, P < 0.01; HR 0.68, P = 0.03; HR 0.68, P = 0.0278 respectively). We then validated, and combined 2 multi-variate prognostic models for OS (Templeton et al, Sonpade et al) after inclusion of CM. Patients taking metformin (HR: 0.729, P = 0.008) and Cox2 inhibitors (HR: 0.708, P = 0.015) had improved OS whilst those taking low molecular weight heparin (HR: 1.342, P = 0.004) had worse OS. Therapeutic drug monitoring (TDM) based on albumin and LDH alone, equivalent in prognostication was established. For docetaxel trials from baseline, baseline neutrophil to lymphocyte ratio was the best predictor of any toxicity (OR 4.23, P = 0.004) after accounting for number of cycles, whilst the lymphocyte count had an inverse relationship with the occurrence of any severe AE (OR 0.31, P = 0.03). The incidence of toxicity after cycle 1 was the best predictor of subsequent adverse events (OR 5.82, P < 0.01) Conclusions: Initial analyses of PDS data in mCRPC allowed for insights into prognostic models and predictors of docetaxel toxicity. Expansion of trials and quality of data will facilitate future analyses.

Association of the prostate cancer risk mutation 84E in HOXB13 with the subtype of ETS fusion negative adenocarcinoma with early age of diagnosis. First Author: Thomas J. Shewmaker, University of Ulm, Medical School, Department of Urology, Ulm, Germany

Background: HOXB13 was discovered as the first prostate cancer (PrCa) specific high-risk susceptibility gene. The most prevalent HOXB13 germ-line mutation in PrCa patients of European descent is HOXB13G84E, which likely originated in Northern Europe. Previous molecular examination of a set of 84E-driven tumors suggested a distinct somatic phenotype, with concomitant ETS gene fusions present at unusually low frequency as compared to the general prevalence of ETS fusions in PrCa (22 % vs approx. 50 %). Methods: We have analyzed 942 cases from three European ancestry populations for the coincidence of HOXB13G84E and the most common ETS fusion, TPMRSS2-ERG(T2E), in corresponding tumor samples. Results: While the prevalence of T2E fusions was similar among study sites (range: 5.6% - 60.7%), the frequency of 84E genotypes differed markedly between US (1.5%), German (3.6%) and Finnish samples (8.3%). Despite the expected frequency gradient among study populations, all subsamples showed a strong enrichment of 84E4E mutation carriers among T2E fusion negative cases as compared to fusion positive cases (center adjusted OR = 4.90, 95%CI = 2.19 - 11.0; p = 0.0001). Consistent with the previous study, the crude frequency of the T2E fusion in HOXB13G84E carriers was 23.5 % (range 16.7 % - 28.5 %). Examination of disease characteristics highlighted age at diagnosis, with fusion positive cases being diagnosed 1.75 (0.87 - 2.63) years earlier than fusion negative cases (p < 0.0001). Age at diagnosis in 84E carriers did not differ significantly from non-carriers (p = 0.26). However, within the subtype of fusion negative carcinoma, which is usually associated with later ages at diagnosis, carriers of 84E4E were diagnosed on average 2.93 (0.49 - 5.37) years earlier (p = 0.02). No associations were seen for tumor stage, tumor grade or diagnostic PSA levels. Conclusions: This study demonstrated a tumor type specific association for HOXB13 G84E mutation carriers having a higher frequency of T2E fusion negative PrCa. Although the T2E fusion negative subtype is known to be associated with later ages of diagnosis, HOXB13 driven tumors within this subtype may represent an early onset subgroup.

PET imaging with 68Ga-hBed-labeled ligand of prostate-specific membrane antigen (68Ga-HBED-PSMA) for staging of biochemical recurrent prostate cancer after radical prostatectomy. First Author: Tobias Maurer, Department of Urology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany

Background: Staging of recurrent prostate cancer (PCa) after radical prostatectomy (RP) remains challenging especially at low PSA values. Prostate-specific membrane antigen (PSMA) shows increased expression on most PCa and might therefore be useful for detection of PCa lesions. Aim of this retrospective analysis of consecutive pts was to evaluate the detection rate of PET hybrid imaging using the PSMA inhibitor Glu-NH-CO-NH-Lys-(Ahx)-(68Ga(HBED-CC)) (68Ga-HBED-PSMA) in pts with biochemical recurrence (BCR) of PCa after RP. Methods: 332 consecutive pts with BCR of PCa after RP and a median PSA value of 1.7 mg/ml (range 0.2-10 ng/ml) were included in this analysis. After injection of 122±17 MBq 68Ga-HBED-PSMA-PET/CT or PET/MR was performed in 256 pts and 76 pts, respectively. One nuclear medicine physician and one radiologist reviewed imaging in consensus. Detection rates according to PSA value were determined. Results: In total, detection rates for 68Ga-HBED-PSMA-PET hybrid imaging were 96.0% (143/149) for PSA values > 2 ng/ml, 92.0% (80/87) for PSA values 1-2 ng/ml, 72.3% (34/47) for PSA values 0.5-1 ng/ml and 53.0% (26/49) for PSA values 0.2-0.5 ng/ml, respectively. In 28.9% (96/332) of pts solely PSMA-PET detected suspicious lesions whereas 2.7% (9/332) of pts only showed positive findings in morphological imaging. Additional lesions were seen in 21.4% (71/332) of pts in PSMA-PET and in 6.3% (21/332) in CT or MRI. Conclusions: 68Ga-HBED-PSMA-PET hybrid imaging shows higher detection rates in pts with recurrent PCa at low PSA values than reported for other PET-tracers like 18F-FDG or choline derivatives. Thus, 68Ga-HBED-PSMA-PET hybrid imaging has the potential to replace PET imaging with these tracers for staging of BCR of PCa after RP in the future.
5024 Poster Session (Board #16), Sat, 1:15 PM-4:45 PM
Statin use at the time of initiation of androgen deprivation therapy and time to progression in patients with hormone-sensitive prostate cancer. 
First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA
Background: Statin use has been associated with improved prostate cancer outcomes such as decreased risk of recurrence after local therapy and a lower risk of prostate cancer mortality. DHEAS is a precursor of testosterone and a substrate for SLCO2B1, an organic anionic transporter. We previously demonstrated that genetic variants of SLCO2B1 correlated with time to progression (TTP) on androgen deprivation therapy (ADT). Statins utilize SLCO2B1 to enter cells, thus, we hypothesized that statin use at ADT initiation might prolong TTP by competing with DHEAS uptake. Methods: To determine if statins interfere with DHEAS uptake, we performed in vitro studies using prostate cancer cell lines. Next, we queried our institutional clinical database for patients treated with ADT for biochemical or metastatic recurrence or de novo metastatic prostate cancer (ADT cohort). The association between statin use and TTP on ADT was estimated using multivariable Cox regression and adjusted for known prognostic factors. Results: In vitro, we demonstrated that statins block DHEAS uptake by competitively binding to SLCO2B1. In our ADT cohort of 926 patients treated between January 1996 and November 2013, 283 (31%) were taking a statin at ADT initiation. After a median follow-up of 5.8 years, 644 patients (70%) had progressed on ADT. Median TTP on ADT was 20.3 months (95% CI: 18.2, 24). Men on statins had a longer median TTP on ADT compared to non-users (27.5 vs. 17.4 months, p < 0.0005). The association remained statistically significant after adjusting for pre-defined prognostic factors (adjusted HR = 0.83 (p = 0.039)). The positive statin effect was observed for both patients with and without metastases. Conclusions: Statin use at ADT initiation was associated with a significantly longer TTP on ADT even after adjusting for known prognostic factors. Our in vitro findings that statins competitively reduce DHEAS uptake and thus, effectively decrease the available intratumoral androgen pool, afford a plausible mechanism to support the clinical observation of prolonged TTP in statin users.

5025 Poster Session (Board #17), Sat, 1:15 PM-4:45 PM
Phase II trial of the PI3 kinase inhibitor BKM120 with or without enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC). 
First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC
Background: PI3K pathway activation is common in mCRPC. BKM120 (buparlisib) is an oral, pan-class I PI3 kinase inhibitor. Preclinical data demonstrated a reciprocal feedback loop between PI3K and androgen receptor (AR) signaling; thus, we evaluated the efficacy of BKM120 in men with heavily pre-treated mCRPC including those progressing on enzalutamide (Enz). Methods: This was a 3 site phase 2 Dept of Defense Prostate Cancer Clinical Trials Consortium open-label trial of BKM120 100 mg once daily with ongoing ADT in men with mCRPC who had failed or were not candidates for docetaxel. Continuation of E was permitted in men progressing on E with subsequent addition of BKM120. The primary endpoint was the rate of composite of radiographic and clinical PSA at 6 months with a goal of 40% vs. a historic rate 25% using a two-stage design with interim futility analysis. Results: Thirty men were accrued: 63% post-docetaxel; median PSA was 70 ng/dl; 83% had >4 prior therapies for CRPC; 43% men received concurrent E. The trial met criteria for futility, with a 6 month PSA rate of 10% (95% CI 2.5-23.6%). Median composite PSA was 1.9 months (95% CI: 1.8, 3.4) and 3.5 months (95% CI 1.2, 5.5) with concurrent E. Median OS was 11 months (95% CI 4.8, 14.4). E did not appear to increase the BKM120 side effect profile. The PSA decline proportion was 23%, but no patients achieved a >50% decline, with median PSA change of +39%. No objective responses were observed. Related SAEs occurred in 3 men including respiratory infection and organ failure (1), urinary tract obstruction due to local progression (1), and severe confusion (1). One seizure was observed in a man who was found to have a new CNS metastasis during concurrent BKM120/E therapy. Grade 3 related AEs were seen in 47% of patients, with 10% stopping for BKM120 due to toxicity. The most common related AEs included grade 1-2 weight loss, diarrhea, nausea, fatigue, anorexia, rash, hyperglycemia, and anxiety and mood disorders. Conclusions: BKM120 did not improve PFS over historic control data in men with mCRPC, either alone or when added to AR inhibition in men progressing on enzalutamide. These data suggest that PI3 inhibition is not sufficient to block mCRPC progression. Clinical trial information: NCT01385293.

5026 Poster Session (Board #18), Sat, 1:15 PM-4:45 PM
National prostate cancer screening rates following the 2012 United States Preventive Services Task Force recommendation discouraging prostate-specific antigen (PSA)-based screening. 
First Author: Michael William Drazer, University of Chicago, Chicago, IL
Background: The prostate cancer screening debate intensified following the 2012 United States Preventive Services Task Force (USPSTF) recommendation discouraging prostate-specific antigen (PSA)-based screening. Previously published USPSTF recommendations did not appreciably reduce screening among groups at high risk for over-diagnosis and overtreatment. The effects of the 2012 guidelines on screening are unknown. Methods: We used the National Health Interview Survey (NHIS), a nationally representative survey, to estimate the proportion of men age 40 and older screened for prostate cancer in 2010 and 2013. We utilized an externally validated nine-year mortality index to analyze screening rates based on remaining life expectancy. We used logistic regression to compare screening rates from 2010 to 2013 and explored which subgroups had significant changes in PSA screening. Results: Screening significantly declined from 2010 to 2013 among all men over 50. Men ages 60-74 were most heavily tested, with 51.2% screened in 2010 and 43.6% in 2013 (P < 0.01). Screening significantly declined for men ages 50-59 (P < 0.01) and over 75 (P = 0.03) but not among 40-49 year olds (P = 0.4). A large percentage of men with a high predicted likelihood (> 52%) of 9 year mortality were screened for prostate cancer, including approximately 32.2% of men over 75. Interestingly, college-educated men had higher screening rates than less college educated men but also had a larger screening decline from 2010 (62.7%) to 2013 (50.2%). Conclusions: Prostate cancer screening significantly declined among men over 50 following the 2012 USPSTF guideline discouraging PSA-based screening. A large proportion of men continued to be screened despite a high risk (> 52%) of nine-year mortality, including 32.2% of men age 75 and older.

5027 Poster Session (Board #19), Sat, 1:15 PM-4:45 PM
The combination of DNA ploidy status and PTEN/6q15 deletions to provide strong and independent prognostic information in prostate cancer. 
First Author: Maximilian Lennartz, Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Background: Aberrant DNA ploidy has been long discussed as a potential prognostic feature in prostate cancer. Methods: In this project, we analyzed the clinical significance of DNA ploidy in combination with the most frequent chromosomal deletions (PTEN, 6q15) with known prognostic impact in a contemporary series of 3,845 prostate cancers. Ploidy status was determined in 3,845 patients in 47% of patients, with 10% stopping for BKM120 due to toxicity. The most common related AEs included grade 1-2 weight loss, diarrhea, nausea, fatigue, anorexia, rash, hyperglycemia, and anxiety and mood disorders. Conclusions: BKM120 did not improve PFS over historic control data in men with mCRPC, either alone or when added to AR inhibition in men progressing on enzalutamide. These data suggest that PI3 inhibition is not sufficient to block mCRPC progression. Clinical trial information: NCT01385293.
Phase 1b study of ARN-509 with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). First Author: Daniel Costin Danila. Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: ARN-509 and AA target the androgen receptor (AR) axis via different mechanisms and may have complementary activity in mCRPC. ARN-509, a potent and selective AR antagonist, inhibits AR nuclear translocation and DNA binding without significant AR agonist properties (Clegg. Cancer Res. 2012). AA is a prodrug of abiraterone, a CYP17 inhibitor that blocks androgen synthesis. No randomized trials are expected for the combination. This phase 1b study evaluates potential PK drug-drug interaction, antitumor activity, and safety of ARN-509 in combination with AA + P (NCT02123758). Methods:Pts with progressive mCRPC and ECOG PS ≤ 2 received AA (1000 mg/d) + P (5 mg BID) beginning on Cycle 1 (C1) with addition of ARN-509 (240 mg/d) on C1D8 in 28-day treatment cycles. Efficacy assessment was based on RECIST and PCWG2 criteria. Results: 29 pts started treatment on study. Median age was 70 years (range 49-83) and median PSA was 56.8 µg/L (range 4.1 - 2597.0 µg/L). Bone, nodal, and visceral disease were present in 25 (86%), 17 (61%), and 8 (29%) pts, respectively. 14 (48%) pts were previously treated with docetaxel, 12 (41%) with AA, 12 (41%) with enzalutamide (ENZ). 22 pts are currently on treatment and 7 discontinued for disease progression. Thus, 41% of pts have had PSA declines >50%; 52% had any PSA decline. Confirmed PSA responses >50% included 3 pts who failed prior ENZ or AA therapy. Most common (≥ 3 pts) drug-related adverse events (AEs) were grade 1-2 and included fatigue (n = 8), dysgeusia (n = 5), vomiting (n = 4), anorexia (n = 4), abdominal pain (n = 3), diarrhea (n = 3), nausea (n = 3). Grade 3 drug-related AEs (hypotension (n = 1), fatigue (n = 1), increased ALT (n = 1), bilateral lower eyelid dermoids (n = 1)) were managed by drug interruption and supportive measures. Conclusions: Interim data indicate that ARN-509 in combination with AA + P is well tolerated in pts with mCRPC. Further study of the efficacy and safety of ARN-509 and AA + P for mCRPC is warranted. Clinical trial information: NCT02123758.

Immune responses and clinical outcomes in STAND, a randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically-recurrent prostate cancer (BRPC) after local therapy failure. First Author: Emmanuel S. Antonarakis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: STAND (NCT01431391) assessed optimal sequencing of sip-T and ADT in men with BRPC at high risk of metastases after local therapy (i.e., prostate specific antigen doubling time [PSADT] < 12 mo). Methods: Men (n = 68) were randomized to sip-T then ADT (1 wk post infusion 3; Arm 1) or ADT (3 mo lead-in) then sip-T (Arm 2). Cellular and humoral immune responses, and clinical outcomes were analyzed. PSA recurrence was defined as ≥ 2 serial rises in PSA and an absolute PSA value of < 0.2 ng/mL (prior radical prostatectomy) or ≥ 2.0 ng/mL (prior radiation therapy alone). PSA post-ADT was analyzed. Time to next anticancer intervention (TTACI) was measured from first ADT to the day of the next systemic therapy. Rate of metastases at 24 mo was also investigated. Results: All men received 3 sip-T doses, and 96% received 12 mo ADT. Cellular and humoral responses to PA2024 (increased following treatment vs baseline [BL]) were sustained at all post-sip-T timepoints through 24 mo (p < 0.05). PA2024-specific T cell proliferation responses were higher in Arm 1 vs Arm 2 (p < 0.001). The number of PA2024 antibody (Ab) responders (post-BL Ab titer ≥ 25,600) was similar between arms. Sip-T-mediated antigen spread was observed in both arms vs BL and maintained at all post-sip-T timepoints through 24 mo.AFP (p = 0.06) and PSA (p = 0.13) were higher at post-sip-T timepoints vs BL, with a trend towards fewer/7.5 ml of blood) in 55% (10/18, 33-77%) of cases. CTC showed a readily detectable STEAP+ signal in EpCAM+ events by FACS in 48% (14/29, 30-67%), confirmed by RT-PCR, with AR (androgen receptor) and KLK3 expression. STEAP+ – events were EpCAM+ in a range from 0-74%. AD activity by IHC and CTC is shown in Table. For STEAP+ IHC imaged pts, PSA decline by ≥ 50% was noted in 4/14 (29%, 8-58%) pts. Time on treatment correlated with bone metastasis SUVmax (r = 0.63). All 8 PET-guided biopsies were confirmed STEAP+ IHC ≥ 3. Conclusions: The best evidence for STEAP+ activity by PSA declines, time, and CTC conversion was seen in high expression tumors. Pts with IHC ≥ 3+ tumors are being prospectively selected in an expansion study where predictive biomarkers are studied as companion diagnostics.

Baseline analysis of circulating tumor cell (CTC) enumeration and androgen receptor (AR) localization in men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY. First Author: Scott T. Tagawa, Weill Medical College of Cornell University, New York, NY

Background: Microtubule-targeted therapy with taxanes is the only chemo with survival benefit in advanced PC. Emerging molecular evidence suggests sensitivity/resistance to taxanes may relate to the ability of microtubulues to inhibit AR nuclear trafficking. CTC represent a real-time biomarker for molecular testing including taxane-induced microtubule stabilization and AR nuclear localization. TAXYNERGY is an international, multicenter phase 2 trial in progressive, chemo-naive mCRPC men randomized (2:1) to docetaxel or cabazitaxel. Pre-treatment CTCs were enriched from 1 ml blood via a prostate-specific microfluidic device, enumerated, and analyzed by multiplex confocal microscopy for AR cellular localization. Nuclear AR % was calculated by integrating fluorescence intensity in the total cell and nuclear area. Bivariate correlations and multiple regressions examined associations between baseline characteristics and % nuclear AR or CTC count. Results: 63 men were randomized (median age 70 (range 53–84), median PSA 89 (2.4–1558), 24 (38%) previously received a CYP17 inhibitor and/or enzalutamide, 17 (27%) had visceral metastases). Of 59 with evaluable samples, CTCs were detected in 48% (28/59, 30-67%). PSA decline by > 50% was noted in 4/14 (29%, 8-58%) pts. Time on treatment correlated with bone metastasis SUVmax (r = 0.63). All 8 PET-guided biopsies were confirmed STEAP+ IHC ≥ 3. Conclusions: Nearly 90% of men with progressive chemo-naive mCRPC have detectable CTCs available for molecular analysis using this platform, with higher CTC counts associated with adverse prognostic variables. Lower percent of nuclear AR was associated with visceral metastases, suggesting progressive visceral CRPC may be less AR-driven. The predictive value of these biomarkers for taxane response is being evaluated. Clinical trial information: NCT01718353.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
5033  Poster Session (Board #25), Sat, 1:15 PM-4:45 PM Performance of CCP assay in an updated series of biopsy samples obtained from commercial testing. First Author: John W. Davis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The cell cycle progression (CCP) score is an RNA-based expression assay, which has improved the prediction of prostate cancer aggressiveness in nine separate retrospective cohorts. In this analysis, we characterized the patient population and CCP score performance in commercial testing. Methods: Formalin-fixed prostate biopsy samples from 4261 patients were submitted by 930 physicians to Myriad Genetic Laboratories for CCP test analysis. Patient clinicopathologic data was obtained from the test request form. The CCP score was calculated based on RNA expression of 31 cell cycle progression genes normalized to 15 housekeeping genes. Patients were sorted into AUA risk categories and on RNA expression of 31 cell cycle progression genes normalized to 15 housekeeping genes. Patients were sorted into AUA risk categories and

5034  Poster Session (Board #26), Sat, 1:15 PM-4:45 PM Radium-223 in an international early access program (EAP): Effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. First Author: Fred Saad, University of Montreal, Montreal, QC, Canada

Background: The pivotal ALSYMPCA study reported improved overall survival (OS) in bone symptomatic mCRCP patients (pts) treated with radium-223 (Ra-223) vs placebo (median 14.9 vs 11.6 months [mos], HR = 0.70). Data from 638 EAP pts recruited from 14 countries (Europe, Canada, Israel) are presented. Methods: In this prospective phase IIb study, mCRCP pts with symptomatic or asymptomatic bone metastases (no visceral disease) received Ra-223 55kBq/kg (iv injection) every 4 weeks for 6 cycles. Primary endpoints were safety and OS. The effects of concomitant medications, baseline (BL) pain, alkaline phosphatase (ALP) and ECOG PS on OS were assessed. Results: 696 pts were treated; 58% received all 6 Ra-223 injections. At BL, median age was 72 years; 88% of pts were ECOG PS 0–1; pain was reported as: no pain, mild-moderate, and severe in 21%, 52%, and 27%, respectively. 60% of pts received prior therapy with docetaxel. For pts treated with concomitant therapy: 22% were with abiraterone; 20% with denosumab; 18% with bisphosphonates and 4% with enzalutamide. Grade 4 AEs were reported in 38% of pts; 21% discontinued Ra-223 due to AE. At the time of median analysis median OS was 16 mos [13–not estimated (NE)]. Median time to first SSE was 18 mos [17–NE]; 24% of pts had >50% confirmed ALP decrease from BL; 8% had >50% confirmed PSA decrease from BL. In post hoc analyses OS was statistically significantly longer in pts with BL: ALP <220 U/L vs ≥220 U/L; ECOG PS 0–1 vs ≥2; no pain vs mild-moderate vs severe. Concomitant denosumab, abiraterone, and concomitant bisphosphonates and enzalutamide were associated with a 30% reduction in OS (log-rank p-value <0.0001). Conclusions: Concomitant bisphosphonates, abiraterone, and enzalutamide are associated with a survival benefit that is >20% vs untreated pts. Median OS was 22 mos [95% CI 16.7–NE]. Clinical trial information: NCT02000279.

5035  Poster Session (Board #27), Sat, 1:15 PM-4:45 PM Circulating tumor cell (CTC) enumeration in men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide post-chemotherapy (phase 3 AFFIRM study). First Author: Martin Fleisher, Memorial Sloan Kettering Cancer Center, New York, NY

Background: CTC enumeration is a biomarker associated with clinical outcomes in patients (pts) with mCRPC. CTC count at baseline (BL) and post-treatment is prognostic for survival. Enzalutamide (ENZA) was approved for post-chemotherapy CRPC based on the overall survival (OS) benefit (AFFIRM trial). In this trial, CTC enumeration was embedded as a biomarker endpoint. Methods: AFFIRM was a phase 3 study (N = 1199, NCT00743131) randomizing men who received ≥2 docetaxel-based chemotherapy regimens to ENZA 160 mg/day or placebo (PBO) (2:1). CTC samples were collected at sites selected for logistics and investigator interest. Conversion rate was defined as a decline from ≥5 (unfavorable) to <5 (favorable) CTCs/7.5 mL of blood from BL to post-BL result. Results: BL CTCs were obtained from 447 of 1199 pts at 89 of 156 study sites; BL demographics and disease history were similar to pts in whom samples were not collected. 382 pts had both BL and post-BL counts; OS, rPFS and select disease characteristics for pts with CTC data are shown in the table. Conversion from unfavorable to favorable CTC counts was observed in 61 of 127 pts (48%; 95% CI 39%-57%) treated with ENZA compared to 6 of 62 pts (9.7%; 95% CI 3.6%-20%) with PBO (p <0.0001). Progression from favorable to unfavorable counts occurred in 18% of ENZA pts compared to 44% with PBO. Conclusions: Unfavorable baseline CTC counts were associated with higher PSA and greater disease burden. The higher rate of conversion from unfavorable to favorable and lower conversion from unfavorable to favorable for ENZA relative to placebo was consistent with observed OS benefit. Clinical trial information: NCT00974311.

5036  Poster Session (Board #28), Sat, 1:15 PM-4:45 PM Enzalutamide (ENZA) in men with chemotherapy-Naive metastatic castration-resistant prostate cancer (mCRPC): Final analysis of the phase 3 PREVAIL trial. First Author: Thomas M. Beer, Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR

Background: PREVAIL (NCT01212991) was a phase 3 trial that investigated the impact of ENZA vs placebo (PBO) on overall survival (OS) and radiographic progression-free survival (rPFS) in asymptomatic or mildly symptomatic chemotherapy-naive men with mCRPC. ENZA improved OS (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.60–0.84; P < 0.0001) and rPFS (HR 0.80; 95% CI 0.75–0.85; P < 0.0001). Concomitant bisphosphonates and enzalutamide were associated with a survival benefit that is >20% vs untreated pts. Median OS was 22 mos [95% CI 16.7–NE]. Clinical trial information: NCT01212991.

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5037 Poster Session (Board #29), Sat, 1:15 PM-4:45 PM
Phase 1 study with expansion cohorts of cabozantinib (C) + abiraterone (A) in metastatic castration resistant prostate cancer (mCRPC): Investigator-sponsored study. First Author: Christopher Sweeney, Dana-Farber Cancer Institute, Boston, MA

Background: A and C (multi-tyrosine kinase inhibitor including MET and VEGFRs) have complementary mechanisms of action and activity in CRPC. In vivo work with LAPC4-CR (castration and A resistant cell line) has shown the combination has enhanced activity. Methods: Phase I, L, 3 + 3 trial with A fixed at 1,000 mg/day and prednisone 5mg BID and escalating daily doses of C (20mg, 40mg, 60mg) in pts with mCRPC was conducted. Cycles were 28 days. Results: 27 patients were enrolled with a median followup of 9.2 months (range 6-29.4 months). 11 pts had prior docetaxel therapy. No DLTs in the first 28 day cycle of dose escalation cohorts. The 60 mg C cohort had Gr 2 adverse events (AEs) of myelosuppression (2), fatigue (2) and DVT (1) in cycles 2 and 3 necessitating a dose reduction to 40 mg (no change to A). Due to a preferable tolerability profile, the 20, 40, and 60 mg C cohorts were expanded to a total of 12 pts each. See Table for activity data. Gr 3 treatment related AEs: 5 pts at 20mg C [skin infection (1), diarrhea (1); anemia (1); transaminase (1); hypophosphatemia (1)]; 7 pts at 40mg C [hypertension (1), hypophosphatemia (2), transaminase (1); colitis (1); lipase incr. (1); thromboembolic (1)]. Dose reductions: 5 pts on 40mg C none on 20mg C. 1 pt had A dose reduction [hypokalemia with Atrial Fib (1)]. The steady-state trough concentration PK data of A and C did not indicate a drug-drug interaction. Conclusions: C at either 20mg or 40 mg is tolerable when combined with standard dose A/pred. The long term tolerability and preliminary efficacy data support the investigation of this combination for further clinical development in mCRPC. Clinical trial information: NCT01574937.

5038 Poster Session (Board #30), Sat, 1:15 PM-4:45 PM
Acute toxicity and early quality of life after dose intensified salvage radiotherapy for biochemically recurrent prostate cancer after prostateactive first results of the PROSECA trial. First Author: Pascal Jaffray, Institute Pierre Ghadjar, Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Berlin, Germany

Background: Patients (pts) with biochemically recurrent after radical prostatectomy may benefit from dose intensified salvage radiotherapy (RT) of the prostate bed. We performed a randomized phase III trial assessing dose intensification. In this first report we report acute toxicity and early quality of life (QoL). Methods: Pts with biochemical recurrence but without evidence of macroscopic disease were enrolled in this randomized phase III trial. Pts were randomly assigned to either 64 Gy (32 daily fractions) or 70 Gy (35 daily fractions). Three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT, or equivalent rotational techniques) were assigned at the sites. The primary endpoint was freedom from biochemical recurrence. Secondary endpoints included acute toxicity according to the CTCAE v4.0 and QoL using the EORTC QLQ-C30 and PR25. Results: We enrolled 350 pts between 02/2011 and 04/2013. Three pts withdrew consent and three were not eligible, resulting in 344 pts in the safety population. Thirty (8.7%) and two (0.6%) pts had grade 2 and 3, respectively, baseline (GU) symptoms. Acute grade 2 and 3 GU toxicity was observed in 22 (13.0%) and 1 (0.6%) with 64 Gy and 29 (16.6%) and 7 (1.7%) with 70 Gy, being not significantly different (p = 0.2). Baseline grade 2 gastrointestinal (GI) toxicity was observed in 1 (0.6%) patient. No baseline grade 3 GI toxicity was observed. Acute grade 2 and 3 GU toxicity was observed in 27 (16.0%) and 1 (0.6%) with 64 Gy and 27 (15.4%) and 4 (2.3%) with 70 Gy, again not significantly different (p = 0.8). Changes in QoL were marginal. However, pts receiving 70 Gy reported a more pronounced and clinically relevant worsening in urinary symptoms (mean difference between 70 Gy and 64 Gy, p = 0.02). The median follow-up time was the same in both arms. Conclusions: Dose-intensified salvage RT was associated with a low rate of grade 2 and 3 GU and GI toxicities. The impact of dose intensified salvage RT on QoL was marginal, with the exception of a worsening in urinary symptoms after 70 Gy. Clinical trial information: NCT01272050.

5039 Poster Session (Board #31), Sat, 1:15 PM-4:45 PM
Testosterone-guided schedule of androgen deprivation therapy (ADT) as an alternative to a fixed schedule in management of prostate cancer. First Author: Saroj Niraula, CancerCare Manitoba and Univ of Manitoba, Winnipeg, MB, Canada

Background: ADT with LHRH agonists that reduce testosterone production is effective initial therapy for treatment of men with advanced prostate cancer. LHRH agonists are usually administered indefinitely at a fixed interval despite their cost and serious toxicity. Methods: We recruited men with prostate cancer who had been on fixed-schedule injections of a LHRH agonist (most commonly given as 12 weekly injections) for at least one year and had castrate levels of serum testosterone (< 1.7mmol/L). We measured their serum testosterone at 6-week intervals, and men resumed their injections only when their serum testosterone was ≥ 1.7mmol/L. We calculated median time to reinstitution of ADT by the Kaplan Meier method and fitted Cox regression analyses to identify factors predicting delay in reinstitution of treatment. Influence of this approach on quality of life (QoL) was measured by the Expanded Prostate Index Composite (EPIC). Results: From November 2009 to May 2014, a total of 82 men were enrolled. Median age at diagnosis was 68 years (range, 51-83 years). Median time to testosterone recovery after the last injection was 30.8 weeks (Inter-quartile range 17-65 weeks). Lower level of baseline testosterone (≤ 1 versus > 1 mmol/L) [Hazard Ratio (HR) 0.32; p = 0.004] and longer duration of disease (≥ 5 versus ≤ 5 years) [HR 0.38; p = 0.03] were independent predictors for prolonged time to testosterone recovery. Statistically significant improvement from baseline was noted in the hormonal domain of EPIC (p = 0.002) but not in overall score. Drug costs (LHRH agonist alone) dropped from a median of $4,550 to $1,900 per patient per year. Conclusions: Implementing a testosterone-guided approach to ADT results in a substantial reduction in exposure to, and symptoms from ADT. Drug cost is reduced by 60% while still maintaining castrate levels of testosterone. Testosterone-guided approach to ADT can have major public health benefits. This approach should be discussed with men on ADT and be considered as the replacement of fixed schedule treatment by physicians and policy makers. Clinical trial information: NCT01007825.

5040 Poster Session (Board #32), Sat, 1:15 PM-4:45 PM
Immune response from STRIDE, a randomized, phase 2, open label study of sipuleucel-T (sip-T) with concurrent vs sequential enzalutamide (enzo) administration in metastatic castration-resistant prostate cancer (mCRPC). First Author: David I. Quinn, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: In mCRPC, data are limited regarding optimal combinatorial or sequential use of available treatments. P12-2 (STRIDE; NCT01981122) is an ongoing, randomized, open-label, phase 2 study evaluating concurrent vs sequential administration of the androgen receptor inhibitor, enz, with the autologous cellular immunotherapy, sip-T. Methods: Fifty-two patients (pts) with asymptomatic or minimally symptomatic mCRPC were randomized 1:1 to receive sip-T infusions with enz starting 2 wks before (n = 25, concurrent arm A) or 10 wks after (n = 27, sequential arm B) sip-T initiation. The primary endpoint is peripheral T cell proliferation response to PA2024, the sip-T immunizing antigen. Secondary endpoints include interferon (IFN)-γ ELISPOT and humoral immune responses to PA2024 and prostate acid phosphatase (PAP), product release parameters (total nucleated cell count, CD54+ cell counts, and antigen presenting cell activation [as measured by CD54 upregulation]), cytokine production, and acute phase responses. Results: Pts through week 26 are described. Results: PA2024-specific T cell proliferative response was significantly elevated at all post-baseline time points (p < 0.001) and was sustained through wk 26, including a > 10-fold increase at wk 20 in both arms. This PA2024-specific response was observed in nearly all pts, 95.8% in arm A vs 92.6% in arm B. Both arms showed a significant and sustained increase in humoral responses to PA2024 and PAP as well as IFN-γ ELISPOT response to PA2024. Sip-T product parameters were similar between arms. Cytokines indicative of immune activation (such as IFN-γ, interleukin-2, and tumor necrosis factor-α) were also elevated in both arms. AEs were observed in 88% (arm A) and 100% (arm B) of pts. The incidence of grade ≥ 3 AEs was similar between arms. Conclusions: Most mCRPC pts receiving sip-T concurrently with or subsequent to sip-T demonstrated significant and sustained peripheral T cell and humoral immune responses through wk 26. These interim data suggest that both schedules were safe, and enz did not impair sip-T production or subsequent immune responses. Clinical trial information: NCT01981122.
Relationship between abiraterone plasma concentration and PSA response in metastatic castration-resistant prostate cancer patients. First Author: Edgar Carton, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France

Background: Abiraterone (ABI) is a standard treatment in metastatic castration-resistant prostate cancer (mCRPC). However, the large interindividual variability in ABI pharmacokinetics could contribute to the lack of PSA regression observed in some patients. We aimed to explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship of ABI in progressive mCRPC patients (pts). Methods: We prospectively included 45 pts receiving ABI, pre-treated or not with docetaxel. ABI was administered once daily at 1000 mg, in a fasted state, with 10 mg of prednisone. Trough ABI plasma concentration (C_min) was assayed using liquid chromatography at month 1, 2 and 3 after treatment initiation, and PSA level was measured at baseline and after 3 months (ms) of treatment. The individual average C_min during the first 3 ms of treatment was used for the statistical analysis. Pts who had a PSA decline of at least 50% after 3 ms were defined as responders, according to Prostate Cancer Working Group 2 (PCWG2). All ABI C_min was available in 48 pts. The median average ABI C_min was 11.2 ng/mL (IQR 7.2 - 16.2 ng/mL). No intraindividual variability in ABI C_min was identified (CV = 23.5%, p = 0.79). The interindividual variability in ABI C_min was large (CV = 70%), but was not influenced by age, body mass index, albumin level, hepatic or renal function.Among 45 pts available for PK/PD assessment, 29 pts (64%, IC95% [50-78]) were responders at 3 ms. The average plasma ABI C_min was significantly higher in the responder group (median 13.1 [IC 95% 10.6 - 15.6] vs 8.5 [5.6-15.7] ng/mL, p < 0.01, respectively). Pts were classified into two groups based on ABI plasma C_min, a low quartile (Q1) and high (Q2-Q4). In 11 pts exhibiting the average ABI C_min below 8.5ng/mL (Q1), 18% were responders. In contrast, 80% of pts in Q2-Q4 were responders (Fisher test, p < 0.001). Conclusions: In addition to molecular profiling, plasma monitoring of ABI C_min could help optimizing its efficacy. We propose 8.5 ng/mL as the threshold ABI C_min to explore the benefit of PK-guided dosing strategy in clinical practice.

Nine-year follow-up for a study of diffusion-weighted MRI in a prospective active surveillance cohort for prostate cancer. First Author: Daniel Robert Henderson, Royal Maraden Hospital NHS Foundation Trust, London, United Kingdom

Background: Active surveillance (AS) for untreated prostate cancer requires accurate selection of patients unlikely to need treatment in their lifetime. Most studies have selected patients on biopsy and PSA criteria alone, but show a significant number requiring treatment for disease progression. Lower tumour apparent diffusion coefficient (ADC) values, derived from diffusion-weighted MRI (dwMRI), are associated with higher risk disease. We hypothesised that ADC values could aid selection of patients for AS. Early results from this study were published in 2009; we now present findings with the benefit of long-term follow up. Methods: We analysed a subset of patients having pre-enrolment dwMRI in a prospective research study of AS. Inclusion criteria: untreated prostate cancer, T1/2a/NOMG, Gleason ≥ 3+4, PSA < 15. Protocol follow up was by biopsy at 18-24 months, then every 24 months, along with regular PSA. To avoid influencing treatment decisions, results of dwMRIs were not available to the AS program. From December 2012 to October 2014, 57 pts were included. Forty-one pts (76%) were dacectaxel-naïve. ABI C_min was available in 48 pts. The median average ABI C_min was 11.2 ng/mL (IQR 7.2 - 16.2 ng/mL). No intraindividual variability in ABI C_min was identified (CV = 23.5%, p = 0.79). The interindividual variability in ABI C_min was large (CV = 70%), but was not influenced by age, body mass index, albumin level, hepatic or renal function. Among 45 pts available for PK/PD assessment, 29 pts (64%, IC95% [50-78]) were responders at 3 ms. The average plasma ABI C_min was significantly higher in the responder group (median 13.1 [IC 95% 10.6 - 15.6] vs 8.5 [5.6-15.7] ng/mL, p < 0.01, respectively). Pts were classified into two groups based on ABI plasma C_min, a low quartile (Q1) and high (Q2-Q4). In 11 pts exhibiting the average ABI C_min below 8.5ng/mL (Q1), 18% were responders. In contrast, 80% of pts in Q2-Q4 were responders (Fisher test, p < 0.001). Conclusions: In addition to molecular profiling, plasma monitoring of ABI C_min could help optimizing its efficacy. We propose 8.5 ng/mL as the threshold ABI C_min to explore the benefit of PK-guided dosing strategy in clinical practice.

Computer automated bone scan index (BSI) as an analytically validated imaging biomarker to quantitate change in bone scan of patients with metastatic prostate cancer. First Author: Aseem Anand, Memorial Sloan Kettering Cancer Center, New York, NY

Background: A consistent imaging biomarker to standardize the evaluation of change in bone scan is an unmet need for patients (pts) with bone metastasis. BSI is quantitative interpretation of bone scan in pts with metastatic prostate cancer (mPca). Here we have performed analytical and clinical studies to evaluate the change in computer automated BSI as a consistent imaging biomarker in pts with mPca. Methods: Analytical studies with bone scan simulation using XCAT phantom and SIMIND-MC program were performed to evaluate the consistency of automated BSI. Specifically, to assess linearity and accuracy, bone scan of 50 phantoms were simulated with tumor burden ranging from low to high disease burden – from 0.10 to 13.0 BSI. To assess precision, another set of 50 phantoms were divided into 5 subgroups, each containing simulated bone scans of 10 phantoms at 0.5, 1.0, 3.0, 5.0 and 10.0 BSI, respectively. To assess variation, another set of 50 phantoms were divided into 5 subgroups, each containing simulated bone scans of 10 phantoms at 0.5, 1.0, 3.0, 5.0 and 10.0 BSI, respectively. Additionally, to evaluate the clinical utility of automated BSI, two follow-up bone scans of 145 pts with progressing mPca, irrespective of therapy regimen, were analyzed for change in BSI. The primary objective was to evaluate the association of change in BSI against overall survival (OS). The computer automated BSI was calculated using the software EXINI bone®. Cox regression and Kaplan Meier analysis were used to evaluate association between BSI and OS. Results: Pearson correlation to evaluate linearity and accuracy was performed. BSI, in the given range from 0.10 to 13.0 BSI, was observed to be 0.995 (N = 50, 95% CI 0.99 - 0.99, p < 0.0001). The mean coefficient of variation indicating precision of BSI at each of the pre-defined tumor burden was observed to be less than 20%. Change in BSI of 145 pts was significantly associated with OS (HR 1.1, p < 0.0001). The median OS for 110 (66%) pts who had a rise in BSI (> 0.10) was 31 weeks, 35 (34%) pts who had a decline or no change in BSI reached a median 72 weeks (HR 1.9, p 0.0002). Conclusions: Computer automated BSI is a consistent biomarker which can standardize the quantitative analysis of change in bone metastasis of pts with mPca. The clinical utility of automated BSI, in multivariate biomarker panel, will be validated in subsequent studies.
Identification of germline mutations in men with early onset prostate cancer. First Author: Patrick Pilie, University of Michigan, Ann Arbor, MI

Background: Prostate cancer (CaP) is generally considered a disease of older men; however, approximately 10% of new diagnoses occur among men (< 65 years) and some of these cases are clinically aggressive. Epidemiological evidence suggests that early age of cancer onset is associated with increased genetic susceptibility. Methods: For this pilot study, we employed a gene panel approach to identify germline mutations in cancer-associated genes among men diagnosed with early-onset (EO) CaP. Fifty-five men with CaP diagnosed before age 55 were selected from the University of Michigan (UM) Prostate Cancer Genetics Project, a large family-based study of familial and EO CaP. Each of the men also had at least one of the following characteristics: 1) family history of breast and/or ovarian cancer, 2) multiple primary cancers in addition to CaP, and/or 3) clinically aggressive CaP defined as death from disease before age 66 and/or of metastatic disease before age 56. All patients provided written consent and this project was approved by the UM IRBMED. Germline DNA from the 55 men was sequenced using the GeneRead Human Comprehensive Cancer Panel (Qiagen) which includes 124 genes previously associated with a variety of cancers. Potentially deleterious variants were confirmed via Sanger sequencing and then tested in all family members with DNA available to assess co-segregation with CaP status. Results: Over 2500 germline variants were identified, including 349 missense, 4 nonsense, and 6 frameshift variants. Seven of the ten protein truncating variants were confirmed. The 7 true positives included nonsense variants in MSH2, ATM, and KRAS, as well as frameshift variants in FGFR3, TET2, and BRCA2. Conclusions: Overall, 7 of 55 (~13%) high selected EO CaP cases harbored protein-truncating variants in one of the genes examined. Although deleterious mutations in BRCA2 and MSH2 have previously been associated with CaP risk, the other genes have been less well-studied for their role in CaP susceptibility. Further studies of this unique patient population will likely uncover additional novel variants and genes linked with CaP risk which may provide new insights into the development of the disease and ultimately suggest new therapeutic targets.

Prognostic index model (PIM) for overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy treated with abiraterone acetate (AA). First Author: Charles J. Ryan, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

Background: Models that predict prognosis may aid in treatment planning for mCRPC. We previously presented a PIM for radiographic progression-free survival from the phase 3 COU-AA-302 trial in mCRPC pts without prior chemotherapy (ECC 2013, #P370). In the final analysis of COU-AA-302, AA + prednisone (P) significantly prolonged median OS vs P (34.7 mos vs 30.3 mos; HR 0.81; 95% CI 0.70 – 0.93; p = 0.0053). Using the final analysis dataset from COU-AA-302, we developed a PIM for OS in mCRPC pts in the AA + P arm. Methods: The complete set of baseline data was available from 493/546 pts (90%), and formed the basis for the modeling. Accepted values for lower (ULN) and upper (ULN) limits of normal were used to dichotomize laboratory factors; other factors were dichotomized for ease of interpretation. Factors were assessed for association with OS through a univariate Cox model and used in a multivariate Cox model with a stepwise procedure. Internal validation of the predictive performance of the final model was assessed by a bootstrap resampling procedure. Model discriminatory power was estimated by the C-index. Results: Four factors associated with poor prognosis were included in the final model: Brief Pain Inventory 2-3 (HR: 1.71, p < 0.0001), lactate dehydrogenase > ULN (294 IU/L) (HR: 2.03, p < 0.0001), alkaline phosphatase > ULN (131 IU/L) (HR: 1.60, p = 0.0004), and 10 bone metastases (HR: 1.92, p < 0.0001). Pts were categorized into good (n = 296), intermediate (n = 117), and poor (n = 131) risk groups based on number of risk factors. Median OS was calculated for each group (Table). The C-index was 0.67 ± 0.016. Conclusions: We identified 4 readily available clinical and laboratory factors to generate a PIM for OS in mCRPC, and categorized pts into 3 distinct risk groups. Further validation of an independent dataset, this PIM may be useful for estimating OS in mCRPC and designing risk-adapted treatment strategies. Clinical trial information: NCT00877198.

Influence of prostate cancer disease state and therapeutic selection on peripheral whole-blood RNA signature. First Author: Bobby Chi-Hung Law, Division of Hematology and Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Prostate cancer is a heterogeneous disease with differences in tumor stromal interactions contributing to variability in treatment response and outcome. Gene expression of peripheral blood cells is altered by interactions with neoplastic tissue. We previously developed a peripheral whole blood six-gene signature prognostic for survival in mCRPC. Here we evaluate how different clinical disease states and treatment with different therapeutic agents impact this signature. Methods: Whole blood was collected in PAXgene Blood RNA tubes in two cohorts of prostate cancer patients, one at Mount Sinai (n = 135), the other in Munich (n = 59), in the context of prospective clinical studies. Whole blood RNA was extracted and the six target genes were amplified using qPCR. Scores were derived using normalized cycle threshold (ΔCT) values of the six genes, according to the model: 2 x ABL2 + SEMA4D + ITGAL – C1QA – TIMP1 – CDKX1A. Patients were categorized by disease state in the Mount Sinai cohort, and by treatment received in the Munich cohort, for data analysis. Results: CRPC is the only disease state with a mean six-gene score (18.06) above the high-risk cutoff (17.9), and is significantly higher than localized or hormone sensitive advanced disease (16.07, 16.52, respectively; p = 0.0002). Among patients with localized disease, there was no significant difference in the mean six-gene scores for patients with low-, intermediate-, and high-risk disease (16.07, 15.33, 16.66, respectively; p = 0.27). In CRPC patients treated with docetaxel, there are significant changes to the six-gene score over the course of treatment (p = 0.002), with a notable percentage decrease (-6.2%) at the 2-8 week time point that is not observed in patients treated with abiraterone or enzalutamide. Conclusions: Gene expression profiling of whole blood is influenced by the clinical state of prostate cancer as seen by differences to the six-gene score from localized to castrate resistant disease. Cytotoxic chemotherapy appears to modulate the six-gene score, something not seen with AR-directed therapies. Further investigation will be needed to understand the significance of these changes.

Association of single nucleotide polymorphisms (SNPs) in ESR1 and PRMT8 and response to treatment with abiraterone acetate (AA) in men with metastatic castration refractory prostate cancer (mCRPC). First Author: Neeral Agarwal, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: Germline variations in genes involved in androgen biosynthesis and metabolic pathways may predict response to AA in men with mCRPC, serve as prognostic and predictive biomarkers, and guide towards more individualized therapy. Methods: 785 single nucleotide polymorphisms (SNPs) from the Illumina OmniExpress genotyping platform within the boundaries of 60 genes reported to be involved in the androgen metabolic pathway were investigated for association with time to treatment failure (TTF) in 49 Caucasian men with mCRPC undergoing treatment with AA. Cox proportional hazard analysis was employed using Gleason score as a covariate and assessing each SNP under an additive genetic model in which the number of minor alleles contributes increasing risk (or protection). Results: Five SNPs in ESR1 (estradiol-binding domain of the estrogen receptor gene), and 5 SNPs in PRMT8 (protein arginine methyl transferase 8 gene) were associated with TTF on AA therapy (p < .005) while controlling for Gleason Score (Table). Conclusions: SNPs in ESR1 and PRMT8 significantly associated with TTF on AA therapy, and may serve as predictive markers to treatment with AA. Further validation is being performed in a larger cohort of men with mCRPC.

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5049 Poster Session (Board #42), Sat, 1:15 PM-4:45 PM
TERRAIN: First Author: Simon Chowdhury, Medical Oncology Department, Guy’s and St. Thomas’ NHS Foundation Trust, London, United Kingdom

Background: Enzalutamide (ENZA), an androgen receptor inhibitor, improves survival and radiographic progression-free survival (rPFS) in patients (pts) with mCRPC. TERRAIN (NCT01288911) compared ENZA to bicalutamide (BIC), which is frequently added to androgen deprivation therapy upon progression in pts with mCRPC. Methods: Pts with mCRPC were randomized 1:1 to ENZA 160 mg/day or BIC 50 mg/day. Primary endpoint was progression-free survival (PFS), defined as time to centrally confirmed radiographic progression, skeletal-related events, or initiation of new anti-neoplastic or death (any cause), whichever occurred first. Radiographic progression was also assessed by investigators. Circulating tumor cell (CTC) counts were evaluated at baseline and on treatment. Favorable conversion was defined as time to centrally confirmed radiographic progression, skeletal-related events, or initiation of new anti-neoplastic or death (any cause), whichever occurred first. Results: 375 pts were enrolled. The median time on ENZA treatment was 11.7 months and 5.8 months on BIC. PFS (primary endpoint) and rPFS outcomes are shown (Table). Among pts with measurable soft tissue disease, objective tumor response rates were 54% (38/70) with ENZA and 11% (8/71) with BIC. Favorable conversion rates at week 25 were 67% (29/43) with ENZA and 43% (19/44) with BIC. Serious adverse events (AEs) were reported for 31% with BIC. Favorable conversion rates at week 25 were 67% (29/43) with ENZA and 43% (16/37) with BIC. Results: 375 pts were enrolled. The median time on ENZA treatment was 11.7 months and 5.8 months on BIC. PFS (primary endpoint) and rPFS outcomes are shown (Table). Among pts with measurable soft tissue disease, objective tumor response rates were 54% (38/70) with ENZA and 11% (8/71) with BIC. Favorable conversion rates at week 25 were 67% (29/43) with ENZA and 43% (19/44) with BIC. Serious adverse events (AEs) were reported for 31% with BIC. Favorable conversion rates at week 25 were 67% (29/43) with ENZA and 43% (16/37) with BIC.

5051 Poster Session (Board #44), Sat, 1:15 PM-4:45 PM
Phase 1-2 study of progesterone receptor (PR) inhibition with extended-release (ER) onapristone (ONA) in patients (pts) with castration-resistant prostate cancer (mCRPC): PK, safety and PR testing results from the dose escalation cohort. First Author: Anuradha Jayaram, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: An urgent need exists for new therapies after progression (PD) on abiraterone (AA) and enzalutamide (ENZ). PR expression increases with castration resistance (Bonnhoff 2001). ONA, a type-I PR antagonist, has clinical activity in other prostate cancers. PR mRNA and protein levels have been shown to achieve continuous exposure, and an IHC companion diagnostic to detect activated PR. Methods: This open-label, phase 1-2 study with dose selection/expansion includes pts with: advanced CRPC, prior PD on AA or ENZ and ≤ 2 chemotherapies. Tumors are biopsied at baseline and on treatment to determine PR status. 1st endpoint for dose escalation is to define recommended phase 2 dose (RP2D). 2nd endpoints include safety and PK. In stage 1a pts were randomized to 10/20 mg ONA BID. Stage 1b escalation. Randomization now includes the 3 higher doses. PK appears acceptable. DLTs or significant LFT abnormalities at 10/20 mg BID. One pt had related G3/4 AEs: G3 nausea/anorexia. Most common related AEs were fatigue (n = 30), nausea/anorexia (n = 28), constipation (n = 21), anemia (n = 16), G3 hyperglycemia (n = 10), G3 hypertension/edema (n = 9) and fatigue (n = 8). To date, at the RP2D, 36 pts will be treated to confirm safety and activity. We present results of stage 1a (n = 10) and a separate biomarker validation cohort (n = 45). Results: Stage 1a is complete. There were no G3/4 AEs: G3 nausea/anorexia. Most common related AEs were fatigue (n = 4) and anorexia (n = 3). 4 SAEs were reported, none considered related to ONA. There were no treatment-related discontinuations for AEs. Mean Cmax/AUC/τ = 10 and 20 mg were 253 ng/mL, 5311 ng*h/mL, 5.98 hours and 384 ng/mL, 10240 ng*h/mL, 4.92 hours, respectively. 3 pts had paired biopsies: 1/3 pts had strong PR expression (> 50%) pre-treatment and no PR expression after 19 days of ONA. In the biomarker cohort, we tested plt-mRNA by inverse-therapy-naïve (TN) and CRPC specimens and identified PR-positive cells (≤ 1% cells) in 15 pts (33%; 5 CRPC and 10 TN). No TN but 4/45 CRPC (9%) biopsies had strong PR expression (> 50% cells). Conclusions: CricPrS expresses PR. The IHC diagnostic method will be used for selective enrichment. The 1st stage of the study concluded with no DLTs, permitting escalation to the randomization dose cohort. PK appears dose proportional. Clinical trial information: NCT02041910.

5050 Poster Session (Board #43), Sat, 1:15 PM-4:45 PM
LBH589 (LBH) and bicalutamide (BIC) in castration-resistant prostate cancer (CRPC) patients (pts) progressing on second line anti-androgen (AA). First Author: Antonio Ferrari, the Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY

Background: Retrospective studies of CRPC pts resistant to 2nd-line AA indicate that progression develops within ~4 months (mo) of a 3rd-line AA treatment (tx). The histone-deacetylase inhibitor LBH decreases expression of androgen receptor (AR) mRNA, splice variants, protein and its targets in CRPC models. Combined with Bic, LBH induces a synergistic anti-proliferative response in resistant PC cells. Targeting androgen signaling by epigenetic modulation of AR alterations and restoration of AA sensitivity, LBH may delay AA-resistant CRPC progression. Methods: AA-resistant CRPC pts were randomized 1:1 to 3-week (wk) cycles of Bic 50 mg daily and LBH 40 mg (arm A) or 20 mg (arm B) tri-weekly 2 wks/cy. Endpoints (E/Ps): Primary (1°), radiographic progression (PR)-free survival (rPFS) at 6 mo and 9 mo with activity declared if > 25% by Fisher Exact Test; Secondary (2°), PSA response, safety and tolerability. Results: 92 pts were randomized to 2°/E Ps; all pts evaluated for 2°/E Ps. Results: 52 pts (28/24, arms A/B) treated. Median (range): age 69 (48-84) years, PSA 14 ng/mL (2-543), previous AA tx, 2 (1-4); 50 pts had mets (mCRPC), 33 each bone/LN. Arm A: Tx cycles before stop (cycles): ≤ 2, 2-7; 7, 12 (1+ ongoing); 8-12 (≥ 6 mo), 8 of which 5 completed 13-25 cycles (> 9 mo).13/28 (46%) pts had LBH dose reduction to 30-25 mg, rPFS was 40% (8/20 pts) at 6 mo (p = 0.006), 25% (5/20 pts) at 9 mo (p = 0.35); 5 pts (25%) had H/P, PSA decline were > 30%; 6 pts; > 10%; 1 pt. Toxicities: Grade(3)4: thrombocytopenia 8; G3 fatigue 2, diarrhea 2; G2 diarrhea 9, fatigue 5. Arm B: Tx cycles before stop (cycles): ≤ 2, 2-7; 7, 12; 18, 12; 4, > 12; 2, Only 1/24 reduced LBH to 15 mg. rPFS was 20% (4/20 pts) at 6 mo, 10% (2/20pts) at 9 mo (p = 0.3); H/P occurred in 7/20 pts (35%); PSA declines were > 30% > 30% > 10% > 10%. Toxicities: Grade(3)4 of which 1, Kaposisi’s, 1, G3 fatigue, 1, diarrhea 2; G2 diarrhea1, fatigue 6. Conclusions: The proportion of mCRPC pts resistant to 2nd-line AA that achieved rPFS at 6 mo was significant after tx with Bic combined with LBH 40 mg and frequent dose reductions to 30-25 mg for tolerance. LBH 20 mg was not effective. Studies combining LBH with new 2nd-line AA are planned to prevent/delay resistance. Clinical trial information: NCT00878436.
Background: Abiraterone acetate (AA) 1000mg, in combination with prednisone (P), 10mg daily is indicated for the treatment of patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). IMAAGEN is a phase II, multi-center study with a primary endpoint that evaluated the ability of AA plus 5 mg of prednisone (AA + 5) to decrease levels in pts with nmCRPC and a rising PSA; primary results have been reported earlier1. Herein we report updated results on secondary endpoints and safety from the IMAAGEN study (Nov 3, 2014 database cut-off date). Methods: All enrolled pts had high risk non-metastatic castration resistant prostate cancer (nmCRPC); PSA value > 10ng/mL or PSA doubling time ≤ 10 months at screening. Pts received AA + 5 daily; each treatment cycle = 28 days. Reported endpoints include time to PSA progression, time to radiographic progressive disease, and safety. Results: At the time of the data cutoff, 62 (47.3%) of the 131 patients enrolled in IMAAGEN remained on treatment in the study. The median duration of exposure was 17.9 months (range 0.1 – 40.7 months). Median time to PSA progression was 28.7 months (95% CI 21.2, NE). There were 21 confirmed radiographic progression events. The median time to radiographic progressive disease was not reached, 95.4% of pts had an adverse event (AE) (54.9% had a Grade 3 or higher) and 38.2% had a serious AE (SAE) with 35.9% having an SAE of Grade 3 or higher. 13.0% of pts had AEs resulting in discontinuation of study treatment. Four pts had AEs resulting in death (coronary artery disease, myocardial infarction, acute respiratory failure, and pneumonia). Conclusions: Treatment of high risk nmCRPC patients with AA + 5 resulted in a median time to PSA progression of 28.7 months. The median time to radiographic disease progression was not reached. The safety profile of AA + 5 reported in this IMAAGEN trial update is consistent with the safety profile from previously reported studies of abiraterone acetate 1000mg in combination with either 5mg or 10mg prednisone.

1ASCO 2014 IMAAGEN primary endpoint poster presentation Clinical trial information: NCT01314118.
5057 Poster Session (Board #51), Sat, 1:15 PM-4:45 PM
Validation of correlation of RECIST changes with survival in metastatic castration-resistant prostate cancer (mCRPC). First Author: Gregory Russell Pond, Ontario Clinical Oncology Group, Vancouver, BC Canada

Background: In patients (pts) with mCRPC receiving chemotherapy, measurable disease response by World Health Organization criteria is prognostic for overall survival (OS). We now explored the association of changes in measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) with OS. Methods: Data from the control arm (n = 612) of the VENICE trial receiving docetaxel, prednisone and placebo (DPP) were available. Data on baseline clinical variables and outcomes were obtained. Cox proportional hazards regression was used to evaluate the prognostic ability of RECIST changes adjusting for known factors for OS using a 90-day landmark analysis. The association was validated using 388 patients in the DPP arm of the MAINSAIL trial who had RECIST measurements prior to day 90 and survival beyond day 90. Results: 363 pts in VENICE had measurable lesions, of whom 296 were evaluable for landmark analysis. 28 (9.5%) had progressive disease (PD) prior to day 90, while 58 (19.6%) had unconfirmed partial response (PR). In a multivariable analysis, the hazard ratio (HR) for OS for pts with PR was 0.64 (95% CI 0.42 – 0.99, P = 0.045) compared to those without PR, and 1.78 (95% CI 1.07 – 2.95, P = 0.026) for those with PD compared to those without PD. PD remained significant (HR = 1.85, 95% CI 1.10-3.12, P = 0.200) after adjusting for PSA changes, but PR was not (P = 0.14). The association of PR (HR 0.51, 95% CI 0.22-1.18, p = 0.12) and PD (HR = 3.51, 95% CI 1.92-6.43, p < 0.001) with OS was externally validated in 388 pts in MAINSAIL who had measurable disease. After adjusting for PSA changes, PD was associated with poor OS (HR = 2.36, 95% CI 1.11-5.04, p = 0.026), but PR was not (p = 0.15). Conclusions: In men with mCRPC receiving first-line docetaxel-based therapy, RECIST changes within 90 days are associated with OS. Given the frequent detection of measurable disease with current imaging and the unclear association of PSA and bone scan changes with outcomes in the setting of new agents, the accrual of patients with measurable tumors in phase II trials to assess RECIST changes may provide a more objective signal of efficacy of new agents.

5059 Poster Session (Board #53), Sat, 1:15 PM-4:45 PM
Tissue-based genomics to augment post-prostatectomy risk stratification in a natural history cohort. First Author: Ashley Ross, The Johns Hopkins University School of Medicine, Baltimore, MD

Background: Genomics has provided insight into the underpinnings of lethal prostate cancer and led to the development and clinical use of RNA expression based gene signatures. We performed genome wide expression profiling on tissue from a large natural history cohort of at risk men undergoing radical prostatectomy (RP). Methods: In an IRB approved study, we utilized a case-cohort design to identify 356 intermediate and high risk men who underwent RP and had no further treatment until the time of metastasis. RP specimens were regraded by 2005 ISUP criteria and index lesions were sampled. RNA was prepared, labelled and hybridized to Human Exon 1.0 ST microarrays from which expression signatures were analyzed. The study followed REMARK guidelines for prospective blinded evaluation and analysis of prognostic biomarkers. Results: Microarray quality RNA was obtained from 260 men (99 of whom metastasized) with a median follow up of 9 years (IQR 6-12). 34 gene signatures were evaluated, including 3 based on commercially available assays (genomic classifier [GC], Decipher), microarray derived (md-CCP, and md-GPS). GC provided the highest c-index to predict metastasis free survival at 10 years post-RP (0.76). Cumulative incidence of metastasis among men with low (< 0.45), intermediate (0.45-0.6) and high (>=0.6) GC scores was 12, 31 and 47% respectively at 5 years post-RP (p < 0.001). GC was independently prognostic of metastasis on multivariable analysis. Stratification by GC was more accurate among patients with PCa. For example, among men with CAPRA-S score of 3-5, 10% with low GC scores would develop metastasis compared to 27% among those with high scores. Addition of expression signatures from other CLIA certified tests (md-CCP or md-GPS) or from the next best performing expression signature (md-Penny, c-index 0.74) did not improve the performance of the GC.

Conclusions: Genomic expression signatures stratify metastatic outcomes and provide additional prognostic information in a natural history cohort of men undergoing RP. Of 34 expression signatures analyzed, GC had optimal performance and captured prognostic information provided via analysis of other signatures.

5058 Poster Session (Board #52), Sat, 1:15 PM-4:45 PM
Development of an imaging approach to detect splice variants of androgen receptor in prostate cancer. First Author: Yusuke Imamura, Genome Sciences Centre, BC Cancer, Vancouver, BC Canada

Background: Resistance to therapies that target androgen receptor (AR) ligand-binding domain (LBD) in prostate cancer patients may be due to expression of constitutively active AR splice variants that lack LBD. EPI small molecules bind to activation function-1 (AF-1) in the AR amino-terminal domain (NTD). Development of a radiolabeled analogue, [123I]-EPI, may be useful for imaging prostate cancer using single-photon emission computed tomography (SPECT). Currently AR is imaged with positron emission tomography with 16F-fluoro-5α dihydroteosterone ([16F-FDHT] that binds to AR LBD. [16F-FDHT] cannot detect AR splice variants lacking LBD. Our approach would sequential imaging with [16F-FDHT] to detect solely full-length [fl-AR] and [123I]-EPI to detect NTD of both fl-AR and variant AR. Discordant distribution or uptake of [16F-FDHT] and [123I]-EPI may reveal expression of AR splice variants lacking LBD.

Methods: Specific activity against AR by I-EPI was confirmed in cells using reporter gene constructs for AR and related steroid hormone receptors. Binding experiments were done using [123I]-EPI with recombinant AF-1 and fl-AR proteins, as well as endogenous fl-AR and variant AR in cells. Evaluation of [123I]-EPI in whole-body distribution included dosimetry in xenografts by small animal SPECT imaging; and temporal evaluation of [123I]-EPI uptake and clearance by quantifying [123I]-EPI in harvested organs.

Results: In cell-based assays, I-EPI was specific for AR and blocked the activity of an AR-driven reporter, while having no effect on transcriptional activities of other steroid hormone receptors. [123I]-EPI covalently binds specifically to AR in living cells and to recombinant fl-AR and AR AF-1. Whole body SPECT imaging showed preferential uptake in LNCaP95 human prostate cancer xenografts that express AR while negligible uptake was observed in PC3 xenografts that lack functional AR. Conclusions: An AR NTD-targeted molecular imaging probe such as [123I]-EPI may be useful to select patients for subsequent antiandrogen therapies, monitor treatment response, and provide insight into the role of all AR species in resistance mechanisms.

5060 Poster Session (Board #54), Sat, 1:15 PM-4:45 PM
Evaluation of the contribution of individual gene groups to a 17-gene prognostic prostate cancer signature. First Author: Dejan Knezevic, Genomic Health, Inc., Redwood City, CA

Background: A 17-gene biopsy-based RT-PCR assay (OncoType DX® Prostate Assay) has been validated as a predictor of adverse pathology and biochemical recurrence (BCR) in clinically very low to intermediate-risk prostate cancer patients. The assay measures expression of 12 cancer and 5 reference genes that are combined to calculate a Genomic Prostate Score (GPS), which can predict biochemical recurrence (BCR) risk for men with clinically very low to intermediate-risk prostate cancer. The cancer genes represent four biological pathways: androgen signaling, stromal response, cellular organization and proliferation. We investigated the association of changes in quantitative expression of individual gene groups on GPS results and prediction of clinical risk.

Methods: The first 3,500 tumor specimens processed in the Genomic Health Inc.’s reference laboratory were included. Expression of individual genes was measured and the expression of the four gene groups and GPS calculated. For each gene group, GPS of patients with the lowest 5% expression levels were contrasted with GPS of patients with highest 5% expression levels.

Results: Percentages of NCCN very low, low and intermediate patients were 28%, 37%, 30%; median age was 65. Mean and median GPS were 24.6 and 23 (range 0-90). Individual gene groups exhibited wide expression ranges (e.g. proliferation-16-fold difference [FD] vs. cellular organization >8000 FD). Large differences in expression of each gene group were reflected in GPS values and, based on a prior clinical validation study, translated into large differences in BCR risk prediction (Table). Next, we examined the associations between the four gene groups. A significant association between the four gene groups show large variations in expression, meaningfully affect the GPS, and contribute to the prediction of PCA aggressiveness.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Effects of preoperative abiraterone acetate (AA) plus enzalutamide (E) and leuprolide acetate (LHRHa) versus AA and LHRHa in localized high-risk prostate cancer (LHRHa). First Author: Elena Stathihu. Alexandria General Hospital of Athens, Oncology Department, Department of Clinical Therapeutics, University of Athens, Athens, Greece

Background: High degree of heterogeneity in cytodestruction has been observed in LHRPC following AA+LHRHa and LHRHa (Tapolin et al, J Clin Oncol 2014;32:3705; Efstatiiou et al, J Clin Oncol 2012:30 (suppl; abs 4556). Rationale exists for AA+E combination and promising efficacy is reported in mCRPC. This study aims to determine effects of AA + E vs AA and modulation of androgen signaling in LHRPC. Methods: Single-institution preoperative study of 24 wks of 1 g AA + 160 mg E + 5 mg prednisone (P) QD + LHRHa (Arm A) vs AA/P+LHRHa (Arm B) (randomized 2:1) in LHRPC pts (clinical stage T1c/T2, biopsy Gleason score ≥ 8, or ≥ T2b with Gleason > 7 and PSA > 10 ng/mL). Safety and treatment effect on pathology stage, androgen metabolites, cellular density (% epithelial component of tumor volume), and link between molecular markers (by IHC) with clinical, pathology, and cellular response were assessed. Results: Study accrued 66 pts; 39 completed 24 wks therapy and had robot-assisted laparoscopic prostatectomy. Preliminary observations in evaluable pts: no perioperative Gr 3 adverse events (AEs); on-treatment Gr 3 AEs; liver function test elevation (7 Arm A, 2 Arm B), hypertension (5 Arm A, 1 Arm B), hypokalemia (1 Arm A), cognitive disturbance (1 Arm A), pulmonary embolism (1 Arm A), fatigue (1 Arm A). Fatigue Gr 1/2 in 38/55 evaluable pts (29/65 Arm A and 9/17 [53%] Arm B). Preoperative PSA was ≤ 0.1 ng/mL in 23/26 (89%) Arm A pts vs 10/11 (91%) Arm B pts (p = ns). To date pathologic downstaging (< yyP2NO) occurred in 11/27 (41%) in Arm A vs 7/12 (58%) in Arm B (p = ns); pCR (2 Arm A, 1 Arm B). Pts segregated by low ≤ 30% (range 0-30%, median 5%) vs high > 30% (65%) median cellular density; low density in 63% Arm A and 77% Arm B. Preoperative testosterone was undetectable in 33/39; when detectable (range 1-10 pg/mL). Pts with pathology stage ≥ yyP2NO had higher AR-N terminal expression (85% vs 58% and AR-CAR-N ratio; p = 0.008). Conclusions: Tumor cytodestruction is dichotomized in the universal serum PSA decline at 6 m preoperative treatment. Planned Comprehensive molecular characterization of androgen biosynthetic flow will mark marker-driven LHRPC treatment strategy. Clinical trial information: NCT01946165.

Methods:

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Contemporary national trends of prostate cancer screening among privately insured patients in the United States. First Author: Simon P. Kim, Yale University, New Haven, CT

Background: Little is known about the degree to which prostate cancer (PC) screening with prostate-specific antigen (PSA) testing has changed in the face of recent clinical research data and theGRADE D against screening from the U.S. Preventive Services Task Force. We used a large private health insurance database to determine the national trends of PSA screening and to investigate which patient characteristics are associated with PSA testing. Methods: Using Optum Labs Data Warehouse, a large private health insurance claims database, we identified males age 40–80 years who underwent PC screening from 2008 to 2013. The primary outcome was use of PSA testing among a privately insured population-based cohort. Demographic covariates included age, census region, race, education level and household income range. The Charlson/Deyo comorbidity index was calculated to assess comorbidity burden. Rates were calculated based on member-years and reported per 1,000 member-years.

Results: Among 11.6 million eligible enrollees, we identified 2.9 million (25%) men who underwent PSA screening from 2008 to 2013 (> 890,000 screened per year). The majority of the screened population were white males, age 50–59 years residing in the Southern census region. The rate of men undergoing PSA screening remained stable from 190.4 per 1,000 member-years in 2008 to 196.4 in 2013 (p = 0.66). Among enrollees aged 50 to 74 years, PSA screening rates were positively associated. However, enrollees who were > 75 years old had a marked decrease in PSA screening from 201.5 to 124.1 per 1,000 member-years from 2008 to 2013 (p = 0.04). PSA screening rates did not vary by racial groups or geographic region over time. Conclusions: In this large population-based cohort of privately insured men, we found little effect of new data and change in clinical practice guidelines on the overall rate of PSA screening. However, older men (> 75) showed a significant reduction in screening over time.

5067 Poster Session (Board #61), Sat, 1:15 PM–4:45 PM
Detecting predictive androgen receptor modifications in circulating prostate cancer cells. First Author: Julie Steinerstel, Clinic of Urology, University Hospital Muenster, Münster, Germany

Background: Molecular modifications of the androgen receptor (AR) can cause resistance to androgen deprivation therapy (ADT) and chemotherapy in prostate cancer patients. When resistance to therapy ensues, lack of representative tumor samples hinders therapy adjustments according to emerging AR-modifications and some patients may thus receive ineffective treatment. Methods: We devised a single-tube assay to detect the two most common AR-modifications (AR-V7 splice variants and AR point mutations) in circulating tumor cells (CTC) using immunomagnetic CTC isolation followed by quantitative real-time PCR and DNA pyrosequencing. We prospectively investigated 47 prostate cancer patients with PSA progression followed by quantitative real-time PCR and DNA pyrosequencing. We estimated the overall benefit from molecularly informed therapy switch by calculating the potential phase 2 dose (Groiss et al, 2009) thus 37 of 43 patients received level 2 dosing. Median age was 65 (50–79) years, PSA 76.6 (0–1847) ng/mL, alkaline phosphatase 114 (37–768) U/L, hemoglobin 12.5 (0.0–15.7) g/dl. Metastatic sites included: bone (38%), lymph nodes 19 (44%), and visceral 8 (17%) pts. Median cycles delivered was 10 (3–21) which included B/E-D maintenance in 24 pts for 3 (1–10) cycles. Maximal PSA decline ≥ 30% and ≥ 50% was achieved in 33 (79%) and 31 (74%) of pts. RECIST responses were assessable in 25 pts with best response complete or partial in 20 (80%) of pts. Hematologic toxicities were the most common treatment related grade ≥ 3 adverse events including: febrile neutropenia 12 (28%), lymphopenia 12 (28%), leukocytosis 10 (23%), neutrophils 9 (21%), and hemoglobin 2 (5%). Non-hematologic grade ≥ 3 AEs included: hypertension 8 (19%), fatigue 3 (7%), and pneumonia 2 (4%). Among 92 have been evaluated by FISH for AR amp, including 36 from bone, 35 from liver, 16 from lymph nodes, 16 from liver, and 5 from other soft tissues. Overall, 64% of mCRPC tumors were AR amplified by FISH and were corroborated by aCGH in 16/21 cases (76%). AR amp was seen in similar proportions in select cases.

Conclusions: The combination of E/B/D demonstrates significant clinical activity against mCRCpts which must be balanced against hematologic and other toxicities. Correlative biomarker studies are ongoing to better define patient subsets which may be more likely to benefit from this therapy. Clinical trial information: NCT00574769.

5065 Poster Session (Board #59), Sat, 1:15 PM–4:45 PM
Safety and efficacy of everolimus (E), bevacizumab (B), and docetaxel (D) for castration resistant prostate cancer (CRPC). First Author: Mitchell E. Gleave, University of Southern California, Los Angeles, CA

Safety and efficacy of Everolimus (E), bevacizumab (B), and docetaxel (D) for castration resistant prostate cancer (CRPC) Background: Based on studies suggesting co-targeting mTOR and angiogenic pathways potentiates chemotherapy, we studied combining mTOR (E, formerly RAD001) and VEGF (B) inhibition with D in CRPC. Methods: Eligible patients (pts) had progressive, metastatic, castration-naive CRPC. D + B was given IV daily with E PO daily on a3 AEs included: hypertension 8 (19%), fatigue 3 (7%), pneumonia 2 (4%). Among 92 have been evaluated by FISH for AR amp, including 36 from bone, 35 from liver, 16 from lymph nodes, 16 from liver, and 5 from other soft tissues. Overall, 64% of mCRPC tumors were AR amplified by FISH and were corroborated by aCGH in 16/21 cases (76%). AR amp was seen in similar proportions in select cases.

Conclusions: The combination of E/B/D demonstrates significant clinical activity against mCRCpts which must be balanced against hematologic and other toxicities. Correlative biomarker studies are ongoing to better define patient subsets which may be more likely to benefit from this therapy. Clinical trial information: NCT00574769.

Conclusions: AR amp status was corroborated with array comparative genomic hybridization (aCGH) in select cases. Results: 150 mCRPC pts have undergone bx to date. To date, 92 have been evaluated by FISH for AR amp, including 36 from bone, 35 from lymph nodes, 16 from liver, and 5 from other soft tissues. Overall, 64% of mCRPC tumors were AR amplified by FISH and were corroborated by aCGH in 16/21 cases (76%). AR amp was seen in similar proportions in liver, bone, or nodal bx, and was present in 9/17 (53%) in AR amp and 5/12 (42%) in AR non-amplified tumors respectively. Conclusions: AR amplification status can be assessed by FISH from mCRPC biopsies. AR amplification was common in Abi/Enz-naive tumors indicating therapeutic resistance. AR amp was less frequent in pts with Abi resistance, suggesting that Abi may select for non-AR amplified cells. Sequential (paired) biopsies from the same pts are being evaluated to test this hypothesis. Preliminary data suggest higher rates of AR amp in pts who are resistant to Enz. The predictive utility of AR amp status and AR splice variants is currently being evaluated.
TPS5069  Poster Session (Board #63a), Sat, 1:15 PM-4:45 PM
Androgen receptor modulation optimized for response: Splice variant (ARNOR3-SV)—Randomized, open-label, multicenter, controlled study of gallantene vs enzalutamide in men with castration-resistant prostate cancer (mCRPC) expressing AR-V7 splice variant. First Author: Mary-Elizabeth Taplin, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: mCRPC patients with tumors expressing the androgen receptor (AR) splice variant 7-AR (AR-V7), a constitutively-active truncated form of the AR lacking the ligand-binding domain, have been shown to have worse clinical outcomes, after AR-targeting drugs than those without detectable AR-V7. Galectone, a small molecule drug, disrupts AR signaling via selective inhibition of CYP17 lystate, AR blockade, and enhanced degradation of the AR protein. In preclinical models, galectone showed activity against the full-length AR and AR alterations including AR-V7 and AR-ADTM splice variants, and against activating AR mutations (eg, AR-T878A, AR-F876L). Given the encouraging results in patients with AR C-terminal loss in the galectone Phase 2 ARMOR2 trial, further research is warranted in this patient subset. Methods: ARNORM3-SV is a Phase 3, randomized, open-label, multicenter study of galectone vs enzalutamide in men with mCRPC expressing AR-V7 mRNA in circulating tumor cells (CTCs). Among other inclusion criteria, eligible patients must continue medical castration or have had surgical castration, and must not have received prior chemotherapy, abiraterone, or enzalutamide. Eligible patients will be prescreened and subsequently enrolled only if AR-V7 is detected in CTCs using a CLIA-certified, analytically-validated assay. A total of 148 patients will be randomized (1:1) to receive once-daily oral galectone 2550 mg or enzalutamide 160 mg. The primary endpoint is radiographic progression-free survival determined by independent blinded, central radiologic review. Secondary endpoints include time to cytotoxic therapy or next anticancer intervention and overall survival. Other endpoints include time to CTC shedding, skeletal related event, decline in PSA, time to PSA progression, and best objective response rate (in men with measurable soft tissue disease).}

TPS5070  Poster Session (Board #63b), Sat, 1:15 PM-4:45 PM
Autologous dendritic cell vaccination (DCVAC/PCa) added to docetaxel chemotherapy in a double-blind, randomized phase III trial (VIABLE) in men with advanced prostate cancer (mCRPC). First Author: Nicholas J. Vogelzang, Carolina Urologic Research Center, The US Oncology Network, Myrtle Beach, SC

Background: Prostate cancer (CaP) is the second most common cancer, and the fifth leading cause of cancer related death among men worldwide. Immunotherapy designed to induce tumor cell specific immune responses capable of destroying tumor cells has emerged as a promising treatment modality in solid malignant tumors. Clinical and preclinical trials have shown that docetaxel chemotherapy can be combined with vaccine without impairing the immune response. Methods: VIABLE is a randomized, double-blind, placebo-controlled, parallel-group, international phase III study to evaluate the efficacy and safety of DCVAC/PCa (active cellular immunotherapy based on dendritic cells) versus placebo in patients with mCRPC eligible for first-line docetaxel chemotherapy. The study was initiated in May 2014 and plans to enroll almost 1200 patients at approximately 300 sites globally. Eligible patients are required to present with metastatic castrate-resistant CaPs defined by both presence and progression of the disease, maintenance of a castrate state with serum testosterone level less than 50 ng/dl, ECOG score 0, 1, and adequate hematologic, hepatic and renal functions. All patients will receive standard of care docetaxel plus prednisone, and will be randomized 2:1 to DCVAC/PCa or placebo. Patients will be stratified by region (US vs other), previous therapy (enzalutamide and/or abiraterone) and ECOG score (0, 1 vs 2). The primary endpoint is overall survival (OS). Secondary objectives include assessments of safety, radiographic progression-free survival, time to PSA progression, time to the first occurrence of skeletal related events (SRE), and quality of life (QoL) assessments based on the FACT-P questionnaire. Clinical trial information: Registration number NCT02111577, EudraCT number 2012-002814-38. Clinical trial information: NCT02111577.

TPS5071  Poster Session (Board #64a), Sat, 1:15 PM-4:45 PM
A phase 3 randomized, placebo-controlled double-blind study of ARN-509 plus abiraterone acetate (AA) in chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). First Author: Dana E. Rathkopf, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: ARN-509, a potent and selective androgen receptor (AR) antagonist, inhibits AR nuclear translocation and DNA binding (Clegg, Cancer Res. 2012). AA directly inhibits androgen biosynthesis and has been approved for the treatment of mCRPC. Although ARN-509 and abiraterone both target the AR, each work through a different mechanism: the former blocks ligand binding, the latter inhibits ligand synthesis. Importantly, lack of sensitivity to one AR-targeted therapy does not necessarily imply resistance to another (Rathkopf, AACR 2014). Inhibiting the AR through multiple mechanisms simultaneously may be more effective than single pathway inhibition and has the potential to have a significant impact on the mCRPC field. This phase 3 trial will compare radiographic progression-free survival (rPFS) in pts with chemotherapy-naive mCRPC treated with ARN-509 in combination with AA + prednisone/prednisolone (P) vs placebo + AA + P. Methods: This multicenter, double-blind, placebo-controlled trial is enrolling men with mCRPC progressing on abiraterone therapy and/or chemotheraphy (enzalutamide and/or abiraterone) and ECOG score (0, 1 vs 2). The primary endpoint is overall survival (OS). Secondary endpoints include time to PSA progression, time to the first occurrence of skeletal related events (SRE), and quality of life (QoL) assessments based on the FACT-P questionnaire. Clinical trial information: Registration number NCT02111577, EudraCT number 2012-002814-38. Clinical trial information: NCT02111577.
Background: Enzalutamide (E) is a newly authorized drug for metastatic CRPC. E inhibits binding of androgens to androgen receptors, nuclear translocation of activated receptors and DNA transcription. E decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. The presence of TMPRSS2-ETS fusion gene rearrangement correlates with the effectiveness of abiraterone (Danila DC, et al 2011). This molecular alteration may also influence E clinical outcome. The aim of this study is to determine whether the efficacy and safety of E when administered to mCRPC before chemotherapy, is influenced by the presence or not of TMPRSS2-ETS fusion gene rearrangement both in primary tumor and circulating blood. Methods: This is a phase II open-label study conducted in chemotherapy naïve mCRPC patients older than 18 years, ECOG 0-1, testosterone < 50 ng/dL and adequate, hematologic, hepatic, and renal function, that progressed to previous castration treatment documented by PSA (PCWG2), radiographic progression (modified RECIST 1.1) or bone scan progression. Patients will receive E treatment (160 mg/d) until clinical and/or radiographic disease progression. Primary objective is to assess the predictive value of the expression of TMPRSS2-ETS gene fusion in primary tumor tissue and circulating tumor cells correlated with progression free survival. Secondary objectives include assessing relationship with time to PSA response, overall soft tissue response rate, time to beginning of cytotoxic chemotherapy, safety of E treatment and circulating tumor cells (CTC) conversion progression rate. In this study is planned to include 98 patients. Sample size has been calculated using a Cox proportional hazards regression model with alpha 0.05, power 80% and 20% drop out rate. Patients will be included in 17 sites in Spain and it is expected to start in February 2015. Clinical trial information: NCT02288936.

TPS5074 Poster Session (Board #65b), Sat, 1:15 PM-4:45 PM
A randomized phase II study of androgen deprivation therapy with or without PD0332991 in RB-positive metastatic hormone-sensitive prostate cancer. First Author: Phillip Lee Palmsbo, University of Michigan Health System, Ypsilanti, MI
Background: Androgens drive proliferation of prostate cancer cells via upregulation of cyclin D which complexes with the CDK4/6 kinases, resulting in phosphorylation of Rb and G1/S progression. Perturbations in this pathway (loss of Rb, upregulation of cyclin D) are felt to promote castration-resistance. PD0332991 (palbociclib) is a novel specific inhibitor of CDK4 and 6. Preliminary PD0332991 inhibited proliferation and promoted G1 arrest in an RB and Cyclin D-dependent manner. 80-90% of early metastatic hormone-sensitive prostate cancers are estimated to retain wild-type RB expression. Addition of PD0332991 to hormonal therapy in ER+ breast tumors demonstrated statistically significant improvements in progression-free survival. Hypothesis: Addition of PD0332991 to initial ADT in patients with newly metastatic RB-positive prostate cancer will significantly increase the efficacy of ADT. Methods: A multicenter randomized phase II study of PD0332991 was initiated (NCT02059213) in which patients (n = 60) with new metastatic hormone sensitive prostate cancer and RB intact tumors based on metastatic biopsy are stratified by disease extent and randomized (1:2) to ADT or ADT plus PD0332991. Primary endpoint is PSA response (< 4 ng/mL) after 7 months of therapy. With 20 patients randomized to ADT and 40 randomized to ADT plus PD0332991 there will be a 64.2% power to detect a 20% difference in proportions with a one-sided type I error of 0.10 using the mid-p-value method of the Fisher’s exact test. Secondary endpoints: safety and tolerability of ADT + PD0332991, rate of undetectable PSA (< 0.2ng/mL), biochemical and clinical progression-free survival, overall PSA and radiographic response rates, assessment of biomarkers which predict therapy response (circulating DNA and tumor cells, tumor protein and transcript analyses) and to establish a repository of metastatic hormone sensitive prostate tumor samples. Support: Movember-PCF Challenge Award, Pfizer. Clinical trial information: NCT02059213.

TPS5076 Poster Session (Board #66b), Sat, 1:15 PM-4:45 PM
Randomized phase-2 study of sipuleucel-T with or without radium-223 in men with asymptomatic/minimally symptomatic bone-metastatic castrate-resistant prostate cancer (CRPC). First Author: Yong Chul Park, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Background: Sipuleucel-T is an autologous cellular immunotherapy indicated for men with asymptomatic/minimally symptomatic metastatic CRPC. Recent analysis of immune responses in men treated with sipuleucel-T showed that antigen-specific immune responses to sipuleucel-T may be associated with survival, confirming the immune-based mechanism of action and suggesting the possibility that producing a robust immune response may translate into better clinical outcomes. Radiopharmaceutical agents have been shown to enhance immune modulation through a variety of mechanisms including enhanced display of tumor-associated antigens. Based on the immunomodulatory effects of radiopharmaceutical drugs, we hypothesized that combined use of radium-223 and sipuleucel-T may enhance the sipuleucel-T-induced immune response and improve clinical outcomes. Methods: This is a randomized phase 2 study comparing antigen-specific immune responses of sipuleucel-T used alone versus sipuleucel-T plus radium-223 in CRPC patients with bone metastases but no visceral involvement. Patients will be randomly assigned (1:1) to receive sipuleucel-T plus radium-223 (Arm 1) or sipuleucel-T alone (Arm 2); men in Arm 2 will receive 3 infusions of sipuleucel-T alone, while men in Arm 1 will receive 6 infusions of radium-223 plus 3 infusions of sipuleucel-T starting after the second radium-223 dose. The primary study objective is to determine whether addition of radium-223 to sipuleucel-T enhances immune response, as measured by peripheral PA2024-specific T-cell proliferation using a tritiated thymidine incorporation assay at 6 wks after the first sipuleucel-T infusion. With 15 men per arm, there is 80% power to detect a 3.6-fold increase in mean proliferation response between the two arms. PSA responses and radiographic responses (in men with measurable disease) will also be assessed. Incidence and severity of AEs will be graded according to CTCAE v4.0. Various immune parameters, both humoral and cellular, will be analyzed at multiple time points during the treatment period, and an exploratory assessment of antigen spread will also be performed.
**TPS5077** Poster Session (Booth #67a), Sat, 1:15 PM-4:45 PM

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: the ANZUP ENZAMET Trial (NCT0130011684).

First Author: Benjamin A. Teply, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Prostate cancer can progress despite androgen deprivation therapy through overexpression of the androgen receptor (AR) and expression of AR splice variants. Almost paradoxically, testosterone given to cancer cells in this state can cause growth inhibition. The AR is normally degraded during progression through the cell cycle, but androgen-bound AR is stabilized, thus arresting the cell cycle and inducing DNA strand breaks through interaction with topoisomerase-IIb. Clinically, supraphysiologic testosterone given to men with castration-resistant prostate cancer was found to be safe in a pilot clinical trial, producing responses and re-sensitizing patients to subsequent anti-androgen therapy. In this context, we designed a randomized phase II study comparing bipolar androgen therapy (BAT) to enzalutamide for patients who have experienced progression on abiraterone. Methods: In this multi-center randomized study, funded by a grant from the Department of Defense, eligible patients have asymptomatic metastatic castration-resistant prostate cancer that has radiographically or biochemically progressed after treatment with abiraterone. Patients are enzalutamide-naïve and have not received docetaxel for castration-resistant disease. Patients randomized to BAT will continue on androgen deprivation therapy and receive monthly intramuscular testosterone injections approved by the FDA. The BAT treatment arm comprises BAT with supraphysiologic testosterone levels with return to castrate levels after one month. Patients randomized to enzalutamide will receive 160mg daily. Crossover is encouraged. The primary endpoint is radiographic progression-free survival (rPFS). The trial is powered to detect a 50% improvement in median rPFS in the BAT arm compared to the enzalutamide arm (expected to be ~6 months), with planned accrual of 90 patients in each arm. The arms will be stratified for time to progression on abiraterone. Secondary endpoints include PSA response rates, safety, and quality of life. Correlative studies include the effect of BAT on AR variant expression. Enrollment opened in February 2015. Clinical trial information: NCT02286921.

**TPS5078** Poster Session (Booth #67b), Sat, 1:15 PM-4:45 PM

Randomised phase 3 trial of enzalutamide in androgen deprivation therapy with radiation therapy for high risk, clinically localised prostate cancer: The ANZUP ENZARAD Trial (NCT02200614).

First Author: Karim Fizazi, Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, Villejuif, France

Background: There is no standard treatment for nmCRPC besides continuing androgen deprivation therapy (ADT). Preventing metastatic disease in nmCRPC is a major unmet need. Patients with nmCRPC who have shorter PSA doubling time (PSADT) are at high risk for metastatic disease or death (Smith et al. J Clin Oncol. 2013;31:3800-6). ODM-201, a novel second-generation oral androgen receptor inhibitor, has shown an excellent safety profile and promising anticancer activity in progressive CRPC (Fizazi et al. Lancet Oncol. 2014;15:975-85). The ARAMIS trial aims to evaluate the efficacy and safety of ODM-201 in high-risk nmCRPC. Methods: This international, randomized, double-blind, placebo-controlled phase 3 trial (NCT02200614) involves over 300 sites in more than 30 countries. 1500 patients on ADT will be randomized 2:1 to ODM-201 600 mg or placebo twice daily. Patients will be stratified by PSADT and baseline use of bone-targeting agent. Eligibility criteria include nmCRPC, PSADT ≤ 10 months, and screening PSA ≥ 2 ng/mL. The primary endpoint is metastasis-free survival based on central independent review of bone scan and CT/MRI every 12 weeks; progression of regional disease is not considered metastasis. Secondary endpoints are OS, time to first symptomatic skeletal event (SSE), initiation of first cytotoxic chemotherapy for prostate cancer, pain progression, and first opioid use. Additional endpoints are FFS, time to first progression or CRPC-related clinical event, progression-free survival, radiographic progression, and time to treatment failure. The trial has 90% power to detect a target hazard ratio of 0.75 based on a 2-sided log-rank test at an overall significance level of 0.05. Kaplan-Meier estimates will be produced for both treatment groups. The ARAMIS trial is open and recruiting, with the first patient randomized in October 2014. Clinical trial information: NCT02200614.
TPS5081  Poster Session (Board #69a), Sat, 1:15 PM-4:45 PM
Prospect: A randomized double-blind phase 3 efficacy study of PROST-VF immunotherapy in men with asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer. First Author: Matthew Smith, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: PROST-VF, a targeted active immunotherapy, is being studied in men with asymptomatic to minimally symptomatic mCRPC in PROSPECT, a global double-blind, randomized phase 3 study. PROST-VF is a prime-boost regimen consisting of subcutaneous administrations of poxvirus-based PROST-VF-Prime (a modified vaccinia vector) and PROST-VF-Boost (a modified fowlpox vector) that encode prostate specific antigen (PSA) as the target antigen with three T-cell co-stimulatory molecules (B7.1, ICAM-1, and LFA-3) also known as TRICOM. A statistically significant overall survival (OS) benefit of 8.5 months (P= 0.0061) with a hazard ratio of 0.56 (95% CI: 0.37 to 0.85), and a favorable risk-benefit profile were reported in a randomized, phase 2 study in mCRPC (Kantoff et al. 2010 J Clin Onc 28:1099-1105). Methods: In PROSPECT, 1200 subjects have been randomized in a double-blind fashion to three arms: PROST-VF, PROST-VF plus GM-CSF, or Placebo at a 1:1:1 ratio. The 5 month treatment regimen comprises one PROST-VF-Prime injection followed by 6 PROST-VF-Boost injections. Enrolled subjects have asymptomatic/minimally symptomatic mCRPC and are chemotherapy-naive. Subjects with rapidly progressing disease and visceral metastases are excluded. The primary endpoint is OS and pre-specified interim analyses are integrated in the statistical plan. Secondary efficacy endpoints include the proportion of event-free subjects at 6 months (radiographic progression, pain progression, chemotherapy initiation, or death) compared to placebo. Exploratory endpoints are planned, including immune responses. An immune monitoring program would inform future immunotherapy studies and potential identification of biomarkers. The trial is fully enrolled. ClinicalTrials.gov registry number: NCT01322490. Clinical trial information: NCT01322490.

TPS5083  Poster Session (Board #70a), Sat, 1:15 PM-4:45 PM
The PRESIDEE trial: A randomized, double-blind, placebo-controlled phase III efficacy and safety study of continued enzalutamide plus docetaxel after disease progression on enzalutamide alone in patients with metastatic castration-resistant prostate cancer. First Author: Simon Chowdhury, Guy’s King’s and St Thomas Hospitals, London, United Kingdom

Background: Enzalutamide (ENZA) is an oral androgen receptor inhibitor approved in the US for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) (US PI, 2014) and in the EU for the treatment of asymptomatic/mildly symptomatic men with mCRPC after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, or those whose disease has progressed on or after docetaxel (DTX) therapy (EU SmPC, 2014). The PRESIDEE study (NCT02288247) will evaluate the efficacy and safety of continued ENZA treatment vs placebo (PBO) when starting docetaxel plus prednisolone (PRED) after disease progression on first-line ENZA in chemotherapy-naive mCRPC patients. Methods: PRESIDEE will consist of an open-label treatment period with ENZA (period 1), followed by a randomized double-blind treatment with continued ENZA or PBO in addition to DTX plus PRED (period 2). Eligibility criteria include confirmed prostate adenocarcinoma, metastatic disease, prostate-specific antigen (PSA) progression on androgen deprivation or surgical castration, Eastern Cooperative Oncology Group performance status 0–1, testosterone ≤ 50 ng/dL, and minimally symptomatic patients (Brief Pain Inventory Short Form, question 3, ≤ 8 in the absence of opiate analgesia). In period 1, all patients will receive open-label ENZA 160 mg/day until radiographic progression or PSA progression with rapidly PSA doubling time. In period 2, patients with confirmed disease progression on ENZA alone will be randomized to either ENZA 160 mg/day or receive PBO. All patients will also receive treatment with DTX 75 mg/m² every 3 weeks plus PRED 10 mg/day. The primary endpoint is radiographic progression-free survival. Secondary endpoints include PSA and pain progression, PSA and radiographic response, opiate use for cancer-related pain, skeletal related events and quality of life. Planned enrolment is 650 patients in 90 sites across Europe for period 1, with ≥ 137 patients in each randomized arm for period 2. Recruitment commenced in December 2014. Clinical trial information: NCT02288247.

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A randomized phase II study of paclitaxel/carboplatin bevacizumab, paclitaxel/carboplatin/tamoxifen and irinotecan/carboplatin/bevacizumab as initial therapy for measurable stage III-IV ovarian cancer, GOG-86P. First Author: Carol Aghajanian, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Paclitaxel (PC) is a standard initial therapy for advanced endometrial cancer (EC). We evaluated efficacy and tolerability of incorporating three novel agents into initial therapy. Methods: Patients (pts) who received no prior therapy. Randomization (1:1:1) was stratified by measurable disease, recurrent disease, prior pelvic RT. Primary endpoint was progression-free survival (PFS). GOG 209 was used as historical control. Results: At least 72% of pts received 6 cycles of therapy (70-83% or P=74-82%); 68% received 6 cycles of I. Pts on arm 1 received a median of 12 cycles (0-78) of Bev compared with 9 cycles (0-53) on arm 3. A median of 8 cycles (0-62) was given on arm 2. Hypertension (G 3/4) was more common in the Bev arms (16%) than in the Tem arm (3%), p < 0.001. Pneumonitis (p = 0.004) and oral mucositis (p < 0.001), more common in the Tem arm. PFS, compared using a log-rank test on data grouped by time intervals, was not significantly increased in any experimental arm (p < 0.039) when each arm was compared to historical control. HR (92% CI) for arms 1, 2 and 3 was 0.81 (0.56-1.21), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively. Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly (p < 0.039) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.95 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively). Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly (p < 0.039) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.95 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively).

Conclusions: PFS is not significantly increased in any Arm. OS is significantly increased in the PC + Bev arm. Clinical trial information: NCT00177574.

5502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxel-bevacizumab (CP-B) in advanced (stage III-IV) or recurrent endometrial cancer: The MITO END-2 trial. First Author: Domenica Longo, MITO and Fondazione IRCCS National Cancer Institute, Milan, Italy

Background: The prognosis of advanced or recurrent endometrial cancer (AEC) is dismal. The antiangiogenic drug Bevacizumab (B) has reported activity in AEC (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively. Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly (p < 0.039) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.95 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively). Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly (p < 0.039) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.95 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively). Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly (p < 0.039) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.95 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively).

Conclusions: PFS is not significantly increased in any Arm. OS is significantly increased in the PC + Bev arm. Clinical trial information: NCT00177574.

5503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact of trebananib plus weekly paclitaxel on overall survival (OS) in patients (pts) with recurrent ovarian cancer and ascites: Results from the phase III TRINOVA-1 study. First Author: Bradley J. Monk, Department of Obstetrics and Gynecology, University of Arizona Cancer Center, Crapehb University School of Medicine at Dignity Health St. Joseph’s Hospital and Medical Center, Phoenix, AZ

Background: Trebananib is an antiangiogenic peptibody that inhibits angiopoetin 1 and 2 binding to the Tie2 receptor. TRINOVA-1 showed significantly longer progression-free survival (PFS) in the trebananib arm (Monk et al, Lancet Oncol 2014;15:799). We evaluated OS, involving clinical and important functional remaining. Most striking differences at 2 years were tingling/numbness (24 vs 7%, p < 0.001) and weakness arm/legs (14 vs 9%, p < 0.001).

Conclusions: CTRT for high-risk endometrial cancer causes significantly higher AE and symptom ratings and reduced HRQL during and after treatment, as compared with RT, with recovery over time, without differences in grade ≥ 3 AE at 2 years. Clinical trial information: NCT00411138.

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Efficacy and safety of chemotherapy (CT) + pertuzumab (P) for platinum-resistant ovarian cancer (PROC): AGO-OVAR 2.20/ENGOT-ov14/PENELOPE double-blind placebo-controlled randomized phase III trial.

First Author: Michael J. Birrer, Massachusetts General Hospital/Dana Farber Cancer Center, Boston, MA

Background: In EOC, the double-blind placebo (PLA)-controlled randomized phase 3 GOG-0218 trial showed significantly improved progression-free survival (PFS) but not overall survival (OS) with CT and continued alone. Plasma BM correaltive analyses identified no predictive BMs for efficacy. Tumor BM evaluation was an exploratory objective. Methods: Patients (pts) with stage III (incompletely resected) or IV OC were randomized to receive 6 cycles of CT with: PLA (CPP); BEV 15 mg/kg q3w → PLA (CPB15); or BEV for 15 mo (CPB15+). Five tumor BMs (CD31, IVEGF-A, VEGFR-2, NRP-1, MET) with a biologic rationale for evaluation were assessed by immunohistochemistry (IHC). BM evaluation was required in a randomized subset of BEV (78%) and BEV/C (31%) but BEV/P (17%) patients. The prespecified primary end point of OS was analyzed using 1st, 2nd and 3rd quartile (Q) expression levels for each BM as the cutoff for high vs low BM subgroups. Correlations between tumor BM levels and OS were analyzed. Results: The BEP, comprising 1455 (78%) of 1873 pts in the ITT population, had very similar baseline characteristics and efficacy to BEP. No prognostic or predictive association was seen for VEGFR-2, NRP-1 or MET. However, when comparing CPB15+ vs control, higher microvascular density (MVD) measured by CD31 IHC showed prognostic (not shown) and potential predictive value for PFS (median 4.3 mo vs 2.6 mo for placebo CT vs placebo + CT). The BEP and BEP/P subgroups showed a survival benefit; BEP (HR 0.55, 80% CI 0.39, 0.79, 95% CI 0.32, 0.95, p = 0.018) vs control, interaction p = 0.0069). IVEGF-A showed potential predictive value for OS (and PFS) for CPB15+ vs control with a Q3 cutoff (> 0.45) and showed favorability in OS (HR 0.38 [95% CI 0.25–0.58]; ≤ 0.54–0.86; interaction p = 0.018) and OS (> 0.39–0.83; ≤ 0.39–0.83; ≤ 0.83–1.27; interaction p = 0.023). Conclusions: These retrospective tumor BM analyses suggest a positive correlation between expression levels of molecular (IVEGF-A) and cellular (endothelial cell) targets of anti-VEGF and magnitude of PFS and OS improvement from BEV in EOC. The predictive value of the BEP and BEP/P for positive correlation between expression levels of molecular (IVEGF-A) and cellular (endothelial cell) targets of anti-VEGF and magnitude of PFS and OS improvement from BEV in EOC. The predictive value of the BEP and BEP/P for BM efficacy markers requires validation in other relevant datasets. Clinical trial information: NCT00268247.

A phase I study of continuous veliparib in combination with IV carboplatin/paclitaxel or IV/IV paclitaxel/cisplatin and bevacizumab in newly diagnosed patients with platinum-sensitive primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study.

First Author: Katherine M. Bell-McQuinn, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Veliparib, a poly-(ADP-ribose)-polymerase inhibitor, increases antitumor activity when combined with platinum chemotherapy and has monotherapeutic activity in BRCA1 or BRCA2 deficient tumors. This study was done to determine the recommended phase II dose (RP2D) of continuous veliparib in combination with initial treatment for epithelial ovarian cancer (EOC) or primary peritoneal cancer. Methods: Eligible patients had newly diagnosed, untreated, stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma or carcinosarcoma. Three regimens (six 21 day cycles) were evaluated: 1, IV q3week carboplatin (AUC 6) and paclitaxel (175mg/m²); 2, IV q3week carboplatin (AUC 6) and weekly paclitaxel (80mg/m²); and 3, IV paclitaxel (135mg/m², day 1), IP cisplatin (75mg/m², day 1 or 2) and IP paclitaxel (60mg/m², day 8). Bevacizumab 15mg/kg started in cycle 2 and continued as monotherapy for cycles 7-22. Veliparib continuous oral BID dosing in cycles 1-6 started at 30mg. A 3 + 3 dose escalation design evaluation dose-limiting toxicities (DLTs) in cycles 1 and 2. One <2/6 patients experienced a DLT, that dose level was expanded to evaluate feasibility over 4 cycles. Results: We enrolled 189 patients; 32 were not evaluable. DLTs at the levels were as seen in the table. Conclusions: The RP2D for all regimens was veliparib 150mg BID. Clinical trial information: NCT00989651.
Results of ARIEL2: A Phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis. First Author: Iain A. McNeish, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland

Background: At least 50% of high-grade serous ovarian cancers (OC) may have homologous recombination deficiency (HRD). Germline BRCA1 and BRCA2 mutations (gBRCAmut) account for ~1/3. Identification of BRCAmut HRD tumors likely to respond to a PARP inhibitor remains as challenging. ARIEL2 prospectively tested a novel next generation sequencing-based HRD assay and algorithm to predict rucaparib sensitivity by assessing tumor BRCA status and genome-wide loss of heterozygosity (LOH). Methods: ARIEL2 enrolled pts with platinum-sensitive, recurrent, high-grade serous or endometrioid OC. The primary objective was to evaluate clinical activity of 600 mg BID rucaparib in 3 pre-defined HRD subgroups: tumor BRCAmut, BRCA-LDHhigh and BRCA-LDHlow. Known gBRCApt enrollment was limited. Tumor HRD status was assessed in pre-treatment biopsies and archival tumor. Response was assessed by RECIST and GCIG CA-125 criteria. Results: In 206 treated pts: median age ~64 (range 31-86); 64% ECOG 0; 96% high-grade serous; 46% with ≥2 prior regimens. Treatment-related AEs ≥1% of pts were: asthenia [9%], nausea [7.9%], vomiting [3.4%], constipation [4.4%], appetite loss [3.4%], pneumonia [2.4%], diarrhea [2.4%] and fatigue [1.9%], and transient ALT/AST elevations with no other evidence of liver dysfunction. Efficacy data for 135 pts indicate RECIST CA-125 ORs of 69%, 39%, and 11% in BRCAmut, BRCA-LDHhigh, and BRCA-LDHlow pts, respectively (Table 1, p < 0.0001, Cochran-Armitage trend test). Responses occurred in both gBRCAmut (14/19, 74%) and somatic BRCAmut (10/16, 63%) tumors. Only 1/16 (6%) gBRCAmut tumors had a loss-of-function mutation or homozgyous deletion in a HR gene; 4/15 (27%) alterations were in RAD51C. All 4 tumors were LOHhigh and responded to rucaparib, suggesting a potential HRD mechanism. Importantly, matched archival and screening tumor analysis revealed an increase in genomic LOH over time in a subset of tumors. Conclusions: ARIEL2 data indicate a tumor HRD assay and algorithm combining BRCA analysis and genomic LOH identified OC pts likely to respond to rucaparib. Clinical trial information: NCT01891344.

Response by HRD status.

<table>
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<th>HRD Subgroup</th>
<th># of Pts</th>
<th>RECIST %</th>
<th>RECIST &amp; CA-125, %</th>
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<td>BRCAmut</td>
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<td>69</td>
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<tr>
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<td>BRCA-LDHlow</td>
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Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase ib study. First Author: Andrea Varga, Gustave Roussy Institute, Villejuif, France

Background: Pembrolizumab is a potent, highly selective humanized monoclonal antibody against PD-1 designed to block interaction with PD-L1 and PD-L2 and reduce the inhibition of T-cell activation against cancer. PD-L1 was found to be overexpressed in ovarian cancer and can contribute to malignancy. We assessed the safety and efficacy of pembrolizumab in pts with PD-L1 advanced ovarian cancer. Methods: KEYNOTE-246 was a randomized, multi-center phase Ib trial of pembrolizumab in pts with PD-L1+ advanced solid tumors. Key eligibility criteria for the ovarian cancer cohort included advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma; failure of prior therapy; PD-L1+ expression in ≥ 1% of cells; and an Eastern Cooperative Oncology Group performance status of 0-1. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with refractory ovarian cancer in an ongoing phase Ib study (NCT01772004). Here we present results from a cohort of patients (pts) with recurrent or refractory ovarian cancer: A phase Ib, open-label expansion trial. First Author: Mary L. Disi, University of Washington School of Medicine, Seattle, WA

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab (proposed INN) (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Here we present results from a cohort of patients (pts) with recurrent or refractory ovarian cancer in an ongoing phase Ib study (NCT01772004). Methods: Pts with ECOG PS 0-1 received avelumab at 10 mg/kg Q2W. Best overall response (BOR) and progression-free survival (PFS) were assessed according to RECIST 1.1. Adverse events (AEs) were evaluated by CTCAE v4.0. A prespecified analysis of 23 pts with follow-up of ≥ 2 months showed improved and confirmed partial responses (PRs), leading to cohort expansion to 75 pts. Results: Seventy-five pts were enrolled from November 2013 to November 2014 (median age 62 [range 38-84]; ECOG PS 0 [41%] or 1 [59%]; median of four prior lines of therapy). As of January 2015, median duration of treatment with avelumab was 10 weeks (range 2-54 weeks), and 27 pts remained on treatment. Efficacy data from the 23 pts followed-up for ≥ 2 months (range 2-8 months) demonstrated 4 pts (17.4%, [95% CI, 5.0%, 38.8%]) achieved an unconfirmed BOR of PR, 11 (47.8%) had stable disease, and 2 pts had >30% tumor shrinkage after progression was reported. Median FFS was 11.9 weeks (95% CI, 5.3, not reached), and the PFS rate at 24 weeks was 33.3% (95% CI, 11.6, 57.2). Drug-related treatment-emergent AEs (TEAEs; all grades) were reported in 18 pts (78.3%), and 2 pts (8.7%) experienced grade ≥ 3 drug-related TEAEs (increased lipase [1] and elevated creatine kinase and autoimmune myositis that led to discontinuation [1]). No drug-related serious AEs occurred. The most commonly reported drug-related AEs (>10%) were fatigue, nausea, and diarrhea. Conclusions: These data represent the largest reported dataset of pts with recurrent ovarian cancer treated with anti-PD-L1 therapy. Avelumab demonstrated an acceptable safety profile and is clinically active in this heavily pretreated ovarian cancer pt population. Clinical trial information: NCT01772004.

Association of POLE-mutated and MSI endometrial cancers with an elevated number of tumor-infiltrating and peritumoral lymphocytes and higher expression of PD-L1. First Author: Brooke E. Howitt, Brigham and Women’s Hospital, Boston, MA

Background: TCGA identified two groups of endometrial cancers with high mutation frequency: an ultramutated group of tumors which harbored mutations in polymerase epsilon (POLE) and a hypermutated group with microsatellite instability (MSI). We hypothesized that these hypermutated tumors may harbor more neoantigens and thus stimulate a stronger immune response compared to tumors with low mutation frequency. In this regard, we evaluated whether hypermutated tumors are associated with an elevated number of tumor-infiltrating lymphocytes (TILs) and peritumoral lymphocytes and higher expression of the immune modulatory molecule PD-L1. Methods: We evaluated 4 POLE-mutated (determined via Sanger sequencing of mutational hotspots), 28 MSI-tumors and 32 microsatellite stable (MSS) endometrioid endometrial tumors. MSI status was determined using immunohistochemistry (IHC). IHC was performed for CD3, CD4, CD8, CD20, PD-1 and PD-L1 using standard protocols. For evaluation of TILs, a photomicrograph (40X) of the area of maximum CD3+ intraepithelial lymphocytes was obtained with corresponding photomicrographs for the additional stains. For peritumoral lymphocytes, a semi-quantitative scoring method was utilized. Results: POLE-mutated and MSI tumors exhibited significantly elevated CD3+ (p < 0.001), CD4+ (p = 0.078) and CD8+ (p < 0.001) TILs compared to MSS tumors. CD20+ TILs were not significantly different between MSI/POLE tumors and MSS tumors. Expression of PD-1 (p < 0.001) and PD-L1 (p = 0.022) was higher in TILs of POLE and MSI tumors compared to MSS tumors. Furthermore, POLE and MSI tumors harbored more peritumoral T-lymphocytes (p < 0.001) and higher expression of PD-1 (p < 0.001) and PD-L1 (p < 0.001) compared to MSS tumors. There were no significant differences in TILs, peritumoral lymphocytes and PD-1/PD-L1 expression between POLE-mutated and MSI tumors. Conclusions: POLE-mutated and MSI endometrial cancers are associated with an elevated number of TILs and peritumoral lymphocytes, and higher expression of PD-1 and PD-L1. These data support trials of immune-checkpoint inhibitors in hypermutated endometrial cancers.
5512 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM
Tumor infiltrating and peritumoral T cells and expression of PD-L1 in BRCA1/2-mutated high grade serous ovarian cancers. First Author: Kyle Stanford, (Origamis Therapeutics, New York, NY) Background: Previous studies have shown that the presence of CD3+ and CD8+ tumor-infiltrating lymphocytes (TILs) and a high CD8+/CD4+ ratio are associated with favorable overall survival in ovarian cancer. Given that BRCA1/2 mutated ovarian cancers are also known to be associated with improved survival, we assessed whether the presence of CD3+, CD8+ and CD4+ and TILs is enriched in these tumors compared to non-BRCA1/2 mutated ovarian cancers. Furthermore, we assessed the expression of PD-1 and PD-L1 in these tumors. Methods: In this pilot study, we evaluated 34 high grade serous ovarian cancers with germline BRCA1 (n = 28) and BRCA2 (n = 6) mutations and 18 tumors without germline or somatic mutations in BRCA1, BRCA2 or other homologous recombination (HR) genes. Immunohistochemistry (IHC) was performed for CD3, CD8, CD19, CD4, CD20, PD-L1 using standard protocols. For evaluation of TILs, a photomicrograph (40X) of the area of maximum CD3+ intratumoral lymphocytes was obtained with corresponding photomicrographs for the additional stains. For peritumoral lymphocytes, a semi-quantitative scoring method was utilized. Results: The number of CD3+ TILs was not significantly different between BRCA1/2-mutated and non-BRCA1/2-mutated ovarian cancers (p = 0.23). However, BRCA1/2-mutated tumors were associated with a strong trend for increased CD8+ TILs (p = 0.06) while demonstrating significantly less CD4+ TILs (p = 0.05) compared to non-BRCA1/2-mutated tumors. Overall, there was a significantly higher ratio of TILs and significantly higher peritumoral T cells. These findings support an additional mechanism for the improved survival of patients with BRCA1/2-mutated ovarian cancers.

5513 Poster Discussion Session; Displayed in Poster Session (Board #71), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
A phase II open-label, multicenter study of single-agent rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious BRCA mutation. First Author: Ronnie Shapira-Frommer, Sheba Medical Center, Ramat Gan, Israel
Background: Rucaparib is a potent oral PARP inhibitor that has shown robust activity in patients (pts) with homologous recombination deficient (HRD) tumors, with the highest response rates observed in ovarian and breast cancer pts with germline/BRCA1/2-mutated BRCA mutations (gBRCAm/BRCAm). In this phase II study (NCT01891344) we evaluated the efficacy and safety of rucaparib in pts with relapsed gBRCAmut high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (EOC/FTC/PPC). Methods: Women with gBRCAmut EOC/FTC/PPC who received 2-4 prior chemotherapy (chemo) regimens and had a platinum-sensitive or platinum-resistant disease were enrolled. ECOG PS 0-1 and adequate organ function were required. Pts received oral rucaparib 600 mg BID in 21 day cycles until disease progression. The primary endpoint was objective response rate (ORR) by RECIST 1.1. Results: 35 pts have been enrolled. Median age was 55 years (range 44-84). The median number of prior chemo regimens was 2 (range 2-4). Fifteen pts (43%) had received ≥ 3 prior chemo regimens. RECIST/CA-125 ORR was 81% (21/26); RECIST ORR was 65% (17/26). RECIST ORR was 88% (7/8) and 56% (10/18), respectively, in pts with PFI 6-12 mo or >12 mos. In pts with ≥ 3 prior chemo regimens, 58% (7/12) achieved a RECIST response. The median duration of response has not been reached. The most common treatment-related AEs (generally grade 1/2) were nausea (55%), anemia (41%), ALT/AST elevations (41%), fatigue (41%), and asthenia (35%). The ALT/AST elevations are transient with no other evidence of liver dysfunction. No pts discontinued treatment due to AEs. No sec or persistent OC, GOG PS ≤ 2, < 4 prior regimens. At DLT at DCAUC4, we escalated BTZ to DL5a without serious toxicity. Of enrolled pts, 32/33 were evaluable for safety. Two pts were withdrawn due to an AE. No secondary malignancies have been observed.

5514 Poster Discussion Session; Displayed in Poster Session (Board #72), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Phase I/II study of the PARP inhibitor (PARPi) olaparib (O) with carboplatin (C) in heavily pretreated recurrent HGSOC pts without gBRCAm. Interactive pharmacokinetics (IP) combination of O/C was feasible and showed promising clinical activity. Tumor biopsies were performed in a 15 patient (pt) expansion cohort where 11 pts were evaluable for safety. PBMCs were collected at baseline, d3, and post-cycle 1 for PAR incorpora-

5515 Poster Discussion Session; Displayed in Poster Session (Board #73), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Results of a phase I pharmacokinetic study of intraperitoneal bortezomib (B) and carboplatin (C) in patients with persistent or recurrent ovarian cancer (OC): An NRG/Gynecologic Oncology Group Study. First Author: Don S. Dizon, Massachusetts General Hospital, Boston, MA
Background: Intraperitoneal therapy (IP) has been shown to improve survival outcomes for women with optimally cytoreduced, newly diagnosed, advanced OC, but whether IP has a role for recurrent OC is unknown. Preclinical data show IP administration of the proteasome inhibitor bortezomib (B) prior to IP carboplatin (C) increased cellular platinum accumulation and results in synergistic cytotoxicity. Hence, we conducted this phase I trial of an IP regimen consisting of B+C in women with recurrent or persistent disease. Methods: We enrolled 33 pts with recurrent or persistent OC, GOG PS ≤ 2, < 4 prior regimens. At DLT at DCAUC4, we escalated B to DL5a without serious toxicity. Of enrolled pts, 35 pts have been enrolled. Median age was 55 years (range 44-84). The median number of prior chemo regimens was 2 (range 2-4). Fifteen pts (43%) had received ≥ 3 prior chemo regimens. RECIST/CA-125 ORR was 88% (7/8) and 56% (10/18), respectively, in pts with PFI 6-12 mo or >12 mos. In pts with ≥ 3 prior chemo regimens, 58% (7/12) achieved a RECIST response. The median duration of response has not been reached. The most common treatment-related AEs (generally grade 1/2) were nausea (55%), anemia (41%), ALT/AST elevations (41%), fatigue (41%), and asthenia (35%). The ALT/AST elevations are transient with no other evidence of liver dysfunction. No pts discontinued treatment due to AEs. No sec or persistent OC, GOG PS ≤ 2, < 4 prior regimens. At DLT at DCAUC4, we escalated BTZ to DL5a without serious toxicity. Of enrolled pts, 32/33 were evaluable for safety. Two pts were withdrawn due to an AE. No secondary malignancies have been observed.
A phase Ib dose-escalation study of binimetinib (MEK162) in combination with weekly paclitaxel in patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. 

First Author: Rachel N. Grisham, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Ovarian cancer is associated with key genetic alterations, including those that lead to activation of the RAS/RAT/MEK/ERK pathway. Binimetinib (BINI) is a potent, selective, allosteric inhibitor of MEK1/2. This study determined the recommended phase II dose (RP2D) of BINI administered on 2 dosing schedules in combination with weekly paclitaxel (PAC) and assessed the safety, pharmacokinetics (PK) and preliminary antitumor activity in female patients (pts) with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.

Methods: Primary objective: To show non-inferiority between PAC and PAC in PFS using CT scans (RECIST) in platinum-sensitive recurrent ovarian, fallopian tube or peritoneal carcinoma. To obtain 379 events of progression 850 were estimated to be accrued (non-inferiority HR = 1.2; α = 0.25 (one-sided); β = 0.8). Patients were randomized to Pcal 250 mg/m² iv 1 hr or Pxel 175 mg/m² iv q3w in PAC. The most common Grade 3/4 AEs noted in 90% in the Pcal group and 87% in the Pxel group. All grade peripheral neuropathy were 29% vs 32% and myalgia 11% vs 13%.

Results: Thirty-four pts were enrolled and treated, with 22 pts on the CONT schedule (14 at DL1; 8 at DL2) and 12 pts on the INTERM schedule. The median age was 63 years (range 42-77), baseline ECOG PS was 0 or 1 (97%), median number of prior systemic therapies was 4 (range 1-14) and the majority of tumors were high-grade serous (HG; 74%) or low-grade serous (LGS; 18%). On the CONT schedule, dose-limiting toxicities (DLTs) of fatigue, nausea, neutropenia, rash and stomatitis were observed; the RP2D was declared as BINI 30 mg BID CONT with weekly PAC. On the INTERM schedule, a DLT of asthenia was observed; the RP2D was confirmed as BINI 45 mg BID INTERM with weekly PAC. The most common Grade 3/4 AEs included asthenia (12%), cough (12%), fatigue, nausea, neutropenia, pulmonary embolism, small intestinal obstruction and stomatitis (9%). When administered in combination, no clinically relevant differences in BINI or PAC exposures were observed. Of the 29 pts with measurable disease, the response rate was 17% with 1 complete response (LGS) and 4 partial responses (1 LGS, 3 HGS). Safety: In this phase I study, the toxicity of BINI on both the CONT and INTERM schedules with weekly PAC had an acceptable safety and PK profile at the RP2Ds. Responses were observed in HGS and LGS pts. Clinical trial information: NCT01649336.

Preliminary single agent activity of IMGN853, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in platinum-resistant epithelial ovarian cancer (EOC) patients (pts): Phase I trial. First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: IMGN853 (mirvetuximab soravtansine) is a FRα-binding antibody conjugated with the potent maytansinoid, DM4.

Methods: A pilot clinical trial was conducted using an IMGN853ADC that comprises a FRα-binding antibody conjugated with the potent maytansinoid, DM4. IMGN853 was administered either at a primary peritoneal cancer. IMGN853 was administered orally either on a continuous (CONT) schedule at 30 mg twice daily (BID); dose level 1 [DL1] or 45 mg BID (DL2), or on an intermittent (INTERM) schedule on Days (D) 1-5 weekly for 3 of every 4 weeks (q3/4w) at 45 mg BID, in combination with PAC 80 mg/m² iv on D1 weekly q3/4w. Results: Thirty-four pts were enrolled and treated, with 22 pts on the CONT schedule (14 at DL1; 8 at DL2) and 12 pts on the INTERM schedule. The median age was 63 years (range 42-77), baseline ECOG PS was 0 or 1 (97%), median number of prior systemic therapies was 4 (range 1-14) and the majority of tumors were high-grade serous (HG; 74%) or low-grade serous (LGS; 18%). On the CONT schedule, dose-limiting toxicities (DLTs) of fatigue, nausea, neutropenia, rash and stomatitis were observed; the RP2D was declared as BINI 30 mg BID CONT with weekly PAC. On the INTERM schedule, a DLT of asthenia was observed; the RP2D was confirmed as BINI 45 mg BID INTERM with weekly PAC. The most common Grade 3/4 AEs included asthenia (12%), cough (12%), fatigue, nausea, neutropenia, pulmonary embolism, small intestinal obstruction and stomatitis (9%). When administered in combination, no clinically relevant differences in BINI or PAC exposures were observed. Of the 29 pts with measurable disease, the response rate was 17% with 1 complete response (LGS) and 4 partial responses (1 LGS, 3 HGS). Safety: In this phase I study, the toxicity of BINI on both the CONT and INTERM schedules with weekly PAC had an acceptable safety and PK profile at the RP2Ds. Responses were observed in HGS and LGS pts. Clinical trial information: NCT01649336.

AutoLOGous oxidized whole-tumor antigen vaccine in combination with angiogenesis blockade to elicit antitumor immune response in ovarian cancer. First Author: Janos L. Tanyi, University of Pennsylvania, Philadelphia, PA

Background: Personalized tumor lysate vaccines can encompass all putative antigens in tumors. Methods: A pilot clinical trial was conducted using an autoLOGous oxidized whole tumor cell lysate dendritic cell (DC) based vaccine (vx) alone or in combination with pembrolizumab (Bev) with or without low-dose IV cyclophosphamide (Cy) and/or oral aspirin (ASA), in recurrent ovarian cancer patients (pts). Pts were treated every 3 weeks. Most of the pts were platinum-resistant and heavily pretreated. Adverse events (AEs) were graded by CTCAE v4.0 and clinical responses by RECIST v1.1. Results: To date, 35 pts (cohort 1 (vx only; n = 5), 2 (vx+bev; n = 10), 3 (vx+bev+Cy; n = 10) and 4 (vx+Bev+Cy+ASA; n = 10) have received over 392 vx doses. The treatment was well tolerated without serious AEs. Immune response to autoLOGous antigen was seen mainly in cohorts 3 and 4, which received low-dose Cy. An increase in the frequency of T cell responses against tumor-specific antigens (WT1, mesothelin, NY-ESO-1) was observed post-vx. Moreover, it is demonstrated for the first time that vaccination with whole tumor lysate-loaded DCs elicited a CDB T cell response against mutated peptides derived from private non-synonymous somatic tumor mutations. Six pts achieved a partial response or were disease-free at end of treatment. The median progression-free survival (PFS) of cohort 1, 2, 3 and 4 were 3.8, 11.1 and 10.1 mos, respectively. The median overall survival (OS) of cohorts 1 and 2 were 35.3 and 11.4 mos, while for cohorts 3 and 4 it has not been reached, with median potential follow up of 19 mos. A historic population (n = 789 patients from the same institution who received Bev; n = 597 vs 582) vs vs in the PFS was 12.2 versus 12.1 months, respectively (HR:0.79; CI:0.56-1.1; p = 0.179). In the subgroup of patients with CTs performed every 3rd month during follow-up the overall survival (OS) was 17.8 vs 16.9 mos, respectively (HR:0.76 vs 0.78; CI:0.55-1.07; p = 0.0938). Response according to RECIST: 67% vs 65%; according to GCIG CA125 criteria: 86% vs 85%; AEs were noted in 90% in the Pcal group and 87% in the Poxel group. All grade peripheral neuropathy were 29% vs 32% and myalgia 11% vs 13%, respectively.

Conclusions: Pcal-treatment is as effective and safe as Poxel, without standard use of premedication and a shorter infusion time. Clinical trial information: NCT00989131.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
perfusion (CTP) parameters are prognostic of progression-free survival

taxel (weekly)/carboplatin with and without bevacizumab per physician

comparing standard paclitaxel (q3 week)/carboplatin to dose-dense pacli-

Ting-Yim Lee, Lawson Health Research Institute, London, ON, Canada

CT perfusion as an early biomarker of treatment efficacy in advanced

dichotomized at zero (\(\text{T0}\)) and at 3- (\(\text{T1}\)) and 4-weeks (\(\text{T2}\)) after chemotherapy initiation. Target

ting neoadjuvant therapy were recruited and underwent CTP studies before

5522 Poster Discussion Session; Displayed in Poster Session (Board #90),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM

Background: Carboblatin (C) plus paclitaxel (P) is among standard options for treatment of advanced or recurrent cervical cancer (ACCC) patients (pts). Cervical cancer cells often express Epidermal Growth Factor receptor (EGFR). Carboblatin (C), an anti-EGFR monoclonal antibody, can be safely combined with CP. MITO-CERV 2 is a comparative randomized phase 2 study, testing the addition of CET to CP. Methods: ARCC pts, < 2 previous chemotherapy, ECOG PS \(\leq 1\), were randomized to CP (C AUC5 + P 175 mg/m², q14d) for 6 cycles +/- CET (400 mg/m²/week) one week before starting CP and then 250 mg/m² (weekly) until the event. Primary endpoint was event-free survival (EFS), i.e. time from randomization to progression, death, definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. With a 4.5 mos expected median EFS and 6.4 mos auspected EFS (HR 0.70), 0.20 one-tailed \(\alpha\) and 80% power, 89 events were required for the final intent-to-treat analysis. Results: 108 pts were randomly assigned to CP (n = 53) or to CP-CET (n = 55). Median age was 50, 69% were PS0, 76% had recurrent disease, \(91\%\) had distant metastasis and \(57\%\) had received previous chemotherapy. A median number of 6 CP cycles was given in both arms. After a median follow-up of 23 mos (95% CI:20-25), 23 (23.8%) and 27 (43.8%) patients in arm A and B, respectively, 97 progressed and 61 died. Median EFS was 4.7 and 6.0 mos (one-tail p = 0.43), median PFS was 5.2 and 7.6 mos (one-tail p = 0.20) and median OS was 17.7 and 17 mos (one-tail p = 0.27), with CP and CP-CET, respectively. One patient died for a stroke during standard treatment. There was no difference in the occurrence of grade 3-4 toxicity, except grade 3-4 skin toxicity reported only with CP-CET (8 cases, 6 with acneform rash, p = 0.004). Out of 86 patients eligible for RECIST, objective response rate was 43% and 38% with CP and CP-CET respectively (p = 0.63). Conclusion: The addition of CET to CP is not worthy of further development. Unselected Advanced cervical cancer treated with CP-CET in this retrospective collect tumor samples for an exploratory biomarker analysis. ClinicalTrials.gov NCT00997009. Partially supported by Merck Serono. Clinical trial information: NCT00997009.

5523 Poster Discussion Session; Displayed in Poster Session (Board #91),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM

The role of PET-CT in treatment decision making for women with locally advanced cervical cancer. First Author: Lorraine Margaret Eilt, McMaster University, Hamilton, ON, Canada

Background: Women with locally advanced cervical cancer (LACC) are treated with concurrent chemotherapy and radiation therapy (CRT) with curative intent. Pre-treatment staging is important to define the extent of disease and guide therapy. Staging with \(^{18}\)FDG PET-CT may detect more extensive disease compared to conventional imaging. We report the results of a phase II study leads to morbidity-sparing approaches in cervical cancer treatment incorporating SLN biopsy alone in negative SLN patients. Clinical trial information: NCT01639820.

5552 Poster Discussion Session; Displayed in Poster Session (Board #79),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM

Effect of sentinel lymph-node biopsy alone on the morbidity of the surgical treatment of early cervical cancer: Results from the prospective randomised study Sentinel2. First Author: Patrice Mathevet, CHU Vaudois, Lausanne, Switzerland

Background: Sentinel lymph node (SLN) biopsy is now part of the management of early cervical cancer. Feasibility and low false negative rate in case of bilateral detection have been demonstrated by several studies. However, patients that have not been demonstrated after SLN biopsy only.

Methods: A multicenter prospective randomised study comparing SLN biopsy alone (Arm A) versus SLN biopsy + pelvic lymph-node dissection (Arm B) in early cervical cancer, has been carried out in France. Patient’s eligibility criteria were: 1) FIGO stage IA1/IB1/IA1 cervical cancer, 2) squamous or adenocarcinoma histology. The primary objective was to compare the surgical morbidity of the 2 arms. The planned sample size was 124 patients per arm for a type I error rate of 5% and a one sided test. The protocol has been funded by the French NCI and has been reviewed by an Ethical Committee. Results: 267 patients were included between March 2009 and July 2012, and 61 patients were not randomized due: to unilateral or no SLN detection, positive SLN at frozen sections and other reasons. Of the remaining 206 patients, 100 were in arm A and 101 in arm B. A median of 6 cycles of chemotherapy was performed in intention-to-treat. The median number of SLN was 3 per patient and 1 per side. No false negative case was identified in arm B. The surgical morbidity related to the lymph-node dissection was largely and significantly reduced in arm A: 33 cases (31.4%) vs 52 cases (51.5%) in arm B (Hazard ratio 0.63, one-tailed \(p = 0.0046\)). No difference in the major morbidity related to the lymph-node dissection was also reduced: 1 case in arm A vs 6 cases in arm B (\(p = 0.06\)). The rate of early post-operative neurological symptoms was significantly reduced in arm A (7.8% vs 20.6% in arm B, \(p = 0.01\)). Conclusions: SLN biopsy may improve the management of early cervical cancer, as it is less surgical morbidity and is able to have full pathologic information of the cancer. This study leads to morbidity-sparing approaches in cervical cancer treatment incorporating SLN biopsy alone in negative SLN patients. Clinical trial information: NCT01639820.

5550 Poster Discussion Session; Displayed in Poster Session (Board #78),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM

MITO (Multicentre Italian Trials in Ovarian cancer): CERV 2 trial—A randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer. First Author: Sandro Pignata, MITO and Istituto Nazionale Tumori di Napoli, Napoli, Italy

Background: Carboblatin (C) plus paclitaxel (P) is among standard options for treatment of advanced or recurrent cervical cancer (ACCC) patients (pts). Cervical cancer cells often express Epidermal Growth Factor receptor (EGFR). Carboplatin (C), an anti-EGFR monoclonal antibody, can be safely combined with CP. MITO-CERV 2 is a comparative randomized phase 2 study, testing the addition of CET to CP. Methods: ARCC pts, < 2 previous chemotherapy, ECOG PS \(\leq 1\), were randomized to CP (C AUC5 + P 175 mg/m², q14d) for 6 cycles +/- CET (400 mg/m²/week) one week before starting CP and then 250 mg/m² (weekly) until the event. Primary endpoint was event-free survival (EFS), i.e. time from randomization to progression, death, definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. With a 4.5 mos expected median EFS and 6.4 mos auspected EFS (HR 0.70), 0.20 one-tailed \(\alpha\) and 80% power, 89 events were required for the final intent-to-treat analysis. Results: 108 pts were randomly assigned to CP (n = 53) or to CP-CET (n = 55). Median age was 50, 69% were PS0, 76% had recurrent disease, \(91\%\) had distant metastasis and \(57\%\) had received previous chemotherapy. A median number of 6 CP cycles was given in both arms. After a median follow-up of 23 mos (95% CI:20-25), 23 (23.8%) and 27 (43.8%) patients in arm A and B, respectively, 97 progressed and 61 died. Median EFS was 4.7 and 6.0 mos (one-tail p = 0.43), median PFS was 5.2 and 7.6 mos (one-tail p = 0.20) and median OS was 17.7 and 17 mos (one-tail p = 0.27), with CP and CP-CET, respectively. One patient died for a stroke during standard treatment. There was no difference in the occurrence of grade 3-4 toxicity, except grade 3-4 skin toxicity reported only with CP-CET (8 cases, 6 with acneform rash, p = 0.004). Out of 86 patients eligible for RECIST, objective response rate was 43% and 38% with CP and CP-CET respectively (p = 0.63). Conclusion: The addition of CET to CP is not worthy of further development. Unselected Advanced cervical cancer treated with CP-CET in this retrospective collect tumor samples for an exploratory biomarker analysis. ClinicalTrials.gov NCT00997009. Partially supported by Merck Serono. Clinical trial information: NCT00997009.
Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in high risk endometrial cancer. First Author: Mostafa Atfi, University Health Network, ON, Canada

Background: To assess if PET-CT improves accuracy of CT to detect lymph node (LN) metastasis in high risk endometrial cancer. Methods: This was a prospective HIPAA compliant ACRIN/GOG multicenter trial. Patients underwent enhanced contrast CT alone in abdomen and pelvic lymph nodes. PET-CT was performed with at least one month interval of CT. Both PET-CT and CT only images in different sessions at least one month apart. Region correlation was performed by reviewing pathologic and clinical data. Results: A total of 207 patients had PET-CT and pathology proof of positive LNs. Reader agreement and correlated analysis of PET-CT vs CT were compared with generalized linear mixed models. Reader average AUCs were compared with Obuchowski’s method. Fleiss’ kappa was used to assess reader agreement. Results: A total of 207 patients had PET-CT and pathology proof of positive LNs. To assess if PET-CT improves accuracy of CT to detect lymph node (LN) metastasis in high risk endometrial cancer.

Efficacy and safety comparison between belotecan and topotecan in patients with recurrent or refractory ovarian cancer. First Author: Roshni Deepa Kalachand, Department of Medical Oncology, Beaumont Hospital, Dublin, Ireland

Background: BRCA1/2 mutations render ovarian cancers (OC) homologous recombination deficient (HRD) and thus sensitive to platinum and PARP inhibitors. Data on BRCA1 promoter methylation in OC, another potential biomarker of HRD, are conflicting and limited. Methods: We searched PubMed and ASCO/ESMO abstracts for studies with survival outcomes in BRCA1/2 mutated OC. Individual patient data were retrieved from 5 studies. Corresponding mean specificities were 0.88 (CI:0.83,0.92) and 0.89 (CI:0.86,0.96) (p = 0.11) and 0.93 (CI:0.82,0.94) (p = 0.27). Mean AUCs were 0.78 (CI:0.66,0.89) and 0.74 (CI:0.63,0.86) (p = 0.39) and 0.82 (CI:0.71,0.92) (p = 0.02) for agreement between PET-CT and pathology. Conclusions: Addition of PET to diagnostic CT significantly increased diagnostic accuracy to detect LN metastasis in abdomen and pelvis. Clinical trial information: ACRIN6671GOG0233.

Efficacy and safety comparison between belotecan and topotecan in patients with recurrent or refractory ovarian cancer. First Author: Hee Seung Kim, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea

Background: Belotecan is a camptothecin derivative with anti-tumor properties. Previous studies suggested the feasibility of belotecan-based chemotherapy for patients with primary or recurrent ovarian cancer. Thus, we conducted a phase IIb trial to compare the efficacy and safety between belotecan and another derivative of camptothecin, topotecan, in patients with recurrent or refractory ovarian cancer. Methods: Patients with recurrent or refractory ovarian cancer were randomized to receive belotecan 0.5 mg/m² (B-arm) or topotecan 1.5 mg/m²(T-arm) intravenously for 5 consecutive days every 3 weeks till 6 cycles or disease progression. The primary endpoint was overall response rate based on RECIST or GCIG criteria, and secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse events according to NCI-CTCAE version 4.0. Results: One hundred and forty one patients were randomized from January 2011 to June 2014. Among all patients, 140 were eligible in full analysis (FA) set where patients received at least one dose (B-arm, n = 71; T-arm, n = 69), and 130 were eligible in per protocol (PP) set where patients completed the study protocol (B-arm, n = 66; T-arm, n = 64). Clinicopathologic characteristics were not different between the two arms. ORR was not different between B- and T-arms in FA and PP sets (29.6% vs. 26.1%, p = 0.60; 95% CI: 0.35-1.01) without significant difference. OS was improved in B- versus T-arm in FA set with marginal significance (median values, 37.1 vs. 21.3 months, log-rank p = 0.053; HR = 0.60; 95% CI:0.39-1.01), and PP set (median values, 37.1 vs. 24.9 months, log-rank p = 0.023; HR = 0.53; 95% CI:0.31-0.93). Grade 3 or 4 adverse events were not different between the two arms. Conclusions: Belotecan may have a similar response and toxicity rates to topotecan in patients with recurrent or refractory ovarian cancer. Moreover, belotecan may prolong OS when compared with topotecan in these patients. Clinical trial information: NCT01630018.
Multicentre trial of carboplatin/paclitaxel versus oxaliplatin/capcitabine, each with/without bevacizumab, as first line chemotherapy for patients with recurrent epithelial ovarian cancer (GECO 1205/NOVA TRIAL). First Author: Yolanda García, Corporate Sanitaria Universitaria Parc Taulí, Universitat Autonoma de Barcelona, Barcelona, Spain

Background: Bevacizumab (Bev) in the neoadjuvant setting has shown to improve surgical feasibility and outcomes in patients (pts) with advanced ovarian cancer. The primary endpoint of severe toxicity (Grade 3 or 4) was a high feasibility rate in the Bev arm (64 vs 88%). Optimal surgery rate also favored the Bev arm (77.7 vs 86.4%) and there wasn’t any patient deemed unresectable at the time of surgery in the Bev arm (2 vs 0). None of these figures were statistically significant. There were lower rates of serious adverse events (grade 3-4) in bev arm (40.6 vs 18.8%, p = 0.05). Three bev related adverse events of special interest were observed in 3 pts (1 G3 entero-vaginal fistulae, 1 surgical dehiscence, 1 deep venous thrombosis). Conclusions: Our preliminary data have shown that NA bev seems feasible and could improve the surgical outcomes in advanced EOC considered initially unresectable. Updated clinical and translational data will be provided. Clinical trial information: NCT01847677.

Poster Session Board #86, Sat, 1:15 PM-4:45 PM
Efficacy and safety of olaparib monotherapy in a subgroup of patients with a germline BRCA1/2 mutation and advanced ovarian cancer from a Phase II open-label study. First Author: Susan M. Domchek, Research Center for BRCA at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Background: Olaparib (Lynparza), an oral PARP inhibitor, has demonstrated antitumor activity in patients (pts) with BRCA-mutated (m) ovarian cancer. Data from the overall cohort of pts in this Phase II study (NCT0178662) have been reported (Kaufman et al, JCO 2014). Presented here are data from a subgroup of pts with germline (g) BRCAm ovarian cancer, stratified by prior lines of chemotherapy (> 3 or 3) and platinum sensitivity. Conclusions: Pts were treated with olaparib 400 mg twice daily (bid); capsule formulation) monotherapy until disease progression according to RECIST v1.1. Objective response rate (ORR) and duration of response (DoR) were assessed for pts with measurable disease at baseline (n = 167). Safety and tolerability were assessed for all pts (n = 193). Results: Of the pts with measurable disease at baseline, 30 and 137 had received 2 (n = 32) or 3 prior lines of chemotherapy (3 prior lines). Adverse events (AEs) most commonly causally related to olaparib were nausea (107/193 pts, 55%), fatigue, 99 pts (51%), and anemia (60 pts, 31%; grade 3 in 163/193 [19%]). Twenty pts (10%) had a serious AE causally related to olaparib. Two pts developed leukaemia and one pt myelodysplastic syndrome; all three had been heavily pretreated. Conclusions: Olaparib 400 mg bid (capsule form) monotherapy demonstrated notable antitumor activity in gBRCAm pts with advanced ovarian cancer, including heavily pretreated, platinum-resistant pts. No new safety signals were identified. Clinical trial information: NCT0178662.

Poster Session Board #88, Sat, 1:15 PM-4:45 PM
A GINECO phase I study evaluating lenalidomide (Le) combined with pegylated liposomal doxorubicin (PLD) and carboplatin (C) in late (>6 months) recurrent ovarian cancer (LROC) patients (pts). First Author: Frédéric Selle, Medical Oncology, Hôpital Tenon, Paris, France

Background: Le is a thalidomide analogue with both immunomodulatory and angiogenic properties. Le has shown efficacy and good tolerability as single agent for LROC pts (Selle F, et al. Ann Oncology 2014). Methods: LROC pts were enrolled in cohorts of 3 to 6 pts and treated with PLD 30 mg/m2 and C AUC 5 day (d1 q4 weeks in combination with daily oral escalation dose of Le (15, 20 and 25 mg) according to different schedules (A: 21 consecutive days from d1; B: 21d from d2; C: 21d from d7; D: 14d from d2). Dose limiting toxicities (DLT) were defined as: treatment delay (> 14d), grade (Gr) 3 febrile neutropenia, Gr 4 neutropenia (2pts) or neurotoxicity (1pt), Gr3 thrombosis (1pt) and Gr3 increase in median PFS for oxaliplatin/capecitabine (B D), or adding bevacizumab (C D). Results: Trial stopped early (2013) due to poor accrual (median follow up 23 months; 31 deaths, 50 pts recruited; n = 13, 13, 11, 13 in arms A-D. Median age 54 yrs; FIGO stage II (n = 15), III (n = 29), IV (n = 4), recurrent (n = 6); ECOG 0 (n = 34), 1 (n = 15), 2 (n = 1). 62, 85, 62, 69% in arms A-D completed 6 cycles of combination therapy, and 36, 46% completed 12 maintenance cycles of bevacizumab (arms C, D). 2.2,4.2 pts (arms A-D) had complete/partial response. Median PFS 10.1 (B > D) vs 8.8 (A + B) months, HR 0.88 95% CI 0.43-1.79, p = 0.72. Grade 3-4 toxicities (most common: neutropenia, & hypertension for bevacizumab) were seen in 62, 62, 55, 92% pts in arms A-D (total 4 pts with grade 4). After specialist pathology review n = 36 so far, 19 were considered to have primary mEOC (many metastatic disease). Setting up & conducting this international trial was challenging in this rare group; correctly assigning histological diagnosis was difficult. Bevacizumab may delay progression (ITT analyses), but without sufficient pts no conclusions can be made. Primary mEOC is rarer than previously thought so different approaches are needed to evaluate new therapies. Clinical trial information: NCT01081262.

Poster Session Board #88, Sat, 1:15 PM-4:45 PM
5530 A GINECO phase I study evaluating lenalidomide (Le) combined with pegylated liposomal doxorubicin (PLD) and carboplatin (C) in late (>6 months) recurrent ovarian cancer (LROC) patients (pts). First Author: Frédéric Selle, Medical Oncology, Hôpital Tenon, Paris, France

Background: Le is a thalidomide analogue with both immunomodulatory and anti-angiogenic properties. Le has shown efficacy and good tolerability as single agent for LROC pts (Selle F, et al. Ann Oncology 2014). Methods: LROC pts were enrolled in cohorts of 3 to 6 pts and treated with PLD 30 mg/m2 and C AUC 5 day (d1 q4 weeks in combination with daily oral escalation dose of Le (15, 20 and 25 mg) according to different schedules (A: 21 consecutive days from d1; B: 21d from d2; C: 21d from d7; D: 14d from d2). Dose limiting toxicities (DLT) were defined as: treatment delay (> 14d), grade (Gr) 3 febrile neutropenia, Gr 4 neutropenia or Gr 4 thrombocytopenia lasting more than 7 d, bleeding with platelet transfusion and all other Gr ≥ 3 toxicity (except vomiting) occurring at cycle 1. Completion of the 6 planned cycles without inacceptable toxicity defined feasibility of the regimen. Secondary objectives were response, progression-free (PFS) and overall survival (OS) rates. Results: 22 pts were enrolled up to Q2/2014 with a median age of 61.4 years (47-73). Pts characteristics were: serous (82%), previous lines (one 68%, two 32%), median platinum-free interval (PFI) 11.4 months and ECOG 0 (73%). Safety: all the 4 schedules were evaluated at a 15mg/d Le dose. With schedule A&B, 2DLT/3pts and 3DLT/4pts were observed. DLT was cycle delay > 14d for neutropenia (2pts) or neurotoxicity (1pt), Gr3 thrombosis (1pt) and Gr3 vision loss (1pt). With schedule C&D, 1DLT/3pts (Gr3 rash) occurred at cycle 1, only 1 pt completed the 6 planned cycles without dose reduction and 6 pts stopped early for toxicity (hematotoxicity for 5pts). Efficacy: complete and partial responses were observed in respectively 10% and 29% of pts. Median PFS and OS were 9.2 months (95% CI, 7.4-11.1) 28 months (95% CI, 18.9-37.1) respectively. Conclusions: Lenalidomide combined with PLD-C was not feasible at the dose and schedules evaluated, mainly due to cumulative hematologic toxicity. Clinical trial information: NCT01111903.

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Use of homologous recombination deficiency (HRD) score to enrich for niraparib sensitive high grade ovarian tumors. First Author: Keith Matthew Winokur, TESARO, Inc., Waltham, MA

Background: The therapeutic potential of PARP inhibitors is predicted to extend beyond patients with germline BRCA mutations (BRCAmut) to those with homologous recombination deficient (HRD) cancers. An HRD test is being applied to patient samples to identify BRCA mutated tumors, provide a categorical determination of tumor HRD, and determine an enrichment strategy for patients with tumors that are sensitive to niraparib treatment.

Methods: Archival FFPE tumor tissue obtained from ovarian cancer patients enrolled in an ongoing Phase III clinical study (ENGOT-OV16/NOVA, NCT 018472774) and a living tumor bank was subjected to HRD testing. The final HRD score is a numeric output ranging from 0-100. A predefined cut-off score of 42 was utilized to determine HRD status of each tumor and classify it as HR deficient (HRD score < 42) or non-deficient (HRD score ≥ 42).

Classification of BRCA mutations from tissue was based on analysis criteria consistent with the laboratory’s approved diagnostic BRCA testing. Niraparib efficacy was evaluated utilizing a living tumor bank of orthotopic patient-derived ovarian xenografts. Intraproductive tumor grafts were monitored for tumor growth with twice-weekly transabdominal ultrasound imaging.

Results: One hundred and six high grade serous ovarian tumors from a living tumor bank were evaluated for HRD, BRCA1/2 mutations, and BRCA1 promoter hypermethylation. Twenty six tumors (25%) were BRCA deficient (a deleterious BRCA1/2 mutation or BRCA1 hypermethylation with a concomitant loss of heterozygosity). All BRCA1/2 deficient tumors had an HRD score of 42 or greater, with the exception of one tumor. The in-vivo response to niraparib monotherapy has been evaluated in 20 unique tumors models across a range of HRD scores. All responding tumors had an HRD score of 42 or above, irrespective of BRCA deficiency. All tumors were classified as HRD deficient (HRD score ≥ 42) or non-deficient (HRD score < 42).

Classifications of BRCA mutations from tissue were based on analysis criteria consistent with the laboratory's approved diagnostic BRCA testing. Niraparib efficacy was evaluated utilizing a living tumor bank of orthotopic patient-derived ovarian xenografts. Intraproductive tumor grafts were monitored for tumor growth with twice-weekly transabdominal ultrasound imaging.

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All 3 mutant pairs had high HRD scores (range 46-76, 12%) comprised only HRD+ tumors. Our data are supportive of the use of HRD testing to enrich for niraparib responders in high grade ovarian cancer.

Conclusions: HRD status appears to be predictive of response to niraparib in our xenograft models.
Background: Ovarian cancer (OC) is a high medical need disease. Most patients (pts) relapse following initial therapy with limited therapeutic options. IMAB027 is the first-in-class monoclonal antibody (mAb) directed against claudin 6 (CLDN6), a cancer specific, embryonic tight junction protein and cancer stem cell marker. CLDN6 is expressed in >55% of OCs and frequently in other cancer types. In preclinical models, IMAB027 executes potent (in)anti-tumor activity via AB-dependent cellular cytotoxicity and complement-dependent cytotoxicity without mediating off-target toxicity.

Methods: This first-in-human, open-label, dose escalation Phase I/II trial assesses the safety/tolerability (NCI-CTCAEv4.0), pharmacokinetics (PK) and clinical efficacy (RECIST 1.1) of IMAB027 in pts with advanced, recurrent CLDN6+ OC. Here we report preliminary data on 12 pts enrolled in the Phase I part of the study as of August 15, 2014. Pts received 100, 300, 600, or 1000 mg/m² IMAB027 (n = 3/group) q3w IV until disease progression. Results: Pts had a median age of 64 (54–75) years, platinum-resistant disease and had received a median of 4 (3–9) lines of previous chemotherapies. All administered doses were safe and well tolerated, no DLT was observed and the MTD was not reached. 108 AEs have been recorded, all but 5 (4 grade 3 [g3], 1 g4) were gr 1–2 (82 and 21 AEs, respectively). 29 AEs were considered IMAB027 related (22 g1, 6 g2, 1 g3 as deemed by investigator). Five AEs (all in 1 pt) were classified as SAEs. No objective responses were seen, with grade 1–2 (g1–2) effects. 84% of IMAB027-treated SAEs were manageable and fully reversible. IMAB027 PK was well described with a 2-compartment model (mean AUC: 20,770–86,160 µg/mLXh; mean Cmax: 151–611 µg/mL for 300–1000 mg/m²). First signs of IMAB027 clinical activity were observed. Conclusions: This is the first clinical study to show the potential of a therapy targeting CLDN6. Based on these preliminary Phase I data, IMAB027 may present a safe and well tolerated treatment option for women with recurrent, advanced OC. This warrants further clinical evaluation of IMAB027 in this patient population with a high medical unmet need. Clinical trial information: NCT02054351.

5536
Poster Session (Board #94), Sat, 1:15 PM-4:45 PM
First Author: Ugur Sahin, TRON GGmbHl, Mainz, Germany
Background: The primary endpoint for clinical trials in PRR/PPS ≥ 3 ROC is progression free survival (PFS) and symptom benefit is not typically measured or reported. The primary aim of GCIG SBS is to validate a patient-reported outcome measure (PROM), the MOS-SF (Symptoms and Treatment concerns), to assess symptom benefit from palliative chemotherapy (PC). The SBS recruited 949 patients; the secondary aims provide insights into symptom burden, patients’ and clinician’s expectations of treatment and outcomes in a “real world” setting. Methods: Patients with PPR/PPS ≥ 3 ROC completed 4 PROMs before each cycle of chemotherapy. They reported expectation of symptom improvement. Clinicians documented the indications for PC, symptoms at baseline, adverse events and estimated the number of cycles patients would receive. Results: Palliation was the major indicator for chemotherapy. The mean number of prior regimens was 2.6 (range 1-10). 60% of patients had PPR and 40% had PPS > 3 ROC. At baseline, most patients were symptomatic; 75% rated at least one symptom as moderate (5 on a 0-10 scale) and 30% rated > 5 symptoms as moderate or worse. The symptoms included pain, fatigue, anorexia, abdominal distension, dyspnea, and constipation. Many had symptoms related to prior chemotherapy (e.g. neuropathy in 28%). Most patients had high expectations of symptom benefit from chemotherapy. 36% of patients received the predicted number of cycles. 25% of patients with PPR-ROC stopped treatment in < 8 weeks mainly due to progression/death. The median number of cycles and median PFS were 4 and 5.6m in PPS > 3 ROC, and the median 3.7m in PPR-ROC respectively. Patients with PPR/PPS ≥ 3 ROC reported a number of significant baseline symptoms. They had high expectations of symptom improvement and this should be measured. The results underscore the importance of incorporating PROMs and including symptom benefit as primary endpoints in trials in patients with PPR/PPS ≥ 3 ROC. Clinical trial information: ACTRN1260700603415.

5539
Poster Session (Board #97), Sat, 1:15 PM-4:45 PM
Tumor biopsies in high grade ovarian cancer: Clinical utility and challenges for biomarker-directed therapy
First Author: Michelle K. Wilson, Princess Margaret Cancer Centre, Toronto, ON, Canada
Background: Molecular profiling of tissue obtained with a biopsy aids detection of predictive and pharmacodynamic biomarkers to guide patient (pt) selection and treatment. This study assesses the safety and success rate of obtaining FFPE tissue and imaging profiling in a large multi-center II RCT. Tumor biopsies were done during initial surgery (open/laparoscopic) and archival tissue. Results: Tissue and DNA samples were collected from 12 pts enrolled in the Phase I part of the study as of August 15, 2014. Pts received 100, 300, 600, or 1000 mg/m² IMAB027 (n = 3/group) q3w IV until disease progression. Pts had a median age of 64 (54–75) years, platinum-resistant disease and had received a median of 4 (3–9) lines of previous chemotherapies. All administered doses were safe and well tolerated, no DLT was observed and the MTD was not reached. 108 AEs have been recorded, all but 5 (4 grade 3 [g3], 1 g4) were gr 1–2 (82 and 21 AEs, respectively). 29 AEs were considered IMAB027 related (22 g1, 6 g2, 1 g3 as deemed by investigator). Five AEs (all in 1 pt) were classified as SAEs. No objective responses were seen, with grade 1–2 (g1–2) effects. 84% of IMAB027-treated SAEs were manageable and fully reversible. IMAB027 PK was well described with a 2-compartment model (mean AUC: 20,770–86,160 µg/mLXh; mean Cmax: 151–611 µg/mL for 300–1000 mg/m²). First signs of IMAB027 clinical activity were observed. Conclusions: This is the first clinical study to show the potential of a therapy targeting CLDN6. Based on these preliminary Phase I data, IMAB027 may present a safe and well tolerated treatment option for women with recurrent, advanced OC. This warrants further clinical evaluation of IMAB027 in this patient population with a high medical unmet need. Clinical trial information: NCT02054351.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Molecular profiling of mucinous epithelial ovarian carcinomas (mEOC): Opportunities for clinical trials.

**Background:** mEOCs are an uncommon subset of epithelial ovarian cancers. Most patients have early stage disease at presentation and a good prognosis. However, patients with advanced stage disease at diagnosis are rare and can be difficult to distinguish from gastrointestinal metastases to the ovary. They have a poor prognosis and a low response to standard platinum /taxane chemotherapy. Rather than assigning chemotherapy according to this tier of origin, selecting treatment based on the molecular characteristics of mEOC should be explored. Molecular profiling of mEOCs may help identify patients for clinical trials with targeted/novel therapies.

**Methods:** 304 mEOCs referred to Caris Life Sciences (from 2009 – 2014) were evaluated. The diagnosis was based on reported pathology. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis.

**Results:** Alternations in the MAP Kinase pathway were common in mEOCs with the most frequent mutations observed in KRAS (49%). The mutation rate in BRAF was 3.5%. Alterations in the mTOR pathway occurred at a less frequent rate (PIK3CA 12% and PTEN 6%). PD-1 positivity was observed in 43% of tumors infiltrating lymphocytes and PD-L1 was positive in 14% of mEOCs. cMET overexpression was seen in 33% of cases, but no cMET amplification was seen. HER2 amplification was seen in 11%. EGFR amplification occurred in 50% of cases and 57% had overexpression of EGFR by IHC. 35% of mEOCs tested (37 of 105 cases) had P53 mutations. P53 occurred in 50% of cases and 57% had overexpression of EGFR by IHC. 35% of mEOCs tested (37 of 105 cases) had P53 mutations. P53 mutated (n = 37) and wildtype (n = 68) mEOCs differed significantly in ER, PR and HER2 expression and BRAF, PIK3CA and PTEN mutation prevalence.

**Conclusions:** Molecular profiling highlights the genomic heterogeneity and distinct molecular subsets in mEOCs and demonstrates the similarities with mucinous gastrointestinal cancers. There are a number of potential treatment targets and therapeutic options that could be investigated in phase 2 basket trials. Given the rarity of advanced stage mEOCs this will require international collaboration.

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A phase I/I trial of multiple dose VB-111 and weekly paclitaxel in recurrent platinum-resistant Müllerian cancer.

**First Author:** Richard T. Penson, Massachusetts General Hospital and Harvard Medical School, Braintree, MA

**Background:** VB-111 is a gene therapy agent consisting of a non-replicating viral particles (VPs) (DL3), followed by repeat doses every 2 months. Ip injection of EGEN-001 is associated with increases in systemic circulation. The study's purpose was to assess safety and efficacy of escalating doses of EGEN-001 with pegylated liposomal doxorubicin (PLD) in recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer (EOC) patients.

**Methods:** Patient eligibility criteria: Females aged ≥ 18 years with persistent or recurrent EOC. Patients were not required to have measurable disease and could have a biochemical recurrence; must have had one prior platinum-based chemotherapy regimen and up to two additional cytotoxic regimens; have adequate organ function; be willing to participate in the study; and have signed an informed consent. Conclusions: EGEN-001 in combination with PLD has clinical benefit in recurrent or persistent EOC and warrants further investigation with escalating doses of EGEN-001.

**Trial information:** NCT#01489371.

**Dose Level** EGEN-001 (mg/m^2/ip) **PLD (mg/m^2 iv)**

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Urinary acetylated polyamines in ovarian cancer.

**First Author:** Johanna Uine, Maenpaa, School of Medicine, University of Tampere, Tampere, Finland

**Background:** Diacetylated polyamines have been detected in the urine of patients with malignant tumors since 1960s but methodological problems have hindered research. We have recently developed a liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the simultaneous analysis of 14 polyamines in free, mono- and diacetylated forms in human urine, without any derivatization. The present study was undertaken to explore urinary polyamine profiles in the differential diagnosis of ovarian tumors in postmenopausal women.

**Methods:** Forty-five postmenopausal women presenting with an abnormal adnexal mass, and as controls, 21 women with genital prolapse scheduled for surgery, were included prospectively. A morning urine sample was obtained before surgery. The urinary concentrations of 14 polyamines were analyzed simultaneously with LC-MS/MS. Preoperative serum CA12-5 concentrations were also determined, and the risk of malignancy indexes (RMI) calculated in the research arm. The statistical analysis was performed by Wilcoxon rank sum test.

**Results:** There were 22 benign and 23 malignant ovarian tumors (16 low malignant potential and 7 high grade tumors). Of the urinary polyamines, N1,N12-diacetylspermine (DiAcSpm) was the best one to make the distinction between the benign and malignant tumors. The urinary levels of DiAcSpm were similar in controls and in women with benign tumors. However, DiAcSpm was elevated in malignant vs. benign tumors (p < 0.0001). DiAcSpm were significantly higher in malignant tumors (p < 0.0001) compared to controls. DiAcSpm III-IV vs. Stage I-II cancers (p = 0.0007), respectively. Also the difference between benign tumors and early-stage cancer (Stage I-II) was statistically significant (p = 0.0006). DiAcSpm had similar specificity (Sp) (65%) and better sensitivity (Se) (91%) (AUC 0.82) as CA12-5 (Sp 65%/Se 68%, with a CA12-5 cut-off value 35, respectively) (AUC 0.72) and as RMI (Se 70%/Sp 68% with a RMI cut-off value 200, respectively) (AUC 0.72). Conclusions: DiAcSpm was elevated in the urine of patients with ovarian cancer as compared to women with benign tumors and with women with genital prolapse. It seems to be able to detect even early-stage cancer, and its performance seems to be at least comparable to CA12-5 and RMI.
A phase I trial and pharmacokinetic study of non-pegylated liposome-encapsulated doxorubicin citrate (NPLD) plus carboplatin in patients with recurrent gynecologic and primary peritoneal cancers. **First Author:** Andres Poveda, Instituto Valenciano de Oncologia, Valencia, Spain

**Background:** Pegylated liposomal doxorubicin (PLD) plus carboplatin is one of the standard treatments for platinum-sensitive recurrent ovarian patients (pts). PLD shortage during 2012 and 2013 was determining in the need to search for an alternative doxorubicin combination with carboplatin. Non-pegylated Liposome-Encapsulated Doxorubicin Citrate (NPLD, Myocet) has been developed in the past decades with proved activity and limited skin-cardiac toxicity. **Methods:** This open multicentric dose-escalation phase I trial aimed to determine the maximum-tolerated dose (MTD) and the pharmacokinetic (PK) profile of Carboplatin+NPLD using a traditional 3+3 design. Main eligibility criteria: measurable or evaluable recurrent gynecologic and/or primary peritoneal tumor, performance status 0-2, no prior normal organ function, no limited number of prior regimens, left ventricular ejection fraction (LVEF) > 50%. Prior anthracycline therapy permitted only for previous responders. Dose Limiting Toxicity (DLT) was defined as G4 hematologic and/or G3 febrile neutropenia and/or G3 non-hematologic toxicity (NCI-CTCAE v4.03). AUC 5 is 60mg/m². The regimen is well tolerated, antitumor activity was observed and 17SD at 8 weeks were observed. PK data will be presented at the meeting.

**Results:** 22/23 evaluable pts were treated with NPLD (40, 50, 60, 70 mg/m²) and carboplatin (AUC 5) every 21 days. ECOG 0/1, 4/8, 2/1. Median age: 57y (40-79), 9 pts had epithelial ovarian, 9 cervical, 5 endometrial CA. Number of prior regimens: 3 (1-7). Previous anthracyclines: 7/22, MTD was LEDD 60mg/m² + Carboplatin AUC 5. DLT were: NPLD 40mg/m²; G3 febrile neutropenia, (1/6); 50mg/m²; G4 thrombocytopenia (1/6); 60 mg/m²; G4 thrombocytopenia (1/6); 70mg/m²; G4 thrombocytopenia (1/4), G3 febrile neutropenia, (1/4). Other non-hematologic G2 toxicities were (%): asthenia (2/6), nausea (0/6), vomiting (1/6), diarrhea (0/6), rash (0/6), alopecia (1/6), and mucositis (1/6). 17SD were reported and 17SD at 8 weeks were observed. PK data will be presented at the meeting. **Conclusions:** The MTD for NPLD when combined with carboplatin AUC 5 is 60mg/m². The regimen is well tolerated, antitumor activity was observed. A phase-II study is ongoing. Clinical trial information: EuDraCT: 2012-003175-25.

**Development and validation of a prognostic nomogram to predict overall survival (OS) in platinum-resistant ovarian cancer (PROC): An AURELIA substudy.** **First Author:** Chee Lee, ANZGOG, NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia

**Background:** PROC describes a heterogeneous group of patients (pts) with a variable but generally poor prognosis and low response to chemotherapy. Predicting OS in PROC would help stratify pts in trials and guide treatment decisions. We developed a nomogram to predict OS in PROC. **Methods:** Data from two randomized phase III trials evaluating chemotherapy for PROC – CARTAKHY (Lortholary Ann Oncol 2012) and AURELIA (Pujade-Lauraine JCO 2014) (chemotherapy-alone arm) – were combined to form the training cohort (N = 331) for nomogram development. Baseline variables significantly associated with OS were identified using Cox regression analysis. Pts were assigned scores based on the weighted sum of the relative importance of each variable in the multivariate model. The nomogram was then validated in the chemotherapy plus bevacizumab arm of the AURELIA trial (N = 166). Nomogram performance was assessed by calculating the c statistic. A classification based on the nomogram’s score was generated to group pts according to prognosis. **Results:** Poor performance status, CA125 > 100 U/mL, ascites, platinum-free interval < 3 months, primary platinum resistance, and largest tumor > 5cm were associated with shorter OS. The nomogram predicted OS with a c statistic of 0.69 (training) and 0.67 (validation). In the training cohort, the median OS in good (N = 93), intermediate (N = 162), and poor (N = 76) prognostic groups was 25.3, 15.6, and 6.9 months, respectively (P < 0.0001). In the validation cohort, median OS in good (N = 50), intermediate (N = 79), and poor (N = 37) prognostic groups was 26.7, 13.8, and 9.0 months, respectively (P < 0.0001). **Conclusions:** This nomogram combining six baseline factors accurately predicts OS in PROC pts treated with chemotherapy either alone or in combination with bevacizumab. It could help to select pts for treatment, counsel pts regarding prognosis, and stratify according to risk in trials. Clinical trial information: NCT00976911.
5548 Posterior Session (Board #106), Sat, 1:15 PM-4:45 PM
Exploratory outcome analyses according to stage and residual disease in the ICON7 trial of front-line carboplatin/paclitaxel (CP) + bevacizumab (BEV) for ovarian cancer (OC). First Author: Antonio Gonzalez-Martín, GEICO and MD Anderson Cancer Center Spain, Madrid, Spain

Background: In ICON7, progression-free survival (PFS) was significantly improved in patients (pts) receiving BEV with front-line CP and continued as a single agent [Perren 2011] but no overall survival (OS) difference was detected in the intent-to-treat (ITT) population. Front-line BEV-containing therapy is approved in Europe for pts with stage IIIb-IV OC. Methods: In ICON7, pts with advanced (stage IIIb–IV) or high-risk early-stage (stage I-IIA and clear cell grade 3) OC were randomized to receive 6 cycles of CP either alone or with BEV 7.5 mg/kg q3w followed by single-agent BEV for a further 12 cycles (total duration 12 months). The primary endpoint was PFS; OS was a secondary endpoint. A post hoc exploratory analysis of subgroups defined by stage and extent of residual disease at diagnosis within the label population was performed. Results: The PFS benefit from BEV observed in the ITT population was seen consistently in all subgroups explored. As in the ITT population, no OS difference was seen in any subgroup except the previously defined ‘high-risk’ subgroup. Safety results in subgroups were in line with the overall population. Conclusions: Adding BEV to CP improves PFS irrespective of stage/residual disease. In pts with stage III >1 cm/IV OC this translates into an OS benefit. No OS difference (benefit or detriment) was seen in other subgroups explored. Clinical trial information: NCT00483782.

5549 Poster Session (Board #107), Sat, 1:15 PM-4:45 PM
Single agent vanucizumab (RO5209855) for platinum (Pt)-resistant recurrent ovarian cancer (OC): Results from a single arm extension phase of the phase 1 FIH study. First Author: Ana Dakin, Vall d’Hebron University Hospital, Barcelona, Spain

Background: Vanucizumab is a bi-specific human lgG1 antibody, simultaneously blocking the complementary roles of Ang-2 and VEGF-A induced tumor angiogenesis. Both, VEGF-A and Ang-2 inhibitors are known to be clinically active in ovarian cancer. Hence, co-targeting of both ligands in a bi-specific manner represents an encouraging approach to improve treatment outcomes. Methods: Eligible pts (pts) had platinum (Pt)-resistant/refractory epithelial OC (measurable by RECIST 1.1). Pts with history of bowel obstruction, >2 prior lines of systemic chemotherapy, or previous treatments with agents targeting Ang/Tie2 receptor axis were ineligible. Pts were treated with vanucizumab (RF2D) at 30 mg/kg q4W until disease progression or unacceptable toxicity. Primarily, primary objective was to determine the optimal recommended phase II dose (ORR) per RECIST 1.1, with tumor re-evaluations every 8 weeks (wks). Results: 41 pts (40 Pts- resistant/ 1 Pt- refractory) with median age of 60 years (range 30-77) were enrolled. 13 (32%) pts were pre-treated with bevacizumab (BEV). All pts had at least 1 tumor re-assessment. At this point in time, twelve (29%) pts achieved partial response (6 confirmed PR/6 unconfirmed PR) including two pre-treated with BEV. Interestingly, a delayed response was observed in 7/12 PRs, following 16 wks (6 pts) or 32 wks (1 pt) of treatment. 22 (54%) pts experienced disease stabilization and 7 (17%) pts progressed. The most frequent adverse events (AE) of any grade (G) were hypertension (53%), asthenia (39%), constipation (36%), abdominal pain (32%), peripheral (24%)/lymphedema (19%), vomiting (24%) and diarrhea (19%). Most common AE ≥ G3 were hypertension (10/24%), pyelonephritis (3/7%), GI-perforation, peritonitis, intestinal obstruction, pulmonary embolism and dyspnea (2/5%). One AE of peritonitis had a fatal outcome 3 months after onset of treatment. In this study, vanucizumab Q2W had an acceptable safety profile while demonstrating encouraging anti-tumor activity in pts with Pt-resistant, recurrent OC that seems to exceed reported results for single VEGF-A inhibition in this setting. Clinical trial information: NCT01688206.

5550 Poster Session (Board #108), Sat, 1:15 PM-4:45 PM
Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSOC). First Author: Ursula Matulonis, Dana-Farber Cancer Inst, Boston, MA

Background: Maintenance mono-therapy with the PARP inhibitor olaparib prolongs progression-free survival in PSOC pts with no adverse impact on HRQoL. BRCAm pts derive greater benefit. Nausea, vomiting, fatigue and anemia are consistently the most common AEs in olaparib trials. Methods: In this randomized, double-blind Phase II trial (NCT00753545), pts received olaparib 400 mg twice daily (capsules; n = 240) or placebo (n = 128). AEs were graded by CTCAE v3.0; the timing and severity of AEs were analyzed.

Results: In this study, AEs were uncommon and manageable (0.03, 0.1% of patients). 3-month

5551 Poster Session (Board #109), Sat, 1:15 PM-4:45 PM
Bevacizumab (BEV) with or after chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (PROC): Exploratory analyses of the AURELIA trial. First Author: Aristotelis Biamis, HECOG, University of Athens, Medical School, Athens, Greece

Background: In the open-label randomized phase III AURELIA trial, adding BEV to CT for PROC significantly improved progression-free survival (hazard ratio [HR] 0.48; p < 0.001) and response rate (27% vs 12%) vs CT alone, but not overall survival (OS). Methods: Eligible pts (pts) had measurable/assessable OC that had progressed < 6 mo after platinum CT. After CT selection, pts were randomized to CT + BEV vs progression (PD), unacceptable toxicity or consent withdrawal. Crossover to BEV at PD was optional in the CT arm but prohibited in the BEV-CT arm. Exploratory post hoc analyses assessed factors potentially affecting the decision to crossover to BEV, and efficacy and safety according to post-PD BEV. Results: 179 pts were randomized to BEV-CT and 182 to CT alone. 72 pts (40%) in the CT-alone arm crossed over to BEV after PD and 110 never had BEV. There were no significant differences in pt characteristics between these subgroups at baseline but at the time of PD, 51% vs 35%, respectively, had ECOG performance status (PS) 0 (p = 0.034). 3-month landmark analyses, excluding 28 pts who died or were lost to follow-up before this time, showed significantly longer OS in pts who received BEV either with CT (HR 0.72, 95% CI 0.54-0.97) or after PD (HR 0.69, 95% CI 0.48-0.99) vs those who never received BEV. These differences remained significant after adjusting for identified prognostic factors for OS (eg., CA-125, platinum interval, ECOG PS). CA-125 baseline levels (median 123 vs 125). When analyzed from the time of PD, the OS HR vs never BEV was 0.84 (95% CI 0.62–1.14) for upfront (pre-PD) BEV-CT and 0.55 (95% CI 0.38–0.79) for BEV after PD. Tolerability was similar with pre-vs post-PD BEV. Conclusions: There appears to be no clear difference in OS between upfront vs post-PD BEV therapy. Pts who never received BEV had the worst OS. These analyses of a non-randomized phase of the study with no information on other post-PD therapies do not allow definitive conclusions about upfront vs post-PD BEV efficacy. Nevertheless, as 60% of pts randomized to CT alone never received BEV, upfront treatment with BEV-CT is important, as receiving BEV until after PD may deny some pts the opportunity to benefit from BEV. Clinical trial information: NCT00976911.
Prognostic and predictive value of primary vs secondary platinum resistance was significantly improved with the addition of bevacizumab (BEV) to standard chemotherapy (CT) for platinum-resistant ovarian cancer (OC) in the randomized phase III AURELIA trial. We examined the relevance of primary (PPR) vs secondary platinum resistance (SPR) on treatment efficacy. Methods: Platinum resistance was categorized as PPR if progression was < 6 months after completing first platinum therapy or SPR if not. We performed exploratory Cox and logistic regression analyses to correlate platinum resistance with PFS, overall survival (OS), and PRO from the time of randomization to CT. Results: Of the 361 randomized patients (pts), 262 (73%) had PPR and 99 (27%) had SPR. Baseline characteristics were generally similar in the two subgroups, except that FIGO stage IV disease and ascites were more common in PPR pts. In the BEV+CT arm (n = 179), SPR was associated with more favorable PFS (median 10.2 vs 5.6 months [mo]) in the PPR subgroup; P < 0.001 and OS (median 22.2 vs 13.7 mo, respectively; P = 0.001) but not PPRO (22.0% vs 21.9% with ≥ 15% improvement in abdominal/gastrointestinal symptoms at week 8/9; P = 0.99). In two separate multivariate analyses, SPR remained an independent prognostic factor for better PFS (adjusted hazard ratio [HR] 0.41, 95% CI 0.25–0.67, P < 0.001) and OS (HR 0.49, 95% CI 0.30–0.80, P = 0.005) in the BEV+CT arm. In the CT-alone arm, the prognostic effect did not reach statistical significance for PFS or OS. The magnitude of benefit from adding BEV to CT appeared greater in the SPR than the PPR subgroup for PFS (SPR: HR 0.30, 95% CI 0.18–0.48, P = 0.001; PPR: HR 0.55, 95% CI 0.42–0.71, P < 0.001; interaction P = 0.07) with a similar direction of effect for OS (SPR: HR 0.62, 95% CI 0.37–1.02, P = 0.06; PPR: HR 0.94, 95% CI 0.71–1.24, P = 0.65; interaction P = 0.18). Conclusions: Median PFS and OS were more favorable in SPR than PPR pts treated with BEV+CT but BEV effect on PRO was similar. The PFS and OS benefit of BEV+CT over CT alone was more pronounced in the SPR than the PPR subgroup. PPR vs SPR should be a stratification factor in future trials of anti-angiogenic therapy for OC. Clinical trial information: NCT00976911.

Early stage ovarian cancer clinical behavior according to FIGO 2014 Staging changes with a focus on IC subtype: data from prospective GEICO registry. First Author: Ignacio Romero, Instituto Valenciano de Oncología, Valencia, Spain

Background: Early stage ovarian cancer (ESOC) represents 10-15% of all Ovarian Cancer (OC) cases and most frequent ESOC subtype (IC) has undergone major changes in FIGO 2014 staging. Methods: A centralized prospective registry of ESOC (I-IIb) patients treated at GEICO (Spanish Group of Ovarian Cancer Research) centers was initiated on January 1998 and updated up to November 2014. We aim at prospectively explore both the robustness of FIGO in ESOC and the role of ascites in terms of prognosis. We analyze FIGO 2014 stage IA-IB (1), IC1-IC2 (2), IC3 citoplasma positive in washing (3) or in ascites (4) and IIA-B (5). Results: A total of 1,178 cases with a median age of 53 yrs. (16-97 yrs) have been included. Histology distribution according to Kurman (Int J Gynecol Pathol 5554) is summarized in table 1, subclassification in IC stage was unavailable in 80% of patients. Distribution of ESOC stages, frequency and Relapse Free Survival (RFS) and Disease Specific Survival (DSS) are summarized in table 1; subclassification in IC stage was unavailable in 80% of cases. With a median follow-up of 77 months (0-285 mo), 16.7% relapsed after a median of 27 months (2-221 mo) and 9.1% died after a median of 42 months (4-181 mo). RFS at 5 and 10 years were 84%, 80% and DSS 93.5% and 87.2% respectively. RFS was inversely associated with stage (p<0.001) (table 1). The presence of positive citoplasma in ascites had worse outcome than in washings. Up to 81% received adjuvant chemotherapy. Conclusions: In this large prospective cohort of ESOC, FIGO 2014 staging system for ESOC is prognostic. We propose to further explore the bad prognostic positivity of citoplasma in ascites.

Epigenome and genome alterations in platinum resistant ovarian cancer. First Author: Daniela Matei, Indiana Univ Simon Cancer Ctr, Indianapolis, IN

Background: Epigenetic changes, particularly DNA methylation aberrations have been implicated in acquired resistance to platinum in ovarian cancer (OC). Methods: An ongoing phase I/II multi-institutional clinical trial uses the novel DNA methyl transferase inhibitor (DNMTI) SGI-110 to re-sensitize platinum resistant OC to carboplatin. Patients enrolled in this trial had recurrent, platinum resistant OC and multiple lines of prior therapy. Tumor biopsies were collected at baseline and after two cycles of SGI-110 administered daily for 5 days (30mg/m²). The objectives of the study were to analyze and integrate global RNA expression and DNA methylation profiles of platinum resistant tumors and to measure genomic and epigenomic changes induced by the DNMTI. DNA and RNA were extracted from 48 and 57 baseline tumors and analyzed using next generation sequencing (RNA-seq) and Infinium HM450 BeadChip array, respectively. Differential gene expression and DNA methylation profiles were generated and used for Ingenuity Pathway Analysis (IPA) to identify significantly altered pathways in response to SGI-110. Results: Analysis of a limited number of paired samples before and after treatment (n = 8) revealed significant changes in global gene expression profiles induced by SGI-110, with 960 significantly altered genes representing immunopathway enrichment, including cytokine production in macrophages and T helper cells by IL-17A and IL-17F, granulocyte/granulocyte adhesion and inflammation, IL-8 signaling, p38 MAPK signaling, CAM-mediated signaling and cytokine receptor activity. Pathway analysis showed a significantly greater number of hypermethylated genes in baseline tumors compared to primary OC samples in the Cancer Genome Atlas (TCGA) and demethylation (decreased beta-values relative to baseline) of a large number of loci (381 gene promoters) after SGI-110 treatment. IPA analysis of baseline tumor transcriptome and methylation data demonstrated significant enrichment in pathways associated with cancer, stem cells, inflammation and the immune system. Conclusions: These data suggest that SGI-110 induces reactivation of immune responses in OC. Correlations between methylation changes and expression profiles are being explored. Clinical trial information: NCT01696032.
5556 Poster Session (#114), Sat, 1:15 PM-4:45 PM
Validation of a second-generation mia (MIA2G) for triage of adnexal masses. First Author: Judith Wolf, Vermillon, Inc., Austin, TX
Background: Many women with ovarian cancer receive non-guideline care. Failure to refer to a gynecologic oncologist is one likely cause. Prior specificity of Multivariate Index Assay (MIA) for ovarian cancer triage, we undertook the re-design and validation of a second-generation test (MIA2G). Methods: A panel of MIA-positive malignant and benign case- controls was used to evaluate candidate biomarkers to improve specificity. These, and the 5 MIA biomarkers were then further ranked and developed into the MIA2G using ranked samples from a previously published prospective, multi-site FDA registration trial of MIA (N = 585). Upon verification, the algorithm was encoded into diagnostics-grade software to calculate MIA2G in subsequent validation studies. Clinical validity was established under a double-blinded protocol using banked samples from the OVA500 trial, a second prospective, multi-site pivotal trial. Samples were assayed at 3 external sites, results were generated at a commercial laboratory and submitted to an independent statistician for decoding and analysis. MIA2G was compared with physician assessment (PA) or MIA. Results were compared for sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratios, concordance and percent overall accuracy. Results: Three MIA markers (CA125-II, transferrin and Apo A-1) and 2 new biomarkers (FSH and HE4) were selected for inclusion in MIA2G. MIA2G results range from 0-10, with a single cut-off separating high- and low- malignancy risk of 10.5. 493 of 519 OVA500 subjects were evaluable (275 pre and 214 post-menopausal). MIA2G specificity (69.1%) and PPV (40.4%) were significantly improved over MIA (53.6% and 31.4%, respectively). Sensitivity and NPV were not significantly different. Overall accuracy was significantly improved from 60.9% (MIA) to 73.2% (MIA2G). When MIA2G was combined with PA sensitivity was 93.5% and specificity was 64.8%. Conclusions: The redesigned multivariate index assay, MIA2G, has significantly improved specificity, PPV and accuracy compared with MIA. These changes enable high-sensitivity detection of malignancy while reducing likelihood of over-referral.

5557 Poster Session (#115), Sat, 1:15 PM-4:45 PM
The PACOVAR trial: A multicenter phase I trial of pazopanib (GW786034) and metronomic cyclophosphamide in patients with recurrent platinum-resistant ovarian cancer. First Author: Michael Robert Ichibaum, St. Marienkrankenhaus Frankfurt, Germany
Background: A combined therapy consisting of the investigational anti-VEGFR tyrosine kinase inhibitor pazopanib (GW786034, paz) and metronomic oral cyclophosphamide may offer a well-tolerable treatment option to patients with recurrent platinum-resistant epithelial ovarian cancer (ECOC). Methods: This study was designed as a multicenter phase I trial evaluating the optimal dose for paz as well as activity of a combination regimen consisting of paz and metronomic cyclophosphamide 50mg daily p.o. in monthly cycles. Patients with histologically proven recurrent platinum-resistant EOC were included. Dose escalation of paz followed a phase I design in three dose levels (DL) of 400mg, 600mg and 800mg daily p.o., respectively. Toxicity and survival data were obtained. Results: 16 patients were treated within this trial, mean age was 66 years. In DL I and II one dose limiting toxicity (DLT) was seen in one patient out of six (AST-elevation, hypotension). Within DL III, two patients out of four showed a DLT (AST-elevation), leading to a maximum tolerated dose (MTD) of 600mg paz daily. Median number of administered cycles was 6 (2-13), with three patients being treated for at least 13 months. Median progression-free survival (PFS) and overall survival (OS) were 6.7 months and 15.2 months, respectively. A total of 254 adverse events (AE) occurred. The most often documented AE were leukopenia in 14.6% of the cases, followed by elevation of ALT (10.2%) and elevation of AST (9.5%). Moreover, 27 AE were probably or very likely related to cyclophosphamide (10.6%) and 55 AE were probably or very likely related to paz (21.7%). A total of five serious adverse events (SAE) occurred in four patients. The events were hypertension as well as sepsis, vomiting, ileus and fatigue. Based on this analysis, which had a favorable outcome, all other SAE were removed. Conclusions: Paz 600mg daily p.o. and metronomic cyclophosphamide 50mg daily p.o. is a feasible regimen for patients with platinum-resistant recurrent, pre-treated EOC. Further evaluation of this palliative regimen in phase II setting is warranted. Clinical trials information: NCT01238770.

5558 Poster Session (#116), Sat, 1:15 PM-4:45 PM
Phase I study of IMGN853, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC) in patients (Pts) with epithelial ovarian cancer (EOC) and other FRa-positive solid tumors. First Author: Hossein Borghaei, Fox Chase Cancer Center, Philadelphia, PA
Background: IMGN853 (mirvetuximab soravtansine) is a FRa-targeting ADC comprising a FRa-binding antibody and potent maytansinoid, DM4. Methods: This Phase 1 trial is being conducted to determine safety, pharmacokinetics (PK), pharmacodynamics, maximum tolerated dose, recommended phase 2 dose (RP2D) and evidence of activity of IMGN853 in pts with EOC or other FRa-positive solid tumors. As previously reported, the occurrence of ocular adverse events (AEs) was associated with peak drug exposure and pt weight. Dosing by adjusted ideal body weight (AIBW) instead of total body weight (TBW) was implemented to decrease PK variability. Two dosing schedules are being evaluated; (A) once every 3 weeks and (B) Days 1, 8, and 15, every 4 weeks. Results: Fifty nine pts enrolled to dose escalation to date, 44 (30 TBW; 14 AIBW) pts in A, 16 (AIBW) in B. RP2D for A was determined to be 6.0 mg/kg, while dose finding in B continues. Exposure to IMGN853 increased with an increase in dose in a more than dose-proportional manner indicating non-linear PK. AIBW enabled IMGN853 to achieve drug exposure with more pts treated at 3 within a clinically relevant therapeutic window. The majority of AEs have been CTCAE grade 1 or 2, generally similar across both schedules: included GI events, ocular events, cough, fatigue, and neuropathy in > 20% of patients. Nausea, vomiting and headache may be more common on schedule B. Diarrhea, anecdotally, is one likely cause. To improve evidence of clinical benefit (CB) (partial PR or complete CR response, CA125 response, SD ≥ 6 cycles) has been observed with both schedules during escalation. In A, CB was observed in 11/44 pts: 4 PRs; 2 confirmed CA125 responses; 5 SD; 2 for 10 cycles. In B, 5/15 evaluable pts had CB: 1 PR; 4 SD, 3 with confirmed CA125 response; six pts remain on study. Benefit was seen in epithelial and transitional cell ovarian cancer, endometrial cancer and NSCLC. Conclusions: With both schedules, IMGN853 demonstrates encouraging clinical activity in heavily pretreated patients during dose escalation with a manageable AE profile. A RP2D has been identified for schedule A, while schedule B continues dose finding. Clinical trial information: NCT01609556.

5559 Poster Session (#117), Sat, 1:15 PM-4:45 PM
A phase I study optimizing the dosing of olaparib tablet formulation combined with cediranib in recurrent ovarian cancer. First Author: Joyce Liu, Dana Farber Cancer Inst, Newton, MA
Background: PARP inhibitors and anti-angiogenics are clinically active in recurrent ovarian cancer (OvCa). Pre-clinical studies suggest these agents can synergize; a phase 2 study demonstrated that combination cediranib/capsule olaparib (C/O) increased progression-free survival (PFS) and response rate (RR) compared to olaparib alone. Olaparib clinical development will proceed using the tablet formulation; we therefore investigated the toxicities and recommended phase 2 dosing (RP2D) of C/O with olaparib tablets. Methods: Cediranib (C) once daily and olaparib (O) twice daily were administered orally in cohorts of 3 patients in a standard 3+3 Phase I design. Eligibility included pts with recurrent ovarian cancer. Pts had measurable disease by RECIST 1.1 or met GCG CA125 criteria. No prior anti-angiogenics in the recurrent setting or prior PARP inhibitor were allowed. Results: 24 pts have been treated since May 2014 at 6 dose levels (C 20mg QD/O 200mg BID (3 pts); C 20mg QD/O 250mg BID (3); C 20mg QD/O 300mg BID (6); C 30mg QD/O 150mg BID (3); C 30mg QD/O 200mg BID (6); C 30mg QD/O 250mg BID). One DLT (gr 3 rotator cuff injury) occurred at the 30mg O/250mg BID dose. Clinical and safety data were obtained. Conclusions: In the 25 evaluable pts the clinical and safety data were not dissimilar to those previously reported. The redesigned tablet formulation showed a DLT (AST-elevation), leading to a maximum tolerated dose (MTD) of 800mg daily p.o. and 200mg daily p.o. respectively. Toxicity and survival data were obtained. Follow-up of patients continued in the 20/300 dosing level. Two pts remained on study 6+ months, respectively. Median progression-free survival (PFS) and overall survival (OS) were 6.7 months and 15.2 months, respectively. A total of 254 adverse events (AE) occurred. The most often documented AE were leukopenia in 14.6% of the cases, followed by elevation of ALT (10.2%) and elevation of AST (9.5%). Moreover, 27 AE were probably or very likely related to cyclophosphamide (10.6%) and 55 AE were probably or very likely related to paz (21.7%). A total of five serious adverse events (SAE) occurred in four patients. The events were hypertension as well as sepsis, vomiting, ileus and fatigue. Based on this analysis, which had a favorable outcome, all other SAE were removed. Conclusions: Paz 600mg daily p.o. and metronomic cyclophosphamide 50mg daily p.o. is a feasible regimen for patients with platinum-resistant recurrent, pre-treated EOC. Further evaluation of this palliative regimen in phase II setting is warranted. Clinical trials information: NCT01238770.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Ovarian carcinosarcomas (OCS) are rare and aggressive malignancies with limited treatment options. It is unclear if this uncommon type of cancer shares similar molecular changes as endometrial carcinosarcoma (ECS) or serous ovarian carcinoma (SOC). We compared the molecular profile of a cohort of OCS to that of SOC and ECS to explore the potential overlap in treatment paradigms. Methods: 110 OCS, 141 ECS and 1587 SOC were evaluated using a commercial multiplexed profiling service (CARIS Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH). Results: TP53 was the most commonly mutated gene in all three malignancies with 76.4% of OCS, 68.8% of ECS and 30.4% of SOC. Alteration of PIK3CA/mTOR/PI3K/AKT/mTOR signaling pathways were noted to be similar in OCS and SOC but was less frequently altered than ECS including mutation in PIK3CA (7.6% and 2.3% vs. 12.5% and 8.9%), PTEN loss (3.7% and 0.8% vs. 12%, p < 0.001) and KRAS (5.2% and 5.0% vs. 13.5%, p < 0.001). For homologous recombination pathway, SOC and ECS were more likely to have BRCA1 (20% and 18% vs. 9%) and BRCA2 mutations (18% and 27% vs. 12%) than OCS. However, the differences were not statistically significant. No difference in alteration of RB, NOTCH, angiogenesis and FGFR pathways were noted among the three cohorts. Estrogen (14.6% and 25.1% vs. 53.1%, p < 0.001) and androgen receptors (18.8% and 12.2% vs. 32.4%, p < 0.001) were expressed less frequently in OCS and ECS than SOC respectively. On the other hand, expression of progesterone receptors was more frequent in OCS and SOC than ECS (62.5% and 30.5% vs. 20.9%, p < 0.001). Conclusions: While ovarian carcinosarcoma and uterine carcinosarcoma (ECS) have similar genetic profiles, we found that OCS has a lower occurrence of PI3K/AKT/mTOR, MAP4K pathways and higher progesterone receptors expression than ECS. Treatment with regimens that are active in ovarian serous could be considered when treating patients with ovarian carcinosarcoma.

5562 Poster Session (Board #120), Sat, 1:15 PM-4:45 PM

Early drug development in advanced gynecologic cancer based on genetic tumor profiling. First Author: Ana C. Garrido-Castro, Vail d’Hebron University Hospital, Barcelona, Spain

Background: The broad spectrum of actionable molecular alterations (MA) detected with new techniques has increased interest in matched targeted therapies (MTT) after failure to standard treatment. Methods: Advanced gynecologic tumor (GYNT) patients (pts) were analyzed in our Molecular Prescreening Program for MA: mutations (mt) detected with Sequenom (SQ) or WH Card Amplicon Seq Panel (VCASP), Notch and PI3K amplifications (ampl), PTEN loss (Hscore ≤ 50) and PDL1 expression. Pts were allocated to Phase I trials with MTT based on MA. Time to treatment failure (TTF) with MTT (TTF2) was compared to TTF with the previous unmatched therapy (TTF1). Results: From Jan 2012 to Dec 2014, 129 GYNT pts (mean age: 52.6y; median no. previous treatments: 3 (0-7)) were screened for MA; 87 ovarian (OC; 23 type I, 64 type II), 27 endometrial (EC; 15 type I, 12 type II) and 15 cervical (CC) cancers. Of 69 pts with MA (53.5%), 33 received MTT (47.8%) including 59/59, respectively, compared to OVA1 improving in 35 stage I/II and 11 low malignant potential (LMP) cases. The specificity and sensitivity of the MIAG2 for the validation set were 60.1% (140/233) and 88.9% (64/72), respectively, compared to OVA1 which had a specificity of 47.2% (110/233) at a sensitivity of 95.8% (69/72). The improvement in specificity was statistically significant (p < 0.001) but the sensitivity was not (p = 0.07). Conclusions: MIAG2, which includes 125 II, ApoA1, TRF, FSH, and HE4. Its algorithm uses two ensembles of classification models, for pre- and post-menopausal women respectively. MIAG2 is a promising tool in early drug development in advanced gynecologic cancer.
Baseline predictors of early treatment failure in patients with platinum resistant/refractory (PRR) and potentially platinum sensitive (PPS) ≥ 3 recurrent ovarian cancer (OC) receiving chemotherapy. Gynecologic Cancer Intergroup (GCIG) Symptom Benefit Study (SBS).

First Author: Felicia T Roncolato, ANZGOG, NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia

Background: Women with PRR/PPS ≥ 3 ROC are a heterogeneous group with unpredictable response to palliative chemotherapy (PC). GCIG SBS recently completed recruitment of 949 patients treated with PC. Primary aim is to validate an instrument to measure symptom benefit. Secondary aims include identifying factors that predict early progression. 25% of patients with PRR-ROC received < 8 weeks of PC. Methods: Physicians recorded baseline characteristics, symptoms (symptomatic ascites, cramping abdominal pain), site/extent of disease and prespecified lab values. Association between baseline characteristics and progression-free survival (PFS) was assessed using time-to-event methods. Median PFS was calculated according to clinically relevant categories and log-rank test applied to assess prognostic value. Cox regression was used to compute hazard ratios and 95% CI to assess the effect of variables on PFS. Results: Sufficient follow up for analysis of PFS was available in 791 patients. Median PFS and overall survival were 4.3 (95% CI: 3.9-4.9) and 12.9 months (95% CI: 11.4-14.0) respectively. In univariate analysis factors with statistically significant associations with PFS included: haemoglobin, PRR-ROC, ascites and abdominal cramps, nodal disease, thrombocytosis, CA125 > 1000, LDH > 600, ECOG status, and elevated c reactive protein. Non-significant factors included: visceral metastases, albumin < 25, lymphocytes < 0.5, tumour volume. Significant variables in multivariable analysis included: ECOG ≥ 2 (HR 1.61 95% CI 1.18-2.19 p = 0.003); nodal disease (HR 1.37 95%CI 1.13-1.67 p = 0.002); ascites (HR 1.54 95% CI 1.24-1.92 p = 0.0001); platinum resistant vs. sensitive (HR 1.39 95%CI 1.12-1.72 p = 0.002); CA125 > 1000 (HR 1.35 95%CI 1.09-1.67 p = 0.005); LDH > 600 (HR 1.88 95%CI 1.36-2.60 p = 0.0001). Conclusions: Several simple clinical variables help predict patients who progress rapidly and will be used to construct prognostic models to aid clinical decisions and trial stratification for clinical trials in PRR/PPS ≥ 3 ROC Clinical trial information: 12607000630415.
Background: Although there are many studies that compared the outcome of neoadjuvant chemotherapy (NAC) and primary surgery in advanced ovarian cancer, most of them showed some limitations such as selection bias and the quality control of surgical procedure. Methods: Data of 1124 patients with advanced epithelial ovarian cancer (stage III-IV) were reviewed retrospectively. To mitigate the possible biases from the retrospective nature of the study, we performed a propensity score analysis. Progression-free survival was assessed using a multivariate Cox-proportional hazards regression model with inverse probability weights to adjust for propensity score. Results: Among the 1124 patients, 198 patients (17.6%) underwent NAC. The factors associated with the use of NAC were old age, non-serous histology, poor histologic grade, stage IV and higher serum CA125 levels (P-value 0.211, 0.050, < 0.001, < 0.001 and < 0.001, respectively). After a propensity score adjustment using these factors, the progression-free survival of the NAC group was not significantly different from that of the primary surgery group (HR 1.24, 95% CI 0.932-1.512, P-value 0.164). Especially, no significant difference was observed between the two treatment strategies in the subgroup from the hospitals with higher surgical standards with the average rate of optimal cytoreduction was over 50% (HR 1.166, 95% CI 0.885-1.536, P-value 0.275). However, when we did not adjust the confounders, the outcome of primary surgery group was superior to that of NAC group (HR 1.24, 95% CI 1.016-1.515, P-value 0.035). Conclusions: Progression-free survival of NAC group did not differ significantly from primary surgery in patients with advanced ovarian cancer. Even in the institutions providing a good standard of surgical care, we did not found any evidence suggesting that primary surgery is better than NAC in patients with advanced ovarian cancer.

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Carboplatin hypersensitivity reactions (HSR) in carboplatin retreatment for recurrent ovarian cancer. First Author: Roisin Eilish O’Carrollhan, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: The reported risk of HSR during carboplatin retreatment is 18-44% and increases with repeated carboplatin exposure. We aimed to prospectively study the effect of an extended incremental infusion of carboplatin on the rate of HSR. Methods: Eligible patients (pts) with recurrent ovarian cancer were consented to an IRB-approved phase II randomized study from 03/2011-10/2015. Pts were randomly assigned 1:1 to standard 30-minute or an incremental 3-hour (1% in 1st hour, 9% in 2nd hour and 90% in 3rd hour) carboplatin infusion. Pts were stratified for concomitant taxane. Based on historical estimates the study was powered to detect a reduction in HSR from 20% to 5% with the extended infusion. All pts were prescribed premedication with montelukast 10 mg nocte x 3 days, dexamethasone 20 mg the night before and morning of, as well as famotidine 20 mg (or ranitidine) and diphenhydramine 50 mg (or hydroxyzine) prior to carboplatin. Pts were deemed evaluable for the study endpoint if they completed ≥ 5 cycles of carboplatin-based treatment or had carboplatin HSR. CTCAE criteria were used. Results: A total of 143 pts with recurrent ovarian cancer were enrolled. Median age was 62 years (35-82). 104 pts (52 in each arm) were evaluable for the study endpoint. Among these pts, 72 (69%), 27 (26%), 2 (1.9%) and 3 (2.9%) pts had 1, 2, 3 and 4 prior platinum-based regimens, respectively. 27 pts (26%) received carboplatin single agent and the remainder a platinum-doublet (46 liposomal doxorubicin, 24 gemcitabine, 7 paclitaxel). There were 15 HSR (14% of pts); 9 HSR in standard arm (9/52, 17%) and 6 HSR in the extended arm (6/52, 12%). There was 1 grade 3 HSR in the extended arm. No pt required hospitalization or epinephrine for HSR. The other 14 HSR were of grade 1 or 2. HSR occurred on cycle #1 (1 pt); #2 (2 pts); #3 (3 pts); #4 (2 pts); #5 (2 pts) and #6 (1 pt). 2/9 HSR pts in standard arm were able to complete therapy with an extended infusion without further HSR.

Conclusions: We did not demonstrate a statistically significant reduction in carboplatin HSR with use of an extended carboplatin infusion. However, the greater than 4-fold lower frequency of severe HSR in both arms suggests there may be a role for prophylactic premedication prior to carboplatin retreatment. Clinical trial information: NCT01248962.

BL1 gene expression subtype to predict outcome in serous ovarian cancers. First Author: Rob Seitz, Insight Genetics Inc, Nashville, TN

Background: A new 2188-gene model classifies triple-negative breast cancer (TNBC) into six distinct subtypes: two basal-like, two mesenchymal-like, immunomodulation and luminal androgen receptor subtype subtypes. Among taxane-treated TNBC patients, significantly higher response rates were seen in patients with BL1 compared to BL2 tumors. Recently we showed a “leash algorithm” of 101 genes could replicate this result in TNBC patients. As TNBC and serous ovarian cancer share many features, similar sub-classification of ovarian cancers may also be clinically important. Methods: A cohort of 592 patients with serous ovarian carcinoma (primarily platinum/taxane-treated) was analyzed. Patients were classified using both the original 2188-gene and 101-gene centroid models. Patients who had an insignificant or multiple statistically indistinguishable correlations with the subtype centroids were considered “unclassified.” Three-year survival was examined using log-rank test and Cox proportional hazard regression analysis. Results: While both models had a higher percentage of unclassified patients in ovarian as compared to TNBC, the 101-gene model classified more patients (60%) than the 2188-gene model (34%). In the subset classified by both models, the models showed 95% agreement. Ovarian cancer patients with BL1 tumors had significantly better 3-year overall survival compared to all other subtypes (hazard ratios of 0.48 and 0.41, p = 0.02 and 0.01, 2188 and 101-gene models respectively). If age and stage—both independent predictors of survival—were included as covariates, only the 101-gene model defined a statistically significant association with outcome (HR 0.47, p = 0.02). Conclusions: There was excellent agreement between the original 2188-gene TNBC classifier and a streamlined 101-gene classifier when applied to an ovarian cancer cohort. BL1-classified ovarian cancer patients had significantly better 3-year survival outcomes than patients with tumors of other subtypes; however, only the 101-gene classification of the BL1 subtype was independent of age and stage. Studies aimed at the refinement of gene expression-defined serous ovarian carcinoma subtypes that can guide therapeutic management will be presented.

A phase Ib/I trial with expansion of patients at the MTD trial of olaparib plus weekly (metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients. First Author: Saul E. Rivkin, Swedish Cancer Inst, Seattle, WA

Background: We established the olaparib tablet maximum tolerated dose, dose limiting toxicities (DLTs) and response to therapy of carboplatin, paclitaxel and olaparib tablet given simultaneously, reported at ASCO 2014. This abstract will include data from both the phase Ib and the phase 2 expansion. Methods: A total of 54 subjects were evaluated in this trial, 14 in phase Ib and 40 in phase II. Eligibility required measurable disease, adequate organ function and ECOG performance status of ≤ 2. Subjects had to have failed first line platinum containing chemotherapy. BRCA testing was conducted as available. Subjects received the metronomic therapy of paclitaxel 60mg/m2 IV and carboplatin AUC 2 IV weekly, 3 weeks out of 4, and olaparib tablets at the MTD of 150 mg bid administered orally for 3 consecutive days (D1-D3), every week for each cycle. Subjects were assessed for toxicity and response according to the protocol. Subjects that reached a confirmed complete remission were transitioned to olaparib tablets only, 300 mg bid, until disease progression. Results: Median age was 58 and median number of prior regimens was 4. There have been no deaths due to the study regimen. One patient had grade 4 neutropenia and an allergic reaction to carboplatin. The common grade 3 toxicities caused by this regimen were neutropenia, anemia and thrombocytopenia. Two subjects had mild GI toxicities. There was no evidence of cardiac, hepatic, or pulmonary toxicities in any of these subjects. 22% of subjects had a complete remission (CR), 30% had PR, 25% had SD and 22.5% had PD. Of the 9 CR’s, 6 were gBRCA mutated. FFS median for gBRCA mutated subjects is 19 months vs 4 months for non-mutated gBRCA subjects. OS median for gBRCA mutated subjects is 24 months vs 16 months for gBRCA non-mutated subjects. 71% of the CR’s are ongoing. Olaparib tablets can be safely administered simultaneously with a weekly regimen of carboplatin and paclitaxel in heavily pretreated ovarian cancer subjects. Olaparib appears to be highly effective in gBRCA mutated. This is the first successful combination of olaparib tablets with carboplatin and paclitaxel that has been well tolerated. Clinical trial information: NCT01650376.

Genomic profile and immune infiltrate in paired ovarian cancer (OC) samples pre- and post-neoadjuvant chemotherapy (NC). First Author: Alexandra Leary, Royal Marsden Hospital, London, United Kingdom

Background: Most studies of OC have analysed tumors at diagnosis, little is known about the evolution of the genomic or immune landscape of OC with NC. Profiling after NC may be informative as the residual tumor may be enriched for resistant clones. Aim: Compare matched post- vs pre-NC tumors to describe changes in immune infiltrate, genomic stability (GS) and characterize the chemo-resistant sub-populations by identifying SC-RAs selectively enriched post-NC. Methods: Analyses included 27 frozen OC samples (13 paired pre/post-NC and 1 subsequent relapse) were subjected to aCGH. GS was evaluated by the % altered genome and the number of altered segments > 15Mbp (W). Changes in copy number alterations (CNA) were considered relevant if log(2)ratio difference in matched post- vs pre-NC samples > 0.5, FFPE samples (N = 66; 33 paired) were scored for % stromal tumor infiltrating lymphocytes (sTILs) on whole sections. Results: Cellularity of frozen samples was high (70-90%) and included 12 high grade serous OC (HGSOC) and 1 low grade SOC. At baseline, HGSOC were unstable with 10 showing N> 10 (range 14-48) and 31%-70% altered genome. LGSOC showed 2% altered genome. GS increased in 8/12 HGSOC resulting in < 2% altered genome post-NC for 3; GS decreased in 2/12 and did not change in 3. CNAs enriched in paired post-vs pre-NC included gains in genes involved in p53 signalling (MDM4, TP53BP2), EMT/senescence (PKD1, ESRR1, RB1CC1), or epigenetic modification (CEBBP, SMARCMB1, RASSF1A). Changes in immune subtype were seen in paired pre- vs post-NC samples (16/33) of paired cases, and 6 tumors had > 60% sTILs pre-NC. An evaluation of changes in PDL1 with NC is ongoing and will be presented. Conclusions: The immune and genomic landscape of OC changes with NC. Surprisingly a proportion showed increasing TILs and GS. Comparative profiling of post- vs pre-NC tumors could be used to select therapies such as immune or targeted therapies to eradicate the residual lethal clones driving relapse.

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Background: Response to DNA-damaging agents, including platinum, is associated with defects in homologous recombination (HR) function. The HRD score is a sum of three previously described metrics (Abkevich et al, Popova et al), and is significantly associated with both tmbBRCA and response to DNA damaging agents. This study examined whether HR deficiency (HRD score >45, or tmbBRCA positivity) is predictive of response or prognosis in a carboplatin monotherapy treated HGSOc cohort from the SCOTROC4 phase II trial (Banerjee et al 2013). Methods: DNA from formalin-fixed archival tumor from 165 HGSOc patients treated with first-line single-agent carboplatin was analyzed for HRD scores and tmbBRCA. Cox proportional hazards analysis was used to test CA125 response, HR deficiency, and tmbBRCA for associations with progression free survival (PFS) and overall survival (OS). HR deficiency and tmbBRCA were evaluated as predictors of CA125 complete response using logistic regression. Results: BRCA1/2 mutations were detected in 26/165 (16%) of primary HGSOc. HR deficiency was present for 53/151 (35%) tumors analyzed. Patients with CA125 complete response (n = 64) had significantly improved PFS (p = 6.6x10-7) and OS (p = 3.3x10-7) compared to no or partial CA125 response (n = 45). HR deficiency predicted CA125 complete response in all evaluable patients (p = 0.0033, n = 96) and in the BRCA1/2 wild type subset (p = 0.034, n = 75). TmbBRCA trended but was not significantly associated with CA125 response (p = 0.079, n = 107). HR deficiency and tmbBRCA were associated with improved PFS (p = 0.00058; 0.012 respectively) and OS (p = 0.0040; 0.026 respectively) in an independent manner from known prognostic variables (age, histology, grade, BRCA1/2 mutations, 2 had HRBRCA1/2 mutations, 2 had HRBRCA1/2 mutations). Mutations in the HRD score is a novel and important biomarker for response to carboplatin monotherapy. HR deficiency was also significantly associated with outcome in HGSOc patients treated with platinum monotherapy. HR deficiency also significantly associated with outcome in the entire cohort, and importantly, in BRCA1/2 wild type tumors. Pending validation evaluation of HR deficiency and tmbBRCA status should be considered in the development of platinum combination therapies.

References:
Progression. Levels of MDSC at time of study enrollment were associated with immunologic synergies and those patients most likely to respond through their respective previous TTP after P alone. The addition of E did not complicate the AE profile of P and was well tolerated.

Dairy [\textsuperscript{3}H1001] multivariate analysis, OC risk was significantly associated with a self-report of dairy (OR = 1.91; 95% CI (1.4-2.4), whole grain (OR = 0.64; 95% CI (0.51-0.87)), fish (OR = 2.7; 95% CI (2.04-3.56), exercise (OR = 1.54; 95% CI (1.19-1.99)) and tobacco smoking (OR = 0.43; 95% CI (0.25-0.74)), respectively. There was no association with fruits, vegetables, and meat consumption on OC risk (see table). Conclusions: Consumption of fish (any serv/day), dairy (> 2 serv/day), whole grains (< 2 serv/day) and exercise (> 120 min/wk) was associated with a decreased risk of OC. Smoking > 40 pack-yr (pyr) showed an increased risk for OC. Further prospective studies are needed to validate our findings.

**Modifiable risk factors in ovarian cancer.**

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<th>p-value</th>
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<td>Fish &lt; 2/day serv vs. &gt; 2/day</td>
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<td>Fruits (&lt; 3/week serv vs. &gt; 3/week)</td>
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<td>BMI (&lt; 30 vs. BMI ≥ 30)</td>
<td>1.00 (0.91-1.02)</td>
<td>0.92</td>
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<tr>
<td>Smoking (&lt;40 gpy vs. &gt; 40 gpy)</td>
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<td>Exercise (&lt;120 min/wk vs. &gt; 120 min/wk)</td>
<td>1.54 (1.19-1.99)</td>
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**Combination therapy with temsirolimus and trabectedin for recurrent clear cell carcinoma of the ovary: A phase II study with biomarker analysis.** First Author: Masashi Takeko, National Defense Medical College, Tokorozawa, Japan

Background: Recurrent clear cell carcinoma (RCCC) of the ovary showed exceedingly chemo-resistant phenotype, especially in the case with recurrent or refractory to previous therapy. A phase II trial to evaluate the effect of combination therapy with temsirolimus and trabectedin for patients with RCCC was performed. Methods: Eligible patients were as follows: (a) ECOG PS 0-2; (b) histologically confirmed ovarian clear cell adenocarcinoma (c) diagnosed as platinum-resistant ovarian cancer (d) written informed consent. Patients with RCCC were treated with weekly regimen using two drugs: 15mg/m\(^2\) of temsirolimus and 0.15mg/m\(^2\) of trabectedin (3 weeks, one week rest). Treatment was continued until development of progressive disease (PD) or unmanageable adverse effects. There was no significant difference of serum level of VEGF according to the response evaluation. Biomarker analyses including serum VEGF and BNP were also conducted. Results: A total of 21 patients were analyzed in the present study. There were no cases that continued the therapy due to toxicities. Median age was 59 years (range: 30-69), and median number of previous chemotherapy was 3 range: (1-6). All cases were assessable by RECIST and CTCAE. One patient (5%) had a complete response (CR), and two cases (10%) achieved a partial response (PR), and 6 patients (29%) had a stable disease (SD) beyond three months, resulting in clinical benefit rate (CBR; CR+PR+SD > 3month) of 43%. Median response duration in CBR case was 3.5 months (range: 3-40+). There were no cases that developed toxicities more than grade2. There was no significant difference of serum level of VEGF according to the response evaluation. Conclusions: Combination therapy with temsirolimus and trabectedin was a candidate for salvage therapy regimen in patients with RCCC. These results warrant further study in clinical settings with biomarker analyses.
Omentin as a biomarker associated with improved overall survival in serous ovarian cancer. First Author: Michaela Onstad, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Omentin is a protective adipokine secreted by the mesothelial cells of visceral adipose tissue. Its expression is inversely related to obesity and low levels have been found to be associated with disease states, such as diabetes and hypertension. Recently it has been found to have tumor suppressor activity in ovarian cancer, leading to decreased ovarian cancer cell proliferation, motility and invasion potential. We sought to explore whether omentin could be used as a biomarker to predict overall survival among patients with serous ovarian cancer.

Methods: Serum samples were obtained from 148 women with serous ovarian cancer at the time of initial surgery. Circulating omentin levels were quantified using a commercially available ELISA kit. Clinical and demographic data were obtained from the electronic medical record. Overall survival was measured from the date of omentin collection to the date of last follow-up or death. A multivariate analysis of overall survival was performed to account for potential confounding variables. Results: Among women with serous ovarian cancer, a higher omentin level (per 100 units) is significantly associated with a decreased risk of death (p = 0.0004). Using a cutoff point of 350ng/mL, a Kaplan-Meier curve demonstrates a significantly improved survival for women with omentin > 350ng/mL at the time of initial surgery (p < 0.0001). A multivariate analysis was performed to consider other risk factors that may contribute to risk of death, including stage and grade of cancer, optimal debulking, use of neoadjuvant chemotherapy, BMI, menopausal status, diabetes and metformin use. After adjusting for these factors, the relationship between omentin and overall survival remained statistically significant (p < 0.0001).

Conclusions: Omentin levels > 350ng/mL are predictive of improved overall survival among women with serous ovarian cancer, after adjusting for potential confounders. This may be reflective of the tumor suppressor activity of this adipokine, or may be due to the ability of ovarian cancer cells to down-regulate production of omentin. These findings warrant validation in another large ovarian cancer dataset.

Omentin as a biomarker associated with improved overall survival in serous ovarian cancer. First Author: Tara Soumerai, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Uterine leiomyosarcoma (uLMS) is a rare gynecologic malignancy affecting 2000 women annually in the United States. It is known about 1500 different somatic mutations in uLMS and targeted therapies are currently approved for this disease. We aimed to describe the genomic alterations present in a cohort of patients with uLMS in order to identify those that are potentially targetable by available or investigational agents.

Methods: Thirty-one tumor samples were prospectively collected from 2/2014 to 1/2015; all had central pathology review at Memorial Sloan-Kettering. Patients were consented to an IRB-approved biospecimen protocol and samples were analyzed in a CLIA-compliant laboratory with the Memorial Sloan-Kettering Integrated Mutation Profiling for Actionable Cancer Targets (MSK-IMPACT). This NGS, bait-capture platform assesses for mutations, copy number variations, and fusions within 341 genes that are common drivers of oncogenic transformation. Variant calls were made against matched germline DNA. Results: All samples were successfully assessed by MSK-IMPACT. The most commonly identified genetic aberrations were deletions/truncating mutations of TP53 in 19 (61%) cases, RB1 in 15 (48%) cases, and ATRX in 10 (32%) cases. MED12 mutations were seen in 3 (10%) cases, 2 of which were hotspot mutations G44A/C. Genetic events activating the PI3K signaling pathway were identified in 9 (29%) cases, including PTEN deletions or truncating mutations, PIK3CA activating mutations, or deletions/mutations of PIK3R1 or PIK3CG. One case was hypothesized (epithelioid LMS) with 65 somatic mutations; 65 tumors were tested for mismatch repair gene deficiency and showed equivocal immunohistochemistry for MSH6. One case had a BRAF V600E mutation and this patient was enrolled on a clinical trial of a BRAF inhibitor. In total, three (10%) patients have been enrolled in clinical trials of targeted therapy matched to their mutational status. Conclusions: Among 31 patients with uLMS, 10 (32%) were found to have potentially actionable somatic tumor mutations. Genomic characterization of uLMS may offer insights into tumorigenesis and identify potential therapeutic targets in this rare and heterogeneous disease.

Utility of PET-CT vs CT alone to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer. First Author: Mostafa Atri, University Health Network, Toronto, ON, Canada

Background: To assess if PET-CT improves accuracy of CT to detect lymph node (LN) metastasis in advanced cervical cancer. Methods: This was a prospective ACRIN/GOG multicenter trial. Patients underwent contrast enhanced PET-CT followed by extra-peritoneal or laparoscopic pelvic and abdominal lymphadendectomy. Seven independent blinded readers reviewed PET-CT and CT only images at least one month apart. Region correlation was performed between pathology and central review results for abdomen (right and left para-aortic, right and left common iliac) and pelvis (right and left external iliac and right and left obturator) regions. Abdomen and pelvic regions were combined, respecting laterality, to calculate accuracy values for these regions at participant level. Reference standard was pathology of resected LNs. Reader average sensitivities/specificities of PET-CT vs CT were compared with generalized linear mixed models. Reader average AUCs were compared with Obuchowski’s method. Fleiss’ kappa was used to assess reader agreement. Results: A total of 153 patients had PET/CT and pathology proof in the abdomen from 169 patients who were enrolled between September 2007 and December 2012. Forty-three of 153 patients had metastasis to abdominal LNs. Forty abdominal positive and 40 randomly selected abdominal negative patients were used for review based on sample size calculation. Reader study cases ranged from 24 to 74 years old (mean;48.9 ± 10.6). Cancer stages were: IB = 25, II = 44, III = 11; sixty-nine squamous cell carcinomas, 6 adenocarcinoma and 5 others. Mean sensitivities of PET-CT/CT alone in abdomen were 0.50 (CI:0.44,0.56)/0.42 (CI:0.36,0.48) (p = 0.052) and in pelvis 0.83 (CI:0.78,0.87)/0.79 (CI:0.73,0.83) (p = 0.15). Corresponding specificities were 0.85 (CI:0.80,0.89)/0.89 (CI:0.84,0.92) (p = 0.21) and 0.63 (CI:0.54,0.70)/0.62 (CI:0.53,0.69) (p = 0.83). Mean AUCs were 0.70 (CI:0.61,0.79)/0.68 (CI:0.59,0.77) (p = 0.43) and 0.80 (CI:0.71,0.88)/0.76 (CI:0.67,0.85) (p = 0.21). Kappa for PET/CT was 0.65 in pelvis and 0.77 in abdomen. Conclusions: Addition of PET to diagnostic CT resulted in statistically borderline increase in sensitivity to detect LN metastasis in abdomen. Clinical trial information: ACRIN6671G00233.

Phase II study of concurrent chemoradiotherapy with weekly CDDP/PTX in patients with locally advanced uterine cervical cancer: JACCCG-GY-01 trial. First Author: Munetaka Takekuma, Department of Gynecologic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Background: A multicenter phase II trial was conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with weekly CDDP/PTX in patients with locally advanced uterine cervical cancer. Methods: The patients with FIGO stages III-IVA uterine cervical cancer who had no para-aortic lymphadenopathy (> 10 mm) assessed by CT were enrolled. Patients received definitive radiotherapy (RT) consisting of external beam whole pelvic RT and HDR-ICBT. The cumulative linear quadratic equivalent dose (EQD2) was 62-65 Gy prescribed at point A. Cisplatin 30 mg/m2 and Paclitaxel 50 mg/m2 weekly was administered concurrently with RT for 5 courses. Results: Of the 70 patients registered, 68 were eligible. The Compete response rate was 76.5% (95%CI, 66.4% to 86.6%). With a median follow-up of 27 months(range: 7.9-33.5), the 2-year progression-free survival rate and pelvic disease progression-free rates were 83.8% (95% CI, 75.1% to 92.6%) and 89.6% (95% CI, 82.3% to 96.9%), respectively. The 2-year overall survival rate was 92.7% (95% CI, 86.4% to 98.9%). The 2-year cumulative late complication rates were 25% for all grades, 13.2% for grade 1, 5.9% for grade 2, 2.9% for grade 3, and 2.9% for grades 4. Conclusions: Concurrent chemoradiotherapy with weekly CDDP/PTX for locally advanced cervical cancer demonstrated favorable antitumor activity, and is feasible and safe with respect to the protocols-specified SAEs and AEs. Evaluation of this regimen in phase III trials is warranted. Clinical trial information: UMIN000002937.
Synergistic effects of cabozantinib to temozolomide and bevacizumab in patients with heavily pretreated relapsed uterine leiomyosarcoma.

First Author: Sayaka Ikeda, Tama-Hokubu Medical Center, Higashimurayama, Japan

Background: Although uterine leiomyosarcoma (ULMS) has been treated with Adriamycin, dacarbazine, ifosfamide, gemcitabine, docetaxel, et al, the effect is not satisfactory. We have reported the effect of temozolomide (T) combined with bevacizumab (B) in heavily pretreated relapsed ULMS (Ref.). In this study, we evaluated the effects of addition of cabozantinib (C) to T and B. Methods: From 2009 to 2014, total 20 patients (pts) with heavily pretreated relapsed ULMS were enrolled. Fourteen of 20 pts were treated with T (80mg/body/day, 3 week one week rest) and B (2mg/kg; days 1, 8 and 15, q4 weeks) (TB, n=14). Since 2013, C (140mg/body/week) was added to TB (TBC, n=6). Treatment was continued until disease progression and/or unmanageable toxicities. The clinical trial was stopped before end of recruitment for toxicity. Clinical trial information: NCT01397877.

Response to TB/TBC in heavily pretreated relapsed ULMS.

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</table>

Data were shown in Table. The response rate (RR) was 20% (4/20) with no difference seen with SD at 12 weeks. Intriguingly, when added C to TB, the effect was significantly reinforced, showing that two (33%) of 6 cases had CR, and the RR and CCR was 50% and 100%, respectively. Toxicity was mild and manageable. Conclusions: Addition of C to T and B in relapsed uterine leiomyosarcoma as shown in Table. These results warrant further prospective and randomized studies.

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Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer: An NRG Oncology Gynecologic Cancer Group study. First Author: Andrea P. Myers, Novartis Institutes of Biomedical Research, Cambridge, MA

Background: Rapamycin analogs have reproducible but modest efficacy in EC. Identification of molecular biomarkers that predict benefit from this class of agents could guide their clinical development. Methods: Fixed primary tumor and whole blood were collected prospectively from patients (pts) enrolled on GOG-248. DNA was isolated from macro-dissected tumors and blood; next-generation sequence analysis was performed on a panel of cancer related genes. Associations between clinical outcomes (Response rate (RR)); 20% overall and progression-free survival (PFS); median 4.9 months) and common mutations (PTEN, PIK3CA, PIK3R1, KRAS, CTNNB1) and other PI3K/mTOR relevant mutations (AKT1, TSC1, TSC2, NF1, FBXW7) were explored. Results: Sequencing data was obtained from tumors of 55 of the 73 enrolled pts. Mutation rates were consistent with published reports: mutations in PTEN (45%), PIK3CA (29%), PIK3R1 (24%), K-RAS (16%), CTNNB1 (18%) were common and mutations in AKT1 (4%), TSC1 (2%), TSC2 (2%), NF1 (9%) and FBXW7 (4%) were less common. Increased PFS (HR 0.16; 95% CI 0.01-0.78) and RR (response difference 0.83; 95% CI 0.30-0.99) were noted for AKT1 mutation. An increase in PFS (HR 0.46; 95% CI 0.20-0.97) but not RR (response difference 0.97; 95% CI 0.34-0.59) was noted for CTNNB1 mutation. There were no statistically significant associations between mutations in PIK3CA, PTEN, PIK3R1, or KRAS and PFS or RR. Six patients had PFS >15 months; of these, two had mutations in CTNNB1, and two had mutations in both CTNNB1 and AKT1. The pt with the longest PFS (on study over 46 cycles) had mutations of NF1, CTNNB1 and PIK3R1 in her tumor. Conclusions: Activating mutations in PI3K/AKT/mTOR pathway are rare in EC, but may predict clinical benefit from temsirolimus. Consistent with a recent report of an association of CTNNB1 mutation with RR in a study of everolimus and letrozole, CTNNB1 mutations were associated with longer PFS on temsirolimus. Studies to elucidate the relationship of the Wnt/β-catenin pathway target expression in endometrial cancers of women with Type II diabetes mellitus? First Author: Dario R. Roque, UNC Durham Division of Gynecologic Oncology, Durham, NC

Background: Metformin, has been found to decrease proliferation and inhibit downstream targets of the mTOR pathway in a phase 0 trial in endometrial cancer (EC) patients. Given this, we aimed to determine molecular differences between ECs from patients with Type II diabetes (T2DM) taking metformin versus those not on metformin. Methods: Patients with T2DM who underwent surgical staging for EC were divided into two cohorts based on whether or not they were on metformin. The use of insulin and other anti-diabetic agents was recorded. Tissue microarrays (triplepic cores) were constructed from formalin-fixed, paraffin-embedded hysterec- tomy specimens. Expression of the estrogen receptor (ER), progesterone receptor (PR), PTEN, LKB1, phosphorylated (p)-AKT, p-4EBP-1, p-S6, p-insulin growth factor-1 receptor (pIGF1R), p-insulin receptor substrate-1 (p-IRS1), PMAT, MATE1 and MATE2 was measured by immunohistochemistry. Results: Of 162 EC patients with T2DM, 102 (63%) were taking metformin and 60 (37%) were not on metformin. There was no significant difference in tumor stage, grade or histology between the two groups. Expression of transporters, hormone receptors, and mTOR pathway targets was similar between the two groups. However, when adjusting for age, BMI, race, tumor grade and stage, there was a trend towards decreased p-AKT expression in metformin users (0.7, 95% CI 0.41-1). In addition, BMI > 30 was associated with increased age (p=0.04, CI 1.2-6.7) and a trend towards higher p-4EBP-1 expression (2.0, 95% CI 1.0-4.1). Conclusions: We did not find a strong relationship between metformin use and transporters, hormone receptors or mTOR pathway targets in EC patients compared to T2DM. However, metformin use trended towards decreased p-AKT expression, which is consistent with its ability to inhibit the mTOR pathway. Obesity is known to activate the mTOR pathway, and was associated with increased expression of p-S6 and p-4EBP-1 in ECs. Further studies should focus on identifying molecular biomarkers in patients with T2DM that may predict response to metformin as an anti-tumorigenic agent.

5595 Poster Session (Board #151), Sat, 1:15 PM-4:45 PM
Onapristone (ONA) in progesterone receptor (PR)-expressing tumors: Efficacy and biomarker results of a dose-excitation phase 1 study. First Author: Patrick Cottu, Institut Gustave-Roussy, France

Background: ONA is a type I PR antagonist, which prevents PR-induced transcription. Immediate release (IR) 100 mg ONA was active in multiple preclinical models and in patients (pts) with breast cancer (BC). We conducted a phase I study of extended-released (ER) ONA to (i) determine a recommended dose and (ii) explore the role of transcriptionally-activated PR (APR), detected as an aggregated subnuclear distribution pattern, as a predictive immunohistochemi- cal (IHC) biomarker. Methods: An open-label, multicenter, randomized, parallel-group, phase 1 study (target n=48; NCT02052128) included female pts ≥18 years with PR+/tumors. APR analysis was performed on archival tumor tissue. Pts were randomized to 5 cohorts of ER ONA tablets 10-50 mg BID, or IR 100 mg QD until progressive disease or intolerability. This abstract reports the APR IHC analysis and clinical benefit (PR/SD≥4 wks). Results: Phase I is complete (n=52). Tumors (n): endometrial carcinoma (EC) 13; breast cancer (BC) 20; ovarian cancer (OC) 13; other 6. Median age was 66 (37-85). No dose limiting toxicity was observed with only transient liver function test elevation, mostly related to liver metastases. PR+/APR tumors (n/total) were: 11/50 BC 8/3, OC 5/1, and 2/0 and 8 pts (6 BC) had missing/non evaluable IHC. Median therapy duration was 8 wks (range 2-44), and 8 pts had clinical benefit ≥24 weeks (see Table). Conclusions: Clinical benefit was seen in heavily-pretreated pts with EC, OC, and BC. Data support ongoing ONA development at 50mg ER BID in APR+ uterine endometrioid endometrial cancer with clinical validation of the APR diagnostic. Meanwhile, further development of APR IHC is needed in OC and BC. Clinical trial information: NCT02052128.

Response and stable disease for ≥24 weeks.

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<th>Tumor type</th>
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<th>ER ONA dose</th>
<th>Response</th>
<th>% change</th>
<th>Dur (wks)</th>
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<tr>
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5598 Poster Session (Board #152), Sat, 1:15 PM-4:45 PM
Does metformin use affect transporter, hormone receptor and mTOR pathway target expression in endometrial cancers of women with Type II diabetes mellitus? First Author: Dario R. Roque, UNC Durham Division of Gynecologic Oncology, Durham, NC

Background: Metformin, has been found to decrease proliferation and inhibit downstream targets of the mTOR pathway in a phase 0 trial in endometrial cancer (EC) patients. Given this, we aimed to determine molecular differences between ECs from patients with Type II diabetes (T2DM) taking metformin versus those not on metformin. Methods: Patients with T2DM who underwent surgical staging for EC were divided into two cohorts based on whether or not they were on metformin. The use of insulin and other anti-diabetic agents was recorded. Tissue microarrays (triplepic cores) were constructed from formalin-fixed, paraffin-embedded hysterec- tomy specimens. Expression of the estrogen receptor (ER), progesterone receptor (PR), PTEN, LKB1, phosphorylated (p)-AKT, p-4EBP-1, p-S6, p-insulin growth factor-1 receptor (pIGF1R), p-insulin receptor substrate-1 (p-IRS1), PMAT, MATE1 and MATE2 was measured by immunohistochemistry. Results: Of 162 EC patients with T2DM, 102 (63%) were taking metformin and 60 (37%) were not on metformin. There was no significant difference in tumor stage, grade or histology between the two groups. Expression of transporters, hormone receptors, and mTOR pathway targets was similar between the two groups. However, when adjusting for age, BMI, race, tumor grade and stage, there was a trend towards decreased p-AKT expression in metformin users (0.7, 95% CI 0.41-1). In addition, BMI > 30 was associated with increased age (p=0.04, CI 1.2-6.7) and a trend towards higher p-4EBP-1 expression (2.0, 95% CI 1.0-4.1). Conclusions: We did not find a strong relationship between metformin use and transporters, hormone receptors or mTOR pathway targets in EC patients compared to T2DM. However, metformin use trended towards decreased p-AKT expression, which is consistent with its ability to inhibit the mTOR pathway. Obesity is known to activate the mTOR pathway, and was associated with increased expression of p-S6 and p-4EBP-1 in ECs. Further studies should focus on identifying molecular biomarkers in patients with T2DM that may predict response to metformin as an anti-tumorigenic agent.
Clinical outcomes in advanced cervical cancer (CC) and endometrial cancer (EC) patients treated in phase I trials of novel molecularly targeted agents (MTAs). First Author: Angela Jain, Fox Chase Cancer Center Ctr, Havertown, PA

Background: To investigate molecular imaging of cervix cancer with combined 3T PET-MRI in cervical cancer patients. Methods: Molecular imaging (3T PET-MRI) using multiple MRI techniques and PET tracers for an improved understanding of tumor biology and heterogeneity. Methods: Ten patients with cervix cancer scheduled for radiation therapy were included in this IRB-approved prospective study. All patients were examined with combined 3T MP PET-MRI. The MRI protocol consisted of a high-resolution T2-weighted, a diffusion-weighted and a T1-weighted sequence with fat-sat before and after the application of contrast agent. All patients underwent 18F-FDG/11F-FMISO PET/CT. PET was injected with approximately 330 MBq 18F-FDG and 11F-FMISO on different days and scanning was started 45 min after injection of 18F-FDG and 180 min after injection of 11F-FMISO. PET and MR image registrations were performed using Mirada RTx (Mirada Medical, Oxford, UK, ver. 1.4.0.23) software. 3T MP PET-MRI was assessed for tumor size, enhancement (EH)-kinetics, restricted diffusivity and 11F-FMISO-avidity. Results: Molecular imaging with 3T MP PET-MRI was successfully performed in all ten patients. Tumor volumes ranged from 6.2-4400 cc (median 129.5cc). All tumors demonstrated restricted diffusivity (mean 0.75 ± 10^-3 mm^2/sec). All tumors showed a strong initial EH and followed by either a wash-out (n = 6) or a plateau (n = 4). All tumors were highly 11F-FMISO-avid (SUVmax mean 17.3). None of the tumors were highly 18F-FDG-avid (SUVmax mean 3.3). In eight patients, 18F-FMISO PET identified 11F-FMISO-avid spots within the 18F-FDG-avid lesion, indicative of areas of tumor hypoxia. There was a weak correlation for tumor volume and 18F-FDG and 11F-FMISO SUVmax indicating that 1F-FMISO-avidity is independent of tumor volume. Conclusions: Molecular imaging with 3T MP PET-MRI in patients with cervix cancer is feasible with unique complementary information on tumor biology and heterogeneity. 3T MP PET-MRI can identify areas of tumor hypoxia, which are more resistant to radiation therapy and necessitate dose-escalation, and thus might improve therapy planning and assessment of treatment response.

Feasibility of a physical activity intervention for ethnically diverse endometrial cancer survivors. First Author: Amerigo Rossi, Long Island University - Brooklyn, Brooklyn, NY

Background: To determine the feasibility of a 12-week physical activity (PA) intervention guided by social cognitive theory for ethnically diverse endometrial cancer (EC) survivors and to evaluate whether such an intervention might improve PA behavior, physical function, waist circumference, and quality of life. Methods: Out of 119 potential participants contacted via telephone, 54 did not respond, 29 declined, and 6 expressed interest but did not complete EC with PR/SD > 40 (402 days) vs EC survivors with PD (174 days) and pts who did not start trial (178 days) (p < 0.0001). Treatments were well tolerated: of 169 toxicities - G1/2: 127 (69%); G3/4: 42 (25%). 27 (15%) PRs were observed in molecularly selected EC pts with PR/SD compared to the control. Furthermore, the results show promising effects that will need to be confirmed in a larger randomized control trial.

Clinical outcomes in advanced cervical cancer (CC) and endometrial cancer (EC) patients treated in phase I trials of novel molecularly targeted agents (MTAs). First Author: Angela Jain, Fox Chase Cancer Center Ctr, Havertown, PA

Background: To investigate molecular imaging of cervix cancer with combined 3T PET-MRI in cervical cancer patients. Methods: Molecular imaging (3T PET-MRI) using multiple MRI techniques and PET tracers for an improved understanding of tumor biology and heterogeneity. Methods: Ten patients with cervix cancer scheduled for radiation therapy were included in this IRB-approved prospective study. All patients were examined with combined 3T MP PET-MRI. The MRI protocol consisted of a high-resolution T2-weighted, a diffusion-weighted and a T1-weighted sequence with fat-sat before and after the application of contrast agent. All patients underwent 18F-FDG/11F-FMISO PET/CT. PET was injected with approximately 330 MBq 18F-FDG and 11F-FMISO on different days and scanning was started 45 min after injection of 18F-FDG and 180 min after injection of 11F-FMISO. PET and MR image registrations were performed using Mirada RTx (Mirada Medical, Oxford, UK, ver. 1.4.0.23) software. 3T MP PET-MRI was assessed for tumor size, enhancement (EH)-kinetics, restricted diffusivity and 11F-FMISO-avidity. Results: Molecular imaging with 3T MP PET-MRI was successfully performed in all ten patients. Tumor volumes ranged from 6.2-4400 cc (median 129.5cc). All tumors demonstrated restricted diffusivity (mean 0.75 ± 10^-3 mm^2/sec). All tumors showed a strong initial EH and followed by either a wash-out (n = 6) or a plateau (n = 4). All tumors were highly 11F-FMISO-avid (SUVmax mean 17.3). None of the tumors were highly 18F-FDG-avid (SUVmax mean 3.3). In eight patients, 18F-FMISO PET identified 11F-FMISO-avid spots within the 18F-FDG-avid lesion, indicative of areas of tumor hypoxia. There was a weak correlation for tumor volume and 18F-FDG and 11F-FMISO SUVmax indicating that 1F-FMISO-avidity is independent of tumor volume. Conclusions: Molecular imaging with 3T MP PET-MRI in patients with cervix cancer is feasible with unique complementary information on tumor biology and heterogeneity. 3T MP PET-MRI can identify areas of tumor hypoxia, which are more resistant to radiation therapy and necessitate dose-escalation, and thus might improve therapy planning and assessment of treatment response.

The use of adjuvant treatment in stage I endometrioid endometrial cancer in the National Cancer Database (NCDB). First Author: Angela Jain, Fox Chase Cancer Center Ctr, Havertown, PA

Background: Women with Stage I endometrioid endometrial carcinomas (EUC) tumors have excellent long term survival. Women may be offered adjuvant radiation if high-risk features are present in the resected tumor. Whole pelvic radiation (EBRT) or vaginal brachytherapy (VB) reduce local recurrence, but do not improve survival. GOG249 looked at the use of chemotherapy with VB in high-grade tumors (HTG). This is a retrospective study using the National Cancer Database to understand national trends in using surgery, radiation and chemotherapy in Stage I EEC. Methods: We identified women with EEC diagnosed between 1998 and 2012 and treated with surgery and/or chemotherapy and/or radiation using the National Cancer Database, with known grade status. Using Chi-squared tests and multivariate logistic regression, we analyzed pathologic stage of EC by age, grade, histology, facility type, race, payer status, income, location, Charlson score, year of diagnosis and facility location. Due to data availability, survival analysis was restricted to patients diagnosed between 2003 and 2007. We used Kaplan-Meier curves and proportional hazards regression to address overall survival in patients treated with adjuvant EBRT vs VB. Results: Among 241,350 patients identified, patients with HTG had decreased use of EBRT over time from 17% to 5%; the use of VB increased from 7% to 24% (p = 0.0001). There were no significant changes for the use of radiation in patients with low-grade tumors. Patients with age > 70 years were less likely to receive chemotherapy - PH chemotherapy > 0.05. Patients with low-grade tumors were less likely to receive chemotherapy (p = 0.0001). The use of chemotherapy in all patients increased from 1% to 14% over time. Multivariate analysis demonstrated that patients with HTG had 84% 5 year survival with VB vs 78% for patients receiving EBRT (HR 0.85 vs 1.16, p = 0.0001). In patients with low-grade tumors there was no advantage for the use of VB and EBRT decreased survival. The use of chemotherapy did not improve survival. Conclusions: The use of VB and chemotherapy has been increasing over time for patients with HTG. However, the use of chemotherapy may not improve survival in this highly curable population, while the use of EBRT is demonstrated to decrease survival.
Background: The poly (ADP-ribose) polymerase (PARP) family of proteins is a family of nuclear enzymes required for the repair of single-stranded DNA damage. Preclinical studies demonstrate that PARP inhibition (PARPi) not only augments the apoptotic response in cervical cancer cell lines, but also sensitizes cells to the effects of alkylating agents like cisplatin. Given the use of cisplatin and paclitaxel as primary treatment for advanced, recurrent or metastatic cervical cancer before the findings of the benefit of adding bevacizumab in GOG 240, we aimed to evaluate whether PARPi can enhance the chemotherapy effectiveness in the treatment of cervical cancer. Methods: Patient eligibility criteria: Females age ≥ 18 years with persistent or recurrent squamous or adenocarcinoma of the cervix with documented disease progression (disease not amenable to curative therapy). Patients were not required to have measurable disease; have had concurrent chemotherapy and radiation for management of their disease; and have adequate organ function. The trial is a standard 3+3 phase I dose escalation with patients receiving paclitaxel 175mg/m2 on day 1, cisplatin 50mg/m2 on day 2, and ABT-888 50mg po bid days 1-7 at dose level 1 and escalating by 50mg every dose level until dose level 8 at 400mg po bid days 1-7. Results: Thirty-seven patients were enrolled from 6/1/11-1/8/14, but only 34 are evaluable. Dose limiting toxicities (DLTs) were assessed during cycle 1 on each dose level of ABT-888 and the three DLTs were as follows: grade 4 dyspnea which was possibly related to the ABT-888 in dose level 2, grade 3 neutropenia > 3 weeks in dose level 4, and febrile neutropenia in dose level 8. Cycles were repeated every 21 days until disease progression. At all dose levels the response rate (complete and partial) (RR) was 34% (95%CI: 20-53%); at the maximum dose level the RR was 60% (95%CI: 23-88%). Translational studies evaluating defects in the Fanconi Anemia pathway are ongoing. Conclusions: PARPi plus chemotherapy appears to have significant clinical benefit in cervical cancer treatment and warrants further investigation with bevacizumab in a clinical trial. Clinical trial information: NCT#01281852.

Comprehensive genomic profiling (CGP) of cervical squamous cell carcinoma (cSCC) to identify targeted therapy options. First Author: Julia Andrea Elvin, Foundation Medicine, Inc., Cambridge, MA

Background: High risk HPV initiates neoplasia in cSCC and progression requires additional genomic alterations (GA). Treatment of localized cSCC is effective but the response to systemic therapy for metastatic disease is inadequate. CGP of 99 advanced stage cSCC was undertaken to identify GA associated with targeted therapeutic options relevant to the systemic treatment of cSCC. Methods: DNA was extracted from 99 FFPE cSCC clinical specimens. Hybridization capture libraries of 236 (FoundationOne, n = 66) or 305 (FoundationOne, n = 33) genes, plus select introns frequently rearranged in cancer were sequenced to high (> 45x0) uniform coverage. HPV16 and HPV 18 viral sequences were detected, but other hrHPVs were not assayed. All classes of genomic alterations (base subduals, small indels, rearrangements, and copy number alterations) were evaluated and reported. CGRA were defined as GA associated with on-label targeted therapies and targeted therapies in mechanism-driven clinical trials. Results: 99 samples (54% primary, 45% metastasis) from women (avg 47.7y) with predominantly advanced stage cSCC were profiled. 368 total GA were identified (3.7 GA per tumor) involving 80 different genes, of which 257 were CRGA (2.57 per tumor). 91% of cSCC cases featured 1 CRGA, including 67 (67%) cases with CRGA in the PI3K/Akt/mTOR pathway. The most common CRGAs observed were: PIK3CA (41%), ML2L2 (18%), PTEN (16%), STK11 (14%), FBXW7 (11%), FGFR3 (4%), ERBB2 (4%), FBXW7 (4%), Kras (4%). To date, we have identified high expression of TOP2A and TOPO1 in SCCC, which may explain the sensitivity to etoposide and topotecan, while low levels of ERCC1 raise concern for cisplatin resistance. Potential druggable mutations include AKT1, KRAS, PIK3CA, and TP53. We have identified one patient with a KRAS mutation treated with a MEK inhibitor who had a complete response and remains in remission at 12 months. Comprehensive genomic profiling (CGP) of cervical squamous cell carcinoma (cSCC) to identify targeted therapy options. First Author: Julia Andrea Elvin, Foundation Medicine, Inc., Cambridge, MA

Methods: DNA was extracted from 99 FFPE cSCC clinical specimens. Hybridization capture libraries of 236 (FoundationOne, n = 66) or 305 (FoundationOne, n = 33) genes, plus select introns frequently rearranged in cancer were sequenced to high (> 45x0) uniform coverage. HPV16 and HPV 18 viral sequences were detected, but other hrHPVs were not assayed. All classes of genomic alterations (base subduals, small indels, rearrangements, and copy number alterations) were evaluated and reported. CGRA were defined as GA associated with on-label targeted therapies and targeted therapies in mechanism-driven clinical trials. Results: 99 samples (54% primary, 45% metastasis) from women (avg 47.7y) with predominantly advanced stage cSCC were profiled. 368 total GA were identified (3.7 GA per tumor) involving 80 different genes, of which 257 were CRGA (2.57 per tumor). 91% of cSCC cases featured 1 CRGA, including 67 (67%) cases with CRGA in the PI3K/Akt/mTOR pathway. The most common CRGAs observed were: PIK3CA (41%), ML2L2 (18%), PTEN (16%), STK11 (14%), FBXW7 (11%), FGFR3 (4%), ERBB2 (4%), FBXW7 (4%), Kras (4%). To date, we have identified high expression of TOP2A and TOPO1 in SCCC, which may explain the sensitivity to etoposide and topotecan, while low levels of ERCC1 raise concern for cisplatin resistance. Potential druggable mutations include AKT1, KRAS, PIK3CA, and TP53. We have identified one patient with a KRAS mutation treated with a MEK inhibitor who had a complete response and remains in remission at 12 months.

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Impact of older age on chemotherapy toxicity and quality of life in women with advanced or recurrent cervical cancer: A NRG Oncology-GOG Ancillary Study. First Author: Emily Meichun Ko, University of Pennsylvania, Philadelphia, PA

Background: To evaluate chemotoxicity and quality of life (QOL) in older women undergoing treatment for recurrent and advanced cervical cancer within Gynecologic Oncology Group (GOG) phase III chemotherapy trials. Methods: 5 trials (GOG 110, 149, 169, 179, 204) were used to characterize chemotoxicity profiles by age. ‘Older’ was defined as age ≥ 65. Toxicity was based on GOG or ECOG scales. Concordant chemotherapy arms between trials were pooled: Cisplatin (C), cisplatin/ifosfamide (CI); cisplatin/topotecan (CT); cisplatin/paclitaxel (CP). Categorical variables were compared using the Pearson chi-square test. The Cox PH model was used to evaluate prognostic factors (at baseline or before a landmark) and to establish age-adjusted effects on survival. Poisson models of toxicity as a function of age were examined. Associations between age and QOL using Fact-G and Fact-Cx (GOG 169,179,204) were assessed with linear mixed models. Results: 1201 women were evaluated (C: 407; CI: 288; CT: 255; CP: 251). Median age was 65 (IQR 58–71) and 107 were age ≥ 65. Being older was associated with improved PFS for C (HR 0.99, 95%CI 0.98-1.00) and CT (HR 0.98, 95%CI 0.96-0.99); and improved OS in CP (HR 0.98, 95%CI 0.97-0.99) in adjusted models. The most frequent grade ≤ 3 toxicities in those age ≥ 65 were leukenopoenia (85% for CP; 80% for CI; 92% for CT), anemia (40% for CT) and thrombocytopenia (40% in CT). Neuprophathy and neurologic toxicity did not differ by age for any regimen. Grade ≥ 3 toxicities that differed significantly by age and were most frequent in older women included leukenopoenia (85%, p = 0.058) for CP; nausea-vomiting (30%, p = 0.03) and metabolic (25%, p = 0.04) for CT. However, age was not associated with overall toxicity for any regimen in the adjusted models. Toxicity did not confound age-dependent outcomes on PFS or OS. QOL did not differ by age group for any regimen. Conclusions: Older age was not associated with severe toxicity or poorer quality of life in women who underwent chemotherapy for advanced or recurrent cervical cancer in phase III National consortia trials. Older patients should be encouraged to participate in cervical cancer trials.

EUTROC PISARRO: A Phase Ib study combining APR-246 with standard chemotherapy in platinum sensitive relapsed high grade serous ovarian carcinoma (HGSOCS). First Author: Charles Gourley, University of Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom

Background: p53 mutations are associated with increased chemoresisistance. APR-246 is a small molecule that restores mutant p53 to wild type conformation and function (Lambert et al., Cancer Cell. 2009; 15(5):376-88). APR-246 also increases reactive oxygen species levels and ER stress; acts synergistically with DNA damaging drugs in vitro; resensitizes ovarian cancer cells to cisplatin and doxorubicin in vitro; and reduces glutathione levels thereby decreasing cellular drug efflux. APR-246 showed no end-organ toxicity in the non-clinical toxicity studies but Cm, related reversible CNS effects were identified. In a previous single agent dose finding study recommended phase II dose and safety profile was determined and signs of clinical activity and p53-dependent biological effects were observed in several patients (Lehmann et al., J Clin Oncol. 2012; 30(29):3633-9). As in animals dose limiting toxicity (DLT) was mainly Cm related reversible CNS effects. PK was linear and displayed no accumulation. APR-246 was concluded to have a safety and PK profile suitable for further development in combination with chemotherapeutic drugs. The rationale for this study was that p53 mutation occurs in > 97% of HGSOCS, thus identifying an appropriate study population for targeted therapy. Methods: Patients with relapsed platinum sensitive HGSOCS and positive p53 immunostaining were treated with APR-246 in combination with carboplatin AUC 5 and pegylated liposomal doxorubicin 30 mg/m2every 4 weeks for 6 cycles. APR-246 was dosed as a 6h IV infusion on 4 consecutive days; on day 4, chemotherapy was given concomitantly with APR-246. A 3+3 dose escalation design with 3 dose levels (35, 50 and 67.5 mg/kg) was used. Endpoints include determination of the appropriate combination APR-246 dose, safety, PK, pharmacodynamic, disease control and multiple translational readouts (transcriptomic and proteomic). Matched pre-treatment and on-treatment radiologically guided biopsies are mandatory. The first two dose cohorts have been recruited with one DLT (GI perforation) in cohort 2. Recruitment to cohort 3 commenced in December 2014. Clinical trial information: NCT02098343.

ENGOT-OV24-NSGO/AVANOVA: Niraparib versus bevacizumab-niraparib combination versus bevacizumab and niraparib as sequential therapy in women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer. First Author: Mansoor Raza Mirza, NSGO, Copenhagen University Hospital, Copenhagen, Denmark

Background: Multiple Phase 1 and 2 clinical studies of PARP inhibitors used as monotherapy to treat patients with recurrent ovarian cancer (ROC) suggest that the agents are active in this population and there is level one evidence that bevacizumab is beneficial in the same population. A phase two randomized study demonstrated that the addition of a PARP inhibitor to an anti-angiogenic drug cediranib improves Progression-free survival (PFS). Our aim is to compare tolerability and efficacy of niraparib alone versus niraparib-bevacizumab combination versus sequential bevacizumab and niraparib. Methods: The ENGOT-OV24-NSGO/AVANOVA study comprises of two parts. Part 1 is a classic phase 1 trial of niraparib and bevacizumab combination. Part 2 is a three-arm, open-label, phase II, 1:1:1 randomized study of niraparib and/or Niraparib-bevacizumab combination against bevacizumab followed by niraparib in women with platinum-sensitive ROC, BRCAmut and or high-grade serous/endometrioid carcinoma patients with platinum-sensitive ROC are eligible. Patients must have disease that is measurable according to RECIST or assessable according to the GCIG CA-125 criteria. Primary objective of phase 1 part is to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the Recommended Phase 2 Dose (RP2D) of bevacizumab-niraparib combination. Primary objective of phase 2 part is to provide clinical evidence of efficacy of bevacizumab- niraparib combination or sequential therapy or niraparib single agent treatment. Primary end-point is PFS. Secondary end-points include PFS in each group according to trial stratification factors; PFS comparison of sequential versus concomitant bevacizumab and Niraparib; Objective response rate; Disease control rate (DCR); Patient Reported Outcomes (PROs); Time to subsequent chemotherapy and survival. Study status: The study is activated and sites are invited to participate. ClinicalTrials.gov Identifier: NCT02354131. Clinical trial information: NCT02354131.

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Centrally randomized Phase II study of AZD1775 plus chemotherapy versus chemotherapy alone in patients with platinum-resistant TP53-mutated epithelial ovarian carcinoma (treatment breakpoint: RECIST v1.1). First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: WEE1 is a DNA damage cell-cycle checkpoint protein that inactivates cyclin-dependent kinase 1 (CDK2) and is overexpressed in a variety of malignancies. Pts with deficient p53 expression rely on the WEE1 kinase to arrest cell-cycle progression at the G2 checkpoint for DNA repair. AZD1775, a highly selective, adenosine-triphosphate (ATP) competitive, small-molecule inhibitor of the WEE1 kinase, is being developed for the treatment of advanced solid tumors with TP53-mutated malignancies. Inhibition of WEE1 allows CDCC2 phosphorylation and subsequent cell-cycle progression despite DNA damage. This G2 checkpoint abrogation thus sensitizes cells to cytotoxic agents. Preliminary efficacy data have been promising when AZD1775 is used in combination with chemotherapy. In this randomized, phase II trial in pts with platinum-resistant, TP53-mutated cancers, AZD1775 will be added to a standard chemotherapy regimen (paclitaxel, gemcitabine, or carboplatin), with the goal of improving efficacy when compared to chemotherapy alone. The primary endpoints are response rate (Part 1), and progression-free survival (Part 2).

Methods: In Part 1, up to 69 pts will be randomized to receive AZD1775 plus paclitaxel, gemcitabine or carboplatin (Arm A: AZD1775 175 mg PO BID Days 1, 2, 8, 9, 15, and 16 plus gemcitabine 1000 mg/m2 IV Days 1, 8, and 15; Arm B: AZD1775, 5 doses of 225 mg PO BID Days 1, 2, 8, 9, 10, and 15-17 plus paclitaxel 80 mg/m2 IV Days 1, 8, and 15; Arm C: AZD1775, 5 doses of 225 mg PO BID Days 1-3 plus carboplatin AUC 5 IV Day 1). In Part 2, up to 108 pts will be randomized 1:1 to the most efficacious AZD1775/chemotherapy combination identified in Part 1, or chemotherapy alone. Pts will be re-staged every 2 cycles and continue treatment until disease progression or unacceptable toxicity. Key eligibility includes: platinum-resistant TP53-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, measurable disease per RECIST v1.1, ECOG PS 0 or 1, QTC < 470 msec, and no known CNS disease. Treatment samples will be collected for evaluation of specific biomarkers. Clinical trial information: NCT02272790.

TPS5610 Poster Session (Board #165b), Sat, 1:15 PM-4:45 PM

The MILO (MEK inhibitor in low-grade serous ovarian cancer)/ENGOT-ov11 study: A multinational, randomized, open-label phase 3 study of binimetinib (MEK162) versus physician’s choice chemotherapy in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. First Author: Bradley J. Monk, University of Arizona Cancer Center and Creighton University School of Medicine at Dignity Health St. Joseph’s Hospital and Medical Center, Phoenix, AZ

Background: Low-grade serous (LGS) carcinomas of the ovary, fallopian tube and primary peritoneum are a unique subset of serous carcinomas for which chemotherapy remains the standard of care. With limited efficacy, KRAS or BRAF mutations, which activate the RAS/RAF/MAPK pathway, have been found in up to 40% of LGS carcinomas. Binimetinib is a potent inhibitor of MEK1/2, a key component of the RAS/RAF/MEK/ERK signaling pathway, is present in many LGS carcinomas. Binimetinib is being developed as a single-agent therapy for LGS ovarian cancer. In a Phase I study (NCT02149874), binimetinib showed activity in advanced LGS carcinomas of the ovary, fallopian tube, and primary peritoneum. Preliminary efficacy data have been promising when AZD1775 is used in combination with chemotherapy. In this randomized, phase II trial in pts with platinum-resistant, TP53-mutated cancers, AZD1775 will be added to a standard chemotherapy regimen (paclitaxel, gemcitabine, or carboplatin), with the goal of improving efficacy when compared to chemotherapy alone. The primary endpoints are response rate (Part 1), and progression-free survival (Part 2).

Methods: In Part 1, up to 69 pts will be randomized to receive AZD1775 plus paclitaxel, gemcitabine or carboplatin (Arm A: AZD1775 175 mg PO BID Days 1, 2, 8, 9, 15, and 16 plus gemcitabine 1000 mg/m2 IV Days 1, 8, and 15; Arm B: AZD1775, 5 doses of 225 mg PO BID Days 1, 2, 8, 9, 10, and 15-17 plus paclitaxel 80 mg/m2 IV Days 1, 8, and 15; Arm C: AZD1775, 5 doses of 225 mg PO BID Days 1-3 plus carboplatin AUC 5 IV Day 1). In Part 2, up to 108 pts will be randomized 1:1 to the most efficacious AZD1775/chemotherapy combination identified in Part 1, or chemotherapy alone. Pts will be re-staged every 2 cycles and continue treatment until disease progression or unacceptable toxicity. Key eligibility includes: platinum-resistant TP53-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, measurable disease per RECIST v1.1, ECOG PS 0 or 1, QTC < 470 msec, and no known CNS disease. Treatment samples will be collected for evaluation of specific biomarkers. Clinical trial information: NCT02272790.
TPS5612 Poster Session (Board #166b), Sat, 1:15 PM-4:45 PM
Open label phase II clinical trial of orteronel (TAK-700) in metastatic or advanced non-resectable granulosa cell ovarian tumors: The Greko II study—GETHI 2013-01. First Author: J.ª Rodriguez-Moreno, Centro Integral Oncológico Clara Campal, Madrid, Spain
Background: Granulosa-cell tumors (GCT) of the ovary are a rare entity characterized by presenting a punctual mutation at the FOXL2 gene 402C→G (C134W) in most cases. Such mutation is responsible for a disorganization and overstimulation of the steroidogenic pathway, that ultimately leads to hormone production. A prior trial by our group (Greko I trial-GETHI 2011-03; NCT01384297) showed promising activity of ketoconazole, a CYP17 inhibitor used to control steroidogenesis in several conditions. Thus, we aim to assess the activity of Orteronel (TAK700), a selective inhibitor of 17, 20-lyase, in GCT. Methods: An open-label phase II single arm clinical trial has been designed for women with metastatic or locally advanced non-resectable granulosa cell ovarian tumor that harbors the somatic mutation FOXL2 402C→G (C134W) and who have not received prior treatment with any CYP17 inhibitor. Treatment will consist on Orteronel 300mg BID, given orally, continuously in a 28-day treatment cycle. The primary objective is clinical benefit rate; secondary objectives are response rate, progression free and overall survival, assessment of the impact of Orteronel in reducing hormonal overproduction and toxicity. Sample size calculation is based on a two stage Simon’s design that will lead to enroll 12 evaluable participants in stage one and 4 participants in stage two if one or more participants achieved a CR, PR or stable disease longer than 6 months. 16 subjects will allow a 80% power to differentiate between a 5% and a 25% clinical benefit rate. Probability of early termination of the trial is .54. 20% of losses have been assumed thus 20 patients will be enrolled in 9 spanish institutions (members of the Spanish Group for Research in Orphan and Unfrequent Tumors-GETHI). Key inclusion criteria are histological diagnosis of GCT, advanced disease (meseasurable or evaluable by RECIST), availability of biopsy material for centralized pathologist review and assessment of the FOXL2 mutation. Key exclusion criteria is prior therapy with orteronel, ketoconazole, abiraterone, aminoglutethimide or enzalutamide. Two patients have already been included. Clinical trial information: NCT02101684.

TPS5614 Poster Session (Board #167b), Sat, 1:15 PM-4:45 PM
Targeting VEGFR resistance through HIF-1α suppression: Phase II clinical trial evaluating CRLX101 as monotherapy and in combination with bevacizu- mab in recurrent platinum resistant ovarian cancer. First Author: Carolyn N. Krasner, Massachusetts General Hospital, Boston, MA
Background: Ovarian cancer (Ov.Ca.) is the leading cause of death among gyn malignancies. Limited treatment options exist for women whose tumors have become platinum resistant. Hypoxia Inducible Factor-1α (HIF-1α) is a master regulator of key cancer cell survival pathways and facilitates resistance to anti-angiogenic therapies. CRLX101, a novel nanoparticle-drug conjugate that differentially delivers camptothecin into cancer cells, durably suppresses HIF-1α and the combination of CRLX101 with anti-angiogenic drugs incl. bevacizumab (Avastin, Genentech/Roche)(BEV) achieves notable drug-drug synergy in pre-clinical models. Phase 2 monotherapy results achieved with CRLX101 and presented at ASCO 2014 exceeded expectations in this setting and established the basis for this follow-on study. Methods: This phase 2 open label, two-stage clinical trial evaluates the combination of CRLX101 plus BEV in pts. with epithelial ovarian, tubal or primary peritoneal cancer progressing through prior platinum-containing chemotherapy. Eligible pts. must have platinum-resistant measurable disease and may have received 1 or 2 prior regimens of chemotherapy that includes no prior topo-1 inhibitors or BEV. Pts. receive CRLX101 15 mg/m2 IV plus BEV 10 mg/kg IV on days 1 and 15 of their 28-day cycles. All pts. undergo CT-based tumor evaluations every 2 cycles. The primary endpoint is progression free survival (PFS) at 6 months (PFS6) and secondary objectives include response rate and assessment of toxicity. A 2-stage design is being employed with the study terminated if ≥ 1/2 stage 1 pts. achieve the PFS6 endpoint. As this gate has now been met, a 2nd stage will enroll 25 additional pts. and the treatment will be considered worthy of further investigation if ≥ 8/13 total pts. achieve PFS6. Enrollment is ongoing and to-date the drug appears well tolerated with no drug-related SAEs, treatment discontinuations, or deaths observed. Clinical trial information: NCT01652079.

TPS5613 Poster Session (Board #167a), Sat, 1:15 PM-4:45 PM
A randomized, placebo-controlled phase II trial comparing gecmbaicine monotherapy to gemcitabine in combination with AZD 1775 (MK 1775) in women with recurrent epithelial ovarian, fallopian tube, or Fallopian tube cancers: Trial of Princess Margaret, Mayo, Chicago, and California consortia. First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada
Background: Platinum resistant ovarian cancer (OC) remains a therapeutic challenge. The majority of high grade serous OC (HGSOCC) harbor TP53 mutations leading to increased dependency on S- and G2-phase checkpoints. Wee1 inhibition with AZD 1775 (MK 1775) induces G2 checkpoint escape. Gecmbaicine is an antimalbolite therapy that kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S phase boundary. Preclinical data have shown that the addition of AZD 1775 to gecmbaicine increased activity in platinum resistant OC cell lines and xenograft models. We propose to evaluate the combination of gecmbaicine/AZD 1775 in patients (pts) with platinum resistant OC. Methods: A multicenter 2:1 randomized phase 2 trial was designed to evaluate the progression free survival (PFS) of subjects with recurrent platinum-resistant/refractory OC receiving gecmbaicine in combination with AZD 1775 compared to subjects receiving gecmbaicine in combination with placebo (NCT02151292). Eligibility requires measurable disease with progression and disease amenable to a paired biopsy for correlative analyses. There is no limitation in the number of prior lines of therapy, but pts with prior gecmbaicine are excluded. All histologic subtypes are eligible, but only pts with HGSOCC are considered for the statistical analysis. AZD 1775/Placebo is given orally at 175mg on D1-2, D8-9 and D15-16 with gecmbaicine 1000mg/m2 IV D1, D8 and D15 in a 28-day cycle until progression or unacceptable AE. The primary objective is an improvement in median PFS (from 3.5 to 7 months). Integrated biomarkers will evaluate loss-of-function TP53 mutations by three complementary methodologies: Sanger sequencing, TAm-Seq and IHC as potential predictive factors of benefit to AZD 1775 and gecmbaicine. The concordance of TP53 mutations in tumor specimens is also determined and followed by TAm-Seq in ctDNA. Current status: This trial was activated in Sept 2014. A total of 10 pts with a median age of 66 are enrolled, all HGSOCC. Clinical trial information: NCT02151292.
PFS and OS. A Simon 2-stage design includes 10 patients in the first stage.

or intolerability. The primary endpoint is objective response rate by RECIST pattern. Pts are treated with ONA 50 mg ER BID until progressive disease PRpos by IHC and APR positivity as interpreted by trained pathologists. PR positivity is defined as central lab using a technically-validated procedure, then centrally inter-

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Phase III randomized trial of standard fractionation radiotherapy (SFX) with concurrent cisplatin (CIS) versus accelerated fractionation radiotherapy (AFRT) with paclitaxel (Pmab) in patients (pts) with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCN): NCIC Clinical Trials Group HN.6 trial. First Author: Lillian L. Siu, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Concurrent administration of anti-EGFR monoclonal antibody with radiotherapy (RT) increases survival compared to RT alone in pts with LA-SCCN. No prospective data are available comparing biologic radiotherapy to standard chemoradiotherapy (CRT) in these pts. Methods: 213 pts with stage T4-5 N0-2 M0, 43% HPV+ were randomized to: 1) SFX: 70 Gy/35/7 wks or 2) AFRT: 70 Gy/35/6 wks plus CIS 100 mg/m² intravenously (IV) on days 1 and 7 and Arm A versus AFRT (70Gy/35 over 6 weeks) plus the anti-EGFR monoclonal antibody Pmab at 9 mg/kg IV for 3 doses on weeks 1, 4 and 7 (Arm A) or AFRT (70Gy/35 over 6 weeks) plus CIS 100 mg/m² IV intravenously for 3 doses on weeks 1, 4 and 7 (Arm B). Primary endpoint was progression-free survival (PFS). A total of 320 patients were accrued from 1/2008 to 11/2011 with a median follow-up of 46.4 months (range: 0.1-64.3). Due to an observed declining event rate, the protocol was amended to analyze data with a clinical cut-off date of October 31, 2014. Results: Of 320 pts randomized, 5 did not receive protocol treatment, 156 received Arm A and 159 Arm B. Demographics: median age = 56 (range 35-80); male = 84%; ECOG 0.1% (71.29% primary site: oropharynx (81%), larynx (11%), hypopharynx (6%), oral cavity (2%); smoking history > 10 pack-years (58%). Of 259 oropharynx pts p16 status was known in 217 (84%), with 176 (81%) p16+ (95% CI: 65-79%) in Arm A and 88% (95% CI: 6-1.5; p = 0.83). Upper bound of HR’s 95% CI exceeded the pre-specified non-inferiority margin. Two-year OS was 85% (95% CI: 78-90%) in Arm A and 88% (95% CI: 82-93%) in Arm B, HR = 0.89; 95% CI: 0.54-1.48; p = 0.66. By multivariable analysis, anatomic location, ECOG PS, p16 status, and T category were significant predictors of PFS (p < 0.05). Incidence of any > grade 3 non-hematologic adverse event (AE) was 88% in Arm A and 91% in Arm B (p = 0.25). QOL is reported separately. Conclusion: With a median follow-up of 46.4 months, PFS in PMab-AFRT was not superior to CIS+SFX in LA-SCCN and non-inferiority was not proven. Clinical trial information: NCT00820248.

Long-term results of GORTEC 2000-01: A multicentric randomized phase III trial of induction chemotherapy with cisplatin plus 5-fluorouracil, with or without docetaxel, for larynx preservation. First Author: Guillaume Janary, Centre Hospitalier et Régional Universitaire, HEN S. Kaplan Center, Clinique d’Oncoologie et de Radiothérapie, Tours, France

Background: To compare the long-term efficacy and safety of induction chemotherapy with cisplatin (P) and 5-fluorouracil (F) with or without docetaxel (T) for larynx preservation. Methods: Operable patients with untreated stage III or - IV larynx or hypopharynx invasive squamous-cell carcinoma and who required a total laryngectomy were randomly assigned to receive three cycles of induction chemotherapy with either TPF or PF, followed by radiation therapy for responders. The primary endpoint was 3-year larynx-preservation rate. Secondary endpoints included larynx dysfunction-free survival (LDFFS), overall survival, disease-free survival, locoregional control rate, cause of death, and last toxicity rates. Results: Two hundred and thirteen patients were treated with a median follow-up for surviving patients of 105 months. The 5- and 10-year larynx-preservation rates were, 74.0% (95%CI; 0.64–0.82) vs. 58.1% (95%CI; 0.47–0.68) and 70.3% (95%CI; 0.58–0.8) vs. 66.5% (95%CI; 0.31–0.63, p = 0.01) in TPF versus PF arm, respectively. The 5- and 10-year LDFFS rates were 67.2% (95%CI; 0.57–0.7) vs. 46.5% (95%CI; 0.36–0.57) and 63.7% (95%CI; 0.52–0.74) vs. 37.2% (95%CI; 0.24–0.52, p = 0.001), respectively. Overall survival, disease-free survival, and locoregional control rates were not statistically improved in the TPF vs. PF arm. Significantly fewer grade 3–4 late toxicities of the larynx occurred with the TPF regimen compared to the PF arm (9.3% vs. 17.1%, g-test, p = 0.038). Conclusions: Long-term follow-up confirms that induction chemotherapy with TPF increased larynx-preservation and larynx dysfunction-free survival. In this larynx preservation approach using induction chemotherapy, TPF should be recommended, followed by radiation therapy. Clinical trial information: NCT00169182.

The effect of age on outcome in prospectiva, phase III NRG Oncology/RTOG trials of radiotherapy (XRT) +/- chemotherapy in locally advanced (LA) head and neck cancer (HNC). First Author: Julie Ann Kish, Moffitt Cancer Center, Tampa, FL

Background: The effect of advanced age on outcome for single agent XRT and combined modality therapy in LA-HNC is not well defined. Methods: The effect of age (< vs > 70 yrs) on outcome and toxicity was examined in LA-HNC patients (pts) on RTOG 0129, RTOG 0522, and RTOG 0522, which compared 3 altered fractionation (fx) XRT schedules versus standard daily XRT (SFX); RTOG 0129 comparing concurrent SFX + cisplatin (DDP) to accelerated fx with concomitant boost XRT (AFX+C) and DDP; and RTOG 0522, testing AFX+C vs combined DDP and cisplatin (C-TPF). Results: Secondary analysis included 2,688 pts. Median follow-up for surviving pts was 5.2 years (range 0.01 to 20.3) overall, 14.1 yrs in RTOG 9003, 7.9 years in RTOG 0129, and 4.5 years in RTOG 0522. Pts age > 70 were more likely to be female with poorer PS, heavier smoking history and pt16 (-) status (p < 0.001 each). Adjusting for covariates, patients age > 70 had worse survival regardless of smoking or p16 status. Adverse effect of patients age > 70 may have been worse in pt16 (+) pts (HR 2.07 vs. 1.30; interaction p = 0.09), (n = 34). Maximum grade stomatitis and other toxicities were similar by age cohort and tx modality. Results: Survival results are excellent and distant failure is very uncommon. Formal comparison with historical data within risk groups and predictive biomarker analysis are ongoing. Clinical trial information: NCT01154860.
A prospective phase II trial of de-intensified chemoradiotherapy for low-risk HPV-associated oropharyngeal squamous cell carcinoma. First Author: Bhaskaraj Shivalingappa S. Chera, UNC Chapel Hill, NC.

**Background:** This is a prospective multi-institutional phase II study of a substantial decrease in chemoradiotherapy (CRT) intensity as concurrent primary treatment for favorable risk oropharyngeal squamous cell carcinoma. **Methods:** The major inclusion criteria were: 1) T0-T3, N0-N2c, M0, 2) HPV or p16 positive, and 3) ≤ 10 pack-years smoking history. Treatment was limited to 60 Gy Intensity Modulated Radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m²). The primary study endpoint was pathologic complete response rate (pCR) based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Power calculations were performed for the null hypothesis that the pCR rate is 87% and N = 40 (type I error = 14.2%, power = 95%, 95% CI = 87% to 90%). Concomitant cisplatin chemotherapy (CTCAE), participant reported symptoms (PRO-CTCAE), quality of life (EORTC QLQ-C30 & H&N35), and penetration aspiration scale (PAS) scores for modified barium swallow studies. Results: The study population was 43 patients. The pCR rate was 86% (37/43). Median time to biopsy/necropsy dissection was 9 weeks (7 - 14 weeks). All 6 non-pCR cases were limited to microscopic foci of residual cancer: 1 primary site, 5 nodal. All patients are alive with no evidence of disease (median follow-up 15 months, 4 - 31 months). Incidence of CTCAE acute Grade 3 toxicity and CTCAE severe/very severe symptoms were: mucositis 34%/45%, pain 5%/48%, nausea 18%/52%, vomiting 5%/34%, dyspnea 39%/35% and xerostomia 2%/75%. Grade 3/4 hematological toxicities were 11%. 39% required a feeding tube, for a median of 15 weeks (5 - 22 weeks). Mean pre- and post-CRT EORTC QOL scores were: Global 80/69 (lower worse, p < 0.01), Pain 15/20 (higher worse, p < 0.001), Swallowing 11/18 (p = 0.04), Cognitive Function 70/48 (p < 0.001), and Sticker/Fatigue 69/25 (p < 0.001). For Saliva 6/49 (p = 0.04). There were no significant differences in PAS scores before and after CRT. Conclusions: Cancer control following 60 Gy of IMRT with weekly cisplatin 30 mg/m² is likely to be very high in favorable risk oropharyngeal squamous cell carcinoma. (ClinicalTrials.gov, NCT01530997). Clinical trial information: NCT01530997.

**Mutational patterns of HPV+ and HPV- squamous cell carcinomas of the head and neck (SCCHN) and their interference with outcome after adjuvant chemoradiation: A multicenter biomarker study of the German Cancer Consortium Radiation Oncology Group. First Author: Inge Tinhofer, Dpts. for Radiation Oncology, Comprehensive Cancer Center, Charite University Medicine Berlin, Berlin, Germany.

**Background:** The genetic landscape of SCCHN is currently being unravelled, but the role of distinct mutations for treatment outcome remains largely unknown. We compared mutational patterns of HPV+ and HPV- tumors with outcome after uniform chemoradiation. **Methods:** Archival tumor specimens from 208 patients with carcinomas of the hypopharynx, oropharynx or oral cavity, all uniformly treated with surgery and adjuvant radiochemotherapy, were included in this study. An in-house gene panel for semiconductor-based next-generation ultra-deep sequencing, covering 211 exons from 45 genes frequently altered in SCCHN was used for mutational analysis. Genetic alterations were correlated with HPV status and patient outcome. Results: Mutational profiles were successfully established for 185 SCCHN cases. Interestingly, HPV+ carcinomas were significantly enriched for activating mutations in driver genes (PIK3CA 27%, ERBB2 4%, AR 3%, BRAF 6%) compared to HPV- cases (P = 0.002). Conversely, HPV- tumors showed an increased frequency of loss-of-function alterations in tumor suppressor genes (TP53 67%, CDKN2A 30%, PTEN 4%, SMAD4 3%) compared to HPV+ cases (P < 0.001). After a median follow-up of 55 months, alterations in tumor suppressor genes significantly increased recurrence and death (HR 2.9, 95% CI 1.5-5.8, P = 0.001), locoregional recurrence (HR 5.4, 95% CI 1.6-18.1, P = 0.006) and distant metastasis (HR 2.3, 95% CI 1.0-5.1, P = 0.04). The occurrence of activating driver gene mutations did not influence outcome in the total cohort of patients; however, they were associated per trend with increased risk of locoregional recurrence and death (HR 3.7, 95% CI 0.7-20.6, P = 0.12) in HPV+ oropharyngeal carcinomas. Conclusions: Overall, loss-of-function tumor suppressor gene mutations negatively interfere with efficacy of adjuvant cisplatin-based chemoradiation, whereas activating driver gene mutations define poor risk specifically in HPV-driven SCCHN. These genes and their signaling pathways might represent therapeutic targets for improving the rates of SCCHN.
PET-NECK: A multi-centre, randomized, phase III, controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT). First Author: Hisham Mohamed Mehmanna, InHANSE, School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom

Background: Planned ND after radical CRT for LANM remains controversial. 30% of ND specimens show histological evidence of tumour, albeit tumour viability cannot be confirmed. Consequently, many clinicians still practice planned ND. PETCT demonstrated high negative predictive values for persistent nodal disease, providing a possible alternative paradigm to ND. This study aimed to determine the efficacy and cost-effectiveness of PETCT guided surveillance, compared to planned ND, in a multicentre randomised setting.

Methods: Eligibility: Patients with LANM of oro-, hypo-, pharynx, larynx, oral or occult HNSCC receiving CRT and fit for ND. Randomisation (1:1): to planned ND before or after CRT (control), or CRT followed by FDG-PETCT 10-12 weeks post CRT with ND only if PETCT showed incomplete or equivocal response of nodal disease (intervention). Balanced by centre, planned ND timing, CRT schedule, disease site, T / N stage. Primary outcome: Overall Survival (OS), minimum follow-up 2 years. Analysis: 560 patients needed to detect non-inferior OS in the intervention arm with 80% power, Type I error 5%, defining non-inferiority as having a hazard ratio (HR) no higher than 1.50. Intention to treat analysis was performed with Cox proportional hazards model. Results: 564 patients recruited (282 ND arm, 282 surveillance arm; 17% N2a, 61% N2b, 18% N2c, 3% N3). 84% had oropharyngeal cancer. 75% of tested cases were p16+ve. Median follow-up 36 months. The HR for OS was 0.92 (95% CI: 0.65, 1.32) indicating non-inferiority. HR margin of 1.50 lies at the 99.6 percentile of this estimate, p = 0.004. There were no differences by p16 status. There were 54 NDs performed in the surveillance arm with 22 surgical complications; 221 NDs in the ND arm with 85 complications. Conclusions: PETCT guided active surveillance showed similar survival outcomes to ND arm, but resulted in considerably fewer NDs, and fewer complications, supporting its use in routine practice. Clinical trial information: NCT00720070.

LBA6008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. First Author: Tanguy Y. Seiwert, The University of Chicago, Chicago, IL

Methods: Patients with locally advanced head and neck squamous cell cancer treated with pembrolizumab (pemb) were eligible, except if disease had progressed during prior CRT. Pts were included if pemb was a last-line therapy. CT scans were performed every 2 months or if clinical progression was suspected. Safety was assessed by collecting adverse events (AEs) and lab abnormalities according to NCICTC version 4.0. Efficacy was evaluated by RECIST v1.1 and measured from first pemb exposure. Patients were followed for OS and PFS. Results: 142 pts were treated with pemb and 135 had data for efficacy and safety analysis. Median age was 61 years; 116 were male; 65% were never-smokers; 54% had stage IVb disease; 25% had advanced HPV-positive disease. 129 pts (90%) received pemb at 200 mg IV Q2W, 3 pts received pemb at 100 mg IV Q3W. Median number of pemb cycles was 5 for all pts; 8 for HPV-negative pts. 53% of pts had grade 3 or 4 AEs, with most common being fatigue (38%), respiratory infection (27%), and diarrhea (23%). Safety was similar across pts with HPV-positive and HPV-negative disease. Efficacy was assessed in 135 pts; ORR was 7% (95% CI 3-12%, 40% complete responders), and median PFS was 1.7 months (95% CI 1.6-1.9, HR 1.25, 95% CI 1.00-1.56, p = 0.051). Median OS was 11.5 months (95% CI 9.0-15.0). Conclusions: Pembrolizumab treatment was generally well-tolerated. ORR and PFS rates were modest in a heavily pretreated, advanced SCCHN population. Longer follow-up and additional endpoints (PFS, OS) will be reported.

LBA6010 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM
Is PET-CT guided management for patients with locally advanced head and neck squamous cell cancer (HNSCC) cost-effective? Results from a UK non-inferiority phase III randomised trial. First Author: Alison Florence Smith, University of Leeds, Leeds, United Kingdom

Title: Despite ongoing controversy, planned node dissection (ND) remains a common treatment strategy after radical chemoradiotherapy (CRT) for locally advanced nodal metastases in patients with HNSCC. Accurate detection of persistent disease using combined Positron Emission and Computed Tomography (PET-CT) could reduce unnecessary and expensive node dissections (ND) in low-risk patients and potentially improve overall outcomes. Methods: 564 patients with N2/N3 oropharyngeal, laryngeal, oral, hypopharyngeal or occult HNSCC were randomized (1:1) to receive either planned ND (before or after CRT), or PET-CT surveillance (CRT followed by PET-CT, with ND administered if incomplete response in the neck nodes). To accurately inform reimbursement decisions, individual patient data from the trial was used to assess within-trial (2-year) cost-effectiveness of PET-CT surveillance versus planned ND from an NHS secondary care perspective. Health benefit was measured using quality-adjusted life-years (QALYs) and costs are reported in 2015 GBP. Probabilistic analysis was conducted using bootstrap methods. Results: PET-CT surveillance was cost-effective over the trial period, producing an average per-person cost saving of £1,415 (95% CI: -607 to -2,218) and a health gain of 0.07 QALYs (95% CI: -0.04 to 0.19) compared to planned ND. The average cost was £12,127 (95% CI: 11,601 to 12,686) for PET-CT surveillance vs. £13,542 (95% CI: 12,968 to 14,131) for planned ND; the average QALYs were 1.26 (95% CI: 1.18 to 1.34) vs. 1.19 (95% CI: 1.10 to 1.27). At a £20,000 per QALY threshold, the probability that PET-CT was the cheapest, most effective and most cost-effective strategy was 99%, 91%, and 98%, respectively. Expanding the analysis to include additional NHS, personal social services and societal costs increased the expected costs for each arm but did not alter the overall cost-effectiveness of PET-CT surveillance. Conclusions: Results of the economic evaluation indicate that PET-CT surveillance is cost-effective over a short time horizon. Clinical trial information: NCT00720070.

6011 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM
Establishing quality indicators for neck dissection: Correlating the number of lymph nodes with oncologic outcomes. NRG Oncology/RTOG 9501-0234. First Author: Vasu Divi, Stanford University, Palo Alto, CA

Background: Quality of head and neck surgery has thus far focused on adherence to clinical national guidelines and margin status. For other solid tumors, an association has been found between lymph node counts from regional nodal dissection and overall survival; as such, lymph node counts have been proposed as measure of quality. Yet, for neck dissection, no prospective metrics for surgical quality have been established for mucosal squamous cell carcinoma. The purpose of this study is to investigate the association between lymph node counts from primary neck dissection, local-regional recurrence, and overall survival (OS). Methods: Secondary analysis of patients in RTOG trials 9501 and 0234 was performed. The number of lymph nodes counted from regional nodal dissection was evaluated for its prognostic impact on overall survival using a multivariate Cox model adjusted for demographic, tumor, and lymph node data, and stratified by postoperative treatment group: (1) radiation or (2) chemoradiation on RTROG 9501 or (3) chemoradiation and cetuximab on RTROG 0234. Models were compared by Akaike Information Criterion (AIC). Results: Five hundred and seventy-two patients were analyzed. Median follow-up for surviving patients was eight years. Median number of lymph nodes recorded on the left and right sides were 24 and 25. Fewer than 18 nodes was associated with significantly worse OS relative to > 18 nodes (hazard ratio 1.38, 95% CI 1.09-1.74, p = 0.007). The model with this cut point had the lowest AIC of all possible models. This cut point was driven by local-regional failure (HR 1.46, 95% CI 1.02-2.08, p = 0.04) but not distant metastasis (HR 1.08, 95% CI 0.77-1.53, p = 0.65). Limited to RTOG 0234, adding p16 status to the model does not affect the hazard ratio for sampled nodes and the effect of nodes is not different by p16 status (p-value for interaction 0.99). Conclusions: Identifying 18 or more lymph nodes was associated with improved overall survival and lower rates of local-regional failure. The benefit is seen in both p16-positive and p16-negative patients. The removal and identification of at least 18 lymph nodes should be considered as a measure of quality in neck dissections for mucosal squamous cell carcinoma.
Background: Cabo inhibits tyrosine kinases including MET, VEGFR2, and RET. EXAM, a randomized double-blind placebo-controlled study in patients (pts) with progressive, locally advanced, or metastatic thyroid cancer (MTC) patients with documented RECIST progression at baseline. First Author: Martin Schlumberger, Institut Gustave Roussy, Villejuif, France

Methods: Eligible pts were randomized 2:1 to receive Cabo (140 mg qd) or placebo (PBO). Preliminary analyses of levels of VEGF and FGF23 may indicate that Cabo is targeting these signaling networks in pts with RR-DTC in SELECT. Preliminary analyses of levels of FGF23, C2D1, and sTie2 were performed. CAFs were assessed at baseline, cycle 1 day 15 (C1D15), day 1 of subsequent cycles, and treatment end. TG and CAF levels (Ang2, VEGF, sTie2, and FGF23) were measured by ELISA.

Results: At the final analysis, median follow-up time was 52.4 mo. 218 events were recorded in the intent-to-treat (ITT) population (N = 330). The estimated median OS was 26.6 mo for Cabo vs 21.1 mo for P (stratified HR = 0.85; 95% CI 0.64–1.12; p = 0.241). For 126 pts with known RET M918T mutations, median OS was 44.3 mo for Cabo vs 18.9 mo for P (HR = 0.60, p = 0.026). 32% of Cabo-treated pts remained on treatment for over 1 year and 2 years, and 10% and 18% for P, respectively. The most common serious adverse events (>2%) on Cabo were pulmonary embolism (3.3%), mucosal inflammation (2.8%), hypocalcemia (2.8%), hypertension, dyspnea, dehydration, and lung abscess (2.3% each). Conclusions: The secondary endpoint of improved OS was not met, with a median OS 5.5 mo longer with Cabo compared to P that did not reach significance. OS for Cabo was consistently higher than for P throughout treatment. Median OS of 44.3 mo for Cabo was superior to the median of 18.9 mo for P in patients with RET M918T mutations, with a 25.4-mo increase in median OS compared to P. The safety profile of Cabo remained consistent with long-term exposure. Clinical trial information: NCT00704730.

6014 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Pharmacodynamic biomarkers of outcomes in the phase III study of lenvatinib in 131I-refractory differentiated thyroid cancer (SELECT). First Author: Makoto Tahara, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Methods: Blood samples from 387/392 (99%) randomized patients (pts) were collected at baseline, cycle 1 day 15 (C1D15), day 1 of subsequent cycles, and treatment end. TG and CAF levels (Ang2, VEGF, sTie2, and FGF23) were measured by ELISA. Results: From cycle 1, VEGF levels were consistently elevated for pts on LEN, whereas Ang2 and sTie2 levels were consistently decreased compared with PBO. FGFR3 levels increased (15.8% C1D15 and 28.6% C2D1). Although TG decreases in LEN pts were correlated with tumor shrinkage (TS; P < 0.0001) and objective response rate (ORR; P < 0.05, through C9D9), TG decreases also occurred in pts with stable or progressive disease. Increased VEGF (P < 0.0001) and decreased Ang2 (P < 0.0001) and sTie2 (P < 0.0001) levels were associated with ORR. Amongst LEN-treated pts with disease progression, decreased levels of TG (31/34 pts, P < 0.0001), Ang2 (32/38 pts, P < 0.0001), and sTie2 (39/42 pts, P < 0.0001) at C2D1 compared to BL were observed. However, at treatment end, increased levels of TG, Ang2, and sTie2 from C2D1 were observed in 79.4%, 78.9%, and 81.0% of these pts, respectively. In some cases, these increases occurred prior to disease progression. Conclusions: TG changes were correlated with TS and ORR in the LEN arm of SELECT; CAF analyses may provide additional information. Increased levels of VEGF and FGFR3 may indicate that LEN is targeting these signaling networks in pts with RR-DTC in SELECT. Preliminary analyses of pts who progressed on LEN included elevated levels of Ang2 and sTie2. Further analyses of the Ang2/sTie2 axis using serum biomarkers are warranted. Clinical trial information: NCT01321554.
Enriched expression of PD-L1 and other immune targets after epithelial-mesenchymal transition (EMT) in squamous head and neck and lung cancers. First Author: Milena Perez Mak, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil

Background: Epithelial-to-mesenchymal transition (EMT) is associated with poor prognosis and resistance to EGFR inhibitors. To determine molecular alterations and novel targets associated with EMT in head and neck squamous cell cancers (HNSCC), we conducted a comprehensive analysis of molecular alterations associated with EMT, using our previously established EMT gene signature. Methods: 504 HNSCCs from two independent patient cohorts and 178 lung squamous (LUSC) tumors were scored using the EMT gene signature. EMT score was correlated with miRNA, miRNA, and protein reverse phase protein array (RPPA) expression and with mutations and HPV status (t-test). Ingenuity Pathway Analysis (PA) software was used for PA. Results: Mesenchymal (M) HNSCCs had higher expression of known EMT markers, such as vimentin and fibronectin, lower levels of E-cadherin and miR-200 family members (p < 0.001 for all), and a higher frequency of TP53 mutations (p = 0.016). In contrast, epithelial (E) tumors were more commonly HPV positive (p = 0.019) and were associated with better survival (p = 0.054). At the protein level, the receptor tyrosine kinase (RTK) Axl was overexpressed in M tumors (p < 0.001), whereas other RTKs, such as phosphoERK (p = 0.005) and phosphoEGFR (p = 0.02) were higher in E tumors. PA revealed a reciprocal enrichment between genes involved with immune trafficking and inflammatory response in M tumors from HNSCC and LUSC. In a supervised analysis, of 20 targetable markers were generated by Kaplan-Meier analysis and tested for significance using Chi-square test for the categorical clinicopathological variables, while patients' survival curves according to EMT score were compared by log-rank test. Conclusion: Among several molecular alterations associated with EMT, we found a strong enrichment in targetable immune checkpoints (PD-L1, PD-L2, PD-1, PD-1L) and immune cell infiltrates in HNSCC and LUSC cohorts. Given our recent findings that EMT promotes immune escape in lung cancer, our data suggests that EMT status could improve patient selection for immune targeting.

PDL1-expressing circulating tumor cells (CTCs) in head and neck squamous cell carcinoma (HNSCC). First Author: George Koutsodroutis, Attkkon Hospital, National Kapodistrian, University of Athens, Athens, Greece

Background: Blockade of PD-1/PD-L1 immune checkpoint pathway emerged as promising novel therapeutic strategy for cancer. Predictive biomarkers for response to anti-PD1 therapy are lacking. Because therapy with checkpoint inhibitors is cost intensive, noninvasive tools for early prediction of responders are of major interest. We assessed gene expression of PDL1 in CTCs at baseline and posttreatment in HNSCC patients (pts). Methods: 70 pts with locally advanced (n = 58) or recurrent/metastatic (n = 12) HNSCC were included in this analysis. Patients with locally advanced disease were treated with cisplatin chemoradiotherapy +/- TPF induction chemotherapy (IC). We assessed PDL1 expression at baseline, after completion of induction chemotherapy, at end of chemoradiotherapy and at relapse. We quantified PDL1 gene transcripts in immunomagnetically positively selected CTCs and 20 healthy individuals. A quantitative real time RT-qPCR assay for PDL1 was developed based on de novo in-silico design of primer and Taqman (TM) probe. The specificity was first tested by homology searches in the nucleotide database (NCBI, nucleotide BLAST). To assess univariate differences of study parameters according to PDL1 expression chi-square test was used for the categorical clinicopathological variables, while patients' survival curves according to PDL1 expression were generated by Kaplan-Meier analysis and significance using the Mantel-Cox log-rank test. Results: From 88 total evaluable CTCs baseline, 26 of 46 were PDL1+ at baseline, 6 of 17 post-IC, 11 of 23 at end of treatment and 1 of 2 at relapse. The assay sensitivity was evaluated using external quantification calibrators ranging from 105 copies/µL to 10 copies/µL. There was trend (p = 0.07) for adverse association between PDL1 expression at baseline and progression-free survival. Conclusion: We report for the first time a highly sensitive, specific and reproducible quantitative real-time RT-qPCR assay for the assessment of PDL1 expression in CTCs. The assay is currently validated in CTCs isolated from a large number of HNSCC pts. Serial PDL1 expression assessment has potential to select and monitor pts for PD-1 targeted therapies.
6020 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Differential impact of cisplatin dose intensity on human papillomavirus (HPV)-related (+) and HPV-unrelated (−) locoregionally advanced head and neck squamous cell carcinoma (LHNSCC). First Author: Anna Spreafico, Princess Margaret Cancer Centre, Toronto, ON, Canada

**Background:** Definitive radiotherapy with concurrent cisplatin (CDDP) is a standard treatment for patients (pts) with LHNSCC. We evaluated the impact of CDDP dose intensity (mg/m²) on overall survival (OS) of HPV+ and HPV–LHNSCC pts. **Methods:** Princess Margaret Cancer Centre (PM) and Istituto Nazionale dei Tumori (INT) LHNSCC cohorts treated from 2000 to 2012 were reviewed. Kaplan-Meier method was used to estimate the 5-year (yr) OS in HPV+ vs HPV– pts. HPV status was determined by p16 staining or in situ hybridization. HPV DNA for all oropharyngeal (OPC), unknown primary (UNK), and <10 pack-year (PY) smoking laryngo-hypopharyngeal cancer (LHC). Untested 16, >10 PY LHC pts were assumed HPV–. **Results:** A total of 659 pts (584 PM; 75 INT) were evaluated. Pts characteristics included: median age 58 (range: 27-81); primary site: OPC 73%, LHC 24%, UNK 3%; non-Epidermoid histology 40%. **Conclusions:** OS was similar for HPV+ and HPV– pts. Median follow-up was 4.3 yrs. Five year OS was inferior for HPV– pts (66%) vs HPV+ pts (70%), HR 0.73 (0.54-0.99, p = 0.03), while no difference was detected in HPV+ CDDP ≤ 200 < 200 mg/m² (83 vs 87%, p = 0.30), confirmed by MVA (Table). In no 3 or 4 HPV+ pts, a trend on OS in CDDP >200 mg/m² (HR = 0.62, 95% CI: 0.30-1.31) was observed. **Conclusions:** In this large multicenter cohort study, CDDP dose intensity ≤ 200 mg/m² had a detrimental impact on OS in HPV– vs HPV+ pts. The impact of CDDP dose intensity on HPV+ pts was not significant. These results warrant prospective validation.

**MVA for OS in HPV+ and HPV– pts:**

<table>
<thead>
<tr>
<th>CDDP (mg/m²)</th>
<th>No. of pts</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200</td>
<td>HPV+ (n=335)</td>
<td>1.00 (0.98-1.02)</td>
<td>0.62</td>
</tr>
<tr>
<td>&gt;200</td>
<td>HPV+ (n=224)</td>
<td>0.73 (0.54-0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>≤ 200</td>
<td>HPV– (n=325)</td>
<td>1.00 (0.98-1.02)</td>
<td>0.62</td>
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<tr>
<td>&gt;200</td>
<td>HPV– (n=334)</td>
<td>0.73 (0.54-0.99)</td>
<td>0.03</td>
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6022 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Safety analysis of a phase III randomized trial of chemotherapy with or without bevacizumab (B) in recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). First Author: Athanassios Argiris, The University of Texas Health Science Center at San Antonio, San Antonio, TX

**Background:** The addition of an anti-VEGF monoclonal antibody, to chemotherapy has improved outcomes in several solid tumors. Pemetrexed plus B in R/M SCCHN showed promising efficacy but significant incidence (15%) of grade 3-5 bleeding (Argiris et al. JCO 2011). **Methods:** Patients (pts) with performance status (PS) 0-1, adequate laboratory parameters, no history of bleeding, not receiving anti-coagulation or having blood vessel invasion were randomized to: A) one of 4 regimens (investigator’s choice): A1: cisplatin (C) 100 mg/m², 5-FU 1000 mg/m²/day x 4 days; A2, carboplatin (Cb) AUC 6, 5-FU 1000 mg/m²/day x 4 days; A3, Cb 75 mg/m², docetaxel (D) 75 mg/m²; A4, Cb AUC 6, D 75 mg/m², every 3 weeks, or B) the same regimen (B1, B2, B3, B4) plus B 15 mg/Kg IV, every 3 weeks, until progression. All pts received prophylactic antibiotics. Chemotherapy could be stopped after 6 cycles after maximum response. The primary endpoint was overall survival (OS) with a sample size of 400. **Results:** We report safety results from a total of 357 pts, 183 in Arm A (A1 = 15; A2 = 10; A3 = 88; A4 = 68) and 174 in Arm B (B1 = 12; B2 = 8; B3 = 88; B4 = 66). PS <0.5; female, 14%; age ≤ 65, 22%. Grade (G) 5 treatment-related adverse events (AEs), 5% in arm A vs 8% in arm B (p < 0.03), cardiac failure (C), 1 vs 0; cardiac arrest, 0 vs 1; gastric hemorrhage, 0 vs 1; tracheal/tracheostomy hemorrhage, 0 vs 2; laryngeal/pharyngeal/bronchial hemorrhage, 0 vs 3; lung infection 1 vs 0; sepsis, 0 vs 1; nervous system/other 0 vs 2. G 5 bleeding AEs, all reported, 1% vs 4% (p = 0.08); treatment-related, 0 vs 3.6 (p = 0.007); G 3-5 bleeding AEs, all reported, 3.2 vs 1.3; neutropenia >3; 2.4 vs 0.8; thrombocytopenia >100, 0.5 vs 0.3; hypertension, 0 vs 0; thromboembolic, 0 vs 0.1. Female gender, age ≤ 65, and presence of G 3-5 AEs were associated with increased incidence of G 5 toxicities was similar to previous phase III ECOG trials. B increased grade 3-5 bleeding but not overall G 5 AEs. Clinical trial information: NCT00588770.

6021 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Symptom reduction from IMRT dose deintensification: Results from ECOG 1308 using the Vanderbilt Head and Neck Symptom Survey version 2 (VHNSS V2). First Author: Anthony Cmelak, Vanderbilt-Ingram Cancer Center, Nashville, TN

**Background:** The prevalence, severity, and functional implications of high-dose radiation for locally advanced head and neck cancer (HNC) are substantial. E1308 allowed dose reduction of IMRT (54Gy) in HPV+ patients if a clinical response was obtained to induction chemotherapy. The VHNSS V2 instrument was used to quantify symptom burden following treatment. **Methods:** The VHNSS V2 is a 50-item survey, scored 0 (none) to 10 (severe) arranged into symptom clusters. The tool was utilized pre-treatment, and at 6 and 12 months to pts with resectable stage III/IVa,b HPV+ oropharyngeal HNC who received IC x3 weeks x 3 with paclitaxel 90mg/m² days (D) 1,8, 15, 75 INT) and standard weekly cetuximab (C). IC response determined IMRT dose independently at primary site and involved nodes: C-IMRT 54Gy/7 if CCR and 69.3Gy/3 if < CCR. Only pts who completed ≥50% of the items in a given symptom cluster were considered evaluable for that cluster. **Results:** 80 pts were enrolled (3 did not receive IMRT) with 44 pts classified as NED at 12 months post-treatment (35 received ≤ 54Gy and 9 received >54Gy). Moderate to severe average symptom cluster scores (scores ≥ 2) appeared numerically reduced with lower IMRT dose: mouth pain 6% vs. 25%, general pain 27% vs. 50%, nutrition 6% vs. 40%, taste/smell changes 31% vs. 50%, voice 13% vs. 25%, speech 13% vs. 25%. Difference in difficulty swallowing solids 35% vs. 100% reached statistical significance (p = 0.01). A composite analysis evaluating moderate to severe symptoms at 12 months for any of these 3 clusters (difficulty swallowing solids, dry mouth, taste/smell changes) was 70% vs. 100%. Difficulty swallowing liquids (60% vs. 25%) and mucous (27% vs. 25%) did not appear to be reduced by the lower IMRT dose. **Conclusions:** The VHNSS V2 instrument provides granular analysis of specific symptoms experienced by HNC patients. Reduction of IMRT dose from 69.3Gy to 54Gy appeared to ameliorate late toxicities in locally advanced HPV+ HNC. This dose reduction in pts with cCR to IC was associated with favorable long-term DFS. VHNSS V2 will be used in subsequent ECOG-ACRIN studies to evaluate treatment effects prospectively. Clinical trial information: NCT01104803.
6024  Poster Session (Board #347), Sat, 1:15 PM-4:45 PM
Ultra-deep targeted sequencing to identify HRAS, TP53, and CDKN2A somatic mutations as molecular prognostic markers in patients with advanced oral squamous cell carcinoma. First Author: Tzu-Chen Yen, Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taoyuan, Taoyuan, Taiwan

Background: Ultra-deep targeted sequencing (UTD-Seq) was used to identify somatic mutations predicting disease-specific survival (DSS) in patients with advanced oral squamous cell carcinoma (OSCC). Methods: Formalin-fixed paraffin-embedded primary tumor specimens were collected from 249 non-squamous OSCC patients, including 147 patients with ECS+ and 102 without ECS+ extracapsular spread. Mutational hotspots of 45 cancer-related genes were examined with UTD-Seq at an average depth of 1000×. Kaplan-Meier plots and Cox regression analyses were used to investigate the association between the mutation status and DSS. Results: Non-synonymous variants were identified in 179 (71.9%) specimens. TP53, CDKN2A, HRAS and PI3KCA were the most frequently mutated genes. The presence of ECS did not statistically significantly influence the mutation spectrum. HRAS mutations were strongly associated with poor DSS independent of ECS. Mutations in TP53 (especially located in the DNA-binding domain) and CDKN2A predicted poor DSS in ECS- and ECS+ patients, respectively. No association between PI3KCA mutations and prognosis was detected. Conclusions: Our findings demonstrate that HRAS, TP53 and CDKN2A mutations identified by UTD-Seq predict DSS in advanced OSCC, potentially serving as molecular markers for individualized patient care through risk-adapted therapy.

6025  Poster Session (Board #348), Sat, 1:15 PM-4:45 PM
New aspects regarding the induction chemotherapy with TPF and radio chemotherapy in head and neck cancer. First Author: Edwin Boelke, University of Duesseldor, Duesseldor, Germany

Background: Induction chemotherapy with docetaxel, cisplatin, and 5 FU (TPF) before radiotherapy (RT) or radio-chemotherapy (RT-CHX) improves the overall survival rate compared to induction chemotherapy with cisplatin and 5 FU in locally advanced squamous cell carcinoma of the head and neck (SCCHN). If TPF induction before RT-CHX improves clinical outcome in comparison to RT-CHX alone is still uncertain. Recently, the results of 5 randomized trials addressing this question have become available. Methods: 1060 patients with locally advanced SCCHN were randomly assigned to receive either TPF induction CHX followed by concurrent RT-CHX or concurrent RT-CHX alone. Platin or taxane based CHX was used during RT. 53,4% of patients had oropharyngeal, 17,3% hyopharyngeal, 6,4% laryngeal, 18,5% oral cavity and 4,4% other SCCHN. Published hazard ratios and hazard ratios extracted from available survival curves for overall survival (OS) and progression free survival (PFS) were basis of the meta-analysis. Meta-analysis of the effect sizes on OS and PFS was performed using a random effects model based on parameter estimates of log hazard ratios in Cox models and their standard errors.

Results: Additional induction CHX with TPF before RT-CHX did not result in a significant improvement of overall survival (Hazard Ratio: 0.950, 95% confidence limits (CL) 0.791-1.140 p = 0.579). Conclusions: Additional induction CHX with TPF before RT-CHX does not improve overall survival in SCCHN.

6026  Poster Session (Board #349), Sat, 1:15 PM-4:45 PM
Phase I trial of intravenous attenuated vaccinia virus (GL-ONC1) with concurrent chemoradiotherapy (CRT) for locoregionally advanced head and neck carcinoma. First Author: Loren K. Mehl, UC San Diego Moores Cancer Center, La Jolla, CA

Background: We aimed to test the safety of GL-ONC1, an attenuated vaccinia virus, delivered intravenously (IV) with concurrent CRT for locoregionally advanced head and neck carcinoma (LA-HNC). Secondary objectives were to test for tumor susceptibility to viral infection in baseline specimens and for tumor infection on mid-treatment biopsies. Methods: This was a 3+3 phase I dose escalation trial for unresected LA-HNC, excluding HPV-positive oropharyngeal cancer (NCT01584284). CRT was given in 33-35 fractions of 2.00-2.12 Gy over 6.5-7 weeks using IMRT with concurrent cisplatin 100 mg/m² given on days 1, 22, and 43. Escalating doses of GL-ONC1 were given as follows: cohort 1, 3x10⁷ pfu on day 3; cohort 2, 1x10⁸ pfu on day 3; cohort 3, 3x10⁸ pfu on day 3; cohort 4, 3x10⁹ pfu on days 3 and 8; and cohort 5, 3x10⁹ pfu on days 3, 8, 15, and 22. Dose-limiting toxicity (DLT) was defined as grade ≥ 4 toxicity or grade ≥ 3 mucositis or skin reaction persisting > 6 weeks after CRT attributed to GL-ONC1. Results: From May 2012 to Dec 2014, 24 patients consented (19 enrolled, 5 screen failures). 18 patients completed CRT, with 1 currently on treatment. Mean age was 56 years. 74% had stage IVB disease. 26% were HPV-positive. One DLT occurred in cohort 4. Maximum tolerated dose was not reached. Adverse events considered unrelated to GL-ONC1 were myocardial infarction (1), pneumonia (1), grade 3 emesis (1), grade 3 neutropenia (1). Of 18 patients completing CRT, 78% had 3 cycles of cisplatin and 22% had 2 cycles. With median 17 month follow-up, Kaplan-Meier estimates of 1-year (2-year) PFS and OS were 82% (75%) and 87% (75%) respectively. Conclusions: This is the first trial to establish the safety of IV GL-ONC1 in LA-HNC patients undergoing concurrent CRT. A phase II trial in this population is warranted. Clinical trial information: NCT01584284.

6027  Poster Session (Board #350), Sat, 1:15 PM-4:45 PM
Can somatic copy number alterations detected by ultradepend targeted sequencing predict prognosis in oral squamous cell carcinoma? First Author: Tzu-Chen Yen, Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taoyuan, Taoyuan, Taiwan

Background: Targeted sequencing technologies have greatly advanced our knowledge of the incidence and functional significance of somatic genomic copy number alterations (CNA) in various malignancies. To understand the underlying genetic alterations in oral squamous cell carcinoma (OSCC) and aid in molecular classification of OSCC and patient prognosis, CNA were analyzed using ultradepend-targeted sequencing (UTD-Seq) with DNA from formalin-fixed paraffin-embedded (FFPE) OSCC specimens. Methods: First, a linear model was developed to overcome uneven coverage across target regions. We then designed 189 primer pairs to selectively amplify mutational hotspots targeting 46 cancer-relevant genes. Samples were obtained from 310 FFPE tissue specimens from OSCC resections and 14 control samples. The 5-year rates of local recurrence, distant metastases, and overall survival served as the main outcome measures. We finally confirmed the prognostic signatures by profiling an additional 105 primary OSCC samples. Results: We found that CNA burden across 16 targeted genes was associated with clinical outcomes in the two cohorts. FGFR1 and PI3KCA amplifications were significant predictors of prognosis independent of traditional risk factors. Moreover, we identified CNA in genes involved in proteoglycan metabolism as well as FOXO and PI3K-AKT signaling pathways, for which targeted drugs are already available or under development. Conclusions: We observed that CNA detected by UTD-Seq may predict prognosis in OSCC patients, complementing the clinicopathological information. Prognostically detrimental CNA can provide added value in the combined molecular and clinical prognostication of OSCC.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Salivary gland carcinoma is an uncommon malignancy. For locally advanced or high risk disease, current standard of care consists of surgery followed by adjuvant RT. Limited data on the efficacy of adjuvant CRT exists. We sought to compare the effectiveness of adjuvant CRT vs. RT alone among older patients in real world setting. Methods: SEER-Medicare database (1992-2008) was searched for beneficiaries 66 years of age or older with Medicare coverage ≥ 1 year following a diagnosis of locally advanced (T3-4 and/or N1-3, M0) major or minor salivary gland carcinoma. Patients must have had definitive surgery within 4 months from diagnosis and adjuvant RT or CRT within 6 months from diagnosis. Results: Analyses included 741 patients: 100 received CRT and 641 received RT. The most common concurrent chemotherapists used were cisplatin or carboplatin (39%), Carboplatin plus Taxane (19%) and Cetuximab (18%). Patients in CRT group were younger (median age 74.2 vs. 76.8 years, p=0.01), with greater node positive disease (73% vs. 64%, p=0.05) than RT group. The median overall survival was 24.0 months with CRT vs. 41.0 months with RT, p=0.012. Multivariable analysis adjusting for patient-, tumor- and treatment-related factors still showed that CRT increased mortality over RT alone: HR 1.40 (95% CI: 1.08, 1.81). Hospitalization with treatment-related toxicity was more frequent in the CRT group: 27.0% vs. 11.5%, p<0.01. An effect modification (p-interaction=0.00) between histology and CRT was present such that an increase in mortality from CRT was observed only among adenoidcystic, mucoepidermoid or acinic cell carcinoma, but not adenocarcinoma or squamous cell carcinoma. Sensitivity analysis performed by changing the adjuvant definition to within 4 months from diagnosis or restricting analytic cohort to those receiving CRT within 2 months post-surgery showed results robust. Conclusions: In this older, population-base cohort, there existed a wide variation in the practice of adjuvant CRT. Adjuvant CRT, when compared with adjuvant RT alone, was associated with an increased risk of mortality and hospitalization with treatment-related toxicity.
Background: Extracapsular spread and positive microscopic surgical margins are known high risk factors of recurrence in head and neck cancer patients. However, molecular biological markers to predict recurrence have not been identified. Here, we aimed to identify markers of recurrence using DNA microarray profiling in patients with squamous cell carcinoma of the tongue (TSCC). Methods: We conducted exploratory Affymetrix gene expression profiling using 26 primary tumor tissue samples from patients meeting the following criteria: 1) histologically confirmed TSCC, 2) surgical resection of the primary tumor and lymph node dissection, and 3) follow-up for longer than one year after surgery. Median age and pathological stage were 60 years (37-85) and pStageIII/IV = 8%/92% (pt: 2/3; a/a = 31/2, pN: 0/1, 2/2/2/2c = 5/5/0/8/8), respectively. The relationship between gene expression pattern and relapse-free survival (RFS) was examined. Predictive candidate genes were independently validated using published survival and gene expression data similarly derived from 23 patients with oral SCC (http://www.ncbi.nlm.nih.gov/geo, GSE31056). Results: Cases were classified into clusters A (n = 10) and B (n = 16) by unsupervised hierarchical clustering analysis. RFS of cluster B was longer than that of cluster A (median RFS: not reached vs. 111days, p = 0.025) with a median follow-up period of 253 days (58-1341). The number of genes highly expressed by more than two-fold their expression in the opposite cluster was 175 in cluster A and 400 in cluster B. We then identified 27 genes with the most predictive value for recurrence, 5 genes highly expressed in the low-risk group (e.g. ALDH3A1) and 22 highly expressed in the high-risk group (e.g. MMP-10). Clustering into high- and low-risk groups based on this gene expression in a validation study also showed a significant association with recurrence (median RFS: low-risk not reached vs. high-risk 25.1 months, p = 0.046) with a median follow-up of 13.27 months (1.43-59.67). Conclusions: We identified 27 genes which could predict recurrence, indicating a promising candidate factor for high-risk relapse. A larger prospective study is warranted.

Conclusions: To our knowledge this is the first time where an early divergence on genomic evolution from PTCTo ATC is suggested challenging the hypothesis of a multistep mutational model that leads from follicular thyroid cell to PTC and ATC. Candidate therapeutically actionable alterations have been identified.
A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). First Author: Joshua David Palmer, Kimmel Cancer Ctr Thomas Jefferson Univ Hosp, Philadelphia, PA.

**Background:** The cisplatin (CDDP)-based CT is considered as the standard regimen for the treatment of moderate to advanced SCCHN. Recently, an alteration is made to carboplatin (CBDCA) because of its similar mode of action. We conducted a meta-analysis to compare the efficacies and toxicities of these two treatments. **Methods:** The search strategy included PubMed, Science Direct, the Cochrane Library, China National Knowledge Internet Web. Statistical analyses were performed using RevMan 5.2. The primary endpoint was overall survival (OS) with secondary endpoints of locoregional control (LRC) and severe toxicity (grade ≥ 3). Hazard ratio (HR) and risk ratio (RR) were calculated using random- or fixed-effect models. Kaplan-Meier curves were read by Engauge-Digitizer. **Results:** Overall 12 studies and 1165 patients were included. CDDP-based CT significantly improved 5-year OS (HR = 0.67, 95%CI 0.49-0.91; RR = 0.01) compared to the CBDCA group. No difference in 3-year OS/LRC was observed (P = 0.08; P = 0.64), but a subgroup analysis showed a better 3-year OS in the CDDP arm for non-nasopharynx carcinoma (non-NPC) SCCHN (HR = 0.66, 95%CI 0.48-0.91; P = 0.01). The CBDP-based CT was associated with more gastrointestinal toxicities (RR = 4.58, 95%CI 1.57-13.37; P = 0.005) and neuropathy toxicity (4/110 = 3.6%) compared to the CBDCA group, but less hematologic toxicities (anemia, leukopenia and thrombocytopenia with HRs of 0.27 0.70, 0.97; 95%CI 0.52-0.96,0.28 0.95%CI 0.15-0.54). Risk of skin toxicity was identical. Moreover, we found that for non-NPC SCCHN, mucositis occurred more frequently and severely in CDDP based treatment (RR = 3.55, 95%CI 1.42-8.88; P = 0.007), whereas less for NPC (RR = 0.20, 95%CI 0.09-0.44; P < 0.0001). **Conclusions:** Patients with CDDP based CT can achieve a higher OS, but there is no significant difference in LRC. The CDDP-based CT is associated with less hematologic toxicities but more gastrointestinal toxicities and neuropathy compared to the CBDCA arm. Risk of mucositis in the CDDP group is higher for non-NPC SCCHN, but lower for NPC. The precise roles of CDDP and CBDCA in the management of SCCHN remain to be determined.

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Comprehensive genomic profiling of salivary gland adenocarcinomas to reveal frequency of druggable targets. First Author: Matthew J. Hawryluk, Fondation Medicine Inc., Cambridge, MA

Background: Salivary gland adenocarcinomas (SAC) are a distinct group of frequently aggressive epithelial tumors. We queried whether the genomic alterations (GA) identified by comprehensive genomic profiling (CGP) in refractory and metastatic SAC could lead to potential targeted therapy selection. Methods: DNA was extracted from 40 microns of FFPE sections from 92 clinically advanced SAC. Comprehensive genomic profiling was performed on hybridization-capture, adaptor-ligation based libraries to a mean coverage depth of 682X for 3,230 exons of 236 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The results were evaluated from each sample for all classes of genomic alterations.

Results: There were 2 grade 1, 27 grade 2 and 63 grade 3 relapsed/refractory tumors in 30 (33%) female and 62 (67%) male patients with a median age of 59.6 years (range 25 to 84 years). There were 27 Stage III and 65 Stage IV cases. The majority (88%) of SAC harbored at least 1 clinically relevant alteration (mean 1.9 per patient) with a mean of 3.7 GA per tumor. GA occurred in 49 different genes including: PIK3CA (25%); HRAS (20%); CDKN2A (17%); ERBB2 (15%); and PTEN and NF1 (9%). NOTCH1 and MCL1 (8%), EGFR (5%), KRAS (4%) and RICTOR, HGF, FBXW7 and CDK4 (3%). The greater frequency of ERBB2 alterations (15%) observed in SAC was significantly higher than observed in 110 similarly studied specialized salivary carcinomas including acinic cell, adenoid cystic and mucoepidermoid carcinomas (1%) (p = 0.001). A similar increase in HRAS alterations of 18/92 (20%) SAC vs 4/110 (4%) in the specialized tumor group was also observed (p = 0.008). PIK3CA was altered in 25% of SAC vs. 5% in 110 specialized tumors (p = 0.001).

Conclusions: SAC are a clinically aggressive and pathologically distinct subset of salivary gland carcinomas. These tumors also differ significantly from the specialized salivary gland tumors in their genomic landscape. The high frequency of clinically relevant alterations in SAC including the 15% ERBB2 alteration frequency suggests that continued molecular analysis of this tumor type has the potential to lead patients to clinical trials employing both established and novel targeted therapies.

The role of cetuximab in induction chemotherapy: Comparison of APF-C (nab-paclitaxel, cisplatin, 5-FU + cetuximab) with APF, both followed by chemoradiation therapy (CRT), in patients with locally advanced head and neck squamous cell carcinoma (HNSCC). First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO

Background: Cetuximab (C) improved overall survival (OS) in patients (pts) with HNSCC when added to definitive RT or to palliative chemotherapy; however, the role of cetuximab in induction chemotherapy is unclear. We hypothesized that improved OS, disease-specific survival (DSS), and lower relapse rates with the addition of C to APF given as induction chemotherapy before CRT. A nab-Paclitaxel-based induction chemotherapy regimen was chosen because we observed better survival outcomes in comparison to a docetaxel-based regimen (CancerMedicine2014). Methods: Two consecutive prospective phase II trials (APF and APF + C) were performed: 30 pts were treated with APF (weekly nab-paclitaxel 100 mg/m² and every 3 week cisplatin 75 mg/m² and 5-FU 750 mg/m²/day x 3) and 30 pts were treated with APF + C (APF + weekly cetuximab 250 mg/m²). Pts were scheduled to receive three cycles followed by CRT (with or without C). Nine (3%). The greater frequency of clinically relevant alterations in SAC including the 15% ERBB2 alteration frequency suggests that continued molecular analysis of this tumor type has the potential to lead patients to clinical trials employing both established and novel targeted therapies.
6044 Poster Session (Board #367), Sat, 1:15 PM-4:45 PM
Augmenting pre-operative risk of recurrence stratification in differentiated thyroid carcinoma using machine learning and high dimensional transcriptional data from thyroid FNA. First Author: Steven I. Sherman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In addition to improving survival, a risk adapted approach to thyroid cancer therapy should minimize risk of recurrence. Currently, patients are classified post-operatively as high, intermediate or low risk of recurrence using 2009 ATA staging. Though clinically useful, this anatomic staging cannot be assessed pre-thyroidectomy, and does not include molecular predictors of outcome. Our goal was to determine if transcriptional data obtained from FNA of malignant thyroid nodules augment risk stratification before thyroidectomy. Methods: We used FNA material from 81 samples preoperatively collected in a previous study and post-surgically diagnosed as PTC. Each patient was categorized as either ATA low risk or ATA intermediate/high risk using established guidelines for recurrence risk stratification. Microarray expression data were obtained on all samples and supervised learning was used to train classifiers (Support Vector Machine (SVM), Random Forest (RF), penalized logistic regression (PLR), and an ensemble of the 3). Performance was measured using 10-fold cross-validation on the training cohort. Results: Classifiers were built using the top 70 genes from LIMMA models that controlled for BRAF status. Maximum classification performance of ATA low risk vs. ATA intermediate/high risk was observed for an ensemble classifier with a maximal area under the ROC curve (AUC) of 0.83. All the classifiers achieved similar AUCs: SVM 0.82, RF 0.82, and PLR 0.82. Genes useful in classification belong to transmembrane signaling pathways including ECM-receptor interaction, focal adhesion, and cell adhesion molecules. When applied to the training cohort, the ensemble classifier correctly identified 72.4% (21/29) of ATA low risk tumors and 82.6% (43/52) of ATA intermediate/high risk tumors. Conclusions: Transcriptional data from FNA of thyroid nodules may improve the pre-operative prediction of risk for post-operative recurrence. If independently validated in a sufficiently large number of patients, such molecular classifiers may augment initial risk stratification and individualization of patient care.

6045 Poster Session (Board #368), Sat, 1:15 PM-4:45 PM
Prognostic value of HPV detection with three primer sets in 255 Head-Neck cancers. First Author: Cristiano Lo Nigro, Laboratory of Cancer Genetics and Translation Oncology, Oncology Dept, S. Croce Teaching Hospital, Cuneo, Italy

Background: HPV-related patients (pts) with locally advanced head and neck cancers (LA-HNCs) have a better prognosis than the HPV-negative ones. This study aimed to investigate the prevalence of HPV infection in a series of LA-HNCs and to compare the prognostic value of E1, E6 and L1 genomic viral fragments, each other, in order to find the best prognosticator among them in terms of Overall Survival (OS) and Progression Free Survival (PFS). Methods: HPV was searched in 255 LA-HNC pts, 89 Oropharyngeal cancers (OPCs) and 166 non-OPCs, by DNA-PYR on formalin-fixed paraffin-embedded (FFPE) tissues using three specific primer pairs for type 16. Each pt was analysed simultaneously for the three viral primer sets and for a housekeeping gene to determine the integrity of tumour DNA samples. Results: One hundred and thirty six out of 255 pts (53.3%) were HPV positive with at least one of the primer pairs used; pos E6 (51%) and L1 (29.8%) samples were the most common; while pos E1 samples were lower (13.7%). OPCs showed a significant higher % of pos samples compared to non-OPCs for each primer set tested and the prevalence proportions for each fragment were kept in both groups, with the highest for E6 and the lowest for E1. Therefore each pt highlighted variable positivity for E1, L1 and E6 viral fragments. In this sense OPCs showed the higher % of pos pts for the three viral fragments concurrently (31.5%) compared to non-OPCs (4.2%), moreover E1 detection was always associated with E6 and L1 one. In term of prognostic value analysed for each fragment by itself, only E1 pos OPC pts showed improved OS (p = 0.012) and PFS (p = 0.036), while pos L1 and E6 ones did not show any gain according to either viral status. Conclusions: Though prevalence in HPV infection by DNA-PYR was significantly higher for E6 and L1 primer sets, the detected HPV viral fragments seemed very weak prognosticators; on the contrary E1 might become a stronger prognostic marker for OS and PFS in OPC pts. In conclusion E1 by DNA-PYR appears to be clinically relevant in the present series of pts.

6046 Poster Session (Board #369), Sat, 1:15 PM-4:45 PM
Association of head and neck cancer (HNSCC) subgroups defined by HPV RNA status, gene expression patterns, and TP53 mutations with lymph node metastasis and survival. First Author: Andreas Dietz, University of Leipzig, Leipzig, Germany

Background: Classification of HNSCC based on HPV16 DNA and RNA status, gene expression patterns, and mutated candidate genes may facilitate patient stratification. Methods: We compared tumors differing in HPV16 DNA and RNA (E6*1) status from consecutively recruited HNSCC patients by gene expression profiling (n = 270, Illumina HT12) and targeted sequencing (n = 226; 50 genes, Ion Torrent). Gene expression was analyzed unsupervised using consensus clustering. Results: HPV16 DNA+RNA+ tumors are molecularly distinct from HPV-negative (HPV DNA-) HNSCC, have elevated expression of cell cycle genes and carry rarely mutations (3.6%, 1/28). HNSCC without transcriptionally active HPV16 (DNA+RNA-) are similar to HPV DNA- tumors in gene expression and TP53 mutation frequency (47%, 8/17, and 43%, 72/167). We identify four gene expression clusters significantly differing in overall survival (OS); P = 0.04, adjusting for UICC stage, age, tumor site, treatment, pack-years smoked, alcohol use, HPV16 status). One cluster with high expression of immune response genes (IR) contains most (77%, 27/35) HPV16 DNA+RNA+ HNSCC. The IR cluster and disruptive TP53 mutations (TP53mut) are associated with lymph node metastasis (OR = 5.7; CI95% 2.2-18.0; P = .001). OR = 2.6; CI95% 1.2-6.0; P = .01) independent of HPV16 status and tumor site. This validates the associations identified by Walter et al. (2013). Consistent with earlier studies, TP53mut has unfavorable prognosis (OS: HR = 2.0; CI95% 1.3-3.6; P = 0.03; PFS: HR = 1.9; CI95% 1.2-3.2; P = .01), adjusting for the UICC stage, age, tumor site, treatment, pack-years smoked, alcohol use, HPV16 DNA RNA status. Conclusions: Elucidation of HPV16 E6*1 and TP53* status are required for patient stratification. The IR gene expression cluster and TP53mut in HNSCC are associated with lymph node metastasis.

6047 Poster Session (Board #370), Sat, 1:15 PM-4:45 PM
Prognostic value of mid-treatment total lesion glycolysis in p16+ oropharyngeal cancer. First Author: Erqi L. Pollom, Stanford University Medical Center, Stanford, CA

Background: To determine whether total lesion glycolysis (TLG) measured during radiation for locally advanced oropharyngeal cancer (OPC) correlates with outcomes. Methods: Patients with Stage III-IVB, intact OPC treated with definitive chemoradiation were included if they underwent both pre- and mid-treatment planning PET scans. The TLG, defined as summation of the total standardized uptake values within the tumor volume, was extracted from within the primary and nodal tumor volumes contoured by the treating physician. TLG velocity was defined as the relative difference between pre- and mid-treatment TLG divided by weeks between the scans. Results: In total, 67 patients who fulfilled inclusion criteria were treated from February 2009 to January 2014 at Stanford. Median age was 59 years (range 27-83), p16 status was positive in 58 patients, negative in 8 patients, and unknown in 1 patient. Ten patients received induction chemotherapy; the majority of patients (58%) received platinum-based chemotherapy concurrently. Patients were treated to a median dose of 70 Gy (range 63.6-70 Gy, in 30-35 fractions). Median follow-up was 18.8 months (range 3.3-67.2 months). Two-year progression-free survival (PFS) and overall survival (OS) were 90% and 98%, respectively. Age, smoking status, p16 status, stage and chemotherapy did not predict for PFS or OS. Higher pre- and mid-treatment nodal TLG predicted for worse PFS/OS, while higher pre- and mid-treatment combined primary and nodal TLG predicted for worse OS. Change in TLG trended toward improved PFS (p = 0.09-0.7), even with controlling for type of chemotherapy. Conclusions: Metabolic response, as characterized by nodal TLG velocity, during radiotherapy predicts for PFS in p16+ OPC patients and may aid with risk-adapting treatment.
Effect of age and lenalidomide treatment on overall survival for patients with 131I-refractory differentiated thyroid cancer in SELECT. First Author: Marcia S. Brose, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Background: Lenalidomide (LEN) significantly prolonged progression-free survival (PFS) vs placebo (PB) in the phase 3 SELECT trial of patients (pts) with 131I-refractory differentiated thyroid cancer (RR-DTC)—a benefit maintained in both younger (≤ 65, median 56 years [y]) and older (> 65, median 71 y) pts. In SELECT, median overall survival (OS) was not reached at data cutoff, and OS was not significantly different between LEN and PB (HR 0.73; 95% CI 0.50-1.07; P = 0.103). Here we examine the effect of age on OS in SELECT. Methods: Pts with RR-DTC and independent radiologic documentation of disease progression were stratified by region, prior VEGF-targeted therapy, and age (younger: LEN, n = 155; PB, n = 81 vs older: LEN, n = 106; PB, n = 50) and randomized 2:1 to LEN or PB. Median follow-up was 17.1 months at primary data cutoff (Nov 15, 2013); 83% of pts on PB crossed over to LEN following confirmed disease progression. Results: Median OS was not reached in any group except in older PB-treated pts (18.4 months; 95% CI, 13.3-20.3). A significant difference in OS was observed in older pts, favoring LEN (HR 0.53, 95% CI 0.31-0.91; P = 0.020). In a related analysis, there was no difference in OS between older and younger pts who received LEN (HR 0.78; 95% CI 0.49-1.26; P = 0.304), but there was a statistically significant difference in the PB arm, favoring younger pts (HR 0.48, 95% CI 0.27-0.85; P = 0.010). No other analyses provided evidence for this difference. Treatment-related death, grade 3-4 neutropenia, and grade 3-4 thrombocytopenia were numerically higher in the older age group. Conclusions: Older PB-treated pts had a significantly longer OS than younger PB-treated pts in SELECT. This effect of age was completely mitigated by LEN treatment resulting in improved overall survival for pts > 65 y treated with LEN. Clinical trial information: NCT01321554.

Randomized phase II study of cabazitaxel versus methotrexate in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) previously treated with platinum-based therapy. First Author: Sylvia Rottey, Ghent University Hospital, Ghent, Belgium

Background: Cabazitaxel (cab) is a second-generation taxane that improves overall survival (OS) of patients with metastatic castrate resistant prostate cancer who progress on/after docetaxel. Caba has activity in SCCHN cell lines as well as in taxanes-resistant cell lines. We investigated cabazitaxel in recurrent SCCHN patients. Methods: Patients with non-curative SCCHN with an ECOG 0-2 and progressive disease within 1 year after platinum-based therapy were randomized between cab (38% T3/T4, 56% with prior chemotherapy regimens 1/2). The primary endpoint was the progression free survival rate (PFSR) at 18 weeks (central review). This trial was a randomized phase II trial (P0 = 0.15, P1 = 0.3, a = 0.1, b = 0.1; Fleming one stage). Results: 101 patients (53 in cab and 48 in MTX) were randomized. The median age was 58 years (range 46-80), 63% had received prior platinum for recurrent disease and 37% as part of the multimodal therapy. 17 were ECOG PS 2. 37% had been previously treated with taxanes. PFSR at 18 weeks was 13.2% (95% IC: 5-25%) for cab and 8.5% (95% IC: 2-20%) for MTX. Median PFS was 1.9 months in both arms. Median OS was 5 and 3.6 months for cab and MTX, respectively. No objective responses were recorded in both arms. Conclusions: PFSR at 18 weeks is the primary endpoint. Caba had no new activity in recurrent SCCHN. Clinical trial information: NCT01527877.
Background: The accuracy of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for predicting immediate failure after radical chemoradiation therapy (CRT) in HNSCC remains poorly characterized. The purpose of this study was to evaluate 1) predictive and prognostic values of PET/CT for immediate failure after CRT, and 2) their impact on clinical decision making for salvage surgery. From January 2005 to 2013, medical records of 132 consecutive LA-HNSCC patients who received radical CRT were analyzed. PET/CTs were taken before CRT and 3-months after CRT. Immediate failure was defined residual disease or locoregional/systemic relapse within one year. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of SUV for predicting immediate failure were estimated. Overall survival (OS) of patients who had/had not salvage surgery according to SUV were compared.

Results: Of the 132 patients, 71 (53.8%) achieved metabolic complete response (mCR) in post CRT PET/CT, mCR group had better OS comparing with non-mCR group (3-year OS rate 95.8% vs. 66.6%, P < 0.001), as well as progression-free survival (PFS) (3-year PFS rate 89.5% vs. 56.9%, P < 0.001). Immediate failure occurred in 4/71 patients with mCR, 24/61 patients with non-mCR (P < 0.001). Among the various metabolic values, the post CRT maximum SUV (postSUVmax) was found to be optimal for predicting immediate failure with corresponding cutoff point of 3.9. The area under the receiver operating curve was 0.82 (95% confidence interval [CI] 0.73-0.92). The sensitivity, specificity, NPV, and PPV were 71.4%, 83.7%, 91.6%, and 54.1%, respectively. Salvage surgery was conducted in 9 of 37 patients with postSUVmax ≥ 3.9. There was no significant difference in OS by immediate salvage surgery based on post CRT PET/CT compared with no immediate salvage operation (3-year OS rate 66.7% vs. 58.1%, P = 0.719). Conclusions: Post CRT PET/CT has prognostic value for OS and is useful for predicting immediate failure with high NPV. However, early detection of immediate failure and salvage surgery based on post CRT PET/CT does not seem to lead OS benefit.

Concurrent chemoradiation using weekly versus tri-weekly cisplatin in locally advanced squamous cell carcinoma of the head and neck (SCHNN): A comparative analysis.

First Author: Man Hu, Department of Radiation Oncology, Shandong Cancer Hospital, Jinan, China

Background: The use of chemotherapy (CT) in the treatment of stage II nasopharyngeal carcinoma (NPC) is controversial. And the reports especially about intensity-modulated radiotherapy (IMRT) have been limited. The purpose of this study is to evaluate the long-term survival outcomes for stage II NPC treated with radiotherapy alone versus combined chemoradiotherapy in the era of IMRT.

Methods: We reviewed records between January 2002 and December 2013 and identified 182 patients who were histologically diagnosed as stage II NPC received RT with or without CT in Shandong Tumor Hospital. Among these patients, 52 were restaged T2N0M0, and the other 130 were restaged T1-2N1M0. One hundred and fifty-nine (38 in T1-2N1M0 and 121 in T2N0M0) received RT with CT (RT/CT) and 23 (14 in T1-2N1M0 and 9 in T2N0M0) underwent RT alone. The overall survival (OS), progression-free survival (PFS), locoregional failure-free survival (LRFF), and disease metastasis-free survival (DMF) were calculated with Kaplan-Meier method.

Results: With a median follow-up of 63.6 months (range 9.4 to 145.7), the 3-year, 5-year and 10-year OS of all stage II patients were 93.2%, 87.5% and 65.4%. For patients with staged T2N0M0, the corresponding rates were 92.3%, 89.9%, 82.6% and for those with T1N0M0, they were 93.6%, 86.6%, and 63.2%, respectively. No significant difference in OS, PFS, LRFF and DMF were observed between RT/CT group and RT alone group (p = 0.768, 0.076, 0.134, 0.161, respectively). No locoregional recurrence occurred in the first 3 years and all distant metastases were developed in patients staged T1-2N1M0, referring more aggressive therapy such as chemotherapy may be indicated for these patients. Conclusions: This is the largest cohort of patients with stage II NPC in the era of IMRT with long follow-up. Chemotherapy showed no additional benefit for patients with stage II NPC. Patients staged T1-2N1M0 had an excellent outcome treated with RT alone. For those staged T1-2N1M0 who had a higher risk for distant metastasis, additional chemotherapy may be preferred.
6056 Poster Session (Board #379), Sat, 1:15 PM-4:45 PM
Genomic landscape of salivary gland tumors. First Author: Sheryl Kresky Elkin, N-Of-One, Inc., Lexington, MA

Background: Effective targeted treatment options for advanced salivary gland tumors are lacking. In order to better understand these tumors, we assessed their genomic landscape. Methods: We studied 117 patients with salivary gland tumors that were, on physician request, tested in a Clinical Laboratory Improvement Amendments (CLIA) laboratory (Foundation Medicine, Cambridge, MA) using next-generation sequencing (182 or 236 genes), and analyzed by N-of-One, Inc. (Lexington, MA). Results: There were 354 total alterations, with 240 distinct alterations identified in this patient population. Only 10 individuals (8.5%) had a molecular portfolio that was identical to any other patient (with four different portfolios amongst the ten patients). The median number of aberrations per patient was three (range, 0 to 10). Most common alterations involved the TP53 gene (36/117 [30.8% of patients]), cyclin pathway (CCND1, CDK4/6 or CDKN2A/B) (31/117 [26.5%]) and PI3K pathway (PIK3CA, PIK3R1, PTEN or AKT1) (28/117 [23.9%]). In multivariate analysis, statistically significant co-existing aberrations were observed as follows: TP53 and ERBB2 (p = 0.01), cyclin pathway and MM2 (p = 0.03), and PI3K pathway and HRAS (p = 0.0001). We were able to identify possible cognate targeted therapies in most of the patients (107/117 [91.5 %]), including FDA-approved drugs in 80/117 (68.4%). Conclusions: Salivary gland tumors are characterized by multiple alterations that mostly differ from patient to patient. Significant associations between alterations in TP53 and ERBB2, the cyclin pathway and MM2, and PI3K pathway and HRAS were identified. Most patients had actionable alterations. These results provide a framework for tailored combinations of matched therapies.

6057 Poster Session (Board #380), Sat, 1:15 PM-4:45 PM
The phase III clinical study about the effect of Kangfuxin Solution (Chinese herbal medicine compound preparation) on the radiation induced oral and upper gastrointestinal mucositis in nasopharyngeal carcinoma patients. First Author: Jin Yi Lang, Sichuan Cancer Hospital and Institute, Chengdu, China

Background: The incidence of oral mucositis in NPC patients treated with radiation. Till now, there was no efficient drug to prevent and treat it. Kangfuxin solution was the Chinese herbal medicine compound preparation, and it could promote angiogenesis and repair mucosa. We aim to observe the effect of it on radiotherapy-induced oral mucositis (OM) and upper gastrointestinal mucositis in NPC patients. Methods: 240 pathologically confirmed squamous NPC patients from five multi-centers clinical departments were included in this study. They were randomized divided into the control group and treatment group in. Stage I, II, III and IV were all included (ACC 2010). All the patients received radical chemoradiotherapy. The treatment group used the traditional Chinese medicine (Kangfuxin Solution, 10ml tid) for mouthwash from the beginning of radiotherapy. The control group used Compound Borax Solution (10ml tid) for mouthwash. CTCAE v3.0 and verbal rating scales (VRS) was used to evaluate the incidence and OM grade, upper gastrointestinal mucositis and the pain grade during in different phases of radiation. Results: 230 effective patients were used for clinical effects evaluation in the study. Compared to control group, the incidence and grade of OM was significantly lower in treatment group (p<0.01). The time from beginning of radiation to different grade of mucositis occurrence (Grade 1, 2, 3) was longer in treatment group (p<0.05), and the accumulated radiation dose was also higher in treatment group comparing to the control group (p<0.05). For upper gastrointestinal mucositis and pains, the grade was lower in treatment group during radiation comparing to the control group (p<0.05). There was no side effect of Kangfuxin solution in the study. Conclusions: Kangfuxin solution could prevent and treat the radiotherapy-induced oral and upper gastrointestinal mucositis to some extent. The incidence and grade were all decreased in the Kangfuxin group. This traditional Chinese medicine was safe and effective, and it might be widely used in the clinical practice in the future.

6058 Poster Session (Board #381), Sat, 1:15 PM-4:45 PM
Mucosaadhesive clonidine (Clonidine Lauriad) in the prevention of severe radioinduced mucositis in head and neck cancer patients: A phase II randomized trial. First Author: Jordi Giralt, Hospital General Val De Hebron Barcelona, Barcelona, Spain

Background: Oral mucositis (OM) is the most frequent and severe complication of chemoradiotherapy (CRT) in head and neck cancer patients. There is currently no effective mechanically-targeted intervention for CRT-induced OM. NF-κB plays a central role in the signaling cascades and pathways responsible for OM. Clonidine reduces NF-κB activation and the subsequent expression of pro-inflammatory cytokines. In preclinical studies, topical clonidine reduced the incidence and duration of severe OM (SOM). The safety and efficacy of 2 doses of clonidine MBT were evaluated in patients with head and neck cancer receiving postoperative CRT.

Methods: This phase 2, multicenter, double-blind, randomized, placebo-controlled, 3-arm study compared clonidine MBT 50μg, 100μg and placebo. Clonidine MBT and matching placebo were applied to the gum once daily 1-3 days prior to RT until the end of CRT. The primary endpoint was the cumulative radiation dose at the onset of SOM (WHO grade 3 or 4) analyzed by the Kaplan-Meier method and the log-rank test. Safety was evaluated by monitoring AEs, clinical laboratory parameters, vital signs, and physical examinations.

Results: Clonidine MBT was administered to 121 patients and placebo to 62. SOM developed in 45.3% of patients in the clonidine MBT group and in 60.0% of patients in the placebo group (p = 0.064). Patients developed SOM at a median radiation dose of 60.0 Gy in the clonidine MBT and placebo groups, respectively (HR = 0.754 [0.484; 1.175]; p = 0.211). The percentage of AEs was similar between placebo (98.4%) and clonidine MBT groups (90.8%) with less nausea (49.6% vs 71%) and dysphagia (32.8% vs 48.4%) in the clonidine MBT groups vs placebo. Conclusion: Here, we present for the first time, that clonidine MBT treatment in head and neck cancer patients undergoing postoperative CRT reduces SOM with minimal toxicity. However, not statistically significant, the observed differences in the incidence and time to occurrence of SOM support the initiation of future confirmatory studies. Clinical trial information: NCT01385748.

6059 Poster Session (Board #383), Sat, 1:15 PM-4:45 PM
Molecular profiling of tumour budding to implicate TGF-β mediated epithelial-mesenchymal transition as a therapeutic target. First Author: David Hebbelstrup Jensen, Rigshospitalet, Copenhagen, Denmark

Background: Tumor budding is an adverse prognostic factor in many types of cancer and understanding of the molecular basis of this phenomenon may provide new therapeutic options. Methods: The number of tumor buds in 199 oral squamous cell carcinoma (OSCC) patients was correlated to metastases, disease-free and overall survival. Tumor buds and paired central-tumor areas were laser-capture-microdissected from 5 OSCC specimens and examined with RNA-sequencing and miRNA-qPCR arrays. Results were validated with immunohistochemistry in 199 and in situ hybridization (ISH) in 20 OSCC samples. Results: The number of tumor buds was predictive of the presence of lymph node metastasis at presentation, and was an independent predictor of overall survival. Compared to cells in the central part of the tumors, budding cells exhibited a particular gene expression signature comprising factors involved in epithelial-to-mesenchymal transition (EMT) and activated TGF-β signaling. Transcription factors ZEB1 and PRRX1 were upregulated concomitantly with a decreased expression of mesenchymal-to-epithelial (MET) transcription factors such as OVO1 in addition to Krüppel-like factors and Grainyhead-like factors. Moreover, the miR-200 family members, was identified to be down-regulated in budding tumor cells. Five markers of the EMT/MET process were validated with immunohistochemistry and ISH. Conclusions: Taken together the results imply that therapeutics based on the inhibition of TGF-β signaling may prove useful in the treatment of oral squamous cancers.
6060 Poster Session (Board #384), Sat, 1:15 PM-4:45 PM
A randomized phase II trial of the MET inhibitor tivantinib + cetuximab versus cetuximab alone in patients with recurrent/metastatic head and neck cancer. First Author: Davide E. Vokes, Department of Medicine, University of Chicago, Chicago, IL

Background: MET signaling has been proposed as a mechanism of resistance to anti-EGFR therapy. MET expression is common in Head and Neck Squamous Cell Carcinomas (HNSCC) (Seiwert et al, Cancer Res 2009). We compared the oral MET inhibitor tivantinib (ARQ197) (T) in combination with cetuximab (C), with C monotherapy, in patients (pts) with recurrent/metastatic (r/m) HNSCC. Patients with pretreatment failure were enrolled from 2012-2014, 40 on the T+C arm, and 38 on the C control arm. 31 pts (40%) were HPV-positive/p16-positive oropharyngeal (OP) cancers. T was given orally 360mg BID, C 500mg/m2 every 2 weeks. Cross-sectional imaging was performed every 8 weeks. Primary outcome was response rate (RECIST 1.1), and 5.3% (N = 2) in the C alone arm (NS). Of note, the response rate in HPV-positive/p16-positive OP HNSCC pts was 0% in both arms in a combined 31 HP-positive/p16-positive OP HNSCC. The response rate in HPV-negative pts was 12.5% (T/C) vs 8.5% (C) (NS). Median PFS in both arms was 4 months (NS), median OS 8 months (NS). Both treatments were well tolerated with a trend towards increased hematological toxicities in the T+C arm (12.5% of pts experience grade 3 leukenopenia).

Conclusions: Tivantinib + Cetuximab given in an unselected population of r/m HNSCC pts does not significantly improve response rate and survival. Consistent with other recent reports (Fayette et al ESMO 2014; Machiels et al ESMO 2014), EGFR inhibitors, including cetuximab appear to be less active/inactive in HPV-positive/p16-positive oropharyngeal HNSCC patients. Clinical trial information: NCT01696955.

6062 Poster Session (Board #386), Sat, 1:15 PM-4:45 PM
Treatment-associated mortality in head and neck cancer receiving chemotherapy and radiation: Meta-analysis of published trials. First Author: Paolo Bosi, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Concurrent chemoradiation (CRT) produces an advantage in survival as compared with RT alone in locally advanced head and neck squamous cell carcinoma (HNSCC), while exposing patients (pts) to more severe toxicities. CRT associated early mortality rate (during and until 90 days after treatment end) has not been consistently described. Methods: We conducted a meta-analysis of phase II-III randomized controlled trials (RCTs), observational studies or case series of HNSCC matching these criteria: concurrent CRT; conducted in both radical and postoperative setting; published from 1/2000 to 6/2014; involving 100+ pts; with available toxicity data. Case series were considered only if presenting homogenous treatment modalities. Early death incidence was weighted and related to the following variables: radical vs postoperative setting, induction chemotherapy, poly vs mono CT concurrent with RT, conventional vs altered RT fractionation and study design (RCT vs observational vs case series). Results: Of 732 papers identified, 36 were included in the analyses (13 case series, 7 observational, 16 RCTs). Data regarding population, acute toxicities and deaths were extracted. A total of 9164 pts were considered with 183 early deaths (incidence rate 2.1% (95% CI 1.5% – 2.8%). Subgroups analyses on the basis of type of study design revealed differences between treatment-associated deaths reported in observational studies (0.8%, 95% CI 0.6% - 1.5%) compared to RCTs (1.5%, 95% CI 1.8% - 4.0%) and case series (2.7%, 95% CI 1.7% - 4.2%). A quantitative interaction seems to exist when the size of the effect is related to the radical intent with respect to postoperative setting (mortality rate 2.4% vs 0.2%; p value 0.03), but no interaction is found with induction chemotherapy, poly or mono CT and conventional or altered RT regimens. Conclusions: CRT in HNSCC resulted in about 2% of early death, with higher rate in the radical setting. Observational studies underestimate mortality, probably due to bias selection or to inconsistent reporting. Early mortality rate reduction may imply better patient selection and more intensive supportive care programs.

6063 Poster Session (Board #387), Sat, 1:15 PM-4:45 PM
MLH1, MSH2, MSH3 and EXO1 polymorphisms and head and neck squamous cell carcinoma risk and prognosis. First Author: Gustavo Jacob Lourenco, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil

Background: MLH1 c.933G > A, MSH2 c.211G > C, MSH3 c.3133G > A, and EXO1 c.1765G > A polymorphisms have been associated with inefficient DNA mismatch repair (MMR). However, it is unknown whether they are involved with increased risk and prognosis of head and neck (HN) squamous cell carcinoma (SCC), therefore, this study aimed to clarify this issue. Methods: Genomic DNA from 450 HNSCC patients and 450 controls was analyzed by PCR-RFLP or real time PCR for discrimination of genotypes. The differences between groups were analyzed by z or Fisher’s exact test. Multivariate analysis using the logistic regression model was carried out to obtain age and tobacco status adjusted crude odds ratios with 95% confidence intervals (CI), and to assess the associations between genotypes and HNSCC. Relapse-free survival (RFS) and overall survival (OS) times were calculated using Kaplan-Meier estimate probabilities and differences between survival curves were analyzed by the log-rank test. The prognostic impact of genotypes was examined using univariate and multivariate Cox regression analyses. Results: MSH2/GG plus MSH3/GG (31.7% vs. 18.7%, P = 0.003) genotypes were higher in laryngeal SCC (LSCC) patients than in controls. Carriers of the respective combined genotype were under a 3.69 (95% CI: 1.54-8.81) fold increased risk of LSCC. The median follow-up time of overall HNSCC patients enrolled in study was 46.0 months (IQR: 4.0-96.0). At 60 months of follow-up, RFS was shorter in patients with EXO1 GG genotype (54.8% vs 61.1%, P= 0.03) and OS was shorter in patients with MSH3 GG genotype (42.8% vs 52.5%, P= 0.02) compared to those with other genotypes, respectively. After multivariate Cox analysis, patients with EXO1 GG and MSH3 GG genotypes had worst RFS (HR: 1.50, 95% CI: 1.03-2.20, P= 0.03) and OS (HR: 1.19, 95% CI: 1.19-2.13, P= 0.002) than those with the remaining genotypes, respectively. Conclusions: Our data present, for the first time, evidence that inherited MLH1 c.933G > A, MSH2 c.211G > C, MSH3 c.3133G > A, and EXO1 c.1765G > A polymorphisms of DNA MMR pathway are important determinants of HNSCC and predictors of patient outcomes. Our findings, once validated in additional studies, will contribute to personalize the therapy of HNSCC patients.
6064 Poster Session (Board #388), Sat, 1:15 PM-4:45 PM
Outcomes of head and neck squamous cell carcinomas (HNSCC) treated with reirradiation (RRT) at Mayo Clinic. First Author: Kelly Kevelin Curtis, Mayo Clinic, Scottsdale, AZ

Background: RRT is offered as definitive (DRRT) or post-operative (PRRT) treatment for patients (pts) with loco-regionally recurrent (LRR) or new primary (NP) HNSCC in previously irradiated volumes. We report the results of a retrospective chart review of all consecutive pts with LRR and NP HNSCC treated with DRRT and PRRT at Mayo Clinic. Methods: We included LRR and NP HNSCC pts treated with DRRT/PRRT from 2003-2011 at all Mayo Clinic campuses. Patient and treatment related data were collected. Loco-regional recurrence rate (LR) and distant metastases rate (DM) at 2 years, and overall survival (OS) from end of RRT using Kaplan-Meier methods, were calculated. Results: We identified 89 pts (68 M, 21 F). 67 pts had LRR; 22 NP. Treatment included salvage surgery with PRRT (10 pts) and DRRT (42 pts). 30 pts received concurrent chemotherapy (CT) with PRRT; 33 DRRT pts received CT. Median prior RT dose was 66.6 Gy (26.4 – 79.2 Gy). Median PRRT dose was 60 Gy (11 – 70 Gy). Median DRRT dose was 69.6 Gy (18 – 76.8 Gy). LR occurred in 42 pts (47%) after RRT; 35 pts (39%) had LR by 2 years (95% CI, 30 – 50%). DM occurred in 20 pts (22%) after RRT; 16 pts (18%) had DM by 2 years (95% CI, 11 – 27%). Median OS was 22.2 mos (95% CI, 17.0 – 29.8 mos) with 2- and 5-year OS 47% and 16%. No difference in OS between LRR- and NP-HNSCC or PRRT and DRRT was found. CT was associated with shorter time to LR (4.3 vs. 12.1 mos, p = 0.008) but not with time to distant metastases or OS. At last follow-up (median 78.1 mos) 21 pts (24%) were alive, with 43.3 mos (95% CI, 27.6 – 52.9 mos) median OS from time of LR/RR. Among surviving pts, 2 cases of osteoradionecrosis (10%) and 1 carotid artery pseudoaneurysm with sentinel bleed (5%) were reported, with no reported spinal cord injuries. OS was better among 70 pts treated to 75% of tumor bed (95% CI, 0.5 – 0.9), compared to 90% of tumor bed (95% CI, 0.7 – 0.8), p = 0.05). Conclusions: RRT cures a small number of pts. 2-year OS of LRR/NP HNSCC pts treated with RRT in the time frame of this study appears superior to published outcomes. Shorter time to LR among pts receiving CT warrants further study, but may signify selection bias toward more aggressive therapy for pts with high risk LRR/NP HNSCC.

6065 Poster Session (Board #389), Sat, 1:15 PM-4:45 PM
Use of chemotherapy with IMRT reirradiation: MDACC experience. First Author: Mark A. Edson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The benefits of adding chemotherapy to radiation, combined with the ability to spare more normal tissue with conformal radiation techniques have led to an increased interest in reirradiation of head and neck cancers (HNC). However, similar to the use of chemotherapy in unirradiated patients with HNC, the use and delivery of systemic therapy in the reirradiation setting is not standardized. We evaluated our 15-year institutional experience using intensity modulated radiation therapy (IMRT) for reirradiation of recurrent HNC, focusing on chemotherapy-related outcomes. Methods: We retrospectively reviewed the records of 206 patients treated between 1999-2014 with IMRT reirradiation to definitive doses ( > 60 Gy). The Kaplan-Meier method was used to estimate loco-regional control (LRC), progression-free survival (PFS), and overall survival (OS). The log-rank test was used to compare variables of interest. Results: Median follow-up was 25 months. Of the 134 patients (65%) who received chemotherapy (CT), 124 (93%) received concurrent chemotheraphy (CCT), and 50 (37%) received induction chemotherapy (ICT). The use of ICT was associated with worse OS (5Y 35% vs 49%, P = 0.04), but not LRC (N.S.) or PFS (N.S.). The use of CCT was associated with improved LRC (5Y OS 55% vs 69%; P = 0.05) but not PFS (N.S.) or OS (N.S.). Sub-group analysis of patients who received CCT showed that the use of platinum-containing doublets (n = 24) was associated with improved LRC (5Y 82% vs 57%; P < 0.05). The use of ICT did not impact clinical outcomes. However, patients who experienced a radiographic complete response after ICT had improved 5-year PFS (5Y 43% vs 9%; P < 0.01) and OS (5Y 44% vs 18%; P < 0.01) but not LRC (N.S.). CT use was associated with increased grade 3 toxicity (5Y 59% vs 34%; P = 0.02), and for those receiving concurrent chemotherapy, grade 4 toxicity occurred in 70% compared to 46% with induction chemotherapy. IC was associated with increased grade 4-5 toxicity (28% vs 8%; P < 0.05). Prior CT use, and type or number of cycles did not affect clinical outcome or toxicity after reirradiation. Conclusions: Chemotherapy given concurrently with IMRT-based reirradiation for HNC appears to improve LRC but not OS. The potential for increased toxicity associated with combined modality treatment warrants careful patient selection.

6066 Poster Session (Board #390), Sat, 1:15 PM-4:45 PM
Double blind multimeric phase III GORTEC trial evaluating the efficacy of oral immune modulating formulae therapy during adjuvant radiochemotherapy in head and neck squamous cell carcinoma (HNSCC). First Author: Pierre Boisselier, Institut régional du Cancer Montpellier, Montpellier, France

Background: A previous phase II study showed that an oral immunomodulating formula could reduce severe toxicities and increased survival for HNSCC with concomitant cisplatin and irradiation treatment (1). We conducted a double blind prospective phase III multicenter trial. Methods: In 60 GORTEC centers pts. with curable HNC treated with standard radiochemotherapy (2, 3), 180 patients were randomly assigned to receive oral supplementation (3 bags/day, a formula enriched with L-arginine, ω-3 fatty and ribonucleic acids vs an isocarlic (isotenicogenous control) for 5 days before each cycle of cisplatin. Statistilcal analysis was done according to an intent-to-treat (ITT) and per protocol (PP) principle. Acute mucositis (RTOG and WHO scales) and 24-months survival survival were analyzed. Results: ITT included 172 patients and PP, the 109 patients with a product compliance ≥ 75%. No difference was identified one month after the end of radiochemotherapy on grade 3-4 mucositis, for ITT and for PP, with both scales, R’s (p = NS) and WHO (p = NS). In accordance with the phase II study, disease-free survival was significantly improved by the immunomodulating formula (p = 0.004) in PP patients, and a statistical trend was observed in overall survival (p = 0.07). In ITT patients, both overall and disease-free survivals were not significant (p = 0.22 and p = 0.25, respectively). The disease-free survival of CR did not reach the level of significance. Conclusions: Oral supplementation with an immunomodulating formula did not reduce grade 3-4 mucositis but showed significant increase of disease-free survival in product compliant patients (PP). Long term follow-up of our study along with further investigations are needed to confirm these findings and perhaps could open a new avenue for standard treatment of HNSCC. Acknowledgements: We thank the Ligue Nationale contre le Cancer and the Fondation Xavier Leverve for funding and Nestlé International for the product. (1) Assenat E et al. Eur J. Clin Nut Met 2011 (2) Cooper JS et al. NEJM 2004 (3) Bernier J et al. NEJM 2004 Clinical trial information: 2009-A00384-53.

6067 Poster Session (Board #391), Sat, 1:15 PM-4:45 PM
Is there a role for induction chemotherapy in the setting of concomitant chemoradiation in locally advanced head and neck cancer: A systematic review and meta-analysis of randomized controlled trials. First Author: Arot Popovitzer, Davidoff Cancer Center, Robin Medical Center, Petach Tiqa, Israel

Background: There is a controversy regarding the role of induction chemotherapy (IC) prior to concomitant chemoradiation (CCRT) in locally advanced head and neck cancer (LAHNC). We performed a systematic review and meta-analysis(MA) of all randomized controlled trials (RCTs) which assessed the added benefit of IC in this setting. Methods: We included RCTs that compared IC followed by CCRT to CCRT alone for LAHNC. The Cochrane Library, MEDLINE and conference proceedings were systematically searched (2000-11/2014). The primary outcome was overall survival (OS). Secondary outcomes were progression-free survival (PFS), disease control (DC), complete response (CR) rate and adverse events. Relative Risk (RR) for dichotomous data and hazard ratio (HR) for time to event data were estimated and pooled. Results: Five RCTs met the inclusion criteria, with a total of 1229 patients with stage III or IV LAHNC. Median age was 55y (35-75). IC consisted of docetaxel, platinum and 5FU (TFU) in 4 trials, and platinum-5FU (PF) in one trial. No statistically significant effect on OS was shown, though a trend towards the IC-CCRT group was observed - HR 0.85 (95%CI 0.71-1.02;p = 0.07). There was no significant difference in PFS HR 0.84 (0.57-1.24). Yet, patients treated with IC had a better DC compared to CCRT alone (HR of progression, treatment failure or death OR 0.44, 95%CI 0.24-0.81; p = 0.02), and to IC with CCRT (OR 0.46, 95%CI 0.20-1.02; p = 0.05). Conclusions: IC was not associated with increased grade 3-4 toxicity (5Y 9% vs 34%; P = 0.02), and for those receiving concurrent chemotherapy, grade 4 toxicity occurred in 70% compared to 46% with induction chemotherapy. IC was associated with increased grade 4-5 toxicity (28% vs 8%; P < 0.05). Prior CT use, and type or number of cycles did not affect clinical outcome or toxicity after reirradiation. Conclusions: Chemotherapy given concurrently with IMRT-based reirradiation for HNC appears to improve LRC but not OS. The potential for increased toxicity associated with combined modality treatment warrants careful patient selection.
Combination of everolimus and sorafenib in the treatment of thyroid cancer: Update on phase II study. First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Everolimus is an oral inhibitor of the mammalian target of rapamycin complex 1 (mTORC1). Laboratory data suggests that mTORC1 activity is required for the growth promoting effects of the oncoproteins RET, RAS, and BRAF in thyroid papillary carcinoma. Everolimus is indicated in both pts with DTC and MTC. Clinical trial information:

- **Patient No:** NCT01141309.
- **Drug:** everolimus is indicated in both pts with DTC and MTC.
- **Clinical Trial Information:**
  - **Purpose:** To evaluate the safety, tolerability, and clinical activity of everolimus in pts with RAIR follicular cell derived thyroid cancers (DTC) and medullary thyroid cancers (MTC).
  - **Methods:** This single institution study used a two-stage phase II design and was initiated on 9/21/10.
  - **Patient Selection:** A pilot, single arm, prospective trial using neoadjuvant rapamycin prior to definitive treatment with VEGF-targeted systemic therapy. Grade 4-5 adverse events at least possibly related to drug were evaluated.
  - **Data Cutoff:** The data cutoff date of 1/21/15. 7 pts are still on study.

**A Phase II study of everolimus (E) and sorafenib (S) in patients (PTS) with metastatic differentiated thyroid carcinoma who have progressed on sorafenib alone. First Author: Marcia S. Brose, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

**Background:** Recently, S became the first drug FDA-approved in 40 years to treat progressive, RAI-refractory thyroid cancer. S inhibits VEGF, PDGFR, Kit and RET. With S, patients achieve a median PFS of 10.8 months. We observed that pts may progress in some sites while maintaining stability in others. We hypothesized that progression on S may depend on increased activity of the oncoproteins AKT/MTOR signaling. Therefore, we conducted a Phase II study to see if the addition of everolimus (E), an oral mTOR inhibitor, to S would have activity in pts who had progressed on S alone. Methods: 35 pts with evidence of progression by RECIST criteria on S were enrolled. Pts would be randomized to continue with S or to switch to S + E (10 mg/d, 7.5 mg/d). Pts were followed for toxicity; if toxicity was seen, the dose of E and then S were incrementally increased to a maximum daily dose of S 800mg/d and E 10mg/d. The primary endpoint was progression-free survival (PFS). Results were evaluated by RECIST every 4 weeks. Results: Of 35 pts enrolled, 33 were evaluable for PFS and response. 17 pts had papillary, 9 had Hürthle cell, 1 had follicular and 6 had poorly differentiated subtypes. 13 pts were successfully dose escalated to full dose of both agents: S 800mg/d and E 10mg/d, 5 pts reached S 600mg/d and E 10mg/d, and 8 pts reached S 600mg/d and E 7.5 mg/d. While increased severity of hand foot skin reaction was anticipated, it was rarely seen. The median PFS was 13.7 mos (95% CI: 7.15-24.75). Complete responses were observed, 1 pt achieved a partial response and 18 achieved a best response of stable disease for > 6 mos. for a clinical benefit rate (CR + PR + SD > 6 mos.) of 58%. Conclusions: The addition of everolimus to sorafenib at the time of progression was tolerated and allowed pts an additional median of 3.7 mos. of disease stability. The addition of everolimus did not result in dose-limiting hand foot skin reaction as had been seen in prior studies in which both were started at the same time, demonstrating that these agents may be successfully combined if started sequentially. Our approach may have implications in other diseases where the combination of a VEGFR inhibitor and mTOR inhibitor may have added activity. Clinical Trial Information: NCT01263951.
Background: Despite the overall decreased incidence of oral cavity carcinoma in younger predominantly female non-smokers has been noted. We sought to explore the landscape of mutational and transcriptional alterations in non-smoking patients with OTC using the TCGA data. Methods: We queried the TCGA data utilizing a novel R-based software Cancer Genome Explorer (http://sourceforge.net/projects/cancergenomeexplorer/) to compare coding mutations, mutation spectra, gene expression and copy number profiles between groups of interest. Results: Sixty two female lifelong non-smokers or current reduced smokers (> 15 years) having cancers of the oral cavity including OTC (n = 29), oral cavity not otherwise specified (n = 17), floor of mouth (n = 6), alveolar ridge (n = 4), buccal mucosa (n = 3) or hard palate (n = 3) were identified in the TCGA clinical data. Seventy life-long non-smoker or reduced smoker male with a similar distribution of oral site cancers were also identified (n = 33, 18, 5, 8, 5, 1 cases respectively). Female versus male OTC exhibited very similar genomic profiles, as did a combined analysis of all of the above sites between males and females. The genomic differences we did detect came primarily from expression and mutation of X and Y chromosome genes. However, male and female OTC (n = 62) had several genomic features that distinguished them from other oral cavity sites (n = 77). These included relative differences in the frequency of CDKN2A, CASP8 and NOTCH1 coding mutations and differential rates of deletion of chromosomes 11q and 13q. Conclusions: Our results point to genomic differences in non-smoking OTC patients when compared to all other oral cavity tumors from non-smokers regardless of gender. These results present an opportunity to develop better understanding of the biology of OTC in non-smokers in addition to an exploration of targeted therapeutic approaches in this group. (This research was supported by a grant NCI R21 CA182661-01A1 to NFS and GZC).
Background: With the advent of immunotherapy, the role of the immune system in cancer patients is increasingly being investigated. The role of lymphocytes as indicators of the adaptive immune response has been reported; however, the relevance of the innate immune response is unclear. Monocytes are the precursor cells to dendritic cells and macrophages. As a crude metric, we sought to determine the predictive value of the pre-operative absolute monocyte count (AMC) in patients being treated for oral cavity squamous cell carcinoma. Methods: We retrospectively reviewed 551 consecutive patients treated at the Stanford Cancer Institute from 1998-2013 for oral cavity squamous cell carcinoma with surgical resection followed by adjuvant therapy if indicated. Patients treated for recurrent disease and metastatic disease were not included. The reference range for AMC is 0.3-0.95 K cells per microliter. For this study, a low AMC was defined as less than 0.5 K cells per microliter. Survival estimates were determined using the Kaplan-Meier method, and recurrence rates were determined using cumulative incidence estimates including competing-risk analyses. Results: In this cohort, 160 patients had a low AMC, and 391 patients had an AMC greater than or equal to 0.5 K cells per microliter. There was no statistically significant difference in T stage and N stage between patients with a low AMC compared to the remainder of the cohort. For the 119 patients who underwent adjuvant radiation therapy, those with a low AMC had improved overall survival at 2 years, 83% vs 53%, and at 5 years, 62% vs 33% (p = 0.02). For patients who did not undergo adjuvant radiation therapy, low AMC did not impact overall survival (p = 0.24). Conclusions: In addition to the adaptive immune system, the innate immune system may be relevant to cancer outcomes. Further investigation is required to understand the mechanisms leading to these observations.

6077 Poster Session (Board #401), Sat, 1:15 PM-4:45 PM
Low pre-operative absolute monocyte count to predict overall survival benefit for oral cavity squamous cell carcinoma. First Author: Timothy Bui, Stanford University, Stanford, CA

6078 Poster Session (Board #402), Sat, 1:15 PM-4:45 PM
Patterns of CD8+ T-cell infiltration and immune escape mechanisms in head and neck cancer. First Author: Vassiliki Saloura, University of Chicago, Chicago, IL

Background: Immunotherapy with PD-1/PD-L1 axis blockade has shown promising preliminary results in patients with head and neck squamous cell carcinomas (HNSCC) (Seiwert ASCO 2014). Using a 12-gene chemokine expression signature (Harlin/Gajewski 2009) 33-47% of HNC have a T-cell inflamed phenotype (TCIP-High) characterized by CD8+ TIL enrichment and PD-L1 expression in both HPV(-) and HPV(+) HNC. In this study, we sought to identify patterns of CD8+ tumor infiltration and describe immune escape mechanisms. Methods: We evaluated the patterns of infiltration of CD8+ TILs in a subset of tumors (N = 73) from the Chicago HNC Genomics (CHGC) cohort using IHC. 58 were also stained for PD-L1 expression. 55 tissues were evaluated with dual CD8/FoxP3 staining. To address potential mechanisms of immune escape, we interrogated the different patterns of CD8+ TIL infiltration in conjunction with the TCIP-high signature. Results: 27% (20/73) of CHGC tumors showed either no CD8+ T-cells (Immunologic Ignorance (II), 8%, 6/73) or CD8+ T-cells limited to the tumor periphery (Excluded Immune Infiltrate (EI), 19%, 14/73). Of these tumors, 75% (15/20) were PD-L1 negative and 25% (5/20) were PD-L1+. 73% (53/73) of tumors showed intratumoral CD8+ TILs. Of these tumors, 38 had available PD-L1 staining results and 63% (24/38) were PD-L1+ (Functional Immune Response (FIR)), while 37% (14/38) were PD-L1 negative (Non-Functional Immune Response (NFIR)). FIR tumors (intratumoral CD8+, PD-L1+) with strong PD-L1 positivity showed significantly higher immune cytolytic activity, by GZMA and PRF1 gene expression, compared to NFIR tumors. Tumors with intratumoral CD8+ TIL infiltrate correlated with the TCIP-High phenotype in both HPV(+) and HPV(-) tumors. FOXP3 staining was significantly higher in HPV(+) tumors. Conclusions: 73% of HNC attract intratumoral CD8+ TILs and 63% of these tumors seem to activate a functional immune response. PD-L1 upregulation may serve as a compensatory immune escape mechanism, making this subset a rational target for PD-L1 blockade. T- regulatory cells seem to play an additional role in immune evasion of HPV+ HNC, suggesting that a combinatorial approach with a T-reg depleting warrants clinical investigation.

6079 Poster Session (Board #403), Sat, 1:15 PM-4:45 PM
Correlation of specific genetic aberrations and signaling pathways with T-cell inflamed phenotype (TCIP) in head and neck cancer and as novel candidate biomarkers for checkpoint blockade therapy. First Author: Zhixiang Zhu, The University of Chicago, Chicago, IL

Background: Anti-PD-1/PD-L1 blockade is active in patients (pts) with head and neck squamous cell carcinoma (HNSCC) (Seiwert ASCO 2014). The T-cell inflamed phenotype (TCIP) (Saloura ASCO 2014) is characterized by CD8+ infiltration and PD-L1 expression in both HPV(+) and HPV(-) HNC. The genetic background of HNC has been described (Poeta 2007, Gross 2014), the impact of effects of specific genetic aberrations on outcome in HNC have been described (Poeta 2007, Gross 2014), the impact of therapies in genetic subgroups remains unknown. We therefore examined in an exploratory, hypothesis-forming analysis two large, genetically annotated cohorts, which preferentially employed different treatment regimens, with respect to impact on outcome in certain genetic backgrounds. Methods: Data of 238 patients (pts) from the Cancer Genome Atlas (TCGA), and 131 pts of the Chicago HNC Genomic Cohort (CHGC) receiving curative intent treatment for locoregionally-advanced HNC were included. Sub-groups of patients were analyzed evaluating anatomic site, HPV status, and 131 pts of the Chicago HNC Genomic Cohort (CHGC) receiving curative intent treatment for locoregionally-advanced HNC were included. Sub-groups of patients were analyzed evaluating anatomic site, HPV status, and primary treatment for locoregionally-advanced HNC. Pts in both cohorts were largely treated at high-volume North American referral centers. Pts in CHGC received more frequently induction chemotherapy and primarily taxane/FHX, non-platinum containing regimens and less frequently surgery. The genetic profiles were very similar between the two cohorts, which preferentially employed different treatment regimens. In both cohorts, HPV status, and primary treatment for locoregionally-advanced HNC were included. Results: In the exploratory analysis, we determined using cumulative incidence estimates including competing-risk analyses. Results: In this cohort, 160 patients had a low AMC, and 391 patients had an AMC greater than or equal to 0.5 K cells per microliter. There was no statistically significant difference in T stage and N stage between patients with a low AMC compared to the remainder of the cohort. For the 119 patients who underwent adjuvant radiation therapy, those with a low AMC had improved overall survival at 2 years, 83% vs 53%, and at 5 years, 62% vs 33% (p = 0.02). For patients who did not undergo adjuvant radiation therapy, low AMC did not impact overall survival (p = 0.24). Conclusions: In addition to the adaptive immune system, the innate immune system may be relevant to cancer outcomes. Further investigation is required to understand the mechanisms leading to these observations.

6080 Poster Session (Board #404), Sat, 1:15 PM-4:45 PM
Comparison of two large, genetically and clinically annotated head and neck cancer (HNC) cohorts (TCGA, CHGC) and differential treatment effects on TP53 mutated, as well as oral cavity cancers. First Author: Johannes Bragelmann, Medical Clinic III; Department of Oncology, Hematology and Rheumatology; University Hospital Bonn, Bonn, Germany

Background: While effects of specific genetic aberrations on outcome in HNC have been described (Poeta 2007, Gross 2014), the impact of therapies in genetic subgroups remains unknown. We therefore examined in an exploratory, hypothesis-forming analysis two large, genetically annotated cohorts, which preferentially employed different treatment regimens, with respect to impact on outcome in certain genetic backgrounds. Methods: Data of 238 patients (pts) from the Cancer Genome Atlas (TCGA), and 131 pts of the Chicago HNC Genomic Cohort (CHGC) receiving curative intent treatment for locoregionally-advanced HNC were included. Sub-groups of patients were analyzed evaluating anatomic site, HPV status, and 131 pts of the Chicago HNC Genomic Cohort (CHGC) receiving curative intent treatment for locoregionally-advanced HNC were included. Sub-groups of patients were analyzed evaluating anatomic site, HPV status, and primary treatment for locoregionally-advanced HNC. Pts in both cohorts were largely treated at high-volume North American referral centers. Pts in CHGC received more frequently induction chemotherapy and primarily taxane/FHX, non-platinum containing regimens and less frequently surgery. The genetic profiles were very similar between the two cohorts, which preferentially employed different treatment regimens. In both cohorts, HPV status, and primary treatment for locoregionally-advanced HNC were included. Results: In the exploratory analysis, we determined using cumulative incidence estimates including competing-risk analyses. Results: In this cohort, 160 patients had a low AMC, and 391 patients had an AMC greater than or equal to 0.5 K cells per microliter. There was no statistically significant difference in T stage and N stage between patients with a low AMC compared to the remainder of the cohort. For the 119 patients who underwent adjuvant radiation therapy, those with a low AMC had improved overall survival at 2 years, 83% vs 53%, and at 5 years, 62% vs 33% (p = 0.02). For patients who did not undergo adjuvant radiation therapy, low AMC did not impact overall survival (p = 0.24). Conclusions: In addition to the adaptive immune system, the innate immune system may be relevant to cancer outcomes. Further investigation is required to understand the mechanisms leading to these observations.

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Background: ACC is chemotherapeutic refractory and there is no standard of care treatment for patients (pts) with metastatic disease. ACC genotyping revealed alterations in the Notch (N) pathway in 13-29% of cases. An ACC patient identified in our institution with an activating Notch1 (N1) mutation achieved a partial response after 2 cycles of a N1 inhibitor in a phase 1 trial. In this study, we investigate the clinical and pathologic characteristics of N1 mutant ACC. Methods: N1 sequencing was performed in 97 pts (71 using whole-exome sequencing and 26 using a 50 gene panel including N1 exons 26, 27, 34). Comparisons between tumor characteristics and clinical outcomes in pts with or without activating N1 mutations (PEST or HD domain) were performed. Results: N1 mutations were identified in 13 pts. Pathway activation was confirmed by IHC for N1 intracellular domain. N1 ACC pts had significantly higher disease stage at diagnosis (p = 0.009, Fisher’s exact test), and solid histologic subtype (p = 0.027). Only 1/38 pts who presented with stage I-III disease had N1 mutation compared with 4/12 pts (33%) who presented with distant metastasis. Although lung is the most common site of metastasis in ACC, N1 mutants developed bone (odds ratio [OR] = 7) and liver (OR = 4.5) metastasis more frequently than lung (OR = 0.44). Recurrence-free survival and OS were significantly shorter in the N1 mutant subgroup (p-value = 0.025, Log-rank test). The clinical correlations identified for the N1 mutants were maintained in an extended analysis that included SPEN and N2 mutations (4 pts), with an even higher impact in OS (p = 0.007).

Conclusions: A subgroup of ACC harbors N1 (13.4%) or other N pathway activating mutations (17%). N activation defines a more aggressive phenotype, with a distinct pattern of metastatic spread, higher risk of relapse, and shorter OS. The identification of genetic events that activate N and the encouraging response observed in an index case support an immense opportunity to further explore this pathway as a therapeutic target in ACC.
Ceritinib in anaplastic thyroid cancer (ATC) with ALK abnormalities. First Author: Saad A. Khan, The University of Texas Southwestern Medical Center, Dallas, TX

Background: ATC is a rare tumor of thyroid epithelium affecting several hundred patients annually, but causing death in almost 100% of them. It has a dismal prognosis with currently ineffective treatment options, particularly in metastatic disease. BRAF V600E mutations have been identified and then targeted with novel agents, which led to striking activity in patients (Rosove et al, NEJM 2013). ALK overexpression and mutation have also been identified in ATC in 11% of patient samples (Murgan et al, Cancer Res 2011). Patients treated with ALK inhibitors show dramatic tumor response (Godbert et al, JCO 2014). Ceritinib is a well-tolerated, highly potent oral ALK-inhibitor that is FDA-approved for use in ALK-rearranged lung cancer. It is critical to develop a framework by which actionable tumor samples can be collected, actionable mutations identified and novel agents rapidly tested. Methods: This multicenter, open label trial (NCT02289144) is collecting tissue from 100 patients with ATC/UTC. A genomic profile will be created by next generation sequencing of all 100 tumor samples. 10 of these patients are predicted to demonstrate ALK abnormalities; either by overexpression, mutations or rearrangements. Upon confirmation of metastatic or unresectable disease, patients with ALK-abnormalities will get 750 mg ceritinib daily. Prior therapy does not affect eligibility. Primary endpoint is progression free survival of 3.5 months, compared to historical controls. As patients are screened, their tumor sample genomic profile will be collected and analyzed for future targets. As genomic profiling provides more information about actionable targets in ATC patients, additional therapeutic arms/sub-studies with other novel agents will be added to this trial. This protocol may serve as the basis by which newer therapies may be tested in this challenging disease. Clinical trial information: NCT02289144.

TP6087 Poster Session (Board #408a), Sat, 1:15 PM-4:45 PM

TPExtreme randomized trial: TPEx versus Extremge regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma. First Author: Joel Guigay, Centre Antoine Lacassagne, Nice, France

Background: The EXTREME regimen (6 cycles of 5FU–cisplatin-cetuximab followed by cetuximab maintenance) is currently the standard first line in recurrent/metastatic (R/M) HNSCC. The GORTEC trial evaluating the TPEx regimen (4 cycles of docetaxel–cisplatin-cetuximab followed by cetuximab maintenance) demonstrated good results (median OS 14 months, ORR 54%) with acceptable safety profile, excellent dose intensity, high rate of patients who started maintenance. The aim of the current trial is to compare TPEx and EXTREME regimens. Methods: International, randomized, open-label trial. Main inclusion criteria are: histologically confirmed R/M HNSCC not suitable for locoregional treatment, age 18-70 years, PS < 2, creatinine clearance > 60 mL/min, prior total dose of cisplatin < 300 mg/m². The control arm EXTREME: 6 cycles, every 21 days, of cisplatin 100 mg/m² day1, 5FU 4000 mg/m² continuous infusion day1-4, and weekly cetuximab 250 mg/m² (1st loading dose 400 mg/m²) followed by weekly cetuximab 250 mg/m² maintenance. The experimental arm TPEx: 4 cycles, every 21 days, of docetaxel 75 mg/m² day1, cisplatin 75 mg/m² day1, and weekly cetuximab 250 mg/m² (1st loading dose 400 mg/m²), followed by cetuximab 500 mg/m² maintenance every 2 weeks. If cisplatin is not tolerated or its total cumulative dose reaches 600 mg/m², it must be replaced by carboplatin AUC5, G-CSF prophylactic administration is mandatory for each cycle in the TPEx arm. Only patients with CR/PR/SD will continue the cetuximab maintenance (weeks until PD or persistence until 12 months). The primary endpoint is OS. Assuming a 2-sided type I error of 0.05, observing 295 deaths will provide a 80% power to detect a hazard ratio of 0.72. 295 deaths are expected out of 416 patients (208 per arm). Secondary endpoints are ORR, best response rate, PFS, TTP, toxicity and QoL. Tumor response assessments (Weeks 6, 12 and 18, then every 8 weeks until PD) will be reviewed by a blinded central image review committee. HPV central analysis and cost-effectiveness study are ancillary studies. GORTEC (France), AIO-Studien-gGmbH (Germany), TTCC (Spain) joint trial in collaboration with French GETTEC, GERCOR, H&N UNICAN-GER groups. Unrestricted grant from Merck Serono. Clinical trial information: NCT02268695.

TP6088 Poster Session (Board #408b), Sat, 1:15 PM-4:45 PM

A Phase 2, multicenter, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic (R/M) squamous cell carcinoma (SCCHN) of the head and neck (H11022/H11022, H11022/H11022). First Author: Dan Paul Zangberg, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD

Background: Patients (pts) with R/M SCCHN have a poor prognosis, with current systemic therapy options after failure of first-line platinum-based chemotherapy yielding objective response rates (ORRs) of approximately 10% and an overall survival (OS) of 6 months. In SCCHN, tumors create a high immunosuppressive environment and evade immune detection by exploiting inhibitory immune checkpoints such as the programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) axis. Upregulation of PD-L1 by SCCHN tumor cells is associated with inhibition of antitumor T-cell responses. Thus, therapeutic intervention with immune-modulating agents targeting this pathway holds promise. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD-80 with high affinity and selectivity. Evidence of clinical activity for MEDI4736 in R/M SCCHN has been seen in a Phase 1 study (NCT01693562), with initial data indicating that PD-L1 expression is associated with a higher ORR. A comprehensive clinical development program of MEDI4736 in SCCHN is underway. Here we describe the HAWK study (NCT02207530), a trial with registration potential, assessing MEDI4736 monotherapy in pts with PD-L1+ R/M SCCHN. Methods: In this Phase 2, open-label, single-arm, multicenter study, 112 PD-L1+ pts will be enrolled from North American and European sites to investigate the efficacy and safety of MEDI4736 (10 mg/kg IV every 2 weeks for up to 12 months). Eligible pts, who are immunotherapy naive and have tumor progression or recurrence during or after treatment with 1 platinum-containing regimen for R/M disease, will receive MEDI4736 monotherapy. The primary outcome measure is ORR (RECIST v1.1), based on independent central review. Secondary outcome measures will further assess disease control rate, duration of response, progression-free survival, and OS (using RECIST v1.1 and immune-related RECIST criteria); safety (CTCAE v4.03) and tolerability; and health-related quality of life. Exploratory outcomes include PK, immunogenicity, and potential biomarkers of response to MEDI4736. Recruitment is ongoing. Clinical trial information: NCT02207530.

TP6088 Poster Session (Board #409b), Sat, 1:15 PM-4:45 PM

Window of opportunity trial of HPV E7 antigen-expressing Listeria-based therapeutic vaccination prior to robotic surgery for HPV-positive oropharyngeal cancer. First Author: Brett Miles, Department of Otolaryngology, Mount Sinai Medical Center, New York, NY

Background: The incidence of human papilloma virus-associated oropharyngeal cancer (HPVOPC) has rapidly risen over the past two decades. Foreign viral antigens make HPVOPC an attractive target for immunotherapy. One exciting approach is the use of live attenuated Listeria monocytogenes-engineered to express the HPV16 E7 protein (LmE7) and elicit a vigorous immune response. We designed a phase II “window of opportunity” trial with robust correlative endpoints to determine the effect of LmE7 vaccination on anti-tumor immunity in the tumor microenvironment and peripheral blood, as well as safety and tolerability in the HPVOPC population. Methods: Trial Design: Non-randomized single-arm phase II clinical trial utilizing a Simon’s two-stage design. HPVOPC patients receive two cycles of LmE7 over 5 weeks prior to standard-of-care transoral surgical resection of their tumor with or without neck dissection. The primary objective is to determine the rate of post-vaccination T cell responses by measuring the pre- and post-treatment mean frequency of peptide-specific IFN-γ expressing T cells in the peripheral blood by ELISPOT. We will conclude that LmE7 is likely highly immunogenic and worth further investigation if post-treatment responses are seen in > 75% of patients. Inclusion Criteria: Previously untreated surgically-resectable stage II-IV HPVOPC, HPV-positive by PCR-based testing. Exclusion Criteria: Prior history of cancer with recurrence within 5 years, or any history of systemic cancer therapy; immunosuppressive disorder or medications, medical contraindications to therapy. Correlative Studies: The pattern of immuneocclusion in the tumor and draining lymph nodes will be assessed by multiplex immunofluorescence; expression profile of immune-related genes assessed by nanotagging; and T cell receptor diversity by deep sequencing. These tissue-based changes will be correlated with comprehensive analysis of immune changes in the peripheral blood. Status: Open, actively accruing. 8 of a maximum 22 (9 in first stage, 13 in second stage) vaccinated patients, and O of a maximum 10 untreated observational cohort patients have been enrolled. Clinical trial information: NCT02002182.

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6500 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

The Technology Enhanced Navigation (TEN) Trial among low-income patients with breast cancer. First Author: Kathy J. Helzlsouer, The Prevention and Research Ctr, Baltimore, MD

Background: Socioeconomic disparities negatively impact adjunct breast cancer treatment completion. A web-based knowledge application was developed in collaboration with breast cancer survivors and evaluated in a randomized clinical trial for the impact on treatment adherence with and without virtual navigator support. The application provides direct links to vetted websites for both study arms, and, for the intervention arm, tailored documents, short instructional videos, and navigator visits via telephone or phone are provided. Methods: Eligible patients were newly diagnosed with non-metastatic breast cancer, low-income (U.S. Department of Housing and Urban Development guidelines) Maryland residents, and recommended to have adjunct treatment. Patients were given a netbook computer, training, and 12 months of wireless internet access and randomized to either the application alone (control arm) or to the application and nurse/social worker navigation support (intervention arm). Adherence was assessed by medical record review and measured by percent initiating/completing recommended treatment. Baseline characteristics and results were compared by study arm using t-tests, chi-square, and Poisson regression analyses. Results: Of 150 eligible patients, 101 were enrolled; 49 on each arm evaluable. The majority were non-white (67%) and unemployed/disability (68%); 47% had a high school education or less. Over 70% of participants on both arms agreed that the computer application was easy to use; confidence in using the application was high (71% intervention arm; 67% control arm). On the control arm, 10 adjunct treatments were refused totally or in part among 6 patients; 2 on the intervention arm (p = 0.04). Three control-arm patients refused multiple treatments: one refused surgery and radiation; another refused radiation and hormone therapy; and another refused chemotherapy and radiation. One patient on the intervention arm refused post-mastectomy radiation and another completed chemotherapy, initiated hormone therapy, but discontinued radiation therapy. Conclusions: Among low-income patients with breast cancer, adherence to adjunct therapy was improved with navigator support compared to application-alone. Clinical trial information: NCT01596179.

6502 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Trends in resource utilization and costs during implementation of a lay navigation program. First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Background: Lay navigators provide support to patients from diagnosis through survivorship or end of life. We hypothesized that integrating lay navigators into the care team would lead to reduced healthcare utilization and cost. Methods: Medicare claims data were obtained for patients ≥ 65 years old diagnosed with cancer in 2008-2014 within the UAB Health System Cancer Community Network (UAB CCN) (12 cancer centers in AL, MS, TN, GA, FL) to identify the percentage with ≤ 1 ER visit, hospitalization, ICU admission, or hospice admission. Analysis period runs from 3/1/2013 to 6/30/2014. The first patient was enrolled in the navigation program in March 2013, and ~30% of patients were navigated by June 2014. Costs for Medicare were assessed, excluding prescription drugs. We used general linear models to evaluate changes in both health care utilization and cost from the pre- (1/11/2-2/28/13) to the post- implementation period (3/1/13-6/30/14). Results: We observed decreases after implementation from 13.4% to 11% for hospitalizations (18% decrease, p < 0.01), 8.0% to 7.1% for ER visits (12% decrease, p < 0.01), 2.9% to 2.5% for ICU admissions (14% decrease, p = 0.04) and an increase of 3.9% to 4.3% for hospice (9.2% increase p = 0.37). Costs decreased about $158 per quarter per beneficiary over the analysis period. A significant pre-post decrease of $952 per beneficiary (p < 0.01) lead to an estimated total reduction in Medicare costs of $18,406,920 for the 1950 enrolled beneficiaries in the UAB CCN for the five quarters post- implementation. Conclusions: Thislay health navigator program may increase hospice use and reduce health care use and costs. Further analysis of its direct impact is warranted. The project described was supported by Grant Number 1C1CMS331023 from the Department of Health and Human Services, Centers for Medicare & Medicaid Services. The contents of this abstract are solely the responsibility of the authors and do not necessarily represent the official views of the U.S. Department of Health and Human Services or any of its agencies.

6503 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

How should we estimate costs of care attributable to cancer? First Author: Aileen B. Chen, Dana Farber Cancer Inst, Boston, MA

Background: Costs of care attributable to cancer are distinct from total costs of medical care, and transparent methods are needed to inform decisions about value of interventions. We measure how alternative strategies for specification of cancer-free control cohorts influences estimation of cancer-attributable costs. Methods: Using SEER-Medicare data, we calculated costs to Medicare from one month prior until 11 months following diagnosis among patients ≥ 66 diagnosed with lung, breast, prostate, and colorectal cancers from 2007-2009. Cancer attributable costs were estimated by subtracting monthly costs for cancer patients from one of 3 alternative reference cohorts: 1) non-cancer Medicare patients individually matched by age, gender, race, and SEER region, 2) non-cancer Medicare patients matched on demographic and comorbidity characteristics with a within-year match on modified Charlson comorbidity score, 3) monthly costs from 2 to 13 months prior to diagnosis, using cancer patients as their own control. Results: Cancer-attributable costs were highest for all patients when using their own pre-diagnosis costs as comparison. Cancer-attributable costs were higher among breast and prostate, but lower among lung and colorectal patients, when using non-cancer controls and matching by comorbidity in addition to demographic characteristics. The greatest variation was seen for prostate cancer, with 39-73% of total costs attributed to cancer depending on reference cohort. Mean total and cancer-attributable costs are summarized in the Table. Conclusions: Choice of reference group can have a substantial impact on proportion of total costs attributed to cancer and should be clearly delineated in analyses of cost and value. Mean Medicare costs in year 1 ($).

<table>
<thead>
<tr>
<th>Total costs</th>
<th>Cancer-attributable costs, by reference group (% total costs attributed to cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cancer patients, demographic match</td>
<td>Non-cancer patients, demographic and comorbidity match</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
</tr>
<tr>
<td>47,366</td>
<td>30,958</td>
</tr>
<tr>
<td>31,703(67)</td>
<td>14,653(47)</td>
</tr>
<tr>
<td>28,725(61)</td>
<td>15,242(49)</td>
</tr>
<tr>
<td>35,476(75)</td>
<td>22,749(73)</td>
</tr>
</tbody>
</table>

6504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Financial burden of cancer clinical trials: Impact of an equity intervention program. First Author: Ryan David Nipp, Dana-Farber / Harvard Cancer Center, Boston, MA

Background: Cancer patients (pts) often experience financial burden, but little is known about the additional burden of clinical trial (CT) participation. Additionally, CT enrollment among underserved groups is lacking. We sought to examine the impact of a cancer care equity program (CCEP) on CT enrollment and to assess pt-reported barriers to CT participation. Methods: We implemented a CCEP at Massachusetts General Hospital (MGH) in 2014 to help fund non-clinical expenses related to CTs (e.g. travel, lodging). To determine the impact of the CCEP on CT enrollment, we compared CT enrollment in 2014 (after initiating the CCEP) to 2012 and 2013. We used multiple regression analysis to evaluate changes in CT enrollment. To assess financial barriers to CT participation, we administered surveys to CCEP pts and a comparison group of non-CCEP pts. We used chi-square tests to compare CCEP and non-CCEP pts. Results: In 2014, CT enrollment increased by 17% and 40% compared to 2012 and 2013. Adjusting for CT availability, phase, and cancer type, CT enrollment increased significantly from 2013 to 2014 (p = 0.02). In 2014, CT enrollment increased among racial minorities (p < 0.01) and those living > 50 miles from MGH (p < 0.01). Comparing CT pts who enrolled in CCEP to those who did not, more CCEP pts were female (68% vs 51%, p < 0.01), under age 65 (74% vs 64%, p = 0.05), with metastatic disease (90% vs 72%, p < 0.01), incomes < $50k/yr (24% vs 15%, p < 0.05), and in phase I CTs (76% vs 50%, p < 0.01). Of 87 pts who completed the financial barriers survey (61% response rate), we received responses from 49 CCEP pts and 38 non-CCEP pts. More CCEP pts reported financial concerns (56% vs 11%, p < 0.01). Compared to non-CCEP pts, more CCEP pts reported concerns with medical costs (47% vs 14%, p < 0.01), travel (61% vs 11%, p < 0.01), and insurance coverage (43% vs 14%, p = 0.01) related to CT participation. Conclusions: CT enrollment increased after the implementation of a CCEP, particularly among underserved groups. While CTs often represent the best option for pts with cancer, pts served by the CCEP report significant financial barriers to CT participation. These findings stress the need to recognize and address the financial burden of CT participation.
6504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Cost of chemotherapy for metastatic colorectal cancer with either bevacizumab or cetuximab: Economic analysis of CALGB/SWOG 80405. First Author: Deborah Schrag, Dana-Farber Cancer Institute, Boston, MA

Background: CALGB/SWOG 80405, a phase III trial, found that adding either bevacizumab or cetuximab to standard first-line chemotherapy for metastatic colorectal cancer (mCRC) resulted in similar survival. We compared the economics of treatment on each arm. Methods: Patients were assigned to standard chemotherapy (Cx) and randomized to either bevacizumab (B, N = 559) or cetuximab (C, N = 578). Quality of life was assessed at baseline and at 8 week intervals using the QLQ-C30 49-item representative subgroup of participants (N = 56 for B and N = 55 for C) to estimate utilities. Because survival and quality of life were similar in each arm, cost-minimization rather than cost-effectiveness analysis was performed. Chemotherapy utilization was tracked from randomization to progression and drug costs were estimated using 4th quarter 2014 average sales price from the US Center for Medicare and Medicaid Services. Resource utilization of acute care including hospitalizations, emergency room visits and ICU care were tracked while patients were on study and costs assigned based on CMS estimates for mCRC patients. End of life and downstream costs were assumed to be comparable per survival month. Out of pocket costs were not tracked. All cost estimates are in 2014 USD.

Results: Acute care costs were similar but drug costs were higher in the cetuximab arm (Table). Results were robust to sensitivity analyses and did not change whether the chemotherapy backbone included oxaliplatin or irinotecan. Conclusions: For first-line chemotherapy treatment of patients with kras wild type mCRC, based on US 2014 drug costs, bevacizumab is preferable to cetuximab from a health economic standpoint. Clinical trial information: NCT00265850.

Mean Costs of treatment for participants in CALGB 80405

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ChemO-B</th>
<th>ChemO-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-directed chemotherapy</td>
<td>$37,124</td>
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<tr>
<td>Acute care costs</td>
<td>$28,951</td>
<td>$29,494</td>
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<tr>
<td>Differences (95% CI)</td>
<td>$7,362</td>
<td>$8,551</td>
</tr>
<tr>
<td>Mean costs of care</td>
<td>$66,076</td>
<td>$105,339</td>
</tr>
<tr>
<td>Comparing B and C</td>
<td>$39,264</td>
<td>$48,521</td>
</tr>
</tbody>
</table>

6506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Value of information analyses for real-time prioritization decisions within a cancer clinical trials cooperative group. First Author: Caroline Savage Bennecke, University of Washington, Seattle, WA

Background: Cancer clinical trials groups face excess demand for limited research funds and patient populations. Value of Information (VOI) analyses are an emerging methodology that can help align research investments with areas that provide the greatest benefit to patients. Prior patient histories and physician expectations remain concerning its feasibility and interpretability in real-world research prioritization decisions. Our objective was to develop and assess a process for calculating VOI in real-time to inform trial approval decisions within SWOG, a large US-based cancer clinical trials cooperative group. Methods: We developed a rapid, reproducible modeling approach to estimate VOI, and applied the method to nine VOI (V1-V9) trials focused on breast, gastrointestinal (GI) and gynecological (GYN) cancer that were reviewed by SWOG leadership between 2008-2013. The decision models for each trial proposal were based on the trial design and informed from the literature. "Clinical" (benefits only) and "economic" (treatment and trial costs) VOI estimates were calculated using Bayesian updating methods. We customized the process using stakeholder input. Results: VOI modeling was feasible for 8 of 9 trial proposals. Model construction and calculation took 1-2 weeks for each proposal. Net VOI results varied widely from proposal to proposal (Table). SWOG leaders felt that VOI analyses would likely be useful to inform future trial proposal evaluations. Conclusions: We developed an efficient and customized process to calculate the expected VOI for cancer clinical trial proposals that is feasible for use in real-time decision-making and acceptable to SWOG stakeholders. Prospective use and assessment of this approach is currently underway within SWOG.

Net VOI metrics for 9 retrospective trial proposals.

<table>
<thead>
<tr>
<th>Proposal ID</th>
<th>Phase</th>
<th>Sample Size</th>
<th>Committee</th>
<th>Per-Patient VOI</th>
<th>Population-level VOI</th>
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<tr>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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<td>120</td>
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<td>$14,476</td>
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<tr>
<td>E</td>
<td>2</td>
<td>92</td>
<td>GI</td>
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<td>F</td>
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6505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Necitumumab in metastatic squamous non-small cell lung cancer (mSqNSCLC): Establishing a value-based cost. First Author: Daniel A. Goldstein, Wayne Cancer Institute of Emory University, Atlanta, GA

Background: The SQUIRE trial demonstrated that adding necitumumab to chemotherapy for patients with mSqNSCLC produces a median overall survival benefit of 1.6 months (hazard ratio 0.84). The objective of this study was to evaluate the range of drug costs for which adding necitumumab to chemotherapy could be considered cost-effective. Methods: We developed a Markov model to compare the incremental cost-effectiveness of standard chemotherapy with or without necitumumab in the first-line treatment of mSqNSCLC. In the model, patients received gemcitabine and cisplatin for 6 cycles or gemcitabine, cisplatin, and necitumumab for 6 cycles followed by maintenance necitumumab. The clinical inputs were the survival benefits and frequency of adverse events (AEs) described in the SQUIRE trial. Weibull models were fitted to the survival curves in the SQUIRE trial. The cost inputs included drug costs based on the Medicare average sale prices, and costs for drug administration and the management of AEs based on Medicare reimbursement rates (all in 2014 US $). Model robustness was addressed by probabilistic sensitivity analyses (PSA) in which we ran 10,000 Monte Carlo simulations sampling from the distributions for all variables. We performed multiple model simulations each time varying Willingness To Pay (WTP) values to evaluate the incremental cost effectiveness ratio (ICER) across a range of values for the cost of necitumumab. Results: In the base case analysis, the addition of necitumumab produced an incremental survival benefit of 0.15 life years (LY) and 0.11 quality-adjusted life years (QALY). The PSAs established that: when necitumumab cost < $563 per cycle there was 90% confidence that the ICER for adding necitumumab would be < $100,000/QALY; when necitumumab cost $1309 per cycle there was 90% confidence that the ICER would be < $200,000/QALY; and when necitumumab cost > $6,628 per cycle there was > 99% confidence that the ICER would be > $500,000/QALY. Conclusions: These findings provide a value-based range for the cost of necitumumab from $563 to $1309 per cycle. This study provides a framework for establishing value based pricing for new oncology drugs entering the US marketplace.
Clinical Science Symposium, Sun, 8:00 AM-9:30 AM
Financial insolvency as a risk factor for mortality among patients with cancer.
First Author: Aasthaa Bansal, University of Washington, Seattle, WA

Background: Patients with cancer are more likely to file for bankruptcy than the general population, but the impact of severe financial distress on health outcomes among cancer patients is not known. Methods: We linked Surveillance, Epidemiology and End Results (SEER) cancer registry records and federal bankruptcy records for Western Washington and identified patients who were diagnosed with cancer from 1995 to 2009. We used propensity score matching to account for differences between patients who filed for bankruptcy and those who did not, with respect to age, gender, race, marital status, residence type, income, stage at diagnosis, and treatment(s) received. In the propensity score matched sample, we used Cox proportional hazards models to compare overall survival between patients who filed and those who did not. Results: Compared to patients who did not file for bankruptcy (n = 226,868), those who filed (n = 4,728) were more likely to be younger, female, non-white, have local or regional (vs. distant) stage disease at diagnosis and have received treatment. After propensity score matching, 7,682 patients remained in the analysis, 3,841 subjects in each group. Both groups had a mean age of 53 (SD 14.7), more men than women (54%), a mean income of $49,000 (SD $12,000), and majorities of white (86%), married (60%) and urban (91%) patients. Most patients in both groups were diagnosed with local or regional stage cancer (84%) and both groups received similar first courses of treatment. Compared to cancer patients who did not file for bankruptcy, the adjusted hazard rate for mortality among patients who filed was 75% higher (HR 1.75, 95% CI (1.61, 1.91)). Excess mortality risk following bankruptcy varied by cancer type, with colorectal, prostate, lung and thyroid cancers having the highest risk. Excluding patients who were distant stage at diagnosis from the analysis had little impact on the mortality risk. Conclusions: Severe financial distress requiring bankruptcy protection following cancer diagnosis appears to be a risk factor for mortality. Further research is needed to understand the process by which extreme financial distress influences survival after cancer diagnosis, and to find factors that could mitigate this risk.

Clinical Science Symposium, Sun, 8:00 AM-9:30 AM
Effect of organizational approaches on safety-net hospitals’ cancer care quality.
First Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Safety-net hospitals, historically at higher risk for delivering poor-quality care, provide a disproportionate amount of care to vulnerable populations. Some safety-net institutions deliver excellent quality cancer care. We undertook this study to determine the impact of organizational factors on breast cancer care quality. Methods: We abstracted charts of 389 breast cancer patients treated in 2009-12 at 9 inner-city safety-net hospitals with high proportions of minority breast cancer patients to measure underuse of needed adjuvant treatment. We interviewed 90 key informants (n = 59 clinical; n = 16 administrative; n = 12 clerical; n = 3 other) about how care is coordinated and delivered. Using Qualitative Comparative Analysis, we defined “conditions”—handoffs, no-shows, organizational culture—that particularly impact care coordination, categorized hospitals into low (< 10%), intermediate (10%-20%) and high (> 20%) underuse of needed adjuvant therapies, and calibrated each of the “conditions.” Hierarchical models assess impact of organizational and patient factors on underuse. Results: Underuse ranged from 8% to 29%. Higher quality sites designated individuals to track & follow-up no-shows; shared clinical information during handoffs; had fully integrated EHRs enabling providers and clerks to transfer responsibility across specialties; had strong system support; paid close organizational attention to clinic patients; and allocated adequate resources for the cancer clinics. Organizations with a patient-centered culture focused on making processes easier for patients. Poor quality sites lacked these organizational characteristics. Multivariate modeling found that beyond older patient age (RR = 1.89; 1.14-3.15), hospitals with strong approaches to follow-up affect underuse rates (RR = 0.24; 0.08-0.738). Conclusions: At safety-net hospitals, underuse of needed cancer therapies is affected by older patient age and organizational approaches to track and follow-up treatment. These findings offer strategies to safety-net hospitals to improve cancer care quality.
A randomized controlled trial (RCT) to improve enrollment to cancer clinical trials.

Methods: Participating sites (n = 34) were stratified into four strata based on 2011 recruitment numbers. Control sites (n = 18) received usual CTMS funds only while intervention sites (n = 16) received usual funds plus additional funds, proportional to the number of patients recruited in 2011. Additional funding was a median increase of 300% (IQR: 112.5%, 459%) relative to usual CTMS funds and was an average 11.8% (IQR: 8%, 12.3%) increase in a site’s budget. Additional funds were provided in early 2013. Sites were to use funds with the aim of increasing recruitment. The primary endpoint was randomized to evaluate the hypothesis that additional funding would improve trial recruitment. Results: The median number of new trial recruits in 2013 was 21 (IQR: 5, 39) in the control arm and 12.5 (IQR: 3.5, 44.5) in the intervention arm. The ratio of the annual recruitment rate of new trial recruits at the intervention sites compared to control sites in 2013 adjusting for 2012 numbers and the number of patients recruited in 2011. Additional funding was a median increase of 300% (IQR: 112.5%, 459%) relative to usual CTMS funds and was an average 11.8% (IQR: 8%, 12.3%) increase in a site’s budget. Additional funds were provided in early 2013. Sites were to use funds with the aim of increasing recruitment. The primary endpoint was randomized to evaluate the hypothesis that additional funding would improve trial recruitment. Results: The median number of new trial recruits in 2013 was 21 (IQR: 5, 39) in the control arm and 12.5 (IQR: 3.5, 44.5) in the intervention arm. The ratio of the annual recruitment rate of new trial recruits at the intervention sites compared to control sites in 2013 adjusting for 2012 numbers. Further evaluation of the MAA’s effect, focused on colon cancer, where longstanding fluorouracil-based regimens were augmented in 2004 with 7 newly-approved drugs (oxaliplatin, bevacizumab, and cetuximab). Methods: Using the 2000-2009 SEER-Medicare data, we examined trends in chemotherapy use and type of antineoplastic received among 59,642 stages II-IV colon cancer patients. Logistic regression models tested the effect of time (pre-post the 2005-2006 reimbursement change) and setting (physician offices implemented reimbursement changes in 2005 vs hospital outpatient departments [OPD] in 2006); interaction terms tested for differential effects of MAA implementation in the 2 settings. Models controlled for patient demographic and tumor characteristics. Results: Overall, 16.3% of stage II, 52.4% stage III and 39.6% stage IV colon cancer patients received antineoplastics. After the reimbursement change in 2007-09 relative to 2000-03, stages II (marginal probability (MP) = -0.06, p < 0.01) and III (MP = -0.04, p < 0.01) patients decreased antineoplastic use, while stage IV use increased (MP = 0.03, p < 0.01). While use of fluorouracil-based therapy decreased slightly after reimbursement changes (MP: -0.07 stage II; -0.04 stage III; -0.04 stage IV; p < 0.01 for all), use of new drugs increased substantially (MP: 0.47 stage II; 0.67 stage III, 0.77 stage IV; p < 0.01 for all). Use of new drugs occurred earlier in physician offices compared to OPDs (p < 0.01). Conclusions: Colon cancer patients saw smaller decreases in treatment with fluorouracil-based chemotherapy, but larger increases in newly approved drugs after the MAA. Trends suggest slightly earlier increases in physician office settings for stage IV patients, consistent with an MAA effect. The effect of the MAA is relatively small, but highlight the responsiveness of providers to changes in reimbursement, and the need to integrate new drugs into payment schema.
Patient-reported care coordination and outcomes of colorectal cancer surgery. First Author: Sarah T. Hawley, University of Michigan, Ann Arbor, MI

Background: Care coordination is an essential component of effective, patient-centered care. Yet little is known about the impact of patient reported care coordination on clinical outcomes, such as postoperative complications following high risk colorectal cancer surgery. Methods: In 2011-13, we surveyed Stage III colorectal cancer patients from Detroit and Georgia SEER registries 4-12 months after diagnosis. The primary outcome was self-report of a postoperative complication. We adapted a validated 6-item scale to assess perceived care coordination across the overall continuum of cancer care (range 6-30). We used a separate 7-item scale to assess perceived care coordination specifically pre- and postoperatively (range 7-35). We compared the association between postoperative complications and overall and pre- /postoperative care coordination with chi-square tests. We assessed associations between complications and care coordination in each phase of care in separate models, using logistic regression to control for age, race, education and insurance. Results: Among 1465 patients who returned surveys (RR = 66%), 23.1% reported a postoperative complication. Most respondents perceived their care coordination to be good overall (mean: 25.9, SD: 3.7), as well as pre- (mean: 29.5, SD 4.6) and postoperatively (mean: 30, SD 4.3). Older, minority and those with more comorbidities significantly more often perceived poorer quality of care (P < .001). In adjusted analyses, postoperative complications were inversely associated with perceptions of good care coordination overall (OR: 0.72, 95% CI: 0.59-0.97) and with better pre- and post-operative care coordination (OR = 0.96, 95% CI = 0.93-0.98; OR = 0.93, 95% CI = 0.91-0.97, respectively). Conclusions: Similar to other large studies, complications in this sample were common after colorectal cancer surgery. Reported care coordination was good for most patients, but less so for certain vulnerable subgroups. Better care coordination was associated with lower rates of surgical complications. Such findings indicate that better care coordination may lead to better clinical outcomes, however further work to confirm and expand these results is needed.

Use of online communication and social media by newly diagnosed breast cancer patients: Results from the iCanCare Study. First Author: Natalie Cook, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Little is known about how email is currently used in healthcare to facilitate patient care. The objective of our study was to understand current practices and preferences of patients (pts) and physicians (MDs) for email communication. Methods: Separate cross-sectional surveys were administered to pts and MDs (staff physicians and clinical fellows) at Princess Margaret Cancer Center. Survey domains included current email and internet use practices, digital literacy skills, perceived barriers and preferences regarding email use to facilitate care. Logistic regression was used to identify factors associated with current email use. Chart review was conducted to assess the impact of email communication on care. Results: The survey was completed by 833 pts, of which 50% reported previous email contact with a healthcare professional (HCP) including administrative assistants (52%), MDs (51%: 36% with specialist; 18% with primary care; 3% both) and nurses (45%). Most pts (87%) were satisfied with this method of communication. Patient factors associated with the likelihood of email contact with a HCP included younger age (p < 0.001), higher education (p < 0.001) and higher income (p < 0.0001). Enrollment in clinical trials (p < 0.001), receipt of multiple treatments (p < 0.001) and receipt of chemotherapy (p < 0.0006) were also associated with higher likelihood of email contact. Patients who had less experience with electronic health care if they had prior email contact with HCPs compared to those with no prior email contact (60% vs. 70%; p = 0.004). Of the 80 MDs who responded to the survey (response rate 30%), 80% had previous contact with a pt via email although only 24% felt this should be used regularly to communicate with pts. All MDs reported email contact with other HCPs about pt related matters and all felt this to be an effective way to communicate. 962 pt charts were reviewed with email correspondence documented in 9% of cases. Conclusions: Email is commonly used for pt care but poorly documented and there may be a mismatch between pt/MD preferences. The use of email in this setting can be developed with appropriate guidance, however there may be concerns about widening the gap for certain groups of pts.
6522 Poster Discussion Session; Displayed in Poster Discussion Session (Board #77), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Disease-specific hashtags for online communication about cancer care. First Author: Matthias S. Katz, Radiation Oncology Associates, Lowell, MA

Background: A majority of patients and health care professionals are now online. Our hypothesis is that disease-specific cancer hashtags may be a way to access accurate health information and positive interactions.

Methods: Based upon two de novo hashtags, #bcsm and #btsm, an organized system of hashtags, the cancer tag ontology (CTO) was designed in July 2013 for online use. We conducted a retrospective study of 25 hashtags used on Twitter April 2011 – September 2014 using data from Symplur, LLC. We classified up to 100 most active users of each hashtag as follows: patient; doctor; non-doctor health care professional (HCP); individual NOS (I); healthcare organization (HCO), other organization (OO), or spam. Two traction analysis was analyzed quarterly for 4 quarters. Results: During the study period, there were a total of 531,765 tweets from 77,454 users. The two original hashtags #bcsm and #btsm had the most use with 249,312 and 110,465 tweets, respectively. The other tags were used exclusively starting Q3 2013 onward. Overall, the most active new tags were those with organized Twitter-based chats: #ayacsm; #gyncsm; #iscm; #mmcm; and #pancsm. These seven accounted for 93% of total Twitter activity. In the cohort, 11% were patients, 20% doctors, 3% HCP, 32% I, 30% HCO, 1% OO, and 3% spam. The most active top users were patients with an median of 46 tweets. Activity increased from 13,778 tweets in Q3 2011 to 79,960 tweets in Q3 2014. For the 23 structured tags, quarterly use increased from 18,098 tweets in Q3 2013 to 39,761 tweets in Q3 2014.

Conclusions: We have demonstrated the feasibility and growth of organized, cancer-specific hashtags on Twitter used by a variety of stakeholders in cancer care. Use of the CTO indicates potential value of online interaction. Further study is needed to determine whether CTO tagging: has any impact on access, outcomes or as a model for other areas of medicine.

6523 Poster Discussion Session; Displayed in Poster Discussion Session (Board #80), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Colonoscopy versus less invasive approaches for colorectal cancer (CRC) screening (Scr): A strategic perspective. First Author: Afsaneh Barzi, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Colonoscopy (CS) is an effective approach to Scr for CRC. Given its invasive nature, interest exists to find other Scr strategies (STs) with DNA stool testing being the most recent. Stool tests (STT) are dichotomous and a positive test typically results in a CS and then a negative CS would dictate the future Scr regime. We compared Scr CS in terms of their effectiveness (E), costs (C), and cost effectiveness (CE) to define the characteristics of a test or ST that can successfully compete or replace CS. Methods: Using a societal perspective, 12 STs and No Scr were compared. Using a Markov model 100,000 simulated individuals (SIs) 50 to 75 years of age with average risk of CRC were followed for up to 35 years. E (life years gained - LGy) and C (C of Scr and CRC) were calculated per SI. Results: CS dominates all other STs and has the highest LGy and lowest C even compared to No Scr. Under various sensitivity analyses (SA) we find that the results remain stable, primarily due to the high sensitivity (Sen) and specificity (Spe) of CS. CS testing is not competitive, even among STT, given its high C and minimal improvement on E. For DNA to be competitive compared to other STT, its C must decrease or its Sen must improve. Conclusions: CS remains the unrivaled Scr test for CRC. Given the high impact on incidence by detecting and eliminating pre-neoplastic polyps, dichotomous stool testing strategies are at a disadvantage. Value proposition for a new Scr ST is in a departure from dichotomous reporting and providing risk levels that can identify pre-neoplastic polyps and influence the Scr regime after a negative CS. This should be regarded as the focus of Scr research and development.
Developing a Cancer genomics Digital Educational Tool to assess the knowledge and expectations of patients with advanced solid tumors (CADET). First Author: Stephen Rosenberg, Department of Health and Human Services, University of Wisconsin, Madison, WI

Background: Genomic testing in cancer (GTC) is increasingly important to guide therapy for patients (pts) with advanced cancers, as eligibility for many early-phase clinical trials is restricted to patients with specific actionable mutation(s). Using a prospectively administered GTC questionnaire, we previously found that only 48% of pts with advanced solid tumors felt that they had sufficient knowledge to make an informed decision to pursue GTC (Blanchette et al, Cancer, 2014). Objective: To develop a digital education tool (DET) to improve pts’ knowledge of GTC, and to assess whether such tool can change pts’ attitudes and expectations toward GTC. Methods: A 5-min video was developed highlighting background information, logistics and rationale for GTC. Pts referred for phase 1 trials and molecular profiling were recruited to view the DET and to complete an identical GTC questionnaire as used in our previous study. These were returned by mail on a voluntary basis. Questionnaire comprised of 12 knowledge of cancer & genomics and 17 attitudes & expectations questions. Results from this cohort (B) were compared with the previously reported cohort (A). Results: Between Aug 2013 and Feb 2014, 118 pts consented to the study with 98 pts completing the questionnaire, representing 83% of pts surveyed. Demographics were similar between the cohorts. In terms of knowledge, as an aggregate, more correct answers were identified from questionnaires administered in B vs. A (72% vs. 67%, OR 1.26; 95%CI 1.06 – 1.51, p = 0.01). Multivariate analysis adjusting demographics, prior work experience in healthcare or having close family members with cancer confirmed better knowledge score in cohort B vs. A (OR 1.22, 95% CI 1.01 – 1.47; p = 0.04). More pts in cohort B felt they had adequate knowledge regarding potential benefits & risks of DNA testing to make an informed decision to pursue GTC (66% vs. 48%, p = 0.013) and agree that DNA testing may improve cancer treatment (79% vs. 64%, p = 0.037). Conclusions: This DET helps fulfill the support pts need, enhancing knowledge and affecting attitudes towards GTC. Evaluation of long-term effect of this DET is warranted.

Poster Session (Board #82), Mon, 1:15 PM-4:45 PM
Utilization of palliative chemotherapy for advanced bladder cancer: Patterns of care in routine clinical practice. First Author: Andrew George Robinson, Kingston General Hospital, Kingston, ON, Canada

Background: Although palliative chemotherapy for advanced bladder cancer is recommended in clinical practice guidelines, patterns of care in routine care is not described. Here we describe utilization rates of chemotherapy and referral rates to medical oncology in the last year of life among patients who die of bladder cancer. Methods: A population based cohort of bladder cancer patients was identified from the Ontario Cancer Registry; the study population included those patients who died of bladder cancer 1995-2009. Electronic records of treatment and physician billing records were used to identify treatment patterns and referral to medical oncology (MO). Log-binomial and poisson regression were used to examine factors associated with chemotherapy utilization and MO consultation. Results: 8005 patients died of bladder cancer; 25% (1964/8005) of whom received chemotherapy in the last year of life. Use of chemotherapy was independently associated with patient age (Relative risk (RR) 0.49 70-79 vs < 50 years, p < 0.001), comorbidity (RR 0.61 moderate comorbidity vs none, p < 0.001), socioeconomic status (RR 0.84 lowest quintile vs highest, p = 0.01) and gender (RR 0.91 females vs males, p = 0.012). Utilization increased over time (from 22% to 26%, p < 0.001) and varied across geographic regions (range 18-30%, p < 0.001); these findings persisted on adjusted analyses. 68% (5426/8005) of patients were seen by MO in the last year of life. Factors independently associated referral rates to MO include age (RR 0.82 70-79 vs < 50 years, p < 0.001), comorbidity (RR 0.90 moderate comorbidity vs none, p < 0.001), socioeconomic status (RR 0.90 lowest quintile vs highest, p < 0.001), and gender (RR 0.96 females vs males, p = 0.023). Referral rates modestly increased over time (66% to 69%, p = 0.006) and varied widely across geographic regions (range 57% to 79%, p < 0.001); these findings persisted on adjusted analyses. Conclusions: Despite clinical practice guideline recommendations, utilization of palliative chemotherapy for bladder cancer in routine practice remains low. Treatment patterns and referral rates to MO vary substantially across geographic regions.

Poster Session (Board #84), Mon, 1:15 PM-4:45 PM
A discrete choice experiment to examine the preferences of patients with cancer and their willingness to pay for different types of health care appointments. First Author: Shu Fen Wong, Deakin University, Waurn Ponds, Australia

Background: Little comparative data exist on how patients with cancer make choices about accessing health care appointments. Our study used a discrete choice experiment (DCE) to better understand patient preferences regarding their cancer care and potential trade-offs between health care appointment characteristics. Methods: Patients diagnosed with cancer at 3 hospitals were recruited to complete a self-administered DCE. Each version of the questionnaire (n = 16) had 8 paired choice scenarios where each health care appointment scenario described 6 attributes (identified through qualitative analysis): expertise of the doctor; familiarity of the doctor with their medical history; waiting time for an appointment; permitted accompanyment by family/friends; travel times to appointments and out-of-pocket costs. Patient preferences were estimated using logistic regression; willingness to pay (WTP) estimates for different aspects were then derived. Results: 185 out of 512 patients (36%) returned the questionnaire. Mean age was 61 yrs (22–92 yrs), and the majority was female (60%). Mean time since cancer diagnoses was 34 mths, 90% had received cancer treatment and 61% had early stage disease. The most important attributes for determining patient preferences were the expertise and familiarity of the doctor with their medical history; distance travelled was least likely to influence patient preferences. The WTP analysis found that patients were willing to pay $70/53 for shorter travelling times to appointments and $342 for shorter travelling times to appointments. Conclusions: Our study could guide the development of patient-centered health care models, with an emphasis on the most important appointment characteristics; models should improve patient access to experienced doctors, and support the role of primary care providers in the community. Interventions to reduce waiting and travel times for appointments and to accommodate medical escorts still influenced patient choices, but to a lesser degree.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Impact of age on the associations between genomic testing in breast cancer (BRCA) and chemotherapy (chemo) use and costs. First Author: Yu-Ning Wong. For Chase Cancer Ctr, Philadelphia, PA

Background: The 21-gene recurrence score assay (Oncomouse Dx) (RS) guides adjuvant chemo use in patients (pts) with BRCA. Since age is associated with chemo appropriateness, we sought to understand if the associations between RS, chemo use, and costs varied by age. Methods: We identified 1,190 pts diagnosed with node-negative, hormone-receptor-positive BRCA during 2007-2010 using the Pennsylvania Cancer Registry and claims from Independence Blue Cross (IBC) or Medicare for 12 months before and after diagnosis. Propensity-score weighted regression models were used to assess the independent effect of RS receipt on chemo use and total 1-year post-diagnosis chemo costs by age group, controlling for demographics, insurance, tumor characteristics, and comorbidities. Results: Mean age was 71 years (range 23-100). 74% were insured by Medicare. Pts who received RS were younger, had fewer comorbidities, were more likely stage 1, and were more likely to have IBC coverage (< .001 for all). The proportion of patients undergoing RS testing increased from 17% among pts in 2007 to 28% in 2010. RS use was associated with reduced adjuvant chemo use and lower chemo spending among younger pts, but had minimal effect on chemo use and chemo spending among older pts (Table, * indicates p < .05). None of the RS recipients over age 85 received chemo. Conclusions: RS testing was associated with lower chemo use in younger pts, but had little effect on chemo use in older pts. The cost savings noted in young pts who underwent the RS test was not seen among older pts. Our results suggest that RS testing is being ordered in many elderly patients for whom chemo is not a realistic treatment option. As additional high-cost genomic tests enter clinical practice, their use should be targeted towards pts in whom the test result will influence clinical decision making.

Table

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6530 Improving veteran access to lung cancer care (iVaLuCancerCare): A quality improvement project at the Louis Stokes Cleveland VA Medical Center (LSVAMC). First Author: Rami Manochakian, Louis Stokes Cleveland VAMC/Case Western Reserve University, Cleveland, OH

Background: At the LSVAMC, one of the largest VA medical centers in the USA, about 190 new cases of lung cancer are diagnosed yearly and 450 veterans are followed for lung cancer care. iVaLuCancerCare is a quality improvement project supported by grant from the VA Office of Specialty Care Transformation. Through this project, a new multidisciplinary lung cancer team was formed in October 2013 to address barriers to access to lung cancer care: timeliness of care, coordination of care and access to palliative care. Methods: To address the gaps, we targeted three specific aims and proposed the following goals: 1) Increase percentage of non-small cell lung cancer (NSCLC) patients who receive first treatment within 28 days from diagnosis from 33% to 50%. 2) Increase percentage of medical oncology visits that are associated with 2 or more additional appointments on the same day from 33% to 50%. 3) Increase percentage of advanced lung cancer patients who receive a palliative care consultation from 10% to 75% and percentage of those who receive ongoing collaborative palliative care from 0% to 30%. In order to reach our goals, we implemented through this project, and with help from the VA Center for Applied Systems Engineering, multiple interventions including a new dedicated multidisciplinary weekly lung cancer clinic, dedicated patient navigator, weekly lung tumor board and module rounds, new lung cancer education clinic, new lung cancer tracking tools, distress screening and management and others. Results: From October 2013 to July 2014, percentage of NSCLC patients who received first treatment within 28 days from diagnosis was 58%. Percentage of medical oncology visits that were associated with 2 or more additional appointments on the same day was 60%. Percentage of advanced lung cancer patients who received a palliative care consultation was 90% and percentage of those who received ongoing collaborative palliative care was 69%. Conclusions: iVaLuCancerCare project at the LSVAMC significantly improved the care for veterans with lung cancer. The project’s goals were met. We plan to sustain and spread the above changes and identify new ways to further enhance our program.

6531 Cancer pain management practices and their impact on quality of life for Asian cancer patients. First Author: Yong-Chul Kim, Department of Anesthesiology and Pain Medicine, Seoul National University School of Medicine, Seoul, Republic of Korea, Seoul, South Korea

Background: In order to implement more effective policies for cancer pain management, a better understanding of current practices and their effects on patients are needed. The ACHEON study was a survey-based investigation of the impact of cancer pain and management practices on patients’ quality of life in 10 Asian countries. Methods: Patients experiencing cancer pain were randomly surveyed in 10 Asian countries with a 33-item questionnaire assessing attitudes and perceptions towards cancer pain management. Patients aged ≥ 18 years with a documented history of cancer pain in the preceding month were selected. Results: Of the 1,190 patients (median age; 53, male/female 805/385) surveyed, 1,026 reported moderate-to-severe pain (median duration, 12 months). The attribution of the pain was 53% from cancer, 18% from cancer-related therapy and 29% from mixed sources. 1,056 (90%) patients were treated for their cancer pain and only 308 patients were receiving opioids, to their knowledge. Patients agreed that their pain affected activities of daily living (86%), sleeping patterns (87%), concentration and focus (92%), as well as causing too much reliance on other people (67%), while only a small proportion reported having a good quality of life (34%). Only 22% of patients were employed, and 44% of those had been absent from work for more than 7 days over the past 3 months due to their cancer pain. It was reported that 42% of the patients who were unemployed had stopped working due to cancer pain. Conclusions: The ACHEON study results show that cancer pain significantly affects multiple aspects of quality of life for patients. The development of more effective management practices for cancer pain will require collaborative efforts from institutional, social and regulatory parties.
State variation in Medicare Part D and choice of initial endocrine therapy for breast cancer. First Author: Liliana E Pezzin, Medical College of Wisconsin, Milwaukee, WI

Background: Evidence suggests that drug utilization under Medicare Part D has been uneven, varying significantly by geographic region. We sought to examine the extent to which geographic variation in Part D plan characteristics contribute to the variation in choice of initial hormone therapy agent among women with incident breast cancer. Methods: Two-stage multivariate regression analyses applied to 23840 Medicare beneficiaries with incident breast cancer in 06-07. The first stage determined the effect of state of residence on the probability of having an aromatase inhibitor (AI, as opposed to tamoxifen) as the initial endocrine therapy, controlling for confounders. The second stage provided estimates of state-specific Part D plan characteristics on state variation in choice of initial hormone therapy. Results: There was substantial residual geographic variation in the likelihood of using an AI as the initial endocrine therapy, despite controls for socioeconomic status, breast cancer treatment, and other factors. Regression-adjusted probabilities of starting an AI ranged from 53.4% in Wisconsin to 82.4% in New York. Nineteen states (38%) had adjusted probabilities significantly different than the national mean: 13 of those were above, while the remaining six states—Wy, MT, MN, IA, NH, AR—were significantly below the national mean. Results from the second stage revealed that variation in characteristics of Part D plans across states explained over one-third (35%) of the overall state-level variability in initiating endocrine therapy with an AI. A higher number of drug plans with cost sharing above the mean, greater spread in deductible costs and a greater spread in monthly drug premiums were associated with lower adjusted state probabilities of initiating an AI. In contrast, a higher number of drug plans with monthly premiums above the state mean and higher mean cost sharing were both positively associated with likelihood of starting on an AI. Conclusions: This study suggests that variability in use of AIs—the newer, more effective breast cancer oral therapy—could be significantly reduced by changing the benefit design underlying states’ Part D plans.

Patients with advanced non-small cell lung cancer (NSCLC): Are research biopsies a barrier to participation in clinical trials? First Author: Charles Henry Lim, University of Toronto, Toronto, ON, Canada

Background: The evolution of targeted therapy in NSCLC has led to growing complexity of clinical research and a heightened expectation of clinical benefit for participants. Clinical trials in NSCLC increasingly require mandatory tumour samples or research biopsies, both potential barriers for trial participation. We assessed the impact of performing research biopsies in advanced NSCLC on clinical trial enrollment. Methods: We conducted a retrospective chart review of patients with advanced NSCLC evaluated for systemic therapy clinical trials at the Princess Margaret Cancer Center from 2010 to 2014. Results: Of 26 clinical trials reviewed, 21 required tumour samples for enrolment. Eleven required confirmation of a pre-specified biomarker in order to receive investigational treatment. Trial participation was offered to 151 patients at 293 unique study encounters (some enrolled in multiple trials). Forty-three percent proceeded to receive study treatment. Those considering trials without mandatory biopsies or tissue requirement were more likely to proceed to study treatment than those considering trials with these requirements (75% vs. 40%, p = 0.009). For trials requiring mandatory tumour samples, 210 consents for participation were obtained, 170 research biopsies were ordered and 88% were performed. Participants proceeded to study treatment in 57% of encounters; 7% of biopsies yielded insufficient tissue and 34% were “biomarker-negative”. The most common barriers to trial enrollment included lack of the pre-defined biomarker (40%), other study exclusion criteria (17%) patient refusal of biopsy (11%), insufficient biopsy tissue (9%), and deteriorating clinical status/death (10%). Conclusions: With the evolution of personalized medicine, a growing number of NSCLC trials require tumour tissue for treatment eligibility. This has emerged as a significant barrier to clinical trial enrollment. Potential solutions include routine tissue banking at diagnosis, facilitating use of available diagnostic samples (e.g. fine needle aspirates) for trials, development of circulating DNA assays for trials, and more resources for timely tissue acquisition.

Analysis of home care coordination activities in oncology: A mixed methods study. First Author: Fatima Yatim, Gustave Roussy, Villejuif, France

Background: Many studies point out the importance of care coordination, but there are few descriptive studies about the content of coordination activities and how it responds to the needs of patients and professionals. Objectives: To identify the skills and competencies needed to perform home care coordination activities. Methods: The study was conducted at Gustave Roussy (Villejuif, France), into the department coordinating outpatient care for patients who need post-discharge home care. In a first step, a data grid was developed (a focus group with the nurses and the head of the department), and then refined during an observation period. After this qualitative analysis, a quantitative analysis studied the phone calls received at the coordination platform of this department (May-June 2014). The following data were systematically collected (date; caller, reason for the call; procedure performed), and then analyzed by two researchers. They identified five categories of actions, one clinical (F1), and four related to managerial and, organizational solutions (F2 to F5), validated by the staff members of the department. Results: 543 calls were analyzed. The callers were patients or their relatives (38%), private nurses (35%), medical devices providers (20%), other primary care providers (7%). Five categories of coordination activities were identified: (F1) Patient monitoring and management of clinical and non-clinical alerts (side effects) (32%); (F2) Helping to understand and navigate through the clinical pathway (information about healthcare professional contacts) (21%); (F3) Managing technical problems linked to the achievement of care (problem about medical devices delivery) (17%); (F4) Explaining some elements of the care protocol (use a medical device) (16%); (F5) Collecting and transmitting the patient medical record information (medical prescriptions) (14%). Conclusions: The majority of requirements for patients and professionals are related to organizational and logistical issues (e.g. navigation, lack of information about specific aspects of the clinical pathway). They require the implementation of new professional managerial skills, especially among nurse navigators and other new professions.

Validation of a clinical trial accrual predictive model. First Author: Wendy R. Tate, The University of Arizona Cancer Center, Tucson, AZ

Background: The costly and extensive process to drug approval highlights the need to streamline the drug pipeline process. We previously reported a novel predictive model with the outcome of anticipated accrual to be used when considering a prospective clinical trial at our center. Here, we present the results of the validation study. Methods: Eligible studies include treatment and supportive care intervention studies permanently closed to accrual between 10/2013 and 01/2015 at our center. Data abstracted from the clinical trials management system (OnCore, Forte Systems, Madison, WI) included: use of investigational drug, disease management team (DMT), use of local IRB, local start date, DMT accrual prediction value, actual total accrual, and clinicaltrials.gov (NCT) number. Abstracted from clinicaltrials.gov were protocol-specific data: number of national sites, national enrollment goal, national start date, and national date of expected primary endpoint completion. Studies were run through the model and actual accrual plotted against predicted accrual. Actual, team- and model-predicted subjects accrued; percent of trials meeting cut-off values; and model sensitivity and specificity were calculated. Results: Sixty-one trials met study inclusion criteria. Total accrual was 373 subjects (mean: 6.1 ± 17.2); 16 (26.2%) studies had zero accrual, 23 (37.7%) accrued 88.7% of the total subjects. The model predicted accrual of 513 subjects (138% of actual) versus the DMT predicted accrual of 1111 subjects (298% of actual). The model correctly predicted whether a study would be met or not within 0.4 of the time. Thirty-six studies (44.3%) correlated perfectly at the category level. Model sensitivity is 70%; specificity is 78%. For the 17 studies not correctly categorized using a cutoff of four, nine (60%) would have been incorrectly opened (predicted 4+; < 4 accrued) and six (40%) would have incorrectly not opened (predicted < 4; 4+ accrued). Conclusions: The identified national and local factors to predict clinical trial accrual at our center are valid, showing it to be an accurate, quick and valuable metric in assessing trial success as well as planning resource allocation. Further research includes national expansion of the model to cancer centers.

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Disparity in insurance status and race in receipt of aggressive and advanced treatments for high-risk prostate cancer/PCa. First Author: Brock R. Baker, UNC Chapel Hill, Chapel Hill, NC

Background: Young and healthy men with high-risk PCa require aggressive treatment. We examined treatment received by these men using the National Cancer Data Base, which contains 70% of incident cancers across the US. We hypothesized a disparity in race and receipt of aggressive and advanced treatment and access to advanced surgical (robotic) and RT (proton or intensity-modulated RTI) technologies. Methods: 12,778 men age < 65 with Charlson comorbidity score 0 diagnosed with NCDB high-risk PCa from 2010-12 were included. Logistic regression examined factors associated with treatment. Results: 97% received definitive treatment (either radical prostatectomy or radiotherapy). However, race was not associated with receipt of RT (73%, Black; 73%, White; p = .001) or receipt of insurance (75%, Black; 76%, White; p = .11). Young/healthy men with high-risk PCa who lacked private insurance or were uninsured were less likely to be with curative intent. 76% of EP patients had significant chest/shoulder pain, cough, haemoptysis). The median length of inpatient stay was 14.31 days (range 0-68 days). Further comparative analysis between countries demonstrates the inter-country variation in patient demographics, presentation and management. Conclusions: The emergency route to lung cancer diagnosis is common across Europe, is associated with specific patient demographics, and represents a significant burden on acute services. The gatekeeper role of the GP does not appear to govern EP rates. Establishing the causes behind EP of lung cancer should allow identification, earlier diagnosis and better outcomes for this vulnerable patient population.

Impact of health insurance transitions on cancer survivors and those with no cancer history. First Author: Katherine S. Virgo, Emory University, Atlanta, GA

Background: 15.4% of the U.S. population was uninsured in 2012. Those without coverage face limited health care access and are more likely to have poor outcomes. Cancer survivors are particularly at risk of insurance gaps due to the long-term nature of the disease. This study examines the association between cancer history and health insurance transition patterns, including insurance gain or loss, and the impact on access to care. Methods: Using longitudinal data from the Medical Expenditure Panel Survey (MEPS) for 2008-2012 (panels 12-16), 2386 cancer survivors and 41,211 individuals with no cancer history ages 18-63 among MEPS survey entry during 2008-2011 were selected. Individuals were categorized as initially uninsured or insured based on first stable consecutive three-month insurance status. Multivariate logistic regressions were used to assess the association between cancer history and insurance loss or gain based on first coverage change, adjusting for the MEPS complex survey design. Results: Uninsured cancer survivors were more likely to gain insurance and insured cancer survivors were less likely to lose insurance than those with no cancer history (42.5% and 34.1%; 9.9% and 14.6%, respectively). In adjusted analyses, cancer history was positively associated with insurance gain and negatively associated with insurance loss; but insignificant (p = 0.06; p = 0.11, respectively). Initially uninsured, younger (18-34), non-Hispanic white, occasionally employed, risk-averse individuals were more likely to gain insurance. Initial insurance status, younger (18-34), low income, occasionally employed males in fair to poor health were more likely to lose insurance. Those remaining uninsured or losing insurance were more likely to experience problems accessing needed medical care and less likely to have a usual source of care. Conclusions: Cancer history is associated with health insurance transition patterns. Different factors impact insurance gain and loss. Cancer survivors need stable health insurance coverage, yet coverage is inconsistent. Providing incentives to those with inconsistent access, such as the young, to enroll in health insurance could decrease volatility in coverage and improve continuity of care.
 Comprehensive genomic profiling of rare tumors in a dedicated community clinic. First Author: William Jeffery Edenfield, Clinical Research Unit – IGCCG, Greenville Health System Hospital, Greenville, SC. 2Foundation Medicine, Boston, MA

Miller2, Ki Chung1 Greenville Health System Cancer Institute, Greenville, SC. 2Foundation Medicine, Boston, MA

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Background: Advances in cancer research indicate that successful treatment may depend more on genomic alterations in the tumor rather than the organ of origin. However, data on the use of off-label molecular testing and targeted treatment is lacking. Our objective was to evaluate off-label use of targeted treatments in a commercially insured population. Methods: We analyzed data from the MarketScan databases, a large employer-based claims repository, from 2011-2013 on the use of off-label molecular tests and targeted drugs for the top 10 incident cancers. We limited the analysis to the metastatic setting using a previously validated algorithm. We defined off-label use as using the test or agent in a fashion not included in an FDA-approved medication label. Results: Test use was limited overall, but rose considerably in 2013 with the most use in lung, colon, and breast cancers. There was also limited though non-negligible use of targeted agents with the most common being erlotinib, imatinib, trastuzumab, vemurafenib, and dasatinib. Drug use rates remained relatively constant over the three-year period. Off-label treatment was most common in breast, lung, and colon cancers. Conclusions: There is limited but non-negligible use of off-label molecular testing and targeted treatment in the top 10 incident cancers. Further work will explore predictors of off-label use and patient outcomes.

Precision oncology: molecular testing and targeted treatment beyond indication. First Author: Josh John Carlson, University of Washington, Seattle, WA

Background: Advances in cancer research indicate that successful treatment may depend more on genomic alterations in the tumor rather than the organ of origin. However, data on the use of off-label molecular testing and targeted treatment is lacking. Our objective was to evaluate off-label use of targeted treatments in a commercially insured population. Methods: We analyzed data from the MarketScan databases, a large employer-based claims repository, from 2011-2013 on the use of off-label molecular tests and targeted drugs for the top 10 incident cancers. We limited the analysis to the metastatic setting using a previously validated algorithm. We defined off-label use as using the test or agent in a fashion not included in an FDA-approved medication label. Results: Test use was limited overall, but rose considerably in 2013 with the most use in lung, colon, and breast cancers. There was also limited though non-negligible use of targeted agents with the most common being erlotinib, imatinib, trastuzumab, vemurafenib, and dasatinib. Drug use rates remained relatively constant over the three-year period. Off-label treatment was most common in breast, lung, and colon cancers. Conclusions: There is limited but non-negligible use of off-label molecular testing and targeted treatment in the top 10 incident cancers. Further work will explore predictors of off-label use and patient outcomes.

Comprehensive genomic profiling of rare tumors in a dedicated community clinic. First Author: W. Jeffery Edenfield1, Ryan Fields1, Siraj M. Ali2, W. Larry Giuck1, Julian Chmeliecki1, Jeffrey S. Ross2, Phillip J. Stephens2, Vincent A. Miller2, Ki Chung2, 1Greenville Health System Cancer Institute, Greenville, SC. 2Foundation Medicine, Boston, MA

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6540  Poster Session (Board #97), Mon, 1:15 PM-4:45 PM

6541  Poster Session (Board #98), Mon, 1:15 PM-4:45 PM

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6542  Poster Session (Board #99), Mon, 1:15 PM-4:45 PM

Social-ecological perspectives on breast cancer care seeking patterns in Karnataka, India. First Author: Arun S. Shet, University of Minnesota, Minneapolis, MN

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6543  Poster Session (Board #100), Mon, 1:15 PM-4:45 PM

Medical Oncologists’ and Surgeons’ approaches to communication of breast cancer recurrence risk. First Author: Aaron Sabolch, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

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6544  Poster Session (Board #101), Mon, 1:15 PM-4:45 PM

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A systematic approach to smoking cessation in Ontario’s Regional Cancer Programs. First Author: William K. Evans, McMaster University, Hamilton, ON, Canada

Background: Smoking cessation (SC) is rarely undertaken in busy cancer centers but potential health benefits in cancer patients include improved general health, improved all-cause and cancer-specific mortality, reduced toxicity, greater response to treatment, decreased risk of disease recurrence and of second primaries. Based on this evidence, Cancer Care Ontario (CCO) undertook a SC initiative for new ambulatory cancer patients in its Regional Cancer Programs (RCPs).

Methods: A steering committee recommended a framework for SC in RCPs in 2012, based on the Ottawa Model for Smoking Cessation. The initiative was piloted in all 14 provincial health regions in 2014. Regional SC “champions” participated in monthly web meetings, data calls and in-person meetings led by a secretariat at CCO. Presentations on the health benefits of SC were made to physicians and other health care providers in the RCPs. New ambulatory cancer patients are screened, advised and referred to internal or external SC services dependent on regional resources. CCO’s data collection processes capture performance metrics. Patient data are aggregated at the RCP-level and provincial performance indicators reported quarterly. A standardized cancer patient resource on SC will be available in both French and English in a print-ready format and adapted for the Aboriginal population by March 2015.

Results: During Q1 and Q2 of the 2014/15 fiscal year, 56.0% (Q1) and 51.5% (Q2) of new ambulatory cancer cases were screened for their smoking status: 25% of those screened were current or recent smokers (within last 6 months); 75% of these were advised of the benefits of cessation; nearly 50% were recommended a referral for cessation services, and about 67% of those referred accepted a referral. Conclusions: CCO’s approach has led to province-wide implementation of a standardized approach in a relatively short timeframe despite limited financial resources. Despite oncologist resistance and limited regional resources, there has been substantial progress. Framing SC as a quality of care issue has been critical to the success to date. Sustainability of the initiative will be dependent on funding for dedicated SC counselors and evidence of program cost-effectiveness.

How TNM stage affects surveillance intensity after treatment for breast cancer. First Author: Daniel Wu, Saint Louis University School of Medicine, Saint Louis, MO

Background: The mean lifetime cost of surveillance for a woman diagnosed with breast cancer at age 45 is estimated to be >$35,000. Based on trials comparing low and high intensity surveillance, ASCO and NCCN have published relative indications encouraging low intensity surveillance for women with breast cancer. We wanted to determine whether ASCO experts carry out surveillance differently for women with breast cancer of varying TNM stages.

Methods: We created a web-based survey instrument with 4 idealized patient vignettes depicting patients with TNM stages 0 to IIIA. Respondents were asked how often they would recommend 12 specific diagnostic modalities for each vignette during post-treatment years 1-5. The survey was e-mailed to 1179 ASCO members who had treated breast cancer as their major clinical focus. We used repeated measures ANOVA for analysis. Results: 1,012 (31%) of the 3245 ASCO members surveyed responded. There were 915 (90%) evaluable responses. Office visit was most frequently recommended. Responders also commonly recommended complete blood count (CBC), liver function tests (LFTs), and mammogram. There was statistically significant variation in recommended surveillance intensity for all 12 modalities according to TNM stage. Conclusions: We have demonstrated significant variability in surveillance after curative-intent treatment. Modalities not recommended by ASCO guidelines, such as CBC and LFTs, are frequently recommended. Physicians’ surveillance recommendations varied depending on the TNM stage of the described patients, but ASCO guidelines do not stratify according to TNM stage. Our results suggest both overuse and underuse of surveillance modalities. Innovative solutions to promote physician and patient education can help physicians follow evidence-based surveillance guidelines and help patients to participate in these decisions. There is a need for new randomized controlled trials to evaluate newer surveillance modalities to guide clinical practice.
Racial differences in 20-year cardiovascular outcomes among childhood and young adult cancer survivors. First Author: Amy M Berkman, University of Pennsylvania, Philadelphia, PA

Background: Individuals diagnosed with childhood (0-14 years) or young adulthood (15-34 years) cancers are at higher risk of cardiovascular disease (CVD) death compared to those without a history of cancer. No study has investigated whether CVD risk differs as a function of race and primary cancer type.

Methods: Case data from the years 1973-2011 were analyzed using the 2013 Surveillance, Epidemiology and End Reports (SEER) registries. We categorized cases according to ICD-0-3 / WHO 2008 Adolescent and Young Adult classification. CVD death was based on ICD-10 codes for: diseases of the heart, atherosclerosis, cerebrovascular diseases or other diseases of the arteries. Hazard ratios were calculated using Fine & Gray methodology for competing risks (all-cause, cancer and CVD mortality) and relative risk ratios were calculated to compare risk of CVD death by race (black : white). Results: A total of 164,316 cases of childhood and young adult primary cancers were identified, of which 16,060 cases were black (10%), 133,932 cases (82%) were white, and 14,314 (8%) were other or unknown. There were a total of 1,584 CVD deaths. Overall, blacks had a higher risk of CVD death compared to whites at 5-years (RR 2.15, 95% CI: 1.65-2.80), 10-years (RR 2.23, 95% CI: 1.80-2.76), and 20-years (RR 1.83, 95% CI: 1.54-2.17) from the date of cancer diagnosis. The relative risk for CVD death between blacks and whites varied by cancer type, with the largest black:white difference among those diagnosed with CNS neoplasms at 10-years (HR 3.02, 95% CI: 1.47-6.18) and melanoma at 5-years (HR 26.9, 95% CI: 3.40-212.08). Conclusions: Black individuals diagnosed with cancer in childhood or young adulthood have a higher risk of CVD at 5-, 10-, and 20-years compared to whites. The risk of CVD mortality among blacks and whites varied by cancer type and time from cancer diagnosis. Further study is needed to understand the etiology of racial differences in this population.

Perceptions of clinical trial participation in African American cancer patients. First Author: Daniel M. Geynisman, Fox Chase Cancer Center, Philadelphia, PA

Background: African Americans (AA) participate in oncologic clinical trials (CT) at lower rates than Caucasians, despite a disproportionally high rate of cancer. While general barriers to participation in CT among AA have been explored, little is known in regard to specific differences of perspectives in those who do or do not participate. Based on an initial and separate qualitative analysis of 16 patients, a perceptual mapping survey was developed to explore barriers and facilitators to participation in CT amongst AA.

Methods: We surveyed AA adult cancer patients at two cancer centers about demographics and knowledge, beliefs, attitudes and perceptions in regard to CT. We asked them to report how much they agreed or disagreed on a 0-10 scale (0 = strongly disagree, 10 = strongly agree) with statements regarding clinical trials’ helpfulness, being informed, having control, value, support from those around them, and beliefs about healthcare providers. We used descriptive statistics and t-tests to assess for differences between those willing to and unwilling to participate in CT.

Results: Of 41 patients recruited, 54% have not participated in a CT within the last 9 months. Mean age was 60 years (27-78), 51% were female, 39% completed high school and 71% had private insurance. CT participants more strongly agreed that their doctor had given them enough information to make a decision about being part of a CT (p < 0.001). Agreement that the benefits of being in a CT outweigh the possible side effects (p = 0.16) and that being in a CT offers the best treatment available (p = 0.015) were also stronger among CT participants. Non-CT participants more strongly believed that being in a clinical trial would make them sicker (p = 0.019), that important information would be withheld from them if they were in a clinical trial (p = 0.008) and that no one talked to them about being part of a CT (p < 0.001). Conclusions: Significant perceptual differences between AA cancer patients who have and have not participated in a CT were noted. Greater attention needs to be given to addressing negative perceptions of CT, as well as ensuring that all AA cancer patients receive clear and sufficient information regarding CT participation in order to make an informed decision about their care.

Factors associated with the large disparities in BRCA testing among high risk Black women. First Author: Tuya Pal, H Lee Moffitt Cancer Ctr and Research Inst, Tampa, FL

Background: Concerns about genomic advances to increase health disparities have been raised. We sought to explore factors associated with receipt of BRCA1 and BRCA2 (BRCA) testing and assess for racial disparities through a population-based sample of young breast cancer survivors.

Methods: Women diagnosed with invasive breast cancer at or below age 50 in 2009-2012 were recruited through the Florida State Cancer Registry with non-sampling of Blacks compared to non-Hispanic Whites (NHW). Participants were asked to complete a baseline questionnaire and a medical records release for verification of genetic test results. Summary statistics, Pearson Chi-square tests and multivariable logistic regression were used to examine associations between dichotomous demographic and clinical variables and access to BRCA testing rates prior to enrollment.

Results: Of the 877 participants included in this analysis, 36.7% (165/450) of Blacks versus 67.7% (289/427) of NHW had BRCA testing (p < 0.001). Medical record verification of the BRCA test result was achieved in over 75% of the sample. In the final logistic regression model, controlling for educational attainment and household income age at breast cancer diagnosis and triage negative status, NHW race remained the strongest predictor for having had BRCA testing with an odds ratio (OR) of 4.2 (95% Confidence Interval: 3.0-6.1). Other highly significant predictors of having BRCA testing included: 1) breast cancer diagnosis at or below age 40 (OR: 3.4); 2) annual income of $25,000 or greater (OR: 2.6); 3) triple negative disease (OR: 1.9); and 4) college education or higher (OR: 1.7) (all p-values < 0.005). Variables not significantly associated with having BRCA testing included having private insurance at the time of diagnosis and having children. Conclusions: Our results demonstrate the enormous disparities in high risk Black women compared to NHW, which is not explained by socioeconomic factors. The rapid diffusion of gene-based care to refine cancer prevention and treatment and ultimately improve patient outcomes underscores the need to systematically understand and address these disparities so all populations may benefit from these scientific advances.
Evaluation of hematologic/oncology patient and physician expectations for integrative oncology in an ethnically diverse population. First Author: Damien Mikael Hansra, Oncology and Radiation Associates, Miami, FL

Background: Many integrative modalities are recommended in NCCN guidelines & evidence shows increased patient (pt) utilization. We aim to compare how integrative services are valued between hematology/oncology physicians (MD) & pts. Methods: Pts & MDs at an academic tertiary care medical center were enrolled to complete a survey. Demographics include: age, gender, race, & ethnicity. Clinical info include: cancer subtype & treatment MD. Survey consisted of 7 questions assessing opinions on integrative care asking: “In addition to standard care, it is important to incorporate/provide” nutrition services, exercise therapy, spiritual/religious counseling, supplement/herbal advice, support groups, music therapy, or other complimentary medicine services (acupuncture, massage, relaxation therapy). Answers recorded on a 5 point scale (1 = highly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = highly agree) & converted into 2 categories (1,2,3 = neutral/disagree vs. 4, 5 = agree). Fisher’s exact test with 2 sided p-value used to compare significance between MD & pt responses. Results: 909 pts and 55 MDs enrolled from June 2013 to January 2015. Pt mean age 55, range 18-88 with 47% male & 53% female. 65% of pts were Hispanic vs. 35% not Hispanic. 81% white, 12% black/African American, 2% Asian/Pacific Islander, & 5% other. 15% of pts had hematologic disorders (93% malignant 7% benign) vs. 85% of pts had solid malignancies. Significance disparities were demonstrated: 82% of pts agree that nutritional advice is important vs. 67% of MDs, p < 0.01, exercise therapy (86% vs. 73%, p = 0.02), spiritual/religious (68% vs. 50%, p = 0.01), supplement/herbal therapies (85% vs. 56%, p < 0.0001), music (64% vs. 30%, p < 0.0001), & “other complementary services” (75% vs. 45%, p < 0.0001). Non statistical favoring of support groups was observed (71% vs. 68% respectively). With exception of support groups, pts value integrative modalities more than MDs. It is expected that increased availability & utilization of integrative oncology modalities at tertiary hospital sites could improve pt satisfaction, quality of life, & other clinical endpoints.

The impact of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) in reducing outcome disparities based on race. First Author: Mark A Fiala, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: The NBCCEDP, created in 1990, provides breast and cervical cancer screening and diagnostic services to low-income and uninsured women. The program’s effectiveness in reducing racial disparities in outcomes is unclear. Therefore, we examined the incidence of breast cancer diagnosis at diagnosis and the mortality rates of women with metastatic disease by race before and after the advent of the NBCCEDP. Methods: Using the SEERStat software, we extracted the case listings of all women diagnosed with breast or cervical cancer from 1981 through 2010 in Surveillance Epidemiology and End Results (SEER)-9 registries database based on the November 2013 submission. Among first time breast or cervical cancer cases, we divided into three cohorts based on the year of diagnosis (1981-1990; 1991-2000; 2001-2010). Socioeconomic status was approximated by median household income of county of residence from the 2000 US census. Incidence rates of metastatic disease were compared using χ² and mortality rates were compared using multivariate cox regression. Results: 224,183 women with breast cancer and 28,532 with cervical cancer were analyzed. Black women represented 15% of the breast cancers and 9% of the cervical. The proportion of women with metastatic disease was consistently higher for black women than white women. The mortality rate of those with metastatic disease, adjusted for year of diagnosis, age, and SES, was also consistently higher for black women than white women (Table 1); neither improved during the two most recent decades. Conclusions: This study confirms earlier studies that black women with breast or cervical cancer face significant disparities in cancer outcomes despite the screening efforts of the NBCCEDP.
Religious beliefs and stage at diagnosis in a biracial sample of newly diagnosed colon cancer patients. First Author: Blase N. Polite, The University of Chicago, Chicago, IL

Background: Blacks are more likely to present with advanced stage colon cancer and more likely to die from this disease than Whites. Blacks are also more likely to place God in control of their health care decision-making. Limited evidence in breast cancer suggests stronger religious beliefs may lead to more delayed care and more advanced stage at diagnosis especially among Blacks. Methods: Newly diagnosed patients with colon cancer were recruited at 9 facilities in metropolitan Chicago (2 public and 4 private non-academic, and 3 academic institutions). Eligible patients had a diagnosis of a first primary invasive colon cancer between the ages of 30 and 79 years, and were non-Hispanic White or non-Hispanic Black. Patients were interviewed on their prior screening and the process of their diagnosis, which was augmented with detailed chart abstraction. A broad range of social and attitudinal constructs were measured including 3 well validated religiosity scales: God Locus of Health Control (GLHC), Religious Problem Solving (RPS), and Religious Coping (Brief RCOPe). The final response rate was 54% and includes 407 patients. Results: Median age of the sample was 60, 52% were Black, 33% had income < $20K, and 13% had < HS education. Cancer stage was available on 372 (91%), and 62% were late stage (stage III, IV). Blacks had significantly higher levels of GLHC than Whites (mean 22 vs. 13, on a scale of 6-30, p < 0.001). Univariate logistic regression models for age, race, sex, income, education, and religiosity items showed that only younger age (p = 0.01) and higher levels of GLHC (p = 0.016) were associated with late stage at diagnosis. These significant associations held in the multivariate model when both were adjusted for. There was no significant interaction between race and GLHC (p = 0.238). Conclusions: In a large bi-racial sample across diverse health care systems, younger age and high scores on the GLHC predicted late stage at diagnosis. While Blacks had significantly higher GLHC scores, race was not associated with stage at presentation. The relationship between GLHC and advanced disease stage was not limited to Blacks. Further work is ongoing to characterize the relationship between religious beliefs and health outcomes.

Effect of demographic factors and histology on stage IV non-small cell lung cancer (NSCLC): A National Cancer Database review. First Author: Brody Slostad, Creighton University School of Medicine, Omaha, NE

Background: Demographic characteristics, especially race and insurance status, affect the incidence of lung cancer diagnosed at Stage IV. This is the largest epidemiological study to determine patient features associated with the development of Stage IV NSCLC. Methods: A population-based study using the National Cancer Database (2000-2012), which contains 70% of all cancer diagnoses in the U.S. from 1658 ACS Accredited-Hospitals. Demographic groups of NSCLC presenting with Stage IV were compared to the entire cohort of NSCLC patients using the Chi square test. Results: Of all NSCLC patients (N = 9,956,237), 36% were Stage IV at presentation. Uninsured (52%), aged 40-49 (47%), Medicaid recipients (46%), aged 50-59 (42%), Hispanic (41%) and Black (41%) patients presented with more Stage IV at diagnosis. Medicare recipients (34%) had worse survival with less Stage IV. Adenocarcinoma (41%) and Squamous Cell (54%) presented with 43% and 25% Stage IV disease at diagnosis, respectively. Uninsured (60%) patients had the most frequent Stage IV disease at diagnosis. Conclusions: AC presents much more frequently than SQ as Stage IV. In particular, uninsured AC patients have the most frequent Stage IV presentation. Similar to a previous NCDB study, this study, which includes 5 times as many lung cancer patients as the previous study, shows uninsured, Medicaid, Hispanic and Black NSCLC patients present with more Stage IV disease (Halipem JT, et al. (2008)) Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. Lancet Oncol 9:222-232). Conversely, Medicare patients present with less Stage IV disease.

Impact of racial residential segregation (RRS) on stage at diagnosis and survival after diffuse large B-cell lymphoma (DLBCL). First Author: Loretta J. Slootrop, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Racial disparities in disease presentation and survival have been reported for DLBCL, which may arise from biological or socioeconomic status (SES) differences that influence treatment and outcomes. We examined the associations between RRS, stage at diagnosis, overall survival (OS) and lymphoma-related survival (LRS) for non-Hispanic Black and non-Hispanic White patients. Hypothesizing that RRS is associated with advanced stage disease and inferior survival for Black pts with DLBCL. Methods: We merged data from the population-based California Cancer Registry for new cases of DLBCL diagnosed during 1996-2007 with 5 Census indices of segregation among Blacks relative to Whites: dissimilarity, exposure, isolation, relative centralization, and spatial proximity. We included a measure of the % of black individuals per neighborhood (%B). Controlling for demographic and clinical factors, we used multivariable logistic regression and Cox regression to examine each RRS measure, modified by %B, on stage and survival, respectively, for Blacks and Whites separately. Results: Among 10,505 White and 749 Black DLBCL pts, Blacks more commonly had advanced stage disease (52 vs 45%) and resided in the lowest SES neighborhoods (28 vs 7%). Among Black pts, medium to high segregation as measured by dissimilarity (HR 2.1; 95% CI 1.1-4.1) and isolation (HR 2.2; 95% CI 1.0-5.0) were associated with advanced stage; however, there were no significant association between any RRS measure and survival. Among White pts, there was no significant associations between RRS and stage; whereas low segregation measured by spatial proximity (LRS HR 1.2; 95% CI 1.2-1.1; OS HR 1.2; 95% CI 1.1-1.4), isolation (LRS HR 1.3; 95% CI 1.1-1.5; OS HR 1.3; 95% CI 1.1-1.4) and dissimilarity (LRS HR 1.2; 95% CI 1.0-1.4; OS HR 1.3; 95% CI 1.1-1.4) in neighborhoods with high %B were associated with worse OS and LRS. Conclusions: Despite association with stage at diagnosis for Black pts, neighborhood composition and segregation had minimal impact for White pts and no impact for Black pts on survival, suggesting that other sociological/biological factors influence racial differences in DLBCL survival.

Patient navigation as a model to increase minority participation in cancer clinical trials. First Author: Mona Foud, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Background: For ethical, social, and scientific reasons, cancer clinical trials require participation of patients from diverse population groups. Less than 10% of all patients enrolled in clinical trials are minorities. The patient navigation model has been used to assist under-resourced cancer patients to access medical care. However, the model has not been evaluated as a tool for increasing the participation of minorities in clinical trials. The project "Increasing Minority Participation in Clinical Trials" (IMPaCT) utilized patient navigation (PN) to enhance the recruitment and retention of African Americans (AA) in therapeutic cancer clinical trials in an NCI-designated comprehensive cancer center. Methods: Lay individuals were recruited and trained to serve as PNs for clinical trials. The training curriculum included content related to clinical trials, the navigation process, interaction with patients, the clinical environment, and case management. The training sessions were co-led by clinical research nurses, physicians, and health educators. AA patients potentially eligible for clinical trials were identified through chart review or referrals by clinic nurses, physicians, and social workers. PNs provided two levels of services to AA cancer patients who consented to receive PN support: 1) Clinic-based education about clinical trials; and 2) Tailored supportive services for patients who enrolled in clinical trials. Results: Two lay individuals matching the demographic characteristics of the patients were trained and hired as PNs. Between June 2004 and 2014, 42 AA were referred to IMPaCT. Of the patients eligible for a clinical trial (N = 378), 302 (79.9%) enrolled in a trial and 270 (71.4%) consented to receive PN support during the trial. Of those receiving PN support, 74.5% completed the trial, compared to 37.5% of those who chose not to receive PN support. The difference in the clinical trial completion rates between participants who received PN support vs. those who did not was statistically significant (P < 0.001; Chi-Square test). Conclusions: This study indicates that PN could address barriers to clinical trial participation in AA cancer patients and improve retention in clinical trials.
Endocrine therapy adherence, side effects, and risk perception among racially diverse breast cancer patients. First Author: Stephanie B. Wheeler, UNC Chapel Hill, Chapel Hill, NC

Background: Differential endocrine therapy (ET) use by race may contribute to disparities in breast cancer outcomes. The goal of this study was to examine racial variation in ET adherence, side effect experiences and perceptions about recurrence risk. Methods: We surveyed 1,507 stage I-III breast cancer patients using a mailed, self-administered questionnaire at 18-months post-diagnosis as part of the Carolina Breast Cancer Study Phase III (CBCS-III), a population-based, prospective cohort study that recruited participants via rapid case ascertainment in 2008-2013. Non-adherence was defined as not taking ET pills every day as prescribed, discontinuing ET pills, or missing >= 3 pills in the past 14 days. Binvariable analyses identified differences in adherence, side effect experiences and risk perceptions by race. Results: Overall, 934 women in our sample were prescribed ET; of these, 43% were African American (AA). The mean age at diagnosis was 54, and the majority were diagnosed with stage 1 (50%) or 2 (37%) disease. Overall, 19% were classified as non-adherent; 22% of AA women were non-adherent (vs.16% of white women, p = 0.014). Comparing to white women, AA women more often forgot to take ET when traveling away from home (25% vs. 16%, p = 0.035); felt sticking to their ET treatment plan was difficult (25% vs. 14%, p < 0.0001), had trouble remembering to take their ET pills (24% vs. 13%, p = 0.0001), and reported cost-related non-adherence (16% vs. 7%, p = 0.0001), and experienced bothersome side effects (25% vs. 18%, p = 0.0033). AA women more often than white women reported experiencing the following side effects frequently in the past 7 days: hot flashes (55% vs. 45%, p = 0.0017), night sweats (41% vs. 30%, p = 0.0002), breast sensitivity (24% vs. 16%, p = 0.0015), and joint pain (46% vs. 38%, p = 0.011). More AA women reported believing there would be no change in their recurrence risk if they stopped ET (20% vs. 8%, p < 0.0001). Conclusions: These data highlight important racial differences in adherence behaviors, side effect experiences and perceptions of recurrence risk. Culturally-tailored interventions that can help women taking ET to better manage side effects and reframe risk perceptions may better motivate adherence.

Utility of surveillance following curative intent resection of metastases. First Author: Richard M. Lee-Ying, BC Cancer Agency, Vancouver, BC, Canada

Background: Surveillance is frequently conducted after the completion of curative treatment in early stage cancers to detect resectable recurrences. As more stage IV patients undergo curative resection of metastases (CRM), surveillance of such cases is increasingly performed, but its utility is unclear. Using a cohort of metastatic colorectal cancer (mCRC) patients, we aimed to 1) characterize surveillance patterns in a population-based setting and 2) examine if surveillance contributed to improved outcomes. Methods: Patients diagnosed with mCRC from 1995 to 2010 and referred to any one of 5 cancer centers in British Columbia were reviewed. Using Cox regression models that adjusted for confounders, we identified predictors of overall survival (OS) in patients who underwent CRM. Recurrences were categorized into those detected by surveillance vs. symptoms and whether further attempts at CRM were feasible. Results: We identified 2082 mCRC patients of whom 254 proceeded to CRM. Median age was 63, 52% were men, 44% had de novo stage IV disease, 56% received perioperative chemotherapy, and 17%/66% had lung/liver metastases, respectively. Sures of OS varied widely, but included clinical examination (85%), CEA (86%), imaging (89%) and endoscopy (28%) in the first 5 years. The median OS of CRM cases was 40.9 months, including 191 (75%) recurrences. The median time to recurrence was 10.2 months. Recurrences were detected by surveillance in 152 (80%) cases, and 52 (24%) of a total of 412 recurrences were detected by symptoms, those based on surveillance were more likely to proceed to another CRM (25% vs. 11%, p < 0.001). Adjusting for confounders, surveillance (HR 0.61 95% CI 0.39-0.94, p = 0.026) and a second CRM (HR 0.53, 95% CI 0.34-0.82, p = 0.004) were indepen- dently correlated with improved OS. Conclusions: In this population-based cohort of mCRC patients, the majority recurred after the initial CRM, but recurrences detected by surveillance were more amenable to a subsequent CRM. While surveillance was performed in most cases, significant variations in practice were observed, underscoring the need for wider dissemina- tion of evidence-based guidelines for the surveillance of selected metastatic disease.

Disparities in hospice use among patients with cancer in the Deep South. First Author: Bradford E. Jackson, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Background: Higher rates of hospice use are an indicator for high-quality end-of-life care for cancer patients, however disparities have been re- ported. Known racial disparities in hospice utilization may be explained by hospital characteristics that would affect the likelihood of referral to hospice. The purpose of this study was to explore variations in hospice use at both the patient and hospital level. Methods: Administrative claims were obtained for Medicare patients ≥ 65 years old diagnosed with cancer within the UAB Health System Cancer Community Network (UAB CCN) from 2008-2014. Enrollment in hospice was assessed for all deceased patients in the 90 days before death. Using logistic regressions we assessed the association between hospice use and patient-level factors (race, gender, and cancer type), as well as hospital-level factors (presence of a board certified palliative care physician and ownership of a hospice facility). Results: are presented as frequencies and percentages as well as odds ratios (OR) and their corresponding 95% confidence limits (95%CL). Results: Sixty-eight percent (n = 7,186) of patients enrolled on hospice in the 90 days before death. In the unadjusted analysis, females were more likely to be enrolled on hospice than males (70% vs 66%; p = 0.002), blacks less likely than whites (62% vs 69%; p = 0.002). Hospice use varied by cancer type (77% for pancreatic cancer patients and 60% for hematologic malignancies). Hospice use was not significantly different for hospitals with board certified palliative care physicians (67% vs 69%; p = 0.178) or those certified to provide (home or inpatient) hospice care (69% vs 67%; p = 0.130). In the multivariable model adjusting for patient- and hospital-level characteristics, we observed lower odds of hospice use for blacks (OR 0.67; 95%CL: 0.57, 0.80); higher odds for hospitals certified to provide hospice care (OR = 1.14; 95%CL: 1.16, 1.21) and no difference for hospitals with palliative care physicians (OR = 0.9, 95%CL: 0.79, 1.04). Conclusions: Disparities in hospice enrollment exist in this hospital network of the rural Deep South. Although patient characteristics may help explain variation in hospice use, our findings show mixed associations with palliative care services.

Trends in use of PET imaging in surveillance of lung and colorectal cancer. First Author: Christine Marie Veenstra, University of Michigan, Ann Arbor, MI

Background: Surveillance PET imaging following curative intent treatment of non-small cell lung cancer (NSCLC) or colorectal cancer (CRC) is not supported by available evidence. ASCO and ABIM’s joint Choosing Wisely campaign recommends against surveillance PET, yet the frequency with which PET imaging is performed during surveillance care is unknown. Methods: 65,748 patients age 66+, diagnosed with stage I-IIIA NSCLC or stage I-III CRC in 2001-2009, who underwent surgical resection were identified in SEER-Medicare data. Eligibility for surveillance started 180 days post-operatively. Use of imaging was assessed during the first year of surveillance and classified as 1) Any PET: receipt of PET or PET/CT regardless of other imaging, or 2) PET-only: receipt of PET or integrated PET/CT only, in patients who did not undergo separate dedicated CT imaging. Unadjusted proportions of patients receiving each category of surveillance were calculated by cancer type, diagnosis year, and stage. Equality of proportions was assessed between diagnosis years with ANOVA. Results: 7,393 NSCLC patients and 35,050 CRC patients met inclusion criteria. PET was more than doubled over the study period in both cohorts. 11% of all NSCLC patients diagnosed in 2001 received any PET vs. 25% diagnosed in 2009 (P < 0.0001). Similarly, 4% of all CRC patients diagnosed in 2001 received any PET vs. 12% diagnosed in 2009 (P < 0.001). PET utilization was more common in higher stage NSCLC and CRC patients compared to lower stage (P < 0.001) and endoscopy (P < 0.001). PET utilization was more common in higher stage NSCLC and CRC patients compared to lower stage. In this same group of patients, 1.5% diagnosed in 2001 received PET-only, compared to 15% diagnosed in 2009. Among Stage III CRC patients any PET use increased from 9% for those diagnosed in 2001 to 27% for those diagnosed in 2009 (P = 0.001), while use of PET-only increased from 1% to 8% over the same period (P < 0.001). Conclusions: Although not indicated in surveillance, PET utilization has more than doubled among NSCLC and CRC survivors over the study period. While surveillance rates may be increasing generally, increased rates of PET-only imaging suggest PET is inappropriately replacing existing surveillance protocols.
**Poster Session (Board #121), Mon, 1:15 PM-4:45 PM**

**Effect of improving guideline-based prophylactic growth factor (pGCSF) use with chemotherapy (CT) on the risk of febrile neutropenia (FN) in non-small cell lung cancer (NSCLC) patients at Cleveland Clinic Taussig Cancer Institute (TCI) Quality Improvement (QI) Project.**

**First Author:** Lindsey Martin Goodman, Cleveland Clinic, Cleveland Heights, OH

**Background:** Per accepted guidelines, pGCSF is not recommended for pts receiving CT regimens with low risk (<10%) for FN. Factors contributing to inappropriate pGCSF use include lack of provider familiarity with national guidelines as well as the presence of standing pGCSF orders in EMR templates. Inappropriate use of pGCSF increases pt morbidity and healthcare costs. **Methods:** A multidisciplinary team performed a QI project through the ASCO Quality Training Program. All NSCLC pts at TCI who initiated a new CT regimen from April 2013 to October 2014 were reviewed. First-cycle pGCSF use was deemed appropriate if prescribed for CT associated with high risk of FN (>20%) or intermediate risk (10-20%) if other risk factors for FN were present. Use with low-risk CT was considered inappropriate. We implemented three QI strategies: education of NSCLC providers, development of TCI Consensus Guidelines for the use of pGCSF in NSCLC, and EMR modification: labeling of CT regimens by FN risk and removal of standing pGCSF orders from low-risk CT. Follow up data were collected from January to October 2014. FN rates before and after the QI interventions were documented. **Results:** 300 NSCLC pts received a new CT regimen during the specified time period. Prior to the interventions, 34/118 pts (29%) treated with low-risk CT received pGCSF (average 2.6 doses/pt). In all other instances pGCSF use was in accordance with guidelines. Following QI interventions, 8/126 (6%) treated with low-risk CT received pGCSF. No patient treated with low-risk CT required inpatient admission for FN during post-intervention follow up. Cost analyses indicate a potential reduction of $1.9 million in charges over 1 year with guideline-based pGCSF use in low-risk CT. Conclusions: Early identification of appropriate use can be improved with focused provider education and EMR modification. The lack of FN admissions in the post-intervention period validates current guidelines. Appropriate pGCSF administration in NSCLC leads to significant cost savings without increasing neutropenic complications.

**Poster Session (Board #123), Mon, 1:15 PM-4:45 PM**

**Utility of pre-operative PET/CT staging in sentinel lymph node-positive melanoma.**

**First Author:** Benjamin Scheier, University of Michigan Health System, Ann Arbor, MI

**Background:** Sentinel lymph node (SLN) mapping is an integral part of melanoma staging. If regional metastases are identified, patients often undergo lymph node dissection (LND) as definitive treatment. The National Comprehensive Cancer Network (NCCN) makes a category 2B recommendation based on "low-level evidence" and a non-uniform consensus that prior to LND, patients may be considered for staging by positron emission tomography with a computed tomography scan (PET/CT). PET/CT, however, lacks data supporting this use, may inconsistently impact treatment decisions and carries a risk of false positives that may detract from clinical utility. **Methods:** A retrospective evaluation of patients seen at the University of Michigan with melanoma and clinically silent regional lymph nodes between July 2013 and September 2014 was performed. We identified patients with positive SLN mapping, 46 of which underwent PET/CT prior to LND. Remaining patients either underwent no staging or CT with brain MRI. Outcomes measured include changes in clinical management and incidence of false positives, defined as biopsy-validated PET/CT findings non-diagnostic for melanoma. **Results:** Of the 46 patients who underwent PET/CT prior to LND, 15 (33%) had abnormal findings distant from the primary tumor and local lymph node basin. 9 of those 15 patients (60%) had abnormalities biopsy-proven prior to LND. Of the 46 patients assessed, only 3 (6.5%) had PET/CT findings that ultimately identified metastatic melanoma and proceeded to LND. The false negative rate of 60% for metastatic distant metastases. There was not a statistically significant association between T and N stage and whether or not patients underwent PET/CT imaging (Fisher’s exact test, p = 0.12 and 0.85, respectively). There was a statistical association between undergoing PET/CT and ulceration status (p = .004). **Conclusions:** The utility of PET/CT staging following SLN mapping in melanoma is unknown, despite its recommended use by the NCCN. In our retrospective review, we found that PET/CT has a high false positive rate and a minimal effect on patient management. PET/CT staging should be reevaluated as a category 2B recommendation by the NCCN and its utility evaluated prospectively in a clinical trial.
Quality of life EQ-5D results from the AETHERA trial: A phase III study of brentuximab vedotin consolidation following autologous stem cell transplantation for HL. First Author: Scott David Ramshey, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: The AETHERA trial demonstrated that early consolidation treatment with brentuximab vedotin (BV) post-ASCT significantly improved PFS in pts with HL (4). Peripheral neuropathy (PN) was the most common adverse event in this trial. Methods: After ASCT, 329 pts were randomized to BV 1.8 mg/kg q3wk or placebo for up to 18 months. The EQ-5D questionnaire, including the visual analog scale (VAS), was administered at each cycle, end of treatment (EOT), and q3 mos during follow up until 24 mos from Day 1. Utility index value scores were calculated using the time trade-off (TTO) method for US- and UK-based value sets. Differences between arms were compared to the lower bound of an estimated minimally important difference (MID) in cancer pts (Pickard et al. 2007). Results: In both arms, EQ-5D scores declined from baseline to 24 mos. Slightly lower scores were seen with BV vs placebo from mos 9-18, but this resolved by end of follow up. In the analysis as randomized (US TTO), the difference between arms was <0.05 (MID) at all timepoints except for mos 15 and 18. Scores by cycle were similar in the 2 arms; mean differences did not reach the MID threshold. In both arms, scores for pts with PD per investigator were lower over time vs. pts with no PD. In the BV arm, scores for pts reporting PN were similar to those who did not. Similar results were obtained with US- or UK-based value sets. EQ VAS scores did not show an important difference between arms at any timepoint. Conclusions: As assessed using the EQ-5D questionnaire, treatment with BV did not have a sustained impact on QoL in HL pts. In both arms, decreased QoL was observed after progression. Clinical trial information: NCT01100925.

US-indexed EQ-5D TTO scores.

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<th>Mean</th>
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Impact of enhanced reimbursement on provider participation: a cancer care quality program and adherence to cancer treatment pathways in a commercial health plan. First Author: Jennifer Malin, Anthem, Inc., Woodland Hills, CA

Background: Payment for treatment planning and care coordination for cancer care in the U.S. has been largely funded through the margin between the acquisition cost and reimbursement of cancer drugs. The Payment for treatment planning and care coordination when oncology patients are treated at academic centers and community practices for breast, lung and colorectal cancers that pose a high risk of recurrence, but its use is frequently generalized to cases in which the probability of recurrence is low and absolute benefit is small. Using a cohort of stage II rectal cancer (RCa) patients (pts), we aimed to examine population-based outcomes stratified by receipt of AC and to characterize pts in whom AC provides benefit. Methods: Prospective collection of data from pts referred to 5 cancer centers in British Columbia for pathologic stage II RCa from 1998 to 2009 were reviewed. Overall (OS), disease-specific (DSS) and relapse-free (RFS) survival were assessed with Kaplan-Meier methods. Cox regression models that adjusted for age at diagnosis, stage, was 9.08% (2.2%), which was statistically significant (P = 0.02). Conclusions: Higher adherence rates were observed after enrollment into our oncology pharmacist-driven oral chemotherapy adherence program. Enrollment of pts into OCAP at the time of initiation of oral anticancer therapy would likely result in increased overall adherence rates. Effects of OCAP on other important outcomes, such as adverse events and costs, are ongoing.

Avoiding overtreatment in rectal cancer when the benefit of adjuvant chemotherapy is unclear. First Author: Jonathan M. Loree, British Columbia Cancer Agency, Vancouver, BC, Canada

Background: Adjuvant chemotherapy (AC) is intended for early stage cancers that pose a high risk of recurrence, but its use is frequently conventionally used to guide AC decisions in early colon cancer. However, these data revealed that AC correlated with improved OS (HR 0.22 95% CI 0.07-0.70, P = 0.001). In multivariate analyses, AC contributed to superior OS (HR 0.46 95%CI 0.35-0.62, P = 0.001), DSS (HR 0.63 95%CI 0.43-0.92, P < 0.05), and a trend to improved RFS (HR 0.70 95%CI 0.49-1.01, P = 0.055). In multivariate analyses, however, AC correlated with better OS (HR 0.61 95%CI 0.42-0.90, P < 0.001), but not DSS (P = 0.25) or RFS (P = 0.46). Subgroup analysis revealed that AC correlated with improved OS (HR 0.50, P = 0.011), DSS (HR 0.25 95%CI 0.07-0.89, P = 0.033) and RFS (HR 0.24 95%CI 0.07-0.85, P = 0.03) only in selected pts who received short course radiotherapy and had ≥ 2 high risk features (n = 49, 12% of pts), such as T4 lesion, poor differentiation, inadequate lymph node sampling or obstruction/perforation. Outcomes in other subgroups were similar regardless of receipt of AC. Conclusions: In this population-based cohort of stage II RCa pts, the majority do not appear to benefit from AC. Risk factors conventionally used to guide AC decisions in early colon cancer should be considered in early RCa. Incorporating molecular tests into future risk stratification may further minimize unnecessary use of AC and potential over-treatment of pts.
Background: Reducing 30-day readmissions is a national policy priority. Readmissions in medical oncology have not been separately evaluated, and may not be reasonably preventable. We examined the impact of interventions focused on reducing oncology readmissions in the palliative medicine (PM) and general medical oncology (GMO) units.

Methods: Baseline rates of readmissions were gathered in the period January 2013 to March 2014. Interventions were initiated in the period leading to April 1, 2014 including: (i) provider education, (ii) within 48 hours post-discharge nursing phone calls, and (iii) within-5-day post-discharge provider follow-up appointments. Calling nurses performed symptom management, education and encouraged prescription/appointment compliance.

Results: There were a total of 3,729 combined admissions and 1,033 readmissions in the baseline period, for a readmission rate of 26% for PM and 27% for GMO units. In the 8-month intervention period (May-Dec 2014), there were 1,694 admissions, and 396 readmissions. Callbacks and 5-day appointments were monitored with a mean compliance of 77% and 70%, respectively, improving during the study period. PM readmission rates declined by 5% to 21% (p = 0.01, relative risk reduction 19%). GMO readmissions also decreased by 3% to 24% (p = 0.02, relative risk reduction 11%). The mean total cost of one readmission was $18,365, suggesting an annual potential cost savings of $2.91 million with the observed reduction in readmissions. Conclusions: Readmission reductions in both units were achieved through better systematic transitions to outpatient care, including follow-up calls and early provider visits; thereby leading to a reduction in utilization of inpatient resources. These data suggest that efforts focused on improving outpatient care transition are effective in reducing oncology readmissions. This is particularly relevant in the transition towards novel bundled payment models in oncology. The observed feasibility and patient/provider acceptance of these interventions suggests sustainability, and will be validated over longer time periods.

Background: Time to initiate breast cancer treatment is increasing in the United States, but controversy surrounds the impact of TTT on survival. The impact of the interval between diagnosis and treatment is a source of concern to patients and clinicians. We investigated the relationship using separate analyses of two of the largest cancer databases in the United States. Methods: Patients had noninflammatory, nonmetastatic, invasive breast cancer, with surgery as initial treatment. The first study used the SEER-Medicare database (SMDB), and second, the National Cancer Database (NCDB). Each analysis assessed survival as a function of time between diagnosis and operation (≤ 30, 31-60, 61-90, 91-120, and 121-180 days) from diagnosis, adjusting for demographics, comorbidity, geographic region, and cancer stage. Results: There were 94,544 patients ≥ 66 years old, diagnosed between 1992 and 2009. With each interval delay increase, adjusted overall survival (OS) was lower for all patients (hazard ratio [HR] 1.09, p < 0.001), and for those having stage I (hazard ratio [HR] 1.13, p < 0.001) and stage II (HR 1.06, p = 0.010) disease. Breast cancer-specific mortality increased with each 60-d interval (subhazard ratio 1.26, p = 0.03). The NCDB study evaluated 115,790 patients ≥ 18 years old, diagnosed between 2003 and 2005. The adjusted overall mortality HR was 1.10 (p < 0.001) for each increasing interval, significant in stages I (HR 1.12, p < 0.001) and II (1.10, p < 0.001) dissections in medical oncology patients have not been extensively related factors and treatment in the SMDB progressively declined from 78.1% for ≤ 30 d to 60.9% for 121-180 d and in the NCDB from 88.0% for ≤ 30 d to 80.4% for 121-180 d. Conclusions: Independent analyses of two national cohorts demonstrate that an increased time to initiate surgical treatment confers lower overall and disease-specific survival for patients with early stage breast cancer. A shortened delay is associated with an outcome benefit comparable in magnitude to the addition of some standard therapies. Although time is required for preoperative evaluation and consideration of options such as reconstruction, efforts to reduce TTT should be pursued when possible to enhance survival.
Background: In 2011, NCI began requesting Corrective Action Plans (CAP) for early phase trials accruing < 50% of their projected accrual rate after Qtr 2 for Phase 1 (Ph1) or Qtr 3 for Phase 2 (Ph2). Study PIs of low accruing trials are asked to complete and return a CAP within 2 weeks and identify reasons and possible actions to address accrual. We report findings from an analysis of CAPs received on all NCI Cancer Therapy Evaluation Program (CTEP) held IND studies active between Aug 2011 and Feb 2013 (N = 327). Methods: Three methods were employed: 1) content analysis of CAPs to categorize slow accrual reasons and proposed actions (3 coders, intercoder reliability = 78%; 100% after post-coding deliberation); 2) analysis of CAP trial timelines and accrual data; 3) assessment of whether closed CAP trials met their primary scientific objectives. Results: CTEP requested CAPs for 150 (46%) of the 327 trials; 135 were eligible for analysis with 51% Ph1 (n = 69) and 49% Ph2 trials, and 88% adult trials (n = 119). CAP trials were open a median of 30 months (14 mo pre- and 16 mo post-CAP), and 70% (n = 94) were closed to accrual at analysis. Of closed CAP trials: 68% (n = 64) met their primary objective but took 3x longer than projected; those not meeting their objective(s) were open 6x longer before closing; and 27% (n = 25) had an accrual rate increase, post-CAP, associated with a greater likelihood of meeting the objective(s). For Ph1 trials, safety delays dominated slow accrual reasons while institutional/administrative reasons were common for Ph2. Site activation delays and access to patients ranked high for both. Only 54% of proposed corrective actions matched the reasons given for slow accrual. Conclusions: CAP requests had a positive impact on accrual for over one-quarter of the trials analyzed; however, most trials receiving a CAP took substantially longer to complete than projected. CTEP’s new Experimental Therapeutics Clinical Trial Network (ETCTN) is poised to address many concerns identified in this analysis. CAPs should be implemented prior to Q2/Q3 to identify and address slow accruing trials earlier. CTEP is standardizing the CAP data collection to develop statistical algorithms to aid decisions related to trial closure for slow accrual.

Outcomes and predictors of life sustaining treatments in patients with metastatic cancer. First Author: Kah Poh Loh, Baystate Medicl Ctr, Springfield, MA

Background: Patients with metastatic cancer admitted to the ICU or requiring invasive mechanical ventilation (IMV) have historically had high mortality rates. However, little is known about how frequently these patients receive life-sustaining treatments (LSTs) or which characteristics are associated with receipt of LSTs. Methods: We used the 2010 California Healthcare Cost and Utilization Project - State Inpatient Database to identify metastatic cancer patients (≥ 18 years), focusing on patients with a medical DRGs. Using ICD-9-CM procedure codes, we examined use of LSTs. We stratified patients by the use of LSTs and cancer types and compared patient characteristics and outcomes with chi-square or Wilcoxon analysis with 51% Ph1 (n = 94) and 49% Ph2 trials, and 88% adult trials (n = 119). CAP trials were open a median of 30 months (14 mo pre- and 16 mo post-CAP), and 70% (n = 94) were closed to accrual at analysis. Of closed CAP trials: 68% (n = 64) met their primary objective but took 3x longer than projected; those not meeting their objective(s) were open 6x longer before closing; and 27% (n = 25) had an accrual rate increase, post-CAP, associated with a greater likelihood of meeting the objective(s). For Ph1 trials, safety delays dominated slow accrual reasons while institutional/administrative reasons were common for Ph2. Site activation delays and access to patients ranked high for both. Only 54% of proposed corrective actions matched the reasons given for slow accrual. Conclusions: CAP requests had a positive impact on accrual for over one-quarter of the trials analyzed; however, most trials receiving a CAP took substantially longer to complete than projected. CTEP’s new Experimental Therapeutics Clinical Trial Network (ETCTN) is poised to address many concerns identified in this analysis. CAPs should be implemented prior to Q2/Q3 to identify and address slow accruing trials earlier. CTEP is standardizing the CAP data collection to develop statistical algorithms to aid decisions related to trial closure for slow accrual.

Determinants of early mortality in 37,568 colon cancer patients participating in 25 clinical trials of the ACCENT database. First Author: Winson Y. Cheung, British Columbia Cancer Agency, Vancouver, BC, Canada

Background: Clinical trials are the gold standard for evaluating novel therapeutics. Accrual of patients (pts) at substantial risk of significant treatment toxicity or early mortality compromises trial integrity, may pose greater harm than benefit, and can complicate trial interpretation. We aimed to define prognostic factors that may be used to guide risk-benefit assessments among pts being considered for phase III adjuvant colon cancer (CC) trials. Methods: A pooled, retrospective analysis of individual level data from CC pts enrolled in randomized trials of adjuvant systemic therapy was conducted. Separate multivariate logistic regression models with different definitions of early mortality (30, 60, 90 days, and 6 months from trial randomization) as outcome variables were constructed, adjusting for clinically and statistically significant variables from univariate and interaction tests. Results: We included 37,568 pts from 25 trials. Median age 61 years (IQR 53-68), 54% men, 90% White, 29% and 71% stage II and III disease, and 79%, 20%, and 1% ECOG performance status (PS) 0, 1, and 2, respectively. Rates of early mortality were low: 109 (0.3%) at 30 days, 215 (0.6%) at 60 days, 281 (0.8%) at 90 days, and 540 (1.4%) at 6 months in the pooled cohort. On univariate analyses, increasing age, male gender, poorer PS, and stage III vs. stage II disease predicted for higher likelihood of early mortality. Race, body mass index, lymph node ratio, micro-satellite status as well as study time era were not associated with outcome. For both models, PS was associated with early mortality at all time-points (age: < p = 0.0001 and PS: p = 0.05 at 6 months), with pts aged ≥ 1 = 80 having a 6 month death rate of 4.6% as compared to < 1 for the youngest and pts with PS 2+ having a 6 month death rate of 4.4% as compared to 1.7% and 1.1% for PS 1 and 0, respectively. Conclusions: Early mortality in adjuvant trials of CC was infrequent. However, it was more prevalent in the elderly and among individuals with PS 2+ underscoring the need for specific trial designs that can accommodate the vulnerabilities of these underrepresented subsets of the population.
Frequency and predictors of hospitalization during chemotherapy: a systematic review. First Author: Rebecca M. Prince, Princess Margaret Hospital, Toronto, ON, Canada

Background: Hospitalization during chemotherapy is a significant event from both the patient and healthcare system perspectives but little is known about how often it occurs and in which settings. We conducted a systematic review to define the frequency of and factors associated with treatment-related hospitalization among cancer patients (pts) undergoing chemotherapy. Methods: A systematic search of Medline and EMBASE databases, from 1946 to September 2013, was undertaken to identify articles reporting rates of hospitalization in pts with cancer undergoing chemotherapy. Observational studies and clinical trials were eligible but articles reporting rates of hospitalization in pts with cancer undergoing chemotherapy. Observational studies and clinical trials were eligible but often only reported hospitalization as a secondary outcome. Therefore, a number of methodological issues regarding reporting of hospitalization parameters were identified such as poor definitions of the groups. Results: Compared to hospitals with low multimodality treatment utilization, patients in hospitals with high utilization were more likely to receive multi-agent chemotherapy (51.0% vs 32.1%, p < 0.001), primary site resection (66.3% vs 62.3%, p < 0.001), metastatic site resection (32.0% vs 10.0%, p < 0.001), or palliative care (9.1% vs 6.9%, p = 0.014), and had longer median survival (15.2 vs 12.4 months, p < 0.001). The observed survival differences across hospitals were eliminated once patients were stratified by treatment modality (adjusted HR for treatment in a high-intensity hospital 1.02 [0.98-1.07]). For example, there were minimal differences in median survival between high and low utilization hospitals for patients treated with multimodality therapy (30.7 vs 29.1 months, p = 0.31), chemotherapy only (12.1 vs 12.6 months, p = 0.04) or palliative care (7.8 vs 7.8 months p = 0.24). Conclusions: There is broad variation in hospital treatment utilization for patients with metastatic CRC. Survival differences across hospitals are minimal, however, when patients receive similar treatments. Higher survival in hospitals with high treatment utilization likely reflects their willingness to utilize cancer treatments, include palliative care, rather than other features of their overall quality of care.

Choosing wisely: Treatment recommendations from 36 Michigan Oncology Clinical Treatment Pathways practices. First Author: Amy Hatfield Seung, CARET, Ann Arbor, MI

Background: ASCO identified ten low value, commonly used practices (Schnipper et al JCO 14:1715, 2012 and JCO 31:4362, 2013) as part of the "Choosing Wisely" (CW) campaign. Pathways is a statewide quality improvement program sponsored by the Michigan Quality Oncology Practice Initiative (MQOPI). Pathways is a peer-reviewed clinical decision support tool that promotes adherence to locally defined treatment pathways (Fineberg et al JOP 8:32s, 2012). CARET, a web-based patient registry was developed to support this program. CARET allows providers to enter treatment data and patient characteristics, and to demonstrate pathway compliance. We report preliminary data for three CW items. Methods: CARET includes records entered by participating physicians for medical anticancer treatment regimens. Provider-reported data is used to describe the results and the Chi-square test was used to compare results. Results: Sixty articles met inclusion criteria: 44 observational studies comprising 189,342 pts and 16 randomized controlled trials comprising 13,086 pts. The majority of articles (80%) focused on chemotherapy given with palliative intent most commonly in breast, lung and colorectal cancers. The proportion of pts hospitalized at least once was significantly higher in observational studies at 32% (range 27-38%) compared with 21% (range 15-27%) in randomized trials (OR 2.13, 95%CI 2.03-2.23, p < 0.0001). A significant difference was seen in both the adjuvant and palliative settings between real life and trial pts with 42 vs 16% (OR 2.94, 95%CI 2.72-3.18, p < 0.0001) of adjuvant and 33 vs 23% (OR 1.44, 95%CI 1.33-1.48, p < 0.0001) of palliative pts being hospitalized, respectively. Factors associated with hospitalization in observational studies included higher comorbidity, type of chemotherapy and geographic location, while performance status and type of chemotherapy were significant predictors in clinical trials. Age was not a risk factor in either population. A number of methodological issues regarding reporting of hospitalization parameters were identified such as poor definitions of the at-risk period and attribution of hospitalization as treatment-related. Conclusions: Hospitalization during chemotherapy is common especially in unselected patient populations. However, few articles report this and often do so poorly.
Prospective clinical study of precision oncology in solid tumors. First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH

Background: Advances in tumor genomic profiling offer the promise of precision oncology but a systematic prospective evaluation is lacking. We conducted a prospective cohort study of tumor genomic testing to identify prevalence of actionable alterations and their impact on management decisions. Methods: Patients provided written informed consent for this prospective cohort study approved by the Cleveland Clinic Institutional Review Board. Eligibility requirements included pathologic diagnosis of select solid tumor malignancies without a known curative option, age ≥ 18 years, and ECOG PS 0-2. Tumor samples were sequenced for up to 315 candidate genes using FoundationOne (Cambridge, MA). Results: A prospective review of 250 tumor samples from 250 patients who met our criteria, of whom 339 (21.3%) had PIM use at baseline. In multivariate analysis, baseline PIM use was associated with higher comorbidity (OR 1.67, 95% CI 1.23-1.26 for 2+ vs. 0) and baseline chemotherapy dose intensity (OR 1.08, 95% CI 1.01-1.15). Baseline PIM use is a predictor of unplanned hospitalizations during cancer care: A Medicare claims analysis. First Author: Noam Avraham VanderWalde, University of Tennessee West Cancer Ctr, Memphis, TN

Background: Unplanned hospitalizations (UH) during cancer care have been identified as a poor outcome that may significantly increase costs of care. We hypothesized that poor quality of care prior to cancer diagnosis, as defined by preventable hospitalizations for Ambulatory Care Sensitive Conditions (ACSCs), predicts for UH during cancer care. Methods: A retrospective claims study was conducted among Medicare fee-for-service enrollees with a first time diagnosis of one of seven cancers (breast, lung, colorectal, lymphoma, melanoma, pancreatic, or thyroid) from 6 different states (TX, OH, ME, NM, GA, and FL) between 2011 and 2012. Date of diagnosis was defined as the first cancer diagnosis claim from inpatient or outpatient claims. At least nine months of pre-diagnosis data was required to identify pre-cancer Charlson comorbidity (CCI) and ACSC hospitalizations as measured by ER and hospitalization diagnosis codes. UHs were defined as hospitalization, with admission type of urgent or emergent within 1 year from diagnosis, excluding those for cancer treatment. Multivariate logistic regression analysis was used to model UH using known patient and county level socio-demographic variables. Results: A total of 21,735 cancer patients were identified. The majority of patients had breast (n=7,548), lung (n=5,841) or colorectal cancer (n=3,904). Median age at diagnosis was 74. Thirty four percent of patients were male. UH were present in 59% of all patients. Among those with UH, 14% had > 2 hospitalizations. We observed a strong association between PIM use during chemotherapy and adverse outcomes. Conclusion: Breast cancer progression is associated with impaired workplace productivity, with greater impairment among those with more advanced disease. Avoiding or delaying disease progression could bring productivity gains to the workplace in addition to the benefits to the patient.

Uncontrolled chronic conditions prior to cancer diagnosis in older adults as a predictor of unplanned hospitalizations during cancer care: A Medicare claims analysis. First Author: Noam Avraham VanderWalde, University of Tennessee West Cancer Ctr, Memphis, TN

Background: Unplanned hospitalizations (UH) during cancer care have been identified as a poor outcome that may significantly increase costs of care. We hypothesized that poor quality of care prior to cancer diagnosis, as defined by preventable hospitalizations for Ambulatory Care Sensitive Conditions (ACSCs), predicts for UH during cancer care. Methods: A retrospective claims study was conducted among Medicare fee-for-service enrollees with a first time diagnosis of one of seven cancers (breast, lung, colorectal, lymphoma, melanoma, pancreatic, or thyroid) from 6 different states (TX, OH, ME, NM, GA, and FL) between 2011 and 2012. Date of diagnosis was defined as the first cancer diagnosis claim from inpatient or outpatient claims. At least nine months of pre-diagnosis data was required to identify pre-cancer Charlson comorbidity (CCI) and ACSC hospitalizations as measured by ER and hospitalization diagnosis codes. UHs were defined as hospitalization, with admission type of urgent or emergent within 1 year from diagnosis, excluding those for cancer treatment. Multivariate logistic regression analysis was used to model UH using known patient and county level socio-demographic variables. Results: A total of 21,735 cancer patients were identified. The majority of patients had breast (n=7,548), lung (n=5,841) or colorectal cancer (n=3,904). Median age at diagnosis was 74. Thirty four percent of patients were male. UH were present in 59% of all patients. Among those with UH, 14% had > 2 hospitalizations. We observed a strong association between PIM use during chemotherapy and adverse outcomes. Conclusion: Breast cancer progression is associated with impaired workplace productivity, with greater impairment among those with more advanced disease. Avoiding or delaying disease progression could bring productivity gains to the workplace in addition to the benefits to the patient.
6589 Poster Session (Board #146), Mon, 1:15 PM-4:45 PM
Creating a national collaborative strategy to enhance trial accrual in NCI’s National Clinical Trials Network (NCTN) in the era of precision medicine.
First Author: Andrea Davis, National Cancer Institute, Bethesda, MD
Background: NCI launched the NCTN on March 1, 2014 to reinvigorate the publically funded cancer trials system. As precision medicine (PM) trials increasingly require screening large numbers of patients to identify a subset of patients whose tumors contain specific molecular targets, national accrual strategies are needed. We report findings from a Network-wide interactive meeting held in Dec, 2014 to explore accrual to PM and adolescent and young adult (AYA) trials. Methods: NCI convened a 2-day meeting of NCTN grantees and NCI staff, with 75 representatives from Groups, Patient Advocates & Lead Academic Participating Sites (LAPS), to discuss accrual in the era of PM. Accrual challenges and strategies were identified via a mixed method approach: pre-meeting worksheets, trial case studies, group and breakout sessions, and a priority ranking activity. Findings were triangulated to determine next steps to maximize future accrual. Results: Key themes identified included the need to streamline trial communication and promotion, emphasize accrual feasibility during trial design and review, better address minority and underserved populations, increase the efficiency and clarity of regulatory processes, and incentivize and enhance participation in trials by investigators and sites. Consensus was reached on the need for a cross-NCTN forum to collaborate on accrual for specific challenging trials and address broader accrual issues. Key themes and recommendations for the forum will be elaborated on in light of PM and AYA trials. Conclusions: A new NCTN Accrual Core Team (ACT) will be formed to collaboratively address identified cross-cutting themes that have implications for accrual to trials. Next steps that may be addressed by ACT include identifying ways to target messaging to promote trials to key groups (including investigators, research teams, and patients), developing templates for trial education, facilitating the pooling of resources currently replicated by sites such as Medicare Coverage Analyses, standardizing trial tools and processes, and developing metrics to monitor accrual enhancement efforts.

6590 Poster Session (Board #147), Mon, 1:15 PM-4:45 PM
Does paid sick leave affect the unmeasured costs of colorectal cancer treatment? First Author: Christine Marie Veenstra, University of Michigan, Ann Arbor, MI
Background: For working patients, the financial impact of colorectal cancer (CRC) diagnosis and treatment can be substantial. Unmeasured costs can include unpaid time away from work and job loss. Although not a provision of the Affordable Care Act or FMLA, paid sick leave may help CRC patients retain their jobs and alleviate some financial burden. Methods: In 2011-13, we surveyed Stage III colorectal cancer patients from Detroit and Georgia SEER registries 4-12 months after diagnosis. The analytic sample was restricted to respondents who were working at the time of diagnosis. We assessed two outcomes, job retention and personal financial burden. We measured personal financial burden using a validated 6-item scale and categorized it as a binary measure indicating low vs. high burden. We assessed associations between 1) paid sick leave and job retention and 2) job retention and personal financial burden in separate models, using logistic regression to control for age, sex, race, education, and income. Results: Among 1469 patients who returned surveys (RR 68%), 38% were working for pay at the time of CRC diagnosis. Overall, 46% of patients did not retain their jobs and 32% reported high financial burden during CRC treatment. In adjusted analyses, availability of paid sick leave was significantly associated with job retention (OR 2.59, 95% CI 1.68 –3.98). After adjustment, job retention was inversely associated with high personal financial burden (OR 0.25, 95% CI 0.160,38). Compared with respon-dents who had paid sick leave available, those without paid sick leave were more likely to be older, have a high school education or less, and have an income of under $50,000 (all p < 0.001). Conclusions: In a robust, population-based study, we found that the availability of paid sick leave during CRC treatment was positively associated with job retention. Further- more, personal financial burden was reduced when working patients were able to retain their jobs throughout CRC treatment. Millions of working Americans do not have access to paid sick leave, but our results indicate that an investment in paid sick leave by employers and government may provide long-term societal dividends.

6591 Poster Session (Board #148), Mon, 1:15 PM-4:45 PM
Impact of maternal death from female cancers on child mortality. First Author: Raymond Malfit Vega, New York University School of Medicine, New York, NY
Background: Cervical and breast cancers are the most common causes of cancer mortality in women of childbearing age. The impact of maternal mortality on child mortality remains an under-investigated area. Elevated mortality rates in offspring are significantly associated with maternal death in both Bangladeshi and Scandinavian cohorts (Ronsmans 2010, Li 2014). This effect is contextual: when a mother dies, a child in Bangladesh is 10 times more likely to die before 10, versus 1.5 times more for a Scandinavian child. By ignoring this impact disease mortality rates underestimate child life lost, and this underestimation affects appropriate resource allocation. We propose a country-specific model to allow for estimates of offspring death rates attributable to breast and cervical cancers in women of childbearing age. Methods: A population model (TreeAge) analyzed a sample population of 1 million 15yo fertile girls of a specific nationality and at risk of dying from cervical and breast cancer. Information was obtained from Globocan and UN World Population Prospects. Criteria included: 1) country-specific life tables for baseline child mortality; 2) risk of dying due to maternal loss until 10 years of age; and 3) definition of a coefficient “Q” – the multiplicative contextual increase in all cause mortality. Bangladesh and Denmark served as two benchmark populations, and coefficient Q was varied. Sensitivity analyses were performed in five nations with the highest breast or cervical mortality. The outcome measurement was relative mortality increase (RMI), such that a value of 2% denotes for every 100 women succumbing to disease, 2 children die in association. Results: Benchmark cases illustrate RMIs of 0.83% in Bangladesh and 0.01% in Denmark. For 19,012 estimated children die in association.

6592 Poster Session (Board #149), Mon, 1:15 PM-4:45 PM
Nationwide utilization of cardiac imaging in patients undergoing cardio-toxic chemotherapy. First Author: Michaela Ann Dinan, Duke Clinical Rsrch Instit, Durham, NC
Background: Current guidelines recommend cardiac evaluation in patients undergoing selected cardiotoxic regimens. However, utilization of cardiac imaging and adherence to guidelines have not been previously examined in a nationally representative patient population. Methods: A retrospective claims-based study of all patients in the SEER-Medicare database with incident cancer of the lung, breast, colon, prostate (metastatic), leukemia (acute) or lymphoma between 2000 and 2012. We examined claims-based receipt of chemotherapy, cardiotoxic chemotherapy (anthracycline, trastuzumab, or bevacizumab) and their association with cardiac evaluation in the year following diagnosis. Results: A total of 346,903 patients met study criteria (Table). Receipt of cardiotoxic chemotherapy ranged from 1% in prostate cancer to 35% in lymphoma. Overall, 43% of patients underwent cardiac evaluation (84% echo, 30% exercise EKG, 9% MUGA, 1% nuclear imaging, 0.2% cardiac PET). Among patients receiving cardiotoxic chemotherapy, 80-90% of breast, leukemia, and lymphoma patients underwent one or more cardiac studies compared to only 40-60% of patients with colorectal, lung, or prostate cancer. Conclusions: Cardiac evaluation appears more common in cancer populations more frequently treated with cardiotoxic chemotherapy than in cancer populations with less exposure to these agents. Increased awareness of cardio-oncologic principles may be warranted among oncologists treating cancer types for which cardiotoxicity has not historically been a concern.
Cardiac imaging utilization by receipt of systemic and cardiotoxic chemotherapy, 2000-2009.

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A prospective evaluation of radiotherapy (RT) related skin reactions in a multi-racial/ethnic population of women with newly diagnosed breast cancer (BC). First Author: Jordan D. Lane, jordan_lane@hms.harvard.edu, Boston, MA

Background: RT-related early adverse skin reactions (EASR) are common in BC patients. EASR occur during/within 2 months post-RT. Predictive biomarkers for EASR are under active investigation. Previous studies have limited sample size/lack racial/ethnic diversity. This study designed to evaluate disparities in EASR of a multi-racial/ethnic BC population. Methods: Stage 0-II BC patients. Inclusion criteria: RT dose > 40 Gy and daily RT 1.8 to 2.7 Gy/ fx. Regional nodal irradiation, mastectomy/ lumpectomy, concur/sequent boost, chemotherapy, hormonal therapy allowed. Exclusion criteria: immediate reconstruction, partial breast RT. Primary outcome: EASR (Oncology Nursing Society (ONS) acute skin toxicity (0-6 scale)) assessed during/2 months post-RT. Mixed effects repeated measures analysis of variance used to assess race/ethnicity and mastectomy/lumpectomy differences in EASR over time. Results: 10/2011-6/2013, 1000 patients accrued (405 non-Hispanic white (NHW), 277 non-Hispanic black (NHB), 241 Hispanic, 62 Asian/Pacific Islanders, 15 other). Both time by race/ethnicity and time by mastectomy interactions were statistically significant (p < 0.001 and p = 0.008, respectively). Based on race/ethnicity cohorts, significant differences in patient characteristics (p < 0.05) existed for age, BMI, marital status, education, health insurance, cancer stage, and medical comorbidities. Mean ONS peaked at last day of RT (2.23), higher: mastectomy vs lumpectomy (2.66 vs 2.19) not different between race/ethnic groups. NHW women greater mean ONS score at 3 weeks into RT than other groups; however, NHB had lower mean ONS at 1 and 2 months post-RT (p < 0.01). ONS grade 4+ skin toxicities occurred: 15% of women at the end of RT, but no difference by race/ethnic cohort. Conclusions: Late EASR peaks at end of RT with variation in time course by race/ethnicity. High grade toxicity uncommon and not different by race/ethnicity. This is first large study of RT EASR in a multi-racial/ethnic BC population. Additional analyses: RT dosimetry, genomics, DNA damage/repair biomarkers, and late effects are forthcoming. Clinical trial information: NCT01407770

Cancer mortality and published research output: Is there any relationship? First Author: Francis Patoa, Division of Cancer Care & Epidemiology, Cancer Research Institute, Queen’s University, Kingston, ON, Canada

Background: The relative distribution of cancer research output across disease sites is not well described. Here we evaluate whether the volume of published research and clinical trials is proportional to mortality by cancer site. We also explore whether research output is proportional to research funding by cancer site. Methods: Statistics from the American and Canadian Cancer Societies were used to identify the top ten causes of cancer death in 2013. The relative distribution of cancer research output across disease sites was estimated using three thresholds: $50,000 per quality adjusted life-year (QALY), $100,000 per QALY, and $150,000 per QALY. A logistic regression was performed to determine how study characteristics including funding source were associated with study findings. Results: Overall, 65 studies were funded by industry (62%). Studies with pharmaceutical company funding were more likely than studies with other funding to report favorable cost-effectiveness estimates (p < 0.05). We identified 19,361 publications and 2,661 clinical trials in 2013. The proportion of publications and clinical trials published in 2013 by US/Canadian authors for these cancer sites. Total research funding in Canada by cancer site was obtained from the 2011 report by Canadian Cancer Research Alliance. Descriptive statistics and Pearson correlation coefficient (r) were used to describe the relationship between research output (volume of publications and clinical trials), cancer mortality, and research funding. Results: We identified 19,361 publications and 2,661 clinical trials. The proportion of publications and clinical trials were substantially lower than the proportion of deaths for lung (41% deaths, 15% publications, 16% clinical trials), colorectal (14%, 7%, 6%), pancreas (10%, 7%, 5%), and gastroesophageal (7%, 5%, 3%) cancers. Conversely, research output was substantially greater than the proportion of deaths for breast cancer (10% deaths, 29% publications, 30% clinical trials) and prostate cancer (8%, 15%, 17%). There was substantial variation in total research investment across cancer sites. There was no difference in total research investment in 2013 in Canada per cancer death was $599 for bladder cancer, $1039 for lung cancer, $2197 for colorectal cancer, $9212 for prostate cancer, and $14,329 for breast cancer. There was stronger correlation between research output and funding (all publications r = 0.8942 p < 0.001; clinical trials r = 0.9258, p < 0.001), than there was between research output and cancer mortality (r = 0.3625, p = 0.3033 and r = 0.3372). Conclusions: Research output is not well correlated to cancer mortality but is correlated to relative level of research funding.

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Trends in the costs and utilization of targeted cancer therapies for the privately insured non-elderly: 2001-2011. First Author: Fabrice Smieliauskas, University of Chicago, Chicago, IL

Background: Studies documenting high costs of cancer drugs often focus on targeted therapies as a whole without differentiating between oral and intravenous agents; such distinction is important because they differ in insurance design. Our study examined recent trends on targeted oral anticancer medications (tOAMs), and targeted IV anticancer medications (tIVAMs) and explored the cost drivers. Methods: We classified cancer drugs as tOAMs, tIVAMs, and non-targeted agents. Using the 2002-2011 LifeLink Health Plan Claims Database, we described trends in utilization and in insurance payments and out-of-pocket (OOP) costs per patient per month (PPPM) and during the first year of systemic therapy among privately insured non-elderly cancer patients. We performed Cochran-Armitage tests and trend-adjusted linear regression testing significance of utilization and cost trends, respectively, and conducted decomposition analysis to disaggregate the cost trend into the increase driven by therapeutic substitution to more expensive classes of drugs vs. increases in drug prices over time. Results: Targeted therapies accounted for 11% of all systemic therapy utilization and 22% of systemic therapy expenditures in 2001, increasing to 42% (28% tIVAMs and 14% tOAMs) of utilization but 63% (38% tIVAMs, 25% tOAMs) of expenditures in 2011. Insurance payments PPPM for tOAMs more than doubled in ten years, growing from $3,381 PPPM in 2001 to $7,370 in 2011 (P < 0.001), whereas PPPPM for tIVAMs remained fairly constant (around $7,000) throughout. Decomposition analyses of two time periods (2001-2005 and 2005-2010) showed that switching to more expensive classes of drugs accounted for the large majority of cost increase. Post-launch price increases contributed a 10-11% of spend increases during the two periods, while the increase in launch price accounted for 65% and 15% of spending growth, respectively, for each period. Conclusions: Payers should consider more aggressive management of pharmacy benefits for tOAMs and payment reforms for injectable drugs to contain the rising costs of cancer care.

Serum tumor marker utilization in patients with advanced solid tumors. First Author: Melissa Kate Accordino, New York Presbyterian Columbia, New York, NY

Background: Despite data on the sensitivity and specificity of serum tumor marker tests, there is no evidence to suggest that early changes in therapy related to rising tumor markers have an effect on survival. Studies have failed to show benefit of surveillance testing in patients with limited disease. We performed a retrospective analysis in patients with advanced cancer to evaluate trends in utilization of tumor marker testing and the associated costs. Methods: Patients at Columbia University Medical Center with advanced or metastatic cancer were identified by ICD9 codes and confirmed with tumor registry and medical record review. Between 7/1/2013-6/30/2014 for each patient, the dates each of the following tumor markers were recorded: alpha fetoprotein (AFP), CA 125, CA 15-3, CA 19-9, CA 27-29 and carinoembryonic antigen (CEA). Subjects with 1 of any single tumor marker over the time-frame were included. We evaluated the maximum number of tests per month and the average number of tests per-month the patient was alive. Costs of each tumor marker were determined using 60% Medicare reimbursement rates. Results: Over the 12 month time frame 996 patients were included in the analysis. The mean number of any individual test per-patient was 7 and the maximum was 35; and the mean number of total tests per-patient was 12 and the maximum was 70. CEA and CA-19-9 were the most commonly ordered tests with an average of 1.94 and 2.18 times per-month, respectively. On average, the number of patients that had at least 1 of any individual test per month was 33%. The most common tests were CA-125, CEA and CA-19-9 (25.3%, 38.2% and 45.6% respectively). Overall 21.9% of patient had ≥ 3 of any individual marker per-month (38% CA19-9 and 25.6% CEA). The mean per-patient annual cost of testing was $421, with a maximum $2,567. Costs per-patient were highest for those with breast cancer (mean $755, max $1,787) and pancreatic cancer (mean $643, max $2,567). Conclusions: Tumor marker testing is frequent, with a large number of patients being tested multiple times per month, every month. Given the rising costs of cancer care, the large number of serum tests, and the frequency of use, efforts should be made to determine the clinical utility of tumor marker testing in metastatic cancer patients.

Assessing financial toxicity in insured patients with multiple myeloma. First Author: Scott F. Huntington, Abramson Cancer Center, Hosp of the Univ of Pennsylvania, Philadelphia, PA

Background: Financial toxicity is increasingly recognized for its potential to adversely impact the quality of life and health outcomes of patients undergoing treatment for cancer. Patients with multiple myeloma (MM) may be particularly vulnerable due to high utilization of novel therapeutics and extended treatment duration. Methods: Patients with at least 3 months of ongoing treatment for MM were invited to participate in a survey during follow-up visits at our institution. The survey was offered from published instruments and included the recently developed 11-item COST measure (financial toxicity score 0 – 44). Electronic health records informed insurance and treatment data. Results: Of 111 patients approached for the study, 100 individuals completed the survey. The median reported annual household income was between $60,000-79,999 and all were insured (43% private, 49% Medicare, 8% Medicaid/dual). Median time from diagnosis was 31 months, 75% had exposure to both lenalidomide and bortezomib, and 58% had undergone autologous transplantation. The majority (59%) labelled treatment costs as higher than expected and 70% endorsed at least minor financial burden. Thirty-six patients reported applying for financial assistance, including 18% of individuals with income over $100,000. Use of savings to pay for MM treatment was common (46%), 21% borrowed money to pay for medications, and 17% reported delays in their MM treatment due to cost. COST scores were normally distributed (median 20.5, range 0-43) and correlated with patient reported incomes, use of savings, borrowing of money, and treatment delays (p < 0.001). After controlling for potential confounders on linear regression, time since diagnosis was directly related (p < 0.03), while age and income were inversely related with COST scores (p < 0.03; p < 0.001). Conclusions: Financial burden and request for financial assistance were common in our insured population with MM. Younger age, lower household income, and time since diagnosis were associated with higher financial toxicity as measured by the COST score. Additional attention to rising treatment costs and cost-sharing is needed to address the growing evidence of financial toxicity impacting patients with cancer.
Impact of site of service on chemotherapy costs: Influence of geographic location and diagnosis. First Author: Michael A. Kolodziej, Aetna, Hartford, CT

Background: Site of service strongly influences the costs of cancer treatment. The migration of community oncology practices to the hospital based practice setting has generated considerable discussion about the cost differential between these sites. Methods: We examined claims paid for chemotherapy by Aetna from August 2013 through July 2014 for all malignancies as well as breast/colon/lung cancer (BCL). Results: Over this period of time, Aetna paid chemotherapy claims for 46,000 unique members, including 17,000 members with breast, colon and lung cancer (BCL). For all members receiving chemotherapy as well as for members with BCL, 69% received chemotherapy in the office setting (O) and 31% received chemotherapy in the hospital outpatient setting (H). Despite this patient distribution, chemotherapy allowable reimbursement share was 42% for H and 58% for O, indicating a disproportional share of chemotherapy reimbursement to H. When considering average chemotherapy allowed per member, patients treated in H for all cancers were 59% more costly per member, while patients treated for BCL were 40% more costly per member. When examining site of service by state, considering only states with more than 100 members treated in H, there was great variation in site distribution, from a high of 79% (Massachusetts) to a low of 15% (Florida). The allowed chemotherapy costs per unique member were 22% more for all malignancies and 190% for BCL in the most costly H state compared to the most costly O state. Paying H the average cost allowed would generate $100 million savings. Conclusions: The impact of site of service on chemotherapy costs is complex. Only 30% of patients treated with chemotherapy receive treatment in H but H received a disproportionate share of reimbursement for all malignancies as well as the most common malignancies (BCL). These differences may be due to factors such as unique toxicity concerns (e.g., history of heart failure). To accelerate the reimbursement process of NGS and potential new targeted therapies, and have a NGS-panel available for patients in the near future, the TA was to conduct a cost-effectiveness analysis. Methods: We constructed a target-based decision model (H-TArget) to estimate the cost-effectiveness of NGS versus single- and no testing. Standard- and targeted therapies in first and second line for 9 targets (BRAF, KRAS, NRAS, EGFR, ERBB/HER, MET, ROS, ALK, RET) over 3 tumor types (melanoma, non-small-cell lung cancer (NSCLC), colorectal cancer (CRC)) were incorporated. A Dutch healthcare perspective and a 5-year time horizon were adopted. Outcomes were incremental cost-effectiveness ratios (ICER) expressed in €/quality adjusted life year (QALY). The threshold for cost-effectiveness is 80k in the Netherlands, which means that the concerning technology is cost-effective if the ICER is below this threshold. Expected Value of Partial Perfect Information (EVP(PPi)) was calculated to quantify the value of further research into particular subsets of uncertain parameters. Results: The expected ICER was €25/€10K/QALY for melanoma, €188K/QALY for NSCLC, and €103K/QALY for CRC. As a weighted average to the three populations, the overall ICER yielded €160K/QALY. The EVP was €25M for melanoma, the subsets of parameters to focus on in future research were: €2M together for failures, prevalence, survival, and €23M for costs. Conclusions: H-TArget model: Early technology assessment for ext generation sequenc-
Background: Both NAB-P+GEM and FOLFIRINOX have shown superior survival efficacy over GE alone as first-line treatment for MPC. Independent cost effectiveness/utility analyses for the US of NAB-P+GEM and FOLFIRINOX have not been performed. Methods: AMarkov model of outcomes and total costs estimated the lifetime utility and quality-adjusted life years (QALY) gained and incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) for patients with MPC using probabilistic sensitivity analyses, discounted at 3%/year, with a lifetime horizon, from a payer perspective, and expressed in 2015 US$. Lacking 3-year head-to-head trial results, we employed a comparative efficacy and safety of NAB-P+GEM and FOLFIRINOX estimated using Bucher indirect comparisons. Total costs included chemotherapy, administration, disease monitoring, adverse reactions and supportive care measures. Results: In direct comparison, NAB-P+GEM was associated with a differential of +0.27 LY and +0.16 QALY gained over GE at an incremental total cost of $23,031; yielding ICER of $80,562/LY and ICUR of $141,338/QALY. In indirect comparison, FOLFIRINOX was associated with a differential of +0.50 LY and +0.26 QALY gained over GE at an incremental total cost of $42,846; yielding ICER of $83,978/LY and ICUR of $164,495/QALY. In indirect comparison, FOLFIRINOX was associated with a differential of +0.23 LY and +0.16 QALY gained over NAB-P+GEM at an incremental total cost of $19,815; yielding ICER of $88,031/LY and ICUR of $202,187/QALY. HR for NAB-P+GEM vs. FOLFIRINOX was 1.26 (95%CI = 0.95-1.67, p = ns) indicating no superior survival in outcome of either regimen. Conclusions: In this indirect comparative economic analysis, the superior survival efficacy of both NAB-P+GEM and FOLFIRINOX over GE in the management of MPC is associated with positive cost-effectiveness and cost-utility. With NAB-P+GEM and FOLFIRINOX not differing statistically in survival benefit, the cost differential of $-4053/LY and $-37,692/QALY gained associated with NAB-P+GEM in the most economically favorable of both regimens as first-line treatment for MPC.
Impact of a Stage IV NSCLC care pathway on front-line (FL) and maintenance (M) chemotherapy use at the Cleveland Clinic Taussig Cancer Institute (TCI). First Author: Marc A. Shapiro, Cleveland Clinic, Cleveland, OH

Background: Care pathways can reduce cancer care costs and variability in NSCLC. Effective implementation requires measurable outcomes and available data in near real-time. Methods: Between 10/1/13 and 7/7/14, TCI developed an evidence and value-based Stage IV NSCLC pathway. For patients with non-squamous EGFR WT/ALK neg NSCLC, ECOG PS 0-2 and sufficient renal function, FL carboplatin/pemetrexed (pem) is recommended standard care while bevacizumab (bev) is not. The pathway recommends best supportive care for pts with ECOG PS ≥ 3. To test feasibility, 4 academic thoracic and 12 community oncologists implemented the pathway into their practices starting 7/7/14. This analysis studies pathway impact on FL and M treatment decisions and charges in patients with metastatic non-squamous EGFR WT/ALK negative NSCLC. 57 pts meeting pathway criteria initiated care with these oncologists from 7/7/14 to 12/31/14 (Cohort A). A retrospective cohort (Cohort B) of 181 pts meeting similar criteria initiated care from 1/1/12 to 7/7/13. Care patterns were defined by manual chart review through 1/8/15. As only 1 Cohort A pt has progressed on M therapy, charge results assume pts who have initiated M pemb will receive the same average of 5.11 doses seen in Cohort B. For Cohort B, actual FL and M therapy charges are reported. 3 Cohort B pts remain on M therapy. Results: Care patterns in Cohorts A and B were compared. 53 (93%) vs 128 (71%) (p < 0.0001) pts received pathway recommended FL care respectively. 42 (74%) vs 110 (61%) received chemotherapy (p = 0.0839). In pts receiving FL platinum-based regimens, 2 (6%) vs 35 (39%) received bev (p < 0.0001) outside of pathway recommendations. In Cohort A, 6 (32%) completing FL therapy initiated M therapy vs 46 (25%) in Cohort B. In pts completing FL therapy, FL and M drug charges per pt were an estimated $107,258 vs $205,431 (48% decrease). Conclusions: Implementation and measurement of adherence to a stage IV NSCLC pathway is feasible at an academic oncology practice with a regional network. This implementation led to a significant improvement in care variation and nearly 50% reduction in chemotherapy charges primarily through decreased bev use.

A network meta-analysis-based cost-effectiveness analysis of systematic therapies in advanced pancreatic cancer. First Author: Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: For advanced pancreatic cancer, there are new treatment options that are more effective than gemcitabine alone (G). In this analysis we utilized data from a recently published Bayesian network meta-analysis (NMAM) to assess the cost-effectiveness of G, G+5-fluorouracil (GF), G+capecitabine (GCap), G+capecitabine and gemcitabine (GCisp), G+erlotinib, G+nab-paclitaxel (G), G+FOLFIRINOX and G+capecitabine and oxaliplatin (GnP) from a Canadian health care perspective. Methods: Analysis was conducted through a three-state Markov model which follows a cohort of patients with advanced pancreatic cancer until death. Analysis used data on the progression of disease with treatment from the G arms of RCTs combined with estimates from the NMA of the effect of the newer regimens on disease progression and adverse events. Estimates of health care costs were obtained from local providers and utilities were derived from the literature. The Markov model estimated the effect of treatment regimens on costs and quality adjusted life years (QALYs) discounted at 5% per annum. Detailed sensitivity analyses were conducted. Results: If a decision maker was willing to pay between $15,259 and $182,723 for a QALY, GF would be the optimal treatment regimen. For a willingness to pay of greater than $182,723, FOLFIRINOX would be optimal. Based on a willingness to pay for a QALY of $50,000, the price of oxaliplatin would need to be reduced by 83.4% for FOLFIRINOX to be cost-effective. Results whilst treating a patient with a total cost of $85,651 for GF, nab-paclitaxel, and erlotinib, the price of GnP would need to be reduced by 93.1% for GnP to be optimal. At this threshold, the probability that GF is optimal is 52.7%, compared to 26.8% for GCisp, 19.0% for GCap and 1.6% for G and 0% for all other treatment regimens. Conclusions: At the current time with current drug prices and from the Canadian health care perspective, GF is the optimal treatment regimen based on the criteria of cost-effectiveness. The acquisition costs of oxaliplatin is expected to decrease significantly once generic, and may make FOLFIRINOX more cost effective in advanced pancreatic cancer. GnP does not appear to be cost-effective regardless of willingness to pay threshold with its current pricing.
Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer.
First Author: Daniel A. Goldstein, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Regorafenib was approved by the FDA in 2012 for the management of previously treated metastatic colorectal cancer (mCRC). It is now the standard of care in the third-line setting. Compared to placebo it improves median overall survival by 1.4 months but is associated with adverse effects and additional cost. The objective of this study was to examine the cost-effectiveness of regorafenib compared to best supportive care for patients receiving 3rd-line treatment for mCRC. Methods: We developed a Markov model to compare the cost and effectiveness of regorafenib compared to best supportive care in the 3rd-line treatment of mCRC based on randomized data from the CORRECT trial. Weibull models were fitted to the published overall and progression-free survival curves, and were used to extrapolate the cause-specific mortality and progression risks. Costs for administration and management of adverse events were based on Medicare reimbursement rates for hospital and physician services, and drug costs based on the Medicare average wholesale prices (all in 2014 US $). Health outcomes were measured in life years (LYs) and quality-adjusted life years (QALYs). Quality of life adjustments were calculated based on health utility values in the CORRECT trial and toxicity disutilities and durations were included for the most common toxicities: hand/foot syndrome, diarrhea, and hypertension. Model robustness was addressed by univariate and probabilistic sensitivity analyses (PSA).

Results: In the model, regorafenib provided an additional 0.04 QALYs (0.13 LYs) at a cost of $39,391. The incremental cost-effectiveness ratio (ICER) was $897,411/QALY. In all one-way sensitivity analyses, the ICER of regorafenib was > $700,000/QALY. The ICER of regorafenib was greater than $200,000/QALY in > 99% of PSAs. Conclusions: This is the first US-based cost-effectiveness analysis of regorafenib in mCRC and our findings show that regorafenib provides minimal incremental benefit at high incremental cost per QALY. The ICER of regorafenib could be improved by use of an effective biomarker to select patients most likely to benefit, or by a lower price for payers.

 Disclosure of industry payments to oncologists: Early open payments data.
First Author: Deborah Catherine Marshall, UC San Diego, Department of Radiation Medicine and Applied Sciences, La Jolla, CA

Background: The Open Payments program discloses industry payments to identified physicians (‘physician payments’). We characterize these payments by oncology specialty. Methods: We analyzed the December 2014 release of Open Payments data on physician payments made from August-December 2013. We characterized physician payments by type (general or research). We also evaluate physician ownership interests in reporting manufacturers. Data were aggregated by physicians and oncology specialty (medical oncology (hematology/oncology, medical oncology, pediatric hematology/oncology); radiation oncology; and surgical oncology (surgical oncology, gynecologic oncology)). We compared the number of physicians receiving payments to the total number of active physicians in each specialty in 2012 (AMA, Physician Characteristics and Distribution in the US. Chicago: AMA; 2014). Results: There were 82,213 payments to 9,893 oncology physicians (50% vs. 46% for all medical specialties) totaling $31 million (‘M’). Table. Payments for food/beverage were most common (79%) but represent only 10% of the total value. The most common nature of payment by total value was compensation for services (excluding consulting and CME) in medical oncology (38%), consulting fees in radiation oncology (30%), and education in surgical oncology (27%). Ownership interests totaled $8M in amount invested and $12M in total value of interest. Medical oncology had the highest proportion of physicians with ownership interests (11.7%) among all oncology specialties. Conclusions: These data can inform policy-making and advocacy efforts for oncology specialties. Partially supported by the NIH (Grant TL1TR00908).

Improving the value of PSA prostate cancer screening with “smarter” strategies and increased use of active surveillance.
First Author: Joshua A. Roth, Fred Hutchinson Cancer Res Ctr, Seattle, WA

Background: Prostate-specific antigen (PSA) screening for prostate cancer is controversial. Epidemiological researchers and guideline groups have suggested many personalized and conservative strategies to improve benefit-risk tradeoffs. The goal of this study is to identify strategies most likely to be cost-effective, and to examine the added value of increased active surveillance (AS) for low-risk cases. Methods: We extended an established CISNET microsimulation model to project life years (LY), quality-adjusted life years (QALYs), and costs for cohorts of U.S. men from age 40 to death in 15 screening strategies with fixed or personalized screening ages, intervals, and PSA biopsy thresholds. We calculated the incremental cost-effectiveness ratio (ICER) for each vs. no screening under “general” or “increased AS” treatment practices. “Contemporary” practices were based on age, stage, and grade-specific initial treatments in the SEER program. “Increased AS” practices immediately treated cases if Gleason sum ≥ 7 or clinical T-stage ≥ T2a and monitored all others. Analyses used a 3% annual discount rate and a willingness to pay of $150,000/QALY. Results: All PSA screening strategies increased LYs (range = 0.014-0.021) and costs (range = $100-900) vs. no screening and were highly cost-effective (ICER range = $25,000-43,000/LY). With “contemporary” treatments, only strategies with biopsy threshold at PSA ≥ 10 mg/L increased QALYs (range = 0.001-0.002), and only quadrennial screening of ages T1a had an ICER < $100,000/QALY. With “increased AS,” all strategies with biopsy threshold at PSA ≥ 10 mg/L increased QALYs (range = 0.003-0.005) and were cost-effective (ICER range = $45,000-95,000/QALY), as was quadrennial screening of ages 55-69 with biopsy threshold at PSA ≥ 3 mg/L (inc QALYs = 0.002, inc Cost = $130, ICER = $65,000/QALY). Conclusions: Personalized PSA screening strategies with conservative screening frequency and/or PSA biopsy threshold appear to be cost-effective vs. no screening, particularly when combined with increased AS for low-risk cases.
Background: The seroprevalence of Hepatitis B virus (HBV) infection among Canadian was 0.4%, and 1.6% among immigrants. Most infected individuals have clinically silent disease. Cytotoxic chemotherapy causes reactivation in 30% of the HBV infected patients. This can be severe and fatal, and may also lead to interruption of chemotherapy. HBV screening before adjuvant chemotherapy (ADJ) for breast cancer (BC) seems to be a plausible strategy. Our objective is to estimate the health and economic effects of HBV screening strategies. Methods: We developed a state transition microsimulation model to examine the cost effectiveness of 3 strategies for 55 year old BC patients undergoing ADJ: (1) No screen, (2) Screen Imm: Screen immigrant only and treat, (3) Screen all: Screen all and treat, with antiviral therapies. In the model, health states were constructed to reflect the natural history of BC and HBV. Model data were obtained from published literature. We used a payer perspective, a lifetime time horizon, and used a 5% discount rate. Results: Screen all would prevent 38 severe reactivations (SR), 9 deaths from reactivation (DR), 21 chemotherapy interruptions (CI), 32 decompensated cirrhosis (DC), 38 HCCs, and 56 HBV deaths per 100,000 persons screened over the lifetime of the cohort. Screen Imm would prevent 29 SR, 7 DR, 16 CI, 23 DC, 27 HCCs, and 41 HBV deaths. Screen all was associated with an increase of at least 0.0034 quality adjusted life years (QALY) and cost $164 more per person, translating to an incremental cost-effectiveness ratio (ICER) of $164,808-76,527/QALY gained compared with No screen, depends on different antiviral therapies. Screen all was the most cost effective, while Screen Imm was ruled out due to extended dominance (ED) by No screen and Screen all. Conclusions: HBV screening before ADJ for BC would prevent a significant number of reactivations, and is likely to be cost effective.

Strategic Cost($) QALYs VS no screen Sequential ICER$(
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Hepatitis B virus screening before adjuvant chemotherapy in patients with early stage breast cancer: A cost-effectiveness analysis. First Author: William W. L. Wong, University of Toronto, Toronto, ON, Canada

Methods: A total of 233 patients who had completed at least 3 months of chemotherapy were assessed. The correlation between the COST and FACT-G was r = 0.42, p < .001. ROC curve analyses produced optimal COST FT grades (G) as follows: G0 ≥ 26 (n = 99 patients, 42%), G1: ≥ 14-25 (n = 71, 31%) and G2: > 0-14 (n = 58, 25%). Five patients (2%) had scores of 0 (G3). On multivariate analyses, pts with G0 had no impact of FT in their HRQoL. G1 had a statistically significant small and meaningful e.s. difference compared to G0 (0.26, p < .05); G2 had a statistically significant and medium e.s. (0.47, p < .001). G3 had a significant and clinically meaningful large e.s. (0.99, p < .005). There was a significant relationship between FT (grades 1-3) and younger age (p < .01), non-Caucasians (< .05), less than a college degree (< .01), unemployment (<.001), Medicaid (< .05), and lower income (< .01). Conclusions: We developed a FT grading system based on clinically meaningful changes in HRQoL. There were 134 (58%) patients with Grades 1-3 FT. Financial distress as it relates to HRQoL is a meaningful event that can be objectively measured, and should be included in the assessment of patient-centered outcomes.

Medical expenditures and productivity loss among colorectal, breast, and prostate cancer survivors in the US. First Author: Chiyuan Zheng, American Cancer Society, Atlanta, GA

First Author: Miranda Kim, Harvard Rad Onc Prog, Boston, MA

Conclusions: Among all Medicare fee-for-service beneficiaries, 18% carried a cancer diagnosis. A cancer diagnosis was far more likely to be present among high-cost patients compared to non-high-cost patients: 26.2% versus 17.1% (p < .001). Cancer diagnoses found more frequently in the high-cost group as compared to the rest of Medicare beneficiaries included colorectal (32.7% vs. 24.8%, p < .001), head and neck (3.2% vs. 0%, p < .001), lymphoma (1.0 vs. 0%, p < .001), pancreatic (9.9 vs. 6.8%, p < .001) and esophageal cancer (2.7% vs. 0.8%, p < .001). There were significantly fewer breast (3.6% vs. 9.2%, p = < .001) and prostate (2.4% vs. 12.3%, p < .001) patients in the high-cost group. Conclusions: Among elderly Medicare recipients, high-cost patients are significantly more likely to carry a cancer diagnosis, suggesting that interventions aimed at reducing cancer costs may be highly effective in reducing overall healthcare spending. Certain cancer diagnoses are particularly overrepresented in this cohort, pointing to a need for further studies aimed at understanding specific components driving cancer costs in this population.

Financial Toxicity (FT) is an important patient-centered outcome. The impact of this toxicity on patients' HRQoL is not well known. We hypothesized that FT can be graded based on statistically significant and clinically meaningful decreases in HRQoL. Methods: FT was assessed by the quantitative COST (Comprehensive Score for Financial Toxicity). Gradations of FT's impact on HRQoL were based on established convention for clinically meaningful small, medium and large effect sizes.) for the FACT-G HRQoL instrument. The optimal COST cutoff scores for FT grades were determined by ROC curve analyses maximizing the sum of the sensitivity and specificity in comparison with normative FACT-G values for the general adult population. Following FACT-G standards, higher FT was represented by lower COST values. Demographics, tumor type, length of disease, chemotherapy use, resource utilization, HRQoL, and symptoms (EORTC QLQ-C30 symptom scales) were collected. Data were analyzed using Pearson correlations, linear regression, and chi-square tests. Results: A total of 233 patients who had completed at least 3 months of chemotherapy were assessed. The correlation between the COST and FACT-G was r = 0.42, p < .001. ROC curve analyses produced optimal COST FT grades (G) as follows: G0 ≥ 26 (n = 99 patients, 42%), G1: ≥ 14-25 (n = 71, 31%) and G2: > 0-14 (n = 58, 25%). Five patients (2%) had scores of 0 (G3). On multivariate analyses, pts with G0 had no impact of FT in their HRQoL. G1 had a statistically significant small and meaningful e.s. difference compared to G0 (0.26, p < .05); G2 had a statistically significant and medium e.s. (0.47, p < .001); G3 had a significant and clinically meaningful large e.s. (0.99, p < .005). There was a significant relationship between FT (grades 1-3) and younger age (p < .01), non-Caucasians (< .05), less than a college degree (< .01), unemployment (<.001), Medicaid (< .05), and lower income (< .01). Conclusions: We developed a FT grading system based on clinically meaningful changes in HRQoL. There were 134 (58%) patients with Grades 1-3 FT. Financial distress as it relates to HRQoL is a meaningful event that can be objectively measured, and should be included in the assessment of patient-centered outcomes.
A framework to assess the cost effectiveness of predictive biomarkers in oncology: Test Incremental Cost Effectiveness Ratio (TICER). First Author: Amol Narang, Department of Radiation Oncology and Molecular Sciences, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Cost effectiveness of predictive biomarkers is currently assessed by Markov Chain (MC) simulations, requiring resources and expertise. Our goal was to develop a practical index to aid clinicians in biomarker cost utility estimation at an early stage of development. Methods: We used decision trees to derive a test incremental cost-effectiveness ratio (TICER) index that combines six parameters including biomarker prevalence, progression free survival (PFS), health-related quality of life (HRQoL) in test of testing, cost of treatment, and cost of progression. We assessed the model on existing HER2, ALK, Oncotype DX and emerging (PDL1 expression) predictive biomarkers. We conducted one-way and multivariate probabilistic sensitivity analyses (PSA) and generated cost-effectiveness acceptability curves (CEAC). Benefits were assessed as quality-adjusted survival years (QALY) and progression-free years (QAPFY). Results: We used literature reported values for base case and varied the parameters over a broad range to estimate the contribution of each variable to TICER. TICER was calculated by one-way PSA for each variable as the median CEAC (cost at 50% probability of acceptance), while sampling the remaining variables from their respective distributions. The table shows the base case and range of TICER compared to literature values and the acceptance probability considering a cutoff of $200k/QAPFY, providing a relative ranking in terms of cost effectiveness. The TICER model is driven primarily by PSA and HRQoL while biomarker prevalence and test costs have a lesser effect. Conclusion: TICER is flexible to a variety of clinical scenarios and does not require assumptions about health states up to death like MC-based methods do. The cost effectiveness of a predictive test is driven by the efficacy and QOL associated with biomarker-directed therapy rather than marker prevalence or assay cost.

Out-of-pocket cost trends for Medicare patients with newly diagnosed cancer. First Author: Amol Narang, Department of Radiation Oncology and Molecular Sciences, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: While rising cancer care costs have been well-documented, the extent to which these costs have translated into increased patient financial burden is unclear. To address this question, we used a nationally, representative panel survey to characterize trends over time in the out-of-pocket (OOP) cost of newly diagnosed cancer patients. Methods: Medicare-eligible, community-dwelling eligible participants in the Biannual Health and Retirement Study who reported a new cancer diagnosis between 2002-2012 were identified. Supplemental insurance was classified in order of increased cost-sharing: public (dual-eligible/VA), private (employer-sponsored/Medigap), or none (Medicare alone). OOP costs included hospital stays, doctor visits, outpatient surgery, prescription drugs, home health, dental, and special facilities. Financial burden was defined as OOP costs over per-capita household income. Multivariable quantile regression was used to assess the median and 90th percentile (p90) of OOP costs and financial burden. Results: Newly diagnosed cancer patients experienced increased annual OOP costs (median: $2222 vs. $1791, p < 0.001; p90: $10,420 vs. $7807, p < 0.001) and financial burden (median: 9.0% of household income vs. 7.4%, p < 0.001; p90: 51.0% vs. 42.4%, p < 0.001). Supplemental insurance significantly affected cancer patients' median financial burden (public: 3.3%, private: 9.9%, none: 16.6%, p < 0.001), which was magnified at the 90th percentile (public: 31.8%, private: 48.3%, none: 106.2%, p < 0.001). Importantly, financial burden at the 90th percentile did not increase following a new cancer diagnosis for patients with public or private supplemental insurance, but significantly increased for patients with Medicare alone (p90: 106.2% vs. 58.1%, p < 0.001). Conclusions: More than 10% of newly diagnosed cancer patients with Medicare alone faced OOP costs greater than their income. Proposals to increase cost-sharing in the Medicare population should include provisions that protect patients from health shocks such as cancer, potentially through OOP cost limits or value-based exceptions.
Background: optimal timing and type of examinations for the follow up (FUP) of head and neck squamous cell cancer (HNSCC) survivors have not been established yet. There is also a need to find out which is the most cost-effective FUP program in this population. The present trial aims at comparing a more intensive radiologic FUP approach with a less intensive one, also evaluating its economical impact on healthcare system. Methods: this is a randomized, phase II, multicenter trial conducted in 15 Centers throughout Italy and Switzerland. Patients with stage III-IV SCC of oral cavity, oropharynx, larynx or hypopharynx having already received radiation therapy as part of their curative treatment and in complete remission at six months are randomized in two arms according to different FUP approaches. A non intensive FUP approach (ARM A) foresees only a radiologic evaluation (locoregional CT scan or MRI) within 6 months since treatment end and subsequently only at signs or symptoms occurrence (according to NCCN guidelines). An intensive FUP approach (ARM B) consists of scheduled radiologic evaluations (CT scan or MRI of head and neck) 2 times/year in the first 2 years and 1 time/year in the third and fourth year; PET scans are requested yearly in the first 3 years for patients with smoking history. FUP visits consist of physical and fiberoptic endoscopic examinations of head and neck district, laboratory tests, quality of life questionnaires and evaluation of out-of-pocket costs and productivity losses; timing of FUP visits is the same in both arms. An estimated 330 patients (randomized 1:1) are being enrolled over the first year; health outcomes and costs will be assessed over the next two years. The percentage of potentially salvageable recurrences or second primaries, as well as the cause-specific survival and the overall survival of recurring patients will be evaluated in both groups. Incremental cost-effectiveness ratio (cost/life year gained) and cost-utility ratios (cost/QALY) will be calculated referring to WHO thresholds of 1-3 times per capita gross domestic product. ClinicalTrials.gov Identifier: NCT02262221. The trial is funded by a grant from the Swiss Bridge Foundation. Clinical trial information: NCT02262221.
7000 Oral Abstract Session, Sat, 1:15 PM–4:15 PM
Correlation of acute myeloid leukemia (AML) stem cell phenotype with cytogenetic/molecular features and prognosis. First Author: Jonathan Michael Gerber, Levine Cancer Institute, Charlotte, NC

Background: Emerging evidence supports the clinical significance of leukemia stem cells (LSCs). We previously found that patients with AML exhibited 1 of 3 distinct LSC phenotypes based on CD34, CD38, and aldehyde dehydrogenase (ALDH): 1. CD34-, 2. CD34+ CD38+ ALDH(low) (ALDHlow), or 3. CD34+ CD38+ ALDH(high) (ALDHhigh). Results: LSCs were CD34+ in 21 cases; ALDHlow in 44; and ALDHhigh in the remaining 33. Poor risk cytogenetics and/or FLT3-ITD mutations were uncommon in the CD34+ (4/21 = 19%) and ALDHlow (17/44 = 39%) cases, but were frequent in the ALDHhigh cases (28/33 = 85%, p < 0.001). NPM1 mutations were detected in 14/21 (67%) of the CD34 LSC patients vs. just 8/77 (10%) of the patients with CD34+ LSCs (p < 0.001). Both patients with (9/11) had CD34+ LSCs (p < 0.001), while antecedent MDS or MPN (p = 0.04) were more common in patients with ALDHhigh LSCs. Only 15/33 patients (45%) with ALDHhigh LSCs achieved complete remission, compared to 29/43 patients (69%) with ALDHlow LSCs, and 19/22 patients (86%) with CD34+ LSCs (p < 0.01). Among patients who did not undergo allogeneic stem cell transplant, long term disease-free survival was 0% (0/6) in patients with ALDHhigh LSCs vs. 31% (4/13) with ALDHlow and 62% (8/13) with CD34+ LSCs (p = 0.04). Conclusions: LSC phenotype correlates with cytogenetic/molecular risk factors and response, permitting rapid risk-stratification of AML patients. This may be of particular use for patients with ALDHhigh LSCs, who appear to be at high risk – more likely to harbor adverse cytogenetic/molecular features and prove refractory to chemotherapy. Earlier identification would facilitate access to clinical trials of novel induction approaches.

7003 Oral Abstract Session, Sat, 1:15 PM–4:15 PM
The International Prognostic Index for patients with CLL (CLL-IPI): An international meta-analysis. First Author: Nadine Kutsch, Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital Cologne, Cologne, Germany

Background: In the era of more effective treatments for CLL, the established clinical staging systems [Rai/Binet] do not accurately discriminate between prognostic groups. There are several new prognostic markers, but no system integrates the major clinical, biological and genetic variables into one widely accepted score. Therefore we performed a comprehensive analysis of 26 prognostic factors to develop an internationally applicable prognostic index for CLL patients (pts) [CLL-IPI]. Methods: Our full analysis set (FAS) was collected from 8 phase 3 trials from France, Germany, UK, USA and Poland [3472 pts at early & advanced stage; median age 61 years (yr) (range 27 - 86); median observation time (OT) 80 months (mos)]. The FAS was randomly divided into training and internal validation datasets (TD, 2308 (67%); IVD, 1164 (33%)). Methods of multivariable statistics were applied and the main end point was overall survival (OS). Handling of missing data was performed by complete case analysis. The model was externally validated in a third dataset comprised of 845 newly diagnosed CL patients (pts) [CLL-IPI]. This model was first applied to 3 phases of the Mayo Clinic Trial [median age 63 yr (range 52 - 84); median OT 63 ms]. Results: Based on 1192 (52%) pts from the TD, 5 independent predictors for OS were identified: age, clinical stage, del(17p) and/or TP53 mutation, IGHV mutation status and β2-microglobulin (B2M) level. Using weighted grading, a prognostic index was derived separating 4 different prognostic groups: low risk (score 0-1), intermediate (score 2-3), high risk (score 4-7), very high risk (score 7-10) with significantly different OS (93%, 79%, 64% and 23% OS at 5 yr for the low to very high risk group respectively, p < 0.001; C-statistic = 0.72 (95% CI, 0.69-0.76)). This multivariable model was confirmed on the IVD (575 (49%) pts; c = 0.777 (0.73-0.82)) and the 4 risk groups were reproduced with 97%, 91%, 68% and 21% 5-yr OS (p < 0.001); c = 0.79 (0.74-0.85)) on the Mayo set. Conclusions: The resulting CLL-IPI combines the most important genetic risk factors (IGHV, del(17p)/TP53 mutation) with clinical stage, age, and B2M in an easily applicable prognostic score for CLL pts. Moreover, it both discriminates between prognostic groups and is informative regarding current treatment recommendations.
Clinical activity of ERY001 (erythrocyte encapsulated l-asparaginase) and native l-asparaginase (L-ASP) in combination with COOPRALL regimen in phase III randomized trial in patients with relapsed acute lymphoblastic leukemia (ALL). First Author: Yves Bertrand, Institut d’Hématologie-Oncologie Pédiatrique, Hospices Civils de Lyon, Lyon, France

Background: Asparaginase is a cornerstone in the treatment of ALL, but its utility is limited by toxicities including hypersensitivity. Clinical allergy is associated with inactivation of asparaginase by antibodies (A-Abs), which can also neutralize asparaginase without any clinical signs of hypersensitivity (silent inactivation). ERY001 improves pharmacokinetics, tolerability and maintain circulating asparaginase (ASP) activity due to the protective barrier of the erythrocyte membrane. Methods: This open, randomized international Phase 3 study enrolled pts with relapsed ALL. The co-primary endpoints were the duration of ASPA activity > 100IU/L and the incidence of ASPA hypersensitivity during induction. Key secondary endpoints were complete remission (CR), minimal residual disease (MRD), event free survival (EFS) and overall survival (OS). The study was powered to detect 3-fold difference in the incidence of allergic reactions between treatments. Pts (n = 80), aged 1-55 years were randomized to ERY001 (150 IU/kg, n = 26) or L-ASP (10,000 IU/m², n = 28), or to ERY001-exp (prior allergy, n = 26). Results: In the non-allergic pts, ERY001 significantly reduced the incidence of ASPA hypersensitivity (0% vs 43%; p < 0.001). ASPA activity > 100 IU/L was 21 ± 5 vs 9 ± 8 days in ERY001 and L-ASP, respectively (p < 0.001). The CR rate: ERY001 (65%, 95% CI: [51.6:89.8]) vs L-ASP (39%, 95% CI: [23.3:63.1]; p = 0.026). Allograft was successfully performed in 65% of ERY001 vs. 46% of L-ASP. The proportion of patients who achieved MRD < 10-3 in F1-F2/VANDA was 35% and 25% in ERY001 and L-ASP arms, respectively. At 12 mo, EFS rate was 65% and 49% in ERY001 and L-ASP arm, respectively. Treatment with ERY001 was well tolerated. Conclusions: ERY001 provides an alternative option for patients with relapsed ALL, which is well tolerated and efficacious. Clinical trial information: NCT 01518517.

Results of the PERSIST-1 phase III study of pacritinib (PAC) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF). First Author: Ruben A. Mesa, Mayo Clinic Cancer Center, Scottsdale, AZ

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.

Long-term follow-up of patients with acute myelogenous leukemia receiving an autologous telomerase-based dendritic cell vaccine. First Author: Hanna Jean Khoury, Winship Cancer Institute of Emory University, Atlanta, GA

Background: A phase II clinical trial was conducted in which subjects with AML were administered a telomerase-based dendritic cell immunotherapy (AST-VAC1; hTERT-DCs). The hTERT-DCs were prepared from leukapheresis collections from 33 subjects and were transfected with an mRNA encoding telomerase (hTERT) and the lysosomal sorting signal, LAMP-1, which enhances immunostimulatory activity. hTERT is essential for maintaining the proliferative capacity of tumor cells. Methods: AML patients were eligible to receive hTERT-DCs if they were in CR1 or CR2 with intermediate or high risk cytogenetics or if they were in early relapse with < 20% marrow blasts. The hTERT-DCs were prepared after induction therapy and before or after completion of consolidation cycles. The hTERT-DCs were administered as 6 weekly followed by 6 biweekly intradermal injections. Results: Twenty-one patients (median age: 55) in complete remission (16 CR1 and 3 CR2) and or early relapse (2) received at least 3 injections of the hTERT-DCs. Only one grade 3 or 4 adverse event, (idiopathic thrombocytopenia), possibly related to the immunotherapy was observed during the first year. The two patients who were vaccinated during early relapse progressed rapidly and did not receive the full dosing regimen of hTERT-DCs. Of the 19 patients that were in CR, 14 received all 12 doses of hTERT-DCs. Fifty-eight percent (11/19) developed cellular immune responses to hTERT as assessed by peptide ELISpot analysis. Eleven of 19 patients (median follow-up 52 mos.) are still in remission as of last follow-up; seven developed detectable cellular immune responses to hTERT. The 19 CR patients, 7 were > 60 yo at the time of hTERT-DC immunotherapy. Four of 7 patients > 60 yo remain relapse free 52-59 months post DC-hTERT immunotherapy with all four developing immune responses to hTERT. The three patients that received DC-hTERT while in CR2 were in remission as of their last follow-up of 24, 50 and 59 months with two having hTERT immune responses. Conclusions: The results suggest that immunotherapy with hTERT-DCs is safe, can stimulate an immune response to telomerase, and may provide anti-tumor immune responses even in high risk patients with AML Clinical trial information: NCT00510133.
Conclusions: Allogeneic transplantation results in long-term survival in the median follow-up was 5.1 months (range, 1.0-37.6 years). 11 pts underwent allo-SCT following the CAR T cells. As of 1/25/15, (81%) and 16/16 pts with MRD (100%) were in complete remission (CR) with a median follow up of surviving patients of 5.1 years (range 1-8.3 years), 3 pts were alive and reported to CIBMTR during 2000-12 were eligible. Pts with large cell transformation and those not receiving rituximab before HCT were excluded. Risk of sCRS correlates with disease burden and can be effectively managed. Donors were matched sibs (19), matched unrelated (23), or mismatched unrelated (4). All patients engrafted with a median time to neutrophil recovery of 13 (7-27) days and a median time to platelet engraftment of 24 (0-268) days. Cumulative incidence (CI) of grade II-IV, grade III, IV acute GVHD, and Chronic GVHD w 22%, 7%, and 40%, respectively. With a median follow up of surviving patients of 5.1 years (range 1-8.3 years), 3 year overall survival (OS), event-free survival (EFS), cumulative incidence (CI) of non-relapse mortality (NRM), and CI of relapse were 96%, 48%, 13%, and 39%, respectively. Multivariate analysis showed that Bu-high dose (HR 0.44; p = 0.07) was associated with lower relapse rate. Bu-high dose (HR 0.5; p = 0.09), DIPPS plus high (HR 2.69; P = 0.01) and Age (HR 1.05; P = 0.01) were predictors of EFS. DIPPS plus high (HR 5.99; P = 0.001) and Age (HR 1.07; P = 0.03) were predictors of OS.

Conclusions: Allogeneic transplantation results in long-term survival in patients with myelofibrosis with better outcome seen in earlier phase of the disease. PK guided myeloablative busulfan (AUC 16,000 μmol/min) appears promising in reducing relapse rate without increasing non-relapse mortality.

Table

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<th>Autogene (%)</th>
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<td>57 (43)</td>
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<td>86 (63)</td>
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<td>105 (77)</td>
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<td>58 (95)</td>
<td>135 (99)</td>
<td>0.05</td>
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<tr>
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<td>9 (15)</td>
<td>8 (6)</td>
<td>0.04</td>
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<td>Chemo A</td>
<td>49 (80)</td>
<td>123 (80)</td>
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<td>Median follow up</td>
<td>57 (3-126)</td>
<td>59 (1-145)</td>
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Efficacy and safety of CD19-targeted 19-28z CAR modified T cells in adult patients with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) have dismal prognosis. We previously reported high anti-tumor activity of autologous T cells genetically modified to express 19-28z chimeric antigen receptor (CAR) targeting CD19 in adult pts with ALL. Herein, we report the long-term outcome of our phase I trial in adults with R/R ALL (NCT01044069). Methods: Adults with R/R B-ALL underwent leukapheresis, and T cells were transduced with a gammaretroviral vector encoding a CAR construct composed of anti-CD19 scFv linked to CD28 and CD3ζ signaling domains (19-28z). All pts received conditioning chemotherapy followed by 1-x300 19-28z CAR T cells/kg. Results: 33 pts have been treated, and 32 pts are evaluable for response. The median age was 54 years (range, 22-74). 12 pts (36%) had Ph+ ALL, 11 pts (33%) had prior allogeneic stem cell transplant (allo-SCT), and 14 pts (42%) had ≥ 3 prior lines of therapy. At the time of CAR T cell infusion, 16 had morphologic disease (> 5% blasts in BM) and the remaining 16 pts had minimal residual disease (MRD). 13/16 pts with morphologic disease (81%) and 16/16 pts with MRD (100%) were in complete remission (CR) after 19-28z CAR T cell infusion, yielding an overall CR rate of 91% (95% CI: 29-32). Of the 28 MRD evaluable patients, MRD negative CR rate was 82%. 11 pts underwent allo-SCT following the CAR T cells. As of 1/25/15, the median follow-up was 5.1 months (range, 1.0-37.6+), with 14 pts having a follow-up of ≥ 12 months. Of surviving patients the OS of all pts or pts with del17p/TP53 mut was not reached. Estimated OS at 36 months was 87% for pts with del17p/TP53 mut, and 36.8 mos for pts without. Med OS for all pts or pts with del17p/TP53 mut was not reached. Estimated OS at 36 months was 87% for pts with del17p/TP53 mut and 78.3% for pts without.

Conclusions: 19-28z CAR T cells can induce a high CR rate of 91% in adult patients with R/R ALL. The risk of sCRS correlates with disease burden and can be effectively managed. These findings strongly support the use of 19-28z CAR T cells in adults with R/R ALL and warrants investigation in a phase II trial. Clinical trial information: NCT01044069.
Dose adherence and baseline exposure analysis of the ibrutinib 420 mg dose administered to patients with previously treated chronic lymphocytic leukemia (CLL). First Author: Paul M. Barr, Wilmot Cancer Institute, University of Rochester, Rochester, NY

Background: Ibrutinib (ibr), a first-in-class, once-daily, oral, covalent inhibitor of Bruton’s tyrosine kinase (BTK), is rapidly eliminated from plasma after oral administration (Advani, JCO 2013). Complete or near complete BTK active site occupancy (median > 90%) is achieved at 4 hours and maintained at 24 hours with ibr 420 mg once-daily (Poggesi, ASCO 2013). At 149±280 mg doses, fewer patients (pts) attained complete BTK occupancy (Poggesi, AACR 2014). This analysis evaluated the effect of the ibr 420 mg once-daily dose on IR-assessed progression-free survival (PFS) in pts with previously treated CLL from the phase 3 RESONATE trial. Methods: Dose intensity (DI) was defined as the proportion of actually administered vs planned doses of 420 mg. DI was also defined in first 8 weeks to compare statistical power of post-week 8 PFS. A steadystate AUCCmax was estimated per NONMEM modeling using 2 timepoint samples (weeks 1 and 4). Missed doses had to be consecutive. Results: Ibr-treated pts (n = 195) had a mean DI of 95% (median 100%) with 8.3 months of treatment. The majority of dose interruptions restarted at 420 mg; 3.6% of pts had 1 and 0.5% had 2 dose reductions due to AEs. Pts with higher DI experienced longer PFS (median NR) compared to lower DI (11 months). Using an adjusted mean DI of 96% in first 8 weeks and post week-8 PFS, this trend was confirmed with HR = 0.4 (P = 0.0127). Pts with higher DI had a lower rate of progression regardless of del17p, p53 mutation, or del11q. In 179 pts receiving ibr 420 mg with PK assessment at weeks 1 and 4, no difference was seen in median PFS with lower vs higher ibr exposure (AUCCmax). There were fewer PFS events in pts not missing > 13.0% (65%) compared with those missing < 10% (83%) PFS in 8 consecutive days (13% vs 31%, respectively), with median PFS of NR vs 11 months, respectively. The mean duration of these missed doses was 26 days. Results: A higher mean dose intensity of ibr is associated with improved PFS, with patients missing more than 1 week of treatment experiencing more PFS events. These results, and the established clinical profile, support the clinical utility of sustained adherence to the once-daily 420 mg dose in patients with previously treated CLL. Clinical trial information: NCT01578707.

Association of relapse of FLT3-ITD AML with normal karyotype with internal tandem duplication allelic burden, base-pair insertion length, and NPM1 status. First Author: Sarah L Sammons, Division of Hematology/Oncology, Department of Medicine, University of Maryland Greenebaum Cancer Center, Baltimore, MD

Background: FMS-like tyrosine kinase internal tandem duplication (FLT3-ITD) mutation in normal karyotype AML (NC-AML) is a poor prognostic feature. The prognostic significance of the mutant to wild type allelic ratio (AB) was calculated as the ratio of ITD to wild type allele expressed as a percentage. Time to failure was analyzed using the Kaplan-Meier estimate (AB) was calculated as the ratio of ITD to wild type allele expressed as a percentage. Time to failure was analyzed using the Kaplan-Meier estimate.

1. A FLT3-ITD mutation was detected as the presence of a migrating band of base pair insertion length (bpInsLng) of FLT3-ITD with or without NPM1 mutation.

2. Dose intensity (DI) was defined as the proportion of actually administered vs planned doses of 420 mg. DI was also defined in first 8 weeks to compare statistical power of post-week 8 PFS. A steadystate AUCCmax was estimated per NONMEM modeling using 2 timepoint samples (weeks 1 and 4). Missed doses had to be consecutive.

3. Of 861 pts tested at enrollment, 29% showed detectable FLT3-ITD mutations. These results, and the established clinical profile, support the clinical utility of sustained adherence to the once-daily 420 mg dose in patients with previously treated CLL. Clinical trial information: NCT01578707.

Activity of the mitochondrial metabolism inhibitor cpi-613 in combination with high dose Ara-C (HDAC) and mitoxantrone in high risk relapsed or refractory acute myeloid leukemia (AML). First Author: Timothy S. Pardee, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC

Background: CPI-613 is a novel agent that targets mitochondrial metabolism. It inhibits mitochondrial respiration in AML cells and in a single agent phase I study was active for several types of tumors with myeloid malignancies.

This trial was designed to determine the maximum tolerated dose (MTD) and efficacy of CPI-613 in combination with HDAC and mitoxantrone in relapsed or refractory AML. Methods: CPI-613 was given daily on days 1 through 5 starting at a dose of 500 mg/m2. Beginning on day 3, HDAC (6,000 mg/m2) was given daily for 3 doses. If residual blasts were present on day 8, an escalated dose of 500 mg/m2 was given on days 1 and 2. If residual disease was present on day 14, a second cycle could be given. Patients who achieved a complete remission with or without complete count recovery (CR or CRi) could receive additional cycles with the goal of stem cell transplantation when possible. Results: A total of 48 patients were evaluable. The median age is 60 (range 21-79). Seventeen patients had refractory disease and 11 received one or more previous lines of salvage therapy. Cytogenetics were poor risk in 23, intermediate in 20, good in 4 and one patient had CML blast crisis. The overall response rate was 48% (18C+4CRi). Three of five patients with FLT3-ITD mutations (range 40-50) had a CRi rate of 46% (12/26). Surprisingly, patients with poor-risk cytogenetics had a CRi rate of 48% (11/23). In a historical cohort of poor-risk patients treated with HDAC, mitoxantrone and asparaginase, only 25% responded. Median survival for the entire cohort is 6.4 months. Six patients with FLT3-ITD and AML at one center were treated with CPI-613 in combination with HDAC and mitoxantrone is a promising salvage regimen and these data support additional studies especially in older patients with high-risk disease. Clinical trial information: NCT01768897.

Visit abstracts.asco.org and search by abstract for the full list of authors and their disclosure information.

7014 Poster Discussion Session; Displayed in Poster Session (Board #4), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

7015 Poster Discussion Session; Displayed in Poster Session (Board #5), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Prognostic testing patterns in CLL pts treated in U.S. practices from the Connect CLL registry. First Author: Anthony Mato, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: Genetic aberrations detected by fluorescence in situ hybridization (FISH) and cytogenetic (CG) testing provide prognostic information for CLL pts. The identification of genetic abnormalities has particular relevance in CD8+, immunocompromised- or kinase inhibitor therapies, SCT or clinical trial. Here, we analyze factors influencing decisions to perform FISH or CG testing. Methods: A total of 944 pts with untreated CLL (91% stage IV) at 179 community sites were enrolled. CG testing results were compared to FISH results. The role of FISH vs CG in clinical decision-making was evaluated using the kappa statistic. Results: CG testing was performed in 65% of pts and FISH testing in 27% of pts (p<0.001). CG testing was more often performed at academic sites (p=0.005), in pts age ≥75 (p=0.002), at enrollment at LOT1 vs. LOT2 (p<0.001), in private insurance pts (p=0.02) and Rai stage ≥2 (p<0.001). Table 1 describes independent predictors of performing genetic testing stratified by LOT and practice setting. Conclusions: Our results indicate that only a fraction of CLL pts are tested/re-tested for genetic alterations by FISH/CG. Given the significance of identifying del17p or complex CG in selecting each LOT, these results indicate a need for increased awareness of the importance of this testing.

MV analysis: Predictors of FISH/CG.

Time point/Pretreatment setting Covariate OR 95% CI

LOT1/All sites

Academic vs community-grt sites

Whites vs others

Private insurance

1.76 1.03-2.99

1.90 1.33-2.77

1.44 1.01-2.00

LOT1/Community-Grt sites

Whites vs other

Age > 75 vs. < 75

Rai stage ≥2 vs ≤1

0.34 0.17-0.68

1.74 1.22-2.71

1.51 1.02-2.57

LOT2a/All sites

Whites vs other

Age > 75 vs. < 75

Rai stage ≥2 vs ≤1

0.41 0.16-1.04

1.65 1.06-2.61

1.52 1.07-2.14

LOT2a/Community-Grt sites

Whites vs other

Age > 75 vs. < 75

Rai stage ≥2 vs ≤1

0.41 0.16-1.04

1.65 1.06-2.61

1.74 1.22-2.71
7016 Poster Discussion Session; Displayed in Poster Session (Board #6), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Safety and tolerability of the combination of ATRA + arsenic trioxide (ATO) + gemtuzumab ozogamicin (GO) in high-risk acute promyelocytic leukemia (APL): Initial report of the SWOG/Alliance/ECOG S0535 trial, First Author: Jeffrey E. Lancet, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: High-risk APL remains a therapeutic challenge, with significant rates of early mortality and relapse. Recent evidence confirmed excellent outcomes in low-risk APL with the combination of ATO and GO (Lo-Coco, NEJM 2013), and a previous pilot study indicated the efficacy of a combination of ATO + ATRA + GO in a subset of high-risk APL (Ravandi, JCO 2009). SWOG designed a larger phase 2 study to confirm the safety and efficacy of this combination in high-risk APL. Primary Objectives: 1) assessment of complete remission (CR) and continuous remission (CR); 2) assessment of complete remission (CR); Methods: Adult patients with newly diagnosed high-risk APL (WBC ≥ 10k/μL) were eligible. Induction therapy consisted of: ATRA (45 mg/m2/day) - day 1 until CR; ATO (0.15 mg/kg/day) - day 10 until CR; GO 9 mg/m2/day. Patients in CR received consolidation with ATO x 2 cycles, followed by ATRA + daunorubicin x 2 cycles, followed by GO x 2 cycles. Subsequent maintenance therapy consisted of ATRA + 6-MP + methotrexate for up to 1 year. Results: From 2008 to 2013, 73 patients were enrolled and evaluable for toxicity. Median age was 46.5 years, with 52% females and 48% males. Sixty-two (85%) patients completed induction therapy as planned, and 48% (35) patients completed all planned consolidation. Six of 73 patients (11%) died within 6 weeks of treatment initiation (95% confidence interval 6-21%), supporting rejection of the null hypothesis (30% early death rate). The most common treatment-emergent grade 3-4 adverse events (AE) during induction therapy were: febrile neutropenia (33%), AST/ALT elevation (12%), hypoxia/differentiation syndrome (11%), hyperglycemia (11%), headache (11%), prolonged QTc (11%). Amongst 59 patients receiving consolidation, the most common treatment-emergent grade 3-4 AE included: febrile neutropenia (52%), headache (14%), fatigue (14%), and nausea (12%). The efficacy of the ATO + ATRA + GO regimen is ongoing. However, the addition of ATRA + ATO + GO appears safe and well-tolerated in patients with high-risk APL, with an acceptable early mortality rate. 3-year CCR assessment is not yet mature. Clinical trial information: NCT00551460.

7018 Poster Discussion Session; Displayed in Poster Session (Board #8), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Effect of long noncoding RNA RUNX1R on the epigenetic regulation of RUNX1 in acute myelocytic leukemia, First Author: Hong Wang, Cancer Center, First Hospital of Jilin University, Changchun, China

Background: RUNX1, a master regulator of hematopoiesis, is the most commonly perturbed target of chromosomal abnormalities in hematopoietic malignancies. About 30%–40% of acute myeloid leukemia (AML) patients carry the t(8;21) translocation. However, little is known regarding patients carry the t(8;21) translocation. However, little is known regarding the molecular mechanisms underlying RUNX1-associated leukemogenesis. Long non-coding RNAs (lncRNAs) have been implicated in a variety of important biological processes by epigenetic mechanisms. Methods: Using a novel R3C (RNA-guided Chromatin Conformation Capture) method developed in our lab, we identified lncRNAs that participate in the regulation of RUNX1 in AML. Full length of lncRNAs was characterized by Marathon cDNA Amplification Kit. Expression of lncRNAs in AML was quantitated by qPCR. Reverse transcription-associated trap (RT) and chromatin conformation capture (3C) assays were used to map DNA/RNA interaction. The protocol of AML patients bone marrow and peripheral blood cell samples was approved by the Human Medical Ethical Review Committee from Jilin University First Hospital and informed consent was obtained from each AML patient and normal donor. Results: 1) We discovered a novel intragenic 216 kb long noncoding RNA within the RUNX1 locus, named RUNXOR (RUNX1 overlapping promoter-derived noncoding RNA). RUNXOR was transcribed from the front of TEL and located in the gene’s exons and introns. 2) RUNXORlncRNA was overexpressed both in AML cell lines and AML patients’ bone marrow, and was upregulated by Chemotherapeutic drug Ara-C. 3) RUNXOR lncRNA interacted with the promoter and enhancer of RUNX1. By recruiting histone methyltransferase EZH2, it induced H3K27 modification and epigenetically regulated RUNX1. 4) Using the 3C assay, we showed that RUNXOR interacted with the most frequent translocation break regions in translocation related genes, including ETV1, ETO, TEL, and CBFAT23. Conclusions: This study identifies RUNXOR as a novel lncRNA involved in long range DNA interaction of RUNX1 in AML. The lncRNA may function as a putative furlong suppressor by epigenetically regulates RUNX1 and scaffold the translocation associated DNA in AML.

7017 Poster Discussion Session; Displayed in Poster Session (Board #7), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Correlation of overall survival (OS) with bone marrow blast (BMBL) response in patients (pts) with myelodysplastic syndrome, First Author: Lewis R. Silverman, Mount Sinai Medical Center, New York, NY

Background: BMBL % is the prognostic variable with the greatest impact on outcome in MDS patients at diagnosis and subsequent time points. Current composite response criteria (IWG, Cheson 2006) do not consistently correlate with OS. Treatment impact of BMBL as an independent response criterion has not been adequately evaluated. Methods: We evaluated the correlation between OS and BMBL in pts with high-risk (HR) MDS from 4 datasets from 7 studies with 887 pts: ONTIME, a Phase III randomized study of 2nd-line rigosertib (RIG) vs best supportive care (BSC) (N = 299; Silverman, ASH 2014); 4 Phase III studies of RIG in pts with MDS/AML (N = 397; Silverman, ASH 2014); AZA-001, a Phase II trial of azacitidine (AZA) vs 3 conventional care regimens (N = 358; Fenaux, Lancet Oncol 2009; Gore, Haematologica 2013; Cancer & Leukemia Group B (CALGB) Study 9221, a Phase II, randomized trial of 1st-line AZA vs BSC (N = 191; Silverman, J Clin Oncol 2002). Change in blasts was defined similarly: BM complete response is BMBL ≤ 5% and ≥ 50% decrease from baseline; BM partial response is ≥ 50% decrease from baseline, but BMBL still > 5%; stable disease is < 50% decrease or increase from baseline. Results: In ONTIME, landmark time-dependent analyses showed correlation of BMBL response/stabilization with OS at 4 wks (P = 0.011) and 12 wks (P = 0.001). In the phase III studies of RIG, BMBL response/stabilization at 4–8 weeks was associated with a quadrupling of median OS (P < 0.001). In Study AZA-001, time-dependent analysis of BMBL stabilization was associated with a significantly reduced risk of death in both treatment cohorts (P < 0.001). In Study 9221, landmark analysis of BMBL response showed BMBL stabilization led to improved OS (P = 0.005). Conclusions: These studies, spanning more than a decade with different therapeutic agents and settings, demonstrate a consistent positive correlation between BMBL response and OS in pts with HR-MDS, including pts on supportive care. This suggests that use of reduction/ stabilization of BMBL as a new clinical response parameter, as an intermediate clinical endpoint for evaluation of new agents, and as a biomarker for disease progression in HR-MDS itself.

7019 Poster Discussion Session; Displayed in Poster Session (Board #9), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

NFAT2 to regulate anergy induction in CLL through Lck, First Author: Melanie Maerklin, Department of Hematology, Oncology and Immunology, University of Tuebingen, Tuebingen, Germany

Background: NFAT2 is a highly phosphorylated transcription factor which regulates developmental and activation programs in diverse cell types. CLL constitutes a heterogeneous disease with some patients exhibiting an indolent course for many years and others progressing rapidly and requiring early treatment. A defined subgroup of patients shows enhanced responsiveness to stimulation of the B cell receptor (BCR) complex and more aggressive disease. In contrast, another subset of CLL patients with more indolent course is characterized by an anergic B cell phenotype referring to B cell unresponsiveness to IgM ligation. Here, we analyzed the role of NFAT2 in the pathogenesis of CLL and in anergy induction in CLL cells. Methods: We crossed conditional CD19-Cre NFAT2 knockout mice with the Eμ-TCL1 transgenic mice, which develop a human-like CLL. We analyzed TClL + NFAT2 ko mice and TCL1 mice without a NFAT2 deletion served as controls. We performed a comparative gene expression analysis, Ca2+ mobilization assay, and in vitro signaling molecules on both CLL cells. Results: Mice with NFAT2 ko exhibited a significantly more aggressive disease course with accelerated accumulation of CLL cells and a dramatically reduced life expectancy. We detected a substantially altered expression profile of genes associated with B cell anergy (23% responsive to all stimuli of these gene’s expressions were significantly less in the absence of NFAT2 with Lck, P < 0.001). In Study 9221, landmark analysis of BMBL response showed BMBL stabilization led to improved OS (P = 0.005). Conclusions: These studies, spanning more than a decade with different therapeutic agents and settings, demonstrate a consistent positive correlation between BMBL response and OS in pts with HR-MDS, including pts on supportive care. This suggests that use of reduction/ stabilization of BMBL as a new clinical response parameter, as an intermediate clinical endpoint for evaluation of new agents, and as a biomarker for disease progression in HR-MDS itself.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
GATA-1, FOG-1, and FLI-1 regulation in essential thrombocythemia independently from JAK2 and CALR mutations. First Author: Ciro Roberto Rinaldi, University of Lincoln, Lincoln, United Kingdom

Background: GATA-1 is the founding member of the GATA transcription factor family and it is essential for cell maturation and differentiation within the erythroid and megakaryocytic lineages. We and others have demonstrated that elevated GATA-1 expression is found in the bone marrow of essential thrombocythemia (ET) patients independent of JAK2(V617F) and CALR mutations. GATA-1 is able to coordinate lineage specification through its ability to bind both DNA and protein partners that include; Friend of GATA (FOG-1) and the Friend leukemia integration 1 (FLI-1) transcription factors. FOG-1 is vital for megakaryocyte and erythroid-lineage commitment and its expression later occurs in non-hematopoietic tissues with that of GATA-1. FLI-1 is an ETS family member that is expressed at high levels in megakaryocytic progenitors. In conjunction with GATA-1, FLI-1 targets those genes responsible for megakaryopoiesis.

Methods: Following on from our earlier work we analyzed the expression levels of GATA-1 in relation to its interacting transcription factors, FOG-1 and FLI-1 in megakaryocyte development. Peripheral blood specimens were collected from 36 patients diagnosed with ET, 17 JAK2 mutated (47%), 4 CALR in megakaryocyte development. Peripheral blood specimens were collected following on from our earlier work we analyzed the expression levels of FLI-1 targets those genes responsible for megakaryopoiesis.

Results: We confirmed the data obtained in bone marrow demonstrating that GATA-1 is significantly up-regulated in ET patients and that GATA-1 overexpression is independent from JAK2(V617F) and CALR mutations. However, the transcription factors FOG-1 and FLI-1 do not appear to be subject to the same regulatory control in ET as that of GATA-1.

Conclusions: These results suggest that GATA-1 is specifically deregulated in essential thrombocythemia.

7022 Poster Discussion Session; Displayed in Poster Discussion Session (Board #12), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Proximity score analysis: Frontline therapy with high-dose (HD) imatinib vs. 2nd generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia in chronic phase. First Author: Koji Sasaki, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The clinical efficacy of the second generation of tyrosine kinase inhibitors (TKI) has not been compared to that of HD imatinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). Methods: Response and survival for 374 pts with newly diagnosed CML-CP enrolled in four consecutive or parallel prospective clinical trials of imatinib 800 mg daily, dasatinib, or nilotinib were reported. Logistic regression was used and a proximity score (PS) calculation from baseline pt characteristics including age at diagnosis, gender, race, Sokal scores, white blood cell, hemoglobin, platelet, blasts in peripheral blood and bone marrow, albumin, urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, the proportion of Philadelphia chromosome by conventional karyotype and fluorescence in situ hybridization, the presence of clonal evolution, the type of BCR-ABL transcript, and time from diagnosis to therapy. PS analysis with 1:1 matching was performed with the nearest matching method. The Kaplan-Meier method was used to calculate OS, EFS, TFS, and FFS. Results: Of the 374 pts analyzed, 158 were treated with HD imatinib, 109 with nilotinib, and 107 with dasatinib. The median follow-up was 124 months, 49 months, and 54 months, respectively. PS matching resulted in 81 pts in imatinib vs. dasatinib and 84 pts in imatinib vs. nilotinib, respectively. The cumulative best response, five-year OS, EFS, and TFS are summarized in the table below. Conclusions: High-dose imatinib may have similar efficacy compared to second generation TKIs without clear difference in response or long-term survival endpoints.

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<th>Method</th>
<th>HD Imatinib</th>
<th>HD Dasatinib</th>
<th>HD Nilotinib</th>
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<tr>
<td>OS (5 years)</td>
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<tr>
<td>EFS (5 years)</td>
<td>72%</td>
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<td>TFS (5 years)</td>
<td>64%</td>
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<td>MR4.5</td>
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<td>MMR</td>
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<td>Spleen size</td>
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<tr>
<td>Death</td>
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Main outcomes after PS matching:

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7023 Poster Session (Board #4), Sun, 8:00 AM-11:30 AM

Results of a phase III randomized, controlled trial evaluating the efficacy and safety of idelalisib (IDELA) in combination with ofatumumab (OFA) for previously treated chronic lymphocytic leukemia (CLL). First Author: Jeffrey Alan Jones, Ohio State University, Columbus, OH

Background: IDELA (Zydelig) is a selective oral PI3Kδ inhibitor approved in combination with rituximab for previously treated pts with CLL. This open-label study (NCT01659021) compared IDELA + OFA v OFA in pts with previously treated CLL. Methods: Pts with CLL progressing ≥ 24 mo from last therapy, who had received ≥ 2 cycles of a purine analogue or bendamustine, were randomized 2:1 to either Arm A (IDELA 150 mg BID continuously plus OFA, 300 mg IV wk 1, then 1 gm IV wks 7 and 4 x wk 4) or Arm B (OFA, same as Arm A) to Arm A ≥ 2 cycles of IDELA for 1 gr complete response. Stratification was performed for relapsed v refractory, del17p and/or TP53 mutation, and MMR mutation, and IRC-assessed response and PD based on imaging using modified IWCLL 2008 criteria. The 1 endpoint was PFS and its 2 endpoints were confirmed ORR, lymph node response (LNR), OS, PFS in pts with del(17p) and/or TP53 mutation, and CR rate. Results are from the final analysis. Results: Pts attributes were balanced in the 2 arms: Med age 67; Rai I(1)/II(1)/III(1)/IV(1), 71%, med no prior regimens 3, refractory 49%, del17p/TP53mut 40%, MGH unmpt 78%. Exposure, disposition, and efficacy are shown in Table. Results were consistent across risk groups. Gr ≥ 3 AE’s in Arm A included thrombosis (18%, 12.7%), and febrile neutropenia (11.6%). Conclusion: IDELA + OFA yielded superior PFS, ORR, and LNR compared to OFA in relapsed CLL, including within high-risk subgroups. Safety was manageable with a profile similar to that previously observed in CLL trials. The open label design may have led to an imbalance in dropout, with a higher rate in Arm B. Clinical trial information: NCT01659021.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A multicenter open-label phase 1b/2 study of ibrutinib in steroid dependent or refractory chronic graft versus host disease (cGVHD). First Author: David Bernard Miklos; Stanford University; Stanford, CA

Background: Chronic GVHD (cGVHD) is a common and serious complication after allogeneic stem cell transplantation (SCT). Both B and T cell-mediated mechanisms have been implicated in the pathophysiology of cGVHD. There are no approved therapies for cGVHD. In murine models, ibrutinib (ibr) reduces the severity of cGVHD (Dubovsky JCI 2014). In humans, ibr was tolerable in post-SCT patients (pts) and may improve donor chimerism and/or graft-vs-host effects while reducing cGVHD (Miklos ASH 2014, Coutre ASH 2014). Methods: This ongoing phase 1b/2 study was designed to evaluate the safety and efficacy of ibr in pts with steroid-dependent refractory cGVHD. Eligible pts had to have ≤ 3 prior regimens for cGVHD and either >25% BSA erythema or an NIH mouth score > 4. Phase 1b was designed to determine the recommended phase 2 dose (RP2D) with the initial being 420 mg. Response was assessed every 3 months using the NIH consensus cGVHD Activity Assessment. Results: 6 pts (median age, 56 yrs, mean Karnofsky score, 85) were enrolled in phase 1b. Median time from transplant was 23 mo. Median time on ibr was 19.3 months using the NIH consensus cGVHD Activity Assessment. Results: 6 pts (median age, 56 yrs, mean Karnofsky score, 85) were enrolled in phase 1b. Most common treatment-emergent AEs included fatigue (n = 5), diarrhea (n = 4), eczymosclerosis (n = 3) and stomatitis (n = 2), all grade 1/2. SAEs (all grade 3) occurred in 2 pts including one pt with pneumonia and another with pyrexia and fungal brain abscesses. The latter was the only event leading to discontinuation of ibr (at 10.9 mo). From ongoing analysis of efficacy for pts receiving at least 3 months of treatment indicated that all 5 evaluable pts achieved PR. The 2 pts evaluable at 6 months remain in PR. Improvements in clinician assessed GVHD-score, skin erythema and mouth score were observed in pts at these early time points. RP2D was determined to be 420 mg. Conclusions: Ibrutinib given for steroid-dependent refractory cGVHD was well tolerated; AEs were consistent with the known safety profile for ibrutinib. The efficacy data observed at this early time point is preliminary and needs confirmation in a larger number of pts for longer duration. Phase 2 enrollment is ongoing. Clinical trial information: NCT02199869.
7028 Poster Session (Board #17), Sun, 8:00 AM-11:30 AM
Association of higher total nucleated cell dose with improved survival in patients receiving donor lymphocyte infusion after allogeneic stem cell transplantation.
First Author: Nathan Singh, University of Pennsylvania, Philadelphia, PA

Background: Donor lymphocyte infusion (DLI) after allogeneic stem cell transplant is an established therapy for disease relapse. Long-term survival after DLI remains poor, and identification of factors associated with improved outcomes is of significant interest. Methods: We retrospectively analyzed the total nucleated cell (TNC) dose of DLIs in 79 patients (pts) who received un-manipulated DLI at the University of Pennsylvania between 2000-2014. We included pts who received DLI for relapse or falling chimerism, but excluded those who received low dose (< 0.5x10^8 TNC/kg) for stable mixed chimerism. Multivariable regression analyses were used to evaluate associations between cell dose, survival, best response and GVHD. Classification and Regression Tree (CART) analysis was used to identify optimal cutoff in the TNC dose. Results: Pts received DLI from sibling (61%) or unrelated (39%) donors, and 10% were HLA-mismatched. Median follow-up was 68 months (range 0.33-156.2). Median age was 53 years (21-75), and diseases included AML (47), MDS (15), NHL (8), ALL (2), CML (2), Hodgkin (2), myelofibrosis (2) and myeloma (1). Six pts received DLI for falling chimerism without overt relapse. The best response to DLI was complete response (CR) in 27 of 70 evaluable pts. Any GVHD and severe GVHD developed in 24 of 61 and 15 of 59 evaluable pts, respectively. We found that pts receiving > 1.6x10^9 TNC/kg had improved six-month (adjusted OR = 0.29, 95% CI [0.07-0.89], p = 0.03), one-year (aOR = 0.16, [0.04-0.77], p = 0.02), and overall survival (aHR = 0.47, [0.27-0.82], p = 0.01). A survival advantage for a higher TNC dose was also significant in the subset of AML and MDS pts (aHR = 0.41, [0.22-0.76], p = 0.005). Higher TNC dose did not correlate with development of any GVHD (aOR = 0.67, [0.22-2.06], p = 0.48) or grade III-IV GVHD (aOR = 0.51, [0.10-2.68], p = 0.43). There were also no significant differences in achieving a CR (aOR = 1.56, [0.40-6.10], p = 0.52). Conclusions: TNC dose of ≥ 1.6x10^9 TNC/kg correlated with improved survival without an increased risk of developing GVHD, and thus higher target TNC doses should be considered in pts receiving DLI.

7029 Poster Session (Board #18), Sun, 8:00 AM-11:30 AM
A randomized controlled trial of ibandronate for the prevention of bone loss following allogeneic stem cell transplantation.
First Author: Xerxes Punjani, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Bone mineral density (BMD) loss occurs rapidly within the first year following allogeneic hematopoietic stem cell transplantation (alloHCT), which can lead to fractures. Nonpharmacologic prophylaxis measures are inadequate in preventing bone loss following alloHCT and the effect of ibandronate has not been evaluated. Methods: We performed a phase 3 single-center open-label randomized controlled trial of intravenous ibandronate to prevent bone loss in adult recipients of alloHCT at The University of Texas MD Anderson Cancer Center. The treatment group received 3 mg of intravenous ibandronate over 15–30 seconds starting within 45 days of alloHCT and at 3, 6, and 9 months after alloHCT. All patients received daily calcium (500 mg) and daily vitamin D (400 IU) oral supplements twice daily for 12 months. We compared changes in BMD in the lumbar spine, femoral neck, and total hip at 6 and 12 months following alloHCT relative to baseline between treatment and control groups. Results: Of 414 patients screened, 78 were enrolled in the trial, 39 randomized to the ibandronate group and 39 to the control group. Baseline, age, sex, race, underling disease, donor type, stem cell origin, hormonal status, and baseline BMD did not differ significantly between the 2 groups. The treatment group had less BMD loss in the lumbar spine at 6 and 12 months than the control group (P = 0.03). Both groups lost more BMD in the femoral neck and total hip than in the lumbar spine at 6 and 12 months, and changes in BMD in the femoral neck and total hip at 6 months (P = 0.33 & P = 0.10 respectively) and 12 months (P = 0.81 & P = 0.44 respectively) did not differ significantly between groups. Both glucocorticoids and tacrolimus reduced BMD in the lumbar spine, but ibandronate had a significant protective effect and prevented this loss. Conclusions: Ibandronate prevents bone loss in the lumbar spine in patients undergoing alloHCT, particularly those who received high doses of glucocorticoids or tacrolimus. However, ibandronate does not completely prevent bone loss at the femoral neck and total hip. Pharmacologic agents with different mechanisms of action should be evaluated in this population for better prevention of bone loss. Clinical trial information: NCT00824993.

7030 Poster Session (Board #19), Sun, 8:00 AM-11:30 AM
Outcomes of hematopoietic stem cell transplant (HSCT) in HIV patients in HAART era.
First Author: Kathan Mehta, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Prior studies have shown that outcomes of HSCT in HIV patients are similar to non-HIV patients since effective implementation of HAART by 1998; but they are limited by small sample size or non-inclusion of recent data. Methods: We queried National Bone Marrow Donor Program (NBMDP) Database for all HIV positive recipients undergoing HSCT (weighted N = 111,925) from 1998 to 2012 for HSCT using ICD9 procedure code 41.0. HIV patients were identified by ICD9 diagnostic code of 042, 043, 044, 008 and 079.53. Primary outcome was in-hospital mortality and secondary outcomes were complications of HSCT. Results: 39,517 Patients who underwent HSCT were identified (weighted N = 192,562). Among these 108 patients had HIV (weighted N = 29,206). Median survival from HSCT was 4.5 months. Mortality was 31.1% (95% CI = 29.3-32.8). Other infections (10.7%), sepsis (10.7%), graft vs host disease (GVHD) (9.0%), fungal infections (8.1%), and CMV (3.1%) were observed. Conclusions: HIV patients undergoing HSCT had similar outcomes to non-HIV patients. Mortality was significantly worse in patients with HIV infection. Further research is needed to prevent the disease in HIV patients after HSCT.

7031 Poster Session (Board #20), Sun, 8:00 AM-11:30 AM
Post-transplantation long-term events in a cohort of HIV-positive patients affected by relapsed/refractory lymphoma.
First Author: Ernesto Zanet, National Cancer Institute CRO Aviano, Aviano, Italy

Background: The advent of highly active antiretroviral therapy (HAART) allowed to extend autologous stem cell transplantation (ASCT) to the HIV-positive population. In the literature data are scarce concerning the long-term events in this population. Methods: We treated consecutively 36 HIV-positive patients (pts) affected by relapsed/refractory lymphomas with ASCT. Ten pts died during or early after ASCT due to progressive disease (4 pts), chemotherapy toxicity (1 pt) and infection (5 pts). We analyzed the post-ASCT long-term data of 26 pts, reaching a complete response after ASCT. All patients received HAART concomitantly to chemotherapy. Results: Two pts experienced a lymphoma relapse, after 4.27 and 3.08 years from ASCT, respectively. Five patients presented with a secondary malignancy (1 patient an anal squamous cell cancer, 1 patient a squamous cell carcinoma of the larynx and 1 patient a cervical intraepithelial neoplasia (CIN) grade 2, 1 patient a melanoma of the skin, 1 patient a HL developed in a patient primarily affected by NHL, respectively), with a median time of 3.01 years from ASCT. Nine patients had OI: 3 patients developed a Pneumocystis Carinii pneumonia, 1 patient a Cytomegalovirus pneumonia, 1 patient a Mycobacterium Avium Complex pneumonia, 1 patient a Herpes Simplex Chronic Uler, 3 patients cutaneous relapsing Herpes Zoster, respectively. The median time of OI appearance was 0.25 years (IQR: 0.11-2.33). Two pts died: one of lymphoma relapse, the other of car accident. With a median of 4.95 years from ASCT, 4 of 36 pts and 30 of the entire sample of pts were 91% and 36% at 10 years, respectively. Conclusions: 24 out of 26 pts are still alive and in long-term complete remission after ASCT. These data confirm the long-term efficacy of ASCT. The appearance of OI is earlier than that of second malignancies after ASCT. The secondary malignancies developed by our pts are non-AIDS-defining cancers and at least three cases are linked to a viral pathogenesis (HPV for both anal cancer and cervical cancer precursor lesion; EBV for HL). Both OI and second malignancies were successfully managed and cured and the only long-term death occurred due to lymphoma relapse.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Engraftment fever (EF) is common in 2nd week post autologous hematopoietic stem cell transplant (auto HSTC). It is difficult to differentiate from infective fever (IF). This leads to unnecessary use and cost of antibiotics. Also timely treatment of EF may prevent progression to full blown engraftment syndrome (ES). We studied the role of total leucocyte count (TLC) to C-reactive protein (CRP) ratio in differentiating EF from IF.

Methods: Consecutive patients with breakthrough fever (BF) from d+7 to d+15 post auto HSTC, from March 2011 to August 2013, were included in this retrospective analysis. BF was defined as new onset fever preceded by an afebrile period of at least 48 hours. BF episodes were classified as IF or EF. Fever was classified as IF if blood culture was positive. There were radiological signs of infection or if fever subsided within 48 hours of change of antibiotics. EF was defined as fever associated with rising counts without any identifiable infective focus responding to steroids. Antibiotics were added at the onset of BF. If fever persisted beyond 48 hours and no infective cause was identified, systemic steroids were started. Daily morning TLC and CRP values were obtained from patients’ records. TLC:CRP ratio was calculated from day of admission to day of discharge. Optimal cut-off value of the ratio on the day of BF was obtained by plotting a receiver operating curve. Sensitivity and specificity were calculated. Optimal cut-off value of the ratio on the day of BF was 10 and 13 respectively. The median day of BF was 9. Sixty two patients had EF, among whom 15 had ES. We found an optimal value of 0.056 for differentiating between IF and EF. Using a ratio > 0.056 for diagnosing IF, sensitivity and specificity were 63% (95% CI – 50 – 75%) and 100% (95% CI – 63 – 100%) respectively. Conclusions: In 2nd week post auto HSTC, a value of the ratio of TLC:CRP > 0.056 on the day of BF is highly specific for EF. Prospective studies are warranted to confirm the results. This could help reduce unnecessary use and cost of antibiotics.

7034 Poster Session (Board #23), Sun, 8:00 AM-11:30 AM
The impact of HBO on early ALC recovery following high-dose therapy and autologous transplantation. First Author: Omar Salah Atljawi, University of Kansas Medical Center, Overland Park, KS

Background: Historically, early absolute lymphocyte count (ALC) recovery (defined as ALC of 500 cells/µl day 15 of transplant) is seen in around 50% of patients receiving autologous stem cell transplantation (ASCT) and is associated with improved survival. Early ALC recovery is related to recovery of natural killer (NK) cells mediated by interluken-15 (IL-15). We are currently conducting a pilot study primarily investigating hyperbaric oxygen (HBO) as a modality to facilitate blood count recovery in ASCT setting. By lowering erythropoietin (EPO) at time of hematopoietic stem cell (HSC)/progenitor cell infusion, HBO appears to facilitate bone marrow homing of HSC/progenitors with retained multi-lineage potential. Accordingly, we hypothesized that HBO pre-treatment might facilitate early ALC recovery.

Methods: Patients treated on the ongoing pilot study were evaluated for ALC recovery, as previously defined. Blood samples were collected at baseline (prior to high-dose chemotherapy), day 0 (prior to HBO and 6 hours later), 24- and 48-hours following HBO therapy, and on the third day of neutrophil engraftment. Plasma IL-15 was measured by ELISA. Results: Of the twenty patients who were treated on study, one patient did not tolerate HBO therapy and 2 patients were released to their oncologist prior to day 15 post-ASCT, accordingly 17 patients were assessable for ALC recovery. 13 out of the 17 patients (76%) achieved ALC 500 prior to day 15, and all achieved ALC 500 by day 18 post-ASCT. In our cohort, the median time to neutrophil engraftment EF, sensitivity and specificity date, twelve patients had IL-15 levels measured in pg/ml for all time points except baseline level which was measured in 5 patients. Average IL-15 level was higher on day 0 prior to HBO therapy compared to baseline level (22.83 +/- 3.20 vs 4.94 +/-1.38) and third day of neutrophil engraftment IL-15 level was higher than baseline level (1.3 +/-1.7 vs 4.94 +/-1.38). IL-15 level peaked 48-hours following HBO therapy (31.9 +/-3.67).

Conclusions: Compared to historic data, the rate of early ALC recovery in our HBO pilot study appears to be encouraging. HBO effects on post-ASCT ALC recovery and IL-15 warrant further evaluation. Clinical trial information: NCT02087657.
7036 Poster Session (Board #25), Sun, 8:00 AM-11:30 AM

Long-term outcomes of rituximab use prior to autologous stem cell transplantation (ASCT) in low-grade follicular lymphoma (FL) at the time of first progression. First Author: Alberto Antonio Ferro, University of Nebraska Medical Center, Omaha, NE

Background: Some studies suggest that prior use of rituximab is associated with poor outcomes following ASCT in relapsed diffuse large B-cell lymphoma (DLBCL). The effects of rituximab use prior to ASCT on long-term outcomes of FL are unclear. Rituximab in addition to ASCT has been associated with an increased risk of secondary primary malignancy (SPM) especially of solid tumors; however, this finding was based on lymphoma subtypes (J Clin Oncol 29:814-824, 2011). Methods: This is a retrospective study of 84 low grade FL patients treated by the Nebraska Lymphoma Study Group between 1987-2013. We used the Chi-square or Fisher’s exact tests to compare characteristics of patients who did vs. did not receive rituximab before ASCT. The Kaplan-Meier method was used to estimate overall survival (OS) and event-free survival (EFS). Results: 34 patients (40%) received rituximab prior to ASCT. Rituximab vs. no-rituximab groups were similar in sex distribution (males 74% vs. 54%, p = 0.07), more likely to be older (mean age of 51 vs. 44 years, p = 0.0004), have received 3 or more prior chemotherapy regimens (53% vs. 24%, p = 0.004) and less likely to have received total body irradiation (TBI) (3% vs. 74%, p < 0.0001). Rituximab group was more likely to be at second complete remission (53% vs. 14%, p = 0.0004) prior to ASCT. At a median follow-up of 10.2 years, 41 patients (49%) died. The 10-year EFS was similar (49% vs. 32%, p = 0.10) but the 10-year OS was better in the rituximab group (74% vs. 46%, p = 0.009). The risk of SPM (excluding non-melanoma skin cancers) was similar in the groups with or without rituximab (18% vs. 12%, p = 0.21). Conclusions: Within the limitations of this study, rituximab use prior to ASCT resulted in similar EFS but improved OS. In addition, we did not find an increased risk of SPM with rituximab use.

7037 Poster Session (Board #26), Sun, 8:00 AM-11:30 AM

Overall survival and treatment response in patients with myelodysplastic syndrome and acute myeloid leukemia treated with DNA methyltransferase inhibitors (DMTI) in 5 randomized trials. First Author: Seongseok Yun, University of Arizona, Tucson, AZ

Background: Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are two of the most common myeloid neoplastic disorders that are characterized by genetic instability and ineffective hematopoesis. DNA methyl-transferase inhibitors (DMTI) have been widely used for elderly MDS and AML patients who are not qualified for stem cell transplantation (SCT), however the outcomes from previous trials were inconsistent. The purpose of current meta-analysis is to assess the efficacy of DMTI compared to conventional care regimens (CCRs) in patients with high risk MDS or AML. Methods: Relevant articles were searched in PubMed, EMBASE, and Cochrane database. Eligible studies were limited to randomized trials comparing DMTI (azacitidine or decitabine) and CCRs (best supportive care, low dose cytarabine or intensive chemotherapy) in adult patients with MDS or AML. Cochrane’s Q statistic was used for the calculation of the statistical heterogeneity. Relative risks and 95% CI were calculated using random effect model and RevMan 5.3 software. Results: Significant OS benefit was associated with DMTI treatment compared to CCR with OS of 33.2% vs. 21.4% (RR 0.83, 95% CI, 0.71 to 0.98, p = 0.03). CR/PR rate was also significantly higher in DMTI group with a response rate of 23.7% vs. 13.4% (RR 0.87, 95% CI, 0.81 to 0.93). In a subgroup analysis, only azacitidine treatment showed OS improvement (RR 0.75, 95% CI, 0.67 to 0.85), but not in decitabine (RR 0.96, 95% CI, 0.92 to 1.01). Additional subgroup analysis according to cytogenetic risk and BM blast counts did not show significant RR difference. Conclusions: In a meta-analysis of randomized trials in patients with MDS or AML, DMTI treatment was associated with treatment response and survival benefit, although the initial treatment response failed to translate into survival benefit in patients treated with decitabine. Collectively, these results suggest that azacitidine may be the best therapeutic option in high risk MDS or AML patients who are not eligible for allogeneic SCT regardless of cytogenetic risk or degree of bone marrow involvement.

7038 Poster Session (Board #27), Sun, 8:00 AM-11:30 AM

Exosome transcriptome analysis to provide novel tools for CLL patient stratification. First Author: Raffaele Calogero, University of Torino, Torino, Italy

Background: Routine diagnostic techniques can detect very low levels of CLL phenotype cells. Monoclonal B-cell lymphocytosis (MBL) is a diagnostic category encapsulating individuals with an abnormal B-cell population but not meeting the diagnostic criteria for a B-cell malignancy. MBL and CLL show similar karyotypes and mRNA/miRNA expression data were hypothetically breaks host tumor tolerance. Methods: We collected data for coding genes, fusion transcripts, long non-coding RNAs, which might be instrumental for CLL patients’ stratification.

7039 Poster Session (Board #28), Sun, 8:00 AM-11:30 AM

Cellular immunotherapy for refractory hematological malignancies. First Author: John Leonard Reagan, Brown University Oncology Research Group, Providence, RI

Background: Allogeneic cellular infusion is a potent immune stimulus. We present data from our FDA approved IND Phase II clinical trial (BUOG 273) where allogeneic haploidentical lymphocytes are infused without prior chemotherapy or radiation to create a rejection response that hypothetically breaks host tumor tolerance. Methods: Eligible patients have relapsed or refractory acute leukemia. HLA haplo donors undergo leu-kapheresis without G-CSF priming, 1-2x10^{10}CD3^+ cells/kg were infused unprocessed immediately after collection. Peripheral blood collected 1-4, 8-24, 34-48, 72-96 and 168-192 hours post infusion were examined for effector cell populations, stimulatory/inhibitory signals, and cytokine release profiles. Wilcoxon rank sum tests were used for statistical analysis. Results: Five patients were infused haplo donor cells. Four developed hyperpyrexia post infusion that lasted 24-48 hours (median T 0-4 hours post infusion 98°F, median Tmax 8-192 hours post infusion 102.4°F, p = 0.009). Host CD8 T cells demonstrated decreased perforin expression post compared to pre-infusion (median pre 77.6%, median post 61%, p = 0.03) with no changes in granzyme A/B, LAMP1, or FasL expression. Rapid up-regulation of PD-1 on host CD8 T cells (median pre 5.6, median post 49.7, p = 0.005) was present. Non-statistically significant upregulation of PD-1 ligands occurred on leukemic blasts from 0-4 to 34-48 hours post infusion. Cytokine release profiles post infusion showed high IL-10 (median 862 pg/mL) with low IFNg (median < 1 pg/mL) and IL-6 (median 7 pg/mL) levels. One of five patients demonstrated a decrease in marrow blast counts post therapy (43% pre to 21% 4 weeks post infusion). No dose limiting toxicities or durable chimerism was seen. Conclusions: Haplo cellular infusions are well tolerated and show biological activity in relapsed AML.

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A meta-analysis of randomized clinical trials in acute promyelocytic leukemia (APL)

First Author: Francesco Lo Coco, University of Rome Tor Vergata, Rome, Italy

Background: All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have dramatically improved treatment outcomes in Acute Promyelocytic Leukemia (APL). To address the question regarding the most effective and safe regimen for 1st-line APL, a meta-analysis was performed following a systematic review of the clinical literature in APL. Methods: A systematic literature search on all published randomized controlled trials (RCT) in APL identified 17 papers. One additional publication was included in the initial discussion with a clinical expert. All trials compared were included if the study population included patients with APL, and was conducted since 1995. Results: The median follow-up was 4 years. Treatment arms comprised ATRA vs. ATRA plus arsenic trioxide (ATO), and chemotherapy (Chemo) regimens. Two trials (365/978, 17.3% each) and 817/817 patients were included. Results showed that event-free survival (EFS) at 4 years (yrs) vs. ATRA plus ATO and ATRA followed by ATO had a higher EFS at 4 yrs (95% CI 89.5-93.1), (t(22): 87% (77.2-94.3), p = 0.001). Relative risks (RR) were not statistically significant. Mean results showed that EFS at 7 yrs for ATRA plus ATO was associated with superior event-free survival (EFS) at 4 yrs (vs. ATRA plus ATO). The median time to progression (TTP) was 81 months, which was not reached, with 58% of patients still alive at a median survivor (PFS) of 7.4 yrs. Conclusions: Results suggest that regimens containing ATRA or IFRT appear to be associated with improved outcomes compared to those which include ATRA plus Chemo without ATO. Furthermore, the regimens which included ATO or RIF were not associated with increased toxicities.

Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia (CLL)

First Author: Nicholas James, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Fludarabine (F), cyclophosphamide (C), and multiple-dose rituximab (R) were evaluated in 65 patients previously untreated CLL. The FCR regimen consisted of 6-28 cycles of IV fludarabine (25 mg/m²/d) and cyclophosphamide (250 mg/m²/d) over 3 days. For cycle 1, rituximab was given at 375 mg/m² on day 1 and at 500 mg/m² on days 2-3. For cycles 2-6, rituximab was given at 500 mg/m² on days 1-3. Results were compared to a historical cohort treated with FCR. Results: The overall response rate to FCR3 was 97%. Forty-eight patients (75%) achieved CR, 10 (16%) achieved nPR, 4 (6%) achieved PR, and 2 (3%) did not respond to FCR3. Response rates were not significantly different from the historical FCR cohort. The median time to progression (TTP) for patients achieving CR, nPR, and PR was 86, 77, and 44 months, respectively (P = 0.14 for CR vs. nPR). MRD negativity by flow cytometry was achieved in 62% of patients. Median TTP was 81 months, which was similar to the median TTP of 84 months with FCR (P = 0.63). Median OS was not reached, with 58% of patients still alive at a median survivor (PFS) of 97.7 months. Of the 361 responders (70% of patients), 24 (6%) achieved CR, 38 (11%) achieved nPR and 14 (4%) achieved PR. Of the 361 responders (70% of patients), 24 (6%) achieved CR, 38 (11%) achieved nPR and 14 (4%) achieved PR. Of the 361 responders (70% of patients), 24 (6%) achieved CR, 38 (11%) achieved nPR and 14 (4%) achieved PR. Median OS for responders was 10.1 years (range 3.6-84 months). Conclusion: In patients with previously untreated CLL, FCR3 resulted in similar response rates, TTP and OS compared to a historical cohort of patients treated with FCR. FCR3 was associated with a significantly increased incidence of therapy-related MDS/AML, which warrants further evaluation.

Impact of unbalanced karyotypes at diagnosis on prognosis of CML

First Author: Ruediger Hehlmann, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

Background: Major route additional cytogenetic aberrations (ACA) at diagnosis of chronic myeloid leukemia (CML) indicate an increased risk of progression and shorter survival. Since all major route ACA are unbalanced it is unclear whether other unbalanced ACA at diagnosis also confer an unfavourable prognosis. Methods: On the basis of 1348 Philadelphia chromosome positive chronic phase patients of the randomized CML-study IV we examined the impact of unbalanced minor route ACA at diagnosis in comparison to major route ACA on prognosis. Results: At diagnosis, 1175 patients (87%) had a translocation t(9;22)(q34.11;q11) and 74 (5.5%) a variant translocation t(22); only, while a loss of the Y-chromosome (–Y) was present in addition in 44 (3.3%), balanced or unbalanced minor route ACA in 17 (1.3%) each. Patients with unbalanced minor route ACA achieved complete cytogenetic remission, major molecular remission, progression-free survival (PFS) and overall survival (OS) at similar rates as did patients with t(9;22), t(22), Y-, and balanced minor route karyotypes. In contrast, patients with major route ACA had a shorter OS and PFS than all other groups (p < 0.005 for all pairwise comparisons with major route). Five year survival probabilities were for t(9;22): 91.4% (95% CI 89.5 – 93.1), (t(22): 87% (77.2– 94.3), Y: 89.0% (76.7 – 97.0), balanced: 100%, unbalanced minor route ACA: 92.3% (72.4 – 100), major route: 52.2% (28.2 – 75.5). Conclusions: We conclude that only major route, but not unbalanced minor route ACA at diagnosis have a negative impact on prognosis of CML. This observation of the prognostic relevance of specific cytogenetic aberrations for a given malignancy may be of importance also to other cancers.

Safety and activity of blinatumomab for older patients (pts) with relapsed/refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) in two phase 2 studies

First Author: Hagop M. Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment options for older pts with R/R ALL are limited. Blinatumomab is a bispecific T-cell engager (BiTE) antibody construct that directs cytotoxic T-cells to CD19-expressing B-cells, and is approved in the US for treatment of Ph- R/R ALL. In two phase 2 adult studies of blinatumomab (Topp MS, et al. J Clin Oncol. 2014;32:4134-40; Topp MS, et al. Lancet Oncol. 2015;16:57-66), 69% and 43%, respectively, achieved complete response (CR) or CR with partial hematologic recovery (CRh*). We report pooled data for the combined subsets of older pts (≥ 65 yrs). Methods: Pts with R/R B-precursor ALL received open-label blinatumomab by continuous IV infusion (4 weeks on/2 weeks off). Pts achieving CR or CRh* after two cycles could receive three consolidation cycles. Response was assessed by bone marrow aspiration. CR required blasts ≤ 5%, ANC > 1000/μL and platelets > 100,000/μL. CRh* required blasts < 5%, ANC > 500/μL and platelets > 50,000/μL. Minimal residual disease (MRD) was detected by ASO-PCR of Ig heavy chain loci. Results: 36 older pts (median age 70 yrs, range 65-79) received multiple cycles of blinatumomab (range of 2 (1-6) cycles. 20 (56%) pts achieved best response of CR or CRh* within two cycles, including 14 (39%) CR and 6 (17%) CRh*. Among responders, 12 (60%) had complete MRD response and 4 other pts had detectable MRD but < 10⁴. With median follow-up of 18.2 months, median (range) relapse-free survival was 9.7 months (0.1-36 months). Of 7 fatal AEs, none were considered related to treatment. Conclusions: Older pts (≥ 65 yrs) with R/R ALL in two phase 2 studies of open-label blinatumomab achieved similar treatment responses and tolerability as pts in the overall study population. Clinical trial information: NCT01209286 and NCT01466179.
7044 Poster Session (Board #33), Sun, 8:00 AM-11:30 AM
Phase 1 study of CW232291 in relapsed/refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CW232291, a novel peptidomimetic small molecule identified via a phenotypic drug discovery screen, shows selective inhibitory activity at submicromolar levels on a Wnt gene reporter and decreases expression of the β-catenin target genes, cyclin D1 and survivin. It has broad anti-cancer efficacy in vitro, with significant preclinical tumor regression following standard cytotoxic AML treatment. Patients with relapsed AML or MDS were infused CW232291 iv over 5-30 minutes for 7 days in 21-day cycles until disease progression in a first in human, 3+3 dose-escalation, Phase 1 design. Results: Results to January 27, 2015 over a dose range 0.5-257 mg/m² in 56 patients (53 AML; 3 MDS) are available. Complete (≥ 10%) patients drug-related adverse events (AE) included nausea (43%), infusion-related reaction (36%), vomiting (29%), diarrhea (16%), and anorexia (11%). Toxicity was mostly ≤ grade 2 (91%), grade 3/4 events comprised 9%, observed similarly across all dose cohorts. Related serious AEs comprised fever, nausea, and anaphylactic reaction, at 19, 54 and 198 mg/m², respectively. Dose-limiting toxicity included nausea, rash and anaphylactic reaction (54, 153 and 198 mg/m², respectively). Toxicity was managed effectively with standard-of-care medications and, in the event of recurrence, could be mitigated with prophylaxis in subsequent cycles. Within 30 minutes CW232291 was completely converted to its active metabolite, CW232204. CW232204, maximum plasma concentration (Cmax) and area under the time-concentration curve (AUC) values were dose proportional. At the highest dose with data (153 mg/m²; n = 6), the mean terminal elimination half-life (t½) was 6.3 hrs, mean Cmax was 9922 ng/mL, and AUC was 6797 ng·h/mL. In the complete blood count, significant changes were seen at 153/118 mg/m², with normalization of neutrophil and platelet counts; maximum reduction from baseline in β-catenin and survivin expression were > 90% and 77%. No other objective responses were seen but higher doses showed significant reductions in these biomarkers. Conclusions: CW232291 single agent efficacy was observed in AML. MTD has not been defined; accrual is ongoing. Clinical trial information: NCT01398462.

7046 Poster Session (Board #35), Sun, 8:00 AM-11:30 AM
Survival of de novo and secondary acute promyelocytic leukemia: A propensity matched analysis of the Surveillance, Epidemiology and End Results database. First Author: Ranjan Pathak, Reading Health System, Wyomissing, PA

Background: Secondary acute promyelocytic leukemia (sAPL) is an uncommon entity with no prior large population-based studies. It is unclear whether there is any difference in the overall survival (OS) of sAPL and de novo APL. Methods: We used the Surveillance, Epidemiology, and End Results (SEER) 13 database and appropriate International Classification of Disease (ICDO-3) histology codes to identify adult patients with sAPL and de novo APL diagnosed between 1992 and 2011. Propensity matching was performed using the MatchIt package of R v2.15.2 to create a matched dataset of sAPL and de novoAPL. Kaplan Meier survival and multivariate analysis (Cox proportional hazard regression model) was performed using SPSS v22.0. Results: sAPL (n = 109) accounted for 5.5% of all APL cases (n = 1964). Crude incidence of sAPL was 0.85 per 10,000 primary malignancies. Patients with sAPL, compared to de novo APL, were more likely to be older (65 vs. 44 years, p < 0.001), White (85% vs. 79%, p = 0.003) and diagnosed after year 2005 (53% vs. 40%, p = 0.008). The two subgroups did not differ by gender (p = 0.665) and marital status (p = 0.745). Mortality rate within 1 month of diagnosis was similar between sAPL and de novo APL (28.9% vs. 23.0%, p = 0.20). One-year (55% vs. 57%, p = 0.70); two-year (51% vs. 54%, p = 0.79) and five-year (42% vs. 50%, p = 0.24) OS rates were similar. In a multivariate analysis, sAPL was not associated with worse OS compared to de novo APL (HR 1.11; 95% CI 0.78-1.58; p = 0.546). OS was worse with older age at diagnosis but better in more recent years. Compared to patients < 55 years, patients 55-70 years (HR 1.86, 95% CI 1.02-3.41, p = 0.043) and > 70 years (HR 4.64, 95% CI 2.54-8.46, p = 0.001) were more likely to have worse OS. Compared to patients diagnosed before 1995, OS was better among patients diagnosed in the recent years (HR after 2005, 2005, 0.37, 95% CI 0.17-0.80, p = 0.012). Conclusions: This is the largest population-based study utilizing propensity matched analysis that demonstrates similar OS in sAPL and de novo APL. This indicates that the patients with sAPL can be managed very similarly to de novo APL and do not need to be excluded from clinical trials of APL.

7047 Poster Session (Board #36), Sun, 8:00 AM-11:30 AM
Four-year minimum follow-up of ongoing patients (pts) with chronic-phase chronic myeloid leukemia (CP-CML) in a phase 1 trial of ponatinib (PON). First Author: Moshe Talpaz, University of Michigan, Ann Arbor, MI

Background: PON, an approved oral tyrosine kinase inhibitor (TKI), has potent activity against native BCR-ABL and resistant mutants, including T315I. A phase 1 trial evaluated PON safety and antileukemic activity; this analysis includes 4-year minimum follow-up of ongoing CP-CML pts enrolled in the phase 1 study of PON-treated pts to date. Methods: Pts (N = 81) with resistant/refractory hematologic malignancies received PON (2–60 mg qd) in this ongoing, open-label, dose-escalation trial (NCT00669020; enrollments 2008–2011; data cutoff, 26 Sep 2014). The median follow-up for 43 CP-CML pts was 49.9 months (range 25–117). The most common treatment-emergent AEs were rash (66%), fatigue (60%), abdominal pain (58%), headache (58%), and arthralgia (53%). Arterial occlusive event (AE/serious AE) rates were 40%/30%, including peripheral vascular (21%/14%), cerebrovascular (7%/5%), and peripheral vascular (14%/9%); venous thromboembolic event rates were 5%/0%. Conclusions: Patients treated with nilotinib exhibited a higher amount of plaques although at a lower CVR score. These data could suggest that patients treated with nilotinib likely develop arterial lesions rather than a systemic arteriosclerotic process. Subclinical cardiovascular biomarkers could provide more targeting options for the personalized follow-up of patients treated with nilotinib. However, these preliminary data need to be confirmed in a larger longitudinal study. Clinical trial information: NCT02161978.
7048 Poster Session (Board #37), Sun, 8:00 AM-11:30 AM
Safety and feasibility of anticoagulation prophylaxis with enoxaparin in acute lymphoblastic leukemia during asparaginase-based intensification therapy. First Author: Hanan Abdulmaoula Sibai, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Venous thromboembolism (VTE) is a well-known complication in adults receiving asparaginase (ASP) for acute lymphoblastic leukemia (ALL). We previously reported 27.3% VTE rate in patients (pts) receiving a modified Dana Farber Cancer Institute (DFCI) intensification phase. Low-dose enoxaparin (ENOX) was not associated with lower rate of VTE. We describe the escalated dose of ENOX in adults treated with this protocol.

Methods: 38 pts with ALL treated with a weekly ASP-based modified DFCI intensification for 21-30 weeks, received ENOX 1 mg/kg subcutaneously daily (adjusted-dose group). The result was compared with a similar group of 41 pts receiving ENOX 40 mg for pts weighing <80 kg, or 60 mg for pts ≥ 80 kg (adjusted-dose group). A total of 19 pts treated with the same protocol, without prophylaxis. Results: There was no significant difference among groups with respect to median age, weight and number of cycles. The actual mean dose of ENOX in the low-dose group was 0.62 mg/kg, as compared to 0.84 mg/kg in the adjusted-dose group. No major bleeding complications were observed. Minor bleeding rate was 5.5% VTE rate in the entire cohort was 22.7%. VTE rate in pts receiving adjusted dose ENOX was 18%, as compared to 26.8% in the low-dose group. There was no significant difference in the VTE rate according to age or gender. Sites of VTE in the prophylaxis groups included lower extremity (9), sagittal sinus (3), central line related (5) and pulmonary embolism (8); some pts had ≥ 1 site. Conclusions: Prophylactic ENOX during intensification in adults with ALL was safe: despite dose increase to 1 mg/kg, no increase in bleeding events was observed. There was trend toward a lower rate of VTE with 1 mg/kg ENOX, particularly in patients weighing ≥ 80 kg; however, a larger cohort is needed to test if the difference is significant.

7049 Poster Session (Board #38), Sun, 8:00 AM-11:30 AM
Elevated blood pressure (BP) and adverse events (AEs) of hypertension (HTN) in panobinostat (PON) leukemia trials. First Author: Hanna Jean Khoury, Winship Cancer Institute of Emory University, Atlanta, GA

Background: PON is a potent, multitargeted tyrosine kinase inhibitor with proven efficacy in resistant Ph+ leukemia. This analysis reports elevated BP and AEs of HTN in PON leukemia trials. Methods: PON safety and efficacy were evaluated in patients (pts) with relapsed/refractory hematologic malignancies in the ongoing phase (ph) 1 trial, in heavily pretreated CML/Ph + ALL pts in the ongoing PACE (ph) 2 trial, and in newly diagnosed CP-CML pts in the terminated EPIC (ph) 3 trial vs imatinib (IM). Ph 1 and EPIC, but not PACE, excluded pts with uncontrolled HTN (untreated systolic/diastolic ≥ 150/100 mm Hg in ph 1, > 140/> 90 mm Hg in EPIC). Elevated BP was defined by single highest measurement (systolic/diastolic): grade (G) 1/pre-HTN 120–129/80–89, G 2 ≥ 140/> 90 mm Hg in EPIC. Any increase in BP grade from baseline was also frequent: 74% in ph 1; 68% in PACE; 68% PON vs 51% IM in EPIC. In PACE, estimated systolic/ diastolic BP increases over time were low: 2.3/0.7 mm Hg. HTN AEs were reported in 38%, 28%, 18%, and 2% of ph 1, PACE, EPIC-PON, and EPIC-IM pts, respectively. Hypertensive crisis was reported in 2 PACE and 2 EPIC-PON pts. HTN AEs did not lead to discontinuation or death. Few pts had dose modifications for HTN AEs (0% ph1; 5% PACE; 3% EPIC-PON; 0% EPIC-IM). A retrospective multivariate analysis of pooled pts showed HTN AEs were significantly associated with PON dose intensity. HTN AEs rarely led to change in therapy. Given BP variability, AE reporting may be a more reliable indicator of clinically meaningful HTN. Clinical trial information: NCT00669592; NCT01207440; NCT01656805.

7050 Poster Session (Board #39), Sun, 8:00 AM-11:30 AM
Phase I trial of α-particle therapy with actinium-225 (225Ac)-lintuzumab (anti-CD33) and low-dose cytarabine (LDAC) in older patients with untreated acute myeloid leukemia (AML). First Author: Joseph G. Jurcic, Columbia University Medical Center, New York, NY

Background: 225Ac-lintuzumab consists of a radiometal that emits 4.6 MeV α-particles and a backbone of an anti-CD33 monoclonal antibody. We are conducting a multicenter, phase I trial to determine the maximum tolerated dose (MTD), safety and feasibility of anticoagulation prophylaxis with enoxaparin in adults receiving asparaginase (ASP) for acute lymphoblastic leukemia (ALL). We previously reported 27.3% VTE rate in patients (pts) receiving a modified Dana Farber Cancer Institute (DFCI) intensification phase. Low-dose enoxaparin (ENOX) was not associated with lower rate of VTE. We describe the escalated dose of ENOX in adults treated with this protocol.

Methods: 38 pts with ALL treated with a weekly ASP-based modified DFCI intensification for 21-30 weeks, received ENOX 1 mg/kg subcutaneously daily (adjusted-dose group). The result was compared with a similar group of 41 pts receiving ENOX 40 mg for pts weighing <80 kg, or 60 mg for pts ≥ 80 kg (adjusted-dose group). A total of 19 pts treated with the same protocol, without prophylaxis. Results: There was no significant difference among groups with respect to median age, weight and number of cycles. The actual mean dose of ENOX in the low-dose group was 0.62 mg/kg, as compared to 0.84 mg/kg in the adjusted-dose group. No major bleeding complications were observed. Minor bleeding rate was 5.5% VTE rate in the entire cohort was 22.7%. VTE rate in pts receiving adjusted dose ENOX was 18%, as compared to 26.8% in the low-dose group. There was no significant difference in the VTE rate according to age or gender. Sites of VTE in the prophylaxis groups included lower extremity (9), sagittal sinus (3), central line related (5) and pulmonary embolism (8); some pts had ≥ 1 site. Conclusions: Prophylactic ENOX during intensification in adults with ALL was safe: despite dose increase to 1 mg/kg, no increase in bleeding events was observed. There was trend toward a lower rate of VTE with 1 mg/kg ENOX, particularly in patients weighing ≥ 80 kg; however, a larger cohort is needed to test if the difference is significant.

7051 Poster Session (Board #40), Sun, 8:00 AM-11:30 AM
Re-exposure to blinatumomab after CD19-positive relapse: Experience from three trials in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R ALL). First Author: Max S. Topp, Medizinische Klinik und Poliklinik II, Universitätshäppen, Würzburg, Germany

Background: Blinatumomab is a bispecific T-cell engager antibody construct designed to link cytotoxic T cells and CD19-positive B cells, inducing tumor cell lysis. In this combined analysis, we evaluated outcomes for patients with R/R ALL enrolled in 3 open-label phase 2 studies (NCT01471782 [study 205], NCT01209286 [study 206], NCT01466179 [study 211]) who received retreatment with blinatumomab following hematologic relapse after initial blinatumomab response. Methods: Patients were < 18 (205) or ≥ 18 (206 and 211) years of age with Ph- R/R B-precursor ALL. Blinatumomab was dosed by continuous IV infusion. A cycle was 4 weeks. The primary endpoint was hematological remission within 2 cycles. Patients with relapse following a response of ≥ 3 months duration could receive up to 3 cycles of retreatment; patients with GVHD or CNS involvement were ineligible. Results: Eleven patients received retreatment with blinatumomab (205, n = 2; 206, n = 5; 211, n = 4). Seven (64%) were male; mean (range) age was 31 (4, 77). At time of initial treatment, 9 (81%) had ≥ 1 line of prior salvage chemotherapy; 7 (64%) had prior HSCT. Among 10 patients who achieved hematological remission during the 2 cycles of initial treatment, the median (range) duration of response prior to relapse was 9 (3-11) mo. Five (45%) patients had HSCT between first blinatumomab response and relapse. Outcomes during retreatment are shown in the one table. Patients were retreated a second time and obtained a CR. Eleven patients (204) with Ph+ R/R ALL (n = 4) had improved following allogeneic HSCT and were considered for second line blinatumomab response. Overall, rates of adverse events occurring during retreatment were similar to those observed in the full studies. Clinical trial information: NCT01471782, NCT01209286, NCT01466179.

Retreated Patients (n = 11)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) duration of treatment, days</td>
<td>28 (4-85)</td>
</tr>
<tr>
<td>Hematological remission (responders)</td>
<td>4 (35%)</td>
</tr>
</tbody>
</table>

1 Minimal residual disease (MRD) responses among responders (n=4)

Complete response MRD < 10^-4 4 (100%)

Patients with any AEs Grade ≥ 3 Cytokine release syndrome Neurologic AEs 8 (73%)

0 (0%) 5 (45%)

1 © 5% marrow blasts and full, partial, or incomplete recovery of peripheral blood counts.
A multidrug resistant engineered CAR T cell for allogeneic combination immunotherapy. First Author: Julien Valton, Collectics SA, Paris, France

Background: The adoptive transfer of CAR T cell represents a highly promising strategy to fight against multiple cancers. The clinical outcome of such therapies is intimately linked to the ability of effector cells to engraft, proliferate and specifically kill tumor cells within patients. When allogeneic CAR T cell infusion on days 1–7. Patients younger than 60 received consolidation therapy with high dose cytarabine along with ODSH. Growth factors were not used during induction. Primary endpoints were safety and tolerability of ODSH, and its effect on platelet count recovery. Secondary endpoints included the effect of ODSH on complete remission (CR) rate. The effect of ODSH on CXCL12/CXCR4 axis in vitro at concentrations achievable in vivo. Conclusions: ODSH is well tolerated when combined with intensive therapy for AML. It may enhance count recovery and treatment efficacy. Further study of this strategy is justified. Clinical trial information: NCT02056782.

Allogeneic hematopoietic cell transplant (HCT) in patients (pts) ≥ 60 years of age with first relapsed or refractory acute myeloid leukemia (R/R AML) after treatment with vosaroxin plus cytarabine (vos/cyt) vs placebo plus cytarabine (pla/cyt): Results from VALOR. First Author: Gary J. Schiller, UCLA, Los Angeles, CA

Background: Increasing numbers of older pts with AML receive HCT due to wider donor availability and improvements in supportive care that reduce transplant-related morbidity/mortality. VALOR, a large phase 3 trial of vos/cyt vs pla/cyt in pts with R/R AML (NCT01191801), provided the opportunity to assess outcomes of HCT in pts ≥ 60 receiving R/R AML. Methods: Pts were randomized 1:1 to receive cyt (1 g/m² IV over 2 hr, d 1-5) plus either vos (90 mg/m² IV over 10 min, d 1 and 4; 70 mg/m² in subsequent cycles) or placebo. In this posthoc subgroup analysis, we assessed complete remission (CR) rates prior to HCT, posttreatment HCT rates, HCT outcomes, and overall survival (OS) by treatment arm in R/R AML pts ≥ 60 y/o. Results: Overall, 451 pts ≥ 60 y/o received vos/cyt (n = 226) or pla/cyt (n = 225). Posttreatment HCTs were performed in 47 (20.8%) pts on vos/cyt and 44 (19.6%) pts on pla/cyt. Of the 91 HCT pts, 27 had achieved CR after vos/cyt vs 16 after pla/cyt. An additional 7 pts (vos/cyt) and 6 pts (pla/cyt) received subsequent therapy and went on to achieve CR, resulting in totals of 34 vos/cyt vs 22 pla/cyt pts who achieved CR prior to transplant. Median OS for pts who underwent posttreatment HCT on the vos/cyt arm was 20.2 mo vs 12.2 mo on the pla/cyt arm (HR 0.699; one sided P = 0.088). There were no clinically meaningful differences in complications associated with HCT (including graft-vs-host and veno-occlusive disease), 100-day mortality, or achievement of engraftment. Conclusions: While HCT rates were comparable between treatment arms in this older R/R AML population, higher pre-transplant CR rates in the vos/cyt arm enabled more pts ≥ 60 y/o to undergo transplant while in CR as compared to the pla/cyt arm. With median OS lengthened by 8 months, a trend toward an OS benefit was observed for vos/cyt-treated pts. Additional follow-up is being conducted to further assess the impact of vos/cyt treatment on posttreatment HCT. Clinical trial information: NCT01191801.
Cardiovascular events in patients with chronic myelogenous leukemia treated with tyrosine kinase inhibitors: A systematic review and meta-analysis. First Author: Anju Chana, Department of Medicine, SUNY-UB School of Medicine, Buffalo, NY

Background: Outcomes of standard induction chemotherapy in older patients (pts) ≥ 60 years old with acute myeloid leukemia (AML) are significantly affected by medical co-morbidities and performance status. The pooled risk ratio (RR) with 95% CIs was calculated using a Mantel-Haenszel random-effects model to compare the effect between nilotinib and imatinib. Results: Here, we evaluated the pooled estimates of the incidence of cardiovascular events in CML patients treated with TKIs. The pooled proportion associated with non-intensive TKI therapy for patients, patients who received imatinib and dasatinib had less cardiovascular events, whereas the incidence was greater among patients receiving nilotinib, ponatinib and bosutinib.

7057 Poster Session (Board #46), Sun, 8:00 AM-11:30 AM
Factors influencing outcomes in patients (Pts) with relapsed/refractory b-precursor acute lymphoblastic leukemia (t/r ALL) treated with blinatumomab in a phase 2 study. First Author: Hagop Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Blinatumomab, a bispecific T-cell engager (BiTE) antibody construct, showed efficacy in t/r ALL in a large phase 2 study (Topp et al. Lancet Oncol 2015;16:57-5). We evaluated associations of baseline characteristics and outcome with BiTE responses. Methods: Pts (n = 388) with t/r ALL were included. We assessed differences in baseline characteristics between Pts with and without a BLAST response. Results: Of 388 pts treated with BiTE/MoAbs within 2 cycles. Median (95% CI) RFS was 5.9 (4.8, 7.3) months. ECOG was significantly associated with OS (p = 0.039) with a life expectancy of 81 (43%) of 189 pts treated with CR/CRh; higher platelet count and lower LDH were associated with longer OS (Table). Conclusions: Blinatumomab has anti-leukemia activity in pts with t/r ALL, including pts with poor prognostic factors. Low baseline BMB count had the strongest association with response, supporting early blinatumomab administration. For pts with higher tumor burden, cytotherapy/higher doses may be options. Clinical trial registration: NCT01461772.
7060 Poster Session (Board #49), Sun, 8:00 AM-11:30 AM

Association between early promoter methylation changes and outcome in older acute myeloid leukemia patients treated on SWOG S0703 (NCT0065884), First Author: Sucha Nand, Loyola Univ Cancer Ctr, Maywood, IL

Background: Treatment of acute myeloid leukemia (AML) in older patients remains a therapeutic challenge. Current treatment options range from supportive care alone to full-dose chemotherapy. Identifying factors that predict response to therapy may help increase efficacy and avoid toxicity.

Methods: The phase II SWOG S0703 study investigated the use of hydroxyurea and azacitidine in gentuzumab ozogamicin in the elderly AML population. This regimen appeared to have efficacy similar to the standard AML regimens, with less toxicity in the poor risk population. Here we report the laboratory findings of samples accrued as part of this study.

Global DNA methylation, promoter DNA methylation of six candidate genes (CDKN2A, CDKN2B, HIC1, RARB, CDH1 and APAF1), and expression analysis of these same genes were determined at several time points before and during therapy.

Results: The goal of this study was to investigate whether DNA methylation or gene expression changes predict clinical response. Global DNA methylation was not associated with a clinical response. Samples from days 3 or 4 of treatment showed significantly decreased CDKN2A promoter DNA methylation in patients achieving complete remission (CR) compared to those who failed to achieve CR. Samples from day 7 of treatment showed significantly decreased RARB, CDKN2B and CDH1 promoter DNA methylation in patients achieving CR and complete remission with incomplete blood count recovery (CRi) compared to those who failed to achieve CR. Of the genes assessed in this study, there was a significant negative correlation (R² = −0.47) between APAF1 promoter methylation and APAF1 gene expression between pre-study and day 3 or 4 samples among patients who later went on to achieve CR.

Conclusions: These findings offer a potentially important early insight that may inform clinicians about the likelihood of success with demethylating agents in the treatment of older patients with AML. Such information may help to decrease toxicity and improve therapeutic efficacy in these patients.

Support: NIH/NCI/NCTN CA180888, CA180819 and in part by Celgene Corporation and Pfizer, Inc.

7061 Poster Session (Board #50), Sun, 8:00 AM-11:30 AM

Azacitidine in older patients with acute myeloid leukemia (AML). Results from the ALMA study according to the MRC risk index score. First Author: Jose Palantes, Hospital Universitario Virgen del Rocio, Sevilla, Spain

Background: Treatment of patients (pts) >60y with AML remains challenging. The MRC and LRF validated a 1y survival risk index score in 2843 older AML pts treated with intensive (IC) and non-intensive (NI) chemotherapy, identifying 3 groups with different risk estimates1. Azacitidine (AZA) prolonged OS in older AML pts vs. conventional care (AZA-AML-001 trial)2. Nevertheless, comparison between AZA and IC was jeopardized by the low number of subjects randomized to AZA or IC. Aim: To assess the impact of AZA in a retrospective cohort of older AML pts, unfit for IC, stratified by the MRC/LRF risk score.

Methods: The ALMA cohort accrued 110 unfit AML pts who received compassionate front-line AZA before 2011 in 22 Spanish sites (Ramos F et al, Leuk Res. 2014). Cytophenetic, age, white blood count (WBC), PS and AML type categorized pts as good, standard and poor-risk, as stated by Wheateley’s score. Results: Characteristics of the ALMA cohort and distribution across MRC/LRF risk categories are shown in Table 1. After accounting for the above 5 parameters, the ALMA cohort included more poor-risk pts than the MRC/LRF series (63% vs. 31%/37% in the AML11/AML14 trials, respectively). After 28 months median follow-up, 1y survival of ALMA cohort was 66%, 40% and 31%, respectively, for the good, standard and poor-risk groups. Comparison of these estimates with those of MRC/LRF trials are also shown in Table 1. Potentially relevant clinical differences are apparent in the poor-risk group when comparing AZA to either approach.

Conclusions: Although retrospective and non-randomized, AZA pts unfit for IC seemed to benefit from AZA to a similar extent to IC. Moreover, in the poor-risk subset (n~70), 1y survival with AZA was equivalent and likely superior to previous AML/MRC strategies.

ALMA cohort.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>75 (56-89)</td>
</tr>
<tr>
<td>PS</td>
<td>0.1 (27-2)</td>
</tr>
<tr>
<td>WBC (&lt;10×10⁹/L)</td>
<td>79 (72)</td>
</tr>
<tr>
<td>Therapy-related AML &amp; AHOD</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>MRC cytogenetics</td>
<td>37 (34.5%)</td>
</tr>
<tr>
<td>Risk categories (AML11 risk)</td>
<td>26 (23.6%)</td>
</tr>
<tr>
<td>1y survival estimates (%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>73 (6.4)</td>
</tr>
<tr>
<td>Standard</td>
<td>60 (5)</td>
</tr>
<tr>
<td>Poor</td>
<td>30 (25)</td>
</tr>
</tbody>
</table>

1: The phase II SWOG S0703 study investigated the use of hydroxyurea and azacitidine in gentuzumab ozogamicin in the elderly AML population. This regimen appeared to have efficacy similar to the standard AML regimens, with less toxicity in the poor risk population. Here we report the laboratory findings of samples accrued as part of this study. Global DNA methylation, promoter DNA methylation of six candidate genes (CDKN2A, CDKN2B, HIC1, RARB, CDH1 and APAF1), and expression analysis of these same genes were determined at several time points before and during therapy. Results: The goal of this study was to investigate whether DNA methylation or gene expression changes predict clinical response. Global DNA methylation was not associated with a clinical response. Samples from days 3 or 4 of treatment showed significantly decreased CDKN2A promoter DNA methylation in patients achieving complete remission (CR) compared to those who failed to achieve CR. Samples from day 7 of treatment showed significantly decreased RARB, CDKN2B and CDH1 promoter DNA methylation in patients achieving CR and complete remission with incomplete blood count recovery (CRi) compared to those who failed to achieve CR. Of the genes assessed in this study, there was a significant negative correlation (R² = −0.47) between APAF1 promoter methylation and APAF1 gene expression between pre-study and day 3 or 4 samples among patients who later went on to achieve CR. CRi.

Conclusions: These findings offer a potentially important early insight that may inform clinicians about the likelihood of success with demethylating agents in the treatment of older patients with AML. Such information may help to decrease toxicity and improve therapeutic efficacy in these patients. Support: NIH/NCI/NCTN CA180888, CA180819 and in part by Celgene Corporation and Pfizer, Inc.

7062 Poster Session (Board #51), Sun, 8:00 AM-11:30 AM

An alvocidib-containing regimen is highly effective in AML patients through a mechanism dependent on MCL1 expression and function. First Author: B. Douglas Smith, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Through multiple Phase I/II studies, alvocidib (flavopiridol) has proven to be highly effective in both frontline and relapsed/refractory AML when sequentially administered before ara-C and mitoxantrone (FLAM). In frontline patients, FLAM resulted in a complete remission (CR) among 70% of patients with secondary (s)AML, FLAM produced 60% CR versus 35% CR in poor-risk sAML, and expression of these same genes were determined at several time points before and during therapy. Results: The goal of this study was to investigate whether DNA methylation or gene expression changes predict clinical response. Global DNA methylation was not associated with a clinical response. Samples from days 3 or 4 of treatment showed significantly decreased CDKN2A promoter DNA methylation in patients achieving complete remission (CR) compared to those who failed to achieve CR. Samples from day 7 of treatment showed significantly decreased RARB, CDKN2B and CDH1 promoter DNA methylation in patients achieving CR and complete remission with incomplete blood count recovery (CRi) compared to those who failed to achieve CR. Of the genes assessed in this study, there was a significant negative correlation (R² = −0.47) between APAF1 promoter methylation and APAF1 gene expression between pre-study and day 3 or 4 samples among patients who later went on to achieve CR. CRi.

Conclusions: These findings offer a potentially important early insight that may inform clinicians about the likelihood of success with demethylating agents in the treatment of older patients with AML. Such information may help to decrease toxicity and improve therapeutic efficacy in these patients. Support: NIH/NCI/NCTN CA180888, CA180819 and in part by Celgene Corporation and Pfizer, Inc.

7063 Poster Session (Board #52), Sun, 8:00 AM-11:30 AM

Ethnic differences in survival of elderly chronic myeloid leukemia patients in pre- and post-imatinib era in the United States. First Author: Dinesh Upreti, Abington Memorial Hospital, Abington, PA

Background: Survival of chronic myeloid leukemia (CML) has improved since FDA approval of imatinib in May 2001. However, there is limited data on survival pattern of elderly patients. We conducted this study to evaluate ethnic differences in survival of elderly CML patients.

Methods: We selected elderly CML patients (>65 years) from the Surveillance, Epidemiology, and End Results (SEER) 18 database. We analyzed one- and five-year relative survival (RS) rates of CML patients by ethnicity during pre-imatinib (1990-2000) and post-imatinib (2001-2006) time periods. We used Z-test to compare survival rates. Results: The database comprised of 5,802 patients. Among them, 3,183 were males and 2,619 were females. Likewise, 5,073 were Caucasians and 394 were African Americans. The median age at diagnosis was 76 years. The median follow up period was 18 months (range: 1 to 60 months). The RS of the patients improved significantly in post-imatinib era as compared to pre-imatinib era (1 year: 65.6 ± 0.9 vs 59.2 ± 1.0, Z score = 4.93; 5 year: 34.6 ± 1.1 vs 22.2 ± 0.9, Z score = 8.45). Survival rates of Caucasians improved significantly (1 year: 59.2 ± 1.1 vs 65.6 ± 1.0, Z score = 4.49; 5 year: 22.3 ± 1.0 vs 34.3 ± 1.1, Z score = 7.59) but there was no significant improvement in survival for African Americans (1 year: 58.8 ± 3.8 vs 61.1 ± 3.7, Z score = 0.49; 5 year: 21.1 ± 3.5 vs 31.1 ± 4.0, Z score = 1.61). There was no difference in survival rates of African Americans compared to Caucasians in post-imatinib era. Conclusions: Survival rates of elderly CML patients have improved significantly in post-imatinib era. This improvement in survival rates is limited to Caucasians.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Combined NPM1-+FLT3- is associated with a favorable prognosis in adults with AML, treated with standard chemotherapy. The impact of this on outcome is however not well defined according to age and different treatment modalities, including chemotherapy with or without hematopoietic cell transplantation (HCT), and hypomethylating agents (HMA). Methods: Out of 620 newly diagnosed AML pts treated between 2007 and 2014, 169 with intermediate risk cytogenetics and known NPM1/FLT3 were analyzed. Results: Estimated 3-yr overall survival (OS) according to age, NPM1/FLT3 status, and treatments are shown in the table. Among adults and elderly treated with chemotherapy alone, those with NPM1-+FLT3- had a superior OS compared to those without this mutational status (P=0.004 and 0.0008, respectively). Adults without NPM1-+FLT3- had a significantly improved OS when treated with HCT in addition to chemotherapy (P=0.0001), and a comparable OS to those with NPM1-+FLT3+ (P=0.43), when treated with chemotherapy alone. Similarly, elderly without NPM1-+FLT3- had a superior OS when treated with chemotherapy followed by HCT (P=0.028), and a comparable OS to those with NPM1-+FLT3- (P=0.83), when treated with chemotherapy alone. Among elderly pts without NPM1-+FLT3-, those treated with HMA alone (n=12) had a similar OS to those treated with chemotherapy without HCT (P=0.86). Conclusions: Combined NPM1-+FLT3- is associated with a favorable prognosis, irrespective of age, in newly diagnosed AML pts with intermediate risk cytogenetics, treated with chemotherapy. In pts without NPM1-+FLT3-, the OS improves with the addition of HCT to standard chemotherapy, irrespective of age. HMA seems to be comparable to chemotherapy alone in elderly pts without NPM1-+FLT3-.

<table>
<thead>
<tr>
<th>Estimated 3-yr OS</th>
<th>55%</th>
<th>95% CI</th>
<th>30%</th>
<th>16%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1-+FLT3-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (18-60 yrs.)</td>
<td>50%</td>
<td>0.005</td>
<td>0.20</td>
<td>0.64</td>
<td>0.16</td>
</tr>
<tr>
<td>Elderly (&gt;60 yrs.)</td>
<td>60%</td>
<td></td>
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</table>

**Other treatments: N=21**

7066 Poster Session (Board #55), Sun, 8:00 AM-11:30 AM

**Digital Fusion-Gene expression profiling in acute leukemia (AL): Clinical validation of throughput molecular technology in laboratory medicine.**

**Background:** AL is a heterogenous and aggressive disease with dismal prognosis. Chromosomal translocations constitute the basis of current WHO classification and are central to AL pathogenesis. FISH technique is utilized to detect variable translocations for patient prognosis and therapy selection. It is a laborious and expensive technique, which may not support rapidly expanding scope of additional translocations of clinical importance. Hence, throughput automation technologies that play a critical in the management of AL patients. Methods: Nanostring platform utilizes a novel digital color-coded automated technology that is based on direct multiplexed measurement of gene expression. The “tCounter Leukemia Fusion Gene Expression Assay Kit” allows profiling a comprehensive set of 25 fusion genes that result from balanced translocations in AL. It also includes probes for 12 clinically proven AL-related biomarkers. RNA extracted from FFPE tissue from 50 AL patients with known balanced chromosomal translocations and validated the fusion gene expression on this platform. Results: We observed highly significant concordance between Nanostring fusion gene results with FISH data in various translocation such as t(9;22) (BCR-ABL); t(15;17) (PML-RARA); t(8;21) (AML-ETO); t(4;11) (MLL-AF4) and Inv(16) (CBFB-MYH11) (P<0.05). Nanostring technology failed to validate fusion gene transcript in patients with t(12;21) (TEL-AML). High expression of BAALC, a prognostic biomarker associated with poor outcome in AL patients was noted in t(9;22) (58%), t(15;17) (12%), t(4;11) (50%), t(12, 21) (20%), (t8;21) (20% ) and Inv(16) (63%). Conclusions: We have validated the application of automated throughput technology for AL patients in a clinical laboratory. Our study provides an efficient, viable and economical solution for the rapidly expanding molecular repertoire of laboratory testing for AL patients, which is critical to determine prognosis and select effective therapy. This approach also provides a promise to seamlessly incorporate newly discovered (up to 800) targets of diagnostic and prognostic importance on this digital platform.

7067 Poster Session (Board #56), Sun, 8:00 AM-11:30 AM

**Construction and characterization of novel CD33/CD3 tandem diabodies (TandAbs) for the treatment of acute myeloid leukemia (AML).**

**Background:** CD33 has been validated as an AML target in randomized studies of the antibody-drug conjugate, gemtuzumab ozogamicin (GO) in a subset of patients, but currently explored CD33-targeted therapeutics are ineffective in many patients. Here, we explored the potential therapeutic activity in AML of a series of novel CD33/CD3-directed tandem diabodies (TandAbs). These tetravalent bispecific antibodies comprised of single chain antibody variable fragments (scFv) have avidity due to two binding sites for each antigen and attractive pharmacokinetics due to a molecular size that is larger than the renal clearance threshold. Methods: CD33/CD3 TandAbs were generated from humanant-CD33 and anti-CD3 scFv domains and expressed in CHO cells. Binding affinities of purified TandAbs were determined via flow cytometry. T-cell activation was assessed via quantitation of CD25 and CD69 on T-cells. Cytotoxic properties of TandAbs were determined in 48-hour assays in the presence of healthy donor T-cells. TandAbs were generated from humananti-CD33 and anti-CD3 scFv domains and expressed in CHO cells. Binding affinities of purified TandAbs were determined via flow cytometry. T-cell activation was assessed via quantitation of CD25 and CD69 on T-cells. Cytotoxic properties of TandAbs against CD33+ AML cell lines and primary specimens from adults with AML, selected across the entire cytogenetic/molecular disease spectrum, were determined in 48-hour assays in the presence of healthy donor T-cells. Results: Our studies demonstrated that CD33/CD3 TandAbs induced potent cytolyisis of CD33+ AML cell lines and patient-derived AML specimens at pM concentrations. Their cytotoxic effect required the presence of T-cells and was quantitatively dependent on the concentration of the TandAb as well as the effector-to-target (E:T) cell ratio. In a series of 29 primary AML specimens, high-affinity CD33/CD3-directed TandAbs were broadly active in vitro, even in leukemias with low CD33 expression, with similar activity profiles in specimens from patients with newly diagnosed AML and those with relapsed or refractory disease. Conclusions: CD33/CD3 TandAbs have potent and selective cytotoxicity for CD33+ AML cells that is independent of disease stage. Our findings identified several TandAbs that merit further study as targeted AML therapeutics.
7068 Poster Session (Board #57), Sun, 8:00 AM-11:30 AM
Long-term bosutinib (BOS) for Philadelphia Chromosome–Positive (Ph+) advanced (ADV) chronic myeloid leukemia (CML) after prior tyrosine kinase inhibitor (TKI) failure.
First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy
Background: ADV Ph + CML pts have worse outcomes vs chronic CML pts. In this first report of BOS activity in this cohort as fully enrolled, we evaluate long-term efficacy and safety of BOS in ADV pts as vs y1 from last enrolled pt.
Methods: Ongoing phase 1/2 BOS study in 79 accelerated (AP) and 64 blast phase (BP) pts with prior TKI failure.
- For AP and BP pts, 18% and 3% remained on BOS at y4 (vs 48%, 13% at y1; y1 – 48 wk), 57% and 28% newly attained or maintained overall hematologic response (ORR; y1 > 12 mo; 40% and 37% attained/maintained major cytogenetic response (MCyR) by 4 y (most by 12 mo).
- Kaplan-Meier (KM) probabilities of MNR, MMR, and CCyR were calculated; des 3 doses (120 mg-250 mg BID) for 7 days on/7 days off (7on/7off).
- Most common AEs occurred gastrointestinal (AP, 96%; BP, 83%), primarily diarrhea (85%; 64%), which was typically low grade (grade 1/2: 96%; 93%), transient (median duration-lymph grade AE: 2 range, [1–9] d); 2 (1–211) d; no pt discontinued due to this AE.
- Newly occurring AEs arose mostly in y1; new cardiac/vascular AEs occurring in y4 were pericardial effusion, sinus bradycardia/1st degree atrioventricular block (same pt), and hypertension (n = 1); those in y1 (+2 pts either cohort) were pericardial effusion (AP, n = 4; BP, n = 1), tachycardia (n = 2; n = 4), hypertension (n = 3; n = 2; Table). Serious AEs occurred in 56% AP and 58% BP pts, most commonly pneumonia (n = 9–11; AP, 7 + BP, 13) and BP pts died within 30 d of last dose; 2 BOS-related (AP, 1/24 morphologic discontinuations were mostly due to PD (AP, 6/0) and AEs in AP (n = 25); 13 BP pts died within 30 d of last dose; 2 BOS-related (AP).

Conclusions: Durable response was seen in ~50% AP responders (~25% NCT01451437.
Long-term bosutinib (BOS) for Philadelphia Chromosome–Positive (Ph+) advanced (ADV) chronic myeloid leukemia (CML) after prior tyrosine kinase inhibitor (TKI) failure. 
First Author: Howard A. Cohen, National Cancer Institute, Tennessee Oncology, PLLC, Nashville, TN
Background: TGR-1202 is a novel, next generation PI3K inhibitor which lacks the hepatotoxicity associated with other PI3K inhibitors and is active in patients (pts) with advanced heme malignancies (ASH 2014). Herein we present updated safety and efficacy results from a Ph I study of TGR-1202 in pts with rel/ref CLL and B-cell lymphoma.
Methods: TGR-1202 is a structurally novel orally once daily following a 3–3 dose escalation design. Eligible pts have rel/ref B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), or other B-cell malignancy and an ECOG PS ≤ 2. Endpoints: safety, PK/PD, and efficacy. Results: As of Feb 2015, 58 pts evaluable for safety including CLL, FL, Hodgkin’s (HL), DLBCL, MCL, and MZL. Median age 63 yo (range: 22-85), 72% male, ECOG 0/1/2: 19/31/1, median prior Tx: 3 (range: 1-14), 48% refractory to prior Tx. Safety: The only Gr 3 AE in ≥ 10% of pts was neutropenia (10%); AEs (all grades, all causality) in > 20% of pts were limited to diarrhea (34%), fatigue (31%), nausea (29%), and cough (26%). All diarrhea events Gr 1/2, except one Gr 3 event occurring in a pt in Cyc 1, which persisted for 2 days and resolved without dose interruption. Notably, in contrast to similar agents, no drug-related hepatotoxicity or colitis has been observed to date (ave time on study 7 Cyc). 2 episodes of Gr 3 fatigue at 1800 mg of a new micrornized formulation met the criteria for DLT. Expansion cohorts are open at 800 mg (CLL) and 1200 mg (NHL). Efficacy: A strong exposure-response relationship has been observed. Of 14 evaluable CLL pts, 13 (93%) achieved a nodal PR (median nodal ↓ of 76%), of which 7 (50%) achieved a PR per Hallek 2008 criteria. Response has been limited in pts with aggressive lymphoma and HL. Of the 12 evaluable FL pts, 8 (67%) remain on study progression-free (range 7 – 99+ weeks), with 3 achieving a PR, notably being the 3 pts exhibiting the highest TGR-1202 plasma concentrations.

Conclusions: TGR-1202 is well tolerated in pts with rel/ref heme malignancies with no reported hepatotoxicity or colitis (41% of pts on study 6 + Cyc) and promising activity in CLL and NHL. Enrollment continues in expansion cohorts. Clinical trial information: 01/677666.
7069 Poster Session (Board #58), Sun, 8:00 AM-11:30 AM
Clinical activity, safety profile, and hepatotoxicity of TGR-1202, a novel once daily PI3Kδ inhibitor, in patients with CLL and B-cell lymphoma.
First Author: Howard A. Cohen, National Cancer Institute, Tennessee Oncology, PLLC, Nashville, TN
Background: TGR-1202 is a novel, next generation PI3Kδ inhibitor which lacks the hepatotoxicity associated with other PI3Kδ inhibitors and is active in patients (pts) with advanced heme malignancies (ASH 2014). Herein we present updated safety and efficacy results from a Ph I study of TGR-1202 in pts with rel/ref CLL and B-cell lymphoma.
Methods: TGR-1202 is a structurally novel orally once daily following a 3–3 dose escalation design. Eligible pts have rel/ref B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), or other B-cell malignancy and an ECOG PS ≤ 2. Endpoints: safety, PK/PD, and efficacy. Results: As of Feb 2015, 58 pts evaluable for safety including CLL, FL, Hodgkin’s (HL), DLBCL, MCL, and MZL. Median age 63 yo (range: 22-85), 72% male, ECOG 0/1/2: 19/31/1, median prior Tx: 3 (range: 1-14), 48% refractory to prior Tx. Safety: The only Gr 3 AE in ≥ 10% of pts was neutropenia (10%); AEs (all grades, all causality) in > 20% of pts were limited to diarrhea (34%), fatigue (31%), nausea (29%), and cough (26%). All diarrhea events Gr 1/2, except one Gr 3 event occurring in a pt in Cyc 1, which persisted for 2 days and resolved without dose interruption. Notably, in contrast to similar agents, no drug-related hepatotoxicity or colitis has been observed to date (ave time on study 7 Cyc). 2 episodes of Gr 3 fatigue at 1800 mg of a new micrornized formulation met the criteria for DLT. Expansion cohorts are open at 800 mg (CLL) and 1200 mg (NHL). Efficacy: A strong exposure-response relationship has been observed. Of 14 evaluable CLL pts, 13 (93%) achieved a nodal PR (median nodal ↓ of 76%), of which 7 (50%) achieved a PR per Hallek 2008 criteria. Response has been limited in pts with aggressive lymphoma and HL. Of the 12 evaluable FL pts, 8 (67%) remain on study progression-free (range 7 – 99+ weeks), with 3 achieving a PR, notably being the 3 pts exhibiting the highest TGR-1202 plasma concentrations.

Conclusions: TGR-1202 is well tolerated in pts with rel/ref heme malignancies with no reported hepatotoxicity or colitis (41% of pts on study 6 + Cyc) and promising activity in CLL and NHL. Enrollment continues in expansion cohorts. Clinical trial information: 01/677666.

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Background: PI3K-δ and PI3K-γ play complementary roles in malignant B-cells and the tumor microenvironment (TME). Inhibition of PI3K-δ blocks cytokine-mediated CLL proliferation, while inhibition of PI3K-γ blocks M2 macrophage polarization and T-cell migration in vitro. Duvelisib, an oral PI3K-δ, -γ inhibitor, has shown clinical activity in a phase 1 study in patients (pts) with advanced hematologic malignancies (Study IPI-145-02), including pts with relapsed/refractory (R/R) CLL in first line activity. 

Methods: Serum from 52 pts with R/R CLL and 30 healthy subjects (HS) was analyzed for 72 analytes (cytokines, chemokines, and matrix metalloproteinases) using Luminex xMAP technology at baseline, Cycle 1 Day 8 (C1D8), C2D1, and C3D1. Median change from baseline was analyzed for statistical significance using parametric (t-test) and non-parametric (Wilcoxon) tests (α = 0.05). Additional cutoffs were applied to multiple hypotheses; threshold for reduction was ≥ 50% of baseline and for increase was ≥ 150% of baseline. Comparison between CLL and HS utilized a 2-sample t-test with Bonferroni correction.

Results: Following treatment with duvelisib, the median serum levels of 12 analytes decreased to ≤ 50% of baseline (p < 0.0002) by C1D8. These included CCL1, CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-6, IL-10, IL-12p40, MPP-9 & TNFα. All of these were significantly elevated (p < 0.0042) at baseline in CLL pts compared to HS and reduced towards normal range following duvelisib treatment. In addition, MMP1 was the only analyte for which median serum levels increased above the threshold of ≥ 150% of baseline (p < 0.0002). Together, these 13 analytes were further explored for potential associations with clinical efficacy. TNFα was significantly elevated (p < 0.0013) at C2D1 & C3D1 in pts who did not exhibit a nodal response.

Conclusions: Most of the analytes reduced following duvelisib treatment had known roles in T-cell responses involved in the communication between CLL cells and the TME. Furthermore, one of these analytes (TNFα) exhibited elevated levels at C2D1 and C3D1 in pts who did not achieve a nodal response. Together, these data indicate that modulation of the TME via PI3K-δ, -γ inhibition may be an important mechanism of action in supporting clinical activity of duvelisib in patients with CLL. Clinical trial information: NCT01476657.

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**Poster Session (Board #63), Sun, 8:00 AM-11:30 AM**

**Early clinical activity and pharmacodynamic effects of duvelisib, a PI3K-δ inhibitor, in patients with treatment-naive CLL. First Author: Manish R. Patel, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL**

**Background:** Signaling via PI3K-δ and PI3K-γ has distinct and complementary effects on malignant B-cells and nonmalignant immune cells in chronic lymphocytic leukemia (CLL). Duvelisib, an oral PI3K-δ, -γ inhibitor, has shown clinical activity in a phase 1 study, IPI-145-02. The activity of duvelisib is monotherapy in pts with treatment-naive (TN) CLL from this study are presented here. Methods: Following dose escalation, an expansion cohort of TN CLL pts was enrolled (n = 18). Response was based on iwCLL (2008) criteria. Safety included AEs and laboratory assessments. Pharmacodynamic assessments included peripheral blood (PB) flow cytometry for cytokines and chemokines. Numbers of PB T-cell subsets were also monitored.

**Results:** As of Oct 2014, 18 TN CLL pts received duvelisib 25 mg BID. The best ORR per iwCLL was 82% (PRs in 14/17 evaluable pts) with a median response duration of 14 months. Reductions in the Ki67 proliferative fraction in both CLL and T-cells was also observed following a single dose and sustained through Cycle 2 Day 1 (C2D1). A reduction in the Ki67 proliferative fraction in both CLL and T-cells was also observed. The overall number of T-cells and T-cell subsets (CD4, CD8, memory subsets) did not change, whereas reductions in the median serum levels of CCL2, CXCL10, IL-10, IL-12p40, MPP-9, IL-16, and TNFα to ≤ 50% of baseline at C1D8 and/or C2D1 (p < 0.01).

**Conclusions:** Duvelisib 25 mg BID shows clinical activity in TN CLL pts. The inhibition of pAKT in CLL cells was rapid and sustained through Cycle 2 Day 1. A reduction in the median serum levels of CCL3, CCL4, CCL7, CCL22, CXCL10, CXCL13, IL-6, IL-10, IL-12p40, MPP-9, and TNFα to ≤ 50% of baseline at C1D8 and/or C2D1 (p < 0.01).

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
Long-term bosutinib (BOS) in patients (pt) with chronic phase (CP) chronic myeloid leukemia (CML) after prior imatinib (IM) failure. First Author: Jennifer Howard Lipton, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: BOS is an Src/Ab1 tyrosine kinase inhibitor for adults with Ph + CML resistant/intolerant to prior therapy. We assess long-term efficacy/tolerability of BOS after ≥5 y vs ≥2 y follow-up from last enrolled pt. Methods: Data were from an ongoing phase 3/4 study of BOS in CP CML pts (500 mg/m2 dose) after IM failure (n = 284). Results: 41% of pts remained on BOS at 5 y vs 54% at ≥2 y (1 y = 48 wk); 60% and 50% had newly attained or maintained major cytogenetic response (MCyR) or complete cytogenetic response (CCyR) in responders was similar at 5 y (71%, 71%) and 2 y (76%, 79%), 6 and 7 pts lost response ≥2 y. Cumulative incidence of on-treatment transformation to AP/BL CML at 5 y was 4%; 55% discontinued without transformation < y; 1/153 pts on-treatment ≥2 y transformed to AP in y3–5. KM overall survival was 84% at 5 y vs 91% at 2 y (40% censored vs y). Median treatment duration was 25.6 (range 0.2–9.4) mo; follow-up: 51.4 (0.6–96.3) mo. 37 pts discontinued BOS y3–5 (vs 13% ≤2 y); mostly for disease progression (n = 11); AE (n = 7): cardiovascular adverse events, scleroderma, renal failure; y4: ascites and serositis (same pt); blood creatinine increased, pulmonary hypertension; y5: thrombocytopenia, and unsatisfactory efficacy (n = 7). Common newly occurring AEs (in > 5 pts) in y3 were cough (n = 7), blood creatinine increased (n = 7), pyrexia (n = 6), and blood creatine phosphokinase increased (n = 6); y4: blood creatinine increased (n = 6), pleural effusion (n = 6), y5, none in > 5 pts. Newly occurring AEs of interest (Table I) were most common in y1; vascular AEs > y2 were primarily hypertension (y3, n = 5; y4, n = 3; y5, n = 2), 4 on-treatment deaths occurred y3–5, none OS-related. Conclusions: BOS showed durable efficacy and manageable toxicity; a large proportion of CP CML pts with prior IM failure remained successfully treated at 5 y. Clinical trial information: NCT00261846.

Newly Occurring AEs

<table>
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<tr>
<th>n (%)</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
<th>Y4</th>
<th>Y5</th>
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<tr>
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<td></td>
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<td>Y2 n = 189</td>
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<td>Y3 n = 148</td>
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<td>Y4 n = 130</td>
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<tr>
<td>Y5 n = 124</td>
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<td></td>
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<tr>
<td>Diarrhea</td>
<td>239 (84)</td>
<td>3 (2)</td>
<td>8 (5)</td>
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<td>0 (2)</td>
</tr>
<tr>
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<td>23 (8)</td>
<td>4 (5)</td>
<td>5 (3)</td>
<td>4 (3)</td>
<td>5 (4)</td>
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<td>14 (5)</td>
<td>2 (2)</td>
<td>8 (5)</td>
<td>7 (4)</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>
*Not experienced by same pt previously (denominator = pts on treatment each y; 1 y = 52 wk)

First Author: Nandita Bose, Biothera, Inc., Eagan, MN

Moxetumomab pasudotox and minimal residual disease in hairy cell leukemia. First Author: Robert J. Kreitman, Laboratory of Molecular Biology, NCI, NIH, Bethesda, MD

Background: Moxetumomab pasudotox is a recombinant immunotoxin containing truncated Pseudomonas exotoxin fused to an anti-CD22 Fv, reported to achieve 46% complete remissions in 28 relapsed/refractory hairy cell leukemia (HCL) patients treated with 5-50 ug/kg every other day for 3 doses (QD) x3 cycles. As a secondary endpoint of this phase I study, minimal residual disease (MRD) was studied in the original cohort and in an additional 21 patients enrolled at the highest dose level, amounting to 33 patients at 50 ug/kg QD x3. Methods: MRD studies included immunohistochemistry (IHC) of bone marrow biopsy (BMBx) and flow cytometry (FC) of blood and bone marrow aspirate (BMA). Results: Real-time quantitative (RQ)-PCR, previously reported to detect 1 HCL cell in 10^5 normal, used immunoglobulin rearrangement (IgH)-specific primers, when patient HCL IgH sequencing was possible. Results: Elimination of MRD by BMA FC, BMBx IHC and BMA FC was achieved in 13 of 46 evaluable patients, 12 (36%) of 33 at 50 ug/kg x3 and 1 (33%) of 3 at 40 ug/kg QD x3, vs 0 of 10 at lower doses (p = 0.04). Of 36 patients at 40/50 ug/kg, 8/10 patients tested positive by BMA FC and BMBx IHC, 5 by both blood FC and BMBx IHC, and 13 by all 3 studies. The median time to resolution of MRD in these 13 patients was 84 days, just prior to cycle 4. Of these 13 MRD-free patients, 11 (85%) remain MRD-free for 28-72 (median 45) months, and all 13 remain MRD-free in blood. In contrast, 7 of 10 patients tested positive by RQ-PCR before and after therapy, and became MRD- in blood (p = 0.0005). RQ-PCR was more sensitive than BMA FC; of 19 patients evaluable for RQ-PCR, 5 of 6 MRD-free by BMA FC were also MRD-free by BMA RQ-PCR. Conclusions: Moxetumomab pasudotox can eradicate MRD in multiply relapsed HCL patients. We are aware of no other non-chemotherapy option with documented multi-year MRD-free. BMA FC in a significant fraction of HCL patients, BMA MRD eradication is associated with lack of HCL progression in blood. Additional testing with RQ-PCR will determine if this more sensitive test is associated with outcome and can be used to help determine the optimal number of cycles. This study of investigator reported data was supported by Medimmune and supported by NCI’s Intramural Research Program and the Hairy Cell Leukemia Foundation. Clinical trial information: NCT00462189.
Correlation of genomic analysis by MyAML with chemotherapy drug sensitivity. First Author: Pamela S. Becker, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Whole genome sequencing has demonstrated tremendous heterogeneity in the mutations and chromosomal translocations associated with acute myeloid leukemia (AML), yet we remain quite limited in our ability to predict outcomes of treatment. Most patients with AML cannot be cured with chemotherapy, and the overall survival remains poor. Thus, new approaches are needed to better tailor treatment for individual patients. Methods: MyAML uses next generation sequencing to identify the coding regions and gene fusion genomic breakpoints of 194 genes associated with AML. Fragmented genomic DNA is captured with a customized probe design, and sequenced with 300bp paired end reads on an Illumina MiSeq instrument to an average depth of coverage > 1000x. Using a custom bioinformatics pipeline, sample nucleotide variants (SNVs) and indels, inversions and translocations are identified and annotated. High throughput drug sensitivity testing was performed against a panel of 160 drugs, of which 56 are FDA approved. De-identified samples from 12 patients with de novo AML and 12 patients with relapsed AML were analyzed. For 2 patient samples, Duplex Sequencing was also performed to detect sub-clonal mutations below the detection limit of conventional next-generation sequencing. Pearson’s correlation was used to examine all possible pairs of missense mutations and the in vitro cytotoxicity response across the sample set. Results: From the 24 patient samples analyzed to date, an average of 129 missense mutations were identified in each sample with an allelic frequency > 5%. These samples also contained an average of over 12 coding indels (~5 frameshift and 7 inframe indels) per sample. In addition, MyAML identified 3 samples with inv(16) and 6 samples with translocations, including the cryptic NUP98-NSD1(5;11) that were not detected by karyotyping. For 2 of the samples, Duplex Sequencing was performed at a depth of > 6000x. The FLT3 DB35 tyrosine kinase domain (TKD) was identified in 2 patients not previously known to have this mutation. Conclusions: Data from disease focused genomics and in vitro chemotherapy sensitivity testing of individual patient samples will likely lead to innovations in treatment and improved outcomes in AML.

Phase II trial of the combination of subcutaneous bortezomib (Bortez) and pegylated liposomal doxorubicin (PLD) for the treatment of patients with acute myelogenous leukemia (AML), First Author: Kent Tomlinson, UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: The proteasome inhibitor Bortez has activity in AML, both as a single agent and in combination with standard induction. Bortez inhibits NF-kB signaling, and NF-kB activity promotes anthracycline resistance. The combination of Bortez and PLD was well tolerated in trials for multiple myeloma. Methods: We performed a phase II trial of Bortez and PLD in subjects who had at least 18 years old with relapsed/refractory AML or treatment naive AML unfit for or who refused standard therapy. Bortez 1.5mg/m² was given subcutaneously on days 1, 4, 8, 11, and 11, and PLD 40mg/m² was given IV on day 4. Cycles were 21 days long. The primary endpoint was objective response rate (ORR), defined as complete remission (CR) plus partial remission (PR). Results: Fifteen subjects (53% male) were enrolled. Median age was 70 years (range 32-83). Four had relapsed, five had refractory, and six had untreated AML. Subjects had a median of two prior lines of therapy (range 0-7), including two with prior allogeneic transplantation. No subjects achieved a CR and three achieved a PR for an ORR of 20%. Two of the subjects achieving PR were treatment naive. There were 12 patients that did not meet response criteria, and all three subjects with a PR progressed after cycle 2. The median number of completed cycles was 1 (range 0-2). Of 14 subjects with circulating blasts, eleven (79%) had a decrease in circulating blasts after the first cycle. Four subjects died from disease-related complications during cycle 1. The most common grade 3-4 adverse events were hematologic and infectious, occurring in 93% and 60% of subjects respectively. Two subjects (13%) had grade 3 peripheral sensory neuropathy. Conclusions: The combination of Bortez and PLD demonstrates modest anti-AML activity in a cohort of AML patients that includes heavily pretreated patients. The combination was well tolerated. Given the modest response rate and short duration of response, outcomes could be improved with modification of the current dosing schedule and/or inclusion of additional agent(s). Responses seen in older treatment naïve subjects suggest that this regimen should be studied further in this patient population. Clinical trial information: NCT01736943.

Clinical outcome of adult acute lymphoblastic leukemia based on Philadelphia chromosome status and socioeconomic status. First Author: Bao Day Dao, The University of Texas Southwestern Medical Center, Dallas, TX

Background: Adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) often relapse with chemotherapy alone. Many undergo allogeneic stem cell transplant (alloSCT) in first complete remission (CR1). Use of tyrosine kinase inhibitors (TKI) with chemotherapy improves outcomes although the standard of care for Ph+ALL remains undefined. Methods: 105 consecutive adult patients with ALL were treated at UT Southwestern Medical Center and its county affiliate Parkland Hospital from 2004-2014. Associations between alloSCT, socioeconomic status, and overall survival (OS) were evaluated using Cox regression methods and Kaplan-Meier analysis. Results: 34 patients had Ph+ALL. Median age was 49 years. 26 patients received chemotherapy + TKI alone. 8 patients underwent alloSCT after initial chemotherapy + TKI. 52.4% of Ph+ALL patients achieved CR1. At median follow up of 18 months, 61.5% of Ph+ALL patients who did not undergo alloSCT were alive compared to 50.0% of patients who did. AlloSCT was not significantly associated with OS (p = 0.74). Survival was not significantly different between Ph+ALL and Ph-ALL (p = 0.58). Impact of socioeconomic status on OS within the Ph+ALL group was limited by small sample size. Within the entire cohort of ALL patients, about half of patients had an indigent care plan and were treated at the county hospital. These patients had an OS of 15.5 months compared to 49 months among privately insured patients (p = 0.008). OS improvement for patients with dialysis coverage was 17.9 months for patients with dialysis coverage compared to 78 months for individuals treated at our university facility (p = 0.0052). In univariate analysis, OS was significantly associated with insurance type (HR = 2.09; 95% CI 1.20-3.64) and treating facility (HR 2.24; 95% CI 1.25-4.00). In multivariate analysis, this association was no longer significant. Conclusions: In the advent of TKI, alloSCT did not significantly influence OS in Ph+ALL patients. Administration of chemotherapy + TKI alone may be a viable alternative given the increased morbidity associated with alloSCT. Socioeconomically disadvantaged patients appear to have inferior survival, but this needs further investigation in a larger cohort.
Background: Renal function has a well-established prognostic role in patients with some hematological malignancies, such as multiple myeloma. However, its impact on survival in patients with CLL hasn’t been explored. Methods: We used the Mayo Clinic CLL database to identify all patients diagnosed with CLL between 01/1995 and 11/2014 using the 2009 iwCLL criteria and seen at our center prior to treatment. Patients for whom we could not calculate a baseline creatinine clearance (Cr-C) due to missing creatinine/weight or who were missing baseline complete blood count (CBC) (n = 466) were excluded from final analysis. Renal insufficiency (RI) was defined as Cr-C < 45 mL/min calculated with the Cockcroft-Gault equation. Logistic regression was used to determine which factors predicted RI. Fisher’s exact test was used to compare treatment types by RI. The Kaplan-Meier method was used for the survival analyses.

Results: The final analysis included 1268 patients. Of these, 87 (7%) had RI at diagnosis. Factors significantly associated with RI on univariate analysis (UVA) were age > 65 years, female sex, hypertension (HTN), hemoglobin < 11 g/dL, and Rai stage III-IV. Factors associated with RI on multivariate analysis (MVA) were age > 65 years, female sex, HTN, and advanced Rai stage. Of the 506 patients who required treatment, 25 had RI. Type of first treatment differed between patients with and without RI (p < 0.001); patients with RI were more likely to receive alkylator-based therapy (48% vs 15%) and less likely to receive purine analogue-based CIT (45% vs 83%). Median overall survival (OS) was 124 months, 59 months for those with RI, and 132 months for those without RI (p < 0.001). Baseline characteristics (age, sex, HTN, diabetes, CBC, CD49d, CD38, ZAP70, IGHV mutation status and FISH) as well as RI were associated with OS on UVA. Conclusions: RI is relatively frequent at time of CLL diagnosis (7% of cases) and has a profound influence on therapy selection among patients requiring treatment. RI at time of CLL diagnosis is associated with overall survival.

Up-regulation of CALR in patients with essential thrombocythemia independent from CALR mutations. First Author: Ciro Roberto Rinaldi, University of UVA.

Background: Somatic mutations in the exon 9 of calreticulin (CALR) gene were recently discovered in patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) lacking JAK2 and MPL mutations, and absent in patient with polycythemia vera (PV). Among patients with ET or PMF with un-mutated JAK2 or MPL, CALR mutations were detected in 67% of those with ET and 88% of those with primary PMF. Over expression of the most frequent CALR deletion caused cytokine-independent growth in vitro owing to the activation of signal transducer and activator of transcription 5 (STAT5) by means of an unknown mechanism. Patients with myeloproliferative neoplasms carrying CALR mutations presented with higher platelet counts and lower hemoglobin levels than patients with mutated JAK2, but also a lower risk of thrombosis and longer overall survival than patients with mutated JAK2. Methods: We analyzed by Real Time PCR, CALR expression in peripheral blood (PB) of 38 patients affected by ET, 17 JAK2 mutated (45%), 4 CALR (10.5%) mutated, 1 MPL mutated (3%) and 14 with no molecular abnormalities, and compared with a cohort of healthy volunteers. Results: We found a significant over expression of CALR (median 5.15; range 1.13-270.08) comparing with controls (median 0.38, range 0.18-1.0). No significant difference was found comparing CALR expression in ET delayed (median 4.9, range 1.51-37.14) and CALR/JAK2 un-mutated patients (4.68, range 1.51-28.7). CALR up-regulation is not mutually exclusive with JAK2 mutations, there was, in fact, no difference in CALR mRNA between JAK2 mutated (median 5.09, range 1.13-270) and wild type ET patients (median 5.08, range 1.51-37). There was no significant difference when we correlated CALR expression with PLT counts, spleen size or type of cytoreductive therapy. Conclusions: CALR mRNA expression is independent from the CALR mutational status and more interestingly is up-regulated also in JAK2 mutated patients. A larger cohort of patients is required to confirm these preliminary findings.

Effect of grade (G) 3 fibrosis on clinical outcome of patients (Pts) with myelodysplastic syndromes (MDS): Mayo Clinic Experience. First Author: Amin Motiei Cheema, Mayo Clinic, Rochester, MN

Background: There have been renewed attempts at characterizing the clinicopathological findings of MDS with fibrosis (MDS-F) in order to determine if it warrants a distinct entity. Most of these studies were small while few studied clinical outcome of MDS-F. Aim: To study clinical outcomes of patients with MDS-F. Methods: A retrospective, single-institution study of MDS cases per WHO classification from 1993-2014 was done. Bone marrow fibrosis (BMF) fibrosis was identified as G 1, 2, or 3 on reticulin stain. Wilcoxon, Pearson tests, Kaplan Meier, multivariate analysis were done via JMP. Results: Initial screen of our database revealed 108 (13%) of 835 pts with MDS as MDS-F. On follow up, 49/108 (45%) had subsequent BMF. In 33/49 (67%) pts, diagnosis changed (median time to diagnosis, 0.6 months, m in G1, 0.2 m in G2, 8 m in G3, p < 0.001). A second change was in 5/14 pts. Final diagnoses in 49 pts were AML/RAEB/RCMD in 18 (37%), 15 (31%), and 8 (17%) (rest were atypical CMML/MDS MPN/RARS/MDS-F). Comparison between fibrosis (n = 108) and non-fibrosis groups (n = 727) showed no statistically significant difference in survival or time to AML. Statistically significant variables between the groups were age (p = 0.0002), platelet (p < 0.0001), multilineage dysplasia (p < 0.0001), dysmegakaryopoiesis (p < 0.0001), peripheral blasts (p = 0.01), cellularity (p < 0.0001) and IPSS-R group (p = 0.01). There was a statistically significant difference in MDS across all grades of fibrosis (33 in G1, 39 in G2, 82 in G3, p = 0.0001). Pts with G3 fibrosis vs all others had a statistically significant lower mOS of 8 vs 29 m (p < 0.0001). In multivariate analysis, only age (p < 0.0001), IPSS-R (p = 0.0001) and G3 fibrosis (p = 0.018) were found to have a statistically significant effect on mOS (but not blast or gender). JAK2 status and CD34 count did not have a role in the risk prediction across the fibrosis group. Conclusions: MDS-F is a small entity with distinct lab and BMF findings. Only G3 fibrosis had a significant negative impact on mOS. On follow up, 55% progressed into AML or RAEB. Age, IPSS-R and G3 fibrosis were the only significant contributors to mOS. Our finding needs to be further investigated within larger sets of MDS pts.

Ruxolitinib in polycythemia vera: Follow-up from the RESPONSE trial. First Author: Srdan Verstovsek, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The RESPONSE trial is a multicenter, open-label phase 3 study evaluating the efficacy and safety of ruxolitinib (Rux) compared with best available therapy (BAT) in patients (pts) with polycythemia vera resistant to or intolerant of hydroxyurea. Results from the primary analysis, 48 wks from last pt first treatment (LPFT), were published (Vannucchi, NEJM 2015). Methods: This was a second preplanned analysis 80 wks after LPFT. The primary response was defined as achieving both hematocrit reduction in spleen volume (SV) by imaging at wk 32. Durability of the primary response, HCT control, spleen volume reduction, and complete hematologic remission (CHR), as well as long-term safety, were evaluated. Results: At data cutoff, 91 (82.7%) pts randomized to Rux (Rux arm) were receiving treatment (median exposure, 111 wks), compared to 93 (84.5%) at the wk 48 analysis (median exposure, 81 wks). No pts remained on BAT, compared to 3 pts at the wk 48 analysis. Of the 23 (21%) pts in the Rux arm who achieved the primary response at wk 32, only 1 lost this response. Fm 50% of pts in the Rux arm who achieved CHR at wk 32, at data cutoff, 23 (21%) pts remained on Rux at wk 48. The probability of maintaining this response for 80 wks from time of initial response was 89%. Of the 98 pts on Rux at wk 32, 90% did not have a PBT from wk 32 to 80. A ≈ 35% SV reduction at wk 32 was achieved in 38% of Rux pts, all maintained their response. CHR at wk 32 was achieved in 24% of pts. The probability of maintaining CHR at wk 80 was 33% (60% at wk 48). Pruritus Symptoms Impact Scale was “very much improved” for 5 of 10 pts in the Rux arm at their end of study visit. The most common nonhematologic adverse events in the Rux arm were headache (21.8% at the wk 80 analysis [ie, entire follow-up] vs 20.5% at the wk 48 analysis), diarrhea (20.0% vs 19.1%), pruritus (20.0% vs 17.3%), and fatigue (17.3% vs 17.3%); most were grade 1 or 2. Grade 3 or 4 anemia and thrombocytopenia occurred in 1.8% and 5.5% of pts, respectively (no increase from wk 48 analysis [ie, entire follow-up] vs 20.9% at the wk 48 analysis), diarrhea (20.0% vs 19.1%), pruritus (20.0% vs 17.3%), and fatigue (17.3% vs 17.3%); most were grade 1 or 2. Grade 3 or 4 anemia and thrombocytopenia occurred in 1.8% and 5.5% of pts, respectively (no increase from wk 48 analysis). The rate of treatment discontinuation in the Rux arm due to adverse events remained low (4.5%). Conclusions: In RESPONSE, Rux responses were durable and treatment was generally well tolerated, with 83% still receiving Rux at a median exposure of 111 wks. Clinical trial information: NCT01243944.
7088 Poster Session (Board #77), Sun, 8:00 AM-11:30 AM

Case series of hypomethylating agents (HMA) effect on myelodysplastic/myeloproliferative neoplasm unclassified (MDS/MPN-U): Mayo Clinic experience. First Author: Anubuddha Dasgupta, Mayo Clinic, Rochester, MN

Background: MDS/MPN-U is a rare myeloid disorder that has both dysplastic and proliferative features, but cannot be parsimoniously classified as either MDS or MPN. There is currently no standard treatment algorithm for MDS/MPN-U and is either based on MPN or MDS best available therapies.

Methods: A retrospective, single-institution study between 1993-2014 of WHO-defined MDS/MPN-U cases was carried after getting appropriate IRB approval. Patients with diagnosis of chronic myelomonocytic leukemia and refractory anemia with ring sideroblasts were excluded. Wilcoxon, Pearson tests, Kaplan Meier, multivarant analysis were done via JMP 10. Results: A total of 63 patients with MDS/MPN-U were identified, 10 of whom were treated with HMA. The indication for treatment was thrombocytopenia in 50%, anemia in 30%, and symptomatic splenomegaly in 20%. Median age was 67.5 years (56-82), with 80% of the patients were males. Median platelet count was 101 x10^9 (14-184), hemoglobin (Hg) of 9.4 g/dL (6.9-16.3), white blood cell (WBC) count of 8.3 x10^9 (1.8-90.7), peripheral blood of 1% (0-6); bone marrow blasts of 5% (3-20). Cyogenetics were diploid in 70%, while splenomegaly was found in 30%. Two HMAAs were used, with decitabine in 60% and azacitidine in the other 40%. There was no statistical significance on overall survival (OS) between the two HMAAs (p = 0.2). The median number of treatment cycles was 5 (1-20), with achievement of complete response (CR) in 20%, partial response (PR) in 10%, stable disease in 40%, and progressive disease in 30%. Transformation to AML was seen in 40%, with a median time of 372 days (248-929). Bone marrow transplant was performed in one patient. Median OS was 15 months. Multivariate analysis revealed bone marrow blasts (p = 0.01) as the only statistically significant factor on OS (but not WBC, Hg or platelets). Conclusions: MDS/MPN-U is a rare entity with no standard treatment algorithm available at present. HMAs yielded an overall response (CR+PR) of 30%, with a median OS of 15 months. On a multivariate analysis only bone marrow blasts had an impact on mOS. Larger studies are needed to confirm our findings in this rare disease.

7090 Poster Session (Board #79), Sun, 8:00 AM-11:30 AM

Hepatitis C virus infection in patients undergoing hematopoietic cell transplantation in the era of direct-acting antiviral agents. First Author: Andreas Kyvernitakis, Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: There is paucity of literature regarding hepatitis C virus (HCV) infection in hematopoietic cell transplant (HCT) recipients. In the study described herein, we aimed to evaluate several aspects of HCV infection in HCT recipients, including the yield of HCV antibody testing, impact of this HCV screening on HCT outcomes, various antiviral treatments, and their impact on HCT outcomes.

Methods: A retrospective, single-institution study conducted from 1/1983 to 12/2014 of HCV-infected cancer patients undergoing hematopoietic cell transplantation in the era of direct-acting antiviral agents (DAAs). A total of 434 HCV-infected cancer patients were identified. The majority (80%) underwent autologous transplantation, with chronic HCV infection seen at MD Anderson Cancer Center from 11/2012-12/2014, whereas those seen from 1/1983-11/2012 were reviewed retrospectively.

Results: Of 434 HCV-infected cancer patients, 59 underwent 64 HCTs. The majority (80%) underwent autologous transplantation, with chronic HCV infection seen at MD Anderson Cancer Center from 11/2012-12/2014, whereas those seen from 1/1983-11/2012 were reviewed retrospectively. 59% of the patients were males with a median age of 48 (range 18-72) years, and 41% had history of injection drug use. Median platelet count was 101 x10^9 (14-184), hemoglobin (Hg) of 9.4 g/dL (6.9-16.3), white blood cell (WBC) count of 8.3 x10^9 (1.8-90.7), peripheral blood of 1% (0-6); bone marrow blasts of 5% (3-20). Cyogenetics were diploid in 70%, while splenomegaly was found in 30%. Two HMAAs were used, with decitabine in 60% and azacitidine in the other 40%. There was no statistical significance on overall survival (OS) between the two HMAAs (p = 0.2). The median number of treatment cycles was 5 (1-20), with achievement of complete response (CR) in 20%, partial response (PR) in 10%, stable disease in 40%, and progressive disease in 30%. Transformation to AML was seen in 40%, with a median time of 372 days (248-929). Bone marrow transplant was performed in one patient. Median OS was 15 months. Multivariate analysis revealed bone marrow blasts (p = 0.01) as the only statistically significant factor on OS (but not WBC, Hg or platelets). Conclusions: MDS/MPN-U is a rare entity with no standard treatment algorithm available at present. HMAs yielded an overall response (CR+PR) of 30%, with a median OS of 15 months. On a multivariate analysis only bone marrow blasts had an impact on mOS. Larger studies are needed to confirm our findings in this rare disease.

7091 Poster Session (Board #80), Sun, 8:00 AM-11:30 AM

Influence of variant allele frequency (VAF) on the phenotypic penetrance of TP53 mutations in myelodysplastic malignancies. First Author: David Andrew Saliman, Moffitt Cancer Center, Tampa, FL

Background: The clinical implementation of next generation sequencing (NGS) has allowed for the quantitative detection of clinically significant somatic mutations in myeloid malignancies. However, the clinical relevance of the VAF in these mutations is unknown. Here we investigate the influence of TP53 mutations on NSG in MDS and AML which is a recognized adverse prognostic feature associated with a complex karyotype. Methods: A training set of NGS profiled MDS or AML cases were retrospectively identified from the Moffitt Cancer Center MDS database. A validation set was obtained from WHO defined MDS cases profiled at Genoptix. Clinical variables and outcomes of MDS patients were characterized at the time of sample procurement. Fisher’s exact and t-tests were used for comparative analyses. Kaplan-Meier estimates were used to estimate overall survival and analyzed from the date of mutation identification. Results: From May 2013 to October 2014, 43 patients of 252 screened cases were identified in our training set with a TP53 mutation. The mean VAF across duplicate libraries was 39.8%. As previously reported, TP53 mutation was strongly associated with complex karyotype (70% vs 6%, p < .0001). When parsed by VAF, 100% of TP53 mutated patients with a VAF > 40% had complex cytogenetics in comparison to 50% of patients with a VAF < 20% (p = .0016). Further, patients with complex cytogenetics had a significantly increased VAF (median 49% vs 18%, p = .0009). MDS patients with a TP53 mutation had a median time to calculated donor neutrophil recovery of 45 d (range 15 d to 60 mo). 4/5 subjects achieved full and sustained donor T-cell and myeloid chimerism, which occurred at a median 9 mo and 6 mo post-transplant, respectively. Among those at risk, 2/4 developed CMV reactivation. None of the subjects developed PTLD. At a median follow-up of 3 yrs, 1 subject developed advanced stage MF/SS while OS was complete remission, 1 subject died 6 mo post-transplant from a second malignancy while OS was complete remission, 1 subject died 6 mo after transplant from a second malignancy while OS was complete remission. Conclusions: TP53-based reduced intensity transplant approach described here is well tolerated and associated with prolonged, GVT-induced complete remissions in patients with advanced stage MF/SS. The trial is ongoing and efforts are underway to permit enrollment of patients with available HLA-matched unrelated donors. Clinical trial information: NCT00047060.
Use of dual donor T-cell chimerism to predict prognosis after double cord blood allogeneic transplantation. First Author: Muhamed Baljevic, The University of Texas Medical Branch at Galveston

Background: Double cord blood transplantation (dCBT) is an important strategy to overcome dose limitation of single CB. By day 21, over 80% of patients (pts) have single unit dominance maintaining long-term hematopoiesis. However, outcomes of pts who have persistence of both CB units after dCBT is unknown. Methods: We retrospectively analyzed 105 pts who underwent dCBT between 2003 through 2014 and had donor T cell chimerism (TCC) of at least 10% from each CB unit at day 100 +/- 30 after transplant (dCBT). Pts alive and free of disease progression at day 100 were evaluable. Results: Of 105 pts, 10 (9.5%) had dTC. Median age was 43 (range: 1-73). Disease diagnosis was AML in 57.1% and ALL in 21.9%. Disease status at dCBT was 1st or 2nd complete remission in 74.2% of the pts. The median dose of CD34+ and total nucleated cells infused was 0.36x10^6/kg (0.12-5.35) and 0.51x10^6/kg (0.3-1.29), respectively. Single TCC (sTCC) and dTCC pts were comparable except for more frequent ≥ 4/6 HLA matching between 2 CB units (66.3% vs. 90%, p < 0.1), and less use of CB manipulation in dTCC (74.7% vs. 50%, p = 0.1). Treatment outcomes were similar between groups with 3-year (yr) overall survival and progression free survival of 40% vs. 41.4% and 40% vs. 32.3%, respectively. Seven of 10 pts with dTCC were evaluable for long-term assessment (>6 months (mo)): 1 pt had autologous regression with progression after 6 mo of dCBT. Unit dominance was observed in 4 pts, within 4 to 20 mo after dCBT; 1 of them produced 5 mo after transfusion and another 1 pt lost function of fusion at 15 mo. Two AML pts had long-term dTCC with units contributing 58%/42% and 84%/16% at 4 and 3.2 yrs after dCBT. Both were alive in remission at last follow-up. Conclusions: The unique situation of TCC from both CB units around day 100 is not associated with worse transplant outcomes in pts receiving dCBT. These provocative results need to be confirmed in larger studies.

"when treated with RIG compared to BSC. Such characteristics should be considered in the design of future 2nd-line studies in MDS patients with IPSS-R VHR. Clinical trial information: NCT01241500."
Background: Therapeutic options in patients with acute myeloid leukemia (AML) who are elderly, unfit, or who relapse after induction therapy remain an unmet need. Studies with primary AML samples and cell lines suggest a role for Bruton’s tyrosine kinase (BTK) as a therapeutic target in AML (Rushworth, 2014). Expression and increased phosphorylation of BTK were detected in AML cells, and treatment with ibrutinib (an oral, covalent inhibitor of BTK) resulted in down-regulation of cell growth, decreased adhesion to the bone marrow stromal cells and cell migration induced by a CXCR4 ligand, SDF1 (Zeitseva, 2014). As such, ibrutinib may have a dual anti-AML effect by (1) a direct anti-proliferative/cytotoxic activity and (2) mobilizing cells from the protective bone marrow microenvironment. In addition, ibrutinib augmented the cytotoxicity of cytarabine and daunorubicin in patient derived AML cells. Methods: PCYC-1311 (NCT02351037) is a phase 2, open-label, non-randomized study of ibrutinib + low-dose cytarabine (LD-AraC) in patients with AML. The study will enroll approximately 67 patients with pathologically documented AML that has failed standard treatment, or patients without prior therapy who declined standard treatment. Initially, the safety of the combination will be assessed in 6–9 patients receiving oral ibrutinib 560 mg once daily continuously + LD-AraC at 20 mg twice daily subcutaneously for 10 days per 28-day cycle. Dose-limiting toxicities (DLTs) will be assessed during the first treatment cycle. If less than 33% of patients experience DLTs, additional patients will be assigned at investigator discretion to receive ibrutinib monotherapy (n = 33), or ibrutinib + LD-AraC (n = 34). Patients on ibrutinib monotherapy who experience treatment-failure or relapse will be permitted to add LD-AraC. The primary endpoints are overall remission rate, safety, and tolerability. Additional endpoints include relapse-free survival, event-free survival, overall survival, clinical benefit rate, pharmacokinetics of ibrutinib ± LD-AraC, and evaluation of prognostic and predictive biomarkers. Safety data will be summarized descriptively. Clinical trial information: NCT02351037.

First-in-human study of FLX925, an orally administered FLT3/CDK4/CDK6 inhibitor, in subjects with relapsed or refractory acute myeloid leukemia (AML). First Author: Naval Gaur, St. Jude Children’s Research Hospital, Memphis, TN

Background: Acquired mutations in oncogenic kinases remains an obstacle between valid therapeutic hypotheses and meaningful patient benefit. The inhibition of FLT3 can be efficacious in AML patients, particularly in FLT3-ITD mutated cancers. However, relapse is common and frequently associated with the acquisition of secondary resistance mutations in FLT3. FLX925 is a next-generation kinase inhibitor that was prospectively designed to address or avoid common mechanisms of resistance to earlier FLT3 inhibitors, with its unique binding mode and potential activity against CDK4/CDK6. FLX925 retains its cellular potency against clinically relevant secondary resistance mutations in FLT3. In addition, FLX925 potently inhibits CDK4/CDK6, central components of the cell cycle machinery. This unique profile may reduce the emergence of resistant clones and extend the therapeutic potential of FLX925 to other malignancies dependent on these pathways (e.g., MCL). This data suggest the unique profile of FLX925 makes it an ideal inhibitor for the treatment of cancers driven by FLT3 signaling, such as AML. Methods: This open label, sequential-group, dose escalation and cohort expansion study includes adult patients diagnosed with relapsed or refractory AML. Eligible patients need to have failed prior induction therapy or relapsed within 12 months of prior therapy. Duration of expansion phase is 124 days and patients are enrolled into 3 cohorts: subjects with a FLT3 ITD or kinase domain mutation with (Cohort A) or without (Cohort B) FLT3 inhibitor treatment, or patients without a FLT3 mutation at screening (Cohort C). The primary objectives of the study are to characterize the safety and tolerability of twice-daily, oral FLX925. Key secondary objectives are to evaluate the pharmacokinetic (PK) profile, pharmacodynamics (PD) effects, and the magnitude and duration of antitumor activity with FLX925, using standard criteria. A Simon 2-stage mini-max approach will be used to test the null hypothesis based on the CRI rate. This trial (NCT02335814) is currently enrolling patients. Clinical trial information: NCT02335814.

GRASPA-AML 2012-01 study (NCT01810705): A multicenter, open, randomized phase 2b trial evaluating ERY001 (L-asparaginase encapsulated in red blood cells) plus low-dose cytarabine vs low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) elderly patients, unfit for intensive chemotherapy. First Author: Xavier G. Thomas, Centre Hospitaller Lyon Sud, Cedex, France

Background: Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells and the most common malignant myeloid disorder in adults, with a median age of 65 years at diagnosis. There is currently no curative therapy for most elderly patients with AML, and who are unfit for intensive chemotherapy. L-asparaginase (L-ASP) plays a key role in all treatment phases for Acute Lymphoblastic Leukemia (ALL). Some leukemic cells, with asparagine synthetase deficiency, need plasmatic L-asparagine for protein synthesis. L-ASP hydrolyses L-asparagine leading to depletion of this amino acid. Normal cells are resistant to L-asparaginase because they can synthesize asparagine using asparaginase synthetase. Several clinical studies and case reports showed a potential benefit of L-ASP in certain AML cell lines or mixed lineage leukemia. ERY001 is a novel platform of RBC encapsulation of L-asparaginase. Antitumor activity of ERY001 as well as any L-ASP is based on depletion in plasmatic asparaginase, which is an essential amino acid for cells survival in almost all lymphoblastic cells. Methods: GRASPA-AML 2012-01 is an international multicenter, open label, randomized, phase 2b trial evaluating clinical activity and tolerability of ERY001 plus low-dose cytarabine (LDAC) vs LDAC alone, in treatment of elderly patients (65-85 years) and patients with newly diagnosed de novo AML and who are unfit for intensive chemotherapy. The primary objective is progression free survival (PFS). The key secondary objectives are: response to treatment, event free survival, overall survival, quality of life, pharmacokinetic and pharmacodynamics profiles, and immunogenicity. Patients are randomized 1:1 to: Arm A: LDAC only (40 mg daily for 10 consecutive days, every 28 days); Arm B, ERY001 (100 IU/kg) in combination with subcutaneous LDAC, for up to 24 months. Patients are assessed every 4-5 days during each cycle. The study is currently in recruiting phase. Seventy-three patients were recruited to date. Clinical trial information: NCT01810705.
A phase 1b trial of duvelisib, a PI3K-δ,γ inhibitor, in combination with obinutuzumab in patients with CLL/SLL previously treated with a Bruton’s tyrosine kinase inhibitor (BTKi). First Author: James Stewart Blachly, Ohio State University Medical Center, Columbus, OH

Background: Abrogating B-cell receptor pathway signaling through BTK inhibition is an effective treatment strategy for CLL. However, some patients (pts) do not respond, or progress despite BTK inhibitor (BTKi) treatment. Duvelisib, an oral inhibitor of PI3K-δ and PI3K-γ, can reduce downstream PI3K signaling even in the setting of BTK C481S mutation, thus providing an alternative for attenuating CLL growth and survival signaling. Early clinical activity observed in a Phase 1 study of duvelisib monotherapy in a subset of pts previously treated with a BTKi, suggest further evaluation is warranted (Porcu, ASH 2014). Combining duvelisib with obinutuzumab may augment clinical benefit through both cell intrinsic and extrinsic mechanisms. This study (NCT02292225) was designed to identify a tolerable dose of duvelisib combined with obinutuzumab, and to evaluate the safety and efficacy of the combination in relapsed/refractory CLL/SLL pts previously treated with a BTKi. Methods: This is a Phase 1b, open-label, dose escalation, safety and tolerability study of duvelisib in combination with obinutuzumab in pts with CLL/SLL whose disease is refractory to or has relapsed while receiving a BTKi therapy. Dose escalation (DE) Cohort 1 will receive duvelisib 25 mg BID in combination with obinutuzumab at its approved dose and schedule. Dose escalation of duvelisib to 50 mg BID or 75 mg BID may occur based on evaluation of dose limiting toxicities. Sequenced administration may be explored if the DE of duvelisib cannot progress when treatments are administered concurrently. An expansion phase is planned to explore the optimal dosing regimen of duvelisib in combination with obinutuzumab. Approximately 64 pts will be enrolled at 5-6 US sites. The primary endpoints are dose-limiting toxicities (DE phase only), AEs, and safety laboratory changes. Secondary endpoints are overall response rate, duration of response, progression-free survival, overall survival, BTK mutation status, and pharmacokinetics. Response will be evaluated according to the modified IWCLL 2008 response criteria. Clinical trial information: NCT02292225.

Phase III randomized, open-label, active-controlled study of momelotinib versus best available therapy in ruxolitinib-treated patients with myelofibrosis. First Author: Vikas Gupta, Princess Margaret Cancer Center, Toronto, ON, Canada

Background: Momelotinib (MMB) is a JAK1/2 inhibitor, and displays potent in vitro inhibitory activity against cells dependent on JAK2 including cells with the JAK2V617F mutation. Dosing of ruxolitinib (RUX), the first JAK inhibitor approved for myelofibrosis (MF), is based on platelet count, with dose reduction indicated for various degrees of hematologic toxicity. In the phase II study of RUX versus placebo (PBO) in MF (COMFORT-I), 70% of subjects in the RUX arm experienced thrombocytopenia of any grade compared to 31% of subjects in the PBO arm, with rates of Grade 3 and 4 thrombocytopenia of 13% and 1% on the RUX and PBO arms, respectively. Grade 3 and 4 anemia rates were 45% and 19% for the RUX and PBO arms, respectively. For those patients who experience significant hematologic toxicities while on RUX, no approved alternative JAK inhibitor therapy is currently available. Methods: 150 subjects with primary, post-polycythemia vera, or post-essential thrombocythemia MF will be randomized in a 2:1 manner to receive either MMB or best available therapy (BAT) for 24 weeks, with the option for eligible subjects to continue open-label MMB in an extended treatment phase for up to an additional 168 weeks. Treatment on the BAT arm may include RUX. Key inclusion criteria are palpable splenomegaly ≥ 5 cm, currently or previously treated with RUX and characterized by either requirement for red blood cell transfusion while on RUX, or dose adjustment of RUX to enhance by hypomethylating agents, providing the rationale for targeting PPARγ.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Bevacizumab 15mg/kg plus cisplatin-pemetrexed (CP) triplet versus CP doublet in Malignant Pleural Mesothelioma (MPM): Results of the IFCT-GFPC-0701 MAPS randomized Phase 3 trial. First Author: Gerard Zalcman, Caen Univ Hosp, Caen, France

Background: MPM median overall survival (OS) did not exceed 13 months with pemetrexed-platinum doublet, with virtually no surviving patients at 5 years. Vascular endothelial growth factor is a potent mitogen for MPM cells. Methods: In this French multicenter randomized phase 3 trial, eligible patients had unse evaluable, histologically proved MPM, age <76, no prior chemo, PS 0-2, no thrombosis, nor bleeding. Standard (1:1) received pem 500 mg/m², CDDP 75 mg/m² at D1, with (arm B) or without bevacizumab (arm A), 15 mg/kg Q21D, for 6 cycles. Arm B non-progressive patients received bevacizumab maintenance therapy until progression or toxicity. Primary endpoint was OS. 445 patients were to be randomized, and 385 events observed, to show a significant OS improvement, with 80% statistical power, 5% α-risk. Results: From Feb 2008 to Jan 2014, 448 patients were included in 73 centers. Males: 75.4%, median age: 65.7 years (range 34.7-75.9), PS 0-1: 96.7%. The IDMC recommended a second interim analysis after 95% of events. On 01-Jan-2015, the duration since last news was < 30 days in 105 out of 106 still living patients. Overall survival was significantly longer in the experimental arm (median: 18.8 months, 95%CI[15.9-22.6] vs. 16.1 months, 95%CI[14.0-17.9]) for the reference arm, (adj,HR = 0.76, 95%CI[0.61;0.94], p = 0.012). With only 46/448 non-progressive patients at the date of analysis, median PFS was 9.6 months, 95%CI[8.5-10.6] in bevacizumab arm vs 7.5 months, 95%CI[6.8-8.1] (adj,HR = 0.62, 95%CI[0.50-0.75], p < 0.0001). G3-4 hematological toxicities did not significantly differ between the two arms (49.5% vs. 47.3%). Significantly more G3 proteinuria (0.0% vs. 3.1%), G3 hypertension (0.0% vs. 2.3%), G3-4 arterial thrombotic events (0.0% vs. 2.7%) were observed in bevacizumab arm. QOL and exploratory biomarkers studies will be also presented at the time of the meeting. Conclusions: Bevacizumab addition to pemetrexed/cis-platin provides a significantly longer survival in pts with MPM, with acceptable toxicity, making this triplet a new treatment paradigm. Clinical trial information: NCT00651456.

Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. First Author: Patrick Alexander Ott, Dana-Farber Cancer Institute, Boston, MA

Background: Treatment options for pts with SCLC that progresses on or after platinum (PLT) chemotherapy are limited. Pembrolizumab, an anti–PD-1 monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2, has shown antitumor activity in multiple advanced malignancies, including non-small cell lung cancer. We assessed the safety and efficacy of pembrolizumab in pts with PD-L1–positive tumors. Seventeen pts were enrolled from March 2014 through January 2015. 9 pts (53%) had prior platinum and etoposide. 9 pts (53%) experienced a drug-related AE of any grade, with diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO; 10% were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO and vinorelbine [V], doxorubicin [D] or supportive care). Primary endpoint was OS. Hypothesis testing: hazard ratio (HR) 0.76, 95%CI[0.61; 0.94], p = 0.012. With only 46/448 non-progressive patients at the date of analysis, median PFS was 9.6 months, 95%CI[8.5-10.6] in bevacizumab arm vs 7.5 months, 95%CI[6.8-8.1] (adj,HR = 0.62, 95%CI[0.50-0.75], p < 0.0001). G3-4 hematological toxicities did not significantly differ between the two arms (49.5% vs. 47.3%). Significantly more G3 proteinuria (0.0% vs. 3.1%), G3 hypertension (0.0% vs. 2.3%), G3-4 arterial thrombotic events (0.0% vs. 2.7%) were observed in bevacizumab arm. QOL and exploratory biomarkers studies will be also presented at the time of the meeting. Conclusions: Bevacizumab addition to pemetrexed/cis-platin provides a significantly longer survival in pts with MPM, with acceptable toxicity, making this triplet a new treatment paradigm. Clinical trial information: NCT00651456.

Phase III trial (NGR015) with NGR-hTNF plus best investigator choice (BIC) versus placebo plus BIC in previously treated patients with advanced malignant pleural mesothelioma (MPM). First Author: Babab M. Gasar, National Cancer Institute, Cairo University, Cairo, Egypt

Background: Currently, there are no standard options for MPM patients who failed a pemetrexed-based chemotherapy (CT). NGR-hTNF, a tumor-targeted antivascular agent, displays antitumor activity through a vessel normalization that improves intratumor CT uptake and T-cell infiltration. Methods: MPM patients who progressed on or after a front-line pemetrexed-based chemotherapy, stratified by performance status (PS) and CT agent, were randomly assigned to receive weekly NGR-hTNF 0.8 μg/m² (arm A; n = 200) or placebo (arm B; n = 200), both with BIC (gemcitabine [G], vinorelbine [V], doxorubicin [D] or supportive care). Primary endpoint was overall survival (OS). Hypothesis testing; hazard ratio (HR) = 0.72, 1-α = 0.05. Results: 393 patients were randomized between arms (A vs B); median age (65 vs 67 years); men (76% vs 74%); PS ≥ 1 (72% vs 69%); nonepithelial histology (15% vs 19%); poor EORTC score (30% vs 23%); prior treatment-free interval (TFI) < median of 4.8 months (47% vs 53%). Investigator-selected CT (n = 381, 95%); G 55%, V 42%, D 3%. Patients completing six CT cycles: 41% vs 32% (p = 0.08); Most common grade 3/4 toxicity: neutropenia (17% vs 19%) and fatigue (5% vs 8%). After a median follow-up of 18.9 months, OS did not differ significantly between arms in ITT analysis (median 8.4 vs 7.9 months; HR = 0.94 p = 0.61). By predefined OS analyses, there was a significant interaction only between treatment group and TFI (p = 0.008). In 189 patients with TFI shorter than 4.8 months after first-line therapy, median OS for NGR-hTNF vs placebo was 9.0 vs 6.3 months and 1-year OS was 39% vs 23% respectively (HR = 0.69 p = 0.02; stratified HR = 0.65 p = 0.01). By CT agent, median OS for NGR-hTNF plus G vs placebo plus G was 9.0 vs 6.3 months (p = 0.07), for NGR-hTNF plus V vs placebo plus V was 9.5 vs 6.9 months. A significant treatment-by-TFI interaction was also observed for PFS (p = 0.009), with 6-month rates in the short TFI subset of 25% for NGR-hTNF and 12% for placebo (HR = 0.71 p = 0.03). Conclusions: Though the primary endpoint was not met, OS and PFS benefit reported with NGR-hTNF plus CT in patients with short TFI deserves a confirmatory first-line phase III trial. Clinical trial information: NCT01098266.

Phase II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. First Author: Scott Joseph Antonia, Moffitt Cancer Center, Tampa, FL

Background: Patients (pts) with SCLC respond to initial platinum (PLT) based chemotherapy (CT), but rapidly progress. Combined blockade of PD-1 and CTLA-4 immune checkpoint pathways has antitumor activity with a manageable safety profile. Nivolumab (NIVO) is a fully human IgG4 PD-1 immune checkpoint inhibitor approved in the US & Japan. Interim safety and efficacy of NIVO +/- ipilimumab (IPI), a CTLA-4 checkpoint inhibitor, in pretreated and for NIVO and IPI as salvage therapy, with NIVO sensitive or refractory and had progressive disease were enrolled regardless of tumor PD-L1 status or number of prior CT regimens. This open-label study randomized pts to NIVO 3 mg/kg IV Q2W or NIVO + IPI (1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) IV Q3W for 4 cycles followed by NIVO 3 mg/kg Q2W. Primary objective was overall response rate (ORR). Other objectives were safety, PFS, OS and biomarker analysis. Results: Seventy-five pts were enrolled (NIVO, n = 40; NIVO+IPI, n = 35); 59% had ≥ 2 prior drug regimens. Drug-related adverse events (DRAEs) in ≥ 10% were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO; a 5% incidence of fatigue (29%), dian (17%) neutropenia (≤ 0.5), nausea, and decreased appetite (11%) with NIVO + IPI. Gr 3/4 DRAEs in ≥ 5% included diarrhea and rash (6% each; NIVO + IPI). Drug-related pneumonitis occurred in 2 pts (1 per arm). One pt experienced a drug-related SAE of myasthenia gravis on study which was fatal. Of 40 evaluable NIVO pts, partial response (PR) rate was 16% (3 of 19 pts (16%)) and stable disease (SD) (DRAEs) only 1 pt had a grade ≥ 3 DRAE. There were no treatment-related deaths or discontinuations due to DRAEs. Four of (16% of 25) evaluable pts had a partial response. One (7%) pt had stable disease, resulting in a disease control rate of 31%. Six (37%) pts had progressive disease as their best response, and 5 pts had no assessment at the time of analysis. Responses are durable, with all responders on treatment for 16+ wks with ongoing response. Conclusions: Pembrolizumab is generally well tolerated and has promising antitumor activity in pts with PD-L1+ SCLC who have progressed on prior platinum-based therapy. Enrollment in the SCLC cohort of KEYNOTE-028 is ongoing. Clinical trial information: NCT02054806.
Clinical trial information: NCT01555710.

CE did not improve survival in ES-SCLC. The safety profile was similar in the majority of pts having an ECOG PS of 0-1. Median OS in the Intent to treat group was 11.4 mos in the control arm, but did have a better safety profile than the Eto arm. As expected, toxicity-adjusted dosing increases side-effects. How-ever, it does not improve the ORR, nor does prolong PFS or OS in advanced SCLC patients. Clinical trial information: NCT00526396.

#### 7504 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

**Results** from a randomized study of carboplatin and etoposide (CE) with or without paclitaxel (Pa) in extensive stage small cell lung cancer (ES-SCLC): The MATISSE trial. First Author: Alexiadis Ibrahim Jalal, Indiana University School of Medicine, Indianapolis, IN

**Background:** Extensive stage small cell lung cancer (ES-SCLC) is a disease with high mortality. SCLC is initially exquisitely sensitive to chemotherapy with carboplatin and etoposide (CE), considered the standard first-line regimen in ES-SCLC in the US. In a previous phase III trial, the combination of cisplatin, etoposide, and ifosfamide (VIP) improved overall survival (OS) as compared to cisplatin and etoposide (CE) but with increased toxicity (UCO 13: 2594-2599,1995). Paclitaxel (Pa), a bi-functional DNA alkyator is the active metabolite of ifosfamide (If) which does not generate toxic metabolites facilitating its combination with CE. This trial was therefore pursued comparing CE with or without Pa in ES-SCLC.

**Methods:** This was a multi-center, open-label trial in chemotherapy-naive patients (pts) with ES SCLC with planned enrollment of 548 pts. Pts were randomized 1:1 to receive CE (C at AUC 5mg/mL/min day 1) or PaCE (Pa at 130mg/m2/day, E at 100mg/m2/day both on days 1-3) or PaCE (Pa at 130mg/m2/day, E at 100mg/m2/day both on days 1-3) and C at 4ug/mg/mL/min day 1). The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival, objective response rate, and quality of life assessment. Pts were stratified based on age, gender, and Eastern Cooperative Oncology Group (ECOG) performance status. **Results:** The MATISSE trial closed prematurely in light of the negative phase III trial evaluating the addition of etoposide to thoracic radiotherapy (RCT). In a large European trial (ES-SCLC pts (N = 188) were randomized to CE (n = 94) or PaCE (n = 94). Pt characteristics were well balanced with median age of 61 and the majority of pts having an ECOG PS of 0-1. Median OS in the Intent to treat population was 10.0 mos (95% CI: 7.7-10.5) with PaCE and 10.4 mos (95% CI: 8.7-13.4) with CE (p value 0.096). Serious treatment-related adverse events were observed in 28.3% pts receiving PaCE and 27.5% pts receiving CE with febrile neutropenia occurring in 4.3% of pts on PaCE arm and 5.5% of pts on CE arm. **Conclusions:** The addition of Pa to CE did not improve survival in ES-SCLC. The safety profile was similar on PaCE and CE, the paclitaxel arm did not lead to increased toxicity. Clinical trial information: NCT01555710.

#### 7506 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

**Final overall survival (OS) results of the phase III PROCLAIM trial:** Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiotherapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nSNSCLC). First Author: Suresh Senan, VU University Medical Center, Amsterdam, Netherlands

**Background:** Efficacy and safety of concurrent Pem+Cis and TRT followed by consolidation Pem+CTX were presented previously (Vokes et al. 2013). **Methods:** Six hundred and ninety-eight patients (pts) with stage III unresectable nSNSCLC were randomized 1:1 to Pem+Cis (Pem 500 mg/m2, d1; Cis 75 mg/m2, d1-5, q3w) or Pem+CTX (60.0 Gy) every 21 days (q21d) x 3 cycles followed by Pem consolidation (66.0 Gy) every 28 days (q28d) x 2 cycles followed by 2 cycles of a consolidation CTX of choice: Cis+Eto, Cis+vinorelbine, or paclitaxel+carboplatin. The primary objective was OS. Progression-free survival (PFS), objective response rate (ORR), and safety were key secondary objectives. This superiority trial was designed to achieve 80% power, assuming an OS HR of 0.74 with 355 events at 0.05 α (two-sided) using a log-rank test. **Results:** Five hundred and fifty-five pts were treated: 283 Pem+Cis, 272 Eto+Cis. Baseline characteristics were balanced between arms (Pem+Cis/Eto+Cis): median age: 65.9 (56.7-74.0) vs 67.5 (57.0-74.0); median PS: 1.0 (0-2) vs 1.0 (0-2); median Karnofsky: 70 (0-100) vs 70 (0-100); median number of chemotherapy cycles: 6 (0-10) vs 6 (0-10). **Conclusion:** Pem+Cis did not improve OS vs the control arm, but did have a better safety profile than the Eto+Cis arm. Clinical trial information: NCT00686959.

#### 7507 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

**A multicenter, randomised, phase III trial comparing fixed dose versus adjusted dose of cisplatin + etoposide in advanced SCLC patients.** The STAD-1 trial. First Author: Alessandra Morabito, National Cancer Institute of Naples, San Nicola La Strada Caserta, Italy

**Background:** Classic dosing of chemotherapy does not account for pts’ variability and some pts could be undertreated. We tested whether toxicity-adjusted dosing of chemotherapy was more active than classic dosing in advanced SCLC pts. (ClinicalTrials.gov NCT00526396). **Methods:** Advanced chemosensitive SCLC pts, aged ≤ 75, ECOG PS ≤ 2, were randomised to either control (fixed-dose cisplatin/etoposide: C 80mg/m2, d1 = E 100mg/m2, d1-3, q3w) or experimental (adjust-dose, C in ES-SCLC pts but escalated with age) (two-sided) using a toxicity-adjusted dose of cisplatin dosing increases side-effects. However, it does not improve the ORR, nor does prolong PFS or OS in advanced SCLC patients. Clinical trial information: NCT00526396.
7508 Poster Discussion Session; Displayed in Poster Session (Board #255), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 1:15 PM-2:30 PM

Final results of phase Ib of tarextumab (TRTX, OMP-59595, anti-Notch2/3) in combination with etoposide and platinum (EP) in patients (pts) with untreated extensive-stage small-cell lung cancer (ED-SCLC). First Author: Maria Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Notch signaling is implicated in cancer stem cell self-renewal and proliferation; thus being an appealing target in the treatment of SCLC. Tarextumab (TRTX), a fully human IgG2 antibody targeting Notch2 and 3 receptors, has shown preclinical efficacy in SCLC models with cisplatin. This Phase Ib study explores the MTD, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of TRTX with EP in chemo-naive ED-SCLC. Methods: Notch signaling is implicated in cancer stem cell self-renewal and proliferation; thus being an appealing target in the treatment of SCLC. Tarextumab (TRTX), a fully human IgG2 antibody targeting Notch2 and 3 receptors, has shown preclinical efficacy in SCLC models with cisplatin. This Phase Ib study explores the MTD, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of TRTX with EP in chemo-naive ED-SCLC. Results: By November 18, 2014, 27 pts were treated with TRTX at dose range from 5 mg/kg to 15 mg/kg. The MTD was not reached and TRTX 15 mg/kg was determined to be the Phase 2 dose. One DLT of Grade 3 nausea and vomiting was reported in the 10 mg/kg dose cohort. Frequently reported (≥ 15%) TRTX-related adverse events were: diarrhea (29.3%), fatigue (44.4%), nausea (40.7%), (25.9%), decreased appetite (25.9%) and vomiting (25.9%); most Grade 2 or 1 and managed with supportive care. The overall response rate was 84%. The median duration of treatment was 128 days (6 cycles) with mPFS and mOS of 124 and 228 days, respectively. The median follow-up for P400 and OS was 89 and 107 days the placebo arm: 32 days. DLT with EP is well tolerated. Encouraging anti-tumor activity has been observed. Final safety, efficacy, PK, immunogenicity and predictive biomarker results will be presented. TRTX at a dose of 15 mg/kg has been selected for the phase 2 randomized, placebo-controlled portion of the study, which is ongoing. Clinical trial information: NCT01895741.

7509 Poster Discussion Session; Displayed in Poster Session (Board #256), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 1:15 PM-2:30 PM

Lurbinitedim (PM01183) with doxorubicin (DOX), an active treatment as second-line therapy in small cell lung cancer (SCLC). First Author: Martin Forster, University College London, London, United Kingdom

Background: PM01183 inhibits transscriptional transduction and acts on the tumor microenvironment. It lacks cross-resistance with platinum. PM01183 and DOX are synergistic in vitro. Recommended dose (RD): 4 mg (or 2 mg for females) + 50 mg/m2 daily for 21 days every 3 weeks. Compelling activity was observed earlier in 2nd line SCLC patients (pts), leading to a cohort expansion. The historical response rate (RR) of DOX-based combinations is around 29%. Methods: SCLC pts < 75 years with ECOG PS 0-1, adequate organ function and 1 prior chemotherapy-containing line were included. Stable asymptomatic brain metastases were allowed. DOX was discontinued before reaching 450 mg/m2, non-progressing pts could continue on PM01183 alone. CSF prophylaxis was not mandatory. Results: 21 pts were treated and evaluable for efficacy (response rate (RR) by RECIST v1.1). Male: 76%; median age: 62 y (48-73); ECOG PS = 0 in 43/57%; 29% had metastases, 62% had bulky disease and 80% responded to 1st line, 5% CRs. Median chemotherapy-free interval (CTFI) was 3.1 months; 48% were resistant (R = CFI < 90 d). Confirmed RR was 67% (95% CI: 43-85%), including –10% CRs. CTFI was predictive of RR (100% vs. 30% in R pts; p = 0.001). Grade (G) 4 neutropenia, thrombocytopenia or anemia occurred in 86%/19%/5%, respectively and febrile neutropenia (G3/4) in 29%. Other toxicities were generally mild: fatigue (G3/4 in 13% of pts), anorexia, nausea, vomiting, alopecia, stomatitis (G3 = 10%), dysgeusia, constipation and pneumonia (10%). Three pts discontinued due to toxicity (myelosuppression, renal failure, dyspnea). No cardiac toxicity or OS events occurred. Of events occurring, 24% of G3/4 events were ongoing. Progression-free survival (PFS) is 4.7 months (95CI: 3.5–not reached). Conclusions: The PM01183 and DOX combination showed compelling clinical activity as 2nd line treatment in SCLC. RR could be comparable to first-line treatment. Response rate and median CTFI was the most frequent and expected side effect; DOX dose adjustment and/or CSF prophylaxis might be appropriate to improve tolerance. A randomized study is planned to help define the role of this combination in relapsed SCLC pts. Updated results will be presented. Clinical trial information: NCT01970540.

7510 Poster Discussion Session; Displayed in Poster Session (Board #257), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 1:15 PM-2:30 PM

Pazopanib (P) or placebo in completely resected stage I NSCLC patients: Survival results of the phase II trial IFCT-0703. First Author: Benjamin Besse, Gustave Roussy, Villejuif, France

Background: P is an anti-angiogenic agent approved in metastatic renal cell carcinoma and sarcoma. We have previously reported compliance. A one-step Fleming design was used with the new dose. Here, we report survival data. Mets: TRXT at a dose range from 5 mg/kg to 15 mg/kg. The MTD was not reached and TRXT 15 mg/kg was determined to be the Phase 2 dose. One DLT of Grade 3 nausea and vomiting was reported in the 10 mg/kg dose cohort. Frequently reported (≥ 15%) TRTX-related adverse events were: diarrhea (29.3%), fatigue (44.4%), nausea (40.7%), (25.9%), decreased appetite (25.9%) and vomiting (25.9%); most Grade 2 or 1 and managed with supportive care. The overall response rate was 84%. The median duration of treatment was 128 days (6 cycles) with mPFS and mOS of 124 and 228 days, respectively. The median follow-up for P400 and OS was 89 and 107 days the placebo arm: 32 days. DLT with EP is well tolerated. Encouraging anti-tumor activity has been observed. Final safety, efficacy, PK, immunogenicity and predictive biomarker results will be presented. TRTX at a dose of 15 mg/kg has been selected for the phase 2 randomized, placebo-controlled portion of the study, which is ongoing. Clinical trial information: NCT01895741.

7511 Poster Discussion Session; Displayed in Poster Session (Board #258), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session, Mon, 1:15 PM-2:30 PM

ARG 197 in patients with previously-treated malignant mesothelioma (MM): A phase II trial from the University of Chicago Phase II Consortium. First Author: Steven Brad Maron, University of Chicago, Chicago, IL

Background: The MET receptor tyrosine kinase plays a key role in MM biology. MET and its ligand, hepatocyte growth factor (HGF), are each over-expressed in ~80% of MM; MET is mutated and/or amplified in ~10% of MM. Cancers with MET over-expression or mutation are potentially more sensitive to MET inhibitors, such as ARQ 197 (tivantinib), which inhibits MM growth and proliferation in preclinical models. Methods: We conducted a multicenter phase II trial of ARQ 197 in previously-treated pts with histologically-confirmed pleural (PL) or peritoneal (PER) MM, measurable disease, PS 0-1, and ≤ 2 prior chemotherapies. Primary endpoint: response. ARG 197 350mg was given orally BID. CT scans were obtained Q8 weeks. A Simon, optimal, 2-stage design required 2 responses in 16 pts to proceed to a 2nd stage. Correlatives: MET mutation, gene amplification, IHC, and serum HGF. Results: 18 pts enrolled at 4 centers between 2/13 and 12/13. Male 61%; median age 66 (range 19-81); PS 0: 50%; epithelial/biphasic/sarcomatoid histology: 89%/9%/2%; ECOG PS ≤ 2: 92%. Median cycles: cycles (2-14). There were no objective responses. Stable disease (SD): 50% (33 PL pts, 71 PER pts). 3 PER pts had SD for 9.7, 11, and 15.2 months, respectively. Median PFS: 1.9 mo (95% CI: 1.6-2.4); PL/PER 1.3/1.8 mo (95% CI: 1.1-2.7). Median OS 12.2 months. ARG 197 was well-tolerated; DLTs were nausea, vomiting, fatigue, infection 6% each. Correlatives: N = 16. HCC expression (0/1+2+/3+): c-MET (38%/31%/19%/13%), p-MET (0%/0%/31%/69%), and p-AKT (0%/13%/56%). One pt had a 1110 mutation in the MET juxtamembrane domain which was overcome in vitro with ARQ 197. In vivo, the combination of ARG 197 HCC expression or mutation and PFS or OS upon preliminary analysis. Conclusion: The trials did not meet its pre-specified response endpoint. However, 43% of peritoneal pts had SD for > 9 months. Though p-MET expression was high, MET HCC expression or mutation did not correlate with disease control. Alternative biomarkers predictive of the activity of ARQ 197 in PER MM pts should be evaluated. Funded by NCI NO1-CM-2011-071C.
A randomized phase II study of TS-1 plus cisplatin versus vinorelbine plus cisplatin with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC): WJOG 5008L. First Author: Takashi Seto, National Kyushu Cancer Center, Fukuoka, Japan

Background: Cisplatin-based chemotherapy and concurrent radiotherapy is the standard treatments for LA-NSCLC. Histrial evaluated two experimental regimens of chemotherapy with concurrent radiotherapy. Methods: Eligible patients with unresectable stage IIIA NSCLC, 20 to 74 years of age, and ECOG PS of 0–1 were randomized to either Arm SP, S-1 (40 mg/m²/dose per oral, b.i.d, on days 1-14) and cisplatin (60 mg/m² on day 1) repeated every 4 weeks or Arm VP, vinorelbine (20 mg/m² on day 1, 8) and cisplatin (80 mg/m² on day) repeated every 4 weeks with concurrent thoracic radiotherapy of 60 Gy at 2 Gy per day fractionation. The primary endpoint was overall survival rate at 2-year (2y-OS). A pick-the-winner design was used to identify the treatment regimen most likely to be superior. The planned sample size was 55 patients per arm, assuming in each arm that the null hypothesis for 2y-OS was 50% versus an alternative hypothesis for 65% with one-sided alpha of 0.10 and power of 80% (Study ID: UMIN000002420). Results: One hundred eleven patients were registered between Sep 2009 and Sep 2012. Of 108 patients for efficacy analysis, the 2y-OS was 76% (95% CI, 62-85%) for SP and 69% (95% CI, 54-79%) for VP. The hazard ratio (HR) of death between the two arms was 0.85 (0.48-1.49). The median progression-free survival (PFS) for SP was 13.4 months and for VP 9.7 months. The Kaplan-Meier curves for overall survival (OS) were 0.92 (0.58-1.44) for SP and 0.80 and 48% of patients completed the protocol treatment in SP and VP, respectively. Common grade 3-4 toxicities in SP vs VP were neutropenia 33.3% vs 75.9%, platelets 9.3% vs 3.7%, hemorrhagic 1.9% v 27.8%, febrile neutropenia 9.3% v 16.7%, diarrhea 5.6% v 0%. There were 4 and 5 treatment-related deaths in SP and VP, respectively. Conclusions: Both arms rejected the null hypothesis for 2y-OS. In this study Arm SP was declared the winner in terms of 2y-OS, PFS, treatment completion, and toxicity. Clinical trial information: 0000002420.

Tridomality therapy in the treatment of stage IIIA non-small cell lung cancer (NSCLC): Analysis of the National Cancer Database. First Author: Madhusmita Behera, Winship Cancer Inst Emory Univ, Acworth, GA

Background: Significant controversy remains regarding the care of patients (pts) with clinical stage IIIA NSCLC. While multi-modality therapy is an acceptable strategy in selected pts, the optimal approach is not firmly established. We analyzed outcomes and predictors associated with tridomality therapy (TT) in the National Cancer Database (NCDB). Methods: The NCDB was queried from 2003-2011 for NSCLC pts diagnosed with stage IIIA disease and treated with chemotherapy (C) and concurrent radiotherapy (CRT). The analysis included 19,373 patients for OS comparison. Results: A total of 29,584 pts were included in this analysis: NS-91.7%, L-7%, and P-1.5%. Pt characteristics: median age 66 years (yrs); males 56%; whites 86%; academic centers 27%; metro locations 78%; government insured 63%; Charlson/Deyo comorbidity score 0 in 66%, Pts < 60 yrs were more likely to receive TT vs P (L 47%, P 60% vs NS 29%; p < 0.001). In pts with academic centers were more likely to get TT than in pts in SP. On MV analysis, L and P had significantly better survival vs. NS: HR 0.43 (0.38-0.48) and HR 0.57 (0.46-0.71) respectively; p < 0.001. The median survival of L, P and NS were 44.5 m vs 25.6 m vs 15.7 m (p < 0.001) and 5- year survival rates (5y-SR) were 64% vs. 33% vs. 14% respectively. 30-day mortality was higher in P vs. L (7% vs. 2.6%; OR 0.26(0.16-0.45); p < 0.001). Pts with < 2 lymph nodes (LN) had better survival than pts with > 2 LNs in L (60% vs. 38%) and worse in NS (13.8% vs. 16.5% and 15.3% vs. 18.5m). On MV analysis of LNs, L had better survival than NS: HR 0.4 (0.35-0.46) in < 2 LN pts and LR 0.56 (0.46-0.69) in > 2 LN pts; p < 0.001. In pts with < 2 LN, L had better survival than P (65m vs. 25.5m; p < 0.0001), and P had better SR than NS in all ages: 48% vs. 33% and 19% in 60 yrs; 42% vs. 30% vs. 14% in 61-70 yrs, 36% vs. 19% vs. 10% in > 70 yrs. Conclusions: TT was associated in less number of pts with stage IIIA NSCLC disease, suggesting high degree of pt selection. In this selected group, TT was associated with favorable outcomes relative to CRT alone.

Programmed cell death 1 (PD-1) and its ligand (PD-L1) expression in thymic epithelial tumors (TETs): Impact on the treatment efficacy and alteration in expression after chemotherapy (C). First Author: Yuki Katsuya, National Cancer Center Hospital, Tokyo, Japan

Background: Recent studies have demonstrated the efficacy of anti-PD-1/L1 antibodies. To understand the clinical impact of PD-L1/L1 expression in TETs, we evaluated the frequency of PD-L1/L1 expression in pre- and post-C (Post) specimens and the correlation between PD-L1/L1 expression and the treatment efficacy. Methods: The expression of PD-L1/L1 was evaluated by immunohistochemistry in patients (pts) with thymoma (TM) or thymic carcinoma (TC) treated by chemotherapy between 2000 and 2014 at the National Cancer Center Hospital. Using formalin-fixed paraffin-embedded tissue samples and a validated PD-L1 antibody (E1L3N), the PD-L1 expression in TET cells was reported in terms of the H-score (0-300), with a score ≥ 1 being defined as positive. PD-1 expression in the tumor-infiltrating lymphocytes was evaluated based on the intensity (0–3) of staining using a PD-1 antibody (NAT105). The objective response rate (ORR), progression-free survival (PFS) and the correlation between PD-L1/L1 expression before and after chemotherapy were evaluated. Results: A total of 29 pts was included; TM/TC, 12/17; male/female, 14/15; median age 57; WHO histology (B1/B2/B3/Squamous/others), 1/7/3/12/6. Pre/Post C chemotherapy included 6-8 cycles of platinum-based C, and the ORR was 18% in TMs and 12% in TCs. The expression of PD-L1 was positive in 9 (75%) of the TMs and 8 (47%) of the TCs. In the PD-L1 positive population, ORR was 56% (5/9) in TMs and 13% (1/8) in TCs. In the PD-L1 negative group, ORR was 0% (0/3) in TMs and 22% (2/9) in TCs. There were no statistically significant differences in the PFS according to the PD-L1 expression status. Increase of the PD-L1 score and PD-1 staining intensity were observed in C in serial specimens of TM; mean Pre/Post PD-L1 score, 41.6±92.5 (p = 0.058); median Pre/Post PD-1 intensity, 0.2/5 (p = 0.055). Conclusions: Although there was no obvious correlation between PD-L1 expression and the efficacy of C in pts with TET, increased expression of PD-L1 after C was observed in the TMs. Further efforts to develop novel therapies, including anti-PD-1/L1 antibodies, are warranted.
Defining the immunologic phenotype of thymic epithelial tumors. First Author: Jarushka Naidoo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Thymic epithelial tumors (TETs) are associated with immune dysfunction and are poorly responsive to conventional therapies. We aimed to characterize the immune microenvironment in TETs, to identify potential targets for immunotherapeutic strategies. Methods: Tumor tissue from 24 TETs was identified. Tumor-infiltrating lymphocytes (TILs; CD3+ and CD8+ T-cells), PD-L1 expression on tumor cells (antibody: E1L3N), and a panel of co-stimulatory (CD137, GITR, OX40, ICOS) and co-inhibitory checkpoint molecules (PD-1, CTLA-4, TIM-3) on immune cells, was investigated by immunohistochemistry. PD-L1 positivity was defined as ≥ 25% of tumor cells with positive membranous staining. TILs and immune cell checkpoint molecule staining were semi-quantitatively scored as: low = 0-1, high = 2-3. Associations between clinicopathologic factors, immune checkpoint molecule expression and TILs, was evaluated. Overall survival (OS) was measured from the time of cancer diagnosis, assuming that immune markers do not change throughout the course of disease. Data was analyzed using Fisher’s exact test, Wilcoxon rank sum and log-rank tests, and Cox proportional hazards model. Results: Tumor tissue from 2/23 thymomas (n = 12) and thymic carcinomas (n = 12) was evaluated. CD8+ TILs was seen in all tumors. Sixty-three percent of TETs (n = 15/24) were PD-L1+. PD-L1 positivity was more common in thymomas than thymic carcinomas (11/12 vs. 4/12, p < 0.01). When analyzed as a continuous variable, PD-L1 expression had an inverse correlation with risk of death (p = 0.02). Eighteen pts with TETs (n = 18/24, 75%) had high TIM-3 expression. Two immunologic parameters correlated with improved survival – PD-L1+ tumor cells (p < 0.01) and high TIM-3 expression (p = 0.01). There was a positive correlation between PD-L1+ tumor cells and CD8+ T-cells (p = 0.02), PD-L1+ tumor cells and high TIM-3 expression (p = 0.03). CD8+ T-cells and high TIM-3 expression rejected the null hypothesis, which supports the idea that TETs possess a robust TIL infiltrate. The majority of tumors have high expression of the co-inhibitory checkpoint molecule TIM-3, and 3-TIM-3 positivity was observed in 15/24 TETs. These parameters may correlate with OS. These data support the immunotherapeutic targeting of the PD-1/PD-L1 and TIM-3 pathways in patients with TETs.

Propective molecular analysis of small cell lung cancer (SCLC) using next generation sequencing (NGS). First Author: Maria Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Recent studies using NGS on resected SCLC have provided insights into the landscape of genetic alterations in this disease. We report our experience with prospective genomic profiling of SCLC patients using the biopsy specimens available in clinical practice and a targeted, hybrid capture-based, NGS assay, MSK-IMPACT. Methods: Utilizing an IRB approved protocol, we are evaluating SCLC tumors of patients in active treatment. FFPE surgical resections, core biopsies, and fine needle aspirates (FNA) are being evaluated by NGS to identify single nucleotide mutations, insertions and deletions, and copy number alterations in a common set of 222 cancer-associated genes shared by pre-clinical and clinical versions of MSK-IMPACT. Clinical data are collected (smoking status; stage [extensive (ES), limited (LS)]; treatment response). Results: Currently, 50 patient samples have undergone evaluation, 58% from core biopsies or FNA. The 50 SCLC patients included 4 never smokers, 58% with ES-SCLC, and 30% resistant to first line therapy. Alterations have been detected in 222 targeted genes. The median number of non-synonymous somatic mutations is 7. Of 526 total non-synonymous mutations, 5% are hotspot COSMIC mutations, 25% are loss-of-function, and 47% are G-to-T transversions, reflective of tobacco induced carcinogenesis. We observe frequent inactivation of RB1 (96%), and TP53 (92%). Other common genomic events include alterations in SOX2 (26%), EPHA5 (22%), Cdkn2c (20%), MYC1 (20%), and PIK3CA (18%). Tumors from the 4 never smokers (0 pk yrs) displayed a median of 3 mutations, of which none were G-to-T transversions, while those from moderate (<20 pk yrs) and heavy (≥20 pk yrs) smoking exhibited 7 and 8 mutations respectively. ES-SCLC patients had a lower median number of mutations (5/mut) than LS-SCLC patients (9/mut). Diverse amplifications, deletions, and mutations are noted in sensitive tumors, while homozygous deletions are more common in refractory tumors. Conclusions: Comprehensive molecular evaluation of SCLC is feasible on resectable specimens using a targeted NGS assay. Prospective analyses allow us to fully characterize the molecular diversity of SCLC in the clinical setting.

Genomic profiling of large-cell neuroendocrine carcinoma of the lung, First Author: Tomohiro Miyoshi, Division of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: Large-cell neuroendocrine carcinoma (LCNEC) of the lung shares many clinical characteristics with small-cell lung cancer (SCLC). However, little is known about the molecular biology of LCNEC. We analyzed lung LCNECs for biologically relevant genomic alterations using a next-generation sequencing-based genomic profiling assay. Methods: Genomic DNAs extracted from surgically resected or biopsy samples were subjected to a 1.499 Mb custom target capturing panel including all exons of 244 cancer-related genes. Seventy eight LCNEC samples including 10 LCNECs combined with other non-small cell lung cancers (NSCLCs) were applied to the target sequencing. In the 10 combined LCNECs, both morphologic components of LCNEC and other NSCLCs (adenocarcinoma: 5, squamous cell carcinoma: 5) were analyzed separately. Frequencies of detected driver gene alterations were compared with those in previous reports regarding SCLC. Results: The demographics of the 78 patients were as follows: median age 70 years (range: 22-94); male 57% (44/78); smoking status: 78% (61/78); performance status (PS) in 18 (52.9%), pursuing alternate therapy in 3 (9.1%), smoking 76 (97%); pathological stage I/II/III = 38/14/3 for 65 resected cases and clinical stage I/II/III = 1/4/8 for 13 biopsy cases. We identified high prevalence of inactivating mutations in TP53 (74%) and RBL (29%), and mutations of histone modifiers, CREBBP (10%) and EP300 (4%), were detected. Conclusions: LCNEC is a heterogeneous tumor with frequent alterations in both PI3K/AKT/mTOR and DNA repair pathways. 11% of all patients had RAS (4%) and KRAS (3%) mutations.
Adjuvant chemotherapy for patients with T2N0M0 non-small cell lung cancer. First Author: Daniel Morgensztern, Washington University School of Medicine in St. Louis, MO

**Background:** Adjuvant chemotherapy (CT) improves overall survival (OS) in patients with completely resected stage I and III non-small cell lung cancer (NSCLC). However, its role in patients with stage IB disease remains unclear. We therefore evaluated the role of adjuvant CT in patients with completely resected T2N0M0 NSCLC.

**Methods:** Patients with pathologic stage T2N0M0 NSCLC who underwent complete (RO) resection from 2003 to 2010 were identified from the National Cancer Database (NCDB). Patients were grouped based on tumor size: 3-3.9 cm, 4-4.9 cm, 5-5.9 cm and 6-7 cm. Survival curves according to the CT status were estimated by the Kaplan-Meier product-limit method and compared by log-rank test. Cox proportional hazard model was used to evaluate whether adjuvant CT was an independent predictor for survival for each tumor size groups.

**Results:** Among the 29,908 patients meeting inclusion criteria, there were 5,209 (17.4%) and 24,699 (82.6%) patients in the CT and observation groups respectively. Patients treated with CT were younger (median age 65 vs 71 years, p < 0.001), had smaller median tumor sizes (3.7 vs 4.1 cm, p < 0.001), and a lower incidence of sublobar resection (5.6% vs 8.2%, p < 0.001). Adjuvant CT improved median OS compared to observation for all tumor size groups in both univariate (UVA) and multivariate (MVA) analyses (Table). **Conclusions:** Adjuvant CT was associated with improved OS in all tumor size groups for patients with completely resected T2N0M0 NSCLC. Despite the biases inherent in a database study, the benefit from adjuvant CT in patients with tumors < 4 cm suggests a possible role in this patient population and the need for revisiting its current status as an exclusion criterion for adjuvant trials.

Adjuvant chemotherapy versus observation.

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>All patients</th>
<th>3-3.9cm</th>
<th>4-4.9cm</th>
<th>5-5.9cm</th>
<th>6-7cm</th>
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<tr>
<td>Median OS (months)</td>
<td>95.6 vs 67.0</td>
<td>97.0 vs 59.7</td>
<td>90.9 vs 64.7</td>
<td>87.9 vs 60.8</td>
<td>86.9 vs 54.6</td>
</tr>
<tr>
<td>5-year OS</td>
<td>67.9 vs 54.6%</td>
<td>70.5 vs 57.7%</td>
<td>66.5 vs 52.7%</td>
<td>63.5 vs 48.3%</td>
<td>60.5 vs 45.6%</td>
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**Proportional hazards regression using 5-year mortality [hazard ratio (HR) 0.55 (0.47-0.64) 0.62 (0.53-0.72) 0.61 (0.55-0.68) 0.70 (0.63-0.77) 0.62 (0.53-0.72)]**

Adjuvant chemotherapy versus observation.

**Validation of a cell cycle progression score for 5-year mortality risk in patients with stage I non-small cell lung cancer.** First Author: Takashi Eguchi, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** The aim of this study was to validate a molecular expression [cell cycle progression (CCP) score] and a Prognostic Score (PS) combination of CCP and pathological stage (IA or IB) that identify stage I non-small cell lung cancer patients with a higher risk of cancer-related death after surgical resection. Methods: Formalin-fixed paraffin-embedded surgical tumor samples from 1200 patients diagnosed with stage I adenocarcinoma who underwent definitive surgical treatment without adjuvant chemotherapy were analyzed for 31 proliferation genes by quantitative RT-PCR. The prognostic discrimination of the CCP score and the PS were assessed by Cox proportional hazards regression using 5-year lung cancer death as primary outcome. **Results:** In a multivariable model the CCP score was a significant prognostic marker of 5-year lung cancer mortality [hazard ratio (HR) = 1.54 per interquartile range (95% confidence interval = 1.10–2.15; p = 0.0110)]. Other significant variables included age, tumor size, lymphatic invasion, morphology grade and type of surgery. Gender, smoking status, pathological stage, pleural invasion and vascular invasion were not significant. In a separate multivariable model the PS was a significant prognostic marker of 5-year lung cancer mortality [hazard ratio (HR) = 1.76 per interquartile range (95% confidence interval = 1.14–2.72; p = 0.0112)]. Using a previously established threshold (85% percentile) of the PS, there was a significant difference in lung cancer survival between low-risk and high-risk patient groups (p < 0.0001).

**Conclusions:** This study validates both the CCP score and PS as independent prognostic markers of lung cancer death in patients with Stage I lung adenocarcinoma treated with surgery alone. Significantly, in the Stage IB population, CCP and PS provide quantitative risk information above that captured by current NCCN high risk features. Patients with resected stage I lung adenocarcinoma and a high CCP and PS may be candidates for adjuvant therapy to reduce cancer related mortality.

**The effect of platinum based adjuvant chemotherapy on survival in the surgically resected lung adenocarcinoma according to the expression of EGFR mutation specific antibody and c-MET.** First Author: In-Ho Kim, Division of Oncology, Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea

**Background:** To assess the role of mutant EGFR and c-MET in survival benefit obtained from platinum-based adjuvant chemotherapy (PBAC) among resected lung adenocarcinoma (RLADC) patients. **Methods:** From 2005 through 2013, the RLADC patients (stage IB-IIIA) receiving either PBAC (Paclitaxel/Caboplatin, Paclitaxel/Carboplatin, or Vinorelbine/Caboplatin) or to be observed were enrolled. We did immunohistochemistry (IHC) study with mutant EGFR-specific antibody (mutEGFR-sAb) and C-MET in tissue microarray with 301 cases. We assessed the effect of PBAC on survival according to the expression of mutEGFR-sAb and C-MET. **Results:** Until Oct. 2014, 85 patients experienced relapse and 65 patients died among 301 patients. The median follow-up period for survival was 22.4 months. 137 patients received PBAC, Clinical characteristics is as follows; F: M = 165:136, stage Ib 170, II 74, IIIa 47. The IHC were positive for mutEGFR-sAb in 78 cases (42 in exon 19, 36 in exon 21) and for C-MET in 1st withexpress. Compared with EGFR mutation by direct sequencing the specificity and sensitivity of mutEGFR-sAb were 99% and 88%, respectively. PBAC prolonged overall survival (OS) in mutEGFR-sAb (+) group of stage II,III patients with statistical significance (p = 0.040), not in mutEGFR-sAb (-) group (p = 0.460). Among all patients, PBAC was an independent prognostic factor for survival free from relapse (HR = 0.74, CI 0.54-0.93, p = 0.034) and OS (HR = 0.17, P = 0.033) in mutEGFR-sAb (+) group. By contrast, in patients with mutEGFR-sAb (-), PBAC was not associated with RFS (HR = 0.63, p = 0.144) and OS (HR = 0.55, p = 0.091). Meanwhile, in C-MET (+) subgroup of stage II and IIIa patients, PBAC showed significantly longer survival (RFS; p = 0.088; OS; p = 0.015), not in C-MET (-) subgroup. (RFS; p = 0.597, OS; p = 0.839). The multivariate analysis indicated that PBAC may be an important factor for increased survival among C-MET(+) patients (RFS; HR = 0.53, p = 0.086; OS; HR = 0.34, p = 0.010) but not among C-MET (-) (RFS; HR = 0.74, p = 0.472; OS; HR = 0.83, p = 0.157). Taken together, our data suggests that overexpression of mutEGFR-sAb and C-MET may be favorable predictive biomarkers for PBAC among RLADC patients.
7524  Poster Session (Board #271), Mon, 8:00 AM-11:30 AM
Therapeutic Interventional Mapping System (TIMS): A novel strategy for the selection of tri-targeted therapy combinations for non-small cell lung cancer (NSCLC). First Author: John Mendelsohn, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Combining three targeted therapies significantly improved outcomes in AIDS. A similar strategy could theoretically benefit patients with metastatic NSCLC, but a scientific method for rational selection of drug combinations is needed. Methods: We assessed genomics and the transcriptome (including miRNA), utilizing defined subsets of relevant gene/protein products, and scored information about the relationships between targeted drugs and genes, based in part on the biological hallmarks of cancer. Interventional points (genes/group of genes) that, when activated, could be blocked by a customized therapy combination, were identified. The underlying algorithm integrates and weighs the genomic (DNA sequencing) and transcriptomic data (miRNA and mRNA) against differential expression between tumor and normal -bronchial mucosa -tissues. Results: Key genes (N = 183) grouped in 24 intervention points forming the Therapeutic Interventional Mapping System (TIMS) were elucidated. Frequency and trends of co-activation derived from 121 NSCLC patients defined a list of candidate triple therapy combinations. The focus, in order to limit toxicity, was on the application of two small molecules (TKI) and an immune-modulator (anti-PD1L). Twenty-eight percent of NSCLC patients displayed the simultaneous activation of PD1L, Ras/Raf and mTor/P13K interventional points. Overall, fifty two percent of NSCLC patients could be targeted by a triple combination that includes an anti-PD1L agent. Most individuals could benefit from two or even more triple combinations to overcome resistance. Conclusions: The TIMS’s strategy enables conversion of thousands of genomic and transcriptomic measurements into a simple and actionable result (a 1 to 10 score) that may be applicable by physicians to select triple drug therapy. Comparing tumor and normal tissue biopsies has proven feasible in the ongoing WINTER trial (NCT01856296). This novel strategy may allow deployment of personalized tri-targeted therapies that will be prospectively tested in a clinical trial with the objective to significantly impact survival in advanced NSCLC and other malignancies.

7525  Poster Session (Board #272), Mon, 8:00 AM-11:30 AM
Prognostic value of cytokine profile on survival in non-small cell lung cancer patients treated with radiotherapy. First Author: Shulian Wang. Department of Radiation Oncology, GRU Cancer Center and Medical College of Georgia, Augusta, GA

Background: Immunomodulatory and inflammatory cytokines play an important role in cancer development and progression. This study is to investigate the prognostic value of cytokine profile on overall survival (OS) in non-small cell lung cancer (NSCLC) patients treated with radiotherapy (RT). Methods: The pre-RT plasma levels of 30 cytokines were measured by Multiplex ELSA in 154 stage I-II NSCLC patients who were enrolled in prospective studies. Cox-regression analysis was performed to evaluate the prognostic values of cytokine levels, clinical factors on OS. Results: With a median follow up time of 21.3 months for patients alive, the 3 and 5-year OS was 38.3% and 18.5%, respectively. In univariate analysis, 6 out of 30 cytokines were identified as prognostic biomarkers for OS. Elevated level of TGFα (p = 0.011), IL-1b (p = 0.000), IL-4 (p = 0.048), IL-15 (p = 0.005), EGF (p = 0.011), scD40L (p = 0.020) was significantly associated with inferior OS. Male (p = 0.034), older age (p = 0.023), poor ECOG performance status (p = 0.002), weight loss (p = 0.036), fatigue (p = 0.005), non-adenocarcinoma histology (p = 0.004), lower RT dose (p = 0.046) were significantly associated with inferior OS. In multivariate analysis, TGFα (p = 0.041), ECOG performance status (p = 0.006), fatigue (p = 0.018), histology (p = 0.019) were independent prognostic factors for OS. Conclusions: Elevated plasma level of TGFα before radiotherapy may represent an independent adverse biomarker for poor OS of NSCLC treated with RT. This result, if validated, will provide important additions to identify risk group of NSCLC patients and guide the development of new targeted therapies. [KFM1]

7526  Poster Session (Board #273), Mon, 8:00 AM-11:30 AM
Final overall survival (OS) analysis of a multicenter phase II study of concurrent high-dose (72Gy) three-dimensional conformal radiotherapy (3D-RT) without elective nodal irradiation with chemotheraphy using cisplatin (DDP) and vinorelbine (VNR) in patients with stage III non-small cell lung cancer (NSCLC). First Author: Hidehito Horinouchi, National Cancer Center Hospital, Tokyo, Japan

Background: We previously reported the adverse events and objective responses in a multicenter phase II study of high-dose chemoradiotherapy. This is a final analysis of the pattern of recurrences, progression free survival (PFS) and OS. Methods: Patients with stage III NSCLC were eligible if they met the following key criteria: age between 20 and 74 years, PS 0-1 and V20 ≥ 30%. Participants received 3-4 cycles of CDDP (80 mg/m2 day 1) and VNR (20 mg/m2 days 1 and 8) every 4 weeks. The 3D-RT was administered at a total dose of 72 Gy divided into 36 fractions from day 1 chemotherapy. The primary endpoint was the 2-year survival rate and the planned sample size was 60 to reject the rate of 45% under the expectation of 65% with a power of 90% and an alpha error of 5%. Results: Thirty-one patients were enrolled between 2009 and 2011. The median follow-up time (range) was 51.4 (28.8-65.6) months at the point of data cut-off. This trial was terminated early due to the slow accrual and appearance of grade 5 pulmonary toxicities in 2 patients. There were 25 men and 6 women with a median (range) age of 59 (32-72) years. Of the 25, 23 had adenocarcinoma and 21 had stage IIIA disease. The median (range) V20 value was 20 (9-30). Among the 20 patients showing disease progression, in-field failure was the most commonly observed (85%) patients associated with 3-5 year mortality risk: adjusted hazard ratio 0.75 (p < .0001) for chemoradiotherapy; 0.86 (p < .002) for radiotherapy; 0.75 (p < .0001) for chemoradiotherapy. Conclusions: Black race, urban residence, and certain facility characteristics (e.g., low resection volume and high percentage of underinsured patients) were independently associated with incomplete resection. Margin involvement significantly impacts survival after lung cancer resection, irrespective of stage. Contributory intra-institutional provider practices should be identified, to minimize this outcome disparity. Postoperative adjuvant therapy mitigates the mortality risk independently of stage, and should be offered to all patients.
Phase II trial of neoadjuvant bevacizumab plus pemetrexed and carboplatin in patients with unresectable stage III lung adenocarcinoma (GASTO 1025). First Author: Si-Yu Wang, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Unresectable stage III non-small cell lung cancer is often treated with concurrent chemoradiotherapy. Bevacizumab has shown its efficacy in advanced non-squamous lung cancer. The aim of this phase II trial is to assess the efficacy and safety of induction bevacizumab (Bev) plus chemotherapy followed by surgery in unresectable stage III lung adenocarcinoma. Methods: This is a Phase II trial. Bev at 7.5 mg/kg plus pemetrexed (500 mg/m²) and carboplatin (AUC = 5) followed by surgery for patients with unresectable, stage III lung adenocarcinoma. Neoadjuvant therapy was administered every 3 weeks for 4 cycles. Surgery was scheduled 3-4 weeks after last neoadjuvant therapy and patients’ resectability was assessed by a medical team, including thoracic surgeons, medical oncologists, and radiologists. The primary endpoint was resectability rate. Results: From April 2012 to April 2014, 42 patients were enrolled and received Bev plus pemetrexed and carboplatin (PC). Grade 3 or 4 neoadjuvant-related adverse events included fatigue in 5 patients, neutropenia in 4, hypertension in 1, anemia in 1 and thrombocytopenia in 1. The adverse events thought to be related to bevacizumab included epistaxis in 3 patients (grade 1; 2; grade 2, 1) and hypertension in 2 patients (grade 1, 1; grade 3, 1). Complete response was achieved in 1 patient, partial response in 22, stable disease in 17, and progressive disease in 2. After neoadjuvant therapy, 31 patients underwent surgery, with pneumonectomy in 11. R0 resection was achieved in 22 patients. Postoperative complications included pneumonia (4 patients), atelectasis (2), bronchial stump insufficiency (1), empyema (1), subcutaneous emphysema (2) and arrhythmia (1). No perioperative hematoma events, thromboembolic events and wound-healing problems were observed. No patient died in the perioperative period. The median event-free survival (EFS) was 15.4 months, and the 1-year EFS was 56.1%. Conclusions: The treatment modality of neoadjuvant Bev-PC followed by surgery appears to be feasible and safe in patients with unresectable stage III lung adenocarcinoma.


Genomic heterogeneity of lung cancers and its potential clinical implications. First Author: Jianjun Zhang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Substantial genomic heterogeneity of lung cancers between different patients, reflecting distinct genetic background and potentially different carcinogen exposures in different patients, has been well documented, particularly under the Cancer Genome Atlas (TCGA) efforts. On the other hand, our recent study (Zhang et al, Science, 2014, 346:256-9) and others (de Bruin, et al, Science, 2014, 346:251-6) have revealed limited intratumor or heterogeneity (ITH) in localized lung adenocarcinomas (LUAD). Our more recent work on synchronous multifocal lung cancers (MSLC) has demonstrated distinct genomic profiles in different tumors within the same patients in spite of identical genetic background and exposure history (Liu and Zhang et al, submitted). Methods: We analyzed data from the two studies on ITH of LUAD (Zhang, et al, Science, 2014, 346:256-9) and de Bruin, et al, Science, 2014, 346:251-6), our MSLC study and data from TCGA LUAD study to assess the genomic heterogeneity of lung cancers under different clinical scenarios. We are currently conducting studies to assess the genomic heterogeneity of primary lung cancers versus distant metastases, versus relapsed diseases, and versus secondary primary lung cancers. Results: The percent mutations in a tumor sample that are identical to mutations from another tumor sample under different clinical scenarios are: 91% between different regions within the same tumors (n = 16); 80% between primary lung cancers and metastatic lymph nodes (n = 4); 70% between patients with stage II and stage III cancers (n = 6) and 0.05% from unrelated patients (n = 519). The data from primary lung cancers versus distant metastases, versus relapsed diseases and versus secondary primary lung cancers. Results: The percent mutations in a tumor sample that are identical to mutations from another tumor sample under different clinical scenarios are: 91% between different regions within the same tumors (n = 16); 80% between primary lung cancers and metastatic lymph nodes (n = 4); 70% between patients with stage II and stage III cancers (n = 6) and 0.05% from unrelated patients (n = 519). The data from primary lung cancers versus distant metastases, versus relapsed diseases and versus secondary primary lung cancers is pending. Conclusions: With the caveat of small sample size, our data suggests that in localized LUADs, metastases resemble matched primary tumor closely while multifocal primary cancers within the same patients have distinct genomic profiles in spite of identical genetic background and exposure history. Genomic profiling may be useful for identification of both synchronous and metachronous multifocal lung cancers.
Prognostic value of miRNAs in resected lung adenocarcinomas. First Author: Sandra Gallach, Fundación para la Investigación del Hospital General Universitario de Valencia, Spain.

Background: Adenocarcinoma (ADC) is one of the most common types of non-small cell lung cancer (NSCLC). Deregulated microRNAs (miRNAs) in tumor were associated with poor prognosis. In this study, we analyzed the prognostic value of 22 deregulated miRNAs identified by NGS in a previous study in a group of early-stage ADCs. Methods: RNA was isolated from fresh-frozen lung ADC specimens (tumor and normal lung) (N = 78). Deregulated miRNA (miR-182, 29a, 191-1, 34a, 339-5p, -590, -31, -181, -21, -135b, -199b, -224, -196b, -451a, -144, -195, -215b, -145, -30a, -126, -139) were analyzed in paired tumor/normal samples by RqPCR using TaqMan microarray assays. Statistical analyses were considered significant at p < 0.05. Results: For survival analysis, continuous variables were dichotomized using the median expression of each miRNA as a cutoff. Of the 22 miRNAs analyzed, high expression levels of miR-34a, miR-145, miR-191-1, miR-29a, miR-339-5p, miR-21, miR-218 and miR-188 were associated with worse OS and/or PFS (Table 1). Furthermore, patients with combined high levels of miR-188 and miR-339-5p had significantly reduced OS and PFS (p < 0.001 and p = 0.001, respectively). The multivariate analysis revealed that this combined variable (miR-188 & miR-339-5p) is an independent prognostic marker for PFS (HR 18.1 vs. 7.6 vs. 2.7; P = 0.001) & current smokers compared to never. Obese & non-obese pts were better for obese vs. cachectic. There were significant differences between survival curves & the majority of patients (pts) were either former (49%) or current (40%) smokers. Obesity (yes/no) was an independent prognostic biomarker in this type of patients. Supported by grants RTICC (RD12/0363/0025), TRACE (TRA09-0132) and Beca Roche Oncohematologia.

miRNAs univariate analysis for OS and PFS.

<table>
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<th>P</th>
<th>PFS Median (months)</th>
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<td>miR-188</td>
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<td>miR-182 + miR-339-5p</td>
<td>&lt;0.001</td>
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<td>15.43</td>
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</table>

Conclusions: Expression of miR-188 and miR-339-5p seems to have a prognostic role in resectable ADC, and the combination of both could be an independent prognostic biomarker in this type of patients.

The burden of healthcare utilization in Medicare service patients aged 67-94 years who were diagnosed with stage I NSCLC from 2007 through 2009 and received curative treatment with either sublobar resection, lobectomy, or stereotactic body radiotherapy (SBRT). We examined healthcare utilization in the 30 days before through 12 months after treatment initiation, determining the total number of days in contact with the healthcare system as well as the number of unique physicians seen. We described care received in the acute, outpatient, post-acute, home care, and hospice settings. Results: Of the 4,214 patients, 90.9% received surgery and 9.1% SBRT. During the first 100 days post-treatment, an average of 1 in 4 days was spent in contact with the healthcare system (mean: 25 encounter-days excluding home health visits). Among patients who survived the entire 13-month follow-up period, there was an average of 50 days with at least one encounter. Approximately 3% of patients had ≥ 10 acute care encounter-days, while 97.7% had > 10 outpatient encounter-days and 23.5% had ≥ 10 homecare encounter-days. The median number of physicians seen was 22 (interquartile range 16-31). Conclusions: The burden of receiving healthcare for older patients with NSCLC is substantial in terms of frequency of encounters and number of providers seen. Interventions are needed to improve patient-centered, streamlined cancer care.

Effects of obesity and smoking on survival in non-small cell lung cancer. First Author: Damien Mikael Hansra, Oncology and Radiation Associates, Mineola, NY.

Background: Obesity is an emerging leading cause of morbidity and mortality in the US & the relationship between obesity, tobacco, & survival in NSCLC is unclear. Methods: Data (n = 87,631) were obtained from linkage of the 1996-2007 FDSC & AHCA databases providing procedure and diagnoses codes. Survival time was calculated from date of diagnosis to date of death. Smoking status was categorized as never, current, and former obesity (yes/no) = ICD9 code = E10. Carcinoma in situ = ICD9 code = E19.0 code "wasting syndrome", & non-obese = non-obese & non cachectic. Cox proportional regression models used to predict survival; demographic, clinical, treatment factors, & comorbidities were included in adjusted models with smoking status and obesity as the main factors. Results: The majority of patients (pts) were either former (49%) or current (40%) smokers, & non-obese (88%). 6.8% of pts were obese & 4.8% of pts were cachectic. There were significant differences between survival curves & median survival (months) for obese vs. non-obese vs. cachectic pts. (20 vs. 10 vs. 7.9; P < 0.001). Former & current smokers had shorter median survival than never smokers (10.8 & 9.2 vs. 11.9; P < 0.001). Survival rates (%) at 1 yr (60.1 vs. 45.2 vs. 37.7; P < 0.001), 5-yr (30.3 vs. 15.4 vs. 9.5; P < 0.001), 10-yr (18.1 vs. 7.6 vs. 7.2; P < 0.001) were better for obese vs. non-obese & cachectic pts respectively. Independent predictor of worse survival in unadjusted model was former (HR 1.08; P < 0.001) & current (HR 1.20; P < 0.001) smokers compared to never. Obese & non-obese pts had better survival vs. cachexia pts (HR 0.52; P < 0.001 & HR 0.80, p < 0.001 respectively) & obese pts had better survival than non-obese pts (HR 0.65, p < 0.001). In the adjusted model, controlling for extensive variables & comorbidities, former (HR 1.11; P < 0.001) & current (HR 1.19; P < 0.001) smokers still had significantly worse survival vs. never smokers. Obese pts still had better survival (HR 0.87; P < 0.001, & HR 0.88, p < 0.001) vs. cachexia & non-obese pts respectively. Survival rate is not significantly different comparing non-obese & cachexia pts. Conclusions: Our results show that being a former or current smoker worsens survival while obesity improved survival when compared with cachexia & non-obese pts.

Association between the EGFR or KRAS mutation status and the FDG-PET findings in surgically resected lung adenocarcinomas. First Author: Kazuya Takamokho, Juntendo Univ, Tokyo, Japan.

Background: 18F-fluoro-2-deoxy-glucose (18F-FDG) positron emission tomography (PET) is a functional imaging modality based on the glucose metabolism. The association between EGFR or KRAS mutations and the standardized uptake value (SUV) of 18F-FDG has not yet been fully elucidated. Methods: Correlations between the EGFR or KRAS mutation status and clinicopathological factors including SUVmax were statistically analyzed in 734 surgically resected lung adenocarcinoma patients. A cap analysis of gene expression (CAGE), a method to determine and quantify the transcription initiation activities of miRNA across the genome reflecting gene expression levels by determining the 5’ ends of capped RNA molecules using high-throughput sequencers, was done to examine the molecular basis between the SUVmax and mutations in 62 lung adenocarcinomas. Results: EGFR and KRAS mutations were detected in 334 (46%) and 83 (11%) of the 734 lung adenocarcinomas, respectively. Univariate analyses showed EGFR mutations to be more frequently observed in females, never-smokers, patients with normal CEA levels, tumors without lymph node involvement and blood vessel invasion, and tumors with lower SUVmax values. In multivariate analyses, the smoking status and the SUVmax were the significant predictors of EGFR mutations. In contrast, no relationship was seen between the KRAS mutation status and the SUVmax. Four genes associated with the glucose metabolism and five genes associated with the cell cycle showed a lower expression in the EGFR mutated tumors than the wild type tumors and a positive correlation with SUVmax. However, no such genes were found for KRAS mutations. Conclusions: Tumors with EGFR mutations show lower values of SUVmax than wild type ones. In contrast, no relationship was found between KRAS mutation status and the SUVmax. These results suggest that tumors with EGFR mutations are less aggressive with likely lower levels of glucose metabolism.
Comparison of concurrent use of carboplatin-Paclitaxel versus cisplatin-etoposide with thoracic radiation for stage III NSCLC patients: A systematic review.

**Background:** The two most commonly used chemotherapy regimens deployed concurrently with thoracic radiation (RT) for patients with unselectable IIIA and IIB non-small cell lung cancer (NSCLC) are carboplatin-Paclitaxel (CP) and cisplatin-etoposide (CE). Because there are no prospective comparisons of these two regimens in this setting, we conducted a systematic review of published trials to compare outcomes and toxicities between CE and CP. Study: Data were extracted from stage II patients receiving RT with CP or CE were identified using electronic databases (MEDLINE, EMBASE, and Cochrane library) and meeting abstracts. Trials were excluded if they were phase I, enrolled less than 10 pts, or included surgical resection. A systematic analysis of extracted data was performed using multivariable Meta Analysis (Version 2.2) software using random and fixed effect models. Clinical outcomes were compared using point estimates for weighted values of median overall survival (OS), progression free survival (PFS), response rate (RR) and toxicities. Two-tailed T-test with a significance level of 0.05 was used for all comparisons. Results: 3194 patients were included from 32 studies in the CE arm, and 3789 pts from 51 studies in the CP arm. Baseline characteristics of patients on the CE arm versus CP arm were: median age 61 vs. 63 years, male 67.5% vs. 78%, squamous histology 39% vs. 40%, and median radiation dose 62 Gy vs. 63 Gy. There was no significant difference in response rates between CE and CP (65% vs. 56%, p = 0.26), respectively. There was no significant difference in median progression free survival (11.5m vs. 9.3m p = 0.2), overall survival (19.8m vs. 18.4m, p = 0.48), or 3-year survival rate (31% vs. 25%, p = 0.4) for CE vs. CP. CE was associated with higher grade 3/4 hematological toxicities than CP, such as neutropenia (53% vs. 23% p < 0.0001), as well as grade 3/4 nausea/vomiting (20% vs. p = 0.018), while rates of grade 3/4 pneumonitis and esophagitis were similar. Conclusions: CE and CP regimens were associated with comparable efficacy when used with concurrent radiotherapy for stage III resectable NSCLC pts. The toxicity profile favored the CP regimen.

<table>
<thead>
<tr>
<th>SEQUENTIAL ALLELES</th>
<th>COMMON (%)</th>
<th>RARE (%)</th>
<th>COMMON &amp; RARE (%)</th>
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Conclusions: The use of PORT for N0-N1 margin-negative NSCLC was associated with comparable efficacy when used with concurrent radiotherapy when compared to CE. CP regimen was favored due to the toxicity profile. CE regimen was associated with higher grade 3/4 hematological toxicities than CP, such as neutropenia (53% vs. 23% p < 0.0001), as well as grade 3/4 nausea/vomiting (20% vs. p = 0.018), while rates of grade 3/4 pneumonitis and esophagitis were similar. Conclusions: CE and CP regimens were associated with comparable efficacy when used with concurrent radiotherapy for stage III resectable NSCLC pts. The toxicity profile favored the CP regimen.

**Methods:** Data on EGFRm in early stage NSCLC are limited. RADIANT was a prospective randomized Phase 3 trial of adjuvant erlotinib (E) to placebo (P) in 973 patients (pts) with completely resected Stage IB-IIIA NSCLC that was E=ER by IHC or FISH (ACOSOG Z0001, ESMO14 #1178P). Methods: EGFRm in exons 18-21 was determined by WAVE HS and confirmed by Sanger sequencing. Two EGFRm groups were defined: Common refers to exon del19 or L858R irrespective of the presence of another EGFRm; Rare Only refers to EGFRm without del19 or L858R. Exploratory analysis of disease-free survival (DFS) was performed by subgroup (June 11, 2014 data cut-off). Results: 921 pts had EGFRm status determined, 198 pts (21.5%) had EGFRm (161 Common, 37 Rare Only). There was no sex difference between the groups, but pts with Rare Only EGFRm were less likely to be Asian (32.4% vs 47.2%) and non-smokers (48.6% vs 62.7%). With a median follow-up of 5 years, updated DFS by mutation type is shown below. The DFS HR was lower in the Common group (HR 0.75, CI 0.48-1.16) than the Rare Only group (HR 1.19, CI 0.44-3.22). Conclusions: The effect of E on DFS in EGFRm subgroups remains inconclusive. Clinical trial registration: NCT00373425.
Further results from ongoing trials are awaited to determine the role of TKI in M and lung, bone and brain in P pts. Among the 13 pts in the Full Analysis Set analysis occurred after final f/u (June 2014 cutoff). There were no new safety concerns.

Methods: Completely resected IB–IIIA NSCLC pts were randomized 2:1 to receive E 150 mg daily or P for 2 years. The primary endpoint was disease free survival (DFS) in the full analysis set (FAS). Secondary endpoints included overall survival (OS) in the FAS and DFS and OS in EGRF mutation (M+) subset (del19/L858R). 973 pts were randomized and the planned final analysis was performed after 410 DFS events (April 2013 data cutoff, ASCO14 #7501). A subsequent exploratory analysis occurred after final f/u (June 2014 cutoff). Results: The median f/u is 59.6m (95% CI 56.7–61.2). There was no statistically significant difference in DFS or OS overall or in the EGRF M+ group. The OS data remain immature with 33.5% deaths in the E arm and 31.4% in the P arm. The most common site of relapse (>15% pts) overall and in EGRF M+ were lung and brain in E treated pts and lung, bone and P in P pts. Among the 13 pts in the EGRF M+ subgroup with brain as site of relapse, 11 of these patients relapsed after E cessation. There were no new safety concerns. Conclusions: Overall adjuvant E did not prolong DFS; a trend for E benefit previously observed (ASCO14 #7513) in EGRF M+ subgroup is no longer apparent. EGRF mutation status was not a stratification factor in this trial and was not a prognostic factor (ESMO14 #1177PD). Further results from ongoing trials are awaited to determine the role of TKi in EGRF M+ early stage lung cancer.

7540 Poster Session (Board #287), Mon, 8:00 AM-11:30 AM Final follow-up (f/u) results from RADIANT: A randomized double blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection in patients (pts) with stage IB–IIIA NSCLC of positive (IHC/FISH) non-small cell lung cancer (NSCLC). First Author: Mary E.R. O’Brien, Royal Marsden Hospital, London, United Kingdom

Background: Adjuvant chemotherapy for NSCLC has reached a plateau. The use of the tyrosine kinase inhibitor (TKI), E, was explored in the adjuvant setting given success in advanced setting. We report final f/u from RADIANT. Methods: Completely resected IB–IIIA NSCLC pts were randomized 2:1 to receive E 150 mg daily or P for 2 years. The primary endpoint was disease free survival (DFS) in the full analysis set (FAS). Secondary endpoints included overall survival (OS) in the FAS and DFS and OS in EGRF mutation (M+) subset (del19/L858R). 973 pts were randomized and the planned final analysis was performed after 410 DFS events (April 2013 data cutoff, ASCO14 #7501). A subsequent exploratory analysis occurred after final f/u (June 2014 cutoff). Results: The median f/u is 59.6m (95% CI 56.7–61.2). There was no statistically significant difference in DFS or OS overall or in the EGRF M+ group. The OS data remain immature with 33.5% deaths in the E arm and 31.4% in the P arm. The most common site of relapse (>15% pts) overall and in EGRF M+ were lung and brain in E treated pts and lung, bone and P in P pts. Among the 13 pts in the EGRF M+ subgroup with brain as site of relapse, 11 of these patients relapsed after E cessation. There were no new safety concerns. Conclusions: Overall adjuvant E did not prolong DFS; a trend for E benefit previously observed (ASCO14 #7513) in EGRF M+ subgroup is no longer apparent. EGRF mutation status was not a stratification factor in this trial and was not a prognostic factor (ESMO14 #1177PD). Further results from ongoing trials are awaited to determine the role of TKi in EGRF M+ early stage lung cancer. Clinical trial information: NCT03373425.

7542 Poster Session (Board #289), Mon, 8:00 AM-11:30 AM Retrospective analysis between PD-L1 expression and prognosis for stage III non-small-cell lung cancer patients who received concurrent chemoradiotherapy. First Author: Takaaki Tokito, Division of Respiratory, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan

Background: Programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway often hijacked by tumors in order to suppress immune control. We investigated whether the expression of programmed death ligand 1 (PD-L1) is related to clinicopathologic or prognostic factors in patients with locally advanced NSCLC who received concurrent chemoradiotherapy (CRT). Methods: We retrospectively reviewed consecutive stage III NSCLC patients who received CRT at Kurume University. The expression of PD-L1 was evaluated by immunohistochemical analysis in specimens of NSCLC. Survival analysis was obtained by Kaplan-Meier methods. Results: A total of 52 patients with a median age of 67 years were eligible for this study. Forty-three patients were men, and 46 patients were current or ever smokers. The most predominant histological type was adenocarcinoma (28 patients), followed by squamous cell carcinoma (21 patients). All of the patients received platinum-based doublets. Expression of PD-L1 in tumor cells was observed in 73%. NSCLC patients with PD-L1-negative tumors showed longer progression-free and overall survival than those with PD-L1-positive (median PFS, 17 versus 11 months; P = 0.31, median OS, 52 vs 25 months; P = 0.38, respectively), and higher progression-free rate at 2 years and overall survival rate (38% and 26%, 83% and 52%, respectively). Conclusions: There was a trend toward a poor survival in expression of PD-L1 in stage III NSCLC patients who received CRT. HR (95% CI) P-Value

7543 Poster Session (Board #290), Mon, 8:00 AM-11:30 AM Correlation between high-resolution computed tomography findings and IASLC/ATS/ERS classification of small lung adenocarcinomas in Japanese patients. First Author: Yujin Kudo, Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan

Background: Small pulmonary nodule detection rates have increased owing to computed tomography (CT) screening of lung cancer, and new image-guided-bronchoscopy techniques have been developed to improve diagnostic yield. Additionally, limited surgical resection for small peripheral lung adenocarcinomas has been reported. Recently, the IASLC/ATS/ERS classification emphasized the prognostic significance of histologic subtypes. We evaluated the correlation between high-resolution CT (HRCT) findings and this classification of small lung adenocarcinomas. Methods: We reviewed the data of 220 consecutive lung adenocarcinoma (≤ 3 cm) patients who received segmentectomy or more extended resection with lymph node dissection in our hospital. From the HRCT findings, the tumors were classified as pure solid, part-solid, or pure ground glass opacity (GGO) nodules. Pathologic tumor invasiveness (pT) was evaluated by the degree of vascular invasion, lymphatic permeation, or visceral pleural invasion. Results: The tumors were classified as pure GGO nodules in 16 patients (7.2%), part-solid in 91 (41.3%), and pure solid in 113 (51.3%) from the HRCT findings. We pathologically diagnosed 44 noninvasive and 176 invasive adenocarcinomas (IAs) (lepidic (LPA), papillar, acinar, solid predominant adenocarcinoma, and invasive mucinous adenocarcinoma). Lymph node metastasis was present in 31 patients (14.1%) and pT in 104 (47.3%) of the IAs. All pure solid and IA were IA with pT1a (3.6%) or lymph node metastasis (26.5%). All pure GGO nodules were non-IAs or LPA. Among the part-solid nodules, IA was detected in 67.0% of the patients and pT in 16.5%. The consolidation/tumor (C/T) ratio and consolidation size were associated with IA (optimal cut-off values: 0.4 and 8 mm) or CT (0.8 and 15 mm). Conclusion: The HRCT findings correlated with the IASLC/ATS/ERS classification and were useful for malignancy evaluation. Most pure solid tumors have malignant potential including pT or lymph node metastasis. For part-solid tumors, the C/T ratio and consolidation size were important for predicting pT or making a diagnosis of IA according to this classification.
Comprehensive analysis of driver mutations in Chinese squamous cell lung carcinomas by targeted next-generation sequencing. First Author: Sheng Yang. Department of Medical Oncology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College Beijing, China, Beijing, China

Background: The aim of the study was to analyze the driver mutation profiles in a large cohort of Chinese SqCLC to identify potential therapeutic targets. Methods: We detected approximately 2,800 COSMIC mutations from 50 oncogenes and tumor suppressor genes on 159 samples by using Ion Torrent semiconductor-based next-generation sequencing. We conducted FISH for fibroblast growth factor receptor 1 (FGFR1) and cyclin D1 (CCND1) amplification on 172 and 246 samples, respectively. In addition, we analyzed PTEN expression by immunohistochemistry on 172 samples.

Results: Somatic mutations were detected in 73.6% (117/159) of patients. The most commonly mutated gene detected in this study was TP53 (89 cases, 56.0%), followed by CDKN2A (14 cases, 8.8%), PIK3CA (14 cases, 8.8%), KRAS (7 cases, 4.4%), and EGFR (5 cases, 3.1%). The incidences of FGFR1 amplification, CCND1 amplification and loss of PTEN expression in this cohort of patients were 16.9% (29/172), 11% (27/246) and 43.6% (75/172), respectively. The frequency of EGFR mutation was significantly higher in female and never smokers, while TP53 mutations were significantly more common in men and smokers. The incidence of FGFR1 amplification in current smokers was significantly higher than that in former smokers and never smokers (P\text{Unadj} < 0.025).

Conclusions: FGFR1 amplification and CCND1 amplification significantly increased with increment of total cigarette smoking dosage (P\text{Unadj} < 0.001 and P\text{Unadj} = 0.006, respectively). Loss of PTEN expression was more frequent in elders (P = 0.047), male gender (P = 0.033), patients with early stage (P = 0.042) and pleural invasion (P = 0.030). No significant association was observed between the molecular abnormalities and overall survival.

Patterns and effectiveness of surveillance after curative intent surgery in stage I-IIIA non-small cell lung cancer. First Author: Christine Agnes Cinci. Hosp of the Univ of Pennsylvania, Philadelphia, PA

Background: The optimal strategy for imaging surveillance of non-small cell lung cancer (NSCLC) patients after curative intent surgery is unknown. Current guidelines recommend computed tomography (CT) every 6-12 months for 2 years and then annually. There are no large population-based studies investigating how patients are managed, or comparing the effectiveness of chest radiography (CXR) and CT surveillance. Methods: We performed a retrospective cohort study using the Surveillance, Epidemiology and End Results (SEER) Medicare data to determine the primary surveillance modality following surgical resection in stage I-IIIA NSCLC between 1998 and 2009. Primary surveillance modality was defined as the imaging study used between 90-365 days after surgery. Comparability of effectiveness of CT vs. CXR surveillance was explored in terms of overall survival (OS) by using a stratified Cox model based on stage and adjusted for age, gender, race, Charlson comorbidity index, and adjunct chemotherapy.

Results: 5,968 (54%) patients were followed by CT, and 5,083 (46%) by CXR. Patients with earlier stage, older age, and lower census median income (CMI) were less likely to undergo CT surveillance (P < 0.001). CT surveillance increased over the study period from 23% in 1998 to 68% in 2009 (P < 0.001). In the analysis of surveillance modality and OS, a significant interaction was identified between imaging and diagnosis year (P < 0.001). The effect of CT surveillance on OS steadily improved over time, and was significantly better than CXR in the most recent time periods of study (Table: Conclusions: OS was improved in patients with CT surveillance in the most recent time periods of analysis supporting surveillance guidelines. Further studies to determine how CT surveillance leads to improved outcomes, to evaluate the appropriate interval of CT imaging, and to elucidate why patients are not followed according to guidelines are warranted.

Multivariant Cox Regression for Overall Survival with CT surveillance as reference group.

**Diagnosis year** | **Adjusted HR** | **95% Confidence Interval**
---|---|---
1998-2000 | 1.09 | 0.97-1.25
2001-2002 | 0.85 | 0.74-0.95
2004-2006 | 0.82* | 0.74-0.91
2007-2009 | 0.69* | 0.61-0.78

*p<0.001

Lung Cancers by Original Stage (n) Two-year Overall Survival Log-rank p value

<table>
<thead>
<tr>
<th>Stage</th>
<th>OS (n)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>340</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IB</td>
<td>243</td>
<td>0.97</td>
</tr>
<tr>
<td>II</td>
<td>58</td>
<td>0.63</td>
</tr>
<tr>
<td>IIIA</td>
<td>61</td>
<td>0.68</td>
</tr>
<tr>
<td>IIIB</td>
<td>10</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Multiple Lung Cancers (108) | IA | 28 | 0.88 |
| IB | 19 | 0.44 |

Recurrent Lung Cancer (341) | IA | 31 | 0.046 |
| IB | 18 | 0.33 |
| IIIB | 13 | 0.08 |

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Utility of 18F-FDG PET and CT to assess response to neoadjuvant chemotherapy. First Author: Jamie E. Chast, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Perioperative chemotherapy improves survival in resected NSCLCs. Neoadjuvant administration allows for in vivo assessment of efficacy. Major pathologic response (MPR), defined as <10% viable tumor tissue in the surgical resection specimen, strongly correlates with improved outcomes in lung cancer. (Hellmann, Lancet Oncol 2014) Unfortunately, it is a minority of tumors that demonstrate MPR after standard induction chemotherapy and adaptive strategies are needed. The understanding of the clinical utility of non-invasive mid- and post-treatment PET and CT scans is essential for adaptive trial design. Methods: This analysis is derived from a completed phase 2 trial of PET response-adaptive therapy that treated 40 pts with clinical stage IIB-IIIA NSCLCs (primary <2 cm & SUVmax <4.5). Pts received 2 cycles of cis- or carboplatin + gemcitabine (squamous) or pemetrexed (adenocarcinoma/other), followed by repeat PET + CT. Pts with suboptimal response (<35% decrease in SUV) were switched to vinorelbine + docetaxel q2 wks. This analysis utilizes non-parametric tests to assess the correlation of % change in SUV of the primary tumor (PERCIST) and the % change in size on CT (RECIST) with MPR after 2 cycles and at completion of induction therapy. Results: 40 pts were treated. 15 pts has <35% decrease in SUV, of whom 13 were switched to vinorelbine/docetaxel, and 2 to definitive radiotherapy only. 27 pts had R0 resections. 6 tumors demonstrated MPR. In all settings, PET response correlated with MPR and CT response did not (see Table). Conclusions: 18F-FDG PET response, but not CT response, in the primary tumor after 2 and 4 cycles of chemotherapy correlates with major pathologic response, a surrogate for survival. The use of early PET response to offer alternative therapies to pts who are not benefiting should be considered. NCT01443078 was supported in part by Eli Lilly. Clinical trial information: NCT01443078

% decrease, median (range) p-value
MPR no MPR
All pts after 2 cycles PET CT 71 (23 – 87) 49 (51 – 86) 0.016
71 (0 – 43) 21 (6 – 38) 0.19
Pts not assigned to switch after 2 cycles PET CT 75 (65 – 87) 54 (36 – 86) 0.007 33 (0 – 43) 24 (2 – 38) 0.094
All pts after 4 cycles PET CT 76 (67 – 94) 64 (24 – 87) 0.034 44 (16 – 51) 38 (6 – 64) 0.26

7550 Poster Session (Board #298), Mon, 8:00 AM-11:30 AM

Conditional survival estimates for lung cancer histologic subtypes in the U.S. (2004-2008). First Author: Kailash Musapunja, University of Nebraska Medical Center, Omaha, NE

Background: Conditional survival (CS) is a more accurate measure of survival probability among cancers associated with a poor prognosis. We calculated lung cancer-specific CS estimates to help clinicians and patients with informed decision making. Methods: Lung cancer patients with at least 3 years of follow-up were identified from the Surveillance Epidemiology and End Results registry (2004-2008). American Joint Committee on Cancer, sixth edition was used to classify patients as non-small cell lung cancer (NSCLC). Stages 1 to 3 SCLC were classified as limited stage (LS), and stage 4 was classified as extensive stage (ES). Multivariate Cox regression models were built separately by stage to calculate the adjusted 1-year survival for each histologic subtype for the years 2004-2008. Generalized estimating equations with an exchangeable correlation structure were used to correct for correlation among patients within the same geographic region, year of diagnosis, radiation, and definitive surgery. Results: A total of 127,992 patients were included in the final cohort. Patients diagnosed with stage IA NSCLC had a 3-year survival probability of 73%. This increased to 76% in patients who were alive at 3 years following diagnosis. The three-year conditional overall survival (OS) estimates from diagnosis (time 0) to 3 years for the other stages were as follows: stage IB: 54% to 68%, stage 2A: 54% to 64%, stage 2B: 37% to 58%, stage 3A: 25% to 51%, stage 3B: 14% to 43%, and stage 4: 6% to 29%. For stage 1A NSCLC 3-year conditional cancer-specific survival (CCSS) estimates improved from 82% to 87%, stage 1B: 63% to 80%, stage 2A: 62% to 74%, stage 2B: 44% to 69%, stage 3A: 30% to 60%, stage 3B: 18% to 54%, and stage 4: 8% to 35%. For LS-SCLC, 3-year CCSS improved from 0% to 53% at 16% to 52% at 3 years; for ES-SCLC it increased from 3% to 47%. For LS-SCLC, 3-year CCSS improved from 19% to 60% at 0 years to 63% at 3 years whereas for ES-SCLC it improved from 4% to 53%. Conclusions: Three-year CS and CCSS estimates improve dramatically over time for survivors with advanced stages. These prognostic data are critical to patients for both treatment and non-treatment related life decisions.

7551 Poster Session (Board #299), Mon, 8:00 AM-11:30 AM

PD-L1, PDL-1, and CTLA-4 as prognostic biomarkers in resected non-small cell lung cancer. First Author: Taofeek Kunle Owonikoko, Emory Univ, Atlanta, GA

Background: Reliable assessment of predictive or prognostic biomarker is critical for successful incorporation of immune checkpoint inhibitors into lung cancer management. We assessed the prognostic relevance of immune checkpoint mediators in resected NSCLC. Methods: We performed PD-L1 expression by immunohistochemistry using our institutional tumor bank samples. Mutations, expression and copy number variations (CNV) in genes encoding for PD1, PD-L1 and CTLA-4 were assessed using TCGA data. Survival estimates were performed by the Kaplan-Meier method. Differences in disease free and overall survival (DFS, OS) between patients with high or low PD-L1 protein expression were assessed by univariate and multivariate survival analyses using Cox proportional hazards model using the X-year conditional survival and overall survival. The multiplicative law of probability was then used to compute the X-year conditional survival estimates for lung cancer histologic subtypes in the SEER region, year of diagnosis, radiation, and definitive surgery. The association between ALK polysomy and ALK gene rearrangement. The association between ALK polysomy and higher stage at diagnosis were independently associated with a higher risk of progression on multivariable analysis. Conclusions: There is inverse association of ALK polysomy and ALK gene rearrangement. Aneuploidy of the ALK gene was present in 46 (73%) cases with 40% aneuploid cells per case. Minimum and maximum number of copies of ALK gene in aneuploid cells were 2.63 (± 0.61) and 4.02 (± 2.03), respectively. There was no association between ALK gene aneuploidy and patient characteristics but ALK gene aneuploidy, percent age aneuploid cells and high ALK polysomy were negatively correlated with presence of ALK FISH rearrangement. Absence of ALK polysomy (HR: 0.29; 0.09-0.95; p=0.040) and higher stage at diagnosis were independently associated with a higher risk of progression on multivariable analysis. Prognostic impact: There is inverse association of ALK polysomy and ALK gene rearrangement. The association between ALK polysomy and higher risk of disease progression is worthy of further study to elucidate the underlying biology.
A phase II feasibility study of preoperative chemotherapy with bevacizumab for resectable stage II/IIIA non-squamous non-small cell lung cancer.

First Author: Yoshihito Miyata, Hiroshima University, Hiroshima, Japan

Background: Bevacizumab (Bev) has been demonstrated to improve response and survival rates in patients with advanced non-squamous non-small cell lung cancer (NSCLC). This phase II trial assessed the feasibility of the addition of Bev to preoperative chemotherapy in resectable non-squamous NSCLC.

Methods: Patients with clinical stage II/IIIA non-squamous NSCLC were recruited from 6 institutions. Three cycles of cisplatin (Cis) (75 mg/m²), and Bev (15 mg/kg) were administered on day 1 and every 21 days thereafter, followed by surgical resection. The primary endpoint was the complete resection rate (CRR) after completion of 3 cycles of chemotherapy. The sample size was set at 30 patients. The treatment was considered feasible if the CRR was > 80%.

Results: Thirty patients were eligible. Grade 3 toxicities included neutropenia (7%), nausea (7%), hypertension (23%), and pulmonary embolism (3%). There were no grade 4 events, and 27 (90%) patients completed 3 cycles with full doses of chemotherapy. Twenty-nine patients (97%) exhibited radiologic tumor reduction. The objective responses to chemotherapy were as follows: complete response, 0%; partial response, 37%; stable disease, 50%; and progressive disease, 10%. Five patients dropped out from the study before surgery due to the patient’s decision in one patient, adverse events in three and disease progression in one. Disease control and surgical eligibility was confirmed in 25 (83%) patients after completion of 3 cycles of induction chemotherapy. These patients underwent surgery, and all achieved complete resection (CRR) after completing three cycles of induction chemotherapy, 83%.

Neither grade 3/4 morbidity with 28 days after surgery nor treatment-related mortality with 84 days after surgery was observed.

Conclusions: Preoperative chemotherapy with combined Cis, Pem, and Bev for clinical stage II/IIIA NSCLC is considered feasible. These data provide further evidence that Bev may be used as a promising candidate for future randomized trial arm for patients with locally advanced NSCLC.

Clinical trial information: UMIN000004278.

Clinicalopathological characteristics of squamous cell carcinoma of the lung with programmed cell death ligand 1 (PD-L1) protein expression.

First Author: Tiffany Huynh, Massachusetts General Hospital, Boston, MA

Background: PD-L1 expression by immunohistochemistry (IHC) reportedly predicts patient response to anti-PD-1/PD-L1 therapies in early phase clinical trials for solid tumors. However, there is limited data on the patient/tumor characteristics associated with PD-L1 expression in squamous cell carcinoma of the lung (SqCC).

Methods: PD-L1 (EI13N, 1:200, Cell Signaling Technology), PTEN, and CD8 IHC were performed on tissue microarrays of resected SqCCs (n = 162). Subsets of patients underwent clinical molecular (SNAPSHOT and FISH) testing. Cases with 10% or more tumor cells exhibiting negative or reduced PD-L1 expression were considered to have PD-L1-.

Results: PD-L1 expression in tumor cells and CD8 expression in tumor infiltrating lymphocytes (TILs) were semiquantitatively evaluated. PD-L1 expression, defined as 5% or more of tumor cells exhibiting membranous staining, was correlated with clinicopathological and molecular features as well as patient outcomes.

Conclusions: For clinical trials of PD-L1-targeting agents, IHC determination of PD-L1 expression may serve as a predictor of patient response to anti-PD-1/PD-L1 therapies. The association of clinicopathological and molecular factors with PD-L1 expression in ADC is not well-defined.

Clinical trial information: NCT01059552.

Clinicalopathological and molecular parameters of lung adenocarcinomas (ADC) associated with programmed cell death ligand 1 (PD-L1) protein expression.

First Author: Tiffany Huynh, Massachusetts General Hospital, Boston, MA

Background: Recent efforts in targeting the PD-1/PD-L1 pathway in solid tumors have resulted in durable responses in early phase clinical trials. Additionally, it has been reported that PD-L1 overexpression by immunohistochemistry (IHC) could serve as a predictor of patient response to anti-PD-1/PD-L1 therapies. However, the association of clinicopathological and molecular features with PD-L1 expression in ADC is not well-defined.

Methods: PD-L1 (EI13N, Cell Signaling Technology) and CD8 IHC were performed on tissue microarrays of 242 resected ADC that underwent detailed histological analysis. Clinical molecular testing had been performed in a subset (n = 128). Membranous expression of PD-L1 (any intensity) in 5% or more tumor cells was defined as positive. CD8+ tumor infiltrating lymphocytes (TILs) were evaluated using a 4-tier grading system (0-3). PD-L1 expression was correlated with clinicopathological and molecular features as well as prognosis.

Conclusions: Clinical trial information: NCT01059552.

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Isolated Thoracic Perfusion with Chemofiltration (ITP-F) for progressive and pre-treated malignant pleural mesothelioma. First Author: Karl R. Aigner, Medias Klinikum, Germany.

Background: Treatment of patients (pts.) with progressive malignant pleural mesothelioma (MPM) after multimodal therapy remains a therapeutic challenge. Survival of the pts. is low and the treatment options are sparse. We report on a phase II study on isolated thoracic perfusion with subsequent chemofiltration as a locoregional therapeutic strategy in this situation. Methods: 21 pts. (19 male, 2 female, mean age 65.5 yrs.) with epithelioid MPM were included in this study after informed consent. 10 pts. had prior surgical resection, all pts. had adjuvant/additive therapy, general including cisplatin and pemetrexed. Following multimodal therapy all pts. demonstrated progress in CT scan. No pt. had abdominal, cerebral or bone metastases. After insertion of a venous and arterial 21 ch. stents, the arterial catheter via a femoral access was inserted into the inferior caval vein was blocked distal the right atrium, the arterial catheter was blocked in the aorta at the diaphragm. Chemotherapy consisted of 60 mg/m² cisplatinum and 15 mg/m² mitoxantrin 3 weeks till progress. The agents were administered via the arterial access, followed by 15 min of thoracic perfusion followed by chemofiltration for 45 min. The procedure was done under general anesthesia. Endpoint of the study was overall survival. Median follow-up was 48 month. Results: A total of 107 cycles (mean 5) were administered. Toxicity was low with leucopenia and thrombocytopenia CTC grad I in 9 pts. and mucositis grad II in 6 pts. Surgical complications CTC grad I occurred in 40 % of the pat. (lymphatic fistula). There was no gastrointestinal or neuro- toxicity. One year survival was 50% (Kaplan-Meier), 2 year survival was 37.5% and 3 year survival was 37.5%. Median survival was 12 months. Conclusions: Intraarterial, isolated thoracic perfusion with subsequent chemofiltration (ITP-F) for pretreated patients with MPM, which are progressing after multimodal therapy, is a valuable additional treatment option with low side effects. It offers in a palliative situation a reasonable survival with good quality of life.

Phase I study of intra-pleural administration of GL-ONC1, an oncolytic vaccinia virus, in patients with malignant pleural effusion. First Author: Lee M. Krug, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: GL-ONC1 is an attenuated vaccinia virus genetically engineered with the insertion of RUC (luciferase)-GFP, LacZ (beta-galactosidase), and gusA (beta-glucuronidase) genes. We investigated the feasibility, safety, and recommended dose of GL-ONC1 when administered intrapleurally. Methods: Pts with pleural effusion from malignant pleural mesothelioma (MPM), NSCLC, breast cancer, or other solid tumor, and a free pleural space were eligible. Single doses of 1x10⁷, 1x10⁸, 1x10⁹, or 3x10⁹ plaque forming units were administered, and escalation used a 3+3 design. Virus was infused with 500cc Ringer’s Lactate over 1hr through a pleural catheter. Fluorescent-imaging guided, thoracoscopic pleural biopsy design. Virus was infused with 500cc Ringer’s Lactate over 1hr through a pleural catheter. Fluorescent-imaging guided, thoracoscopic pleural biopsy. The most common toxicities were fever (7 pts), chills (6), and flu-like symptoms (5), all grade 1/2 occurring mostly in the 24hr after infusion. One patient at dose level 4 had transient grade 3 ALT/ALTE elevation. 1/28 urine and 5/28 pleural fluid post-treatment samples had VPA. Positive GL-ONC1 infection of tumor specimens was identified in 6 of 8 pts with epithelioid MPM based on VPA, IHC and GFP imaging. 5 of the 9 pts with epithelioid MPM had time to progression ≥ 9 mo (18 mo in one pt.) Pts with NSCLC and breast cancer progressed quickly after viral plaque assays (VPA). No chemotherapy or radiation was administered during the course of the study (14 days to 60 days). Results: 14 pts have been treated: MPM (11), NSCLC (2), breast (1). Among 13 evaluable pts (1pt with NSCLC was not evaluable due to the rapid development of brain metastases) no dose limiting toxicities occurred. The most common toxicities were fever (7 pts), chills (6), and flu-like symptoms (5), all grade 1/2 occurring mostly in the 24hr after infusion. One patient at dose level 4 had transient grade 3 AST/ALT elevation. 1/28 urine and 5/28 pleural fluid post-treatment samples had VPA. Positive GL-ONC1 infection of tumor specimens was identified in 6 of 8 pts with epithelioid MPM based on VPA, IHC and GFP imaging. 5 of the 9 pts with epithelioid MPM had time to progression ≥ 9 mo (18 mo in one pt.) Pts with NSCLC and breast cancer progressed quickly at metastatic sites. Conclusions: Single dose, intrapleural administration of GL-ONC1 is safe, but is best suited for patients with MPM whose disease is limited to the pleura. We are now exploring multi-day treatment, and also treatment in conjunction with pleurectomy for pts with MPM. Supported by Genelux Corporation (NCT01766739). Clinical trial information: NCT01766739.
7560 Poster Session (Board #308), Mon, 8:00 AM-11:30 AM
The association of T cells with survival in mesothelioma. First Author: Serena J Chee, Mesothelioma Applied Research Foundation, Alexandria, VA

Background: Mesothelioma is a rare, aggressive cancer associated with asbestos inhalation. Treatment results are poor regardless of the modality used, with median survival of 4–18 months. Immunotherapy is now established as an important therapeutic option in many solid tumours including mesothelioma, but predictive markers for benefit are absent. Previous studies suggest that CD8 infiltration in mesothelioma may confer survival benefit. TIL density may therefore identify patients with ongoing immune attack, accessible for boosting by immune activation. Methods: Tissue Microarrays (TMA) were constructed with triplicate 1mm cores from a consecutive series of 213 formalin-fixed paraffin-embedded samples from mesothelioma patients. TMA slides were stained for T-cell populations - CD3, CD4, CD8 and CD45RO. Positive cells in 3 high-powered fields (X40) per core were manually scored. The mean score was used to account for tumour heterogeneity. Medians were used as cut point between high and low counts and correlated with clinical data. Results: In contrast to previous smaller studies (Yamada et al, 2010; Ankur et al, 2008), density of tumour infiltrating CD3, CD4 and CD8 cells was not associated with survival outcomes (p = 0.224, p = 0.205, p = 0.243 respectively). However, a high CD4:CD8 ratio ( > 0.61) was associated with better survival (p = 0.007) with significant ROC curve analysis (AUC = 0.764, p = 0.001). Furthermore, a low CD45RO level was also associated with better survival (p = 0.002) in this cohort. Conclusions: In this unselected mesothelioma cohort, better survival is associated with a high CD4:CD8 ratio and low density of CD45RO memory T cells. Comparison with data from other cancer types suggest that, disease specific immune regulation controls outcome, which is reflected in the particulars of the immune infiltrate in each case. However, a high CD4:CD8 ratio is similarly associated with better survival in cervical cancer (Shah et al., 2011) but not in colorectal cancer (Diederichsen et al., 2003). A better understanding of these immunological drivers and comparative immunometry with other solid tumours types is needed to tailor disease-specific choices for immunotherapy in mesothelioma.

7562 Poster Session (Board #310), Mon, 8:00 AM-11:30 AM
MicroRNA prognostic signature in malignant pleural mesothelioma. First Author: Francesco Grossi, Lung Cancer Unit, IRCCS AOU San Martino - IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor mainly associated with asbestos exposure and characterized by a poor outcome (median overall survival (mOS) < 1 year), therefore requiring novel therapeutic approaches. MicroRNA (miR) play a role in tumorigenesis and progression in MPM. This study aimed to identify miR associated with poor prognosis. Methods: We identified 26 unresected MPM patients (11 long survivors (LS), OS > 3 years and 15 short survivors (SS), OS < 1 year). Total RNA, from formalin-fixed paraffin-embedded biopsy and 3 normal pleura (NP) samples, were miR profiled using the Agilent Human miR Microarray including 2006 miR. Expression data were normalized by GeneSpring software (v12.6). Class-comparison analysis between MPM/NP and SS/LS was performed using a t-test adjusted for multiple comparisons using Benjamini-Hochberg. OS curves were estimated using the Kaplan-Meier method and compared with the log-rank test. In silico validation was performed using miRseq data from TCGA portal based upon 16 patients (LS: 8; SS: 8). Candidate miR were assessed by univariate analysis using Kaplan-Meier method and median as cutoff. Results: Patients’ characteristics: median age 67 years (53-77); 81% males, 19% females; 73% epithelioid histotype, 12% sarcomatoid, 12% biphasic, 3% not otherwise specified. No differences in age, gender and histotype observed among LS and SS. Class-comparison analysis reported 30 miR significantly up-regulated and 11 down-regulated in LS vs SS. After adjustment, reported 14 miR significantly associated with OS and differentially expressed in MPM. A miR signature, based on the top prognostic miR (miR-99a, miR-125b, let-7b, let-7c, let-7i, miR-1224), classified patients into low or high-risk. The latter had a significantly shorter mOS (4.1 months, 95CI 2.2-5.9) compared to low-risk patients (mOS not reached. Log-rank p < 0.001). In silico validation confirmed low expression of miR-99a, miR-125b and let-7c associated with shorter OS. PI3K/AKT, WNT were associated with these top miR by pathway analysis. Conclusions: A prognostic miR signature was identified by profiling a cohort of un-resected MPM, underlying the clinical potential of miR as predictors of survival.

7563 Poster Session (Board #311), Mon, 8:00 AM-11:30 AM
High throughput therapeutic screening of malignant pleural mesothelioma (MPM) to identify correlation of sensitivity to FGFR inhibitors with BAP1 inactivation. First Author: Constantine Alifrangis, Imperial College London, London, United Kingdom

Background: Small molecule inhibitors have failed to find a role in the treatment of MPM patients. We utilised a high throughput therapeutic screen to identify novel compounds with efficacy in MPM, and performed comprehensive molecular characterisation to identify clinically relevant subgroups within a panel of MPM cell lines. Methods: 26 MPM cell lines including immortalised and primary early passage lines underwent Illumina whole exome sequencing, copy number analysis and Affymetrix array transcription profile. In parallel a high throughput drug screen was performed utilising a panel of targeted therapeutic agents. Results: From a drug screen of 896 cancer cell lines across all tumour types, MPM lines featured amongst the most sensitive 5% to FGFR inhibitors. We validated this sensitivity in a panel of early passage MPM cultures and with multiple FGFR inhibitors and also siRNA silencing of FGFR family members. We did not detect FGFR mutations or amplifications in the MPM. However we identified BAP1 loss, either through truncating mutations or promoter methylation-induced silencing, in those MPM lines with enhanced responses to FGFR inhibition. This association was further confirmed using BAP1 overexpression constructs and BAP1 shRNA knockdown, which modulated response to FGFR inhibition in mesothelioma cell lines. Baseline gene expression pathway analysis shows significant activation of MPM with BAP1 mutant status. Furthermore, we observe significantly increased levels of both FGFR1 and FGFR3 receptor transcripts and of FGFR9 and FGFR18 in BAP1 mutant versus wild type MPM cell lines. We validated this observation in a panel of 54 human MPM tumours. Conclusions: We show that a subgroup of mesothelioma-malignant pleural mesothelioma carries exquisite sensitivity to FGFR inhibition when compared to other tumour types. We identify BAP1 loss as a potential biomarker for FGFR inhibitor efficacy to define this subgroup and furthermore describe activation of FGFR signalling in BAP1 inactivated MPM. This data would suggest a clinically relevant MPM subgroup against which FGFR inhibition could be directed in future clinical studies.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**Background:** Efforts to elucidate tumorigenic mutations in mesothelioma are essential to advance therapy. Prior efforts to characterize the molecular heterogeneity of this disease have been limited by sample condition and testing platforms. Herein, we describe efforts to prospectively test patients using next-generation sequencing with matched patient germline controls.

**Methods:** Sequential mesothelioma patients were approached for consent to our IRB protocol NCT01775072 to perform MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a comprehensive molecular profiling platform based on solution-phase exon capture and next generation sequencing to detect somatic genetic alterations in FFPE tumor specimens. MSK-IMPACT involves hybridization capture and deep sequencing of all genes that are druggable by approved therapies or are targets of experimental therapies being investigated in clinical trials at MSKCC. Among 37 samples with results, 40 patients with mesothelioma underwent MSK-IMPACT testing (see Table 1). 6 samples had low tumor content and in 3 of those no alterations were identified. In 2 samples with sufficient tumor content, no alterations were identified. Among 37 samples with results, BAP1 was the most common alteration (57%).

**Conclusions:** Using MSK-IMPACT, BAP1 inactivation is the most common alteration. Other aberrations previously identified inactivation is the most common alteration (57%).

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**Background:** Immune escape correlates with an inflamed phenotype in malignant mesothelioma. **First Author:** Arun Khattri, The University of Chicago, Chicago, IL

**Background:** Malignant mesothelioma (MM) is commonly associated with an inflammatory reaction, although the specific patterns of immune escape remain incompletely understood. We used emerging, high-fidelity gene expression data from the TCGA Mesothelioma cohort to interrogate subgroups based on expression of immune related genes, and determined association of immune escape mechanisms. **Methods:** RNA-seq data from 76 MM from TCGA were analyzed using genes representative of 1. T-cells, 2. NK-cells, 3. neutrophils, 4. dendritic cells/macrophages, as well as genes associated with immune escape (immune checkpoints and cellular immune escape). Using this gene set, unsupervised, hierarchical clustering was performed to identify intrinsic immune subgroups. Groups were correlated with T-cell infiltration (Kindler ASCO 2014) and on the 12-gene inflammation signature (Harlin/Gajewski Cancer Res 2009).

**Results:** MM tumors readily clustered into two large groups with 35% of tumors showing high levels of inflammation (group 1), presence of all four immune cell components, and 80% of tumors showing a TCP-high phenotype. Non-inflamed tumors (group 2) showed low immune cell related gene expression and were 85% non-T-cell inflamed. Prominent immune escape was present in all group 1 tumors, including expression of PD-1/PD-L1, CTLA4, LAG3, and FOXP3 (however not B7H3). Inflammation strongly correlated with presence of immune escape (functional immune response) in group 1, while group 2 tumors exhibited neither infiltration with immune cells, nor immune escape (immunological ignorance).

**Conclusions:** MM can be classified into inflamed/group 1 and non-inflamed/group 2 tumors. Group 1 tumors show simultaneous infiltration with multiple immune cell components, and prominent immune escape. Inflamed and non-inflamed MM may require differential treatment strategies for immunotherapy.

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**Background:** Mesothelin-targeted immunotherapy CRS-207 in combination with standard of care chemotherapy as treatment for malignant pleural mesothelioma (MPM), **First Author:** Arun Khattri, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** MPM is an aggressive disease with poor prognosis and is relatively refractory to currently available therapies. CRS-207 is live-attenuated Listeria monocytogenes engineered to express the tumor-associated antigen mesothelin. Stimulation of potent innate and adaptive immune response by CRS-207 is synergistic with combination chemotherapy that alters the tumor environment to be more susceptible to immune-mediated killing. **Methods:** Eligible patients were chemotherapy-naive with unresectable MPM, good performance status (ECOG 0 or 1) and adequate organ function. Patients received 2 prime vaccinations with CRS-207 (1 × 10^8 CFU) 2 weeks apart, followed by 6 cycles of pembrolizumab (500 mg/m^2) and cisplatin (75 mg/m^2) 3 weeks apart and 2 CRS-207 boost vaccinations 3 weeks apart. Subjects were followed every 8 weeks until disease progression. Clinically stable patients received CRS-207 maintenance vaccinations every 8 weeks. Objectives of the study include safety, immunogenicity, objective tumor responses and tumor marker kinetics.

**Results:** Twenty-six subjects (98% male; median age: 69) have been enrolled as of Jan 15 2015. As of Jan 2015, 10/26 were on treatment. Median time on treatment was 7.1 months (range: 1.0-22.5). No treatment-related unexpected toxicities have been observed. The most common adverse events related to CRS-207 were Grades 1/2 infusion-related fever, chills/rigors, hypotension and nausea/vomiting. Of 24 subjects evaluable, 63% (15/24) had confirmed partial response (PR) post CRS-207 and chemotheraphy and 29% (7/24) had stable disease (SD). Median duration of response was 4.8 months (range: 3.6-7.2) and PFS was 7.5 months (range: 7.1-8.6) for those 16 subjects enrolled. Treatment, follow-up, and overall survival and immune response evaluations are ongoing and will be presented at the meeting.

**Conclusions:** CRS-207 can be safely combined with chemotherapy and showed encouraging anti-tumor activity with 63% of subjects having objective tumor responses and 92% disease control. These results are considerably better than those expected with chemotherapy alone and warrant further evaluation. Clinical trial information: NCT01675765.
Prophylactic cranial irradiation (PCI) and consolidation thoracic radiotherapy (TRT) for extensive stage small cell lung cancer (ES-SCLC): A systematic review and meta-analysis. First Author: Yu Yang Soon, National University Cancer Institute, Singapore, Singapore

Background: The role of PCI and TRT in ES-SCLC is controversial. We performed a systematic review of all comparative studies to investigate the benefits and harms of PCI and TRT in ES-SCLC. Methods: We searched MEDLINE, CENTRAL from date of inception and various conference proceedings from 2009 to November 2014 for eligible studies. The primary outcome is overall survival. Secondary outcomes include progression-free survival (PFS), freedom from brain metastasis and toxicity. The Cochrane risk of bias instrument was used to assess the risk of methodological bias and the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach was used to assess the quality of evidence. Hazard ratios (HR), confidence intervals (CI), p values (p) was estimated with random effects models using Revman 5.3. Results: We found 2 randomized controlled trials (RCTs) and 3 non-RCTs, including 2192 patients comparing PCI versus no PCI; 4 RCTs and 1 non-RCT including 782 patients comparing TRT versus no TRT. The risk of methodological bias was low for 2 RCTs evaluating PCI and 2 RCTs evaluating TRT. Meta-analysis of these low risk bias RCTs showed that PCI decreased the risk of brain metastasis development (HR 0.43, 95% CI 0.30 to 0.60, p < 0.001, high quality evidence) but did not improve OS (HR 0.95, 95% CI 0.48 to 1.91, p = 0.89) or PFS (HR 0.91, 95% CI 0.63 to 1.32, p = 0.62) (moderate quality of evidence). There was high quality evidence that TRT improved OS (HR 0.82, 95% CI 0.69 to 0.97, p = 0.02) and PFS (HR 0.76, 95% CI 0.64 to 0.89, p < 0.001). The incidence of grade 3–4 toxicities of PCI and TRT ranged from 1 to 20%. Conclusions: There was high quality evidence that PCI reduced the risk of brain metastasis development and TRT improved survival in ES-SCLC. Toxicity rates were variable and are probably related to dose and treated volume effects.

New ARCHITECT plasma pro-gastrin-releasing peptide assay and lung cancer: Implications for diagnosis, follow-up, and prognosis. First Author: Benjamin Nisman, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Background: Pro-gastrin-releasing peptide (proGRP) is a precursor of the neuropeptide hormone produced by small cell lung cancer (SCLC) and considered as a potential serum marker for this disease. However, proGRP was shown to be more stable in plasma compared to serum. In this prospective study we evaluated the new proGRP assay in plasma format. Methods: Plasma proGRP was determined using the ARCHITECT I System (Abbott Diagnostics, Wiesbaden, Germany) in four cohorts: healthy individuals (n = 100) and patients with benign lung diseases (BLD, n = 102), non-small cell lung cancer (NSCLC, n = 241), and SCLC (n = 90). Results: The median (95 percentile) concentrations of plasma proGRP in healthy, BLD, NSCLC and SCLC were 39 (121) and 680 (241), and 38 (64), 39 (64), 40 (121) and 680 (241) ng/ml, respectively. There was no association with age, gender or smoking. The proGRP assay proved to be effective in distinguishing SCLC from NSCLC with area under the curve 0.941, 95% CI 0.906-0.975, 84.4% sensitivity, 95% specificity, at a cut-off 121 pg/ml. False-negative results in SCLC were associated with lack of hCG transcription factor (Fisher’s Exact Test, P = 0.0006). False-positive results in NSCLC were associated with large cell neuroendocrine carcinoma (LCNEC) (Fisher’s Exact Test, P < 0.0001). The elevated proGRP was found in 44.5% (5 of 11) patients with LCNEC. Fifty patients with SCLC were followed by plasma proGRP during chemotherapy. The decline of proGRP below a cut-off (121 pg/ml) was associated with objective image based response (Fisher’s Exact Test, P = 0.0003). Multivariate Cox regression analysis the proGRP response adjusted for imaging response and ECOG performance status independently affected progression free survival (PFS), hazard ratio (HR) = 0.38, 95%CI 0.20-0.74, P = 0.009) and overall survival (OS, HR = 0.32, 95% CI 0.16-0.63, P = 0.003). Conclusions: Plasma proGRP is a highly specific and sensitive marker supporting diagnosis of high grade neuroendocrine lung tumors, mainly SCLC. Evaluation of proGRP in NSCLC is associated with LCNEC. The changes in the plasma proGRP during SCLC chemotherapy showed a significant association with imaging responses of response, PFS and OS.
Phase II study of topotecan and cisplatin with sequential radiotherapy in elderly small cell lung cancer patients (Okayama Lung Cancer Study Group; OLCSG 0102). First Author: Yoshihito Aono, Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan

**Background:** The standard treatment for elderly patients with localized small cell lung cancer (LD-SCLC) has not been established. The Okayama Lung Cancer Study Group previously performed a phase I trial using low-dose split cisplatin and topotecan (TP) therapy for elderly SCLC patients and determined the recommended dose. Here, we performed a phase II trial using low-dose split TP therapy with sequential thoracic radiotherapy (TRT) for elderly LD-SCLC patients. **Methods:** Patients aged ≥76 years with untreated LD-SCLC and a performance status of 0–2 were enrolled. Topotecan (1.0 mg/m², days 1–3) and cisplatin (20 mg/m², days 1–3) were administered for a maximum of four courses, and sequential TRT (1.8 Gy/day for a total of 45 Gy) was added. The primary endpoint was the overall response rate (ORR). We assumed that an ORR of 0.90 in eligible patients would indicate potential usefulness, whereas an ORR of 0.70 was the lower limit of interest, with α = 0.05 and 1 − β = 0.80. **Results:** A total of 22 cases were registered between 2004 and 2014. Of these, 19 individuals were male, the median age was 79 years, and the median Charlson Comorbidity index value was 3. The median number of chemotherapy courses was 3, the proportion of patients who could initiate TRT was 63.6%, and the proportion of patients who could complete whole planned treatment was 45.5%. The ORR was 0.68 (15/22 cases; 95% confidence interval, 0.47–0.89), which was below the threshold. The median progression-free survival and overall survival were 9.1 months and 22.2 months, respectively. The observed grade 3–4 toxicities included neutropenia in 95.5% of patients, thrombocytopenia in 50.0%, anemia in 36.0%, and febrile neutropenia in 32.0%. **Conclusions:** Although low-dose split TP and sequential TRT exerted positive effects on survival, the primary endpoint was not met and severe bone marrow suppression was observed. Therefore, further consideration of the regimen including the timing of TRT is required.

Clinical trial information: C000000134.

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Detection of circulating tumor cells in the peripheral blood of patients with small cell lung cancer (SCLC) using both the CellSearch system and immunofluorescence: Correlation with clinical-pathological features.

**First Author:** Ippekkos Messartakis, Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, Greece

**Background:** The diagnosis of SCLC is based on morphology and immunocytochemistry using cytokeratins and neuroendocrine markers. We aimed to evaluate the clinical significance of the detection of Circulating Tumor Cells (CTCs) in patients with SCLC using the CellSearch system (CS) and immunofluorescence (IF). **Methods:** Peripheral blood was obtained from 101 patients with SCLC before treatment, 68 patients after one cycle of 1st line chemotherapy (etoposide/platinum) and 52 patients at the time of disease progression. CTCs were detected by double immunofluorescent staining of one million PBMC’s on cytospins using anti-CD45 and anti-CD45 antibodies, and by the CellSearch system. **Results:** Prior to the initiation of 1st line treatment, 61% of patients had detectable CTCs by IF and 78% with the CS (range: 1-169 and 2-10000 CTCs, respectively). After 1 cycle of chemotherapy, the positivity of CTC detection decreased to 44% (range: 1-56 CTCs) and 45% (range: 1-4882 CTCs) using IF and CS, respectively; at the time of disease progression (PD) the detection of CTCs almost reached the baseline levels (60% and 74%; range: 2-186 and 1-11143 CTCs for IF and CS, respectively). The detection of CTCs at baseline, after 1 cycle of chemotherapy and on PD was significantly associated with decreased PFS (7.0 vs 8.5 months, p = 0.021; 5.6 vs 8.1 months, p = 0.018; 5.7 vs 7.6 months, p = 0.014, respectively) and OS (11.0 vs 26.0 months, p = 0.021; 8.9 vs 17.0 months, p = 0.009; 10.0 vs 17.0 months, p = 0.021, respectively) compared to the patients with undetectable CTCs. Multivariate analysis revealed that performance status, disease stage and the detection of CTCs at 1 cycle of chemotherapy were predictors of PFS and OS. **Conclusions:** Detection of CTCs using either immunofluorescence or the CellSearch is an adverse prognostic factor correlated with poor clinical outcome in patients with SCLC receiving 1st line chemotherapy.
7576 Poster Session (Board #324), Mon, 8:00 AM-11:30 AM
Identification of RICTOR amplification as a recurrent and potentially actionable alteration in small cell lung cancer patients. First Author: Snehal Dabir, Case Western Reserve University, Cleveland, OH

Background: Genomic analysis of SCLC is in its infancy relative to NSCLC and no known correlations to clinical outcomes have been reported for any SCLC mutation. Thus, we tested SCLC cancer diagnostic biopsies for genomic mutations by targeted exome sequencing of a panel of cancer-related genes using FFPE tissue. We identified recurrent RICTOR amplification in 5 of 36 total patient tumors examined. Here we report the clinical importance of RICTOR amplification in our SCLC cohort and its potential to represent a new actionable subgroup in this disease. Methods: Survivor distribution was estimated using Kaplan-Meier methods and the difference of OS, PFS between/among groups was examined by log-rank test. All tests are two-sided and p-value ≤ 0.05 were considered statistically significant.

Results: RICTOR amplification was found in 4 men and 1 women, with a median age of 63 years. RICTOR typically co-amplified with the nearby genes IL7R and FGF10, suggesting a focal amplification of these genes on chromosome 5p13. RICTOR was the most frequent amplified gene identified in our SCLC cohort; greater than FGFR1 and MYC. The OS of patients with RICTOR amplification was significantly decreased (p = 0.036) while PFS approached significance (p = 0.062). Cell growth inhibition studies with SCLC cell lines demonstrated sensitivity towards mTORC1/2 inhibitors (NVP-BEZ235 and AZD2014) by cells with higher CNV for RICTOR. Ongoing experiments will expand the number of cell lines studied to determine the correlation between RICTOR CNV, protein and growth inhibition.

Conclusions: Amplification of RICTOR may represent a clinically significant mutation in SCLC and may represent a predictive marker for targeted therapy with mTORC1/2 inhibitors in small cell lung cancer patients.

7578 Poster Session (Board #326), Mon, 8:00 AM-11:30 AM
Small cell lung cancer: Why has it become an orphan disease? First Author: Shakan M. Malik, Clinical Investigations Branch CTEP/DCTD, Rockville, MD

Background: Lung cancer remains the leading cause of death in US and worldwide. Substantial progress has recently been made in non-small cell lung cancer (NSCLC) with the discovery of molecular targets leading to the targeted drug development. Patient characteristics have led to the development of a number of highly effective targeted therapies in NSCLC. However, therapies for small cell lung cancer (SCLC) have lagged behind with the current standard treatment reflecting the prevailing status-quo. In the early 1980s, we wanted to identify the reasons for the lack of progress in the treatment of SCLC. Methods: We searched all the randomized clinical trials of SCLC through a search of the National Cancer Institute Drug Therapy Evaluation Program database (through June 31, 2014). We also conducted a search of Medline with the MeSH terms “Small Cell Lung Carcinoma”, “phase III”, and “phase II”, for peer-reviewed randomized clinical trials. Results: Trials for limited-stage SCLC have decreased over time with 39/44 trials being positive. Of these 9 positive trials, 8 studied radiation dose/sequencing. In extensive-stage SCLC, there were 14 positive trials, with a greater than 60% of trials being positive. Of these 9 positive trials, 8 studied radiation dose/sequencing. The discovery of molecular drivers in SCLC that are targetable lag far behind NSCLC. The number of randomized trials studying new drugs in SCLC trials is limited. Since the approval of topotecan in 1996 the US FDA has approved no new drugs for the treatment of small cell lung cancer patients.

Randomized comparative trials in SCLC

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7577 Poster Session (Board #325), Mon, 8:00 AM-11:30 AM

Background: Conditional survival (CS) has emerged as a clinically useful measure of prognosis for cancer patients with poor prognosis. We examined the efficacy of prophylactic cranial irradiation (PCI) on cancer-specific CS estimates for small cell lung cancer (SCLC) patients. Methods: SCLC patients on whom PCI data was available were identified from the Surveillance Epidemiology and End Results registry (SEER) from 1988-1997. PCI data were only available after 1997. Multivariate Cox regression models were built separately by each stage to calculate the adjusted 1-6 year cancer-specific survival and overall survival. The multiplicative law of probability was then used to compute the X-year conditional survival where the (x+y) year survival is divided by y years of patients who have survived. Variables adjusted for included age, sex, ethnicity, marital status, SEER region, year of diagnosis, and radiation. Results: On data on 9,134 patients was included. Utilization of PCI in limited stage (LS)-SCLC increased from 18% in 1988 to 23% in 1997 (P < 0.001). Patients with LS-SCLC from Midwest were less likely to receive PCI (36% vs. 40%, P < 0.001) compared to other SEER regions and those aged 50-79 years with LS-SCLC were less likely to receive PCI (59% vs. 16%, P < 0.001). The 3-year conditional overall survival (COS) from diagnosis (time 0) to 3 years for LS-SCLC receiving PCI improved from 23% (all patients at diagnosis) to 54% (patients alive at 3 years from diagnosis) whereas similar estimates for those not receiving PCI were 17% and 48%. For extended stage (ES)-SCLC receiving PCI, the 3-year COS improved from 4% to 49% whereas the 3-year COS for those not receiving PCI improved from 5% to 50%. Three-year conditional cancer-specific survival (CSS) for LS-SCLC receiving PCI improved from 28% to 65% and for those not receiving PCI improved from 20% to 59%. For ES-SCLC receiving PCI, the 3-year CSS improved from 5% to 60% whereas in those not receiving PCI, it improved from 6% to 62%. Conclusions: Three-year COS and CSS estimates improve dramatically over time for SCLC survivors. These prognostic data provide more accurate prognosis helping clinicians and patients with informed decision making.

7579 Poster Session (Board #327), Mon, 8:00 AM-11:30 AM
Impact of accurate staging with 18F-FDG-PET and brain MRI on clinical benefit of prophylactic cranial irradiation (PCI) in patients with limited stage (LS) small cell lung cancer (SCLC). First Author: Mitong Choi, National Cancer Center, Goyang, South Korea

Background: The latest randomized study using brain MRI as initial brain assessment has suggested PCI had a negative survival effect in extensive stage SCLC (Abstr 7503, ASCO, 2014), which is contrary to the results of earlier studies that had not necessarily included brain MRI and PET as initial evaluation. Furthermore, as the survival of LS-SCLC pts improves, there been a great need to critically address the benefit-risk issue of PCI (Lee J et al, J Clin Oncol, 2006). Thus, we sought to evaluate the effect of initial brain MRI and PET evaluation on the clinical outcome and benefit of PCI in LS-SCLC pts. Methods: We retrospectively collected data from 264 pts with histologically-proven LS-SCLC who had complete or partial response after concurrent chemoradiotherapy including platinum-based regimen from April 2001 to April 2013 at National Cancer Center Hospital (Goyang, Korea). Among them, 130 pts who had both brain MRI and whole body 18F-FDG-PET as initial staging work-up are included in this analysis. Results: In the 130 pts, the 5-year cumulative brain metastasis (BM) rate was 39.6% and the 5-year overall survival rate was 53.2%. Among them, 46 received PCI (25 or 30Gy in total) and 84 did not. There was no difference in clinical characteristics such as age (60 v 63 years; p = 0.140) and TMM stage (I-IIIA/IIIB) (22/2845% v 24/43/33%; p = 0.147). Between the two groups (PCI vs No PCI), there was no significant difference in the 5-year cumulative BM rate in patients with stage I-IIIA SCLC (n = 79) (29.5 vs 41.7%, P = 0.985). Subgroup analysis showed PCI tended to decrease the 5-year cumulative BM rate in patients with stage I-IIIA SCLC (n = 79) (29.5 vs 41.7%, P = 0.104) but not in patients with stage IIIB SCLC (n = 51) (46.5 vs 41.3%, P = 0.876).

Conclusions: LS-SCLC pts accurately staged with brain MRI and PET exhibited excellent overall survival with the 5-year survival rates after achieving objective response after CCRT, exceeding 50% regardless of PCI. Considering the risk of overtreatment, the role of PCI should be more critically readdressed in this group of LS-SCLC pts with greater potential for long-term survival and even cure.
Phase II trial of single agent amrubin (A) in patients (pts) with previously treated advanced thymic malignancies (TM). First Author: Heather A. Wodruff, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA.

Background: There are limited treatment options for pts with TM and chemotherapy efficacy is often restricted by cumulative toxicity such as neuropathy (taxanes) and cardiomyopathy (anthracyclines). This trial investigated single agent amrubin (A), a third generation anthracycline and topoisomerase II inhibitor with minimal cardiac toxicity, in TM pts. Methods: This was an open-label investigator-initiated clinical trial at 2 institutions with overall response rate (RR) as the primary endpoint. Eligible pts had TM (thymoma (T) or thymic carcinoma (TC)) with progressive disease (PD) or relapse after ≥ 1 prior chemotherapy regimen, and adequate organ function including left ventricular ejection fraction (LVEF) of > 50%. The initial treatment plan consisted of A at 40 mg/m² IV days 1-3 repeated in 21-day cycles with growth factor support. Results: 33 pts (14T/19TC) enrolled from 7/2011 to 4/2014: 14 women/19 men; age 30-81 yr; 9 Asian, 1 African-American, 23 White. A high rate of febrile neutropenia (FN) led to an amended starting dose of 35 mg/m² IV 1-3 of 21-day cycles. In total, 7 pts experienced FN with 1 related death. All but 3 grade 3/4 possibly related events included thrombocytopenia (n = 3), neutropenia (without fever, n = 3), anemia (n = 7), lethargy/fatigue (n = 7), perirectal abscess (n = 2), palmar-plantar erythrodysesthesia (n = 3), syncope (n = 2), venous embolism (n = 2), and 1 pt each with sepsis, oral abscess, pneumonia, UTI, mucositis, chest pain, and epigastric pain. Other toxicities were mild and A was generally well tolerated. No significant changes in LVEF were noted on serial echocardiograms. RR was 18% (n = 6, all partial); 29% (n = 4) in T and 11% (n = 2) in TC. Disease control rate (DCR) at first evaluation was 88% overall (n = 29): 100% (n = 14) in T and 78% (n = 15) in TC. 4/7 pts (57%) with PD or disease progression (DP) had ≥ 4 pts received at least 4 cycles, and 17 received 10 or more cycles, with 34 cycles as the highest number to date. 5 pts remain on therapy. Conclusions: Amrubin, at 35 mg/m² IV days 1-3 on a 21-day cycle, shows promise as a single agent in pre-treated pts with T and TC with an 18% RR and no unexpected toxicity. Further exploration as a single drug or in combination is warranted. Clinical trial information: NCT01364727.

Effectiveness of somatostatin analogs plus prednisone in aggressive histotype and advanced stage thymic epithelial tumors. First Author: Margaret Ottaviano, Department of Clinical Medicine and Surgery and Rare Tumors Reference Centre Campania Region, University, Naples, Italy.

Background: Thymic epithelial tumors (TETs) are rare neoplasms characterized by histological variability. Efficacy of octreotide/lanreotide with or without prednisone in TETs OctreoScan positive has been widely demonstrated by histological variability. Efficacy of octreotide/lanreotide with or without prednisone in TETs OctreoScan positive has been widely demonstrated. Methods: Eighteen patients (nine women and nine men, median age 54.5 years; range 32-78) with advanced thymic tumors (seven patients with stage III; seven with IVa; Four with IVb according to the Masaoka-Koga staging system), histotype sec WHO revised by central review (three AB, two B1, five B2, three B3/B2, two thymic carcinoma) with a partial response or stable disease to conventional chemotherapeutic regimens platinum or not platinum-based, after performed OctreoScan, were enrolled in this monocentric referral center study. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly), until progression of disease was documented. Median time to progression and toxicity were evaluated. Results: Median follow-up was of 43 months with a median time to progression of 14.5 months (range 77-2). Treatment was generally well tolerated with acceptable toxicity: Grade 1 diarrhea (5 patients), Grade 2 hyperglycemia (4 patients). No patients interrupted treatment because of toxicity. Conclusions: The current study indicates that single-agent somatostatin analogs maintenance therapy is a potential treatment strategy for advanced TETs OctreoScan positive which respond to previous conventional chemotherapy. In particular, somatostatin analogs may provide an effective maintenance treatment duration regardless of histotype and stage of disease with an acceptable toxicity and an improved patients’ compliance.

ALCHEMIST: a clinical trial platform to bring genomic discovery and molecularly targeted therapies to early-stage lung cancer. First Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX.

Background: There are limited treatment options for pts with TM and chemotherapy-based regimens platinum or not provide an effective treatment strategy for advanced stage disease according to the Masaoka-Koga staging system, histotype sec WHO revised by central review (three AB, two B1, five B2, three B3, three B2/B3, two thymic carcinoma) with a partial response or stable disease to conventional chemotherapeutic regimens platinum or not platinum-based, after performed OctreoScan, were enrolled in this monocentric referral center study. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly), until progression of disease was documented. Median time to progression and toxicity were evaluated. Results: Median follow-up was of 43 months with a median time to progression of 14.5 months (range 77-2). Treatment was generally well tolerated with acceptable toxicity: Grade 1 diarrhea (5 patients), Grade 2 hyperglycemia (4 patients). No patients interrupted treatment because of toxicity. Conclusions: The current study indicates that single-agent somatostatin analogs maintenance therapy is a potential treatment strategy for advanced TETs OctreoScan positive which respond to previous conventional chemotherapy. In particular, somatostatin analogs may provide an effective maintenance treatment duration regardless of histotype and stage of disease with an acceptable toxicity and an improved patients’ compliance.

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TPS7584  Poster Session (Board #331b), Mon, 8:00 AM-11:30 AM
Neoadjuvant erlotinib in stage III NSCLC patients (pts) with activating EGFR mutations (EVENT trial). First Author: Cengiz Inal, Albert Einstein Coll of Medcn, Bronx, NY

Background: Results with standard chemoradiotherapy for stage III NSCLC pts have plateaued and systemic relapse remains the biggest challenge. Genomic driven strategies are desperately needed as there is yet to be an approved targeted agent for locally advanced disease. Erlotinib improved objective response rate (ORR) and prolonged progression free survival (PFS) compared with chemotherapy in pts with EGFR-mutated advanced NSCLC. Neoadjuvant therapy is a consistent surrogate marker for long term survival. We aim to evaluate rates of pNO following neoadjuvant erlotinib in stage III NSCLC pts with activating EGFR mutation. Methods: 3 out of 55 planned pts have been enrolled in this single arm, open label phase II study. Based on historical data, pNO rate of > 30% will justify further study and the rate of < 15% will be considered ineffective. With optimal two-stage design, if ≥ 3 out of initial 19 pts have pNO, additional 36 pts will be accrued in the second stage. Neoadjuvant erlotinib will be considered for further studies if pNO is observed in > 12 among total 55 pts. With 80% power and type I error of 0.05, the probability of early stopping at the first stage is 68.4% if the true response rate (TR) is 15% and 13.3% if TR is 30%. Total of 55 pts will ensure that the 95% CI for the estimated TR will be within +/- 15.7% by the end of this study. Stage IIIA/B NSCLC patients with N2 disease, activating EGFR mutations, ECOG PS 0-2, preserved organ function and no prior chemotherapy or radiation are eligible. Pts are treated with neoadjuvant erlotinib 150 mg PO daily for two months and then restaged. Pts with significant clinical down staging and deemed medically fit for surgery will have surgical resection. Pts with non-progressive disease who do not undergo surgery will have mediastinal restaging. Therapy after surgery or mediastinal restaging is at the discretion of the treating physician. The primary objective is to estimate the rate of pNO after neoadjuvant erlotinib. Secondary objectives include PFS, OS, ORR from neoadjuvant erlotinib, and surgical resection rate. The translational studies in pre and post erlotinib tumor biopsy are also planned. Clinical trial information: NCT01857271. Clinical trial information: NCT01857271.

TPS7585  Poster Session (Board #332a), Mon, 8:00 AM-11:30 AM
NCT01912625. Clinical trial information: NCT01912625.

Background: Concurrent chemoradiotherapy is the standard management approach for unresectable, non-metastatic locally advanced non-small cell lung cancer (NSCLC). However, progress has been slow in making substantial improvements in the outcomes of these patients. Preclinical data suggests that adding molecular targeted drugs affecting specific pathways could enhance radiation effects, and KRas mutated NSCLC may be particularly susceptible for MEK1/2 inhibition for radiation sensitization. This trial tests the safety of combining trametinib (GSK1120212), a potent MEK1/2 inhibitor, with standard carboplatin and paclitaxel chemoradiotherapy, for the treatment of locally advanced NSCLC. Methods: This is a multi-center, NCI UM1-sponsored, phase I clinical trial. Patients with unresectable stage II-III NSCLC with KRas mutation who can receive concurrent carboplatin (AUC 2.0) and paclitaxel (50 mg/m2) with once-daily trametinib and 60 Gy radiotherapy delivered in 30 fractions are eligible. Two additional cycles of consolidation chemotherapy (carboplatin AUC 6.0 and paclitaxel 200 mg/m2) are given after completing concurrent chemoradiotherapy. Trametinib is delivered at the starting dose level of 1.0 mg, and Time-to-Event-Continuous Reassessment Method (TiTE-CRM) is used for dose escalation at 4 levels (0.5, 1.0, 1.5, and 2.0 mg). CTCAE v4.0 is used to determine dose-limiting toxicity (DLT), with the Pr(tox) within 70 days of start of therapy, as well as pharmacokinetic studies. Secondary objectives include response rate, overall survival, patterns of recurrence, dose delay and percentage of dose delivered, and biomarker exploratory endpoints. The maximum number of patients is 30. Conduct to Date: The trial was activated October 28, 2013 at MD Anderson, and recently at Ohio State University. So far 7 patients have enrolled on study. Clinical trial information NCT01912625. Clinical trial information: NCT01912625.

TPS7586  Poster Session (Board #332b), Mon, 8:00 AM-11:30 AM
Phase I/II study of tumor-infiltrating lymphocyte (TIL) infusion and low-dose interleukin-2 (IL-2) in patients with advanced malignant pleural mesothelioma (MPM). First Author: Mark Doherty, Department of Medical Oncology, University College Hospital Galway, Galway, Ireland

Background: MPM is a disease with poor outcomes, and only modest benefits from existing systemic therapies. Preclinical studies have shown that MPM often contains populations of TILs, and that these can be expanded ex vivo. Therapy using autologous TIL infusions and IL-2 following lymphodepleting chemotherapy has been successfully used in advanced melanoma. The therapeutic potential for TILs in MPM has not yet been explored. Methods: This is a single arm, phase I/II study to evaluate the feasibility, safety, and efficacy of TIL therapy for advanced MPM at the Princess Margaret Cancer Centre. Eligibility criteria include: advanced MPM, suitable surgical candidate for TIL harvesting from tumor, ECOG performance status 0-1, adequate organ function, and successful expansion of TILs. TILs are harvested from fresh tumor tissue, evaluated for suitability, and expanded ex-vivo. Patients are treated with a lymphodepleting chemotherapy regimen containing cyclophosphamide (60/mg/m2 x 2 days) and fludarabine (25/mg/m2 x 5 days), followed by infusion of expanded TILs. This is followed by low-dose IL-2 therapy (125/000 IU/kg/day subcutaneously) for 2 weeks. The treatment protocol is adapted from that used in melanoma TIL studies, and no dose exploration is planned. The primary objective is determining the maximum tolerated dose (MTD) and safety of trametinib as measured by rate of grade 3 or worse non-hematologic toxicities attributed to chemoradiation within 70 days of start of therapy, as well as pharmacokinetic studies. Secondary objectives include response rate, overall survival, patterns of recurrence, dose delay and percentage of dose delivered, and biomarker exploratory endpoints. The maximum number of patients is 30. Conduct to Date: The trial was activated October 28, 2013 at MD Anderson, and recently at Ohio State University. So far 7 patients have enrolled on study. Clinical trial information NCT01912625. Clinical trial information: NCT01912625.
AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion trial LUX-Lung 8 (LL8). First Author: Jean-Charles Soria, Gustave Roussy Cancer Campus and University Paris-Sud, Paris, France

Background: Treatment options for pts with advanced SCC of the lung progressing after platinum-based chemotherapy are limited. Overexpression of EGFR, ErbB receptors and the dysregulation of their downstream pathways are implicated in SCC pathobiology. Primary analysis of LL8 (2nd line A, an irreversible EGFR family blocker vs T790M resistant) showed significant EGFR tyrosine kinase inhibitor (TKI; only TK1 approved in this setting), in pts with SCC of the lung showed significantly better progression-free survival (PFS) with A. OS and updated PFS are reported here. Methods: Pts with stage IIIIB IV disease were randomized 1:1 to receive A (40 mg/day) or E (150 mg/day) until disease progression. Primary endpoint: PFS; key secondary endpoint: OS. Other endpoints: objective response (ORR), disease control (DCR), patient reported outcomes and safety. 632 events and a sample size of 800 pts was needed to detect a HR of 0.8 with 80% power for OS. Results: OS was significantly better with A (n = 398) vs E (n = 397), with a 19% reduction in risk of death (7.7 vs 9.8 months; HR [95% CI] 0.81 [0.69–0.95]; p = 0.008). Significant differences in OS were seen at 6 (63.6 vs 54.6%; p = 0.01), 12 (36.4 vs 28.2%; p = 0.016) and 18 (22.0 vs 14.4%; p = 0.013) mos. PFS (median 2.6 vs 1.9 mos; HR [95% CI] 0.81 [0.69–0.96]; p = 0.010), ORR (5.6 vs 2.6%; p = 0.055) and DCR (39 vs 32%; p = 0.007) were higher on A. Therapy was better tolerated with a lower incidence of drug-related grade 3/4 diarrhea (9.9/0.5 vs 2.3/0.3%), G3 stomatitis (4.1 vs 0%) with A and a higher incidence of G3 rash/ acne with E (5.9 vs 10.4%). Preliminary data from FoundationOne analysis of tumor blocks will be shown. Conclusions: A significantly improved OS vs E in pts with SCC of the lung in a 2nd line setting. PFS and DCR were also significantly better. With a manageable AE profile, added QOL benefit, and symptom control seen in LL8, A should be preferred over E for these pts. Clinical trial information: NCT01523587.

Cabozantinib (C), erlotinib (E) or the combination (C+E) as second- or third-line therapy in patients with EGFR wild-type (wt) non-small cell lung cancer (NSCLC): A randomized controlled trial (E1512). First Author: Joel W. Neal, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA

Background: Cabozantinib (C) is a small molecule inhibitor of multiple receptor tyrosine kinases, including MET, VEGFR2 & RET. Cabozantinib (C) is a small molecule inhibitor of multiple receptor tyrosine kinases, including MET, VEGFR2 & RET. MET is involved in the progression of various cancers, including NSCLC. Cabozantinib-based regimens are promising for further investigation in this disease setting. PFS and DCR were also significantly better. With a manageable AE profile, added QOL benefit, and symptom control seen in LL8, A should be preferred over E for these pts. Clinical trial information: NCT01523587.

Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). First Author: Lecia S. Sequist, Massachusetts General Hospital, Boston, Massachusetts, Ingam, The Winship Cancer Institute of Emory University, Atlanta, GA

Background: Rociletinib is an oral inhibitor of mutant EGFR, including the T790M resistance mutation. We reported robust activity in T790M positive pts identified by tumor genotyping treated at 500mg-1000mg BID (active doses) (NCT01526928). We now report updated data from the first phase I/II study before plasma genotyping. Methods: For the first phase one 1/2 study, pts had EGFR-mutant NSCLC and treatment with ≥ 1 EGFR inhibitor, ECQ PG 0-1. Brain metastases were permitted. In phase 2, T790M pos pts were included. We performed AE comparison to historically T790M pos pts, regardless of genotype method. ORR was 33-36% among T790M neg pts, (see Table). There were 17 pts T790M pos in plasma but with neg (9) or failed (8) tissue genotyping, and 5/17 responded. There were 16 pts T790M pos in tissue but with neg plasma genotyping and 6/16 responded. 3/8 who were neg by both methods responded. The majority of T790M negative responders were on an EGFR TKI immediately before rociletinib (10/12 tissue and 10/10 plasma). Serial plasma data typically showed a decrease in the levels of T790M over time. Related all grade AE in 15% patients were: hyperglycaemia (40%), diarrhea (23%), fatigue (21%), decreased appetite (8%). Conclusions: Rociletinib is associated with durable response and is well tolerated in pts with mutant EGFR T790Mpos NSCLC. One-third of T790M neg pts also respond, which cannot be explained by retreatment effect. Serial plasma data shows T790M decrease in most pts, including non-responders, suggesting T790M is not always the dominant growth driver. Plasma genotyping by BEAMing may be a complementary method to select patients. Clinical trial information: NCT01526928.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: N is a second-generation platinum compound with lower nausea/vomiting and nephrotoxicity than C. N plus D (ND) showed a promising efficacy with acceptable toxicity for advancedSqLC in the previous phase II study. Methods: Eligible patients (pts) were those with pathologically proven SqLC with stage IIIb/IV or postoperative recurrence, aged 20-74 and ECOG PS 0-1. Pts were randomized 1:1 to ND (N 100 mg/m² and D 60 mg/m² intravenous, q3w, up to 6 cycles) or C plus D (CD) (C 80 mg/m² and D 60 mg/m² intravenous, q3w, up to 6 cycles) according to stage, gender and institution. The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS), response rate (RR) and adverse events (AEs). Target sample size of 350 provided 90% statistical power to detect a hazard ratio of 0.71 with one-sided type I error of 0.05. Results: Between July 2009 and July 2012, 355 pts were randomized. Of 349 for efficacy analysis (ND 177; CD 172), 305 (86%) completed 6 cycles. OS HR was 0.81 (90%CI, 0.67-0.98) with a median OS of 13.6 months [m] for ND and 11.4 m for CD. RR of 35% vs 29% (p = 0.050) with a HR of 0.83 (0.69-1.00) and a median PFS of 4.9 m in ND and 4.5 m in CD. RR was 54.5% in ND vs 52.9% in CD (p = 0.829). Grade 3 or higher AEs of nausea (4.0% vs 13.4%), fatigue (3.4% vs 10.9%), hypotension (3.6% vs 30.3%) and hypokalemia (2.3% vs 8.6%) are more frequent in CD. Grade 3 or higher AEs of neutrophils (82.5% vs 70.3%) and platelets (9.0% vs 0.0%) are more frequent in ND, but there was no difference in grade 3 or higher febrile neutropenia (13.6% vs 15.4%). Treatment related deaths occurred in 4 and 3 pts in ND and CD, respectively. Conclusions: ND showed a significantly longer OS as compared to CD with different toxicity profile. ND will be considered as a new standard treatment for advanced or relapsedSqLC. Clinical trial information: UMIN000002015.

Background: RET rearrangements are found in 1-2% of non-small cell lung cancers and responses can be durable. This study has met its primary endpoint. A larger, confirmatory, multi-center trial is now warranted.

Conclusions: This is the only large randomised trial evaluating the utility of WBRT in this disease. Although the results include the pre-specified non-inferiority margin, the estimate of the difference in QALYs suggests WBRT provides no additional clinically significant benefit for this group of patients. Clinical trial information: 3826061.
Efficacy and safety of the ALK inhibitor alectinib in ALK+ non-small-cell lung cancer (NSCLC) patients who have failed prior crizotinib: An open-label, single-arm, global phase II trial (NCT01801111).

**Background:** The ALK inhibitor crizotinib is approved for patients (pts) with ALK-rearranged (ALK+) NSCLC, but most pts progress within a year and CNS progression is common. The NP28673 study (NCT01801111) investigated the efficacy and safety of alectinib, a highly selective, CNS-active ALK inhibitor, in ALK+ NSCLC pts who had progressed on crizotinib. Aims: Eligible pts (≥ 18 yrs; locally advanced/metastatic ALK+ NSCLC by FDA-approved FISH test; failed on/interolerant to crizotinib) received alectinib 600mg p.o. BID until progression, death or withdrawal. Crizotinib was the only prior ALK inhibitor permitted. Primary endpoint was objective response rate (ORR) by independent review committee (IRC) using RECIST v1.1. Secondary endpoints included ORR by investigator; duration of response (DOR); CNS ORR and DOR; progression-free survival (PFS); disease control rate (DCR); CNS progression rate, overall survival, and safety. Results: 138 pts from 16 countries were enrolled by the 18 Aug 2014 cut-off. Median age 52 yrs; 80% had prior chem; 60% had baseline CNS mets (60/83 treated). Median follow-up was 30 wks. In the response-evaluable population assessed by IRC (122 pts with measurable disease at baseline), ORR was 49.2% (95% CI 40.0–58.4; all PRs); DCR was 79.5% (95% CI 71.3–86.3). For patients with prior chem and crizotinib (n = 96), ORR was 43.9% (95% CI 33.6–54.3); DCR was 78.1% (95% CI 68.5–85.7). For pts with baseline measurable CNS disease (n = 34), IRC-assessed CNS ORR was 55.9% (95% CI 37.9–72.8), including five CRs. Updated ORR, DOR and PFS data will be presented. Overall, 27.5% of pts had grade 3–5 adverse events, most commonly dyspnea (3.6%) and pulmonary embolism (2.2%); rates of discontinuation were (19.6%), reductions (8.7%), and withdrawals (8.0%) due to AEs were seen. Conclusions: Alectinib was well tolerated and achieved a robust treatment response, including excellent intracranial activity, in ALK+ NSCLC pts who had progressed on crizotinib; most had also failed prior chem and had CNS mets. A phase 3 trial of first-line alectinib versus crizotinib and an expanded access program are ongoing. Clinical trial information: NCT01801111.

**Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in ZL/3L NSCLC (POPLAR).**

**First Author:** Alexander I. Spira, Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA

**Background:** MPDL3280A (anti-PDL1) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor-infiltrating immune cells (IC) and/or tumor cells (TC) (Horn et al, ASCO 2015). Methods: Previously treated NSCLC patients (pts) were stratified by PD-L1 IC status, TC0, 1, 2 or 3 and IC0, 1, 2 or 3. The primary endpoint was OS (data cutoff, 33.6–54.3); DCR was 78.1% (95% CI 68.5–85.9). For patients with baseline measurable CNS disease (n = 34), IRC-assessed CNS ORR was 55.9% (95% CI 37.9–72.8), including five CRs. Updated ORR, DOR and PFS data will be presented. Overall, 27.5% of pts had grade 3–5 adverse events, most commonly dyspnea (3.6%) and pulmonary embolism (2.2%); rates of discontinuation were (19.6%), reductions (8.7%), and withdrawals (8.0%) due to AEs were seen. Conclusions: Alectinib was well tolerated and achieved a robust treatment response, including excellent intracranial activity, in ALK+ NSCLC pts who had progressed on crizotinib; most had also failed prior chem and had CNS mets. A phase 3 trial of first-line alectinib versus crizotinib and an expanded access program are ongoing. Clinical trial information: NCT01801111.

**Efficacy and safety of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D.** First Author: Amanda Patnaika, START, San Antonio, TX

**Background:** Pembrolizumab is a potent anti-PD-1 monoclonal antibody, IPI, an anti–CTLA-4 antibody, has shown activity in advanced NSCLC. In melanoma, combined anti–PD-1 and anti–CTLA-4 treatment has shown robust efficacy and manageable toxicity. We report interim results from a phase II study evaluating pembro + IPI in patients (pts) with recurrent NSCLC. Methods: Pts with stage IIIB/IV NSCLC that recurred after ≤ 2 prior regimens received pembro + IPI every 3 wks for 4 cycles followed by the maintenance pembro. Based on emerging data from the nivolumab + IPI advanced NSCLC study, doses were reduced from 10 mg/kg to 2 mg/kg for pembro and from 3 mg/kg to 1 mg/kg for IPI. Primary endpoint was safety and incidence of dose-limiting toxicities (DLTs) in the first 3 wk of dosing. Response was assessed every 6 wk per RECIST 1.1 by investigator review. Results: As of Dec 2014, 17 pts were enrolled; 3 at pembro 10 mg/kg, IPI 3 mg/kg; 3 at pembro 10 mg/kg + IPI 1 mg/kg, and 11 at pembro 2 mg/kg + IPI 1 mg/kg. No DLTs or dose modifications were reported for the 15 pts treated at the time of analysis. 10 pts experienced drug-related AEs (DRAs); none led to discontinuation or death. There were 2 gr 3 ADRs, both rash. Gr 2 ADRs were diarrhea and vomiting (n = 2 each) and chills, cough, decreased appetite, decreased weight, dehydration, depression, dysphonia, fatigue, myalgia, pruritus, and pyrexia (n = 1 each). Responses were seen in all dose groups among the 11 pts on treatment for ≥ 6 wk at the time of analysis, including 1 CR (9%) and 5 PRs (45%); Table 1 shows all pts achieved disease control. 12 pts remain on treatment (≥ 26 + 3 pts discontinued for PD). Conclusions: Preliminary data from KEYNOTE-021 cohort D demonstrate an acceptable toxicity profile and robust antitumor activity for pembro + IPI in pts with recurrent NSCLC. The use of lower pembro and IPI doses did not appear to negatively impact efficacy. Clinical trial information: NCT02039674.
Clinical correlation and frequency of programmed death-ligand 1 (PD-L1) expression in EGFR-mutant and ALK-rearranged non-small cell lung cancer (NSCLC). First Author: Justin F. Gainor, Massachusetts General Hospital Cancer Center, Boston, MA

Background: PD-L1 expression has recently been associated with response to PD-1 blockade. Given recent clinical interest in combining PD-1/PD-L1 inhibitors with EGFR and ALK tyrosine kinase inhibitors (TKIs), we evaluated PD-L1 expression patterns and clinical outcomes in EGFR-mutant and ALK-positive patients (pts). Methods: PD-L1 (Clone E1L3N, Cell Signaling Technologies) and CD8 immunohistochemistry were performed on biopsy and resection specimens from pts with metastatic NSCLC. Membranous expression of PD-L1+ tumors was defined as positive. PD-L1+ tumor infiltrating lymphocytes (TILs) were evaluated using a 4-tier grading system (0-3). Results: We evaluated PD-L1 expression and CD8+ TILs in pts with metastatic, EGFR-mutant (N = 68) and ALK-positive (N = 28) NSCLC (Table). Median progression-free survival (mPFS) on EGFR TKIs was similar in PD-L1+ and PD-L1- pts at baseline (6.7 vs. 13.2 months; P = 0.08), as was overall survival (OS): 31.8 vs. 35.63 months; P = 0.307. mPFS on ALK TKIs was similar in PD-L1+ and PD-L1- pts at baseline (5.6 vs. 11.1 months; P = 0.28), but mOS was shorter among PD-L1- pts (26.5 vs. 51.6 months; P = 0.045). To evaluate whether targeted therapy affects PD-L1 expression, we also compared pre- and post-TKI biopsies in each cohort. Among individual EGFR-mutant pts with paired, pre- and post-TKI biopsies (N = 58), PD-L1 expression levels varied between biopsies in 13 (22%) pts. Among individual ALK-positive pts with pre- and post-TKI biopsies (N = 8), PD-L1 expression levels varied between biopsies in 2 (25%) pts. Conclusions: EGFR-mutant and ALK-positive lung cancers may express PD-L1 and demonstrate CD8+ TILs. Expression is dynamic in a subset of pts with changes in PD-L1 expression and immune infiltrates observed over time and following treatment.

8014 Poster Discussion Session: Displayed in Poster Session (Board #336), Mon, 8:00 AM-11:30 AM, Discussion in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

AS8P273, a mutant-selective irreversible EGFR inhibitor in patients (pts) with NSCLC harboring EGFR activating mutations: Preliminary results of first-in-human phase I study in Japan. First Author: Yasushi Goto, National Cancer Center Hospital, Tokyo, Japan

Background: AS8P273 is a small molecule, irreversible tyrosine kinase inhibitor (TKI) that inhibits the kinase activity of EGFR activating mutations and T790M resistance mutation, with higher potency than wild type EGFR. Methods: This open-label, dose escalating study was performed in pts previously treated with at least one TKI. We were enrolled into this open-label Phase I study which consists of a dose escalation cohorts only pts with T790M were enrolled (NCT02192697). First-in-human phase I study of EGF816, a third generation, mutant-selective EGFR tyrosine kinase inhibitor, in patients (pts) with non-small cell lung cancer (NSCLC). First Author: Daniel Shao-Wen Tang, National Cancer Centre Singapore, Singapore, Singapore

Background: The emergence of T790M resistance mutations (mt) occurs in up to 50% of patients (pts) with NSCLC harboring a sensitizing EGFR mt treated with erlotinib or gefitinib. EGF816 is a cobaloxime, irreversible, EGFR TKI that has nanomolar inhibitory potency against activating mt (L858R, ex19del) and T790M mt, with up to 60-fold selectivity over wild type (wt) EGFR in vitro. Methods: This multicenter, dose escalation study to determine the safety, tolerability and antitumor activity of EGF816, enrolled NSCLC pts with locally or centrally confirmed T790M status. Oral EGF816 was administered on a continuous 28-day schedule. Dose escalation started from 75 mg QD and was guided by an adaptive Bayesian logistic regression model to determine the maximum tolerated dose. Paired tumor biopsies were performed to evaluate pharmacodynamics. NCT02108964.

8015 Poster Discussion Session: Displayed in Poster Session (Board #337), Mon, 8:00 AM-11:30 AM, Discussion in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Activity of AUY922 in NSCLC patients with EGFR exon 20 insertions. First Author: Zofia Piotrowska, Massachusetts General Hospital Cancer Center, Boston, MA

Background: EGFR exon 20 insertions (ins20) represent a rare subtype (4%) of EGFR mutations and are refractory to EGFR-specific tyrosine kinase inhibitors (TKIs). The effective targetable properties for existing EGFR TKIs on ins20 PFS on the irreversible EGFR TKI Afatinib is 2.8 months (mos). A pt with EGFR ins20 achieved a durable RECIST partial response (PR) to AUY922, a Heat Shock Protein 90 (Hsp90) inhibitor, in a previous study (NCT01124864), so we designed this phase II investigator-initiated trial to assess the activity of AUY922 in NSCLC pts with EGFR ins20. Methods: This was a single-arm, multi-center, open-label study of AUY922 in advanced NSCLC pts with EGFR ins20 mutations. A Simon two-stage design was used, with a plan to enroll 19 pts in the 1st stage and an additional 19 pts in the 2nd stage if >1 PR or stable disease (SD) lasting >3 mos was observed in the 1st stage. All pts were treated with AUY922 at 70mg/m2 IV weekly. The primary aim was to evaluate objective response rate (ORR) to AUY922. Here we report the complete results from the 1st stage. Results: Ten pts, including 7 females and 3 males, average age 55 (range 44-69) were enrolled. Median number of prior therapies – 1 (range 1-6), 3 had received a prior EGFR TKI; none responded to TKI monotherapy. The most common toxicities were grade 1-2 visual changes (9 pts), diarrhea (9) and fatigue (8). The only treatment-related grade 3 toxicity was hypertension (2). Among the 10 pts, we observed 1 PR and 3 SD lasting >3 mos, triggering full enrollment to the 2nd stage of the study (Table). Median PFS estimate is 5.1 mos (95% CI, 1.2 to NR). Updated results and correlation with specific ins20 mutations will be presented. Conclusions: AUY922 may be an effective therapy for pts with EGFR ins20 mutations with med PFS 6.1 mo and is generally well-tolerated, though reversible low-grade ocular toxicity is common. To our knowledge, this is the first trial designed specifically for pts with this rare genotype. Further study of AUY922 in this population is warranted. Clinical trial information: NCT01849254, Clinical trial information: NCT01824534.
A phase I study of twice weekly pulse dose and daily low dose erlotinib as initial treatment for patients (pts) with EGFR-mutant lung cancers. First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pts with EGFR-mutant lung cancers treated with EGFR tyrosine kinase inhibitors (TKI) develop clinical resistance, most frequently due to acquisition of EGFR T790M. Modeling suggests that a twice weekly pulse dose, and daily low dose erlotinib schedule may delay the emergence of EGFR T790M. Pulse dose erlotinib may have superior central nervous system (CNS) penetration. Methods: We evaluated toxicity, pharmacokinetics, and efficacy of twice weekly pulse-dose and daily low dose erlotinib in pts with EGFR-mutant lung cancers (NCT01967095). Using a 3+3 dose escalation, we assessed escalating pulse-dose doses (weekly 1–2 doses at 200mg) and daily low dose erlotinib on days 3–7 (D3–7) weekly. Six pulse dose levels of erlotinib were tested: 600, 750, 900, 1050, 1200, and 1350 mg. Response was evaluated by RECIST 1.1. After the maximum tolerated dose (MTD) was determined, we treated an additional 10 pts at the MTD.

Results: From Nov 2013 to January 2015, 34 pts were enrolled. Median age: 60; Women: 20 (59%); never-smoker: 23 (68%); EGFR L858R: 11 (24%) and Ex19del: 22 (65%). Three DLTs were seen: transaminis (1050mg), mucositis (1350mg) and rash (1350mg) during the dose-escalation period. The MTD was determined to be erlotinib 1200mg D1, D2 and 50mg D3-7 weekly. In total, 16 pts were treated at the MTD. Treatment-related AEs were all grade 1–3. The most common treatment-emergent AEs (any grade) were rash (85%), diarrhea (79%), elevated AST (50%) and nausea (41%). Of the 16 pts treated at the MTD, 3 (19%) required a dose reduction of the pulse dose. Of 27 evaluable patients, 22 partial responses were seen (81%). Median-progression free survival is 11 months. 20 pts remained on study (74%) at 6 months and 16 (59%) at 1 year. Effective CNS activity was observed in 6 pts who had CNS metastases at baseline. When pts with baseline measurable and non-measurable CNS disease were both included (21%) for toxicity and 2 (6%) for non-adherence. Of those who progressed, 5/8 (62%) had EGFR T790M identified upon biopsy (none at MTD). Twelve pts (35%) had CNS disease at diagnosis; no pts came off study due to progressive or new CNS metastases. Conclusions: This kinetics-based EGFR TKI dosing scheme for twice-weekly pulse continuous and daily concurrent TKI dose optimization may enhance efficacy. Further studies are planned in pts with brain metastases. Clinical trial information: NCT01967095.
Detection of frequent MET exon 14 skipping events in pulmonary sarcoma-like tumors and response to targeted inhibition. First Author: Xuewen Liu, Columbia University Medical Center; Sun Yat-sen University Cancer Center in China, New York, NY

Background: Pulmonary sarcomatoid carcinoma (PSC) represents a category of highly aggressive carcinomas associated with a poor prognosis. New therapeutic strategies based on better knowledge of the molecular pathogenesis of PSC are needed. We recently identified a high frequency of MET exon 14 skipping in a subset of PSC samples. In this study, we analyzed a larger cohort of PSC to confirm this finding and investigate its potential as a target for treatment.

Methods: Whole-exome sequencing in a discovery set and targeted MET mutation screening in an independent validation set of PSC were performed. RT-PCR and Western blotting were performed to validate MET exon 14 skipping in paired samples. Metastatic tumor cell lines with MET exon 14 skipping were used to test the sensitivity to MET inhibitors.

Results: Alterations affecting MET exon 14 splice sites, including deletions at the 5’ splice site (n = 3) and point mutations at the 3’ splice site (n = 5) were found in 22% (8/36) of PSC. One PSC harbored MET exon 14 skipping and a concurrent PIK3CA mutation. RT-PCR and Western blotting confirmed the presence of MET exon 14 skipping in tumor and in H966 and H974 cells. Both MET siRNA silencing and crizotinib decreased cell proliferation and inhibited downstream AKT and MAPK activation in H974 cells, whereas effects were modest in H966 cells and negligible in controls. MET exon 14 skipping potentiated crizotinib and PI3K inhibition, although H11022 cells, which harbor a MET-associated insert, had less sensitivity to crizotinib. Migration/invasion assays in H966 and H974 cells, as well as functional studies utilizing specific MET exon 14 expression constructs are ongoing.

Conclusions: Our study finds that MET exon 14 alterations are a frequent and potentially targetable event in PSC. Our studies also suggest that concurrent PIK3CA mutations require combined treatment. Clinical studies assessing biomarker-driven MET/PI3K inhibition should be explored in PSC as well as other malignancies harboring MET exon 14 events.

Clinical and molecular characteristics of NF1 mutant lung cancer. First Author: Amanda J. Redig, Dana-Farber Cancer Inst, Boston, MA

Background: NF1 is a tumor suppressor that negatively regulates Ras, thus NF1 mutations may also be sensitive to inhibitors of MAP kinase signaling. NF1 variants occur in lung cancer, but their clinical significance is unknown. We evaluated clinical and molecular characteristics of NF1 mutant lung cancers, with comparison to KRAS mutant tumors. Methods: From 07/13-10/14, 591 lung tumors at our institution underwent targeted mutation screening in a 275 gene panel. 80% M F (20) MET c.3024_3028delAGAAGGTATATT crizotinib

8023 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM
Assessing the performance of Watson for oncology, a decision support system, using actual contemporary clinical cases. First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY

Background: IBM Watson for Oncology (WFO), trained by Memorial Sloan Kettering (MSK), is a cognitive computing system designed to assist medical oncologists making treatment decisions for individual patients. Recommendations are consistent with established guidelines and published evidence, as reflected in MSK’s practice and historical cases. Treatment options are classified as Recommended (WFO-REC), For Consideration (WFO-FC), or Not Recommended (WFO-Not REC). Published evidence, medical logic, and drug information are presented for each treatment option. We sought to assess the current performance of WFO to improve its accuracy and identify areas for development. Methods: 20 de-identified cases were selected from the practices of two MSK thoracic medical oncologists. Patients presented for initial consultation regarding first-line systemic therapy during 2014 and all necessary information to make a treatment decision was available at the time of initial consultation or within two weeks, including molecular pathology. Cases were entered into WFO using structured attributes. WFO recommendations were compared to those of the MSK thoracic medical oncologist (MSKMD-REC).

Results: WFO-REC and MSKMD-REC matched 50% of the time. 25% of the MSKMD-REC appeared as WFO-REC or WFO-FC. All choices were within established guidelines. Cases where the MSKMD-REC appeared as WFO-Not REC involved elderly patients with co-morbidities not yet included in WFO. Conclusions: While WFO’s choices today fall within evidence-based standards, WFO has the capacity to provide greater precision through iterative training and development. Elderly patients for whom care choices are heterogeneous based on co-morbid illnesses represent a challenge. Benchmarking against actual cases has helped us to prioritize development work to increase the number of attributes to include more co-morbid conditions and to incorporate patient preferences to improve precision.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
8024  Poster Discussion Session: Displayed in Poster Session (Board #346), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Electronic medical record as a research tool: Virtual clinical trial comparing pembrolizumab and gemcitabine, both given with cisplatin, in patients with lung adenocarcinomas. First Author: Alexander Grigorenko, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The electronic medical record (EMR) is a tremendous research resource, but its use for exploring hypotheses relies heavily on accurately and reliably identifying patient cohorts. We have created a system that uses advanced computational techniques and Memorial Sloan Kettering’s (MSK) EMR data to overcome these challenges. To validate our system, we sought to replicate a phase III clinical trial comparing cisplatin/pemetrexed (CP) to cisplatin/gemcitabine (CG) in patients with lung adenocarcinomas (Scaglotti J Clin Oncol 2008). Methods: We created a system that can identify a patient cohort by extracting structured cancer and outcomes data from the EMR, algorithmically identifying chemotherapy regimens, and using natural language processing to extract functional and smoking status from physician notes. Using the earlier clinical trial’s eligibility criteria, we identified a patient cohort and analyzed survival on an intent-to-treat basis. Our analysis relied on the extensive data warehouse of MSK’s EMR information, which contains data on the care of over a million patients since 1989. Results: Our system successfully extracted structured data, and accurately categorized treatment regimens (F-measure = 0.985), functional status (F-measure = 0.998), and smoking status (F-measure = 0.993). 281 patients were automatically identified as eligible. The median overall survival (OS) of patients with lung adenocarcinomas receiving CP and CG was 14.7 and 12.6 months with a hazard ratio (HR) of 0.69 (95% CI: 0.52 - 0.90) favoring CP. These results are similar to those of the prospective trial (Table). Conclusions: Our system replicated the results of a prospective clinical trial, highly-accurate computational tools to extract structured and textual data from the EMR are feasible and can help address pending clinical research questions. Future steps will focus on expanding data extraction capabilities to support a broader range of hypotheses within the EMR.

8025  Poster Session (Board #347), Mon, 8:00 AM-11:30 AM
First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 (PD-1) in advanced non-small cell lung cancer (NSCLC): Safety, efficacy and correlation of outcomes with PD-L1 expression.
First Author: Scott N. Gatterman, Yale Cancer Center, New Haven, CT

Background: NIVO, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has demonstrated durable responses and tolerability in heavily pretreated patients (pts) with advanced NSCLC. This phase I study evaluated the efficacy and safety of NVO monotherapy in pts with advanced NSCLC. Methods: Pts (N=52) with squamous (SQ) or non-SQ advanced NSCLC received NIVO 3 mg/kg IV Q2W until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) for the randomized to 2 or 10 mg/kg Q3W). Pembro was given until unacceptable toxicity. The primary endpoint in both studies was the objective response rate (ORR) (RECIST v1.1). Planned sample size was 30 pts for SQ and 67 pts for NSCLC and at least one prior chemotherapy including platinum containing regimen. Pts received nivolumab 3 mg/kg IV Q2W until progression or unacceptable toxicity. The primary endpoint in both studies was the objective response rate (ORR) (RECIST v1.1). 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Background: MPDL3280A (anti-PDL1) has shown activity across a number of tumor types, in FIR, we assessed the efficacy of MPDL3280A in NSCLC pts based on PD-L1 expression. Methods: F,IR is a single arm study of MPDL3280A in stage IIIIB or IV NSCLC. Cohort 1 included chemo-naive pts, pts with 2L without brain metastases and cohort 3 included 2L pts with treated asymptomatic brain metastases. Pts received 1200 mg MPDL3280A IV q3w (last pt entered Jun 27, 2014). Here, we report investigational ORR per RECIST v1.1 (data cutoff Oct 23, 2014). PD-L1 expression was centrally assessed by an SP142 IHC antibody in archival or fresh tumor biopsies (required for cohorts 2 and 3) and scored as IC 0, 1, 2 or 3 and TC 0, 1, 2, or 3. Pts with PD-L1 TC 2/3 or/and IC 2/3 tumors were enrolled. Results: Of 1,009 pts screened, 205 pts were selected based on tumor PD-L1 status. Of the 138 pts that were enrolled, 137 pts were safety-evaluable. The median age was 66 y (range, 42-85 y) and 58% of pts were male. The AE profile was similar across cohorts. Treatment-related AEs occurred in 67% of pts, most often fatigue (26%), nausea (15%) and decreased appetite (14%). Related Grade 3-4 AEs occurred in 15% of pts, with one related death due to constrictive pericarditis. 114 pts were efficacy-evaluable with 3-8 mos follow up in cohorts 2 and 3. The highest ORR was seen in pts with PD-L1 TC3 or IC3 tumors (Table). The median DOR has not been reached in cohorts 1 and 2 (Table). Conclusions: MPDL3280A showed clinical efficacy in both chemo-naive and previously treated NSCLC. High PD-L1 expression (TC3 or IC3) was associated with a higher ORR. The safety profile of MPDL3280A in pts with NSCLC is similar to that reported in previous reports. (NCT01846146) Clinical trial information: NCT01846146

Efficacy results.

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<th>Population</th>
<th>Cohort 1a</th>
<th>Cohort 2b</th>
<th>Cohort 3b</th>
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<tr>
<td>ORR (95% CI), %</td>
<td>31 (29-34)</td>
<td>25 (23-27)</td>
<td>24 (22-27)</td>
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<td>TC3 or IC3</td>
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<td>12 (10-14)</td>
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<td>24</td>
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<tr>
<td>TC3 or IC3</td>
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<td>12 (10-14)</td>
<td>12 (10-14)</td>
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<td>31 (27-35)</td>
<td>32 (28-36)</td>
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<td>17 (14-19)</td>
<td>12 (10-14)</td>
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<tr>
<td>All</td>
<td>31 (29-34)</td>
<td>25 (23-27)</td>
<td>24 (22-27)</td>
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*Unconfirmed ORR. **Confirmed ORR. *Pts with unknown IC STatus. Median not reached.

8030 Poster Session (Board #352), Mon, 8:00 AM-11:30 AM


Background: MPDL3280A, which preserves the PD-L2/PD-1 interaction to potentially diminish autoimmune lung toxicity, has promising activity in advanced NSCLC. Platinum-based doublet chemotherapy (chemo) remains standard first-line (1L) treatment for NSCLC with ORRs historically of ~30%. Preclinical data show that chemo may prompt tumor antigen release and enhance MPDL3280A activity. Here, we studied MPDL3280A+chemo in untreated NSCLC pts. Methods: This Ph Ib study evaluated MPDL3280A combined with carbo/pemetrex + either paclitaxel (Arm C), pemetrex + either nab-paclitaxel (Arm E) n pts with chemo-naive locally advanced or metastatic NSCLC. Pts received MPDL3280A 15 mg/kg IV q3w with standard chemotherapy for 4-6 cycles followed by MPDL3280A maintenance therapy until progression. Unconfirmed ORRs were assessed by RECIST v1.1 in pts dosed by Jun 29, 2014 (data cutoff Sep 29, 2014). PD-L1 expression was centrally assessed using the SP142 IHC antibody. Results: 37 pts were safety evaluable (Arm C, 8; Arm D, 14; Arm E, 15). Across arms, 54% of pts were male, median age was 65 y (range, 40-82 y). 81% had no-squamous and 19% had squamous NSCLC. Median follow-up for safety was 154 d (range, 1-346 d). The most frequent all-grade AEs regardless of attribution across arms included those commonly associated with chemo, such as nausea (Arms C & D, 50%; Arm E, 73%), fatigue (Arm C, 38%; Arm D, 36%; Arm E, 73%) and constipation (Arm C, 25%; Arm D, 71%; Arm E, 27%). The most common MPDL3280A-related G3-4 AEs included anemia (Arms D & E, 7%), neutropenia (Arm C, 13%; Arm D, 7%) and thrombocytopenia (Arms D & E, 7%). No pneumonitis was seen. One MPDL3280A-related G5 AE due to candidemia after prolonged neutropenia was seen in Arm D. 30 pts were efficacy-evaluable (Arm C, 5; Arm D, 12; Arm E, 13). Across all arms, the ORR (95% CI) was 67% (48%-82%); 60% (19%-92%) in Arm C (3 PRs), 75% (45%-93%) in Arm D (9 PRs) and 63% (33%-83%) in Arm E (6 PRs & 2 CRs). Responses were seen in each arm independent of PD-L1 expression. Conclusions: MPDL3280A + standard 1L chemo was well tolerated with no unexpected toxicities, showing promising clinical activity in advanced NSCLC pts. Phase III studies are ongoing. Clinical trial information: NCT01633970.

8031 Poster Session (Board #353), Mon, 8:00 AM-11:30 AM

Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021. First Author: Leora Horn, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: As monotherapy, the anti-PD-1 antibody pembro has shown robust antitumor activity in advanced NSCLC patients (pts). KEYNOTE-021 evaluated the safety, tolerability, and activity of pembrolizumab (PDC) for treatment-naive advanced NSCLC. Methods: Pts with stage IIIIB or IV NSCLC and no prior systemic therapy were randomized 1:1 to pembro 2 mg/kg q3w + pemetrexed 200 mg/m2 (Arm A; any histology) or pembro 10 mg/kg q3w + pemetrexed 500 mg/m2 (Arm C; squamous without sensitizing mutation or ALK translocation only). Pts received pembro + PDC for 4 cycles followed by pembro maintenance in Arm C and pembro monotherapy in Arm A. Key eligibility criteria included ECOG PS 0-1, measurable disease, and adequate tumor sample for PD-L1 assessment. Response was assessed every 6 wk until confirmed progression (RECIST v1.1, investigator review). Results: As of Dec 2014, 44 pts (20 in cohort A and 24 in cohort C) were treated; One DLT was reported (hospitalization for grade 3 rash; C [pembro 10 mg/kg]). Gr 3-4 treatment-related AE rate was 27% (15% in A, 38% in C); AEs were reversible transamnase elevation (n = 3 in C), anemia (n = 1 in A, 2 in C), rash (n = 1 in A, 1 in C), and colitis (n = 2 in C); no gr 3-4 febrile neutropenia was observed. One pt in C discontinued due to treatment-related gr 3 rash. No treatment-related deaths have occurred. Preliminary ORR (confirmed and unconfirmed) is 30% in A and 88% in C (Table). At the time of analysis, 16 pts in A and 21 pts in C remained on treatment. Conclusions: These data suggest that pembro + PDC has a reasonable safety profile and provides antitumor activity as front-line therapy for stage IIIIBIV NSCLC. Based on the promising ORR observed for pembrolizumab + pemetrexed, this combination is being evaluated in a larger cohort. Clinical trial information: NCT02039674.
Avelumab (MSB0010718C), an anti-PD-L1 antibody, in advanced NSCLC patients: A phase 1b, open-label expansion trial in patients progressing after platinum-based chemotherapy. First Author: James L. Gulley, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against cancer. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody being investigated in clinical trials. We report safety and clinical activity in patients (pts) with advanced NSCLC progressing after platinum-based chemotherapy. Avelumab was treated with avelumab at 10 mg/kg Q2W until progression, confirmed complete response (CR), or toxicity. A prespecified analysis of 184 pts with ≥ 3 months follow-up (range 3-13) was performed. Tumors were assessed every 6 weeks (w) (RECIST 1.1). Conclusions: Responses are durable; ORR appears to be higher in squamous NSCLC and PD-L1+ pts. A broad development program of M alone and in combination with other treatments is underway in NSCLC. Antonia S, et al. Poster presented at ESMO 2014, 1325P Clinical trial information: NCT01693562.
**8036** Poster Session (Board #358), Mon, 8:00 AM-11:30 AM

Validation of ERCC1 (E1) for response prediction to platinum-gemcitabine.

*First Author: Gerold Bepler, Karmanos Cancer Institute, Detroit, MI*

**Background:** E1 had been suggested as a predictive marker for platinum drugs. However, there are 4 different isoforms with differential DNA repair functions, antibodies used for quantitation lack specificity, and a phase 3 trial designed to validate E1’s predictive power failed to demonstrate the anticipated benefit (trial A). We investigated the interaction of E1 mRNA levels with therapeutic benefit from various therapeutic doublets in pts with advanced NSCLC. **Methods:** FFPE specimens from trial A were microdisected; RNA was extracted, and analyzed for E1 levels using commercially validated primers and probes. Median and optimized cut-offs were investigated for interaction of E1 levels with survival and validated using a second randomized phase 3 trial (trial B, Ann Oncol 25: 2147–55, 2014). **Results:** E1 expression analysis on 84 pts in trial A, 38 treated with PG and 46 with other doublets, showed a significant (p = 0.044), inverse association between E1 mRNA levels and disease response in pts treated with PG; i.e., the higher the E1 levels the worse the tumor response. An analysis for treatment interaction (PG vs others) using the optimized E1 cut-off level of 1.44 showed E1 was highly predictive of OS and PFS in pts on PG, with high levels predicting short survival (Cox model interaction p = 0.002 for OS and 0.003 for PFS). Using the median E1 level of 1.73, the interaction p-value was 0.028. E1 levels were not associated with histology, sex, age, and smoking status. Specimens from 86 pts in trial B yielded sufficient RNA for a successful E1 analysis. 19 pts had been treated with PG, 55 with P-doxetaxel, and 12 with docetaxel; E1 values were similar across the three trials in trial A. Using the optimized E1 cut-off level of 1.44 from trial A, we found a log-rank p-value of 0.029 for PFS, with high levels predicting shorter survival for pts treated with PG. A 2nd validation on pts treated with PG in Torino, Italy is in progress. We also attempted to develop an RT-PCR assay specific for the E102 isoform. Despite optimized same RNA isolation, reverse transcription, and validation using in vitro samples, the majority of FFPE samples failed analysis. **Conclusions:** E1 mRNA levels, as determined by a commercially available and CLIA/CAP certified assay, are predictive of treatment benefit from PG in advanced NSCLC.

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**8038** Poster Session (Board #360), Mon, 8:00 AM-11:30 AM

Smoking status to predict sensitivity to PARP inhibitor, veliparib, in patients with advanced NSCLC.

*First Author: Sunesh S. Ramalingam, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Tobacco-related non-small cell lung cancer (NSCLC) is associated with reduced survival and greater genomic instability. Veliparib (V) is a PARP inhibitor that augments platinum-imduced DNA damage in preclinical studies, and Phase 2 trials of V in advanced NSCLC showed improved survival (HR 0.80; CI 0.54–1.18) when V was added to carboplatin (C) and paclitaxel (P). Here we report outcomes based on smoking status from a randomized Ph 2 study of CP with either V or placebo in advanced NSCLC. **Methods:** Patients (pts) with previously untreated advanced/metastatic NSCLC were randomized 2:1 to CP with either V at 120 mg BID or placebo (pre-specified stratification by histology and smoking status). 25% of pts (257 of 1027) were former smokers. Plasma samples and index of recent tobacco use. Results: Of 158 pts, 68% were male, and 49% had squamous NSCLC. At study entry, 60% of pts were self-reported current smokers (CS), 27% former smokers, and 13% never smoked. There were no significant differences in V PK parameters between the COT-high and low pts. Most common AE in CS were neutropenia (41%), CP (7% CP), alopecia (36%); and, anemia (31%, 40%), G3/4 AEs were elevated in CS treated with VCP vs CP (66% vs. 40%, p = 0.026); all-grade AEs and SAEs were similar between the two groups. In a COT sensitivity analysis of OS, HR VCP/COP for COT-high was 0.52 (0.29–0.92) and COT-low was 1.07 (0.63–1.61). **Conclusions:** Smoking status was a strong predictor of efficacy for veliparib-chemotherapy combination in advanced NSCLC. No differences in PK of V were seen based on plasma COT; toxicity of VCP was acceptable regardless of smoking history. A Ph 3 study has been initiated in pts with smoking history. Clinical trial information: NCT01560104.

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**8037** Poster Session (Board #359), Mon, 8:00 AM-11:30 AM

Pre-treatment 5-methyltetrahydrofolate levels and response to pemetrexed in stage IV adenocarcinoma of the lung. *First Author: Stephen Joseph Black, University of Pennsylvania, Philadelphia, PA*

**Background:** The anti-folate drug pemetrexed (PMX) is used in treatment regimens for non-small cell lung cancer (NSCLC). Recent evidence suggests that differences in cellular folate metabolism may confer variation in tumor response to PMX. We investigated whether the pre-treatment intra-erythrocyte (RBC) level of 5-methyltetrahydrofolate (5-MTHF), a key component of folate metabolism, is associated with response to PMX-based chemotherapy in stage IV lung adenocarcinoma. **Methods:** We conducted a single-center, prospective cohort study of patients with newly diagnosed stage IV lung adenocarcinoma receiving first-line chemotherapy with a PMX-containing regimen. RBC 5-MTHF levels were quantified using a mass spectrometry-based method from blood drawn prior to initiation of chemotherapy. **Results:** Clinical response to chemotherapy was determined by radiographic tumor response after 4-6 cycles of PMX-based chemotherapy and categorized as partial response, stable disease, or progression. We explored the relationship between pre-treatment RBC 5-MTHF levels and response to PMX-based chemotherapy. A log-binomial model was used to adjust for age and sex. Results: 54 patients were enrolled; the median age was 61 (IQR 55–68) and 29 (54%) were female. RBC 5-MTHF ranged from 37 to 1,667 nM (mean 588, median 518). Following 4-6 cycles of chemotherapy, 23 patients (43%) had an objective radiographic response and 15 (28%) had stable disease. The remaining 16 patients (29.6%) had progression (7 during cycles 1-3, 9 during cycles 4-6). Patients with 5-MTHF levels in the lowest quartile were significantly less likely to achieve radiographic response compared to patients in the highest three quartiles (response rate 8% vs. 54%; risk difference 0.46, 95% CI 0.25–0.67). After controlling for age and sex, there remained a significantly higher likelihood of lack of response to PMX for patients in the lowest 5-MTHF quartile (HR 8.86, 95% CI 1.01–46.92). **Conclusions:** Low pre-treatment RBC 5-MTHF levels are associated with an inferior response to PMX-based chemotherapy in stage IV lung adenocarcinoma. Multicenter prospective studies are needed to validate RBC 5-MTHF as a predictive marker of response to PMX in NSCLC.

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**8039** Poster Session (Board #361), Mon, 8:00 AM-11:30 AM

An open-label, randomized, multicenter, phase III study of S-1 and cisplatin versus docetaxel and cisplatin in patients with untreated advanced non-small-cell lung cancer. *First Author: Jianxing He, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, Guangdong Province, China*

**Background:** Platinum-based doublet chemotherapy is the standard chemotherapy regimen for treatment-naïve advanced Non-Small-Cell Lung Cancer (NSCLC). S-1, an oral fluoropyrimidine, combined with cisplatin or carboplatin (CDDP) has shown no less efficacy than standard doublet chemotherapy in Japanese NSCLC patients. However, the effectiveness in Chinese NSCLC patients is uncertain. We aimed to compare the efficacy and safety of these chemotherapy regimens in Chinese NSCLC patients. **Methods:** In this study, we recruited patients aged 18-70 years with stage IB, II, IV or recurrence, histologically or cytologically confirmed NSCLC. ECOG performance status of 0-1, have at least one measurable lesion, and adequate organ function. Patients were randomized in 1:1 ratio to receive either S-1 (80–120 mg/day, PO, BID, days 1 to 21) with 60 mg/m² CDDP on day 8 every 5 weeks (SP) or docetaxel and CDDP (both 75 mg/m²) on day 1 every 3 weeks (DP), for up to 6 cycles. The primary endpoint was progression-free survival (PFS) and all CT scans were externally reviewed by Independent Review Committee (IRC). Non-inferiority study design was employed as upper confidence interval (CI) limit for hazard ratio (HR) < 1.33. **Results:** Between March 2011 and November 2012, 246 patients from 21 institutions in China were randomly assigned to receive S-1 and CDDP (122) or SP (124). Follow-up period from the last patient randomized. In the SP and DP group, median PFS was 5.9 and 5.7 months (HR = 0.68; 95% CI, 0.48 to 0.96) respectively, median overall survival was 19.1 and 14.8 months, respectively (HR = 0.84; 95% CI, 0.61 to 1.14). The most common grade 3 or worse adverse events in both treatment groups were neutropenia 3.3% vs 55.1%, leukopenia 1.7% vs 39.0%, and febrile neutropenia 0.8% vs 5.9%, of 121 patients in the SP group and of 118 patients in the DP group, respectively. **Conclusions:** The efficacy of SP was non-inferior to DP. Well-tolerated safety could be provided by SP regimen. SP would be a first-line chemotherapy regimen for Chinese patients with advanced NSCLC. Clinical trial information: Jiap C-1114797.
8040 Poster Session (Board #362), Mon, 8:00 AM-11:30 AM
SWOG 0709: A randomized phase II ‘pick-the-winner’ trial of erlotinib (ERL) vs. ERL plus carboplatin/paclitaxel (CT) in patients (pts) with advanced non-small cell lung cancer (NSCLC) and impaired performance status (PS 2) as selected by serum proteomics. First Author: Primo Lara, UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: Advanced NSCLC pts with Zubrod PS 2 are often excluded from clinical trials and platinum-based therapy. In SWOG 0341, ERL in PS 2 pts yielded median progression-free survival (PFS) and overall survival (OS) of 2.1 and 5 months respectively. In a trial of ERL vs CT in PS 2 pts (Lilenbaum, JCO 2008), PFS for ERL and CT were 1.9 and 3.5 months. Early reports suggested a potential role for serum proteomics in predicting ERL benefit beyond that of OS and PS-2 status. We conducted a trial in PS 2 pts enriched by serum proteomics (Veristrat-good). Methods: NSCLC pts with PS 2 and Veristrat-good status were randomized to either Arm A (ERL 150 mg po QD) or Arm B (ERL 150 mg po QD d2-16 + carb AUC 5 IV day 1, paclitaxel 200 mg/m2 IV d1 x 4 cycles, then ERL 150 mg QD). Cycles were q3 weeks. Arm B agents were pharmacodynamically separated to mitigate potential antagonism. The arm with superior observed median PFS would be selected for further evaluation, but only if ≥ 3 months. A sample size of 96 pts was based on a varied assumption of PFS probabilities for each arm. The trial prematurely closed after the FDA determined an IDE application was required for VeriStrat; however SWOG had limited resources available for such filings. Results: Of 156 pts screened, 83 (59%) were VeriStrat-good, of which 59 (60%) met trial eligibility & were randomized. Treatment-related grade 4 adverse events were seen in 2 pts in Arm A (DVT, hypomagn): 1; 5 pts in Arm B (neutropenia 5, febrile neutropenia 1, leukopenia 1). Conclusions: In PS 2 pts with advanced NSCLC and Veristrat-good status, ERL + C/T (vs. ERL alone) had better observed median PFS/OS and surpassed the protocol-specified benchmark of PFS/OS > 3 months required for further study. Clinical trial information: NCT015661193.

8042 Poster Session (Board #365), Mon, 8:00 AM-11:30 AM
Intercalating and maintenance use of gefitinib plus chemotherapy versus chemotherapy alone in selected advanced NSCLC (SCCAN, CTONG-1102): A multicentre, open-label, randomised, phase 3 study. First Author: Hsien-Te Lee, Taipei Medical University; National Taiwan University Hospital; Graduate Institute of Oncology & Cancer Research Center, National Taiwan University, Taipei, Taiwan

Background: This study investigated whether intercalating and maintenance use of gefitinib and chemotherapy improves clinical outcomes versus chemotherapy alone in selected patients with advanced NSCLC after receiving two cycles of chemotherapy with stable disease. Methods: We undertook an open-label, randomized, phase 3 trial at 14 centers in China. We assigned previously untreated patients in China who had stage IIIB or IV advanced non-small cell lung cancer (NSCLC) and impaired performance status (PS) to firstly receive two cycles of gemcitabine plus carboplatin (GC alone). In the absence of disease progression, chemotherapy was continued to receive gefitinib or observation until disease progression or death. After which time patients continued to receive gefitinib or observation until disease progression or death. The trial was registered at ClinicalTrials.gov, number NCT01404260, and has completed enrolment. Results: 109 patients were randomly assigned to receive intercalating and maintenance use of gefitinib plus chemotherapy and 110 to receive chemotherapy alone. 109 in the intercalating and maintenance group (Arm A) and 108 in the chemotherapy-alone group (Arm B) completed enrolment. Median progression-free survival was significantly longer in the intercalating and maintenance use of gefitinib-treated patients than in those on chemotherapy alone (10.0 vs 4.4 months; hazard ratio 0.475, 95% CI 0.349-0.646; p < 0.0001). The addition of gefitinib to chemotherapy was well tolerated and not an alternative to discontinuing GC. Conclusions: Intercalating and maintenance use of gefitinib plus carboplatin led to a significant improvement in PFS for advanced pulmonary adenocarcinoma Chinese patients with nonsmoking and EGFR mutation status unknown after receiving two cycles of gemcitabine/carboplatin with stable disease. Clinical trial information: NCT01404260.

8043 Poster Session (Board #366), Mon, 8:00 AM-11:30 AM
Maintenance therapy with gefitinib (G) plus pemetrexed (P) versus P alone after induction therapy with Platinum for metastatic lung adenocarcinoma (PLATINUM): A Phase II randomized open-label study to compare P vs. G in the maintenance setting. First Author: Chun-Ming Tsai, Division of Thoracic Oncology, Department of Medicine, National Taiwan University Hospital, Taipei, Taiwan

Background: Synergistic EGFR-tyrosine kinase inhibitor (TKI)-chemotherapeutic interaction in lung cancer cells has 3 bases: no platinum, cells not sensitive to TKI, and using a synergistic chemo partner, e.g., Pemetrexed (P) + gefitinib (G). The study found no significant difference in progression-free survival (PFS) between PC/G and G in the overall population. As reported for PFS, there appeared to be better outcomes with G in the EGFR mutation subgroups (especially Ex19del) and with PC/G in the wild-type subgroup. Clinical trial information: NCT01579630.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase Ib study of the anti-cancer stem cell agent demethylzeb (DEM), pemetrexed (PEM) & carboplatin (CARBO) in pts with 1st line non-squamous NSCLC. First Author: Dusan Kotasek, Adelaide Cancer Centre, Kurralta Park, Australia

Background: Delta-like ligand 4 (DLL4) activates the Notch pathway & is important for cancer stem cell (CSC) survival. DEM is a humanized IgG-anti-DLL4 antibody that has been shown to inhibit tumor growth, decrease CSC frequency & cause dysfunctional sprouting of new vessels resulting in an antiangiogenic effect in human tumor xenograft models. Most AEs related to DEM were grade (G) 1-2. In pts receiving DEM (2.5 or 5 mg/kg), PEM 500 mg/m² & CARBO (AUC = 6) every 3 weeks X 4 cycles followed by maintenance DEM (cohorts 1-4) or truncated DEM (5 or 7.5 mg/kg), PEM 500 mg/m² & CARBO (AUC = 6) every 3 weeks X 4 cycles followed by maintenance DEM (cohorts 5 & 6). The objectives were to determine the MTD, safety, efficacy, immunogenicity, pharmacokinetics & biomarkers of Notch signaling, pharmacodynamics (PK), antitumor activity, and patient (pt) reported outcomes.

Methods: Notch signaling was assessed in tumor specimens or plasma circulating tumor DNA from study pts. For those pts with only blood samples, a repeat or alternative test was used to confirm the status of DEM wt Notch. The parent study was designed to detect an increase in median progression-free survival (mPFS) by 50%, i.e., a hazard ratio (HR) of ≤ 0.67. Results: 59 (79%) of 75 eligible pts had confirmed DEM wt (N=52) or DEM-mutant (N=7) genotype. The results are summarized in Table 1. Longer PFS was observed in pts with DEM wt NSCLC treated with the combination (Arm B). Conclusions: PFS of DEM and Erl as 2nd-line therapy appears to have promising clinical activity in pts with advanced, DEM wt non-squamous NSCLC, which comprises 85% of non-Asian NSCLC pts, and warrants further confirmation. (U.L.) RR24146, P30CA093373, Astellas, Eli Lilly. Clinical trial information: NCT00950365.

Clinical efficacy in pts with DEM wt NSCLC.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arm (N=75)</th>
<th>Median mPFS (mo)</th>
<th>1 year PFS (% 95% CI)</th>
<th>2 year PFS (% 95% CI)</th>
<th>3 year PFS (% 95% CI)</th>
<th>4 year PFS (% 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (N=31)</td>
<td>5.4 (4.8-7.2)</td>
<td>59% (46%-72%)</td>
<td>36% (25%-50%)</td>
<td>24% (15%-41%)</td>
<td>19% (10%-37%)</td>
<td>13% (5%-31%)</td>
</tr>
<tr>
<td>B (N=44)</td>
<td>3.9 (3.0-6.0)</td>
<td>47% (35%-60%)</td>
<td>28% (17%-43%)</td>
<td>21% (11%-42%)</td>
<td>15% (8%-33%)</td>
<td>11% (5%-29%)</td>
</tr>
</tbody>
</table>

**HR (95% CI)**: 0.63 (0.4-1.1) 0.77 (0.4-1.4) 0.64 (0.3-1.2) 0.70 (0.4-1.1) 0.81 (0.4-1.5) 0.76 (0.4-1.4)

**p value**: 0.05 0.05 0.08 0.07 0.07 0.07

**DCR 3mo**: 32% (9%-49%) 26% (11%-45%) 30% (10%-51%) 25% (10%-48%) 22% (8%-40%) 18% (5%-34%)

**DCR 12mo**: 29% (9%-48%) 19% (8%-39%) 31% (11%-54%) 23% (10%-43%) 21% (8%-40%) 18% (5%-34%)

**mPFS**: 1.9 (0%-5.9) 2.3 (0%-6.7) 3.9 (2.7-7.3) 4.7 (3.3-11.8) 4.2 (3.0-7.7) 4.1 (2.8-7.6)

**95% CI**: 95% confidence interval

**Results**: 39 patients were enrolled: 40 received DEM (2.5 mg/kg), 6 received DEM (5 mg/kg), 1 received DEM (7.5 mg/kg), 9 received PEM (500 mg/m²), 2 received PEM (750 mg/m²), and 4 received PEM (875 mg/m²). 30 had received prior chemotherapy (20 in arm A, 10 in arm B). AEs were grade (G) 1-2 in 89% of pts. Notch, B-type natriuretic peptide (BNP) & anemia (21%). Increased BNP values are an early indicator of the cardiac effects of DEM & mildly elevated values are being used to initiate cardioprotective therapy with an ACE inhibitor or cardeniol. Two pts receiving 5 mg/kg developed reversible pulmonary hypertension & heart failure on days 167 & 183, respectively. As a result, DEM treatment was limited to days 51 in cohorts 5 & 6. One of 33 (3%) evaluable pts had a RECIST CR, 15 (45%) had a PR & 13 had SD. The Kaplan-Meier estimated median progression-free survival for the 2.5, 5, truncated 5 & truncated 7.5 mg/kg pts were 4.3, 5.3, not yet reached & 4.4 months, respectively. Eight pts who discontinued the study for the above other than toxicity reasons were rechallenged (6 continued DEM & 2 were rechallenged with pem). 2 pts were progression-free through Days 314+, 408+, 448+, 456+, 677+ 680+ & Day 850. Conclusions: This therapy was generally well tolerated with nausea, fatigue & hypertension being the most common drug related toxicities. Encouraging early clinical activity has been observed. Biomarker data showed modulation of the Notch pathway. Final data will be presented. Clinical trial information: NCT01189968.
Individual patients data analysis (IPD) of three randomized studies comparing erlotinib (E) with chemotherapy (CT) in patients with advanced wild-type epidermal growth factor receptor-activated non-small cell lung cancer (NSCLC). First Author: Valter Torri, IRCCS-Mario Negri Institute, Milano, Italy

Background: While the benefit of EGFR tyrosine kinase inhibitors in EGFR mutated NSCLC patients (pts) is undisputed, their usefulness in wtNSCLC pts is still questioned. The TAILOR, DELTA and PROSE trials singularly showed a significant gain in Progression-Free Survival (PFS) favoring CT. We present here the mature results from the IPD analysis of the three studies. Methods: In each trial, pts with eGFR stage IIIb/IV NSCLC, progressing after first line platinum-based therapy, were randomized 1:1 to receive either E or CT at standard doses. Primary endpoints of this IPD were PFS and Overall Survival (OS); summary measures were Hazard Ratio (HR) and Difference in Mean Survival Time (DMST), which is the difference in the areas under the Kaplan-Meier curves of two treatment arms. Cox regression analyses were used to estimate the HR. All analyses were stratified by trial. Results: The analysis included all 587 pts randomized into the trials (Overall ECT 303/284; TAILOR 109/110; DELTA 109/90; PROSE 85/84); 646 deaths and 570 progressions or deaths were observed. Compared with CT, E treatment was associated to an increased risk of both progression (40%) and death (12%) (HR-PFS: 1.40, 95%CI: 1.18-1.65, p < 0.0001; HR-OS: 1.12, 95%CI: 0.93-1.35; p = 0.221). Importantly, patients treated with CT gained 1.6 and 1.5 months, in progression-free and life-time respectively (DMST-PFS 95%CI: 0.6-2.1; DMST-OS 95%CI: -0.5-3.4). Results were preserved after adjustment by age, gender, smoking habit, performance status and histotype. Conclusions: The IPD analysis of TAILOR, DELTA and PROSE conclusively confirm the superiority of CT over E in the disease control of eGFR NSCLC patients, and corroborate the original results of each single trial.

Results: The final analysis of EMPHASIS did not show a differential activity on PFS of E vs D in SqNSCLC pts stratified by VS status. These results are at variance with trial assumptions and previous studies. In addition to the EMPHASIS results (PFS & OS), we will present a combined PFS/OS analysis with the subgroup of SqNSCLC from the PROSE study. EudraCT number: 2012-001896-35. Clinical trial information: NCT01652469.

Conclusions: PK-guided dosing of paclitaxel combined with carboplatin in advanced non-small cell lung cancer (NSCLC) patient. First Author: Markus Joerger, Cantonal Hospital, St. Gallen, Switzerland

Background: Variability of chemotherapy exposure may cause severe toxicity or lack of efficacy. Paclitaxel (PTX) exposure (time above a plasma concentration of 0.05mM, Tc > 0.05) has been shown to predict toxicity. Whereas carboplatin dose is adapted to kidney function, PTX dosing only accounts for body-surface area. We developed a PTX dosing algorithm for avoidance of supra- or subtherapeutic PTX exposure based on Tc > 0.05 determined from a single blood sample drawn 18-30 hours after starting PTX infusion. This study was initiated to validate PK-guided PTX dosing in advanced NSCLC patients. Methods: 304 patients with advanced NSCLC were randomly assigned to receive up to 6 cycles of first-line 3-weekly carboplatin AUC 6 combined with PTX either at a standard dose of 200mg/m2 (Arm A) or at a PK-guided dose (Arm B). Initial PTX dose in Arm B was between 150 to 200 mg/m2 based on age and sex, and subsequent PTX doses were adjusted according to the previous cycle PTX Tc > 0.05 to target a Tc > 0.05 between 26 and 31 hours. Dose reductions were performed in both arms for cumulativeasthanated toxicity. The study had a power of 90% to detect a 11% reduction of grade 4 neutropenia with PK-guided PTX dosing. Results: Major patient characteristics were male gender in 67%, current smokers in 38%, ≥ 65 years of age in 50%, performance status of 2 in 8%, squamous-cell histology in 21%. Compared to standard dosing, PK-guided dosing of PTX for the first cycle of grade 4 neutropenia (measured on day 15 of each cycle) (15% v 21%, P = 0.029), grade ≥ 2 neuropathy (14% v 27%, P = 0.001), and grade ≥ 3 neuropathy (1% v 8%, P < 0.001). Median PTX dose at cycle 6 was significantly lower with PK-guided dosing (132 v 197 mg/m2, P < 0.001), and the proportion of patients with subtherapeutic PTX exposure was reduced from 41% in cycle 1 to 2% in cycle 6. Objective response rate was 32% and 29% in Arms A and B (P = 0.70). Progression-free survival was 5.2 and 4.7 months in Arms A and B (hazard ratio 1.1, 95% CI 0.8-1.4, P = 0.54). Conclusions: PK-guided dosing of PTX improves the risk-benefit profile in patients with advanced NSCLC, primarily by a substantial reduction of PTX-associated neuropathy. Clinical trial information: 2010-023688-16.
8053 Poster Session (Board #376), Mon, 8:00 AM-11:30 AM
Exposure-response relationship for ramucirumab (RAM) from the randomized, double-blind, phase III REVEL trial (docetaxel [DOC] vs DOC plus RAM) in second-line treatment of metastatic non-small cell lung cancer (NSCLC). First Author: Egbert F. Smit, Cancer Center Amsterdam, Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands

Background: An exploratory exposure-response analysis for RAM was performed using data from the REVEL trial (NCT01168973). Methods: Patients received RAM (10 mg/kg) or placebo (PL) + DOC (75 mg/m²) every 3 weeks (q3w). Sparse pharmacokinetic (PK) samples were collected; a population PK (PopPK) analysis was conducted. PopPK model-predicted RAM exposure parameters (C_{0.05}, C_{1} and C_{95}) were used to evaluate the relationship between RAM exposure and measures of efficacy and safety. C_{0.05}, C_{1} and C_{95} are presented. Kaplan-Meier, Cox regression, and ordered categorical analyses evaluated these relationships. Results: Analyses included 376 RAM + DOC pts and 366 PL + DOC pts. Similar trends were seen for all four exposure parameters. RAM exposure increased, greater improvements (smaller HRs) were seen in OS and PFS (table below). A statistically significant correlation was also seen for RAM exposure and grade ≥ 3 febrile neutropenia and hypertension. Conclusions: Results from exposure-response analyses suggest improvements in efficacy and increased toxicity may occur with increasing RAM exposure. RAM at a dose of 10 mg/kg q3w in combination with DOC is appropriate for the NSCLC indication. Clinical trial information: NCT01168973.

8054 Poster Session (Board #377), Mon, 8:00 AM-11:30 AM
Docetaxel + ramucirumab (DR) versus docetaxel + placebo (D) as second-line treatment for advanced non-small cell lung cancer (NSCLC): A randomized, phase III, double-blind, multicenter trial in Japan. First Author: Yukio Hosomi, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

Background: A randomized global phase III trial (REVEL) demonstrated statistically significant improvement in OS and PFS for DR versus D in patients (pts) with advanced NSCLC; a limited number of East Asian pts were given docetaxel (DOC) at 75 mg/m², higher than 60 mg/m² used in the REVEL study. A similar phase II study was conducted in Japan to evaluate the efficacy of DR for stage IV NSCLC following disease progression during or after prior platinum-based chemotherapy. Pts with EGFR mutant NSCLC who received prior EGFR tyrosine kinase inhibitor (TKI) therapy were enrolled as exploratory. Eligibility criteria included ECOG PS 0-1, age ≥ 20 years, and adequate organ function. Pts were randomized 1:1 to receive DOC 60 mg/m² + ramucirumab 10 mg/kg IV or placebo on Day 1 of a 21-day cycle until disease progression. Stratification factors: PS, gender, prior maintenance therapy. The primary endpoint was PFS to be analyzed after observing 134 PFS events for pts without prior EGFR-TKI therapy (primary population). The number was designed to show a high likelihood of observing PFS HR < 1. Secondary endpoints: safety profile, OS, objective response rate (ORR), disease control rate (DCR), patient-reported outcomes. We report the results of the primary population. Results: 157 pts (DR 76; D 81) were randomized and treated. Pts characteristics were balanced between arms. The median PFS was 3.7 vs 3.8 months (m) (95%CI 3.52, 6.97) for DR and 4.2 m (2.83, 5.62) for D; hazard ratio (HR) 0.83 (0.59, 1.16). ORR: 28.9% (DR), 18.5% (D). DCR: 78.9% (DR), 70.4% (D). The median OS at the time of primary PFS analysis was 15.2 m for DR and 14.0 m for D (data are immature). Main Grade 3-4 toxicities (DR vs D) were neutropenia 90% vs 86%, febrile neutropenia 70% (vs 68%), febrile neutropenia (33% vs 20%) and anorexia (7% vs 5%). The Grade 3/4 febrile neutropenia did not lead to any fatal events and incidence of Grade ≥ 3 infections was 1% vs 10%. Conclusions: Efficacy results were consistent with those from REVEL. DR has shown clinical benefit over D in terms of PFS, ORR, and DCR in Japanese NSCLC pts. DR was well tolerated, with manageable toxicity. Clinical trial info: NCT01703091. Clinical trial information: NCT01703091.

8055 Poster Session (Board #378), Mon, 8:00 AM-11:30 AM
Exploratory analysis of safety by histology and efficacy in a nonsquamous NSCLC subgroup in REVEL: A randomized phase III study of ramucirumab (RAM) plus docetaxel (DOC) vs DOC for second-line treatment of stage IV non-small cell lung cancer (NSCLC). First Author: Luis Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: REVEL, a study inclusive of nonsquamous (NSQ) and squamous (SQ) NSCLC, led to FDA approval of second-line RAM + DOC for patients (pts) with advanced NSCLC resistant to platinum-based therapy. Neutropenia, febrile neutropenia, gastrointestinal and pulmonary hemorraghic events were similar across histologies. Additional outcomes are presented. Methods: A total of 1,253 pts with SQ or NSQ NSCLC received DOC (75 mg/m²) plus RAM (10 mg/kg; N = 628) or placebo (N = 625) after disease progression on platinum-based therapy (NCT01168973). Endpoints evaluated in specified histologic subgroups were OS, PFS, response rates, safety, and QoL. OS and PFS were analyzed using Kaplan-Meier (KM) method and Cox proportional hazard model. Response was assessed using the Cochrane-Mantel-Haenszel test. The primary QoL analysis was time to deterioration (TID) of the Lung Cancer Symptom Scale (LCSS) using the KM method. Results: Of the 73% (N = 912) of NSQ tumors, the majority were adenocarcinoma (79%; N = 725). Efficacy outcomes for pts with adenocarcinoma were similar to the NSQ population (see table). Incidences of pts with grade ≥ 1 treatment-emergent adverse event (TEAE), ≥ 3 serious adverse event, TEAEs grade ≥ 3, and TEAEs leading to dose adjustment or discontinuation were similar between treatment arms and across NSQ and SQ histologies. The TID for total LCSS score was similar between treatment arms in NSQ and SQ subgroups. Conclusions: REVEL demonstrated an acceptable benefit/risk profile for RAM + DOC, with favorable efficacy and manageable safety outcomes across the major histologic subtypes of NSCLC. Clinical trial information: NCT01168973.

8056 Poster Session (Board #379), Mon, 8:00 AM-11:30 AM
Bevacizumab beyond disease progression after first-line treatment with bevacizumab plus chemotherapy in advanced nonsquamous non–small cell lung cancer (WJOG 5910L). An open-label, randomized, phase II trial. First Author: Masayuki Takeda, Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan

Background: Bevacizumab combined with platinum-based chemotherapy has been established as a standard treatment option in the first-line setting for advanced nonsquamous non–small cell lung cancer (NSCLC). However, there have been no evidence-based studies to support the use of bevacizumab beyond disease progression in NSCLC patients receiving such treatment. Methods: WJOG 5910L was designed as a multicenter, open-label, randomized, phase II trial of docetaxel (60 mg/m²) versus docetaxel (60 mg/m²) plus bevacizumab (15 mg/kg) every 3 weeks in patients with recurrent or metastatic nonsquamous NSCLC whose disease has progressed after first-line treatment with bevacizumab plus platinum-based doublet. The primary endpoint was progression-free survival (PFS). Results: One hundred patients were randomly assigned to receive docetaxel (Doc, n = 50) or docetaxel plus bevacizumab (Doc + Bev, n = 50). The median PFS was 4.4 months for the Doc + Bev group and 3.4 months for the Doc group, with a hazard ratio (HR) of 0.71 (95% confidence interval [CI], 0.47–1.09) and stratified log-rank P value of 0.058, which met the predefined value for statistical significance (P < 0.2). The median overall survival also tended to be longer in the Doc + Bev group (13.1 months; 95% CI, 10.6–21.4) than in the Doc group (11.0 months; 95% CI, 7.6–16.1), with a HR of 0.69 (95% CI, 0.46–1.02). Conclusions: In the first-line setting, events of grade ≥ 3 included neutropenia (90% in the Doc + Bev group vs 82% in the Doc group), leukopenia (64% vs 52%, respectively), and febrile neutropenia (26% in both groups). There were two treatment-related deaths (one in each group). Conclusions: The addition of bevacizumab to docetaxel in the second-line setting shows promising efficacy with regard to PFS for patients with nonsquamous NSCLC whose disease has progressed while receiving bevacizumab plus a platinum-based doublet. The addition of bevacizumab was associated with a slight increase in toxicity, although the combination regimen was tolerable. Phase III studies of this combination are warranted. Clinical trial information: 000004715.
Efficacy and safety of BCD-021, bevacizumab biosimilar candidate, compared to Avastin. Results of international multicenter randomized double-blind phase IIIB study in patients with advanced non-squamous NSCLC. First Author: Olga Filip, CJSC BIOCAD, St. Petersburg, Russia

Background: BCD-021 demonstrated equivalence to Avastin in a comprehensively comparable exercise that included physicochemical, PK and PD studies, as well as phase I PK clinical study in patients with non-squamous NSCLC. Methods: 138 patients with advanced non-squamous NSCLC (stage IIIb/IV) were randomly assigned into 2 groups at a ratio of 1:1 to receive either BCD-021 or Avastin at a dose of 15 mg/kg in combination with paclitaxel (175 mg/m²) and carboplatin (AUC 6 mg/ml/min) every 3 weeks up to 6 cycles of therapy or until progression or unbearable toxicity. Results: ORR (primary endpoint) in both groups had no statistically significant differences: 42.59 % (95% CI 30.33 - 55.83) in BCD-021 group and 39.29 % (95% CI 27.58 – 52.27%) in Avastin group. The lower limit of 95% CI for ORR difference between the groups (<14.96%) did not exceed the non-inferiority margin, hence BCD-021 is non-inferior to Avastin. There were also no differences between the groups for all other efficacy parameters: CR (1.85% vs 1.79%), PR (40.74% vs 37.50%), stable disease (51.95% vs 51.79%) and progression rate (5.56% vs 8.93%) in BCD-021 and Avastin group, respectively. AEs profiles of BCD-021 and Avastin were equivalent. Rate of all observed AEs including severe AEs had no statistically significant difference between the groups. Most AEs were associated with chemotherapy - neutropenia (85.29% vs 78.7%), anemia (88.24% vs 94.85%), leukopenia (79.41% vs 75.76%), thrombocytopenia (69.12% vs 62.12%), hyperglycemia (61.76% vs 56.06%), LDH increase (48.53% vs 37.88%), ALP increase (35.29% vs 30.30), ALT increase (26.47% vs 28.79%), alopecia (30.88% vs 24.24%), etc. Reactions specific for bevacizumab included: arterial hypertension (26.47% vs 22.73%), weakness (17.65% vs 16.67), lung bleeding (5.88% vs 3.03%), proteinuria (2.94% vs 0%), GIT perforation (0% vs 1.52%) and VTE (0% vs 1.52%). Binding and neutralizing antibodies were transient and detected only in 1 patient in each group that indicated to low immunogenic potential of both drugs. Conclusions: BCD-021 demonstrated non-inferiority to Avastin in patients with NSCLC. Clinical trial information: NCT01763645.

ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). First Author: Tany Mos, Chinese University of Hong Kong, Shatin, Hong Kong

Background: In the ASCEND-1 study ceritinib showed clinical activity in pts with ALK+ NSCLC, including in brain metastases (BM). ASCEND-2 (NCT01685060) evaluated efficacy and safety of ceritinib in ALK+ NSCLC pts pre-treated with chemotherapy (≥ 1 platinum doublet) who progressed ≥30 days from last treatment with CRZ. Methods: At August 2014 data cut-off, 140 pts receiving oral ceritinib (750 mg once daily) were evaluable. Most pts received prior BM (75%) and intracranial (IC) therapy (79%). ALK status was assessed by fluorescence in situ hybridization. Results: Of 140 pts median age (range) 51 (29–80) years; 50.0% male; 60.0% Caucasian; 40.3% had BM, of which 46% had no prior brain radiation (BRT). Median time from initial diagnosis to treatment start was 13.5 (1.0–283.1) mos; median exposure duration was 8.0 (0.1–16.2) mos. Progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) were assessed in all evaluable pts. Conclusions: Ceritinib provided durable responses even in pts with no prior BRT. Safety outcomes were similar to those seen in ASCEND-1. Clinical trial information: NCT01685060.

ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve pts. First Author: Enriqueita Felip, Vall d’Hebron University, Barcelona, Spain.

Background: Ceritinib demonstrated clinical activity in ALKi-pretreated and -naive pts with ALK+ NSCLC, including those with brain metastases (BM; pivotal ASCEND-1 study). ASCEND-3 (NCT01685138) evaluated efficacy and safety of ceritinib in ALKi-naive pts. Methods: At 27June 2014 data cutoff, 124 pts enrolled worldwide received oral ceritinib 750 mgid. Whole brain (WB) and intracranial (IC) therapy were evaluated by investigator. Prior chemotherapy (≤3 lines) was permitted. Results: Median age of enrolled pts was 56 (27–82); 40.3% were male, 59.7% Asian and 38.7% Caucasian; 40.3% had BM, of which 46% had no prior brain radiation (BRT). Median time from initial diagnosis to treatment start was 13.5 (1.0–285.1) mos; median exposure duration was 8.0 (0.1–16.2) mos. Conclusions: Ceritinib achieved robust ORR and promising DOR/PFS in pts with and without BM. ASCEND showed brain responses even in pts with no prior BRT. Safety outcomes were similar to the ASCEND-1 trial. Clinical trial information: NCT01685138.
A phase I/II study with a CNS-penetrant, selective ALK inhibitor alectinib in ALK-rearranged non-small cell lung cancer (ALK+ NSCLC) patients (pts): Updates on progression free survival (PFS) and safety results from AF-001JP.

**Background:** Alectinib, a CNS-penetrant, selective ALK inhibitor with a novel scaffold, was granted approval in Japan 2014, since it showed good efficacy and safety for longer period. Since safety profile was consistent with the one in the previous reports, high tolerability of long term administration of alectinib was observed. The results suggested that alectinib showed high efficacy and safety for longer period.

**Conclusions:** Alectinib is a novel therapeutic option for the treatment of ALK+ NSCLC, since in ALK+ NSCLC pts without previous ALK inhibitor treatment, alectinib demonstrated early efficacy and tolerability for longer administration. Clinical trial information: JapCITI-101264.

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**Phase (Ph) 1/2a study of TMS-011, a potent inhibitor of ALK and TRK, in advanced solid tumors including crizotinib-resistant ALK positive non-small cell lung cancer. First Author: Hendrik-Tobias Arkenau, Sarah Cannon Research Institute, London, United Kingdom

**Background:** Both intrinsic and acquired resistance mechanisms to ALK inhibitors have been observed in ALK rearranged (ALK+) non-small cell lung cancer (NSCLC). TMS-011 inhibits ALK (IC50 = 0.7 nM), tropomyosin receptor kinase (TRK) A, B, and C (IC50 < 0.01 nM), and tumor growth in vivo. Methods: A Ph 1/2a study is underway to evaluate safety, pharmacokinetics (PK), and preliminary efficacy of TMS-011. The ongoing Ph 1 is evaluating patients (pts) with ALK+ tumors, including those progressing on, or with intolerance to ALK inhibitor therapy. Results: Forty-six pts with advanced cancer, including 19 ALK+ and 11 TRK+ pts, have been treated at total daily doses of 30 to 480 mg, administered 1, 2 or 3 times a day. Dose-limiting toxicities (diaphoresis, QTc prolongation) were observed above 120mg/day, not with the fractionated dosing up to 120mg/day. PK modeling showed that a fractionated schedule achieves sustained trough concentrations above the ALK IC50, and minimizes peak exposure associated with QTc prolongation. TMS-011 at the current dose level of 40mg q8h is well tolerated (Table). In evaluable ALK+ pts, 3/3 achieved a response at or above 120mg total daily dose, and 5/9 achieved disease stabilization for >7 months or longer at lower doses; investigation with the 40mg q8h cohort continues. Duration on TMS-011 exceeded that of previous ALK in a majority of patients with clinical benefit, up to 20 months longer than prior ALK for a pt still continuing on study. Conclusions: TMS-011 is a well-tolerated, promising second-generation ALK, oncogene safety and ECO findings: Development of TMS-011 in pts with ALK+ NSCLC at a fractionated schedule. Development of a controlled release formulation is planned. Clinical trial information: 02048488.

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**Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non–small cell lung cancer (NSCLC). First Author: D. Ross Cancer Center, University of Chicago, Chicago, IL

**Background:** Brigatinib is an investigational oral tyrosine kinase inhibitor with preclinical activity against rearranged ALK and clinically identified crizotinib-resistant mutants. Methods: A phase (ph) 1/2 single-arm, open-label, multicenter study in patients (pts) with advanced malignancies is ongoing. Pts received brigatinib (30–300 mg/d total daily dose, ph 1; 90 mg/d, 180 mg/d, or 90 mg/d for 7 d followed by 180 mg/d; ph 2). Safety was evaluated; efficacy in all 11 pts was evaluated in all 79 ALK+ NSCLC pts. NCT01449461. Results: Median age: 57 y; 58% female. As of 4 Aug 2014, 47% of total pts and 71% of ALK+ NSCLC pts remained on study. Median and maximum time on treatment were 5.5 mo and 29 (ongoing), respectively. Most common treatment-emergent adverse events, grade 1/2, included: nausea 45%; diarrhea 36%; fatigue 36%; cough 26%; headache 26%. Early-onset pulmonary events, observed n = 7 after starting treatment, included dyspnea, hypoxia, or new pulmonary opacities on chest computed tomography suggestive of pneumonia or pneumonitis and occurred in 13/137 (9%) pts (6/44 [14%] pts started at 90 mg qd [pts treated with 90 mg qd or 90 mg qd for 7 d followed by 180 mg qd]). Of 72 evaluable ALK+ NSCLC pts, 52 (72%) responded: 45/65 (69%) with prior crizotinib and 7/7 crizotinib-naive pts. Median duration of response: 49 wks. Median progression-free survival (PFS): 56 wks; 47 wks with prior crizotinib. In a post hoc independent radiological review of pts with baseline intracranial central nervous system metastases, 6/12 pts with lesions ≥10 mm had a brain response (≥30% decrease in sum of longest diameters of target lesions) and 8/26 pts with only nonmeasurable lesions had disappearance of all lesions. Median intracranial PFS for these pts: 97 wks. Conclusions: Brigatinib is promising antitumor activity in ALK+ NSCLC pts with and without prior crizotinib, including pts with brain metastases. Early-onset pulmonary events were observed less frequently with the 90-mg starting dose compared with higher doses. A randomized ph 2 trial of brigatinib 90 mg qd vs 90 mg qd for 7 d followed by 180 mg qd in crizotinib-resistant ALK+ NSCLC (ALTA) is underway. Clinical trial information: NCT01449461.
Crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). Preliminary results of the AC5e phase II trial. First Author: Denis Moro-Sibilot, Thoracic Oncology Unit Teaching Hospital A Michallon, INSERM U823, Grenoble, France

Background: Molecular alterations of crizotinib (crz) targets (ALK, MET, ROS1) are found in a wide range of malignancies. To avoid uncontrolled off-label use and allow for a nationwide safe access to crz for patients (pts) with an ALK, MET or ROS1 positive (+) tumor, the French National Cancer Institute (INCa) launched the Ac5e program, funding both access to tumor molecular diagnosis and an exploratory 2-stage phase II trial. We report the preliminary results of the ROS1+ NSCLC cohort.

Methods: ROS1 status was determined in 28 regional INCa molecular genetic centers by break-apart FISH assays. Patients with ROS1 rearrangements, progressing after at least one standard treatment (including a platinum-based doublet, unless pts were considered as unfit for chemotherapy) were proposed to receive crz 250 mg BID. Responses were centrally assessed using RECIST v1.1. The objective response rate (ORR) and disease control rate (DCR) were assessed every 8 weeks. Results: From Aug 5, 2013 to Dec 12, 2014, 34 pts with ROS1+ NSCLC were enrolled out of 37 expected pts; 32 pts had received crz, including 3 recently enrolled pts, leading to 29 pts with clinical information. Median age: 62 years (range 33–81), 69% females, 93% non-squamous histology, and 93% metastatic disease at study entry. Median number of prior treatments: 2 (range 1–12). Twenty one pts were still on treatment at the cut-off date, 8 had stopped crz (5 PD, 2 adverse events (AEs), 1 death). Among the 24 pts evaluable for response at 8 weeks, we observed 1 CR, 14 PR, 6 SD and 3 PD, leading to ORR = 63% [95% CI:41-81], and DCR = 88% [68-97]. DCR at 6 months was 53% and disease control was achieved in 8/15 evaluable pts. Crz was well tolerated with only 9 grade ≥ 3 AEs or SAE. Most common AEs, mainly grade 1 were visual disorders (62% of pts), peripheral edema (55%), diarrhea (51%), nausea (41%), and elevated transaminases (51%). Conclusions: Crz was well tolerated and achieved a robust treatment response rate in ROS1+ NSCLC. These results underline the interest of integrating ROS1 in biomarkers routine screening. Survival data and duration of response will be presented. Clinical trial information: NCT02034981.

Outcomes with chemotherapies and molecular characteristics of HER2-mutant lung cancers. First Author: Juliana Eng, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Human epidermal growth factor receptor 2 (HER2, ERBB2) aberrations have been identified as oncogenic drivers and potential therapeutic targets in lung cancers. The molecular associations of HER2 protein overexpression, HER2 gene amplification and HER2mutation in lung cancers have not been distinctly defined. To explore these associations, Memorial Sloan Kettering and the University of Colorado combined their data on HER2 in lung cancers. Methods: Tumor specimens from 175 patients with lung adenocarcinomas with no prior targeted therapy were evaluated for the presence of HER2 overexpression, HER2 amplification and mutation. Overexpression was assessed by immunohistochemistry (IHC) using the 4B5 Ventana antibody. Amplification was assessed by fluorescence in-situ hybridization (FISH) using FDA approved probe sets (PathVysion, Abbott and HER2 IQFISH pharmDx, Dako) and defined as HER2/CEP17 ratio ≥ 2.0. Mutation was assessed by fragment analysis and mass spectrometry genotyping for indels and recurrent point mutations in exon 20, respectively. The frequencies of HER2 overexpression, HER2 amplification and mutation were calculated and their concordance examined. Results: HER2 amplification by FISH was detected in 5 of 175 (3%) cases, and 46 (26%) showed polysomy (HER2 copy ≥ 4 but HER2/CEP17 ratio < 2). HER2 overexpression (2+, 3+) on IHC was not detected in the 25% of cases tested. HER2 mutation testing, amplified and negative, identified 32 (20%) cases, with 4 (62%) of FISH results on FISH. HER2mutation was detected in 4 of 145 (3%) specimens, including 3 identical 12bp insertions ([p.A775_G776insYVMA c.2324_2325ins12]) and a 9bp insertion, in 23 (62%, 95% CI 45-78%) patients. In addition, there were 4 identical insertions, all 4 vs 9bp insertions, and five 3bp insertions in exon 20, and four single base pair substitutions (3 exons, R1 exon 8). The median overall survival from date of diagnosis of stage IV disease was 2.3 years (95% CI 1.2-2.7). The median duration of all chemotherapy was 8 months (range 0.8-43 months). Median duration of treatment was 6 months for pemetrexed ±platinum/bevacizumab, 3 months for taxane ±platinum/ bevacizumab, 4 months for erlotinib, 5 months for vinorelbine and 5 months for mitomycin vinblastine. The median duration of targeted therapy was 3 months for trastuzumab, 4 months for small molecule HER2 tyrinos kinase inhibitors, 3 months for erlotinib. No objective responses were noted with trastuzumab (n = 2) or lapatinib (n = 4). Conclusions: The HER2-mutant lung cancers harbored a specific 12bp in-frame inser-
tion (YVMA) in exon 20. In our cohort, the median duration of treatment with chemotherapy was shorter than that of HER2-targeted therapies. Pemetrexed-containing regimens had the longest duration of treatment. As we search for better targeted therapies for patients with HER2-mutant lung cancers, chemotherapy remains an important component of care.
EGFR mutation pattern in African American population in a community-based academic center. **First Author:** Hyaiing Cheng, Montefiore Medical Center, Eastchester, NY

**Background:** The two most common EGFR mutations, L858R in exon 21 and deletions in exon19, represent around 90% of all EGFR mutations in NSCLC and convey sensitivity to EGFR TKIs. Little is known about the patterns of EGFR mutations in different racial groups. Montefiore Medical Center (MMC), a community based academic center, treats a large minority patient population. For example, 33% (693/2104) of patients with lung cancer were identified as African American from 01/2009 to 06/2014. We initiated reflex molecular testing on all non-squamous NSCLC patients in 01/2012 at MMC. **Methods:** We retrospectively reviewed our cancer registry database from 01/2009 to 06/2014 and analyzed all non-squamous NSCLC patients with pathology available in our system for rates and patterns of EGFR mutations. EGFR testing was performed by Integrated Oncology (Labcorp) by PCR-based technology. **Results:** 1032 patients with non-squamous NSCLC had their pathological diagnosis at MMC: 386 (37.4%) were African American, 475 (46%) white, 46 (4.5%) other (Asian and others), and 125 (12.1%) race unknown, respectively. EGFR mutation analysis was performed in 446 patients and 63 were positive for EGFR mutations. The EGFR mutation rate was 14.1% (63/446) for all races, 12.4% (22/178) for African Americans and 14% (27/193) for whites. Interestingly, 25.4% (16/63) of mutations were uncommon EGFR mutations on exon 18 or exon 20, which is higher than the rates reported in the literature (~10%). In particular, 31.8% (7/22) of African Americans with EGFR mutations had uncommon mutations. The mean age at diagnosis of these 7 patients was 66 years, 5 were female, 2 never-smokers, and 5 had stage 3 or 4 disease. The types of uncommon mutations included S768I, V769L, N771_H773dupNPH, V773L, V774M mutations in Exon 20, G719X mutations in Exon 18. **Conclusion:** This is the first report of a high uncommon EGFR mutation rate in African American lung cancer patients. Most uncommon EGFR mutations are less sensitive to EGFR TKIs than L858R and del19 and these results justify consideration in larger cohorts of patients.

Clinical predictors of 5-year survival in patients with EGFR-mutant metastatic NSCLC treated with EGFR-TKIs. **First Author:** Jessica Jyeong Lin, Brigham and Women's Hosp, Brighton, MA

**Background:** Activating mutations of the epidermal growth factor receptor (EGFR) were discovered over 10 years ago. EGFR mutations predict clinical benefit in patients with advanced NSCLC with common EGFR mut (Del19 or L858R). EGFR mutations in other exons other than exon 19 (n = 60; 43.9%) were found in 21% of patients. **Methods:** A retrospective analysis was performed of pts with metastatic NSCLC treated with EGFR-TKIs at Dana-Farber Cancer Institute between Jan 1, 2002 and Sept 30, 2009. Pts alive at time of analysis must have had at least a 5-year survival. OS was compared based on clinical features using log-rank test. Cox's proportional hazards models were used to estimate hazard ratios. **Results:** Among 134 pts, median PFS and OS were 13.1 mos (95% CI, 10.8-14.6) and 30.9 mos (95% CI, 28.2-35.7), respectively. 19 pts (14.2%) were long-term survivors (>5 years), of whom 10 remained alive at the time of analysis with median follow-up of 89.8 mos (range, 60.1-91.6). Multivariate analysis adjusted for factors significant at the 0.10 level in univariate models revealed that sensitizing EGFR mutations in exons other than exon 19 (n = 55) (HR 1.53; 95% CI, 1.05-2.23; p = 0.03) were associated with longer OS (p = 0.01), and HER2 (p = 0.02), histology (p = 0.02), and stage (p = 0.02) were associated with shorter OS. In this cohort, age, gender, disease stage at diagnosis, liver or adrenal mets at diagnosis, specific TKI (erlotinib vs gefitinib), or line of TKI treatment did not correlate with OS. **Conclusion:** Our data estimate 5-year OS among EGFR-mutant metastatic NSCLC pts treated with EGFR-TKIs at 14% vs less than 5% in historic results for an unsellected population with distant-stage NSCLC. Planned studies will elucidate the genetic alterations that may co-occur with EGFR mutations and influence treatment outcomes.
Reduced-dose versus full-dose erlotinib for advanced EGFR-mutant non-small cell lung carcinoma (NSCLC): A retrospective analysis. First Author: Amanda J. Redig, Dana-Farber Cancer Inst, Boston, MA

Background: Erlotinib is an EGFR tyrosine kinase inhibitor (TKI) which is FDA-approved at the maximum tolerated dose (MTD) of 150mg daily with dose limiting toxicities of diarrhea and rash. Preclinical data and small clinical series suggest that lower doses of erlotinib are biologically active against EGFR mutations. However, this has not been systematically studied. We aimed to study whether reduced-dose erlotinib is as effective as full-dose erlotinib for EGFR-mutant NSCLC. Methods: An institutional database was reviewed to identify patients (pts) who received erlotinib for advanced NSCLC carrying an EGFR exon 19 deletion or L858R mutation. Using a retrospective chart review, erlotinib dose was determined at treatment start and after 4 months of therapy. Progression free survival (PFS) was calculated from time of treatment start until date when the treating clinician documented clinical disease progression. Results: 206 eligible pts were identified: 118 exon 19 del, 88 L858R; 144 1st-line, 62 later-line. 34 pts (17%) initiated erlotinib at a reduced dose: 100mg (n = 29), 50 mg (n = 4), 25 mg (n = 1). Reduced-dose pts were older than full-dose pts (median age 70 vs. 64 yrs, p < 0.01), but otherwise clinically similar (Table). Reduced-dose pts had a median PFS of 8.8 months, not significantly different from those at full-dose (11.2 months, HR = 1.3, p = 0.14). Of 173 pts who had not progressed at 4 months, the 86 (50%) on reduced-dose erlotinib at that time had a significantly lower median PFS (11.7 vs. 14.0 months, HR = 1.5, p < 0.05). Conclusions: This is the largest series to date describing outcomes when initiating treatment for EGFR-mutant lung cancer with reduced-dose erlotinib. PFS was acceptable when treating at a reduced biologically active dose, though trends towards a lower PFS than with MTD dosing. A multivariate analysis controlling for baseline differences is underway.

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8087 Poster Session (Board #401), Mon, 8:00 AM-11:30 AM
Clinical implications of repeat tumor biopsy (RTB) in patients (pts) with advanced lung cancer (LC): The Cleveland Clinic (CC) experience. First Author: Eberachi Sandra Adega, Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH

Background: RTB at disease progression (PD) is increasingly used to profile tumor biomarkers and identify drug resistance mechanisms. However, information on safety and clinical consensus on the use of RTB remain lacking. Methods: The aim of this study is to review RTB patterns and safety in LC pts at CC and impact on treatment (Rx) decisions. Pts who were diagnosed and underwent RTB for suspected LC PD between 2007 and 2013 were studied. Statistical analysis is primarily descriptive. Results: The study involved 184 (56% male) pts. Median age at diagnosis was 65y (21-87); 100 (54%) were treated initially with traditional RX (surgery – 41%, chemo – 39%, Radiation – 17%, targeted therapy – 9%) and 83 (45%) with multimodality RX (2-modality guided bx (5.9%, n = 17; targeted therapy – 9%) and 3-modality guided bx (5.9%, n = 11) & others (2.7%, n = 5). Lung was the most common biopsy site (46%) followed by LN (15%). Complications occurred in 13 of 181 (7.2%) pts at 1st RTB (data missing in 3 pts), 3 of 61 (4.9%) at 2nd RTB, 1 of 25(4%) at 3rd RTB, and 0 of 4 (0%) at 4th RTB. The 17 (6.2%) complications are shown in the table below. Histologic change was seen in 13 cases, including adenosis-to-squamous carcinoma (at erlotinib resistance) and vice-versa, and non-small cell to small cell histology. The T790M-EGFR mutation was noted in 6 cases, the PIK3CA mutation in 1, and in a change in ALK status in 3. Medical decision making was impacted in 16% of cases. Conclusions: RTB can be safely performed using minimally invasive techniques and can benefit LC Rx decision making.

Complication n

Bleeding without hemodynamic compromise 6
Bleeding requiring transfusion 5
Pneumothorax 2
Hemorrhagic instability after premedication 1
Cerebral salt wasting 1
Tracheoesophageal fistula 2
Severe cough 1
Incomplete procedure 1
Deaths 2

8079 Poster Session (Board #403), Mon, 8:00 AM-11:30 AM
Early prediction of response to tyrosine kinase inhibitors by quantification of EGFR mutations in plasma of non-small cell lung cancer patients. First Author: Conino Maria Lucia, Center of Predictive Medicine, SS. Annunziata Hospital, University G. D’Annunzio, Chieti, Italy

Background: Several studies have investigated the feasibility of detecting EGFR mutations in liquid biopsies of Non-Small Cell Lung Cancer (NSCLC) patients. However, the potential to accurately quantify EGFR mutations in plasma for clinical purposes is largely unexplored. Methods: Plasma samples were obtained from 79 subjects: (a) 42 NSCLC patients with EGFR mutation positive primary tumors, from a prospective trial, where biopsy samples were collected at baseline prior to first-line erlotinib therapy and immediately after progression; (b) 15 previously untreated stage IIB-IV NSCLC patients, with EGFR mutation positive tumor specimens, where plasma samples were collected at baseline and serially at 4-60 days during TKI therapy; (c) 11 patients receiving EGFR mutation inhibitors and in whom plasma was conducted by the cobas EGFR Mutation Test (EIGFR test, under development, RMS, Pleasanton, CA) and ultra-deep next generation sequencing (UDNGS) by Roche 454-QS Junior and Illumina MiSeq. A semi-quantitative index (SQI) was derived from a dilution series of known mutation copy numbers. Clinical response, expressed as percent tumor semi-quantitative index (SQI) was derived from a dilution series of known mutation copy numbers. Clinical response, expressed as percent tumor decrease in the EGFR semi-quantitative index (SQI) during therapy in all of the patients, starting from the 4th day of treatment in 90% of cases. The rate of SQI decrease was more than 50% at 15 days in 73% of patients (rapid responders) and less than 50% at 15 days in 27% of patients (slow responders) and was correlated with PTS at 2 months.

Conclusions: Quantification of EGFR mutations with the cobas test in plasma is feasible. The variation of EGFR SQI during therapy could be used for early prediction of response and diagnosis of relapse, with further implications for patient management. A prospective trial has been planned to confirm these results. Clinical trial information: EudraCT Number: 2010-023892-2.

8080 Poster Session (Board #404), Mon, 8:00 AM-11:30 AM
Association of plasma EGFR T790M ctDNA status with clinical outcome in advanced NSCLC patients with acquired EGFR-TKI resistance. First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, South Korea

Background: EGFR T790M mutation occurs in around half of non-small cell lung cancer (NSCLC) patients with acquired EGFR-TKI (TKI) resistance, based on tumor tissue re-biopsies using an invasive clinical procedure. Here, we evaluated the feasibility of detecting T790M mutation in circulating tumor DNA (ctDNA), using serial plasma samples from NSCLC patients receiving TKI to further investigate its association with clinical outcome. Methods: Patients with advanced or recurrent NSCLC receiving TKI were enrolled consecutively and blood samples were taken every 2 months, including post-TKI failure. Upon TKI failure, patients were given continued TKI alone or TKI plus chemotherapy at the discretion of the physician. EGFR ctDNA in plasma was measured using Droplet Digital PCR (ddPCR) assay. Overall survival (OS) of starting from initial TKI treatment was analyzed according to the T790M ctDNA status detected in plasma.

Results: Among 318 patients, 117 who acquired TKI resistance (with 391 plasma samples) were eligible for the analysis. T790M ctDNA was detected in the plasma of 55/117 (47%) patients. Almost half of the T790M ctDNA positive patients were identified at a median time of 2.2 months prior to clinical progressive disease (PD). Furthermore, T790M ctDNA positive patients had significantly shorter OS compared to negative patients (median OS: 808 versus 1083 days, P = 0.0418). Conclusions: Our study demonstrates the feasibility of monitoring EGFR mutation dynamics in serial plasma samples from NSCLC patients receiving TKI therapy. T790M ctDNA can be detected in plasma before and after PD and represents a potential poor prognostic factor.
8081  Poster Session (Board #405), Mon, 8:00 AM-11:30 AM

Kinetic monitoring of EGFR T790M in urinary circulating tumor DNA to predict radiographic progression and response in patients with metastatic lung adenocarcinoma.

Author: Hatim Husain, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Acquisition of the EGFR T790M resistance mutation is a hallmark of disease progression in patients with metastatic EGFR mutant lung adenocarcinoma treated with anti-EGFR inhibitors. Biopsies are challenging in relapsed patients and a non-invasive approach to detecting T790M is desired. We sought to monitor urinary circulating tumor (ct)DNA for the early acquisition of T790M and understand ctDNA kinetics in patients on anti-EGFR treatment.

Methods: In a biomarker study of 100 patients with EGFR-mutated metastatic lung adenocarcinoma (39 patients enrolled), urine samples were obtained at different time points up to 8 months prior to radiographic progression on anti-EGFR tyrosine kinase inhibitors (TKIs) and second line TKI therapy. Urinary ctDNA was extracted by a method that preferentially isolates short, fragmented ctDNA. Quantitative analysis of T790M was performed using PCR coupled with next generation sequencing (MiSeq), with standardized reporting of mutant allele copies per 10⁷ genome equivalents.

Results: Interim analysis was conducted in 22 patients. EGFR T790M mutation was detected in the urine of 15 out of 22 (68%) patients who received anti-EGFR treatment. Of 15 patients positive for T790M by urine, 10 patients had T790M mutation in tissue biopsy (CLIA test). Three patients, who were tissue T790M negative (n = 3) but had a very high clinical suspicion of T790M, had detectable T790M in both urine and plasma. EGFR T790M was detected in urine up to 3 months prior to the detection of radiographic progression on anti-EGFR TKIs. Examination of urine samples collected daily after initiation of anti-EGFR TKIs and second line therapy revealed early peaks in ctDNA one day after therapy which predicted radiographic response.

Conclusions: We demonstrate for the first time that T790M can be successfully detected in urinary ctDNA months before progression on anti-EGFR TKIs. Urinary ctDNA testing identifies additional patients who are potentially eligible for anti-T790M treatment. Urine monitoring can enable dynamic assessment of response and progression from a completely non-invasive sample.

8082  Poster Session (Board #406), Mon, 8:00 AM-11:30 AM

EML4-ALK rearrangement in blood platelets and outcome to crizotinib in non-small-cell lung cancer patients.

First Author: Niki Karachaliou, Quirón University Hospital, Biomedical Research Unit, Barcelona, Spain

Background: Non-small-cell lung cancer (NSCLC) with EML4-ALK rearrangements is sensitive to crizotinib. However, despite initial response most patients (p) will eventually relapse and monitoring EML4-ALK rearrangements over the course of treatment may help identify them. Challenges associated with serial tumor biopsies have highlighted the need for blood-based assays for monitoring biomarkers. Platelets can sequester RNA released by tumor cells and are an attractive source for non-invasive biomarker assessment.

Methods: EML4-ALK rearrangements were analyzed by reverse transcription-polymerase chain reaction (RT-PCR) in platelets and plasma isolated from blood obtained from 77 NSCLC p, 38 of whom had EML4-ALK-rearranged tumors. In a subset of 29 p with EML4-ALK-rearranged tumors treated with crizotinib, EML4-ALK rearrangements in platelets were correlated with progression-free survival (PFS) and overall survival (OS).

Results: The study was designed with three parallel objectives: firstly, to determine the sensitivity and specificity of detecting EML4-ALK rearrangements in platelets with plasma serving as a control biosource; secondly, to examine the potential impact of EML4-ALK rearrangement in platelets on outcome to crizotinib; thirdly, to test the feasibility of monitoring p a throughout treatment with EML4-ALK rearrangement assessment in platelets. RT-PCR demonstrated 65% sensitivity and 100% specificity for detection of EML4-ALK rearrangements in platelets. In the subset of 29 p treated with crizotinib, PFS was 3.7 months for p with EML4-ALK + platelets and 16 months for those with EML4-ALK – platelets (hazard ratio, 3.5; P = 0.02). Monitoring EML4-ALK rearrangements in platelets of one index p over a period of 30 months revealed crizotinib resistance two months prior to radiographic disease progression.

Conclusions: Platelets may provide a useful source for non-invasive assessment of EML4-ALK rearrangements and may prove useful for predicting outcome to crizotinib. Serial analyses of EML4-ALK rearrangements in platelets may help improve clinical decisions based on radiographic imaging alone by detecting resistance to therapy sooner.

8083  Poster Session (Board #407), Mon, 8:00 AM-11:30 AM

Phase I dose escalation study of ASP8273, a mutant-selective irreversible EGFR inhibitor, in subjects with EGFR mutation positive NSCLC.

First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ASP8273 is a mutant selective, third generation irreversible inhibitor of EGFR activating mutations and the EGFR T790M resistance mutation, with less effect on wild type EGFR. Methods: In a phase I dose escalation study, subjects diagnosed with EGFR mutation positive NSCLC who were previously treated with an EGFR TKI were enrolled at multiple centers in the United States into dose escalation and expansion cohorts. ASP8273 was administered once daily at doses of 25 mg to 400 mg. Endpoints included safety and tolerability, PK and preliminary anti-tumor activity. Response expansion cohorts enrolled subjects with known EGFR T790M mutation and required submission of tissue samples for central confirmatory testing.

Results: As of 08 January 2015, 35 subjects were enrolled; 24 subjects in 6 dose escalation cohorts (25-400 mg) and 11 subjects in 2 expansion cohorts (100-200 mg). The majority were female (71.4%), median age 65 (38-85), all (100%) received prior erlotinib, and the median number of prior therapies was 2. The most common treatment emergent AEs included nausea (9; 25.7%) and diarrhea (6; 17.1%); one treatment was CTCAE Grade 1, manageable and none required dose reductions. Of 5 evaluable subjects enrolled at 400mg, 2 DLTs were observed requiring dose reduction including one event of G3 hyponatremia and one event of G3 anorexia. No ILD-like events, QTc prolongation or hyperglycemia have been reported. PK profile is as expected for a T790M TKI.

Conclusions: We demonstrated for the first time that T790M can be successfully detected in urinary ctDNA months before progression on anti-EGFR TKIs. Urinary ctDNA testing identifies additional patients who are potentially eligible for anti-T790M treatment. Urine monitoring can enable dynamic assessment of response and progression from a completely non-invasive sample.

8084  Poster Session (Board #408), Mon, 8:00 AM-11:30 AM

Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non-small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI).

First Author: Keunchil Park, Division of Hematology & Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: HM61713 is an orally available EGFR mutation-specific inhibitor with sparing EGFR WT tumors that previously showed promising efficacy in T790M positive tumors at the dose of 300 mg (overall response rate: 29.2%). We report here on updated data from the ongoing phase I/II study of HM61713 in pts with advanced NSCLC who had failed previous EGFR-TKIs (NCT01588145). Methods: Advanced NSCLC pts with EGFR mutation positive tumor were enrolled in dose escalation cohort and received doses ranging from 75-1200 mg/d. After safety evaluation, separate expansion cohorts opened for pts who failed prior EGFR TKI pts at 800 mg QD dose, respectively to investigate efficacy and tolerability of HM61713 in pts with centrally confirmed T790M positive NSCLC.

Results: As of 15 Dec 2014, 173 patients were enrolled, 55 and 118 in dose escalation and expansion parts, respectively. Maximum tolerated dose (MTD) was established as 800 mg once daily (QD). Dose limiting toxicities (DLTs) included abdominal pain, diarrhea, idiosyncratic drug reaction, and elevation of aspartate aminotransferase, alanine aminotransferase, amylase and lipase. Treatment-related adverse events occurred in 87.3% of 165 pts; mainly diarrhea, rash, skin exfoliation, nausea, pruritus, decreased appetite and dry skin. In the 34 pts with centrally confirmed T790M who received HM61713 with a dose more than 650 mg, the overall response rate was 58.8% (10 confirmed/10 unconfirmed partial responses) and 13 pts achieved disease stabilization (disease control rate: 97.1%). Updated data will be presented at the meeting. Conclusions: HM61713 showed an encouraging clinical anti-tumor activity with good tolerability in pts with T790M positive NSCLC. Clinical trial information: NCT01588145.
A phase II, single-arm, efficacy and safety study of poziotinib (NOV120101) in Korean patients with advanced or metastatic lung adenocarcinoma who have acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. First Author: Ji-Youn Han, National Cancer Center, Goyang, South Korea

Background: Poziotinib is an oral irreversible inhibitor of EGFR, HER2 and HER4, and has shown preclinical activity in lung cancer models with EGFR mutations including T790M. This phase II study was aimed to access the efficacy of poziotinib in patients with EGFR-mutant lung adenocarcinoma and acquired resistance to erlotinib or gefitinib. Methods: Eligible patients had documented activating EGFRmutations and developed acquired resistance after treatment with erlotinib or gefitinib based on Jackson criteria. Patients received poziotinib at a dose of 16 mg once daily in 28-day cycles. The primary endpoint was PFS. All tumor responses were evaluated by independent review and, in a supportive manner, by investigator. Results: A total of 39 patients were treated with poziotinib in this study (29 women, median age 62 years (range, 43-84)). Most patients received erlotinib or gefitinib as first-line (n = 27) or second-line therapy (n = 11). The median time on erlotinib or gefitinib was 13.1 months (range, 3.4-33.2). Genotyping using tumor biopsy acquired at study entry was determined in 37 patients; 19 patients had EGFR T790M mutation, 2 PIK3CA mutation and no MET-amplification. Partial response with poziotinib was confirmed in 3 patients (8%; 95% CI, 2-21). Twenty patients (51%; 95% CI, 35-68) had disease control of at least stable disease for ≥ 8 weeks. The median PFS and overall survival were 2.7 (95% CI, 1.8-3.7) and 15.0 months (95% CI, 9.5-not estimable), respectively. The most frequently reported AEs of grade 3 by preferred term were rash (59%), stomatitis (18%), and diarrhoea (10%). Two patients were discontinued due to treatment-related AEs (one grade 3 rash and one grade 3 myositis). Conclusions: Poziotinib showed modest efficacy in patients with EGFR-mutant lung adenocarcinoma who had progressed on erlotinib or gefitinib. Obvious clinical evidence suggesting that poziotinib may overcome acquired resistance secondary to EGFR T790M mutation was not captured in this study. Clinical trial information: NCT01718847.

Biomarker analysis of a phase II trial of caboctinib and erlotinib in patients (pts) with EGFR-mutant NSCLC with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) resistance: A California Cancer Consortium Phase II Trial (NCI 9303). First Author: Karen L. Reckamp, City of Hope, Department of Medical Oncology and Therapeutics Research, Duarte, CA

Background: Modulation of the MET and VEGF signaling pathways are associated with resistance to EGFR TKI therapy in addition to acquired T790M mutation (mt). Caboctinib is a TKI that targets MET and VEGFR2, among other receptors. Axitinib, imatinib, and cabozantinib 40 mg daily were given on a 28 day cycle and ORR was the primary objective. Pts were required to have archival tissue available, and a subset had had documented activating EGFR mutations and developed acquired resistance to erlotinib or gefitinib. Methods: Eligible patients had had documented activating EGFR mutations and developed acquired resistance to erlotinib or gefitinib. First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, South Korea

Background: Aftatinib (A) is a potent irreversible ErbB family blocker and nimotuzumab (N) is a humanized anti-EGFR mAb. In this phase Ib/II study, we aimed to assess the safety and activity of A plus N in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib. In our preclinical study, using a mouse xenograft model, Nimotuzumab enhanced the antitumor efficacy of Aftatinib. Methods: Major inclusion criteria were advanced NSCLC with activating EGFR mutation or disease control for at least six months with previous gefitinib or erlotinib therapy. In phase Ib study using classic 3+3 dose escalation method, patients were treated with A either 40mg/d or 30mg/d in combination with N either 100mg/w or 200mg/w. One cycle was composed of 4 weeks of treatment. In phase II study, patients were treated with A plus N in the level of RP2D defined in phase Ib study. Results: Overall, fifty pts were enrolled and treated: 13 in phase Ib and 37 in phase II. The median age of the patients was 55 years and 62% were female. EGFR mutation types were as follows: del19 (N = 23, 46%), L858R (N = 15, 30%), and others. All patients had received prior gefitinib (N = 34, 68%) or erlotinib (N = 16, 32%). At the first cohort (A 40mg/d + 100mg/w), 1 out of 6 pts experienced 1 DLT (G3 diarrhea), and 2 out of 6 pts experienced DLTs (G3 diarrhea and G3 neutropenia, respectively) during the 1st cycle in the next cohort (A 40mg/d + 200mg/w). Thus, RP2D was accordingly determined as A 40mg/d + N 100mg/w per protocol. In phase II part, there was no treatment related death and 27% (10/37) of patients experienced any grade 3 adverse events (no one in grade 4 or 5), including diarrhea and skin rash. In phase II part, the response rate was 38% (14/37), disease control rate 81% (30/37), duration of response 4.0 months (range, 1.8-8.5 months) and the median PFS was 4.2 months (95% CI, 0.5-10.3). Conclusions: Combination of A and N showed an acceptable safety profile and promising antitumor activity in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib. Clinical trial information: 1200.189.
Response to tyrosine kinase inhibitors in non-small-cell lung cancer with concomitant c-MET overexpression and driver genes. First Author: Na-na Lu, Guangdong Lung Cancer Institute & Guangdong Academy of Medical Sciences, Guangzhou, China

Background: The common driver genes in non-small cell lung cancer (NSCLC) include EGFR, ALK and KRAS. We investigate the frequency of MET overexpression coexisting with oncogenic drivers and response to tyrosine kinase inhibitors (TKIs).

Methods: We screened 806 consecutive NSCLC patients for the presence of MET overexpression by immunohistochemistry (IHC), in which ≥50% tumor cells with moderate to high intensity staining were defined as MET positive. MET amplification and ALK rearrangements were detected by fluorescence in situ hybridization (FISH), and FISH positive was defined as gene focal amplification or high polyomy (at least 15% cells with ≥5 copy numbers). Meanwhile, KRAS and EGFR mutations were tested by DNA sequencing or Scorpion amplification refractory mutation system (ARMS).

Results: The frequency of MET overexpression was 31.9% (257/806) in NSCLC. Among c-MET positive patients, the frequency of EGFR mutation was 38.1% (98/257) and that of ALK rearrangement was 8.7% (22/257). Response rate (RR) of EGFR-TKIs was 22.2% (9/36) in advanced NSCLC patients with concomitant EGFR mutation and c-MET overexpression, and 56.8% (21/37) in those with only EGFR mutation, P=0.033. However, there was no significant difference in RR between the patients with concomitant ALK rearrangement and c-MET overexpression and those with only ALK rearrangement, 61.5% (8/13) vs. 75.0% (6/8), P=0.656. Among 2 cases with concomitant MET amplification and EGFR mutations, one responded to gefitinib, but the other had stable disease. Dramatic response was observed in one with concomitant MET amplification and KRAS mutations.

Conclusions: Advanced NSCLC patients with concomitant MET amplification and MET overexpression have significantly low RR with EGFR-TKIs, indicating that MET overexpression potentially causes intrinsic resistance to EGFR-TKIs. Similar response was observed in ALK positive patients with or without c-MET overexpression treated with crizotinib.

Response to tyrosine kinase inhibitors in non-small-cell lung cancer with de novo c-MET overexpression. First Author: An Na Li, Guangdong Lung Cancer Institute, Guangzhou, China

Background: c-Met gene amplification has been identified as one of the acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and de novo activation in advanced non-small-cell lung cancer (NSCLC). However, it is not clear whether c-Met overexpression could be as the biomarker for de novo. Methods: Advanced NSCLC patients with de novo c-Met expression were detected by immunohistochemistry (IHC), ≥50% tumor cells with moderate to high intensity staining were defined as c-Met positive. Gene copy numbers have been detected by FISH. By Cappuzzo scoring system ≥5 copies were positive or METCEP7 ratio ≥1.8 was defined as c-MET amplification. The statuses of METover expression could be as a biomarker for de novo c-Met amplified NSCLC. KRAS and ROS1 were also tested. Results: From January 2013 to December 2014, 24 eligible patients with c-Met IHC overexpression received crizotinib treatment (3 female, median age 59 years), with 19 evaluable for response. Eleven of them achieved partial response (PR), 3 were stable disease (SD) and 5 were progressive disease (PD). All responders had high c-Met IHC status, and 8 with FISH positive. Table 1: Adverse events of grade 3 or 4 toxicities have been found in 1 patient. For one death, with interstitial lung disease, causality to crizotinib was not ruled out. The most frequent drug-related AEs were grade 1-2, including nausea (14/19), anorexia (14/19), vomiting (10/19), visual impairment (6/19). EGFR, ALK, KRAS and ROS1 were all negative. Conclusion: c-Met overexpression could be as a biomarker for de novo c-Met amplified NSCLC. c-Met inhibitor against de novo MET overexpressed NSCLC is a good strategy. IHC seems not worse than FISH in predicting efficacy for c-Met inhibitor.

Targeting c-Met overexpression for overcoming acquired resistance to EGFR TKIs in NSCLC. First Author: Lan-yang Gou, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Background: c-Met amplification and T790M are both recognized as the mechanisms of resistance to EGFR TKIs in advanced NSCLC. Advanced NSCLC patients with AR to EGFR TKIs were detected for c-Met overexpression by immunohistochemistry ≥ 50% tumor cells with moderate to high intensity staining were defined as c-Met positive. The statuses of EGFR, ALK, KRAS and ROS1 were tested. c-Met, p-Met, EGFR, p-EGFR, ERBB3, p-ERBB3, AKT, p-AKT, MAPK, p-MAPK, which were important markers in MET and EGFR signal pathway, were tested by IHC. Results: From January 2013 to January 2015, 126 advanced NSCLC patients with AR to gefitinib or erlotinib were enrolled prospectively. The frequency of c-Met overexpression was 28.6% (36/126), c-Met overexpression + T790M 13.5% (17/126), T790M 24.6% (31/126), SCLC or squamous cell transformation 1.6% (2/126), KRAS mutations 0.8% (1/126), ALK fusion 0.8% (1/126), ALK fusion 0.8% (1/126) and unknown mechanism 20.3% (27/126). Response rate was 25% (3/12). Eleven c-Met overexpression patients received gefitinib plus c-Met inhibitors crizotinib. Response rate (RR) by RECIST was 45.5% (5/11), Disease control rate (DCR) was 54.5% (6/11), Progression disease (PD) was 45.5% (5/11). For patients with c-Met overexpression and without T790M DC was 100% (5/5), and for those patients with c-Met and T790M DC was 30% (2/6). The longest duration of response to date is >6 months. For patients with both c-Met/T790M positive no RR was found. We detected the protein expression of c-Met, p-Met, EGFR, p-EGFR, ERBB3, p-ERBB3, AKT, p-AKT, MAPK, p-MAPK in tumor of 9 cases with c-Met/T790M by IHC. The results showed that all of the markers were positive in ≥50% cases (each marker was positive in at least 5 cases, respectively). Conclusions: c-Met overexpression could be as a biomarker for AR. Combination of EGFR TKIs and c-Met inhibitor is a good strategy to overcome AR for c-Met overexpressed patients, but not effective in c-Met/T790M-coexisting cases. One of the possible mechanism of resistance could contribute to both MET and EGFR signal pathway active.
Lung Cancer–Non-Small Cell Metastatic
8093 Poster Session (Board #417), Mon, 8:00 AM-11:30 AM
Nationwide genomic screening network for the development of novel targeted therapies in advanced non-small cell lung cancer (LC-SCRUJ-Japan). First Author: Takahiro Mine; Makoto Suzuyama; Hiroshi Nishio; National Cancer Center Hospital East, Kashiwa, Chiba, Japan
Background: Various driver gene alterations have emerged as critical targets for molecular therapies in non-small cell lung cancer (NSCLC), but these alterations other than EGFR mutations occur in rare populations. A nationwide genomic screening network in Japan (LC-SCRUJ-Japan) was established in February 2013 for the development of novel targeted therapies against advanced NSCLCs harboring these rare alterations. Methods: Advanced non-squamous NSCLCs without EGFR mutations were eligible for inclusion in LC-SCRUJ-Japan. The tumors were analyzed for ALK/RET/ROS1 fusions using RT-PCR, and detected fusions were confirmed by FISH. Between November 2013 and March 2014, one of 186 institutions across Japan were participating and 1347 patients had been enrolled in LC-SCRUJ-Japan. Among 1271 available samples, ALK/RET/ROS1 fusions were detected in 24 (2%), 31 (3%), and 55 (4%) cases, respectively. The NGS analysis was performed in 201 cases without the fusions, and 82 cases (41%) had driver mutations, including 45 KRAS mutations (22%), 10 BRAF mutations (5%), 9 ERBB2 mutations (4%), 2 PIK3CA mutations (1%), and 1 NRAS mutation (0.5%). MET and ERBB2 amplifications were also detected by the NGS in 4 (2%) and 2 (1%) cases, respectively. Among a total of 198 cases harboring targetable gene alterations, 16 with RET fusions, 26 with ROS1 fusions, and 2 with BRAF mutations were enrolled in clinical trials for vandetanib (LURESTudy, Japan), crizotinib (2012-01, East Asia), and dabrafenib (Zelboraf), respectively. Conclusions: This nationwide and population enrichment screening system enabled various rare driver gene alterations to be efficiently detected in advanced NSCLC, thereby contributing to the rapid accrual of matched patients in clinical trials for targeted therapies.

8094 Poster Session (Board #418), Mon, 8:00 AM-11:30 AM
Migration to next-generation sequencing and the identification of RET and ROS1 rearrangements plus PTEN and MET protein expression in tumor specimens from patients with lung adenocarcinomas. First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY
Background: LCMC 1.0 demonstrated that multiplexed genomic platforms can assay 10 oncogenic drivers at diagnosis in tumor specimens from patients with lung adenocarcinomas and this information can guide care. (Kris JAMA 2014) The number of molecular lesions that can be targeted with TKIs continues to grow and Next-Generation Sequencing permits more comprehensive testing of more aberrations with less tumor tissue. To translate these advances, we initiated LCMC 2.0 to test initial tumor specimens for 12 oncogenic drivers and to provide the results to clinicians for treatment decisions and research. Methods: The 16 site LCMC 2.0 is testing tumors from 1000 patients with lung adenocarcinomas in CLIA laboratories for KRAS, EGFR, HER2, BRAF, PIK3CA, MAP2K1, AKT1, and NRAS mutations, RET amplification, rearrangements in ALK, RET, and ROS1, and PTEN mutation (Mab 138G4) and MET (Mab SP44) expression by immunohistochemistry. All patients were diagnosed with stage IIIIB/IV after May 2012, had a performance status 0-2 and available tumor tissue. Results: Of 986 patients registered, data is now reported for 617. An oncogenic driver has been found in 52% (95% CI 49 to 56%). Drivers detected 13 RET (2%, 95% CI 1 to 3%), 17 ROS1 (1%, 95% CI 1 to 2%), 155 KRAS (22%, 95% CI 19 to 25%), 77 EGFR (13%, 95% CI 13 to 15%), 20 ALK (3%, 95% CI 2 to 5%), 18 BRAF (3%, 95% CI 2 to 4%), 4 PIK3CA (<1%, 95% CI <1 to 1%), 9 HER2 (2%, 95% CI 1 to 3%), 12 MET amplification (2%, 95% CI 1 to 3%), 3 NRAS (<1%, 95% CI <1 to 1%), 1 MAP2K1 (<1%, 95% CI 1 to 1%), 0 AKT1, 26 had >2 findings (4%, 95% CI 3 to 6%). PTEN loss was detected in 15% (95% CI 12 to 17% and MET expression in 54% (95% CI 50 to 58%). Next-Generation Sequencing platforms were used at 81% of LCMC 2.0 sites. Results were used to select a targeted therapy or trial in 16%. Conclusions: Next-Generation Sequencing is rapidly becoming routine practice at LCMC 2.0 centers with use going from 0 to 81% of sites since 2012. LCMC 2.0 identified additional targets (RET and ROS1 rearrangements and PTEN loss) and detected an actionable oncogenic driver in the majority of initial lung adenocarcinoma specimens. Supported by Free to Breathe Clinical trial information: NCT01014286.

8095 Poster Session (Board #419), Mon, 8:00 AM-11:30 AM
Clinical implementation of anchored multiplex PCR with targeted next-generation sequencing for detection of ALK, ROS1, RET and NTRK1 fusions in non-small cell lung carcinoma. First Author: Anna F. Farago; Massachusetts General Hospital, Boston, MA
Background: Chromosomal rearrangements resulting in expression of oncoprotein kinase fusion genes occur in a subset of epithelial malignancies and can underlie sensitivity to tyrosine kinase inhibitors. In non-small cell lung cancer (NSCLC), rearrangements involving anaplastic lymphoid kinase (ALK), ROS proto-oncogene 1 (ROS1), and RET proto-oncogene (RET) occur at frequencies of approximately 4%, 1% and 1%, respectively. Rearrangements involving neurotrophic tyrosine kinase receptor type 1 (NTRK1) have been described, though the frequency is not well characterized. Methods: We implemented a multiplex polymerase chain reaction (PCR) technology, Anchored Multiplex PCR (AMP), for detection of fusion transcripts using targeted next-generation sequencing of cDNA generated from clinical samples (Zheng et al., 2014). The sequencing library targets known fusion exons in ALK, ROS1, RET and NTRK1. We retrospectively reviewed the NSCLC cases assessed by this method. Results: Between July 2013 and January 2015, 663 clinical NSCLC cases from our institution were assessed, providing >99% power to detect at least one fusion event at an underlying frequency as low as 1%. 584 cases were adenocarcinoma histology. We detected fusions involving ALK, ROS1, RET and NTRK1 at frequencies of 2.6%, 0.9%, 2.0% and 0.0% (17, 6, 13 and 0 cases), respectively. All were mutually exclusive. The histologic subtype distribution of adenocarcinomas in all fusion positive cases was 75% adenocarcinoma, 25% squamous cell lung cancer, none were undifferentiated (BR11) 3928). Among 174 pts from our institution during the study period were identified from an institutional database. The rate of test utilization, assay failure, and detected genomic alterations were studied. Results: 174 pts with squamous NSCLC presented to our institution from 7/1/2013-11/18/2014. Of these, 100 consented to targeted NGS. Median age was 65, 89% and 11% were heavy versus light/never smokers, 66% were stage IIIIB/IV. The majority of patients underwent core biopsy (52 core, 30 resection, 14 FNA, 3 cytology) Targeted NGS was successful in 74 patients, pending in 12 patients and failed in 13 patients due to insufficient tissue (5 FNA/cytology, 8 core). The mutational rates for each target of the LungMAP study were as follows: PIK3CA mutation 12% (9), CCND1-2 amplification 17% (12), FGFR1-4 amplification 24% (18), FGFR1-4 mutation 7% (5) and MET amplification 3% (2). Of these, 12% (9) pts had multiple targets detected. 18% (6/33) of these amplification events were high level (ploidy estimate >5 copies). Conclusions: NGS in a real-world squamous NSCLC cohort is feasible and yields a high rate (51% pts) of potentially targetable genetic alterations. The majority of amplification events are low-level (2-5 copies) which may be challenging to therapeutically target. Our findings support the use of targeted NGS as a tool to facilitate trial enrolment in studies such as the NCI LungMap and Match studies.
KEAP1-mutations in patients with non-small cell lung cancer (NSCLC).

First Author: Rieke Frank, Lung Cancer Group Cologne, Department I of Internal Medicine, University Hospital of Cologne, Center for Integrated Oncology (CIO) Köln Bonn, Cologne, Germany

Background: Mutations in genes of the KEAP1-NFE2L2 pathway of patients with NSCLC are associated with an increased tumor growth, resistance towards cytostatic drugs and reduced survival rates. KEAP1 suppresses NFE2L2 under physiological conditions. Oxidative stress or electrophiles cause NFE2L2 to stabilize and translocate to the nucleus, resulting in the transcription of various cytoprotective genes. Mutations in KEAP1 are described for diverse tumor entities with a relatively high frequency causing an increased level of NFE2L2. This leads to resistance of cancer cells against anti-cancer drugs and irradiation. This study was performed to characterize KEAP1-mutated NSCLC clinically and genetically. Methods: Tumor tissue collected from 446 patients within a regional screening network was analysed for KEAP1 mutations using next-generation sequencing (NGS). Clinical, pathological and genetic characteristics of these patients are described and compared with a control group of patients without KEAP1 mutation. Results: So far, we identified 33 patients with KEAP1 mutations. Among these we found 34 different mutations, of which the majority was not previously described. KEAP1 mutations were not restricted to a special exon. In 30 patients (90.9%), additional driver aberrations in KRAS, EGFR, FGFR1, FGFR3, STK11, ALK, DDR2, HRAS, BRAF, PIK3CA, PTEN, NFE2L2, EP300, TSC1, CREBBP, NRAS, MET and CYP2D6 could be detected, as well as mutations and polymorphisms in TP53. KEAP1 mutations occurred in both genders (male/female ratio 3/1), in squamous-cell carcinoma (36.4%) and adenocarcinoma (60.6%) and were significantly associated with smoking. The prognostic and predictive impact of KEAP1 mutations in a prospective cohort will be presented. Conclusions: Our data suggest a role of KEAP1-mutations as a cofactor in addition to classical driver mutations underlying the malignant phenotype of lung cancer cells. So far, this is the largest cohort of patients with KEAP1-mutations analysed and described. Further survival and treatment analyses will reveal the role of these mutations for the outcome of these patients.

Maximum severity score (MSS) of baseline patient-reported Lung Cancer Symptom Scale (LCSS) as a prognostic and predictive factor for overall survival (OS) in the Phase III SQUIRE study. First Author: Martin Reck, Lung Clinic Grosshadern, Airway Research Center North (ARCN), Member of the German Center for Lung Research (DZL), Grosshadern, Germany

Background: SQUIRE, a randomized, phase III study (N = 1093) demonstrated that the addition of nectumumab (N) to gemcitabine-cisplatin (GC) improved OS in patients with stage IV squamous NSCLC. We further analysed the results by baseline MSS and other cofactors that preliminary models suggested were prognostic for OS in this study. Methods: This post-hoc analysis defined the MSS for each patient as the worst (highest) score of any individual LCSS item at baseline. MSS was evaluated as a prognostic and predictive factor for OS and progression-free survival (PFS) using Cox and Kaplan-Meier methods. Cox models included baseline ECOG performance status, sum of target lesions, number of metastatic sites, body mass index, platelets, hemoglobin, and leukocytes. Results: As a continuous variable, MSS was prognostic for OS (p < 0.001) with a statistically significant interaction (p = 0.006) with treatment effect. These results manifested as subgroup differences shown in the table below. Results for PFS and OS were consistent. Conclusions: Prognosis for survival worsened with increasing LCSS severity, as shown with the MSS. The addition of N to GC was increasingly effective as severity increased, providing the greatest survival benefit in patients with more severe symptoms or more severely reduced functional ability or quality of life. This observation suggests baseline LCSS can provide information supporting treatment choice. Clinical trial information: NCT00981058.

Afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: Patient-reported outcome (PRO) data from the LUX-Lung 8 Phase III global trial. First Author: Shirish M. Gadgeel, Karmanos Cancer Center, Detroit, MI

Background: A is an irreversible ErbB family blocker that has shown clinical activity in pts with SCC of the head/neck and lung. The LUX-Lung 8 Phase III global trial compared A and E in pts with SCC of the lung following failure of platinum-based chemotherapy. Between Mar 2012 and Jan 2014, 795 stage IIIB/IV SCC pts were randomized 1:1 to receive A (40 mg/day) or E (150 mg/day) until progression. The primary endpoint of PFS, assessed after 414 events, was significantly higher for A than E (median: 2.4 vs 1.9 months; HR [95% CI]: 0.82 [0.68–1.00]; p = 0.04). PRO analyses of the PFS dataset are presented here. Updated PRO analysis of the OS dataset (to be undertaken after 632 deaths) will be available at the meeting. Methods: PROs were collected every 28 days until progression using the EORTC QLQ-C30/LC13 questionnaires. Percentage of pts improved on therapy, time-to-deterioration (TDD) and changes over time were analyzed for the pre-specified SCC symptoms: cough, dyspnea, and pain. Results: Improvement in global health status (GHS)/QoL was significantly greater with A than E (36.4 vs 27.1%; p = 0.026). More pts had an improvement in cough with A vs E (43.6 vs 32.6%; p = 0.010). The proportion of pts with improvements in dyspnea and pain were 49.4 vs 44.8% and 37.5 vs 37.5% with A and E, respectively. There were no significant differences in TDD of symptoms between treatment groups. However, trends favoring A were reported for dyspnea (HR [95% CI]: 0.82 [0.66–1.01]), fatigue (HR [95% CI]: 0.89 [0.73–1.09]), physical (HR [95% CI]: 0.81 [0.64–1.02]), and role (HR [95% CI]: 0.83 [0.67–1.03]) functioning. Changes in mean scores over time significantly favored A for dyspnea (p = 0.002) and fatigue (p = 0.04), including chest pain, as well as fatigue (p = 0.006) and role (p = 0.001) functioning. Conclusions: Compared to E, A improved SCC symptoms, SCC symptoms over time, and overall GHS/QoL. PRO analyses of LUX-Lung 8 complement the significant improvement observed in PFS with second-line A vs E in pts with SCC of the lung; Clinical trial information: NCT01523587.
Impact of crizotinib on patient-reported general health status compared with chemotherapy in patients with no prior systemic treatment for advanced non-squamous ALK-positive NSCLC.

Methods: Patients in the phase III PROFILE 1014 study (Pfizer; NCT01154140) were randomized to crizotinib (250 mg PO BID n = 172) or chemotherapy (pemetrexed + cisplatin n = 172) and followed up to progression or discontinuation. The primary end point is PFS per RECIST 1.1 by central review. Secondary end points are ORR, OS, and safety. Enrollment is ongoing and will continue until approximately 300 patients are enrolled. Clinical trial information: NCT02142738.

Background: The present analysis compares patient-reported general health status between crizotinib and chemotherapy in patients who had received no prior systemic treatment for advanced non-squamous ALK-positive NSCLC. Patients with EGFRm advanced NSCLC.

The mean (SD) scores at baseline were comparable between crizotinib and chemotherapy for VAS (70.78 [19.65] vs 66.64 [21.89]) and EQ-5D index scores (0.72 [0.30]) vs (0.71 [0.26]). The proportion of patients reporting presence of a problem at baseline for crizotinib and chemotherapy respectively were: mobility (27% vs 34%), self-care (13% vs 13%), usual activities (44% vs 46%), pain (56% vs 68%), and anxiety/depression (41% vs 39%). The overall mean VAS scores on treatment were statistically significantly higher (p < 0.05) in the crizotinib arm compared with the chemotherapy arm. The overall mean EQ-5D index scores on treatment were significantly greater (p < 0.05) in the crizotinib arm compared with the chemotherapy arm. The overall mean EQ-5D index score for health status between crizotinib and chemotherapy in patients who had received no prior systemic treatment for advanced non-squamous ALK-positive NSCLC.

Recruitment is ongoing and will continue until approximately 300 patients are enrolled. Clinical trial information: NCT02142738.

Conclusion: Treatment with crizotinib leads to significantly greater overall general health status scores compared to chemotherapy in patients with NSCLC with EGFRm.

TPS802
Poster Session (Board #427a), Mon, 8:00 AM-11:30 AM
A randomized, phase III study (FLAURA) of AZD9291, a novel EGFR-TKI, versus gefitinib or erlotinib in treatment-naive patients with advanced non-small cell lung cancer (NSCLC) that expresses programmed cell death ligand 1 (PD-L1).

First Author: Suresh S. Ramalingam, The Winship Cancer Institute of Emory University, Atlanta, GA

Background: EGFR-TKI is the recommended treatment for advanced NSCLC for which have an EGFR-TKI-sensitizing mutation (EGFRm). However, most patients develop resistance, and in ~60% of cases the EGFR T790M mutation is the cause. AZD9291 is an oral, potent, irreversible EGFR-TKI selective for EGFRm and T790M mutations. Preliminary data from a Phase I/II study demonstrated clinical activity and a manageable tolerability profile for AZD9291 as first-line treatment of patients with EGFRm advanced NSCLC. Eligible patients must have pathologically confirmed adenocarcinoma harboring an EGFR Ex19del or L858R mutation, alone or in combination with another EGFRm, determined by local (accredited laboratory) or central testing. Patients ≥ 18 years of age (≥ 20 in Japan), WHO performance status 0–1, will be randomized 1:1 to receive either AZD9291 or SoC EGFR-TKI, stratified by mutation status (Ex19del or L858R) and race (Asian versus non-Asian), until RECIST v1.1 defined progression or a discontinuation criterion is met. Patients may continue randomized treatment beyond RECIST defined progression if they continue to show clinical benefit, as judged by the Investigator. The primary objective is to compare progression-free survival (PFS) for AZD9291 to SoC EGFR-TKI. PFS in patients with tumors harboring T790M is a key secondary objective. The secondary objectives include PFS by Ex19del or L858R detectable in circulating tumor DNA, objective response rate, duration of response, disease control rate, depth of response, overall survival, PK, health-related quality of life, patient satisfaction with treatment, and the safety and tolerability profile of AZD9291 compared with SoC EGFR-TKI. The study was opened to accrual in November 2014. Clinical trial information: NCT02296125.

TPS804
Poster Session (Board #428a), Mon, 8:00 AM-11:30 AM
A phase III study of MEDI4736 (M), an anti-PD-L1 antibody, in monotherapy or in combination with Tremelimumab (T), versus standard of care (SoC) in patients (pts) with advanced non-small cell lung cancer (NSCLC) who have received at least two prior systemic treatment regimens (ARC-TIC). First Author: David Planchard, Gustave Roussy, Villejuif, France

Background: M is a human IgG1 mAb that blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1 and CD80 with high affinity and selectivity. T is a soluble human IgG2 mAb inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA-4). Both M and T are monoclonal antibodies against PD-1, have shown antitumor activity as first-line therapy for NSCLC, particularly in patients whose tumors strongly express PD-L1.

Methods: In the international, open-label, multi-centre, phase III study (NCT02352948) is designed to evaluate the efficacy and safety of M vs SoC (gemcitabine, vinorelbine or erlotinib) in NSCLC pts with PD-L1-negative tumours (Sub-study B). Eligible pts include pts (PS of 0–1) with locally advanced or metastatic NSCLC, who have received at least 2 prior treatment regimens including 1 platinum-based chemotherapy. Pts with known EGFR mutations and ALK rearrangements are not eligible. Approximately 300 pts will be randomised 1:1 to receive M (300 mg qd) or SoC (gemcitabine, vinorelbine or erlotinib) in each NSCLC pts (pts) with advanced non-small cell lung cancer (NSCLC) (squamous vs nonsquamous), and region (Asia vs rest of world). Pathways may have additive or synergistic antitumor activity. Furthermore the Phase I/II dose-escalation/expansion study of M+T in advanced NSCLC (NCT02000947) shows a manageable safety, and early signs of clinical activity. The study was opened to accrual in November 2014. Clinical trial information: NCT02296125.

TPS103
Poster Session (Board #427b), Mon, 8:00 AM-11:30 AM
KEYNOTE-024: Phase III trial of pembrolizumab (MK-3475) vs platinum-based chemotherapy as first-line therapy for patients with metastatic non-small cell lung cancer (NSCLC) that expresses programmed cell death ligand 1 (PD-L1). First Author: Julie R. Brahmer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: The current standard-of-care first-line therapy for patients with advanced NSCLC who lack EGFR sensitizing mutations or an ALK translocation is platinum-based combination chemotherapy with or without maintenance therapy. Median OS with platinum-based chemotherapy ranges from 10-12 months. Pembrolizumab, a humanized monoclonal antibody against PD-1, has shown antitumor activity as first-line therapy for NSCLC, particularly in patients whose tumors strongly express PD-L1.

Methods: In the international, open-label, multi-centre, phase III KEYNOTE-024 trial (NCT02142738), adults with previously untreated, advanced NSCLC without EGFR sensitizing mutations or ALK translocation that expresses PD-L1 (PD-L1) in ≥ 50% of tumor cells are randomized 1:1 to receive a 200-mg fixed dose of pembrolizumab intravenously every 3 weeks or investigator’s choice platinum-based combination chemotherapy (carboplatin or cisplatin with pemetrexed or gemcitabine or carboplatin with paclitaxel). Patients with lung tumours NSCLC may receive pemetrexed maintenance therapy, PD-L1 expression is determined by immunohistochemistry at a central laboratory. Randomization is stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and region (Asia vs rest of world). Pembrolizumab will be given for up to 35 cycles or until disease progression, intolerance to therapy, or withdrawal of consent. Pembrolizumab recipients who experience disease progression after completing 35 cycles or who stop treatment after achieving complete response may be eligible for 1 year of pembrolizumab retreatment. Patients assigned to chemotherapy who experience progression may cross over to receive pembrolizumab. Tumor response is assessed every 9 weeks by RECIST 1.1 per central review. AEs will be monitored throughout the study and graded according to NCI CTCAE v4.0. Primary end point is PFS per RECIST 1.1 by central review. Secondary end points are ORR, OS, and safety. Enrollment is ongoing and will continue until approximately 300 patients are enrolled. Clinical trial information: NCT02142738.
Eligible pts with advanced PD-L1/H11001 chemotherapy as first-line therapy for PD-L1 phase 3 KEYNOTE-042 trial (ClinicalTrials.gov, NCT02220894) will ongoing after a median follow-up of 36 wk. The randomized, open-label naive, PD-L1

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TPS8109  Poster Session (Board #430b), Mon, 8:00 AM-11:30 AM
TIGER-3: A phase 3, open-label, randomized study of rociletinib vs cytotoxic chemotherapy in patients (pts) with mutant EGFR non-small cell lung cancer (NSCLC) progressing on prior EGFR TKI therapy and platinum-based doublet chemotherapy. First Author: James Chih-Hsin Yang, Department of Oncology, National Taiwan University Hospital; Graduate Institute of Oncology & Cancer Research Center, National Taiwan University, Taipei, Taiwan

Background: Rociletinib is a small molecule inhibitor that selectively targets mutant EGFR and has been shown in preclinical studies to inhibit L858R, del19 and T790M while sparing wild-type EGFR. TIGER-X, a phase 1/2 dose-ranging trial, has provided evidence that rociletinib is associated with durable response and is well tolerated in pts with NSCLC and positive T790M status following progression on a TKI. TIGER-3 is designed to investigate single agent rociletinib vs chemotherapy in pts who have failed EGFR therapy and platinum-based doublet chemotherapy, a setting of acquired resistance and a high unmet need of targeted therapeutic options. TIGER-3 will evaluate pts with T790M positive and negative status based on blood and tumor tissues, and biomarkers of response or resistance. Methods: Pts with histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC, with radiological progression on the most recent therapy will be enrolled in a phase 3, randomized, open-label study (NCT02322281). Pts must have documented evidence of a tumor with ≥ 1 EGFR activating mutations excluding exon 20 insertion, and prior treatment with an EGFR TKI and platinum-containing doublet chemotherapy. Pts will be randomized 1:1 to receive rociletinib twice daily or single agent cytotoxic chemotherapy (investigator choice specified before randomization) until disease progression according to RECIST 1.1. Pts will be stratified by presence or absence of brain metastases, EOG performance status (0 vs 1), and race (Asian vs non-Asian). The primary endpoint is progression-free survival (PFS). Secondary endpoints include objective response rate, duration of response, disease control rate, and overall survival. Kaplan-Meier methodology will assess time to event variables. The stratified log-rank and the hazard ratio (HR) will be used for comparing PFS distributions. Survival analysis will be carried out based on standard adverse event reporting. Planned enrolment is 600 pts with study start planned by end of May 2015. Sequist LV J Clin Oncol. 2014 Clinical trial information: NCT02322281.

TPS8110  Poster Session (Board #431a), Mon, 8:00 AM-11:30 AM
IFCT-1003 LADIE trial: Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-estrogen in women with non-squamous advanced stage NSCLC. First Author: Julien Mazières, Hôpital Larrey CHU Toulouse, Toulouse, France

Background: The incidence of lung cancer is increasing dramatically in women and displays some specific epidemiological, radiological, clinical and pathological characteristics. Two main mechanisms emerged from recent findings in the field of lung carcinogenesis in women: the preferential involvement of the EGFR pathway and the potential impact of hormonal factors. The interaction of estrogen receptors with growth factor receptor signalling has also been shown. Preclinical data have shown that the combination of an EGFR-Tyrosine Kinase Inhibitor (TKI) with an anti-estrogen could overcome resistance to EGFR-TKI by postponing the reactivation of the PI3K-AKT pathway through the estrogen-mediated non-genomic pathway. Methods: We launched an open-label phase II randomized trial dedicated to women with advanced stage adenocarcinoma. Patients are treated by gefitinib (250 mg/d) vs. gefitinib + fulvestrant 500 mg MI / month (with a supplementary dose at day 15) in the EGFR mutated group (EGFR +) in first or second line setting and by erlotinib (150 mg/d, according to marketing authorization at trial initiation) vs. erlotinib + fulvestrant in the EGFR wild-type group (EGFR WT) in second or third line setting. Treatments are given until progression or unacceptable toxicity. Follow-up is performed in both arms every month to minimize the potential bias due to monthly fulvestrant injection. Primary objective is progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR + patients, respectively. Secondary objectives are safety, overall survival and quality of life. Exploratory objective is biomarkers analysis. The main inclusion criteria are histologically-confirmed non-squamous NSCLC, available tumor tissue for EGFR mutation analysis, post-menopausal women, PS 0-2. The study has been approved by all ethical committees. First patients have been enrolled in May 2012. To date, 223 patients (89 EGFR +, 134 EGFR WT) have been enrolled and 394 (204 EGFR +, 190 EGFR WT) are expected. Clinical trial registry number NCT01556191. Clinical trial information: NCT01556191.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: MOR208 is an Fc-engineered humanized monoclonal antibody that targets the B-cell-specific antigen, CD19. There remains a high unmet medical need for new therapies for patients (pts) with relapsed or refractory (R-R) B-cell NHL. Methods: This is a non-randomized, open-label, multicenter, two-stage, phase Ila study of MOR208 in pts with R-R NHL previously treated with rituximab, who were not candidates for high-dose chemotherapy with stem cell support. Adult pts with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), or other indolent NHL (iNHL), were treated with single-agent MOR208, 12 mg/kg intravenously, weekly, over two 28-day cycles. Pts with at least stable disease by the 2007 International Response Criteria were to continue MOR208 treatment for another cycle. Pts with complete or partial response (CR or PR) could then receive maintenance MOR208 every 2 or 4 weeks, depending on investigator decision, until progression. Overall response rate (ORR) was the primary endpoint. Results: By 17 November 2014, all pts (n = 89) had been enrolled (DLBCL, n = 35; FL, n = 31; MCL, n = 12; iNHL, n = 11). Thirty-five (39%) pts were female, median age 67 (range 35–90), 78 (88%) had stage III–IV disease, and the median number of prior lines of therapy was 2 (1–4). The mean number of cycles completed was 2.2 (0–3). The investigator-assessed ORR across all NHL subtypes was 22% (20/89) with clinical activity seen in the DLBCL (26% [9/35]; 2 CR, 7 PR; preliminary median duration of response (mDoR) 7.7 months), FL (23% [7/31]; 1 CR, 6 PR; preliminary mDoR 2.6 months) and iNHL (36% [4/11]; 1 CR, 3 PR) cohorts (MCL, 0/12 responses). Grade 3/4 adverse events (AEs) per CTCAE V4.03. AEs G3/4 presented. Clinical trial information: NCT01691898. Results: As of Feb 2015, 10 pts were evaluable for safety: 4 follicular (FL), 3 CLL/SLL, 1 marginal zone (MZL), 1 mantle cell (MCL) and 1 Richter’s DLBCL. Med age 61 yo (range 51–76); 8 M/2 F; median prior Tx 3 (range 1–4). No DLTs have occurred up to the current dose (600 mg TGR-1202). AEs (all causality) included: diarrhea, constipation and fatigue (30% each, no G 3/4). Dan 1 patient related reactions at 20% (no G 3/4) and neutropenia at 20% with 1 event G 3/4. 7 pts were evaluable for efficacy. ORR was 86% with all pts except the Richter's responding (FL 2), CLL/SLL (2), MZL (1) and MCL (1). All responses were observed by week 8 (1 CR / 5 PR's). Patients remain on study from 1 – 5+ months. Conclusions: To date, this is the first combination of an anti-CD20, a PI3K and a BTK inhibitor. UTX + TGR-1202 + ibrutinib was well tolerated with significant early activity across heavily pre-treated and high-risk B-cell malignancies. Dose escalation continues with TGR-1202 at 800mg. Based upon the early activity of the triplet, Ph II studies are planned. Clinical trial information: NCT02006485.

8500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM
Phase Ila study of single-agent MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL). First Author: Wojciech Jurczak, Jagiellonian University, Krakow, Poland

8501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM
Safety and activity of the chemotheraphy-free triplet of ublituximab, TGR-1202, and ibrutinib in relapsed B-cell malignancies. First Author: Natalie M. Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Multiple novel targeted agents are emerging for B-cell malignancies, but few studies have successfully and safely combined these agents. Ublituximab (UTX) is a novel glycoengineered mAb targeting a unique epitope on the CD20 antigen. TGR-1202 is a next generation, once daily, PI3Kδ inhibitor, active in patients (pts) with rel/ref hematologic malignancies (Burris, 2014). This Phase 1 trial evaluated the safety of the first triplet combination of a novel anti-CD20 + PI3Kδ + BTK inhibitor in pts with B-cell malignancies. Methods: Eligible pts had rel/ref CLL (including Richter's) or B-cell NHL with an ECOG PS ≤ 2 w/o limit to number of prior therapies. Pts refractory to prior PI3Kδ or BTK were eligible. CLL & NHL cohorts were evaluated independently in a 3 + 3 dose escalation design to evaluate safety and dose limiting toxicities (DLT). UTX was dosed at 900mg on D 1, 8, 15 of Cy 1 & 2 and D 1 on Cy 4, 6, 9 & 12. TGR-1202 was dose escalated (400mg, 600mg, 800mg, 1200mg). Ibrutinib was dosed at 420mg (PLL) and 560mg (NHL). Preliminary efficacy was examined (CLL per Hallek 2008 / NHL per Cheson 2007). Results: As of Feb 2015, 10 pts were evaluable for safety: 4 follicular (FL), 3 CLL/SLL, 1 marginal zone (MZL), 1 mantle cell (MCL) and 1 Richter's DLBCL. Med age 61 yo (range 51–76); 8 M/2 F; median prior Tx = 3 (range 1–4). No DLTs have occurred up to the current dose (600 mg TGR-1202). AEs (all causality) included: diarrhea, constipation and fatigue (30% each, no G 3/4). Dan 1 patient related reactions at 20% (no G 3/4) and neutropenia at 20% with 1 event G 3/4. 7 pts were evaluable for efficacy. ORR was 86% with all pts except the Richter's responding (FL 2), CLL/SLL (2), MZL (1) and MCL (1). All responses were observed by week 8 (1 CR / 5 PR's). Patients remain on study from 1 – 5+ months. Conclusions: To date, this is the first combination of an anti-CD20, a PI3K and a BTK inhibitor. UTX + TGR-1202 + ibrutinib was well tolerated with significant early activity across heavily pre-treated and high-risk B-cell malignancies. Dose escalation continues with TGR-1202 at 800mg. Based upon the early activity of the triplet, Ph II studies are planned. Clinical trial information: NCT02006485.
8504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Evaluation of complete response rate at 30 months (CR30) as a surrogate for progression-free survival (PFS) in first-line follicular lymphoma (FL) studies: Results from the prospective analysis of the Follicular Lymphoma FLASH Analysis of Surrogacy Hypothesis (FLASH) analysis with individual patient data (IPD) of 3,837 patients (pts). First Author: Daniel J. Sargent, Mayo Clinic, Rochester, MN

Background: Although PFS is the standard endpoint for new drug approvals in first-line FL, advances in efficacy (median PFS >7 y) coupled with the indolent nature of FL necessitate extended patient follow-up in clinical trials. The FLASH group conducted a meta-analysis to examine whether treatment effects on CR30, an earlier endpoint, could accurately predict treatment effects on PFS. Methods: Correlation of CR30 odds ratio (OR) with PFS hazard ratio (HR) was evaluated using both linear regression (R²_WLS) and copula bivariate (R²_Copula) models. Prespecified criteria for CR30 surrogacy required either R²_WLS > 0.80 or R²_Copula > 0.85, with a lower bound of the 95% confidence interval (CI) ≥ 0.60, with neither estimate < 0.70. The minimum CR30 difference to predict significant PFS difference was calculated. Results: Data from 13 randomized first-line trials (8 induction, 5 maintenance trials) with IPD for 3837 pts were included. The prespecified threshold for surrogacy was met: R²_WLS of 0.88 (95% CI, 0.77-0.96) and R²_Copula of 0.86 (95% CI, 0.72-1.00), Table), supporting the hypothesis that treatment effects on CR30 predict effects on PFS in pts with previously untreated FL. Multiple sensitivity and IPD surrogacy analyses supported the robustness of the primary analysis. A minimum 10% absolute improvement in CR30 over a control CR30 of 50% predicted significant improvement in PFS. Conclusions: This large IPD meta-analysis of chemo/immunotherapy trials establishes CR30 as a surrogate endpoint for PFS in first-line FL trials and supports its use to expedite therapeutic development.

Trial type Trials, N (pts) R²_WLS (95% CI)* R²_Copula (95% CI)*
Overall 13 (3837) 0.88 (0.77-0.96) 0.86 (0.72-1.00)
Rituximab included 9 (2661) 0.89 (0.75-0.97) 0.89 (0.75-1.00)
No Rituximab 4 (986) 0.91 (0.05-1.00) 0.96 (0.90-1.00)
Maintenance 8 (1630) 0.93 (0.84-1.00) 0.89 (0.71-1.00)

8505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Brentuximab vedotin plus AVD for non-bulky limited stage Hodgkin lymphoma: A Phase II trial. First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA

Background: ABVD plus radiation is standard therapy for limited HL, but carries risks of bleomycin-lung injury and radiotoxicity. Brentuximab vedotin is highly active in relapsed HL. We evaluated brentuximab plus AVD (A-ABD) for non-bulky stage I-II HL. Methods: This is a multicenter phase 2 study. Patients received a lead in cycle of brentuximab monotherapy 1.2 mg/kg on days 1 and 15, followed by a PET scan. Patients then received 4 cycles of A-ABD, based on interim PETCT. The primary endpoint was complete response rate (CRR). A sample size of 34 was required to detect a CRR of 93% with 91% power and alpha error of 0.10. Results: 34 patients were enrolled. Median age was 36 (20–75). Risk was easily favorable in 62%, unfavorable in 38%. The best CRR was 100%. After the monotherapy lead in, 18/34 patients (53%) were in CR. After 2 cycles of A-ABD, 33 were in CR (97%), and 1 was removed for toxicity. At end of treatment (EOT), 30 (88%) were in CR, 2 were interpreted as progressive disease (PD), and 2 were removed for toxicity. At EOT, 8 subjects had PET scans interpreted as positive on central review, 6 of which were felt to be reactive by investigators. All 6 subjects were in confirmed CR on brief follow-up scan with no intervening therapy, confirming false positive scans. Two cases were considered PD at EOT, 1 of whom received 2 further cycles of AVD alone and was back in CR, suggesting that scan may also have been a false positive. At a median follow-up of 14 months, the PFS and OS are 90% and 97%. The most common adverse events were peripheral neuropathy (74%), fatigue (71%), nausea (24%), neutropenia (68%), anemia (56%), constipation (56%), diarrhea (35%), abdominal pain (32%), ALT elevation (29%) and febrile neutropenia (29%). Grade 3-4 toxicity occurred in 26/34 patients: neutropenia (56%), febrile neutropenia (29%) and peripheral neuropathy (24%). One elderly patient died of neutropenic sepsis in the first A-ABD cycle. One patient was removed for grade 2 hypersensitivity despite premedication. Brentuximab reductions were required in 38%, most for peripheral neuropathy. Conclusions: A-ABD x 4 produced a high CRR but with more toxicity than expected from AVD alone. False positive PET scans were common on EOT imaging and warrants further attention. Clinical trial information: NCT01534078.

8506 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Allogeneic or autologous transplantation as first-line therapy for younger patients with peripheral T-cell lymphoma: Results of the interim analysis of the AATT trial: First Author: Norbert Schmitz, Asklepios Hospital St. Georg, Hamburg, Germany

Background: AlloSCT gives encouraging results in pts with relapsed PTCL. We did the AATT (Allogeneic or Autologene Transplantation in T-Cell Lymphoma) study in newly diagnosed PTCL and present results of an interim analysis leading to termination of the trial. Methods: We compared alloSCT with autSCT in younger pts with PTCL. Pts were randomized after enrollment. Treatment was four courses of CHOP-E4. Pts achieving CR/PR/SD proceeded to HDAP and stem cell collection in pts randomized to autSCT or without suitable (HLA 10/10) donor. BEAM high-dose therapy and autSCT or myeloablative conditioning and alloSCT followed within 4-6 weeks. Results: 58/104 pts were eligible: median age was 50 yrs, 64% of pts were male. 11/30 pts randomized to autSCT did not proceed to transplantation because of progressive disease / no response (n=8), infection (n=1) or change of histology (n=2). 13/28 pts (46%) randomized to alloSCT received it. Fifteen pts were not allografted due to progressive disease (n=10) or lack of a fully matched donor (n=5). Twenty-one pts have died 68-705 days after randomization. Twelve pts died of lymphoma (7 in the auto and 5 in the allo arm), 2 pts died from salvage therapy (1 in each arm) and 1 pt from EBV-pos PTLD. Two allografted pts died early (d 21, +65) and 2 late from infections (d +549, +577). Two pts died from acute GVHD (d +24, d +85). One-year event-free survival was 41% (95% CI 24%, 54%). FAQs will be answered to the best of our knowledge for the target population. Conclusions: This pre-planned interim analysis showed no significant survival differences for pts randomized to autSCT or alloSCT. 38% of randomized pts did not proceed to transplantation mostly because of early lymphoma progression. A conditional power calculation showed a low probability that the primary endpoint (25% EFS improvement by allo SCT) could still be met. The data safety monitoring board decided to prematurely stop patient accrual.

Methods:
PET scans were common on EOT imaging and warrants further attention. First Author: Norbert Schmitz, Asklepios Hospital St. Georg, Hamburg, Germany

Background: AlloSCT gives encouraging results in pts with relapsed PTCL. We did the AATT (Allogeneic or Autologene Transplantation in T-Cell Lymphoma) study in newly diagnosed PTCL and present results of an interim analysis leading to termination of the trial. Methods: We compared alloSCT with autSCT in younger pts with PTCL. Pts were randomized after enrollment. Treatment was four courses of CHOP-E4. Pts achieving CR/PR/SD proceeded to HDAP and stem cell collection in pts randomized to autSCT or without suitable (HLA 10/10) donor. BEAM high-dose therapy and autSCT or myeloablative conditioning and alloSCT followed within 4-6 weeks. Results: 58/104 pts were eligible: median age was 50 yrs, 64% of pts were male. 11/30 pts randomized to autSCT did not proceed to transplantation because of progressive disease / no response (n=8), infection (n=1) or change of histology (n=2). 13/28 pts (46%) randomized to alloSCT received it. Fifteen pts were not allografted due to progressive disease (n=10) or lack of a fully matched donor (n=5). Twenty-one pts have died 68-705 days after randomization. Twelve pts died of lymphoma (7 in the auto and 5 in the allo arm), 2 pts died from salvage therapy (1 in each arm) and 1 pt from EBV-pos PTLD. Two allografted pts died early (d +21, +65) and 2 late from infections (d +549, +577). Two pts died from acute GVHD (d +24, d +85). One-year event-free survival was 41% (95% CI 24%, 54%). FAQs will be answered to the best of our knowledge for the target population. Conclusions: This pre-planned interim analysis showed no significant survival differences for pts randomized to autSCT or alloSCT. 38% of randomized pts did not proceed to transplantation mostly because of early lymphoma progression. A conditional power calculation showed a low probability that the primary endpoint (25% EFS improvement by allo SCT) could still be met. The data safety monitoring board decided to prematurely stop patient accrual.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Carfilzomib and dexamethasome (Kd) vs bortezomib and dexamethasome (Vd) in newly diagnosed multiple myeloma (RMM): Results from the phase III study ENDEAVOR. First Author: Meletios A. Dimopoulos, National and Kapodistrian University of Athens, Athens, Greece

Background: ENDEAVOR (NCT01568866) is comparing Kd with Vd in pts with RMM. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), overall response rate (ORR), rate of peripheral neuropathy (PN), and safety. Methods: Adults with RMM and 1–3 prior treatments were eligible; planned enrollment was 888 pts who were randomized and stratified by prior V or K or V vs vs K, then by line of treatment (1 vs 2–3), ISS stage (1 vs 2–3), and intended route of V vs SC. The Kd arm received K (30-min IV infusion) on days (D) 1, 2, 8, 9, 15, and 16 of a 28-day cycle (20 mg/m² on D1 and 2 (cycle 1); 56 mg/m² thereafter) and dexamethasone (DEX; 20 mg) on D1, D2, 8, 9, 15, 16, 22, and 23. The Vd arm received V (1.3 mg/m²; IV or SC on D1, 4, 8, and 11 of a 21-day cycle) and dex (20 mg) on D1, 2, 4, 5, 8, 9, 11, and 12. Cycles were repeated until disease progression or unacceptable toxicity.

Results: Data are presented for Kd then Vd. In total, 929 pts (Kd: 464; Vd: 465) from 27 countries were randomized. In the Vd arm, 83.6% of pts received SC V. At the preplanned interim analysis, median exposure was 39.9 and 26.8 weeks. Kd showed a significant improvement in median PFS vs Vd (18.7 months [mo] vs 9.4 mo; hazard ratio [HR] = 0.53; P < 0.0001). OS data were immature (75 and 88 deaths) and continue to be followed. ORRs were 76.9% and 62.6% (P < 0.0001); 54.3% and 28.6% had a very good partial response or better, and 12.9% and 4% of pts had a complete response or better. Treatment discontinuation due to adverse events (AE) occurred in 14.0% and 15.7% of pts. On-study death due to an AE occurred in 3.9% and 3.4% of pts. AEs of interest (grade ≥ 3) included hypothyroidism (10.2% vs 4.9%), diabetes (7.8% vs 4.2%), and renal failure (grouped term; 4.1% vs 2.6%). Rates of grade ≥ 2 PN (grouped term) were 6.3% vs 32.0% (P < 0.0001). Conclusion: Kd demonstrated statistically significant and clinically meaningful superiority over Vd in RMM, with a two-fold improvement in median PFS. In addition, Kd had a favorable benefit-risk profile; these data suggest that Kd is a potentially best-in-class agent for RMM. Clinical trial information: NCT01568866.
The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
Pre-infusion chemotherapy regimens were EPOCH (2); cyclophosphamide 20 mg/m2 and fludarabine 150 mg/m2. Twenty pts received CTL019 per protocol dose (12 DLBCL; 7 FL; 1 MCL). The median prior therapies were 4 (range: 1-8), and pts with prior ASCT 9 (31%). At enrollment, stages were: IV, 16 pts (55%); II, 3 pts (17%); 11, 6 pts (21%); IE, 2 pts (7%); LDH was increased in 20 pts (69%). Eight pts are not evaluable for response (DLBCL 7; FL 1): 3 pts removed from study before T cell infusion due to progressive disease; 1 pt withdrew consent; 3 pts had adequate T cell expansion; 1 pt received < protocol specified dose. Twenty pts received CTL019 per protocol dose (12 DLBCL; 7 FL; 1 MCL). Pre-infusion chemotherapy regimens were EPOCH (2); cyclophosphamide (9); radiation + cyclophosphamide (2); bendamustine (6); cyclophosphamide-fludarabine (1). Cytokine release syndrome occurred in 15 pts (13 evaluable for response (DLBCL 7; FL 1): 3 pts removed from study before T cell infusion due to progressive disease; 1 pt withdrew consent; 3 pts had adequate T cell expansion; 1 pt received < protocol specified dose). Twenty pts received CTL019 per protocol dose (12 DLBCL; 7 FL; 1 MCL). Pre-infusion chemotherapy regimens were EPOCH (2); cyclophosphamide (9); radiation + cyclophosphamide (2); bendamustine (6); cyclophosphamide-fludarabine (1). Cytokine release syndrome occurred in 15 pts (13 evaluable for response (DLBCL 7; FL 1): 3 pts removed from study before T cell infusion due to progressive disease; 1 pt withdrew consent; 3 pts had adequate T cell expansion; 1 pt received < protocol specified dose).

Conclusions: CTL019 cells induce durable responses in pts with r/r DLBCL and FL with high complete response (CR) rates and low progression-free survival.

**Background:** Eomesodermin is a master regulator of T cell effector function in the generation of cytotoxic CD8+ T cells. We sought to determine whether Eomesodermin expression correlates to activity of T cells against hematologic malignancies.

**Methods:** We performed a single institution, prospective, open label study to evaluate whether Eomesodermin expression in peripheral blood mononuclear cells (PBMCs) is a predictor of response to anti-CD19 CAR T cells. PBMCs were collected at baseline and post-infusion from 26 patients with r/r B cell malignancies. The primary end point was objective response to CAR T cells.

**Results:** Baseline Eomesodermin expression was significantly lower in patients who had a complete or partial response compared to non-responders. The trend in change in expression was significant at post-infusion. In univariable analysis, the hazard ratio (HR) for achieving a complete response decreased from 0.92 [95% confidence interval (CI): 0.84-0.99] to 0.78 [95% CI: 0.70-0.86] after adjustment for CD38 and bet2 expression.

**Conclusions:** Eomesodermin expression may serve as a predictive marker for response to anti-CD19 CAR T cells.

**Background:** One of the key challenges in cancer treatment is the resistance to therapy that is frequently observed in cancer patients. T cells are pivotal immune cells that recognize and kill tumor cells through their surface receptors. However, T cells often fail to recognize tumor cells due to the presence of tumor-specific antigens that are not displayed on the cell surface. This is known as tumor immune escape (TIE). TIE is a major mechanism by which cancer cells evade the immune system and accumulate drug-resistant clones. TIE can be overcome by activating the T cells and enabling them to recognize and kill tumor cells. This is achievable using CAR T cells, which are T cells engineered with chimeric antigen receptors (CARs) that recognize tumor-specific antigens.

**Methods:** In this study, we performed a retrospective analysis of 26 patients with r/r B cell malignancies who received CTL019 cells at our institution. We evaluated the expression of Eomesodermin in PBMCs at baseline and post-infusion. The primary end point was objective response to CAR T cells.

**Results:** Baseline Eomesodermin expression was significantly lower in patients who had a complete or partial response compared to non-responders. The trend in change in expression was significant at post-infusion. In univariable analysis, the hazard ratio (HR) for achieving a complete response decreased from 0.92 [95% confidence interval (CI): 0.84-0.99] to 0.78 [95% CI: 0.70-0.86] after adjustment for CD38 and bet2 expression.

**Conclusions:** Eomesodermin expression may serve as a predictive marker for response to anti-CD19 CAR T cells.

**Background:** In the phase III randomized, placebo-controlled AETHERA trial, patients with CD19+ acute lymphoblastic leukemia (ALL) who were in first complete remission (CR1) were randomized to receive brentuximab vedotin (BV) or placebo every 3 weeks for up to 16 cycles. The primary endpoint was PFS per investigator assessment.

**Methods:** A total of 329 patients were randomized to receive BV 1.8 mg/kg q3wk (n = 164) or placebo (n = 165) or up to 16 cycles. The primary endpoint was PFS per investigator assessment. Multivariate analyses of PFS by investigator assessment.

**Results:** The median age was 16.5 years, 58% male, and 70% had CD19+ ALL. The most common grade 3 and 4 adverse events were febrile neutropenia (21%), anemia (17%), thrombocytopenia (13%), and infection (12%). Overall, 31% of patients had grade 3 or 4 adverse events. The most common grade 3 and 4 adverse events were febrile neutropenia (21%), anemia (17%), thrombocytopenia (13%), and infection (12%). Overall, 31% of patients had grade 3 or 4 adverse events.
8520 Poster Discussion Session; Displayed in Poster Session (Board #337), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Interim analysis of a phase I study of INCB040093, a PI3Kδ inhibitor, alone or in combination with INCB039110, a selective JAK1 inhibitor, in patients (pts) with relapsed or refractory (r/r) B-cell malignancies. First Author: Tyecl Jovelle Phillips, University of Michigan, Ann Arbor, MI

Background: Inhibiting the PI3K or JAK-STAT pathways may be therapeutic in B-cell malignancies due to their contribution to tumor growth and survival and effects on the tumor microenvironment. Blocking both pathways may be synergistic due to JAK-STAT augmentation of BCR activation of the NF-κB pathway. Methods: This ongoing dose escalation study with expansion cohorts enrolled adult pts with r/r B-cell malignancies. INCB040093 was given at doses between 100–300 mg QD or BID alone or 150–300 mg QD or BID with INCB039110 at 400–600 mg QD. Safety, efficacy, and pharmacodynamics were evaluated. Results: A total of 83 pts have been enrolled on the study with n = 20 on INCB040093 alone and 15 CLL/SSL n = 13; others n = 19. Median age was 61 and 70% were men. The median number of prior regimens was 4 and 24% underwent HSCT. Median exposure was 185 days (range: 5–491 + [ongoing]) for INCB040093 alone and 99 days (range: 6 – 337 + [ongoing]) for INCB040093 + INCB039110. The most common AEs were fatigue (28%), headache (19%), pyrexia (19%) and the most common grade ≥ 3 AE was pneumonia (6%). The most common laboratory abnormalities were liver enzyme elevations and cytopenias. One pt had a DLT on INCB040093 100 mg BID (GL bled secondary to gastric DLBCL regression). Doses of INCB040093 100 mg BID and INCB040093 100 mg BID + INCB039110 400 mg QD were selected for expansion cohorts based on the incidence of liver enzyme elevations with INCB040093 and cytopenias with INCB039110 + INCB040093 at higher doses. pAKT was decreased by ~90% at trough on INCB040093 and IL6-induced pSTAT3 was decreased an average of 65% on INCB039110. Of 75 pts thus far evaluated for a response, 28 responses have been reported. Notably, ORR of TCL was 43% (2 CR, 6 PR, 1 SD) at a median of 18 months. The selected dose was expanded to enroll additional cohorts of pts with r/r B-cell malignancies such as DLBCL and CHL, and a Phase II study in pts with r/r CHL was initiated. Clinical trial information: NCT01905813.

8522 Poster Discussion Session; Displayed in Poster Session (Board #339), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Prognostic index for chronic and smoldering types adult T-cell leukemia/lymphoma. First Author: Hiroo Katsuya, Fukukawa University, Fukukoa, Japan

Background: Adult T-cell leukemia/lymphoma (ATL) has been divided into 4 clinical subtypes: acute, lymphoma, chronic and smoldering. The prognostic index for patients with chronic and smoldering type ATL is better than the others, but they have not been treated uniformly because of diverse clinical courses even in the same clinical type. The aim of this study is to develop a novel prognostic index (PI) for chronic and smoldering type ATL. Methods: We conducted a nationwide retrospective survey of ATL patients in Japan newly diagnosed between 2000 and 2009. Among chronic and smoldering types, fully eligible 248 individuals were used for this analysis; this is a largest study in chronic and smoldering ATL. We randomly selected subjects equally into training and validation samples, and developed a PI. Results: In univariate analysis, gender, performance status, log10(soluble interleukin-2 receptor (sIL-2R)) as well as the number of neutrophil and lymphopenia showed P values lower than .05 in the training sample. A multivariate analysis was performed in factors above, and sIL-2R was only identified as an independent prognostic factor in the training sample. Using a regression coefficient of this variable, a prognostic model was formulated to identify different levels of risk: Indolent ATL-PI (ATL-PI < 1.5) x log10(sIL-2R (U/ml)). The values calculated by IATL-PI were formulated to identify different levels of risk: Indolent ATL-PI (ATL-PI < 1.5) x log10(sIL-2R (U/ml)). The values calculated by IATL-PI were stratified into 3 groups: low (ATL-PI < 1.5), medium (1.5 ≤ ATL-PI < 3), and high (ATL-PI ≥ 3). The median survival rates were 6.5, 1.5 and 1.1 years, respectively in the low, medium, and high risk groups, respectively in the validation sample. The Kaplan-Meier survival curve showed a significant difference in OS between the groups (log-rank test, P < .0001). Conclusion: This ongoing dose escalation study with expansion cohorts enrolled adult pts with r/r B-cell malignancies. INCB040093 alone and 99 days (range: 6–337 + [ongoing]) for INCB040093 + INCB039110. The most common AEs were fatigue (28%), headache (19%), pyrexia (19%) and the most common grade ≥ 3 AE was pneumonia (6%). The most common laboratory abnormalities were liver enzyme elevations and cytopenias. One pt had a DLT on INCB040093 100 mg BID (GI bleed secondary to gastric DLBCL regression). Doses of INCB040093 100 mg BID and INCB040093 100 mg BID + INCB039110 400 mg QD were selected for expansion cohorts based on the incidence of liver enzyme elevations with INCB040093 and cytopenias with INCB039110 + INCB040093 at higher doses. pAKT was decreased by ~90% at trough on INCB040093 and IL6-induced pSTAT3 was decreased an average of 65% on INCB039110. Of 75 pts thus far evaluated for a response, 28 responses have been reported. Notably, ORR of TCL was 43% (2 CR, 6 PR, 1 SD) at a median of 18 months. The selected dose was expanded to enroll additional cohorts of pts with r/r B-cell malignancies such as DLBCL and CHL, and a Phase II study in pts with r/r CHL was initiated. Clinical trial information: NCT01905813.

8523 Poster Discussion Session; Displayed in Poster Session (Board #340), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Updated analysis of CALGB/ECOG/BMT CTN 100104: Lenalidomide (Len) vs. placebo (PBO) maintenance therapy after single autologous stem cell transplant (ASCT) for multiple myeloma (MM). First Author: Sarah A. Holstein, Roswell Park Cancer Institute, Buffalo, NY

Background: CALGB 100104 studied Len vs. PBO maintenance following ASCT for newly diagnosed MM patients (pts), demonstrating improved time to progression (TTP), overall survival (OS) and increased progression free survival (PFS) for Len.Pts of progression free survival (PFS) for Len. Median OS has not been reached for the Len arm and is 86/128 PBO pts without PD chose to cross over to Len. Starting dose was 10 mg daily and was escalated to 15 mg daily after 3 months. Primary end point was TTP (time of progressive disease (PD) or death from any cause). After several interim analyses, the study was unblinded at 18 mos median follow-up and 86/128 PBO pts without PD chose to cross over to Len. Results: SPMs diagnosed after randomization but before PD included 14 hematologic and 11 solid tumor SPMs in the Len arm vs. 3 hematologic and 7 solid tumor SPMs in the PBO arm. Conclusion: There is an increased incidence of SPMs for Len compared to PBO. Post ASCT Len maintenance continues to demonstrate significantly improved TTP and OS. Clinical trial information: NCT00114101.

SPM Type

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PBO cross over to Len B-cell ALL(2) MDS (1) Endometrial (1) Melanoma (1) Invasive SCC (1) Ovarian/endometrial (1) Lung carcinoma (1)
FIRST study: Updated overall survival (OS) in stem cell transplant (SCT)-ineligible newly diagnosed multiple myeloma (NDMM) patients (pts) treated with continuous lenalidomide plus low-dose dexamethasone (Rd) vs melphanal, prednisone, and thalidomide (MPT). First Author: Thierry Facon, Service des Maladies du Sang Place de Verdun, Lille, France

Background: MPT is considered a standard treatment (Tx) option in many countries for SCT-ineligible pts with NDMM. The FIRST trial showed that continuous Rd improved progression-free survival (PFS) and was associated with an OS advantage vs MPT (Bennoubker, NEJM2014). This abstract presents an updated OS and safety analysis, not initially planned, but requested by regulatory authorities. Methods: SCT-ineligible NDMM pts were randomized 1:1:1 to Tx with continuous Rd (28-day cycles), Rd for 18 cycles (Rd18), or MPT for 12 cycles (42-day cycles). The primary endpoint was comparison of PFS (Rd vs MPT) based on IRAC review. Secondary endpoints included OS, overall response rate, and safety. Time from randomization to second progression or death (PFS2) was an additional analysis. Results: 1623 pts were randomized; 535 pts received continuous Rd, 541 received Rd18, and 547 received MPT. As of March 3, 2014, 91 pts remained on Tx with Rd, 697 pts (42.9%) have died (38.9% Tx with Rd, 42.1% with Rd18, and 47.7% with MPT). With a median follow-up of 45.5 mos, median OS was 58.9 vs 56.7 vs 48.5 mos for pts treated with continuous Rd, Rd18, and MPT, respectively (HR [95% CI]: 0.75 [0.62-0.90]). Average Tx duration for continuous Rd, Rd18, and MPT was 22.3 mos, 6.8 mos, and 5.1 mos, respectively. Discontinuation of lenalidomide vs thalidomide due to AEs was 22.6 vs 27.0%. Conclusions: In this updated analysis from the FIRST trial, OS benefit was maintained with continuous Rd and it was better tolerated vs MPT in SCT-ineligible NDMM pts. PFS2 improvements suggest benefit of continuing continuous Rd, though Rd18 confers similar OS but is associated with increased toxicity compared with MPT. Safety profile remained consistent with the interim analysis. These findings reinforce continuous Rd as a new standard of care for the studied population. Clinical trial information: NCT00689936.

8526 Posterior Discussion Session; Displayed in Poster Session (Board #343), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1. First Author: Jesus F. San Miguel, Clinica Universidad de Navarra, Pamplona, Spain

Background: Panobinostat (PAN) is a potent pan-deacetylase inhibitor (pDACi) that targets multiple biological pathways in multiple myeloma (MM), including epigenetics and protein metabolism. PAN + bortezomib (BTZ) and dexamethasone (Dex; PAN-BTZ-Dex) led to a clinically relevant and statistically significant increase in progression-free survival (PFS) of ~4 months compared with placebo + BTZ and Dex (PAN-BTZ-Dex) in patients (pts) with relapsed or relapsed and refractory MM in the PANORAMA 1 phase 3 clinical trial. Methods: The study design was described previously (San-Miguel, Lancet Oncol. 2014;15:1195-206). For this subanalysis, pts who received prior BTZ and IMiDs (lenalidomide or thalidomide) were analyzed for outcomes and safety. Results: A total of 193 pts (26%) received prior BTZ and IMiDs (PAN-BTZ-Dex [n = 94] or Pano-BTZ-Dex [n = 99]). Median PFS as determined by investigator assessment for the PAN arm was 10.6 mos (95% CI, 7.6-13.8) vs 5.8 mos (95% CI, 4.4-7.1) for the Pbo arm (HR 0.56 [95% CI, 0.39-0.80]; P = .0011). Most (76%) received 2 prior lines and the difference in PAN vs Pbo PFS increased in these pts: PAN arm (n = 73): 12.5 mos (95% CI, 7.3-14.0); Pbo arm (n = 74): 4.7 mos (95% CI, 3.7-6.1); HR 0.47 [95% CI, 0.32-0.71]; P = .0003). For all pts who received prior BTZ and IMiDs, overall response rate was 58.5% (95% CI, 47.9%-68.6%) vs 41.4% (95% CI, 31.6%-51.8%; P = .0179) and ≥ complete response rate was 22.3% (95% CI, 14.4%-32.1%) vs 9.1% (95% CI, 4.2%-16.6%) in the PAN and Pbo arms, respectively. Common grade 3/4 adverse events and laboratory abnormalities in each arm included thrombocytopenia (68.5% vs 48.0%), lymphopenia (50.0% vs 46.5%), neutropenia (35.9% vs 17.2%), diarrhea (11.0% vs 13.1%), and upper respiratory tract infection (12.0% vs 11.2%). The percentage of on-treatment deaths in each arm was similar (6.4% vs 5.1%). Conclusions: PAN-BTZ-Dex demonstrated efficacy, with an increased median PFS of 4.8 months among MM pts who received prior BTZ and IMiDs, demonstrating a clinical benefit in pts with a clear unmet need. The safety profile is consistent with that in the overall PANORAMA 1 population, although on-treatment deaths were similar. Clinical trial information: NCT0123308.

8527 Posterior Discussion Session; Displayed in Poster Session (Board #344), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Updated results from CHAMPION-1, a phase II/III study investigating weekly carfilzomib with dexamethasone for patients (Pts) with relapsed or refractory multiple myeloma (RRMM). First Author: James R. Berenson, Institute for Myeloma & Bone Cancer Research, Los Angeles, CA

Background: Carfilzomib (K) is a selective proteasome inhibitor that is approved for the treatment of relapsed and refractory multiple myeloma in the US. CHAMPION-1 (NCT01677858) is a multicenter, single-arm, phase II/III study evaluating the safety, efficacy, and optimal dose of carfilzomib with dexamethasone (dex; Kd) in pts with RRMM. Methods: Pts who received 1–3 prior regimens were eligible. In the phase 1 portion, pts received K as a 30-min IV infusion on days 1, 8, 15, and 21 of a 28-day cycle using a 3+3 dose-escalation scheme. Pts received K at 20 mg/m2 on day 1 of cycle 1; subsequent doses started at 45 mg/m2 and were escalated to 56, 70, or 88 mg/m2 until the maximum tolerated dose (MTD) was reached for use in the phase 2 portion. Pts received dex 40 mg (IV or oral) on days 1, 8, 15, and 22 of cycles 1–8; dex was omitted on day 22 in cycles ≥ 9. Kd was administered until disease progression or unacceptable toxicity. Results: The MTD was reported previously (70 mg/m2). As of Jan 1, 2014, 104 pts were enrolled at the MTD (phase 1, n = 15; phase 2, n = 89). Median pt age was 68.5 y (range, 41–88). Pts received a median of 1 prior regimen (range, 1–3); 82% of pts had received prior bortezomib (BTZ). A total of 48% of pts were BTZ-refractory, 28% were lenalidomide (LEN) refractory, and 16% were refractory to both BTZ and LEN. The median treatment duration in the ongoing study was 5.3 mo (range, 0.03–18.8). The overall response rate (≥ partial response) was 72% (95% confidence interval [CI]: 63%–81%); the clinical benefit rate (≥ minimal response) was 80% (95% CI: 71%–87%). Median PFS was 10.6 mo (95% CI: 7.2–not estimable). Survival was 85% (95% CI: 77%–93%) at 1 year. 57% of pts received subsequent treatment due to an adverse event (AE). The most common grade ≥ 3 AEs were fatigue (9%), thrombocytopenia (6%), dyspnea (6%), back pain (6%), anemia (5%), and acute renal failure (5%). Four pts died on study: 1 pt had sepsis, respiratory distress, pneumonia, and acute renal failure; and 1 pt each had acute renal failure, cardiopulmonary arrest, and disease progression. Conclusions: At the MTD (70 mg/m2), weekly Kd had acceptable safety and tolerability with promising efficacy in pts with RRMM. Updated results will be presented at the meeting. Clinical trial information: NCT01677858.
transplant-eligible, previously untreated, NDMM were randomized to four Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

A phase II study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. First Author: Ajai Chari, Mount Sinai, New York, NY

Background: Preclinical data support deacetylation of oncopgenic proteins/histones with the pan histone deacetylase inhibitor (HDACi) panobinostat (pan), which renders MM cells more susceptible to other anti-MM agents. Clinically, pan added to bortezomib (b) & dexamethasone (dex) in the PANORAMA 1 phase III study resulted in improved CR & PFS by 3.9 months. However, grade 3/4 dexamethasone also increased from 8% to 25%. Though the MTD of panobinostat was attained in a phase 1b study of Rel Ref MM (Mateo et al, ASCO 10), 4 day pulses of dex *3 per cycle was toxic. We modified that regimen; pan 20 mg D1, 3, 5, 16, 19 + len 25 mg qd D1-21 + dex 40 mg D1, 8, 15 in 28 day cycle. Methods: Pts with RRMM with PD, measurable disease, & adequate PS/hematopoetic function were eligible. Use of QTC prolonging agents & prior HDACis were prohibited. Evaluation of the ORR was the primary objective & safety. ORR, OS, & PFS were secondary objectives.

Results: 20 evaluable pts median age 64 yo (45% = 65 yo) with 3 median lines of Rx over 4 years were enrolled. 13 (65%) had high molecular risk, 16(75%) were len- refr & 35, 45, 30% were refr to each: pom, btx, & ctz. Responses include 1 CR, 3 VGRs, 5 PRs, 8 MRs, & 2 SD, for an ORR of 45%, CBR of 85% & a median PFS of 7.5 mos. In the 16 len-refr pts, there were 3 VGRs, 3 PRs, 7 MRs, with a median PFS of 6.5 mos. Grade 3/4 toxicities (regardless of drug attribution) were primarily heme, with neutropenia (55%), thrombocytopenia (40%) & anemia (3%) respectively. Grade 3/4 nonhematologic events included infections in 4 (1 while neutropenic), 3 diarrhea (transient) & 2 PEs and 1 pt each with: neck pain, QTc prolongation, fatigue, & weight loss. Pts requiring dose reductions of len/pan respectively were 4/2 for ANC, 2/1 for pts, & 1 len for fatigue, & 1 pan for anemia. 3 pts experienced dose reductions for both len & pan. Conclusions: In RRMM, the completely oral pan len dex demonstrates durable responses, even in high risk len-refr pts, indicating the essential role of pan in attaining responses. In notable contrast to PANORAMA 1 there were no significant GI toxicities & primarily expected hematologic toxicities. Updated results of planned 27 pts, including correlatives, will be presented at the annual meeting. Clinical trial information: NCT01651039.

Lenalidomide and low-dose dexamethasone (Ld) is equivalent to Ld plus autologous stem cell transplant (ASCT) in newly diagnosed multiple myeloma (NDMM). Results of a randomized, phase III trial. First Author: Suzanne Lentzsch, Columbus University Medical Center, New York, NY

Background: Upfront ASCT is the current standard of care for transplant-eligible NDMM. However, its use has come into question with the emergence of novel agents such as lenalidomide. This randomized phase III study evaluated the role of upfront ASCT in NDMM, with Ld administered as induction therapy. Methods: Patients aged 18–75 years with transplant-eligible, previously untreated, NDMM were randomized to four 28-day cycles of lenalidomide (25 mg days 1–21) plus low-dose dexamethasone (40mg days 1, 8, 15, 22) followed by stem-cell mobilization and: ASCT conditioned with 200 mg/m2 melphalan (Arm A; Ld + ASCT); or Ld for 4 additional cycles (Arm B; Ld). Patients subsequently received maintenance lenalidomide (10–15 mg) for ≤ 2 years or until disease progression. Patients with stable disease prior to stem-cell collection, or with progressive disease at any time, went off study. The primary objective was to compare best response in Arm A versus Arm B. Secondary objectives were comparisons of the duration of response, progression-free survival (PFS), and overall survival (OS). Results: Sixty patients were randomized to the two arms between February 2009 and August 2014: 31 into Arm A, and 29 into Arm B. Baseline characteristics were similar in the two arms. The mean age was 62 years (range 48–75), and 43.3% of patients had International Staging System stage 1 disease. In an intention-to-treat analysis, neither the overall response rate nor the partial response rate (39% vs 36%, p = 0.74) differed significantly between Arm A and Arm B. The median follow-up time for the entire study population was 53.5 months (95% confidence interval (CI): 49.5–58.3). OS and PFS at 4 years were estimated at 79.0% (95% CI: 62.9–90.8) vs. 86.5% (95% CI: 67.3–95.4) (p = 0.31) and 69.3% (95% CI: 47.6–83.4) vs. 56.8% (95% CI: 34.3–74.2) (p = 0.30) in Arm A vs. Arm B, respectively. Conclusions: Ld without upfront ASCT appears to provide similar treatment response, OS, and PFS benefits to Ld plus ASCT in NDMM. Clinical trial information: NCT01731886.

8529 Poster Discussion Session; Displayed in Poster Session (Board #346), Sun, 8:00 AM-11:30 AM

Idelalisib efficacy and safety in follicular lymphoma patients from a phase 2 study. First Author: Gilles A. Salles, Hospices Civils de Lyon, Université Claude Bernard, Pierre Bénite, France

Background: There is an unmet need for new treatment options in FL, particularly for heavily pretreated, high-risk patients refractory to anti-CD20 and chemotherapy. Idelalisib, a PI3Kδ inhibitor, showed antitumor activity and acceptable tolerability as monotherapy in a pivotal phase 2, open-label study in indolent non-Hodgkin lymphoma (iNHL) refractory to rituximab (R) and an alkylating agent (NCT01228424). This post hoc analysis evaluated efficacy and safety in the FL patient subset. Methods: Double refractory patients with histologically confirmed iNHL received oral idelalisib 150 mg BID until disease progression (PD) or unacceptable tolerability; patients with FL (grade 1, 2, or 3a; n = 72) were included in this analysis. Responses were evaluated by an independent review committee using standardized criteria. The primary endpoint was the overall response rate (ORR). Results: At study entry, patients’ median age was 62 y, 54% had a high-risk FLIPI score, 22% had bulky disease, and 17% had FL grade 3a. Median (range) number of prior treatments was 4 (2–12); 86% were refractory to their last therapy (32/50 to bendamustine). At data cutoff, median (range) treatment duration was 6.3 (0.6–31.0) mo, with 65 (90%) patients off treatment (PD; 38, adverse events [AEs]; 15); investigator decision; 7, death; 5). Lymph node size decreased during treatment by ≥ 50% SPD in 57%. The ORR (95% CI) was 56% (43–67; P = 0.001), including 10 complete responses (CR) and 30 partial responses. Kaplan-Meier (KM)—estimated median (range) time to response was 2.6 (1.6–11.0) mo, median response duration was 11 mo (27 mo in patients with CR), and progression-free survival was 11 mo, substantially longer vs the last regimen. Median overall survival (OS) was not reached; KM-estimated OS at 1, 1.5, and 2 y was 87%, 74%, and 68%. The most common AEs (grade ≥ 3) were fatigue (38%), dyspepsia (23%), neutropenia (20%), anemia (14%), constipation (10%), nausea (7%), and diarrhea (4%). Median Karnofsky performance status (KPS) was 90% at study entry, 70% at progression. Conclusions: I delalisib demonstrated rapid, durable responses and acceptable safety in highly refractory, relapsed FL patients with limited treatment options. Clinical trial information: NCT01228424.
Poster Session (Board #349), Sun, 8:00 AM-11:30 AM

8532

Idelalisib monotherapy and durable responses in patients with relapsed or refractory Waldenstrom's Macroglobulinemia (WM). First Author: Steven Cohen, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA

Background: Idelalisib (Zydelig), a selective oral inhibitor of PI3K, demonstrated considerable anti-tumor activity in patients with relapsed/refractory INHL in phase 1 (p1; Finn, 2014), and refractory INHL in phase 2 trials (p2; Gopal, 2014). This analysis evaluates the outcomes with idelalisib in the subset with WM. Methods: Eligible WM patients (pts) included those with relapsed/refractory disease (p1), or those with disease refractory to both rituximab and an alkylating agent (p2). Idelalisib dosages were 150 mg QD, 90 mg QD, 225 mg QD, 300 mg QD, and 375 mg PO BID (p2) and were administered continuously until disease progression. WM response was assessed by IGm levels and CT-imaging (Owen, 2013). Results: Enrolled pts (p1 N = 9; p2 N = 10), had a median age of 63 and 60 years (range 42-83) and 78% and 80% were male, respectively. Patients had received a median of 4 prior regimens in both groups. Overall response rate (ORR) was 59% (56%), and 8/10 (80%; Table 1). Median time to first or second responses was 12 months, and most responses continued to improve over 6 months or longer. Median DOR was 32.8 months (p1), and not yet reached (p2), 67% have continued response at 2 years (p2). Median PFS is 33.3 months, and 22.1 months, respectively. Interestingly, > 3 gram/dL improvements in hemoglobin were noted in 5/9 and 7/10 subjects respectively over 3-6 month timeframe. Grade 3 adverse events included increased ALT/AST 5/9, and 1/10, and diarrhea/colic 1/9, and 3/10. One G3 ALT elevation and 1 G3 diarrhoea resulted in study discontinuation. Conclusions: These combined data suggest single agent idelalisib monotherapy is active in Waldenstrom’s macroglobulinemia. Durable responses were seen in the majority of subjects. Marked improvements in hemoglobin level and are also associated with response. The safety profile was acceptable and manageable, with no apparent disease specific safety signals. Phase 3 clinical trials of idelalisib with combination therapy are in progress for WM.

8533

A phase I study combining bendamustine with rituximab, etoposide and carboplatin (TREC) in patients with aggressive relapsed or refractory lymphoma. First Author: L. Elizabeth Budde, City of Hope National Medical Center, Duarte, CA

Background: Traditional multi-agent salvage strategies for lymphoma are less effective after failed modern front line therapies. Bendamustine (Treanda, T) has considerable anti-lymphoma activity and a favorable toxicity profile. We hypothesized that bendamustine could replace ifosfamide within the (R)ICE regimen yielding a feasible and effective salvage strategy (TREC). Methods: This multicenter, phase I study used a two stage design followed by 2 expansion cohorts for patients with diffuse large B cell lymphoma (DLBCL) and Hodgkin lymphoma (HL). Eligibility included measurable relapsed/refractory lymphoma, ECOG performance status ≤2, adequate blood counts and organ function. The primary objective was to define a maximally tolerated dose (MTD) of bendamustine associated with a dose limiting toxicity (DLT) rate of ≤25%. Therapy consisted of bendamustine ranging from 60 mg/m2 to 120 mg/m2 daily on days 1 and 2 with standard doses of carboplatin, etoposide, and rituximab (CD20+ disease only) used in the RICE regimen every 21 days for 2 cycles. Results: A total of 46 treated patients with median age of 58 years and median of 1 prior therapy, were enrolled with 3 at the dose escalation cohorts and 43 at the recommended phase 2 dose (RP2D). MTD was not reached. Primary feasibility of dose or early relapse was seen in 13 (65%) patients with HL (n = 20) and 14 (74%) patients with DLBCL (n = 19). All cycles were successfully given in the outpatient setting. Fourteen patients suffered ≥ grade 3 non-hematologic adverse events but without DLTs. The most common ones were febrile neutropenia (n = 4, 9%), and rash (n = 3, 4%). Per Cheson 2007 criteria overall response rates were 67% with 84% (14 CR, 2 PR) in HL, and 63% (6 CR, 4 PR) in DLBCL. Mobilization of peripheral blood stem cells (PBSC) was successful in all attempts and the administration of G-CSF prophylaxis and DLT criteria; bPrimary reasonable possibility due to allopurinol; pt discontinued.

Poster Session (Board #350), Sun, 8:00 AM-11:30 AM

8534

A phase I study of gemcitabine and bendamustine in relapsed/refractory Hodgkin’s lymphoma. First Author: Jonathon Brett Cohen, Emory University, Atlanta, GA

Background: Salvage regimens for Hodgkin lymphoma (HL) can be challenging due to either need for inpatient admission or frequent dosing. Based on previously reported single agent activity of bendamustine (benda) and gemcitabine (gem), we conducted a phase I study of benda and gem in patients (pts) with relapsed/refractory classical HL who failed at least 1 prior therapy to determine the maximum tolerated dose. Methods: Utilizing a continuous every 28 days (d/C) schedule, d/C 1 to 6 cycles, with cycle lengths of 28 (dose levels [DL] 1-3) and 21 (DL 4-5) days. The BR regimen was 6 C: B (2 Cycles of 60 mg/m2 to 120 mg/m2 daily on days 1 and 2 of each cycle for up to 6 cycles, with cycle lengths of 28 (dose levels [DL] 1-3) and 21 (DL 4-5) days. Dose limiting toxicity (DLT) was determined during cycle 1. Results: Fourteen pts (8 males) with a median age of 38.5 years (range: 23-60) and a median of 4 (range: 1-7) prior lines of therapy have completed a median of 4 cycles at DL 1 (n = 3), 2 (n = 3), 3 (n = 3), 4 (n = 4), and 5 (n = 1). Seven pts had a prior autologous transplant (ASCT), and 1 pt had a prior ASCT and autologous transplant. One pt only received day 1 of therapy in cycle 1 at DL 4 and was thus not considered in dose escalation determination. The benda dose was 60 mg/m2 for 3 pts, 90 mg/m2 for 6 pts, and 120 mg/m2 for 4 pts. No DLTs have been observed. Four pts have required hospitalization, including 2 heavily pretreated pts with pulmonary symptoms after cycle 2. One underwent a biopsy that was consistent with a drug-induced pneumonitis likely gem-related, while the other had grade 5 respiratory failure that was deemed secondary to infection although a relationship with gem could not be ruled out. Additional grade 3-4 toxicities include: hypophosphemia (n = 10) thrombocytopenia (n = 2), atrial fibrillation (n = 1), fever (n = 1), renal failure (n = 1), hypertension (n = 1), pneumonia (n = 1), hypothyreoidism (n = 1), hypokalemia (n = 1), and rash (n = 1). In 13 evaluable pts, the response rate was 77% (21/28); CR, n = 7; PR, n = 7; SD, n = 2; PD, n = 1. Two pts have had an ASCT with collection of 5.1 x 10^6 CD34+ cells over 2 days and 4.94 x 10^6 CD34+ cells over 3 days. Conclusions: The combination of benda 120 mg/m2 with gem 1000 mg/m2 is tolerable and appears efficacious. We continue to monitor closely for additional responses and complete accrual accruing with the maximally tolerated dose level using a 21-day cycle. Clinical trial information: NCT01359524.

8535

Poster Session (Board #352), Sun, 8:00 AM-11:30 AM

Interim results from a dose-escalation study of the BCL-2 inhibitor venetoclax (ABT-199/GDC-0199) plus bendamustine (B) and rituximab (R) in patients with relapsed/refractory (RR) Non-Hodgkin’s Lymphoma (NHL). First Author: Sven De Vos, Department of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Venetoclax (VEN) is a selective, potent, orally bioavailable BCL-2 inhibitor that has shown single agent activity in R/R NHL. The current study examined VEN with BR, an active regimen used for NHL. Methods: Objectives were safety, PK, preliminary efficacy, MTD, and recommended Phase 2 dose. Dose escalation (DE) used a 3+3 design on a 28 day (d) cycle (C) with 3 VEN (50 – 400 mg) schedules: 3, 7, and 28 d/C. The BR regimen was 6 C: B (2 d/C, 90 mg/m2) and 1 R (1 d/C, 375 mg/m2). DLTs for DE were assessed during C1. Responses were first assessed on C1 d. Pts who completed VEN + BR with continued tolerability and without disease progression could continue VEN monotherapy up to 2 yrs. Results: As of 1/9/15, 33 were treated: 20 (61%) FL, 10 (30%) DLBCL, and 3 (9%) MCL. Median age was 62 (29-90) yrs. All had prior R or R-combination, of which 32 (97%) had R-based chemotherapy and 8 (24%) had prior B or BR. 16 (48%) pts are active; 17 discontinued (12 PD, 2 AE, 1 each withdrew consent, non-compliance, pt decision). Median time on study was 90 d (1-876); 15 (45%) completed C of the combination. The most common AEs (in >25%) were nausea (58%), anemia, neutropenia (each 42%), thrombocytopenia, diarrhea (each 39%), hyperglycemia (36%), and vomiting, hypokalemia, fatigue (each 27%). The most common gr 3/4 AEs (in >10%) were neutropenia (30%), leukopenia, thrombocytopenia, lymphopenia (each 21%), and anemia (18%). The most frequent SAE was febrile neutropenia (9%). There were no drug-related AEs that led to death. Co-administration of BR did not significantly impact VEN PK. 29 pts had ≥1 assessment: 6 (21%) CR and 13 (45%) PR. The ORR was 66% in all pts and 74% in pts with FL. Conclusions: Primary end points demonstrated a tolerable safety profile and early interim responses were seen across all cohorts. Cohort 9 is enrolling at 600 mg 28 d/C. Clinical trial information: NCT01944229.
Lymphoma and Plasma Cell Disorders

8536  Poster Session (Board #353), Sun, 8:00 AM-11:30 AM
Development of the molecular diagnostic (MDx) DLBCL Lymphoma Subtyping Test (LST) on the nCounter Analysis System. First Author: Brett Watson, NanoString, Inc., Seattle, WA；Co-Author: Naomi Sanders, NanoString, Inc., Seattle, WA

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin’s lymphoma with two distinct molecular cell-of-origin (COO) subtypes known as germinal center B-cell (GCB) or activated B-cell (ABC). DLBCL subtypes have been reported to be prognostic and potentially predictive of treatment benefit, underscoring the need for a precise and accurate MDx test. NanoString’s LST is based on the Lymph2Cx gene expression profile (GEP). These studies describe the development of the LST and analytical robustness and clinical accuracy of the Linear Predictor Score (LPS) and DLBCL subtypes (ABC and GCB). Methods: 51 banked formalin fixed, paraffin embedded (FFPE) DLBCL specimens were used to recalibrate the algorithm using a clinical grade assay. The subtype accuracy of the final locked algorithm was verified by testing 68 independent specimens with gold standard (GS) GEP results. Analytical precision was measured across 2 operators and 3 reagent lots by testing 10 FFPE DLBCL RNA samples. Reproducibility was measured across 2 operators and pathologists by testing replicate tissue sections from 64 FFPE DLBCL blocks following independent pathology review of H&E slides. Following guided macrodissection of pathologist identified tumor tissue, isolated RNA was tested on the NanoString nCounter system. The assay was evaluated across the assay RNA input range (62.5-1000 ng) and with the inclusion of adjacent non-tumor tissue. Results: The estimated classification rate compared to the GS result was 5.9% (95% CI: 4.0%-7.7%). The total standard deviation in LPS was < 2% of the score range, including all sources of assay variation, with no significant differences between operators or reagent lots. Average LST subtype concordance with independent pathology review was > 95% with no GCB to ABC misclassifications (or vice versa). The LST was robust across the specified range and against the inclusion of tissue interferents. Conclusions: The NanoString LST is a highly precise and accurate method for determining the COO from FFPE DLBCL tissue. The assay is well suited to clinical applications and is being used to select ABC patients for a Phase III study investigating lenalidomide (REVLIMID) in DLBCL.

8538  Poster Session (Board #353), Sun, 8:00 AM-11:30 AM
Phase II study of Hyper-CVAD with pegylated liposomal doxorubicin alternating with melphalan and cytarabine (HCVIDD/MA) in patients with newly diagnosed T- and NK-cell lymphoma (T/NKCL). First Author: Dai Chihara, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prognosis of T/NKCL is poor after standard CHOP therapy. To prospectively evaluate the role of dose intensified chemotherapy, we conducted a phase II trial of HCVIDD/MA in patients with newly diagnosed T/NKCL. Methods: Eligible patients were adults with newly diagnosed untreated T/NKCL excluding ALK positive ALCL. Patients received HCVIDD/MA every 21 days for up to eight cycles. In this trial, pegylated liposomal doxorubicin at 25mg/m² was used instead of conventional doxorubicin at 45mg/m². We conducted a phase II trial of HCVIDD/MA in patients with newly diagnosed T/NKCL excluding ALK positive ALCL. Patients received HCVIDD/MA every 21 days for up to eight cycles. In this trial, pegylated liposomal doxorubicin at 25mg/m² was used instead of conventional doxorubicin at 45mg/m². Methods: We profiled 43 DLBCL RNA samples. Reproducibility was measured across 2 operators and pathologists by testing replicate tissue sections from 64 FFPE DLBCL blocks following independent pathology review of H&E slides. Following guided macrodissection of pathologist identified tumor tissue, isolated RNA was tested on the NanoString nCounter system. The assay was evaluated across the assay RNA input range (62.5-1000 ng) and with the inclusion of adjacent non-tumor tissue. Results: The estimated classification rate compared to the GS result was 5.9% (95% CI: 4.0%-7.7%). The total standard deviation in LPS was < 2% of the score range, including all sources of assay variation, with no significant differences between operators or reagent lots. Average LST subtype concordance with independent pathology review was > 95% with no GCB to ABC misclassifications (or vice versa). The LST was robust across the specified range and against the inclusion of tissue interferents. Conclusions: The NanoString LST is a highly precise and accurate method for determining the COO from FFPE DLBCL tissue. The assay is well suited to clinical applications and is being used to select ABC patients for a Phase III study investigating lenalidomide (REVLIMID) in DLBCL.

8537  Poster Session (Board #354), Sun, 8:00 AM-11:30 AM
Phase I first-in-human trial of oral CUDC-907, a dual inhibitor of PI3K and HDAC, in patients with refractory/relapsed lymphoma or multiple myeloma. First Author: Jesus G. Berdeja, Sarah Cannon Research Institute, Nashville, TN

Background: CUDC-907 is an oral inhibitor of class I PI3K and II HDAC enzymes. Anti-tumor effects of CUDC-907 have been demonstrated in B-cell lymphoma and multiple myeloma xenografts via inhibition of PI3K, MAPK, and STAT pathways. Methods: In a 3+3 dose escalation and expansion trial, CUDC-907 was administered on 3 dosing schedules: once daily (QD), intermittent (ie, twice [BIW] or thrice [TIW] weekly), or five days on/two days off (5/2) in 21 day cycles. Re-staging was performed every 2 cycles. Results: 45 subjects received CUDC-907 at doses up to 60 mg on the QD or 5/2 schedules, and up to 150 mg on the BIW or TIW schedules. Dose limiting toxicities occurred in 3 subjects: 1 at 60 mg BIW (hyperglycemia and diarrhea); 1 at 150 mg BIW (hyperglycemia); and 1 at 150 mg TIW (diarrhea). No DLT occurred on the 5/2 schedule. The most common treatment-related adverse events (AEs) included diarrhea (44%), fatigue (29%), nausea (16%) and thrombocytopenia (11%). 38 subjects are evaluable for response. 4/8 subjects with DLBCL or t-FL/DLBCL (median of 4 prior therapies) achieved objective responses and long-term SD across multiple tumor types and dosing schedules, with objective response achieved in a heavily pretreated DLBCL patient population. Though MTD was not reached in the interim or 5/2 schedules, expansion is being studied at 120 mg TIW and 60 mg 5/2 dose levels based upon their efficacy and toxicity profiles. Clinical trial information: NCT01742988.

8539  Poster Session (Board #356), Sun, 8:00 AM-11:30 AM
Pre-treatment circulating tumor DNA as a biomarker for disease burden in diffuse large B cell lymphoma (DLBCL). First Author: Florian Scherer, Division of Oncology, Stanford University School of Medicine, Stanford, CA

Background: Patients with DLBCL reveal striking heterogeneity in clinical outcomes. Plasma cell-free DNA (cfDNA) levels have been shown to be adversely prognostic. Both circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) can be used for DLBCL monitoring with ctDNA reported to be superior (Kurtz et al 2014 ASCO). However, the relationship between ctDNA and CTC levels with DLBCL clinical responses remains newly defined. Methods: We profiled 45 DLBCL patients treated with R-CHOP based therapy and quantified their pre-treatment ctDNA, cfDNA and CTC levels. Pre-treatment ctDNA levels were determined by high-throughput sequencing of tumor specific immunoglobulin genes (Ig-HTS) of plasma cfDNA, and CTCs were enumerated by Ig-HTS of blood leukocytes. Results: Mean cfDNA and ctDNA levels varied widely (2.8-1,713.5 ng/mL, median: 12.6), as did ctDNA and CTC levels. Pre-treatment ctDNA levels were strongly associated (r = 0.73, P < 0.0001) and correlated with LDH (r = 0.79 and 0.74, P < 0.0001) and MTV (r = 0.62 and 0.53, P < 0.0001 and P = 0.002). ctDNA was detectable in 14 of 19 patients (74%) with normal LDH levels. Higher cfDNA and ctDNA levels were associated with lower MTVs, fewer metabolic perturbations. Conclusions: Our study demonstrates that, in contrast to CTCs, ctDNA levels better capture disease burden in DLBCL, including tumor volume and metabolic properties. The prognostic value of cfDNA levels appears directly related to ctDNA levels, and not to CTCs. Therefore, ctDNA is a specific biomarker of tumor burden in DLBCL and, compared to cfDNA, less prone to physiological perturbations.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Bendamustine and rituximab and lenalidomide (BBR) in the treatment of relapsed and refractory low grade non-Hodgkin lymphoma (NHL). Final results of phase 1 study NCT01908821/ALLIANCE. First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN

**Background:**

The combination of bendamustine and rituximab is effective in the treatment of low grade NHL. Lenalidomide shows significant synergy when combined with rituximab and rituximab-containing chemotherapy. The primary aim of this phase 1 study was to establish a maximum tolerated dose (MTD) of bendamustine, rituximab and lenalidomide. Secondary endpoints included toxicity, overall response and progression-free survival. **Methods:** Eligible patients had relapsed or refractory low grade NHL. Treatment was with at least a 1-st phase regimen. A 3-3 phase was used. Dose levels are shown in the Table. Bendamustine was given on day 1 and 2, rituximab on day 1 and lenalidomide orally, daily, days 1-10 of 28-day cycle for up to 6 cycles. Pegfilgrastim was given on day 3 of the cycle. **Results:** 15 patients were enrolled. The median age was 58 years (47-71), 15 patients were female, 12/15 patients had stage 4 disease. The histological subtypes were: follicular lymphoma grade 1 and 2 (6/15 pts), marginal zone lymphoma (5/15 pts) and lymphoplasmacytic lymphoma (4/15 pts). The left-limiting toxicity was seen. Dose escalation beyond 25 mg daily of lenalidomide was not performed, since 25 mg is considered a biologically effective dose. The most common toxicity was hematological, with 2/15 pts experiencing grade 3 neutropenia. The overall response was 100% (Table). Only 1/15 pts experienced grade 3 or more non-hematological toxicity (grade 3 urticaria). All patients remain alive with median follow up of 17 months (6-28) and only 1 pt disease progression at 12 months. **Conclusions:**

Lenalidomide at 25 mg/day, days 1-10 of a 28-day cycle can be safely combined with the standard dose bendamustine rituximab regimen and is well tolerated. The encouraging response rates in a relapsed setting warrant a larger randomization of the current combination in larger trials. Support: U10CA180821, U10CA180882, CA025224 Clinical trial information: NCT01429025.

**Dose escalation and response summary.**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Lenalidomide</th>
<th>Bendamustine</th>
<th>Rituximab</th>
<th>Day 1-2</th>
<th>Day 1</th>
<th>DLTs</th>
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<td>1</td>
<td>15 mg</td>
<td>70 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
<td>0/0</td>
<td>0/0</td>
<td>CR, PR</td>
</tr>
<tr>
<td>2</td>
<td>20 mg</td>
<td>70 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
<td>0/0</td>
<td>0/0</td>
<td>CR, PR</td>
</tr>
<tr>
<td>3</td>
<td>20 mg</td>
<td>90 mg/m²</td>
<td>375 mg/m²</td>
<td>0/3</td>
<td>0/0</td>
<td>0/0</td>
<td>CR, PR</td>
</tr>
<tr>
<td>4</td>
<td>25 mg</td>
<td>90 mg/m²</td>
<td>375 mg/m²</td>
<td>0/6</td>
<td>0/0</td>
<td>0/0</td>
<td>CR, PR</td>
</tr>
</tbody>
</table>

Telomere profile of Reed-Sterenberg and Hodgkin cells in diagnostic biopsy in Hodgkin lymphoma as a predictor of clinical response. First Author: Jeffrey B Tompkins, Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada

**Background:**

Markers that predict poor response to primary therapy in Hodgkin’s lymphoma (HL) are currently lacking. Much of the difficulty stems from the rarity of the malignant mononuclear Hodgkin’s (H) cells and multinuclear Reed-Sterenberg (RS) cells in the tumor. We have developed a 3D quantitative fluorescent in situ hybridization (3D qFISH) telomere profiling system with telomere fluorescent intensity, number, distribution and aggregation, as markers of genomic instability. Telomere profiles differ between H and RS cells; increased genomic instability accompanies the switch from H to RS phenotype. Cases of relapsed/refractory HL have greater H cell genomic instability compared to those entering stable remission. Telomere profiles of H and RS cells at time of diagnosis may predict aggressive disease behavior, as indicated by relapse or refractoriness to therapy. **Methods:** Incidence cases of classic HL from 2002-2010 were retrospectively identified from the provincial cancer registry in Manitoba, Canada. Patients with only palliative treatment or who had insufficient biopsy material for analysis were excluded. Primary outcome was treatment failure (primary refractory, relapse or death from HL). H and RS cell telomers in the initial diagnostic biopsies were subject to 3D qFISH with telomere specific probes. Resultant images were analyzed with TeloView software. Subhazard ratios (SHR) were computed using competing risk models. **Results:** 235 patients were diagnosed with HL of which 145 met the eligibility criteria, and 28 had treatment failure. Median follow up was 4.0 years. H cell mean telomere intensity (SHR 0.77; 95% CI 0.59-1.00; p = 0.048), total telomere intensity (SHR 0.90; 95% CI 0.83-0.98; p = 0.013) and the ratio of RS/H cell total intensity (SHR 1.54; 95% CI 1.43-1.67; p = 0.003) were predictive of primary refractory or relapsing HL. Conclusions: Genomic instability of the H and RS cells measured by telomere 3D qFISH is predictive of primary refractory or relapsing HL independent of disease stage and is a potential biomarker of disease behavior at time of diagnosis.

Analysis of “double-hit” lymphoma cases by genetic subtype. First Author: Daniel Jeffrey Landsburg, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

**Background:**

“Double-hit” lymphoma (DHL), defined as a B cell non-Hodgkin lymphoma harboring rearrangements in c-MYC as well as BCL2 and/or BCL6, carries a poor prognosis. Here we report characteristics and outcomes of DHL patients (pts) by genetic subtype. **Methods:** We reviewed the largest reported series of DHL pts (B2014 124:2354-61), we identified cases which underwent cytogenetic testing for c-MYC as well as both BCL2 and BCL6 rearrangements. Cohorts were defined by the presence (+) or absence (-) of rearrangements: c-MYC+/BCL2-/BCL6- (BCL2-DHL), c-MYC-/BCL2+/BCL6+ (BCL6-DHL) and c-MYC+/BCL2+/BCL6+ (THL). Therapy was given at the discretion of the treating physician. Data from 17 cases were included. Pts with BCL6-DHL were more likely to have extranodal disease as compared to BCL2-DHL (p = 0.04) and THL (p = 0.04) pts. Treatment received and outcomes are described in Table. Univariate analysis revealed that elevated LDH, stage ≥ 3 disease, IPI ≥ 4 and bone marrow involvement in BCL2-DHL pts and IPI ≥ 4 and bone marrow involvement in THL pts predicted for inferior overall survival (OS). **Conclusions:** Analysis of the largest reported series of BCL2-DHL, BCL6-DHL and THL pts by genetic subtype did not reveal significant differences in outcome, potentially due to small cohort sizes. Nevertheless, high rates of primary refractory disease and relapse seen across all subtypes provides a rationale for offering novel therapeutic approaches to these pts in the frontline setting.

Treatment received and outcomes.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>BCL2-DHL</th>
<th>BCL6-DHL</th>
<th>THL</th>
<th>BCL2-DHL vs. BCL6-DHL</th>
<th>BCL2-DHL vs. THL</th>
<th>BCL6-DHL vs. THL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of DE1</td>
<td>%</td>
<td>%</td>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Complete (CR1)</td>
<td>55%</td>
<td>44%</td>
<td>65%</td>
<td>0.42</td>
<td>0.35</td>
<td>0.19</td>
</tr>
<tr>
<td>CR/PR</td>
<td>54%</td>
<td>75%</td>
<td></td>
<td>0.77</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>If receiving DE2</td>
<td>55%</td>
<td>86%</td>
<td>63%</td>
<td>0.22</td>
<td>0.77</td>
<td>0.37</td>
</tr>
<tr>
<td>Bone cell/marrow</td>
<td>36%</td>
<td>22%</td>
<td>55%</td>
<td>0.47</td>
<td>0.31</td>
<td>0.18</td>
</tr>
<tr>
<td>Primary refractory disease</td>
<td>32%</td>
<td>31%</td>
<td>33%</td>
<td>0.18</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Relapse (if responding)</td>
<td>25%</td>
<td>14%</td>
<td>14%</td>
<td>1.0</td>
<td>0.71</td>
<td>1.0</td>
</tr>
<tr>
<td>Med. OS (months)</td>
<td>34.8</td>
<td>14.5</td>
<td>17.2</td>
<td>0.89</td>
<td>0.69</td>
<td>0.90</td>
</tr>
</tbody>
</table>

1DE=dose-escalated frontline chemotherapy (EPOCH, hyperCVAD, COO02-A, CVAD). 2Median length of follow-up ≥ 12 months (range 0.1-85.6). 3Not yet reached.
Phase 1 trial of brentuximab vedotin in combination with gemcitabine for pediatric and young adult patients with relapsed or refractory Hodgkin lymphoma, a Children's Oncology Group report. First Author: Peter D. Cole, The Children’s Hospital at Montefiore, Bronx, NY

Background: Salvage therapy followed by autologous stem cell transplantation improves outcomes for patients with primary refractory Hodgkin lymphoma (HL) or early relapse. Brentuximab vedotin (Bv) and gemcitabine each produce high overall response rates in this context. Compared to alternate retrieval regimens, this combination offers the advantage of avoiding agents that are associated with late treatment sequelae such as anthracyclines, alkylators, or epipodophyllotoxins. This phase 1 trial was conducted to describe the toxicity of the combination and to define a recommended phase 2 dose (RP2D) for Bv when given with gemcitabine.

Methods: Patients ≥ 30 years old with primary refractory HL or early relapse were eligible. Bv was given on day 1 of each 21-day cycle, at two dose levels (DL): DL1, 1.4 mg/kg and DL2, 1.8 mg/kg. Gemcitabine 1000mg/m² was given on day 1 and 8. Dose limiting toxicity (DLT) was assessed during cycle 1 to define the RP2D, and response after every 2 cycles. Results: Fifteen patients have enrolled (14 evaluable for hematologic toxicity), with median age of 17 years (range 5-28). No DLTs were seen among 3 patients treated at DL1. Two of six patients experienced non-hematologic DLT at DL2: one with grade 3 hypotension and one with asymptomatic Grade 3 elevation of liver enzymes. Both had resolution of all toxicity and continued on study treatment with dose reduction of Bv to 1.2 mg/kg. An expansion cohort of six patients was enrolled at DL2; none experienced DLT. Grade 3-4 neutropenia was common (13 of 14 patients during cycle 1) but self-limited. No grade 4 non-hematologic toxicity occurred. No cases of interstitial pneumonitis or pulmonary toxicity attributable to study therapy were observed. Conclusions: Bv can be safely given in combination with gemcitabine. The RP2D of Bv is 1.8 mg/kg. The ongoing Phase 2 trial will early describe the complete response rate observed within four cycles of Bv with gemcitabine. Clinical trial information: NCT01780662. Clinical trial information: NCT01780662.

Treatment of refractory/relapse vitreoretinal lymphoma: Result of a multicenter retrospective study from the LOC network on temozolomide in monotherapy. First Author: Sylvain Choquet, APHP-CHU Pitit-Salpétrière, Paris, France

Background: Vitreoretinal lymphoma (VRL) is a rare subset of non-Hodgkin lymphoma. Its overall survival (OS) is from 35% to 68% at 5 years (Riemens et al Jama ophthalmol 2014) in first line, but relapse/refractory (R/R) VRL survival is usually of few months. Temozolomide (Tz) has been described effective in some cases of CNS lymphoma. Methods: VRL not eligible for IV chemotherapy or local treatment were proposed to be treated by Tz at 150mg/m² 5 days/month. Diagnosis of VRL was made by vitrectomy with a cytological, phenotypical and molecular analysis, dosages of IL10 and IL6 were also made. Extra-ocular localizations were searched in brain MRI, lombar puncture and CT-scan or PET-scan. Results: 16 patients were included, mean age was 75 years (35-90). 12 previously received systemic chemotherapy with high dose methotrexate or cytarabine, 8 were in second line, 3 in third, 2 in forth and 1 in fifth who relapsed after autologous stem-cell transplantation (ASCT). The 2 patients treated in first line where more than 80 years old. All but one had an isolated VRL, one an association with a cerebral localization. Median duration of treatment was 5 months. The median follow-up (fu) is 16 months. Overall response rate is 75%, with 10 CR (63%) and 2 PR (13%). At the last fu, 6 patients are still in CR. The median disease free survival is 12,3 months. The patient treated after ASCT relapse is still in CR at 77 months. The two old patients treated in first line are in CR at 40 months. One patient had a persistent ocular and cerebral CR. Three patients were treated a second time by Tz after relapse, obtaining 2 new CR, one of 4 months and one persistent at 12 months, and one new persistent PR. Median OS is not reached. Only 2 patients experienced hematological grade 3/4 toxicity. There was no treatment related deaths. Conclusions: This work represents the biggest study with an homogeneous treatment in R/R VRL. Temozolomide appears as a safe and efficient treatment of R/R VRL and first line VRL in patients in bad condition, even after high dose chemotherapy and/or in elderly patients. Longer follow-up, prospective and larger studies are necessary to confirm these data.

Survival of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and peripheral T-cell lymphoma (PTCL): A propensity matched analysis of the Surveillance, Epidemiology, and End Results (SEER) database. First Author: Samyak Manandhar, UPMC Mercy, Pittsburgh, PA

Background: SPTCL is a rare entity with no prior population-based study. Using the SEER database, we compared the characteristics and survival of SPTCL and PTCL. Methods: We used the SEER 18 database to identify adult patients with SPTCL and PTCL diagnosed between 1973 and 2011. Prior to 2008, T-cell receptor gamma/delta phenotype of SPTCL was not recognized as a separate entity, hence could not be excluded from this study. Actuarial, relative and cause specific survival of SPTCL were computed. The actuarial survival of SPTCL was compared to a propensity matched cohort of PTCL. Kaplan Meier survival curves were plotted. Multivariate analysis was conducted using weighted Cox proportional hazards regression model. Results: Patients with SPTCL (n = 118), compared to PTCL (n = 3296), were more likely to be younger (median age of 47 vs. 62 years, p < 0.01), women (67 % vs 40%, p < 0.01) and diagnosed with stage I/II disease (46% vs. 36%, p = 0.01). The five year actuarial, relative and cause specific survival for SPTCL was 40%, 57% and 64% respectively. After propensity matching, the 5-year overall survival (OS) of SPTCL was better than that of PTCL (57% vs. 40%, p < 0.01). In a multivariate analysis, mortality was significantly lower among SPTCL vs. PTCL (hazard ratio, HR 0.54; 95% CI 0.39-0.75; p < 0.01) after adjusting for age, gender, race and stage of the disease. Among patients with SPTCL, advanced age (p < 0.01) and diagnosis before the year 2008 (p=0.02) were predictors of worse OS in a multivariate analysis. Conclusions: Our study provides characteristics and OS of a large cohort of this rare entity, which can be used for patient education and may provide background information for future research. As compared to PTCL, SPTCL patients were more likely to be younger, female and diagnosed at an early stage. Even though T-cell receptor gamma/delta phenotype, which has an unfavorable outcome, could not be excluded, the OS of SPTCL was found to be better than PTCL. Advanced age and year of diagnosis were the predictors of OS among patients with SPTCL.
8548 Poster Session (Board #366), Sun, 8:00 AM-11:30 AM

Ubilutiximab plus TGR-1202 activity and safety profile in relapsed/refractory B-cell NHL and high-risk CLL. First Author: Matthew Alexander Luning, Pennsylvania State University Cancer Institute, Hershey, PA

Background: Ubilutiximab (UTX) is a novel glycoengineered anti-CD20 mAb. TGR-1202 is a novel once daily oral PI3Kδ inhibitor. UTX + TGR-1202 has shown strong synergistic activity in-vitro (Lugano 2013). This phase I trial evaluated the safety and efficacy of the combination of UTX + TGR-1202 in patients (pts) with heavily pre-treated rel/ref NHL and CLL. Methods: A 3 + 3 design is utilized with rel/ref NHL or CLL pts accruing independently. No limits on prior therapies (Tx). Pts refractory to prior PI3Kδ inhibitors were eligible. UTX administered 150 mg/m² on days 1, 15, and 28 with a 49-day cycle, followed by D 1 of Cy 4, 6, 9 & 12. TGR-1202 is daily, with an improved micronized formulation introduced in later cohorts. Primary endpoints: Safety and dose limiting toxicities (DLT). Secondary endpoints: Efficacy (ORR, CR rate). Results: 32 pts enrolled and evaluable for safety. 12 CLL/SLL, 10 FL, 8 DLBCL, 1 MZL and 1 Richter’s. Med age 64 yo (range 35-84); 20 M/12 F; Median prior Tx = 3 (range 1-9). AE’s (all causality) include: Day 1 infusion reactions at 44%, neutropenia 41% (31% Gr 3/4), diaphoresis 34% (0% Gr 3/4), and nausea 28% (0% Gr 3/4). To date, TGR-1202 related hematotoxicity has not been reported. One DLT occurred: a pt with Gr 3 neutropenia at study entry which worsened (cohort 1). A dose-response relationship has been observed with TGR-1202. 2B/32 are evaluable for efficacy with best response in the table below. To date, of all 32 pts, 89% (16/18) in the higher dose cohorts remain progression-free compared to 57% (8/14) in the lower dose cohorts. Of the 10 CLL pts, all remain progression-free at a median of 8 months (range 2 – 12 + months). Conclusion: The combination of UTX + TGR-1202 is well tolerated with activity in rel/ref NHL and CLL with a dose-response relationship observed. Dose escalation continues with enrollment ongoing at the highest dose cohort and in recently opened expansion cohorts. Clinical trial information: NCT02006485.

TGR-1202 Higher dose TGR-1202 Lower dose

<table>
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<th>Type</th>
<th>CR</th>
<th>PR</th>
<th>ORR</th>
<th>PD</th>
<th>CR</th>
<th>PR</th>
<th>ORR</th>
<th>PD</th>
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</thead>
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<tr>
<td>CLL/SLL</td>
<td>2</td>
<td>3</td>
<td>3 (100%)</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>50%</td>
<td>4</td>
</tr>
<tr>
<td>DLBCL</td>
<td>4</td>
<td>2</td>
<td>1 (75%)</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>57%</td>
<td>-</td>
</tr>
<tr>
<td>FL</td>
<td>6</td>
<td>1</td>
<td>2 (50%)</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Richter’s</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>1</td>
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</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>3</td>
<td>9 (64%)</td>
<td>14</td>
<td>4</td>
<td>4 (29%)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Higher dose, 1200 original and 600/800 micronized; Lower dose, 800 original and 400 micronized.

8550 Poster Session (Board #368), Sun, 8:00 AM-11:30 AM

Breast implant-associated anaplastic large cell lymphoma: Proposal for optimal management. First Author: Mark Warren Clemmens, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a newly identified lymphoma arising around breast implants placed for cosmetic or reconstructive indications. Patterns of disease progression and optimal treatment strategies have not been described. Methods: The literature was reviewed for all published cases of BI-ALCL from 1997 to November 2014, contacted corresponding authors to update clinical follow up, and compared the combination with individual cases. A novel clinic-pathologic TNM staging system is proposed and was compared to traditional Ann Arbor staging to determine prognostic value for overall survival (OS) and progression free survival (PFS). A Pretice, Williams and Peterson (PWP) model was used to assess treatment effect on progression events. Results: We identified 128 unique cases of BI-ALCL, including 91 previously reported and 37 unreported cases. Pathologic slides were available in 56 patients for pathologic staging. Average follow up was 45 months (30–217 months). The median OS was 13 years, OS rate 93% at 3-years and 89% at 5-years. 18 progression events were noted and median PFS was 13 months, with 3-year and 5-year PFS at 79.4%. Total capsulectomy with implant removal (TCIR) prolonged OS (p = 0.022) and improved PFS (p = 0.014), and the effect of definitive surgery was statistically significant for PFS benefit (HR = 0.14, 95% CI = 0.05-0.46, p = 0.001). After definitive surgery, patients had 4% of risk of having events by the end of the first year while the rates were 18%, 24% and 60% when patient had radiation, chemotherapy or limited surgery. The PFS was significantly different by Ann Arbor staging (p = 0.013) and by the newly proposed clinical staging (p = 0.030). Conclusions: Advanced stage, presence of mass, incomplete resection, and delay in definitive surgical treatment were associated with poor OS and PFS in patients with BI-ALCL. Surgical management with definitive excision and oncologic surveillance is adequate for most patients with BI-ALCL. The role for chemotherapy, targeted immunotherapy, and/or radiation for advanced disease requires further research in larger series.

8551 Poster Session (Board #369), Sun, 8:00 AM-11:30 AM

Rituximab maintenance Therapy in B-cell lymphoma: A meta-analysis. First Author: Yucai Wang, Rutgers New Jersey Medical School, Newark, NJ

Background: The role of rituximab (R) maintenance therapy (MT) in B-cell lymphoma is controversial. We reviewed data from clinical studies and conducted a meta-analysis to evaluate the efficacy and safety of R MT in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Methods: A systematic review of ASCO, ASH, and PubMed was performed for eligible clinical studies to date that investigated survival outcomes (OS, PFS, DFS and/or TTP) and adverse events of R MT in FL, DLBCL and MCL. Pooled hazard ratios (HRs) for survival outcomes and risk ratios (RRs) for AEs were calculated. Results: 22 clinical studies of 6785 patients, including 15 randomized controlled trials (RCTs) and 7 cohort studies, were included for meta-analysis. In RCTs, R MT significantly prolonged PFS (HR = 0.60, 95% CI = 0.52-0.68, P < 0.001) and OS (HR = 0.79, 95% CI = 0.69-0.93, P = 0.005) in B-cell lymphoma. Improvement of PFS with R MT was demonstrated in all types of lymphoma studied. R MT increased OS in FL (HR = 0.76, 95% CI = 0.61-0.94, P = 0.010) but not DLBCL (HR = 0.88, 95% CI = 0.64-1.21, P = 0.47); and MCL (HR = 0.77, 95% CI = 0.57-1.07, P = 0.036) in B-cell lymphoma. For the treatment of limited-stage natural killer (NK)/T-cell lymphoma, the role of R MT needs further study. Conclusions: R MT significantly improved PFS in FL, DLBCL and MCL as well as OS in FL. Whether R MT improves OS in DLBCL and MCL needs further study.

**Survival benefits of rituximab maintenance therapy in B-cell lymphoma.**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Survival</th>
<th>Type</th>
<th># of trials</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>RCT</td>
<td>PFS</td>
<td>FL</td>
<td>9</td>
<td>0.52</td>
<td>0.42-0.64</td>
<td>0.000</td>
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<tr>
<td></td>
<td>DLBCL</td>
<td>7</td>
<td>0.67</td>
<td>0.50-0.92</td>
<td>0.010</td>
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<tr>
<td></td>
<td>MCL</td>
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<td>0.55</td>
<td>0.41-0.73</td>
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<tr>
<td></td>
<td>OS</td>
<td>FL</td>
<td>7</td>
<td>0.76</td>
<td>0.61-0.94</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>DLBCL</td>
<td>7</td>
<td>0.60</td>
<td>0.42-0.85</td>
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<td></td>
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<td>0.47-1.27</td>
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</tr>
<tr>
<td></td>
<td>OS</td>
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<td>0.77</td>
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<tr>
<td></td>
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<td>0.48-1.01</td>
<td>0.047</td>
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<tr>
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<tr>
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<td>OS</td>
<td>FL</td>
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<td>0.62</td>
<td>0.42-0.91</td>
<td>0.015</td>
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<tr>
<td></td>
<td>MCL</td>
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<td>0.62</td>
<td>0.42-0.91</td>
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<tr>
<td></td>
<td>All</td>
<td>FL</td>
<td>15</td>
<td>0.76</td>
<td>0.56-0.98</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
CD30+ expression in Peripheral T-cell lymphomas (PTCLs): A subset analysis from the international, prospective T-Cell Project. First Author: Massimo Federico, Dept of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

**Background:** CD30 is a member of TNF-alpha receptor family that might have important therapeutic implications with the advent of targeted therapies. Several PTCLs subtypes have been reported in literature to be associated to variable CD30 expression. We investigated the frequency of CD30 expression on PTCLs subtypes registered in the T-Cell Project and correlated it with clinical features and outcome. **Methods:** The T-Cell Project is a prospective, international study in patients (pts) with newly diagnosed aggressive PTCLs. Clinical, laboratory and disease localization data at diagnosis as well as therapy details and follow-up information are collected at a dedicated website via secure HTTP protocols. Central review of diagnostic biopsy is planned. **Results:** From Sept 2006 to Jan 2015, 1038 pts were registered in the T-Cell Project by 73 sites from 14 countries world-wide. As from the 792 pathology forms filled out by site local staff CD30 expression was tested in 490 pts (62%) and reported as CD30+. CD30- in 349 (71%) and CD30- in 141 (29%). Frequency of CD30 expression in different subtypes is shown in the Table. CD30+ pts tended to be younger (54 vs 58 yrs, P = 0.03) with less extranodal involvement (65% vs 78%, P = 0.01) than CD30-. CHOP like regimens were the most common irrespective of CD30 status (63% in both groups, P = 1.0). In the group of pts with any histology but ALCCL, no difference in CR rate (44% vs 51%, P = 0.26), 5-yr PFS (29% vs 22%, P = 0.57) and OS (44% vs 29%, P = 0.17) was observed between CD30+ and CD30- pts. Brentuximab use in first line was noted in only 5 pts enrolled in clinical trials. **Conclusions:** Data from the T-cell project confirm that CD30 is expressed in many PTCLs other than ALCCL, thus suggesting a routine assessment for all PTCLs. Again, this analysis suggests that CD30 expression has no prognostic significance. The very limited use of anti CD30 targeted therapy in this sample doesn’t allow to establish the predictive value of CD30 expression in PTCLs.

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**PTCL, NOS** 85.41 120, 59
**AITL** 16.42 50, 76
**ALCL** 0.0 14, 100
**NKTCL** 13.48 14, 52
**EATL** 11.46 13, 54
**Other** 16.70 7, 30

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**8554** Poster Session (Board #372), Sun, 8:00 AM-11:30 AM Outcomes and prognostic factors in marginal zone lymphoma: Case comprehensive cancer center cumulative experience of 358 cases. First Author: Adam Starr, Case Western Reserve University, Cleveland, OH

**Background:** MZL are uncommon B-cell lymphomas. The outcomes and prognostic factors of MZL remain poorly defined. **Methods:** We retrospectively identified 485 cases of MZL diagnosed between 1994-2014 from 2 institutions. Diagnoses had been confirmed by expert hematopathologists. We excluded 127 cases because of limited data and overlapping features with other lymphoma subtypes. **Results:** Of the 358 patients (pts) included in the analysis, 216 (60%) had extranodal MZL (EMZL) with the remainder arising from stomach (32%), 56 (16%) nodal MZL (NMZL), 64 (18%) splenic MZL (SMZL), and 22 (6%) had typical MZL phenotype but were unclassifiable. Median age was 66 (range 13-95) years, 171 (48%) pts had stage III/IV disease at diagnosis. B-symptoms were present in 33 (9%) pts and 20 (18%) had > 1 node (LN) involved. If time from diagnosis to treatment was 33 (2-1883) days and median duration of follow-up was 40.3 (2.2-236.4) months. Among treated pts, initial treatment was rituximab (R) (33%), chemotherapy +/- R (22%), radiation (16%), surgery (16%), and antibiotics (13%). Progression-free survival (PFS) and overall survival (OS) for the whole group was 5.15 (95% confidence intervals; CI: 2.8-10) and 19 (95% CI: 10-19) years respectively and there was no significant difference in PFS or OS between EMZL, NMZL, SMZL, or atypical MZL. On univariate analysis, age > 60 (p = 0.002), elevated serum lactate dehydrogenase (LDH) (p = 0.003), involvement of > 4 LN (p = 0.019), follicular lymphoma International Prognostic Index (FLIPI) score (p = 0.0005), and hemoglobin (Hb) level < 12 g/dL at presentation (p = 0.003) were associated with inferior OS. In a multivariate analysis, only age (hazard ratio (HR) = 5.48, p = 0.002) and Hb (HR = 2.97, p = 0.009) retained significance. Transformation to aggressive lymphoma occurred in 29 (8%) pts and was associated with high serum LDH and higher FLIPI at diagnosis. In pts treated with R +/- chemotherapy, R maintenance was associated with improved OS (p = 0.04). **Conclusions:** In our MZL series, one of the largest reported, prognosis of MZL is good with a median OS of 19 years. Age > 60, Hb < 12 g/dL, elevated LDH, and > 4 LN involved are associated with inferior OS.

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**8555** Poster Session (Board #371), Sun, 8:00 AM-11:30 AM A phase I trial of lenalidomide maintenance after autologous stem cell transplant (ASCT) in patients with high-risk relapsed/refractory lymphoma. First Author: Jaimie Lymphoma and Plasma Cell Disorders, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

**Background:** Lymphoma patients (pts) with residual hypermetabolic lesions on PET imaging after salvage chemotherapy have extremely poor outcomes and may benefit from continued therapy after ASCT. Lenalidomide (len) has been used as maintenance in other hematologic malignancies, but its toxicity and efficacy are not well known in lymphoma pts following ASCT. Methods: We conducted a phase I trial of len maintenance after ASCT in lymphoma pts at high risk for relapse defined by residual PET positive lesions of SUV > 2.5 immediately prior to ASCT. Our primary objective was to determine the safety and dose-limiting toxicity (DLT) of len maintenance. A 3+3 de-escalation design was utilized with a starting dose of len at 10 mg on days 1 through 28 of each 28 day cycle (C). Len was initiated 28-100 days post-ASCT and planned for twenty four Cs. DLT was defined as non-hematologic toxicity ≥ grade (G)3 or hematologic toxicity ≥ G4 during the first 28 days of len. Enrollment began in 5/2012; reported data were collected through 1/2015. **Results:** Eight pts were enrolled and 6 pts are evaluable (4 diffuse large B-cell and 2 Hodgkin lymphomas). One pt withdrew consent and one progressed prior to initiation of len. Median age was 51 yrs (29-61), ECOG PS 0-1, prior therapies 3-25. Median time on len was 7 Cs (2-24). Len was well tolerated and no DLT was observed at the 10 mg dose. Two pts required dose reduction to 5 mg due to treatment-related toxicities (after C7 and C3). Four pts had ≥ G2 non-hematologic adverse events possibly related to len including fatigue, bronchitis, and thrush. Three pts had transient ≥ G3 neutropenia. Two pts discontinued len (1 due to progression, 1 at investigator’s discretion). No secondary malignancies or study-related deaths were observed. Four of 6 pts continued on len and 4 of 6 were progression-free at median follow-up of 195 days. **Conclusions:** We established safety of len after ASCT in pts with relapsed/refractory lymphomas and determined that len 10 mg daily is a well-tolerated maintenance dose in this setting. Preliminary clinical outcomes observed in this cohort of high-risk lymphoma pts are encouraging and will be validated in the ongoing phase II trial. Clinical trial information: NCT01575860.
8556 Poster Session (Board #374), Sun, 8:00 AM-11:30 AM

Background: RTK families are attractive therapeutic candidates. One of the families is the ROR receptors. ROR1 is of importance during embryogenesis but down-regulated in most adult human tissues. ROR1 has been shown to be expressed in cHL as well as in other hematological malignancies and solid tumors and is constitutively phosphorylated. ROR1 siRNA transfection of cHL cells induced apoptosis. We have produced and explored the activity of a new class of compounds, acting as inhibitors of phosphorylation of the tyrosine kinase domain of ROR1 (ROR1-TKI). We describe for the first time the activity of a lead ROR-TKI, KAN0439834.

Methods: ROR1 inhibitors were derived from a high-throughput screen (HTS) using HTRF assay based on recombinant intracellular kinase domain of ROR1. The lead compounds were then optimized in an in vitro and in vivo pharmacokinetic setting. Results: KAN0439834 induced apoptosis in vitro of fresh cHL cells from patients with non-progressive and progressive disease as well as from patients with fludarabine resistant disease with and without 17p abnormalities (EC50 for cHL cells < 200 nM and for normal PBMC > 14 µM). In vitro incubation resulted in dephosphorylated ROR1, Src, PIK6, AKT, mTOR and CREB. 6 h incubation was sufficient to induce full apoptosis at 24 h. In NOD-SCID mice xenografted with human cHL cells orally bioavailable KAN0439834 induced a significant reduction of ROR1+ cells, dephosphorylated pROR1, downregulated Mcl-1 and upregulated cleaved PARP. PK analyses showed a blood concentration of KAN0439834 to be sufficient to induce apoptosis of cHL cells. Minimal animal toxicity could be noted. Conclusions: The ROR1 inhibitor is expressed in cHL cells and of importance for survival. Targeting ROR1 by a TKI induced a strong killing of leukemia cells in vitro. The drug depleted the activated ROR1 as well as PI3K/AKT/mTOR. In an animal cHL model the lead ROR1 inhibitor compound significantly reduced xenotransplanted cHL cells with minimal animal toxicity. This is a first report of a novel class of candidate drugs targeting ROR1. The candidate drug will be further evaluated in preclinical in vivo efficacy and safety models before proceeding to clinical evaluation.

8557 Poster Session (Board #375), Sun, 8:00 AM-11:30 AM
BRD4 degrades produce long-lasting loss of BRD4 Potein and robust efficacy in Burkitt’s lymphoma cells. First Author: Kevin Coleman, Arvinas, North Haven, CT.

Background: We have created specific BRD4 degraders using PROTAC (PROteolysis TArgeting Chimera) technology. This involves creating bifunctional molecules, with one end having a ligand for BRD4 and the other end creating an element for the E3 ligase cereblon. These PROTACs promote the interaction of BRD4 with cereblon, resulting in its degradation via the proteasome degradation machinery.

Methods: Treatment of NA-MALWA, Ramos, CA-46 and Daudi Burkitt’s lymphoma cells with BRD4 PROTACs leads to rapid loss of BRD4, with near complete loss observed within 4 hours. This effect is potent and long lasting, with the most effective molecules having DC50s in the pM range, and with 1 hour treatment of cells resulting in BRD4 loss over a 3 day period. We examined the functional effects of BRD4 PROTACs in several Burkitt’s lymphoma cell lines, comparing their effects to those observed with the clinical BRD4 inhibitor OX015. Results: We found that treatment of cells with the BRD4 inhibitor OX015 led to a rapid and robust hyper-acclimation of BRD4 that, together with the reversible nature of binding to BRD4, may have accounted for the observed moderate suppression of MYC expression, modest inhibition of cell proliferation and lack of cellular apoptosis. In contrast, BRD4 PROTACs maintained suppression of BRD4 protein throughout the several day experiment, maintained near complete MYC suppression and caused both pronounced suppression of proliferation and robust apoptotic responses, as measured by PARP cleavage. Conclusions: These data imply that degradation of BRD4 can provide a more robust therapeutic approach to MYC-driven hematological cancers.

8558 Poster Session (Board #376), Sun, 8:00 AM-11:30 AM
A phase 1 study of INCB040093, a PI3Kδ inhibitor, alone or in combination with INCB039110, a selective JAK1 inhibitor: Interim results from patients (pts) with relapsed or refractory (r/r) classical Hodgkin lymphoma (cHL). First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL.

Background: Efficacy of treatment options for pts with r/r cHL is limited. Evidence suggests blocking the PI3K or JAK-STAT pathways may be efficacious in cHL directly and through modulation of the tumor microenvironment. Blocking both pathways may provide synergistic efficacy. Methods: Adult pts with r/r B-cell malignancies were enrolled in this ongoing single institution, phase 1 dose escalation study. INCB040093 was given at doses of 100–300 mg QD or BID alone or 150–300 mg QD or BID with INCB039110. Data from the r/r cHL pts are reported herein. Results: A total of 17 pts with r/r cHL have been enrolled: median age = 34 yrs, 59% men, median of 5 prior regimens, 82% underwent HSCT, and all had failed brentuximab vedotin. Minimal animal toxicity could be noted. Conclusions: The ROR1 inhibitor is expressed in cHL cells and of importance for survival. Targeting ROR1 by a TKI induced a strong killing of leukemia cells in vitro. The drug depleted the activated ROR1 as well as PI3K/AKT/mTOR. In an animal cHL model the lead ROR1 inhibitor compound significantly reduced xenotransplanted cHL cells with minimal animal toxicity. This is a first report of a novel class of candidate drugs targeting ROR1. The candidate drug will be further evaluated in preclinical in vivo efficacy and safety models before proceeding to clinical evaluation.

8559 Poster Session (Board #377), Sun, 8:00 AM-11:30 AM
High throughput in vitro combination sensitivity screen in hematologic malignancies with the phosphoinositide-3 kinase (PI3K)-δ,γ inhibitor, duvelisib. First Author: Kerrie Fala, Infinity Pharmaceuticals, Cambridge, MA.

Background: Duvelisib (IP1-145) is an orally active inhibitor of the PI3K-δ and PI3K-γ isoforms in clinical development in HM. To gain mechanistic insights into the cellular response to duvelisib and identify novel pairings for duvelisib in HM, a high-throughput in vitro combination screen was conducted. Methods: Duvelisib was evaluated alone and in combination with 35 compounds comprising a diverse panel of standard-of-care agents and emerging drugs in development for HM. These compounds were tested in 20 cell lines including diffuse large B-cell (DLBCL), follicular, mantle cell, and mantle cell lymphomas, and multiple myeloma. Growth inhibition (GI) was measured by ATPLite (Perkin Elmer) in a 6x6 or 9x9 dose combination matrix. Results: Single agent activity was seen in 14 cell lines treated with duvelisib, with a median GI50 of 0.59 µM. A scalar measure of the strength of synergistic drug interactions (Synergy Score) was devised and filtering on scores exceeding the mean self-cross plus twice the standard deviation revealed a synergy hit rate of 19.3% across the matrix of drug combinations and cell lines. Synergy was most prominent in DLBCL and follicular lymphoma cell lines and seen with approved and emerging drugs used to treat HM, including, but not limited to, dexamethasone, inotuzumab and gemtuzumab ozogamicin. Conclusions: These studies support enhanced activity of combined PI3K-δ and PI3K-γ inhibitors in lymphoma models and identified synergistic pairings with the PI3K-δ and PI3K-γ inhibitor, duvelisib. These results provide a rationale for exploring the combination of duvelisib and other therapeutic agents in clinical studies.
Early high-dose therapy and autologous stem-cell transplantation in angio-immunoblastic T-cell lymphoma: Outcome study using the National Cancer Data Base. First Author: Pawan Kumar Karanam, Gundersen Health System, Lacrosse, WI

Background: Angioimmunoblastic T-cell lymphoma (AITL) is a rare aggressive non-Hodgkin lymphoma with a poor outcome. The role of high-dose therapy followed by autologous stem-cell transplantation as a consolidation strategy (early SCT) remains undefined. We studied the outcome of AITL patients who received early SCT using the National Cancer Data Base (NCDB). Methods: Patient level data were obtained from the NCDB Participant User File. The NCDB collects hospital cancer registry data representing 70% of newly diagnosing cancer cases in the US population. We identified AITL patients (ICD-O-3: 9705) diagnosed in 1998-2011 for demographics, disease and treatment characteristics. We included patients diagnosed from 1998-2006 in the overall survival (OS) analyses. Patients who received SCT as part of their first course of treatment were considered to have early SCT. Results: From 1998-2011, 515,026 patients were diagnosed with NHL and 3,160 (0.6%) had AITL. The median age at diagnosis was 69 years (range, 18-90+) and 52.8% were males. The stage distribution was as follows: I (58.5%), II (6.7%), III (35.4%), IV (34.8%), and unknown (17.3%). The median overall survival (OS) for the entire cohort was 17.7 months. Compared to those diagnosed in 1998-2000, patients diagnosed in 2001-2003 (HR: 1.09; 95% CI: 0.94-1.28) and 2004-2006 (HR: 0.99; 0.86-1.16) had similar OS. There were 201 patients (6.4%) who received early SCT. The use of early SCT steadily increased over time from 1.0% in 1998 to 9.5% in 2011 (P < 0.001). The unadjusted OS was superior among patients who had early SCT (median 94.8 versus 16.7 months; HR: 2.46; 1.68-3.60). On multivariable analysis, age > 70 years (HR: 1.65; 1.40-1.95), Black race (HR: 1.39; 1.10-1.76), stage IV (HR: 1.39; 1.24; 1.04-1.70), and not having early SCT (HR: 1.89; 1.28-2.79) were associated with inferior OS. Conclusions: This is the largest series of AITL reported to date. The OS remains poor and has not improved during the study period. The use of early SCT has increased ten-fold in the past decade. Early SCT may improve long term outcome and warrants further evaluation.

Role of radiation (RT) in primary mediastinal large B-cell lymphoma (PMBCL): An analysis of the Surveillance, Epidemiology, and End Results (SEER) database. First Author: Smith Girli, The University of Tennessee Health Science Center, Memphis, TN

Background: In the rituximab era, patients with PMBCL demonstrate high complete remission rate and a plateau in survival curve beyond 2-3 years. The use of RT in these young patients may predispose to the risk of cardiopulmonary toxicities and secondary malignancies. Methods: We used SEER 18 database and histology code 96791 to identify adult patients with PMBCL between 1973 and 2011. FDA approved rituximab for diffuse large B cell lymphoma in 2006. Hence, using the year 2006 as a cutoff, we compared the survival differences among patients treated with and without radiotherapy. Kaplan Meier survival curves with log rank test were plotted to compare survival statistics. Chemotherapy regimen could not be ascertained. Cox proportional hazard regression model was done to adjust for other covariates including age, year of diagnosis, race, Ann Arbor stage and gender. All p-values were two-sided and level of significance was chosen at 0.05. Results: Of 358 PMBCL patients, 50.5% patients (n = 181) received RT. Those who received radiation were more likely to be younger than 50 years (90% vs. 81%, p = 0.01) but were similar in terms of gender, race and stage at diagnosis. The unadjusted five-year overall survival (OS) was higher for RT vs. non-RT group (84% vs. 74%, p = 0.02). When stratified by year of diagnosis, OS was higher for RT vs. non-RT group in pre-rituximab era (before 2006) but not in post-rituximab era (after 2006). In multivariable analysis, RT remained an independent predictor of improved OS in pre-rituximab era (HR 0.36; 95% CI 0.17-0.79; p = 0.01) but not in post-rituximab era (HR 0.96; 95% CI 0.45-2.05; p = 0.93) after adjusting for age, year of diagnosis, gender, race and stage at diagnosis. Conclusions: Our study suggests that the effect of rituximab may reduce the benefit of RT in select patients such as patients treated with R-EPOCH or those with important risk factors for breast cancer/coronary artery disease. However, select patients such as those with large masses, positive PET scan after chemotherapy or those treated with R-CHOP may still benefit from RT. Resolving these questions is an important topic for future research.

Lymphoma and Plasma Cell Disorders
The outcome of ALK positive and ALK negative anaplastic large cell lymphoma (ALCL) following DA-EPOCH. First Author: Catherine Lai, Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: Systemic anaplastic large cell lymphoma (ALCL) is a clinically and molecularly heterogeneous type of peripheral T-cell lymphoma (PTCL). It may be subdivided into cases with or without translocation of the anaplastic lymphoma kinase gene (ALK), leading to overexpression of ALK. While the outcome for patients with ALK positive ALCL - particularly in pediatric patients - has been very favorable following doxorubicin-based therapy, ALK negative cases have fared more poorly. Approaches such as autologous transplantation have been studied in this group in an attempt to improve outcome (d’Amore et al. J Clin Oncol, 2012). Methods: 23 patients with newly diagnosed ALK positive (15) and ALK negative (8) ALCL underwent treatment with 6 to 8 cycles of dose-adjusted infusional etoposide, vincristine and doxorubicin with prednisone and cyclophosphamide (DA-EPOCH). Both groups had similar IPI characteristics (shown below). Results: 19/23 (83%) patients achieved CR or CRu. 3/23 (13%) a PR and 1 patient had PD. At the median potential follow-up time of 13 years, event free survival (EFS) in ALK positive and ALK negative ALCL was 72% and 62.5% (p = 0.50) and overall survival was 76% and 87.5% (p = 0.82), respectively. Toxicity was assessed on all 135 cycles. Neutropenic fever and thrombocytopenia <25,000/mm3 occurred on 10% of cycles, respectively. Absolute neutrophil count (ANC) less than 500 cells/mm3 occurred on 35% of cycles. Conclusions: Following DA-EPOCH, the outcome of ALK negative ALCL is equivalent to ALK positive ALCL. The incorporation of etoposide, infusional scheduling and dose adjustment may play important roles in ALCL therapeutics. DA-EPOCH should be considered a reasonable front-line regimen in ALCL and especially in older patients where approaches such as transplantation may not be feasible. Clinical trial information: NCT00001337.

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Outcome comparison of allogeneic vs. autologous stem cell transplantation in transformed low grade lymphoid malignancies: A meta-analysis of comparative studies. First Author: Seongseok Yun, University of Arizona, Tucson, AZ

Background: Low grade lymphoid malignancy is incurable disease with a chronic relapsing disease course, requiring recurrent therapeutic interventions. Stem cell transplantation (SCT) has become the cornerstone in the cure of this disease. While both allogeneic and autologous SCTs have been shown to improve survival compared to conventional chemotherapy, allogeneic SCT is associated with overexpression of ALK, leading to overexpression of ALK. While the outcome for patients with ALK positive ALCL - particularly in pediatric patients - has been very favorable following doxorubicin-based therapy, ALK negative cases have fared more poorly. Approaches such as autologous transplantation have been studied in this group in an attempt to improve outcome (d’Amore et al. J Clin Oncol, 2012). Methods: 23 patients with newly diagnosed ALK positive (15) and ALK negative (8) ALCL underwent treatment with 6 to 8 cycles of dose-adjusted infusional etoposide, vincristine and doxorubicin with prednisone and cyclophosphamide (DA-EPOCH). Both groups had similar IPI characteristics (shown below). Results: 19/23 (83%) patients achieved CR or CRu. 3/23 (13%) a PR and 1 patient had PD. At the median potential follow-up time of 13 years, event free survival (EFS) in ALK positive and ALK negative ALCL was 72% and 62.5% (p = 0.50) and overall survival was 76% and 87.5% (p = 0.82), respectively. Toxicity was assessed on all 135 cycles. Neutropenic fever and thrombocytopenia <25,000/mm3 occurred on 10% of cycles, respectively. Absolute neutrophil count (ANC) less than 500 cells/mm3 occurred on 35% of cycles. Conclusions: Following DA-EPOCH, the outcome of ALK negative ALCL is equivalent to ALK positive ALCL. The incorporation of etoposide, infusional scheduling and dose adjustment may play important roles in ALCL therapeutics. DA-EPOCH should be considered a reasonable front-line regimen in ALCL and especially in older patients where approaches such as transplantation may not be feasible. Clinical trial information: NCT00001337.

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Is rituximab sub-optimally dosed in indolent B cell lymphoma? First Author: Yazed Sawahla, Cleveland Clinic, Cleveland, OH

Background: Rituximab (R) pharmacokinetics (PK) are affected by gender, age and weight (WT) and can affect outcomes in aggressive B cell lymphoma (Pfreundschuh et al. Proc ASCO 2014). Less is known about PK of R in indolent B cell lymphoma (iNHL). Methods: We analyzed effects of gender, age, WT, BSA and BMI on outcomes for 303 consecutive patients (pts) at the Cleveland Clinic treated with 1st line R-based regimens for iNHL from 1997-2014. We divided pts into 3 treatment cohorts: R only (N = 119), R + Chemotherapy (CTX) (N = 120) and R-CTX followed by R maintenance (Rm) (N = 64); and by follicular (FL) (N = 184) or non-FL (N = 119) histology. Event-free survival (EFS) was based on date of relapse, progression, transformation, loss of follow-up, initiation of 2nd therapy or death. Characteristics among the 3 cohorts were compared using ANOVA and logistic regression. Results: The 3 cohorts were compared using ANOVA and logistic regression. Differences in baseline characteristics among the 3 cohorts were significant differences in baseline characteristics among the 3 cohorts. An event has occurred in 52%. Cut points determined were WT > 81.8 kg, BSA > 2 m² and age > 70. For all pts combined, higher WT was significantly associated with inferior EFS (HR = 1.75, p = 0.007) with or without adjustment for gender and age. Univariable analysis by cohort revealed only R-CTX cohorts had a difference only in R-CTX cohort with high WT associated with lower EFS (HR = 2.0, p = 0.008). For FL within the R-CTX cohort, WT (HR 2.54, p = 0.003) and BMI (HR 2.02, p = 0.024) were associated with worse EFS. Elderly females in this group had better EFS (HR = 0.32) though this did not reach statistical significance (p = 0.098). Conclusions: Our results concur with DLBCL studies in which higher WT was associated with faster R clearance and worse outcomes for R-CTX. As this is not observed in pts after R alone or R-CTX followed by Rm, we hypothesize that higher levels of weekly R and/or prolonged R exposure exceed therapeutic threshold despite more rapid clearance. Pts with iNHL, and FL specifically, treated with R-CTX may be sub-optimally dosed with R.
8558  Poster Session (Board #386), Sun, 8:00 AM-11:30 AM
Relationship of distinct B-cell receptor (BCR) isotype in diffuse large B-cell lymphoma (DLBCL) with ABC and GCB genetic signatures and association with signaling mediators of clinical outcomes
First Author: Abid Qureshi, University of Calgary, Calgary, AB, Canada
Background: DLBCL is a heterogeneous disease. Gene expression profile (GEP) based distinction into ABC and GCB sub-types, provides basis for risk stratification in DLBCL patients. GEP is an intricate platform, which is not routinely available in clinical laboratories. Hence, surrogate markers for distinction between ABC vs GCB subtypes of DLBCL are needed. Methods: We used Nanostring nCounter system for gene expression analysis, utilizing RNA from diagnostic biopsy tissues. We correlated, flow-cytometry based BCR-isotype (IgM/IgG) expression with mRNA levels in a series of ABC/GCB related genes (n = 54). We also investigated gene set (n = 48) related to TLR, NF-kB and JAK/STAT pathways to determine, if BCR- isotype expression was distinguishable on specific molecular pathways. Results: Median expression for each gene was compared across two BCR isotype groups utilizing fisher’s exact test. Results: Our cohort (n = 44) comprised of IgG* (n = 13; 30%) and IgM* (n = 31; 70%) DLBCL patients. BCR-isotype expression showed significant association with specific molecular signature related to cell of origin. IgG expression was linked with GCB genetic profile and IgM expression allied with ABC related genes (P < 0.001), thus confirming a previous single report (Leukemia. 2011 Apr; 25 (4):681-8). IgM expression related well with higher median expression of BLNK, LYN, BCL10, CARD 11 (P < 0.001); while SYK/BTK expression showed no significant differences (P > 0.01). In NF-kB pathway, expression levels of p100, p52, IKKx were significantly higher in IgM* DLBCL, compared to IgG* DLBCL patients (P < 0.001); thus suggesting higher NF-kB activity. Genes related to TLR and PI3K/STAT pathway showed no significant differences between two BCR-isotype groups (P > 0.182). In relation to JAK/STAT signalling pathway, IgM* DLBCL showed significantly higher expression of STAT3/JAK2 genes (P < 0.001). Conclusions: Our data stipulates some preliminary observations that BCR-isotype is distinct between ABC and GCB subtypes of DLBCL. We have also shown linkage of BCR-isotype with some critical pathways related to disease biology in DLBCL.

8569  Poster Session (Board #387), Sun, 8:00 AM-11:30 AM
Overall survival in patients with Hodgkin lymphoma: Disparities by insurance status. First Author: Rahul Panikh, Mount Sinai Beth Israel; Mount Sinai Health System, New York, NY
Background: The association between insurance status and outcome has not been well established for patients with Hodgkin Lymphoma (HL). The purpose of this study was to examine the disparities in overall survival (OS) by insurance status in a large cohort of patients with HL. Methods: We used a prospectively collected nationwide database—the National Cancer Data Base (NCDB) to evaluate clinical features and survival outcomes among patients with HL diagnosed with stage I-IV HL from 1998 to 2011. The association between insurance status, co-variables, and outcome was assessed in a multivariate Cox proportional hazards model. Survival was estimated using the Kaplan-Meier method. Results: Among the 76,672 patients with HD within the NCDB, a total of 45,777 patients with stage I-IV disease were evaluated. We found that insurance status was significantly associated with the risk of death among all stages of disease especially in those less than 70 years old. All patients in the public insurance group had worse overall survival compared to private insurance group (HR = 1.21, 95% CI: 1.16-1.26, P < 0.001). However, among patients with advanced stage disease, this difference was not observed. Conclusion: Our study reveals that patients with Medicaid or uninsured have inferior outcomes than patients with more favorable insurance. To our knowledge, this study represents the largest dataset examining the role of insurance status on survival for patients with HL. Targeting this subset of patients with limited access to care may help improve outcomes.

8570  Poster Session (Board #388), Sun, 8:00 AM-11:30 AM
Distinct early response dynamics of circulating tumor DNA and circulating tumor cells during therapy of B-cell NHL. First Author: David Matthew Kurzt, Division of Oncology, Stanford University School of Medicine, Stanford, CA
Background: Both circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have been used for disease monitoring in non-Hodgkin lymphoma (NHL) (Armand BJH 2013; Kurzt ASCO 2014; Roschewski ASH 2014). However, it remains unclear how these compartments compare during induction of active therapy in NHL. Using immunoglobulin high-throughput sequencing (lg-HTS), we compared the dynamics of ctDNA and CTCs in response to systemic therapy. Methods: We performed 206 lg-HTS assays from 104 serial blood samples in diverse patients with NHL receiving their first cycle of systemic therapy at Stanford University. Tumor samples were used to define tumor specific DNA sequences by Ig-HTS. Identified sequences were used to track ctDNA and CTCs. Results: A total of 17 patients with NHL were enrolled (DLBCL = 10, FL = 3, transformed FL = 4). All patients received Rituximab-containing regimens. In patients with high-grade disease, CTCs and ctDNA decreased by a mean of 94% (61%-100%) and 95% (68%-100%) after 1 cycle of therapy respectively. CTCs and ctDNA decrease in intensity on cycle 3 and 5 patients by cycle 2. However, a dramatic increase or ‘spike’ was seen in ctDNA levels within hours of Rituximab (median increase 8.0x, range 0.3x to 264x). In contrast, a dramatic decrease was seen in CTCs (median decrease 72%, range -23% to 93%), indicating their rapid clearance. This ctDNA spike was observed in 6 out of 10 patients, but not in 2 transformed FL patients (post 0.02). The size of the ctDNA spike was significantly associated with the burden of pretreatment CTCs (p < 0.001) and the magnitude of decrease in CTCs (p < 0.001), but was not associated with the pretreatment ctDNA level (p = 0.88). Four of eight patients achieving CR and 2/3 patients not achieving CR had a spike in ctDNA (p = 1.0). Conclusions: While ctDNA and CTCs can be used to monitor NHLs, their dynamics in response to therapy are distinct. Although both clear during therapy, a rapid increase in ctDNA is seen in response to Rituximab, indicating cell death of CTCs. This ctDNA spike is associated with therapeutic effect on CTCs, but not with outcome in this small cohort. Circulating tumor DNA is a potentially useful method to measure cell death in NHL and other malignancies.

8571  Poster Session (Board #389), Sun, 8:00 AM-11:30 AM
Effect of prednisone and rituximab prephase on early toxicity in older DLBCL patients (pts) receiving RCHOP within a NHL specific comprehensive geriatric assessment (CGA) trial. First Author: Colette Ngzi Owens, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Older pts with DLBCL are increasing in the US and are most vulnerable to treatment related toxicities and mortality (TRM). Effective tools to predict and mitigate toxicity are essential in these pts. The RICOVER-60 trial implemented a “pre-phase” of vincristine and prednisone (Pred) to reduce disease symptoms and improve KPS, reporting decreased early TRM. This prospective pilot study in older DLBCL pts employs a pre-phase of Pred and rituximab (R) as part of a larger CGA validation study in NHL (n = 200; NCT01829958). Methods: Eligible pts (n = 30) had de novo DLBCL/DLBCL, age ≥ 70 yrs or ≥ 60 yrs with KPS ≤ 80%, and planned RCHOP-like therapy for 2+ cycles. CGA consisted of CARG and CRASH scores as largely self administered assessments. CA was assessed at baseline, post pre-phase, with each cycle, and at end-of-therapy. Pre-phase included Pred 50-100mg x 5-10 days and R. Results: A total of 17 patients with NHL were enrolled (DLBCL = 10, FL = 3, transformed FL = 4). All patients received Rituximab-containing regimens. In patients with high-grade disease, CTCs and ctDNA decreased by a mean of 94% (61%-100%) and 95% (68%-100%) after 1 cycle of therapy respectively. CTCs and ctDNA decrease in intensity on cycle 3 and 5 patients by cycle 2. However, a dramatic increase or ‘spike’ was seen in ctDNA levels within hours of Rituximab (median increase 8.0x, range 0.3x to 264x). In contrast, a dramatic decrease was seen in CTCs (median decrease 72%, range -23% to 93%), indicating their rapid clearance. This ctDNA spike was observed in 6 out of 10 patients, but not in 2 transformed FL patients (post 0.02). The size of the ctDNA spike was significantly associated with the burden of pretreatment CTCs (p < 0.001) and the magnitude of decrease in CTCs (p < 0.001), but was not associated with the pretreatment ctDNA level (p = 0.88). Four of eight patients achieving CR and 2/3 patients not achieving CR had a spike in ctDNA (p = 1.0). Conclusions: While ctDNA and CTCs can be used to monitor NHLs, their dynamics in response to therapy are distinct. Although both clear during therapy, a rapid increase in ctDNA is seen in response to Rituximab, indicating cell death of CTCs. This ctDNA spike is associated with therapeutic effect on CTCs, but not with outcome in this small cohort. Circulating tumor DNA is a potentially useful method to measure cell death in NHL and other malignancies.
A phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rMM). First Author: Marc S. Raab, University Hospital Heidelberg, Heidelberg, Germany

**Background:** MOR202 is a HuCAL-derived fully human IgG1 anti-CD38 antibody, with high efficacy in preclinical models of MM. **Methods:** This is an open-label, dose-escalation study (3 + 3 design) to evaluate the safety and preliminary efficacy of MOR202 in adult patients (pts) with rMM. We present the data of pts previously treated with ≥ 2 prior therapies including an immunomodulatory drug and a proteasome inhibitor. Pts received 2-hour IV MOR202 every 2 weeks (q2w) (8 dose levels [DLs] from 0.01–16 mg/kg) without dexamethasone (DEX), or 4 or 8 mg/kg (DLs 6 and 7), weekly (q1w) +/- DEX. MOR202 16 mg/kg (DL 8) q1w +/- DEX and combination cohorts with lenalidomide (LEN)/melphalan (POM) + DEX are planned, as well as confirmation cohorts. **Results:** As of December 31, 2014, 138 pts had been treated; 29 and 9 pts in the q2w and q1w DLs, respectively. Median age was 70 (44–80) yrs. The median number of prior therapies was 4 (2–10) for all pts. 36 pts (94.7%) developed AEs.

**Conclusions:** The prognostic value of interim positron emission tomography/computing tomography (PET/CT) according to the Deauville criteria (as negative or positive), and by this retrospective study. All images were reviewed and interpreted visually according to the Deauville criteria (as negative or positive), and by computing ∆SUVmax, lymphopenia (2.6%). Infusion-related reactions occurred in 13 pts (34%). No deaths occurred. PK data demonstrate a significant target-mediated drug disposition effect for most pts treated q2w. In 4/6 pts in the q1w 4 mg/kg cohort MOR202 trough levels show the start of target saturation. Only 1 pt (MOR202 0.15 mg/kg q2w) generated a transient anti-drug antibody response to MOR202. The MTD has not been reached, MOR202 is safe and well tolerated. PK data show the potential for full target occupancy in the majority of pts receiving 8 and 16 mg/kg q1w. These latter DLs of MOR202 will be tested as monotherapy or in combination with DEX, LEN + DEX and POM + DEX in the upcoming cohorts. Efficacy analyses are ongoing. Clinical trial information: NCT01421186.

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Phase I interim safety and efficacy of venetoclax (ABT-199/GDC-0199) monotherapy for relapsed/refractory (R/R) multiple myeloma (MM). First Author: Shaji Kumar, Mayo Clinic, Rochester, MN

Background: The anti-apoptotic protein BCL-2 has been implicated in mediating the survival of MM cells. Venetoclax (VEN) is a potent, selective, orally bioavailable small-molecule BCL-2 inhibitor. VEN induces cell death in MM cell lines and primary samples in vitro, especially in CD38- and t(11;14)-positive (t11;14) clones which express a high ratio of BCL2 to MCL1 (VEN resistance factor). The current Ph I study evaluates safety and efficacy of VEN in pts with R/R MM. Methods: Primary objectives are to evaluate safety, PK, and efficacy of VEN and PPTD; other objectives include preliminary efficacy and impact of chromosomal abnormalities. In dose-escalation cohorts, VEN was given PO daily at 300, 600, 900, or 1200 mg after preliminary safety and efficacy, which included 21 of 28 pts were evaluable for preliminary efficacy. Best response by t(11;14) status shown in Table. Conclusions: VEN monotherapy was well tolerated in heavily pretreated R/R MM. Responses (including CR) and longer ToS were observed in group 2 (21-day cycle). Among newly diagnosed pts, the median follow up was 42 mos. Eligible pts could receive SCT (auto and/or allo). Visited abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

8578 Poster Session (Board #396), Sun, 8:00 AM-11:30 AM
Outcome at first relapse after frontline RVD regimen plus lenalidomide maintenance in transplant eligible MM patients. First Author: Manuile Roussel, Hematology Department, IUCT Oncopole-CHU Purpan, Toulouse, France

Background: The IFM 2009 trial recruited 700 MM pts between 2010-2012. Pts were randomly assigned to received RVD (5-8 cycles) and 1-yr Len maintenance +/- upfront ASCT. More than 250 pts relapsed. We aimed to analyze response rates (RR) and survival outcomes after salvage therapy. Methods: Pts who relapsed during RVD cycles or first 2 months of maintenance (group 1) were considered Relapsed and Double Relapsed and were likely to receive CVAD or DCEP regimen. Pts who relapsed during or early after maintenance (Group 2) were considered Relapsed and Len Refractory and were likely to receive VCD, CPAD or pomalidomide based regimen (PCD). Pts who relapsed during FU (Group 3) were standard Relapsed. Eligible pts could receive SCT (auto and/or allo). Results: 83 pts were retrospectively analyzed. Median age was 56 years (28-65), ISS 2/3=37/22, 27 pts had High Risk (HR) cytogenetics. Group 1 comprised 15 pts (10 relapsed during RVD induction/consolidation). Eight pts received CVAD, 3 DCEP and 1 PD. Three pts died before any tx. Group 2 comprised 40 pts; 14 received VCD, 8 CPAD, 4 DCEP and 11 PCD. Group 3 comprised 28 pts; 12 received VCD, 3 CPAD and 11 PCD. RR and survival outcomes are listed in table 1. ORR was 40, 67.5 and 75% in groups 1, 2 and 3 respectively. Conclusion: Relapsed pts within 1 year of RVD induction/consolidation have impaired prognosis after salvage therapy.

8579 Poster Session (Board #397), Sun, 8:00 AM-11:30 AM
Preliminary safety and efficacy of evosofosfamide (TH-302), an investigational hypoxia-activated prodrug, combined with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma (RR MM). First Author: Jacob Laubach, Dana-Farber Cancer Institute, Boston, MA

Background: The presence of hypoxia in the diseased bone marrow presents a new therapeutic target for multiple myeloma (MM) (Colla, Leukemia 2010). Evosofosfamide (EVO; formerly TH-302) is a novel 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide mustard that is selectively activated under hypoxia and is investigated in multiple Phase 1-3 trials. Synergistic induction of apoptosis in MM cells by EVO and bortezomib (Bor) was shown in vivo and in vitro (Hu et al, Mol Cancer Ther 2013). An ongoing phase I/II study investigates EVO in combination with Bor and dexamethasone (Dex) in RR MM (NCCT01522872). Methods: This phase I/II open-label multicenter study investigates EVO (240-480 mg/m2), IV or SC Bor (1.3 mg/m2), plus PO D (40 mg) on Days 1, 4, 8 and 11 of a 21-day cycle. At the maximum tolerated dose, a Simon two-stage optimal design was implemented to pursue a regimen with ≥ 50% response rate or discontinue if ≤ 25% (85% power, 10% alpha). Results: Nine patients (pts; 4 male, 5 female) have been reported (3 at 240 mg/m2 EVO and 6 at 340 mg/m2 EVO) with the log-rank pre-treated median number of prior therapies was 8 (4 – 12). Median age was 57 years (45 – 68). All had previously received Bor and lenalidomide or thalidomide. No pt had a dose limiting toxicity and the recommended phase 2 dose (RP2D) was established at 340 mg/m2 EVO. The most common ≥ Grade 3 adverse events were thrombocytopenia (6 pts), nausea (5 pts), vomiting, anemia (2 pts) and neuropathy (2 pts). Limited skin toxicity has been observed (2 pts, grade 2 rash or skin lesions). Four pts had SAEs; one SAE of thrombocytopenia was related to EVO. Seven pts discontinued for progressive disease; no pts have discontinued due to an AE. IMWG assessments were completed on 12 Pts. 4 PR, 4 SD and 2 PD (1 CR and 2 PRs out of 6 pts at 340 mg/m2 EVO). Two pts with a CR and PR continue on study. To date, 17 of 24 pts have been enrolled to evaluate safety and efficacy at the RP2D. Conclusions: EVO can be administered at 340 mg/m2 twice a week with Bor and D. Preliminary clinical activity has been noted in pts with heavily pre-treated RR MM. Data from pts treated at the RP2D will be updated and presented at the meeting. Clinical trial information: NCT01522872.
8580 Poster Session (Board #398), Sun, 8:00 AM-11:30 AM
Phase 1b interim results: Venetoclax (ABT-199/GDC-0199) in combination with bortezomib (BTZ) and dexamethasone (Dex) in relapsed/refractory (RR) multiple myeloma (MM). First Author: Cyrille Touzeau, CHU de Nantes, Hotel Dieu—HME, Nantes, France

Background: The anti-apoptotic proteins BCL-2 and MCL-1 promote MM cell survival. BTZ can inhibit MCL-1 activity by elevating the MCL-1 antagonist, NOKA. Venetoclax (VEN) is a selective, orally bioavailable, small-molecule BCL-2 inhibitor, which enhances BTZ efficacy in in vitro and in vivo pharmacologic models. In this phase 1b study evaluates VEN with BTZ and Dex in patients (pts) with RR MM. Methods: Objectives include safety, PK, preliminary efficacy, and MTD of VEN with BTZ and Dex. Pts received VEN 50-500 mg PO daily in cycles (C) of 28 days followed by designated dose escalation (DE) cohorts (continual reassessment); BTZ (1.3 mg/m² on days [D] 1, 4, 8, 11) and Dex (20 mg/m² on D1, 4, 5, 8, 9, 11, 12) in C1-8 (21D), BTZ D1, D2, D8, 15, 22 in C9-11 (35D), and VEN alone ≤ C12. Results: 32 pts were enrolled as of 1/12/2014; median age 65, 12/20 F/M. 12 were ISS stage I, 7 stage II, 10 stage III. Median (range) prior therapies: 5 (1–15). 26 pts received prior BTZ (10 refractory), 26 had prior lenalidomide, and 20 auto-HSCT. AEs (≥ 25% pts: constipation (41%), diarrhea (38%), peripheral edema (28%), thrombocytopenia (31%), peripheral neuropathy (28%), insomnina (28%), dyspepsia (25%), anemia (22%). Grade 3/4 AEs (≥ 10%): thrombocytopenia (25%), anemia (13%), 14 pts had SAE: none VEN-related. Reason for discontinuation (D/C): n (N) = 17; PD (n = 14), AEs (n = 2): adrenocarcinoma, cardiac and respiratory decompensation, consent withdrawal (n = 1), 3 deaths occurred (due to PD); 1 DLT at 300 mg (cardiac decompensation attributed to DEX). No TLS occurred. Dose-normalized exposure when given with BTZ + Dex (n = 30) was similar to VEN alone. Preliminary efficacy (best response) by BTZ status. Conclusions: Venetoclax with BTZ and Dex has an acceptable safety profile in heavily pretreated MM. This combination targeting BCL-2 and MCL-1 resulted in anti-tumor activity and longer TOS in pts naive or sensitive to prior BTZ. DE continues at 600 mg. Clinical trial information: NCT01794507.

8581 Poster Session (Board #399), Sun, 8:00 AM-11:30 AM
Total marrow irradiation (TMI) with helical tomotherapy and peripheral blood progenitor cell rescue (PBPC) following high-dose melphalan (MEL) conditioning and PBPC as part of tandem autologous transplant (TAT) for patients with multiple myeloma. First Author: George Samolo, City of Hope, Duarte, CA

Background: Ablative dose total body irradiation (TBI) of 800 cGy in combination with high-dose melphalan (MEL) was found to be too toxic. TMI, an image-guided targeted TBI using TomoTherapy intensity modulated radiotherapy, given as the sole ablative regimen for the second cycle (C) of TAT was tested in patients (pts) with stable (SD)/responsive MM, in a phase I-II trial. Here we present a long-term update on outcome. Methods: We enrolled pts with Durie-Salmon stages (DS) I-III MM in response or with SD, who were ≥ 70 years old and ≤ 18 months from diagnosis. Pts received MEL 200 mg/m² and AT (C 1), and, after recovery, TMI (MTD: 1600 cGy) and AT (C 2) followed by maintenance therapy with dexamethasone and an IMID. Results: 54 pts started treatment (23 F/31M). The median age was 54 years (31-67). DS stages were: I (N = 4), II (N = 18), III (N = 32). 44 of the 54 pts received TMI (28 of 36 pts enrolled at the MTD received TMI). 10 pts did not receive TMI due to post-MEL toxicities or pt or doctor's choice. The median time between MEL and TMI was 65 days (range 47-125). All pts engrafted. 9/14 (64%) experienced febrile neutropenia (FN) following MEL, and 8/44 (18%) experienced FN after TMI; less frequent grade 3 or 4 non-hematologic toxicities were similar between MEL and TMI. Best responses included CR (N = 22, of which 3 were in CR to MEL), very good partial response (VGPR, N = 8, of which 2 were in VGPR prior to MEL) and PR or SD (N = 14). Median follow-up of alive pts is 73 months (27-117). Second malignancies included 2 skin, 1 breast, 1 thyroid carcinoma, and 1 acute myeloid leukemia. In intent-to-treat analysis median PFS for the 54 pts is 52 months (95% CI 34.4- NR), and median OS is not reached. PFS and OS at 5 years is 43% (95% CI 31-59) and 66% (95% CI 53-79), respectively. For pts enrolled at 1600 cGy, the PFS and OS at 5 years were 48% (34-69) and 73% (59-90). Conclusions: TMI of 1600 cGy is feasible following MEL in MM patients. The long-term safety and PFS/OS are encouraging, and further assessment of TMI is warranted. Clinical trial information: NCT01112827.

8582 Poster Session (Board #400), Sun, 8:00 AM-11:30 AM
Overall survival in newly diagnosed MM patients with del(17p): A report from the Connect MM Registry. First Author: Jatin J. Shah, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Del(17p) is detected in 10%-15% of patients (pts) with MM and is associated with early relapse and short survival. There are limited data, no uniform or optimal treatment (Tx) approach, and questions on role of autologous stem cell transplant (ASCT). Connect MM, a prospective, observational, US, multicenter disease registry, contains the largest cohort of pts with newly diagnosed MM (NDMM) and del(17p). Disease characteristics and OS were analyzed in this cohort. Methods: Connect MM started data collection in Sep 2009. Data from pts (n = 4743) at 234 sites were collected at baseline and quarterly thereafter. Outcomes data through Jun 30, 2014 for pts enrolled up to Dec 2011 (N = 1493) at 234 sites were collected at baseline and quarterly thereafter. Conclusions: There is clear need to improve outcomes in this pt segment.

8583 Poster Session (Board #401), Sun, 8:00 AM-11:30 AM
Outcomes of high, t(11;14), and standard cytogenetic risk multiple myeloma following early high dose therapy and autologous hematopoietic cell transplantation (SCT). First Author: Gregory Peter Kaufman, Mayo Clinic, Rochester, MN

Background: Current cytogenetic risk stratification in newly diagnosed multiple myeloma (NDMM) is not derived from recent patients (pts) treated with novel agents. High dose melphalan and SCT is a preferred management strategy for transplant eligible NDMM pts following novel agent induction. We investigated outcomes of high cytogenetic risk (HR), t(11;14), and standard cytogenetic risk (SR) NDMM treated with early SCT. Methods: Following Mayo Clinic IRB approval and in accordance with the Declaration of Helsinki, all pts treated at Mayo Clinic Rochester with SCT for NDMM between 2003 and 2012 were identified (n = 941). We excluded pts without FISH cytogenetics from diagnosis (dx) and those who did not undergo SCT within 12 months of dx. HR was defined as a composite of smSMART high and intermediate risk abnormalities including del(17p), t(4;14), t(14;20) or t(1;14). Response and progression were defined per IMWG criteria. Overall survival (OS) and progression free survival (PFS) were calculated from dx. Results: The study cohort had 409 pts [SR: t(4;14), t(11;14) = 69, HR = 96], with a median estimated follow up of 43 months from dx. Novel agents (IMiDs or proteasome inhibitors) were used in 95% of pts prior to SCT, and 80% of pts achieved partial response. Median PFS for HR, t(11;14), and SR pts was 24.9 (23,30), 28.1 (21.31), and 30.4 (28-34) months respectively (p = 0.034). Median OS for HR, t(11;14), and SR was 70.1 (66.7), 70.1 (66.7), and 93 (98,113) months respectively (log rank < 0.0001). When only pts who received post-transplant maintenance therapy were evaluated (IMiDs or proteasome inhibitors), there was no difference in OS at 5 years from diagnosis between HR and SR pts treated with early SCT (p = 0.19). Conclusions: Following novel agent induction and early SCT, pts with t(11;14) NDMM have inferior OS compared to a SR cohort of similarly treated pts. This is contrary to the current classification scheme. HR pts have similar OS at 5 years from diagnosis compared to SR pts with the use of early SCT and maintenance therapy.
A phase I/II trial of very low to low-dose continuous azacitidine in combination with standard doses of lenalidomide and low-dose dexamethasone in patients with newly diagnosed or relapsed/refractory multiple myeloma. First Author: Christoph Johann Heuck, Univer-

Impact of total therapies on clinical outcome of myeloma stratified by risk

8586 Poster Session (Board #402), Sun, 8:00 AM-11:30 AM

until the maintenance phase. Interestingly with dose dense therapy in TT5 treatment failure was not seen to improve survival in HRMM. For HRMM treated on TT2 and 3, treatment correlated to treatment phase. CR rates in high-risk (HR) MM are similar to standard arm. However patients with adverse cytogenetics had improved lower intensity treatment arm TT4-L had inferior outcomes compared to the molecular subgroup, it had no significant impact on MF cases. Outcomes

Results:

sion profiling (GEP) data enrolled on Total Therapy 2–5, stratified by Therapy (TT) trials, stratified by risk status and molecular subgroup. treatment response we examined clinical outcomes in our series of Total (MM) is a disease with unpredictable clinical course consistent with it

Discussion: NCT00869232.

upon treatment used at induction opens the potential for adjusting can define distinct clinical response and outcome patterns dependent upon which is now a setting where novel approaches can be used. For LRMM we

treatment failure from the inter-transplant to the maintenance phase, treatment and guide development of CDA inhibitors. Clinical trial informa-

development of the HPLC assay to select patients for aza nucleoside

maximize epigenetic effects and safety. Continuous administration should

refractory multiple myeloma (RRMM).Continuous administration should

CR (CBR) and 22.5% response rates. Median time on study was 90 days. Responses lasted between 3 months and 2 years. Five pts remain on study. Plasma CDA activity at screening and during the study (q wk x4, then q 28d) inversely correlated with achieving > MR (p < 0.03, p < 0.01, respectively, Wilcoxon exact test) and varied by median 17%. Pts with screening CDA activity above 1000 pmol/mg SC twice a wk was reached. One DLT (neutropenic fever without documented infection) occurred in 1 of 6 pts treated with 40mg/m² AZA twice a week). Grade 3/ 4 toxicities possibly drug related were seen in 23 pts (58%), neutropenia (13), thrombocytopenia (5), fatigue (3), infection (2), anemia (2), pleural effusion (1), fever (1), and atrial fibrillation (1). Twelve pts achieved > MR, 9 > PR (3 VGP) yielding 30% clinical benefit response (CRB) and 22.5% response rates. Median time on study was 90 days. Results with

Background: Despite the therapeutic benefit of novel agents, majority of multiple myeloma (MM) patients inevitably relapse leading to poor clinical outcomes. During the past decade, there has been an unprecedented pace of new anti-myeloma compound discovery tested through phase I trials, mostly in relapse/refractory setting. In the same period of time, at least 9 agents have been FDA approved for relapse MM that makes the decision making between standard therapy vs. recruitment on phase I trial poorly defined and occasionally ethically challenged. Further, the current perception of low therapeutic benefit from participation in phase I trials is the main obstacle for patient recruitment and make the phase I trial as a “last resort” in overall therapeutic plan. Here, we present a global assessment of therapeutic benefit and toxicity of all MM phase I studies over the past decade that may lead to optimal timing of patients recruitment on phase I trials. Methods: We reviewed 43 phase I trials from 2004 until 2014 in a systematic fashion. Quality and rate of response, adverse effects and mortality from single agents as well as combination of the experimental agents with immunomodulators (IMiDs) and proteasome inhibitors (PIs) are reported. Results: 41 trials with total of 946 participants were analyzed. 21 were single agents and the reminder tested a combined regimen. Overall response rate (ORR), i.e., partial response or better, was observed in 34% of all patients, 16% with single agents and 42% with combination therapy. Patients participated in trials with combination therapies had more grade III-IV toxicity than single agents (HR: 1.35, p-value: 0.04). There were only 5 patients (less than 1% of all participants) who had therapy-related death. Single agents with anti-CD38 agent, daratumumab and oral PI, ixazombi, had the best single agent response rate, 45% and 36%, respectively. Conclusion: Median ORR from MM phase I trials even with single agents is higher than reported response rate from classic chemotherapy phase I trials (i.e. 5%), therefore phase I participation should not count as the “last resort” and MM patients should be offered the opportunity to participate in these trials at any stage after failure on IMiDs and PIs.

Background: Despite the introduction of new agents multiple myeloma (MM) is a disease with unpredictable clinical course consistent with it being composed of a variety of subtypes with distinct molecular features. In order to shed light on the impact of this molecular heterogeneity on treatment response we examined clinical outcomes in our series of Total Therapy (TT) trials, stratified by risk status and molecular subgroup. Meaning of CDA activity included 1318 patients with available baseline gene expression profiling (GEP) data enrolled on Total Therapy 2–5, stratified by GEP70-defined risk and molecular subgroup. We analyzed their effect on outcomes and timing of treatment failure in relation to protocol phase. Results: For GEP70-defined low risk (LR) MM, PFS and OS has incrementally improved with addition of thalidomide in TT2 and bortezomib (Bz) in TT3a and 3b. While Bz improved outcomes for LRMM within the MS molecular subgroup, it had no significant impact on MF cases. Outcomes for patients on TT4 designed for LRMM were similar to TT3a/b. The lower intensity treatment arm TT4-L had inferior outcomes compared to the standard arm. However 3 patients with adverse cytogenetics had improved outcomes on TT4-L. Treatment failures in LRMM were rare and not correlated to treatment phase. CR rates in high-risk (HR) MM are similar to LRMM. Yet a more dose-dense chemotherapy in Total Therapy (TT) 5 failed to improve survival in HRMM. For HRMM treated on TT2 and TT3, treatment failure was observed in the inter-transplant to the maintenance phase. Interestingly with dose dense therapy in TTS treatment failure was not seen until the maintenance phase. Conclusions: HRMM has a distinct clinical course with high rates of primary refractory disease and early relapse. Changing therapy for HRMM from dose intense to dose dense has shifted treatment failure from the inter-transplant to the maintenance phase, which is now a setting where novel approaches can be used. For LRMM we can define distinct clinical response and outcome patterns dependent upon GEP-defined molecular subgroups. This differential response dependent upon treatment used at induction opens the potential for adjusting maintenance to take account of the disease subtype. Clinical trial information: NCT01155583.

Pre-clinical translational studies of daratumumab in patients with myeloma or AL amyloidosis undergoing autologous hematopoietic stem cell transplantation (SCT). First Author: Chakra Panth Chaullagain, Cleveland Clinic Florida, Weston, FL

Background: Daratumumab (DARA) is a human IgG1 that binds to CD38 and kills tumor cells expressing CD38 through immune-mediated cytotoxicity. CD38 is expressed on plasma cells in multiple myeloma (MM), AL amyloidosis (AL) and on myeloid progenitor cells. Since SCT remains a standard therapy for MM and AL the effect of DARA on progenitor cells was evaluated. Ability of DARA to induce complement dependent cytotoxicity (CDC) of progenitor cells was assessed in progenitor cell assay (PCA). DARA-mediated antibody-dependent cytotoxicity (ADCC) of progenitor cells, its correlation with FcγRIIIA polymorphism and stem cell potential were examined using NK-cells from post-SCT patients (n = 10, n = 6 MM and n = 4 AL) as effectors against a MM target cell line. Methods: ADCC was performed with post-SCT NK cells and MM.15 cells in the presence of 100 ng/ml DARA or isotype control (ICA). DARA-mediated CDC was evaluated in PCA: unselected or CD34-selected mobilized cells were incubated in complement-rich serum with no antibodies, or DARA or anti-CD59 (BRIC 229) or both. The effect of these antibodies on CFU-GM and BFU-E was evaluated twice weekly. The results were analyzed by two-tailed paired t tests with P < 0.05 as significance level. Results: MedianADCC of MM.15 target cells by primary post-SCT NK cells was 39% and 7% using DARA or ICA, respectively (P < 0.05). Of the 10 NK donors, 6 were Vf/Cf or Vf and lymphokine-activated. Of targets, 65% were CD34+ and 13% (8/65) were positive for CD138. There was no decrease in CFU-GM or BFU-E with unselected mobilized cells, with CD34-selected cells with DARA, or with CD34-selected cells incubated with DARA (500 or 1000 ng/ml) +/- BRIC 229 indicating that DARA did not induce CDC on the CD34-selected progenitor cells. Conclusions: DARA is active in ADCC assays with post-SCT NK cells from patients with MM or AL and its activity correlates with FCGRA3A-15B/F polymorphism. DARA did not inhibit progenitor cell growth by CDC in unselected or CD34-selected cells suggesting that administration of DARA may not cause undue harm to the progenitor cells after SCT. These findings support consideration of clinical trials of DARA consolidation post-SCT in MM and AL. CPC: MMRF fellow.

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8588 Poster Session (Board #406), Sun, 8:00 AM-11:30 AM
Effect of IMiD compounds on CD38 expression on multiple myeloma cells: MOR202, a human CD38 antibody in combination with pomalidomide. First Author: Rainer Boxhammer, MorphoSys AG, Martinsried/Planegg, Germany

Background: MOR202 (MOR03087), a human CD38 antibody currently under evaluation in a phase I/IIa trial, mediates antibody-dependent cell-mediated cytotoxicity/phagocytosis (ADCC/ADCP) of multiple myeloma (MM) patient-derived cells with high potency (EC50 ~200 pM). IMiD compounds such as lenalidomide (LEN) or pomalidomide (POM), both approved in MM, were evaluated in vitro for their ability to modulate CD38 expression and enhance the cytotoxicity of MOR202. Methods: CD38 expression +/- LEN and +/- POM on MM cell lines was analyzed by flow cytometry. The antitumor activity of POM combined with MOR202 was evaluated in vitro, analyses included the induction of direct cytotoxicity of MM cells and the upregulation of immune effector cells. On a functional level, the combinatorial effects of MOR202 with POM were assessed in ADCC assays. Different incubation schemes were used to separate the effect of POM on target and effector cells, as well as in the evaluation of the combined effects. The observed combination effects were analyzed for synergistic potential using the fractional product concept. Results: POM and LEN mediated a substantial CD38 upregulation on MM cell lines. POM as a single agent showed activation of effector cells and with high potency (EC50 ~150 nM), cytotoxic effects on MM cell lines. Additionally, POM dose-dependently induced an up to 3-fold CD38 upregulation (EC50 ~20 nM) on CD38-expressing MM cell lines. POM-mediated effects were time-dependent, with the most pronounced effects after 72 h incubation. Combining MOR202 with POM led to a synergistic enhancement of cytotoxic activity. The synergy benefit ranged between 1.2-3.1-fold above theoretical additivity, depending on the cell line used, and was most prominent in the case of strong CD38 upregulation. In a mouse xenograft model, upregulation of CD38 was mediated by both LEN and POM and may represent a prominent in the case of strong CD38 upregulation.

Conclusions: Upregulation of CD38 was mediated by both LEN and POM and may represent a theoretical additivity, depending on the cell line used, and was most pronounced in the case of strong CD38 upregulation. Combining MOR202 with POM led to a synergistic enhancement of cytotoxic activity. The synergy benefit ranged between 1.2-3.1-fold above theoretical additivity, depending on the cell line used, and was most prominent in the case of strong CD38 upregulation. In a mouse xenograft model, upregulation of CD38 was mediated by both LEN and POM and may represent a prominent in the case of strong CD38 upregulation.

8589 Poster Session (Board #408), Sun, 8:00 AM-11:30 AM
Assessing clinical response in multiple myeloma (MM) patients treated with monoclonal antibodies (mAbs): Validation of a daratumumab IFE reflex assay (DIRA) to distinguish malignant M-protein from therapeutic antibody. First Author: Christopher McCudden, Dept. of Pathology & Lab. Medicine, The Ottawa Hospital University of Ottawa, Ottawa, ON, Canada

Background: Residual therapeutics mAbs can be detected by assays intended to monitor clonal myeloma protein (M-protein). Daratumumab, a human anti-CD38 IgG1k mAb in MM clinical trials, has been characterized. We examined the levels of phosphorylated Akt, mTOR, ERK, and STAT3 expression by immunohistochemistry (IHC) in MM, SMM, and MM and assessed their impact on clinical outcomes. Methods: First, biopsy samples were stained with antibodies to p-Akt, p-mTOR(Ser2448), p-ERK1/2(Thr202/Tyr204), and p-STAT3 (Tyr705). Staining intensity was scored as: 0 (no staining), 1 ( 50% of cells), 2 (> 50% and 3 (dark staining of all cells). Nominal variables were compared with Fisher’s exact test and time to progression (TTP) was assessed using Kaplan Meier analysis. Results: Twenty-one MMGS, 20 SMM, and 18 MM patients were reviewed. Strong expression of p-Akt (2-3+ IHC score) was present in 15% of MMGS cases versus 62% of SMM and 61% of MM patients (P = 0.037). Strong p-mTOR expression was observed in SMM and MM patients compared to MMGS patients (100% and 94% versus 45%; P = 0.001). 61% of MM cases exhibited strong p-ERK expression versus 34% in SMM and 15% in MMGS (P = 0.042). There was non-significant trend toward higher p-STAT3 expression in MM versus SMM/MMGS (39% in MM versus 12% and 10% in SMM and MMGS; P = 0.15). Increased p-mTOR activity correlated with high expression of p-Akt (S473) in all patients (P = 0.025). TTP in SMM patients with high versus lower p-ERK activity was significantly shorter (76 months vs 16 months; P = 0.046). No other signaling pathways demonstrated statistical differences in TTP or overall survival. Conclusions: Comprehensive IHC analysis across the spectrum from MMGS to MM and MMD demonstrated increased expression of multiple key signaling pathways as disease progression occurs. Expression of p-Akt(S473) and p-mTOR in SMM and MM is significantly higher than MMGS patients, suggesting an upregulation of these pathways is an early event in pathogenesis. Activation of p-ERK and p-STAT3 was more frequent in MM versus MMGS/MM, suggesting they may be more active in advanced disease.

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Clinical outcomes in t(11;14) multiple myeloma. First Author: Muhamad Alhaj Moustafa, Mayo Clinic, Rochester, MN

Background: Chromosomal translocations involving the immunoglobulin heavy chain region on chromosome 14 are common abnormalities in multiple myeloma (MM); with translocation t(11;14) being the most common (15-20%). Our study focuses on the outcomes of this group and response to different therapies. Methods: We identified 254 patients with MM, who had fluorescence in situ hybridization (FISH) performed between 2004 and 2012 for MM and had t(11;14) abnormality. We included 199 patients who had FISH studies before MM diagnosis or within 2 years of diagnosis. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Results: The median age at diagnosis was 63 years (range, 22-95) and 129 (56%) were male. The estimated median follow up for the whole cohort was 69 months; 100 (50%) patients are alive. The PFS for the whole cohort was 15 months (95% CI; 11, 18) and the OS was 68 months (95% CI; 54, 88). Twenty-seven (14%) patients received conventional therapies for induction, whereas 172 (86%) received novel agents (116 IMiDs, 33 proteasome inhibitors, 23 both); 115 had stem cell transplant (SCT). Partial response (PR) or a better response to induction was seen in 55%. Median OS for those receiving an SCT was 72 months compared with 35 months for the initial therapy; 68 months vs. 70.5 months, respectively. The time to progression (TP) was the median time to progression (95% CI; 11, 18) and the OS was 68 months (95% CI; 54, 88). Some inhibitors, 23 both); 115 had stem cell transplant (SCT). Partial response (PR) or a better response to induction was seen in 55%. Median OS for those receiving an SCT was 72 months compared with 35 months for the initial therapy; 68 months vs. 70.5 months, respectively. The time to progression (TP) was the median time to progression (95% CI; 11, 18) and the OS was 68 months (95% CI; 54, 88).

8594 Poster Session (Board #413), Sun, 8:00 AM-11:30 AM
Outcomes and treatment of patients with POEMS syndrome experiencing progression or relapse after first line treatment. First Author: Taxiarchis Kourelis, Mayo Clinic, Rochester, MN

Background: While clinical improvement is almost universal with first line chemotherapy and/or radiation therapy in patients with POEMS syndrome, outcomes and management of patients who relapse or progress (R/P) after first line treatment has not been described. Here we report the outcomes of patients with POEMS syndrome treated at the Mayo Clinic from 1974-2014. Median follow-up for survival and R/P were 68 months and 51 months, respectively. Results: For the 78 documented R/P patients (27%), 22% of patients had been treated with R2 agents, 11% with a different agent, 11% with a different chemotherapy regimen, and 11% with a different radiation therapy or a combination of therapies. Median survival following R/P was 44 months (range 3-273 months). The median OS from randomization by response status at C3 was 15.3 months for SD, 6.3 months for PD, and 17.5 months for OR. The difference in OS at C3 between SD and PD was significant (P < .001); that between SD and OR was not (P = .32). A similar pattern was observed at C5 and C7. The time-dependent survival analysis showed a lower risk of death for pts with SD or OR vs PD (HR, 0.25 [95% CI, 0.17-0.44] and HR, 0.06 [95% CI, 0.02-0.16], respectively). For the HiDEX arm, small pt numbers per group (due to the lower response rate, 21% randomization, and shorter OS vs POM + LoDEX) made interpretation challenging. Conclusions: In the PO+ LoDEX group, pts with SD at C3, C5, and C7 had OS comparable to pts who achieved a response by those times. Pts with either SD or OR had a longer OS than those with PD at the same time points. Clinical trial information: NCT01311687.

8595 Poster Session (Board #414), Sun, 8:00 AM-11:30 AM
Phase III trial of stem cell transplantation compared to melphalan and dexamethasone in the treatment of immunoglobulin light chain amyloidosis (AL). First Author: Maria A. Gertz, Mayo Clinic, Rochester, MN

Background: Autologous stem cell transplant is widely performed for the management of select patients with AL amyloidosis in the United States. There are no phase III trials that document improved overall survival. This phase III trial assessed patients to select between melphalan and dexamethasone or autologous stem cell transplantation. Methods: Eighty-nine patients with biopsy-proven AL amyloidosis elected to receive melphalan and dexamethasone (n = 34) or stem cell transplantation (n = 54). Patients were selected to exclude those for whom cardiac involvement would not have permitted safe autologous stem cell transplantation. Results: Allowing patients to select their preferred treatment resulted in an imbalance of patients between the two arms. Patients that selected melphalan and dexamethasone were younger, were more likely to be male, and were more likely to have a history of smoking. Patients receiving melphalan and dexamethasone had a three-year progression-free survival of 29% and overall survival of 58.8%. Patients receiving stem cell transplant had a three-year progression-free survival of 51.7% and overall survival of 83.6%. An imbalance to match patients between the two arms, in terms of risk, produced 24 matched triplets with no difference in hematologic response. Conclusions: This trial, which did not meet its accrual goals, failed to demonstrate a survival advantage for matched patients undergoing autologous stem cell transplantation. Clinical trial information: NCT00477971.

Differences between those who chose SCT and those who chose melphalan with dexamethasone.

8596 Poster Session (Board #415), Sun, 8:00 AM-11:30 AM
Analyzing the relationship of response and survival in patients with refractory or relapsed and refractory multiple myeloma (RRMM) treated with bortezomib, lenalidomide, and low-dose dexamethasone (VTD) and LoDEX in the MM-003 trial. First Author: Katja Weisel, University Hospital of Tuebingen, Tuebingen, Germany

Background: RRMM patients (pts) previously exposed to bortezomib (BORT) and lenalidomide (LEN) have short overall survival (OS). The phase 3 MM-003 trial (NCT01311687) demonstrated significantly longer TTR in RRMM pts treated with POM + LoDEX vs HiDEX (HR, 0.74 [95% CI, 0.56-0.97], P = .0285). This post hoc analysis investigated OS based on the response status of pts at different cycles. Methods: Landmark analyses at the start of cycles C3, 5, and 7 were performed using Kaplan-Meier methods and unadjusted Cox regression models. Time-dependent survival analyses captured response status over time. For both approaches, survival of pts with stable disease (SD) was compared to that of pts with progressive disease (PD) or overall response (OR: Ρ: partial response). Results: At C3, 38.4% of pts (116/302) randomized to POM + LoDEX attained SD, 14.6% PD, and 19.2% OR; 28% had no response data, most due to early discontinuation. The median OS from randomization by response status at C3 was 15.3 months for SD, 6.3 months for PD, and 17.5 months for OR. The difference in OS at C3 between SD and PD was significant (P < .001); that between SD and OR was not (P = .32). A similar pattern was observed at C5 and C7. The time-dependent survival analysis showed a lower risk of death for pts with SD or OR vs PD (HR, 0.25 [95% CI, 0.17-0.44] and HR, 0.06 [95% CI, 0.02-0.16], respectively). For the HiDEX arm, small pt numbers per group (due to the lower response rate, 21% randomization, and shorter OS vs POM + LoDEX) made interpretation challenging. Conclusions: In the POM + LoDEX group, pts with SD at C3, C5, and C7 had OS comparable to pts who achieved a response by those times. Pts with either SD or OR had a longer OS than those with PD at the same time points. Clinical trial information: NCT01311687.
**8596 Poster Session (Board #415), Sun, 8:00 AM-11:30 AM**

Survival trends in young patients with Waldenstrom macroglobulinemia (WM). First Author: Nishanth Vallumsetla, Mayo Clinic, Rochester, MN

**Background:** Data in young patients (pts) with WM are sparse and the few available studies utilizing SEER data have included inconsistent results possibly overestimating survival, in part related to inclusion of asymptomatic pts. Herein, we investigate trends in overall survival (OS), including the Rituximab era, in a cohort of young symptomatic WM pts enrolled in the Mayo Clinic over 5 decades. **Methods:** Of 1181 pts with WM seen consecutively between 1960 and 2013, 127 (11%) were <50 years (y) at diagnosis, and 123 of those received therapy. Pts were categorized into 3 equal year groups based on the timing of initiation of therapy: Group 1 (1960-77), Group 2 (1978-95) and Group 3 (1996-2013), and their OS was analyzed using the Kaplan-Meier method. We also compared their outcomes with a control cohort of pts, ≥50 y and matched (1:1) by the timing of diagnosis. **Results:** Follow-up from initiation of therapy was similar in the 2 cohorts (median: 10.7 y in young vs 10.4 y in control cohort). The median OS from initial therapy was 15.5 y (95% CI 13-18) for young compared to 7.3 y (CI 5-8) for the control arm. In the young pts, 92% of deaths with known causes were WM related compared to 59% in control arm (p = 0.0004). While there was no significant OS difference observed with the use of Rituximab-based initial therapy in the young (median 11.4 y [CI 6-21.8] versus 15.6 y [CI 13-21] for all other therapies, p = 0.13), the control arm showed superior OS for pts who received Rituximab based initial therapy (median 9.1 y [CI 7-27.9] vs 5.8 y [CI 5-8] for other therapies; p = 0.03). Among young pts, there was no OS improvement from initial therapy across the 3 groups (p = 0.47) while the OS trends for the controls showed improvement across the 3 groups (p = 0.002; Table). **Conclusions:** Survival of young pts with WM remains unchanged over the past 50 years. In contrast to the patients aged ≥65, Rituximab use did not translate to improved survival in young pts.

**8598 Poster Session (Board #417), Sun, 8:00 AM-11:30 AM**

A national study on conditional survival and excess mortality after high dose therapy with autologous stem cell transplantation for Non-Hodgkin lymphoma (NHL) in a national cohort. First Author: Knut Bjøøro Smeland, National Advisory Unit on Late Effects, Department of Oncology, Oslo University Hospital, Oslo, Norway

**Background:** The aim of this study was to investigate conditional survival and standardized mortality ratios (SMR) after high-dose therapy with autologous stem cell transplantation (HDT) for NHL in Norway during 1960-2013. **Methods:** All patients ≥ 18 years treated with HDT for NHL in Norway 1967-2008 were included (n = 578). Information about cause of death from the national Cause of Death Register in Norway and second malignancies from Cancer Registry of Norway were linked with clinical data. **Results:** One and 5-year overall survival (OS) was 52% (95% CI 48%-55%) and 49% (95% CI 44%-53%), Conditional 5-year OS are shown in the table. SMR was 12.7 (95% CI 10.5-16); n = 216, 77% of deaths (n = 165) were NHL related compared to 59% in control arm (p = 0.02) predicted better OS. Patients treated with RT had 17.6% did not receive surgery or RT. OS at 10 years was higher in patients with age < 60 vs age > 60 (62.5% vs. 22.2%, p < 0.01) and for other races vs Whites vs African Americans (51.1% vs. 40.1% vs. 34.5% respectively, p < 0.01). Use of RT and surgery resulted in better 10-year OS (51%) than surgery alone (44.1%), RT alone (39.8%) or no RT/surgery (21.2%) (p < 0.01). Multivariate analysis, age > 60 (HR 3.01, 95% CI 2.61-3.46; p < 0.01), Whites vs other races (HR 1.35, 95% CI 1.02-1.77; p = 0.03) and African americans vs. other races (HR 1.52, 95% CI 1.11-2.08; p < 0.01) predicted worse OS, while the use of RT (HR 1.42, p = 0.02) and RTM was (HR 1.73, p = 0.070-0.97; p = 0.02) predicted better OS. Patients treated with RT had more SMR as compared to general population- all sites standardized incidence ratio (SIR) 1.49, with more leukemia/lymphoma (SIR 6.37) and bone tumors (SIR 19.93) (p < 0.05). **Conclusions:** Our study demonstrates that the use of RT and surgery for NHL significantly improves the OS, despite an increased risk of SPM with RT. Our study also shows a significant racial disparity in the long-term OS of PP.
Background: The activated B-cell like subtype (ABC) of diffuse large B-cell lymphoma (DLBCL) is associated with inferior PFS and OS with R-CHOP-based chemotherapy. Lenalidomide demonstrated significant single agent activity in relapsed/refractory DLBCL, predominantly in ABC-type DLBCL. In first line therapy, lenalidomide + R-CHOP (R2-CHOP) showed improved efficacy over R-CHOP controls in two independent, single arm phase II trials from Mayo Clinic and Fondazione Italiana Linfomi groups. R2-CHOP appears primarily to improve outcomes in ABC-type DLBCL. The objective of this multicenter, international trial is to compare the efficacy and safety of lenalidomide–R-CHOP (R2-CHOP) vs placebo–R-CHOP in patients with previously untreated ABC-type DLBCL. A phase III placebo-controlled, double-blinded trial (DLC002; NCT02285062), patients with ABC-type DLBCL are randomized 1:1 to oral lenalidomide (15 mg, days 1-14/21-day cycle) plus standard-dose R-CHOP or placebo–R-CHOP, every 21 days for 6 cycles ± 2 additional doses of rituximab until PD, intolerability, inadequate response, or withdrawal of consent. Key eligibility criteria include previously untreated, histologically confirmed ABC-type CD20+ DLBCL (WHO classification), age 18-80 years, IPI score ≥2, Ann Arbor stage II-IV, and adequate organ function. ABC-type will be determined by central pathology lab within 3 days by real-time gene expression profiling (GEP) using the NanoString nCounter Analysis System (Scott et al. Blood. 2014;123:1214-1217) on FFPE biopsy samples. Primary endpoint is PFS; secondary endpoints are EFS, OS, ORR, CR, duration of CR, time to next lymphoma therapy, and health-related QOL. Additional biological analyses for MRD detection are planned. Responses will be confirmed by central pathology using IHC with WHO criteria. After R2-CHOP, patients will be randomized during the estimated 34 month-accrual period. Enrollment began in January 2015, with expected accrual completion in October, 2017. To our knowledge, this is the first phase III trial in DLBCL using real time GEP to assess patient eligibility, thus allowing precision therapy of patients with DLBCL. Clinical trial information: NCT02285062.

Methods: A phase I study with an expansion cohort of the combination of ipilimumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma: E4412 is the first clinical trial targeting the HL tumor microenvironment in conjunction with HRS tumor cell targeting. We hypothesize that this immuno-chemotherapy approach may overcome tumor cell resistance and deepen clinical response. E4412 is the first clinical trial targeting the HL tumor microenvironment in conjunction with HRS tumor cell targeting. Methods: E4412 is currently open at 7 sites within ECOG. A modified 3+3 dose escalation design is used; 6 patients are tested at each dose level if no more than one DLT is observed in the first patient at each dose. In the first cycle (1 cycle = 21 days), the primary endpoint is the maximum tolerated dose (MTD) of the combination. Secondary endpoints include complete response (CR) rate, partial response (PR) rate, overall response (ORR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS). Response criteria are reported per the International Harmonization Project (IHP). DOR, PFS and OS are estimated using Kaplan-Meier methodology. BV is given at 1.8mg/kg and ipilimumab at 1mg/kg (cohort 1) and 3mg/kg (cohort 2) every 21 days for 4 cycles. From cycle 5 BV is given q 21 days, and ipilimumab on cycles 8, 12, and 16. Once the MTD is established, 9 patients are treated in an expansion cohort with BV at 1.8mg/kg and ipilimumab at MTD. Eligibility Criteria include: age ≥18, relapsed HL, measurable disease, no prior relapse on BV, no active GVHD or immunosuppressive therapy, ECOG 0-2, FEV1/FVC >60%, hematology and chemistry labs within standard parameters, no uncontrolled systemic illness. Cohorts I and II have been completed. Expansion cohort enrollment opened on February 3rd, 2015. Clinical trial information: NCT01896999.

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Phase I/II study of intratumoral injection of SD-101, an immunostimulatory CpG, and intratumoral injection of ipilimumab, an anti-CTLA-4 monoclonal antibody, in completely resected low-grade non-Hodgkin's lymphomas. First Author: Michael Siavash Khodadoust, Stanford University, Stanford, CA

Background: Immunotherapy is a promising treatment modality for low grade non-Hodgkin’s lymphomas. SD-101 (DynaRx Technologies) is an immunostimulatory synthetic CpG molecule that activates toll-like receptor 9. Intratumoral CpG injection produced local and abscopal anti-lymphoma immune responses with minimal systemic toxicity in a phase I/II clinical trial (Brodly J et al. J Clin Oncol. 2010). Resistance to CpG is thought to be due to the induction of immune tolerance following an initial immune stimulation. Ipilimumab (Bristol-Myers Squibb) is a monoclonal anti-CTLA-4 antibody that interrupts inhibitory signaling on the surface of T cells, leading to the release of cytokines and production of systemic immune responses. The combination of the immunomodulatory agent lenalidomide (Revlimid) with ipilimumab and local radiation to produce systemic immune responses with minimal toxicity. Methods: Up to 12 patients will be enrolled in the phase 1 dose escalation design to determine maximum tolerated dose of intratumoral ipilimumab with a set dose of SD-101, and an additional 15 patients will be enrolled in the phase 2 expanded cohort at the chosen ipilimumab dose. All patients initially receive two fractions of 2 Gy radiation. After radiation, patients receive intratumoral SD-101 (1mg) and ipilimumab (10mg or 25mg depending on dose cohort). Weekly SD-101 intratumoral injections continue for a total of 5 doses. The primary objective is to determine the safety and tolerability of increasing dose levels of intratumoral ipilimumab with SD-101. Eligible patients must have relapsed/refractory low grade B-cell lymphoma with a disease site amenable to intratumoral injection and a second measurable disease site to assess abscopal effects. This study is currently accruing and is supported by a grant from the NIH (CA188005). Clinical trial information: NCT02254772. Clinical trial information: NCT02254772.

TPS8606 Poster Session (Board #42b1), Sun, 8:00 AM–11:30 AM

MAGNIFY: A randomized, phase 3b trial in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) investigating lenalidomide plus rituximab (R) induction followed by maintenance R2 followed by lenalidomide versus R2 induction followed by rituximab (R) maintenance. First Author: David Jacob Andorsky, Rocky Mountain Cancer Centers, Boulder, CO

Background: Combination of the immunomodulatory agent lenalidomide (Revlimid) with rituximab (R) is a promising therapeutic option for patients with R/R NHL. As frontline therapy, R2 provided a 90% overall response rate (ORR) in patients with follicular lymphoma (FL), marginal zone lymphoma (MZL) and small lymphocytic lymphoma (Fowler, Lancet Oncol, 2014) and 89% ORR in MCL patients (Ruan, ASH, 2014). In phase 2 trials of R2, patients with R/R MZL, FL, and MCL achieved ORRs of 80% (55% complete response [CR]), 73% (36% CR), and 57% (36% CR), respectively (Raderer, EHA, 2014; Leonard, ASCO, 2012; Wang, Lancet Oncol, 2012). These trials support further investigation of R2 therapy in R/R NHL. Methods: The efficacy and safety of 12 cycles of combination R2 for induction with randomization to R2 (Arm A) vs R (Arm B) maintenance will be compared in R/R FL, MCL, or MZL patients as part of the phase 3b MAGNIFY trial. Approximately 500 patients will be randomized 1:1 to 28-day (d) treatment cycles (C). Both patient groups will receive R2 induction with lenalidomide (20 mg/d on d 1-21) + 12 + C (375 mg/m² on d 1, 8, 15, 22 in C1; d1 of C 3, 5, 7, 9, 11). Patients in Arm A will receive R2 maintenance with lenalidomide (10 mg/d on d 1-21; C13-30) + R (375 mg/m² on d 1 of every other C from 13 to 29), followed by lenalidomide (10 mg/d on d 1-21) until progression. Following 12 cycles of induction with R2, patients in Arm B will receive maintenance R (375 mg/m² on d1 of every other C from 13 to 29). Eligibility criteria include R/R FL grades 1-3b, transformed FL, MCL, or MZL; previous systemic therapy; ≥ 1 measurable lesion and adequate bone marrow, liver, and renal function. Progression-free survival is the primary endpoint. Secondary endpoints include rate of CR/CR unconfirmed (CRu), overall survival, ORR, duration of response, duration of CR/CRu, and safety. An exploratory endpoint, health-related quality of life will be measured using the FACT-Lym questionnaire. The MAGNIFY study is closed to accrual 35 patients have been enrolled as of January 30, 2015 (NCT01996865). Clinical trial information: NCT01996865.

TPS8605 Poster Session (Board #42a1), Sun, 8:00 AM–11:30 AM

Phase III trial of brentuximab vedotin and CHP versus CHOP in the frontline treatment of patients (pts) with CD30+ mature T-cell lymphomas (MTCL). First Author: Owen A. Williams, Columbia University Medical Center, New York Presbyterian Hospital, New York, NY

Background: MTCL including systemic anaplastic large cell lymphoma (sALCL) are aggressive neoplasms. Anthracycline-based multigent chemotherapy regimens have demonstrated response rates ranging from 76 to 88%. Five-year overall survival rates range from 12 to 49% depending on the histologic subtype. Brentuximab vedotin is an antibody drug conjugate that has shown efficacy in a pivotal phase II study as a single agent in relapsed sALCL (Pro et al., J Clin Oncol, 2012) and evidence of clinical activity in combination with CHP in the frontline treatment of MTCL including sALCL in a phase I study (Fanale et al., ASH 2012). Methods: This randomized, double-blind, placebo-controlled, multicenter, phase III study (NCT01777152) is evaluating the safety and efficacy of 1.8 mg/kg brentuximab vedotin with CHP (A+B+CHP) vs CHOP for frontline treatment of CD30+ MTCL. Pts must have FDG-avid disease by PET and measurable disease of at least 1.5 cm by CT. Approximately 300 pts will be randomized 1:1:1 to receive A+CHP or CHOP for 6–8 cycles (q3wk). Randomization will be stratified by ALK+ sALCL vs other histologic subtypes and IPI score (0–1, 2–3, or 4–5). The target proportion of pts with a diagnosis of sALCL will be 75%. The primary objective is to compare progression-free survival (PFS) between the 2 treatment arms as determined by an independent review facility (IRF). Secondary objectives include comparisons of PFS per IRF in sALCL patients, safety, overall survival, and complete remission rate between the 2 arms. After completion of treatment, pts will be followed for disease progression, medical resource utilization, quality of life, and survival. Post-treatment stem cell transplant is permitted. Efficacy assessments will use the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). CT and PET scans will be performed at baseline, after Cycle 4, and after the completion of treatment. CT scans will also be performed at regular intervals during follow-up until disease progression, death, or analysis of the primary endpoint. Safety assessments will occur throughout the study until 30 days after last dose of study treatment. Enrollment for this global trial began in early 2013. Clinical trial information: NCT01777152.

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A randomized open-label study of bortezomib, melphalan, and prednisone (VMP) versus daratumumab (DARA) plus VMP in patients with previously untreated multiple myeloma (MM) refractory to high-dose bortezomib/lenalidomide/dexamethasone (RE-DVd) in first-line therapy. Patients with MM who meet the inclusion criteria included previously untreated patients who are ineligible for high-dose therapy, as well as in combination with VMP or Vd alone in relapsed/refractory MM. For both studies, the main inclusion criteria are documented MM satisfying the CRAB criteria, measurable disease, and newly diagnosed and not considered a candidate for high-dose chemotherapy with SCT. Approximately 700 eligible patients will be stratified by International Scoring System, region (Europe vs others), and age (<75 vs ≥75 y) and randomized in a 1:1 ratio to VMP or DARA + VMP. All patients will receive up to 9 cycles (1 cycle = 6 wk) of VMP (bortezomib 1.3 mg/m² SC twice weekly (Weeks 1, 2, 4, and 5) in Cycle 1, then once weekly (Weeks 1, 2, 4, and 5) in Cycles 2-9; melphalan 9 mg/m² PO Day 1-4 of each cycle). Patients in the DARA + VMP arm will receive DARA 16 mg/kg IV weekly x 4 wk (Cycle 1), then every 3 wk for Cycles 2-9; patients will then continue to receive DARA every 4 wk thereafter. The primary endpoint is progression-free survival (PFS). An Independent Data Monitoring Committee will conduct reviews of the efficacy and safety data. The primary analysis will occur when approximately 360 PFS events have been observed. Approximately 200 sites in 24 countries will participate. The first patient was enrolled in January 2015. Clinical trial information: NCT02195479.

Denosumab compared with zoledronic acid for the treatment of bone disease in adults with newly diagnosed multiple myeloma: An international, randomized, double-blind trial. First Author: Noopur S. Raje, Massachusetts General Hospital, Boston, MA

Background: A characteristic feature of multiple myeloma (MM) is osteoclast-mediated breakdown of the bone. Patients with MM and bone lesions often experience debilitating pain and skeletal complications including pathologic fractures, need for radiotherapy or surgery to bone, and spinal cord compression, collectively termed skeletal-related events (SREs). RANKL is the key mediator of osteoclast activity. Denosumab, a fully human monoclonal antibody specific to RANKL, inhibits the formation, function, and survival of osteoclasts, thus decreasing cancer-mediated bone destruction. The primary endpoint of this trial is to determine whether denosumab is noninferior to zoledronic acid (ZA) in delaying the time to 1st-on-study SRE in patients with MM. Secondary endpoints include superiority of denosumab vs ZA in delaying the time to 1st-on-study SRE and time to 1st-and-subsequent SRE and overall survival. Safety endpoints will be assessed. This trial is registered (ClinicalTrials.gov NCT01345019) and sponsored by Amgen Inc. Methods: Targeted enrollment is ~1520 adults with newly diagnosed MM and ≥1 bone lesion receiving first-line treatment. Patients with ≤30 days of anti-myeloma therapy, ≤1 prior dose of IV bisphosphonate, an ECOG status of ≥2, and adequate organ function are eligible. Use of any approved anti-myeloma therapy is permitted. Enrolled patients are stratified by whether they intend to undergo autologous stem cell transplant; use of novel vs non-novel anti-myeloma agents as first-line therapy; stage at diagnosis per the International Staging System (I, II, or III); SRE at time of presentation; and geographic region. Randomized (1:1) patients receive either SC denosumab 120 mg IV placebo or IV ZA 4 mg (adjusted for CrCl) – SC placebo once every 4 weeks. Daily calcium (≥500 mg) and vitamin D (≥400 IU) supplements are strongly recommended. The primary analysis is planned when ~800 patients experience an on-study SRE. Enrollment is currently ongoing and enrollment rates are as planned.
A multicenter, randomized, open-label, phase 2 study of carfilzomib with or without ARRY-520 (filanesib) in patients with advanced multiple myeloma.

**Background:** Light chain (AL) amyloidosis is a rare disease caused by the deposition of misfolded proteins that cause dysfunction of vital organs (eg, heart and kidneys). There are no approved therapies. Current therapeutic approaches target the plasma cells that produce the pathogenic light chain proteins and are typically associated with significant adverse effects. Therefore, there is a substantial need for a safe and effective therapy that specifically targets the misfolded light chain proteins responsible for the underlying organ dysfunction. NEOD001 is a monoclonal antibody that targets these misfolded proteins, and it is hypothesized to neutralize circulating soluble protein aggregates and clear insoluble aggregates from organs. In an ongoing phase I/II study in 27 patients with AL amyloidosis and persistent organ dysfunction, NEOD001 was safe and well tolerated, with monthly infusions producing meaningful decreases in cardiac and renal biomarkers by best response. Supported by these positive results, the current study (VITAL; NCT01989325) is designed to assess the efficacy, safety and pharmacokinetics (PK) of CFZ ≤ filanesib in 75 patients with measurable MM who have received at least 2 prior treatment regimens (including BTZ and an IMiD) and have disease refractory to their last myeloma therapy (NCT01989325). Patients at community and academic centers in the United States are stratified by BTZ-refractory disease status and randomized to receive CFZ + filanesib (≤50 patients) or single-agent CFZ (≤25 patients) in continuous 28-day cycles until disease progression or unacceptable toxicity. CFZ (20/27 mg/m²) is administered intravenously (IV) on Days 1, 2, 8, 9, 15 and 16. Filanesib is administered as 1.25 mg/m²/day IV on Days 1, 2, 15 and 16 with prophylactic filgrastim. Crossover from single-agent CFZ to combination treatment is permitted upon confirmed disease progression. The primary endpoint is PFS; secondary endpoints include PFS rate at 6 months, ORR, duration of response, time to best response, clinical benefit rate, disease control rate, safety, and PK. No formal comparisons will be made between treatment arms. exploratory measurements of alpha 1-acid glycoprotein (AAG), a potential predictive biomarker for filanesib treatment, will be performed. Clinical trial information: NCT01989325.

The VITAL study: A randomized, double-blind, placebo-controlled, global, phase III study of NEOD001 in patients with AL amyloidosis and cardiac dysfunction.

**Background:** Immunomodulatory agent (IMiD)/bortezomib (BTZ) combination therapy is the standard of care for multiple myeloma (MM). Despite high initial objective response rates (ORR) and prolonged progression-free survival (PFS), almost all patients eventually relapse. Treatment for relapsed or refractory disease typically includes regimens that maintain IMiDs and/or proteasome inhibitors (PIs) as a foundation. Filanesib is a highly selective, targeted kinesin spindle protein (KSP) inhibitor that has shown promising preliminary activity and manageable toxicity as a single agent and in combination with dexamethasone, BTZ and carfilzomib (CFZ). Due to a distinct mechanism of action, filanesib demonstrates activity in patients with myeloma that has become resistant to (MI)Ds and PIs, potentially addressing a significant unmet medical need. Methods: This multicenter, randomized (2:1), open-label Phase 2 study is designed to assess the efficacy, safety and pharmacokinetics (PK) of CFZ ≤ filanesib in 75 patients with measurable MM who have received at least 2 prior treatment regimens (including BTZ and an IMiD) and have disease refractory to their last myeloma therapy (NCT01989325). Patients at community and academic centers in the United States are stratified by BTZ-refractory disease status and randomized to receive CFZ + filanesib (≤50 patients) or single-agent CFZ (≤25 patients) in continuous 28-day cycles until disease progression or unacceptable toxicity. CFZ (20/27 mg/m²) is administered intravenously (IV) on Days 1, 2, 8, 9, 15 and 16. Filanesib is administered as 1.25 mg/m²/day IV on Days 1, 2, 15 and 16 with prophylactic filgrastim. Crossover from single-agent CFZ to combination treatment is permitted upon confirmed disease progression. The primary endpoint is PFS; secondary endpoints include PFS rate at 6 months, ORR, duration of response, time to best response, clinical benefit rate, disease control rate, safety, and PK. No formal comparisons will be made between treatment arms. exploratory measurements of alpha 1-acid glycoprotein (AAG), a potential predictive biomarker for filanesib treatment, will be performed. Clinical trial information: NCT01989325.
The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the Annual Meeting Proceedings online supplement to the June 20, 2015, issue of the Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 066 study. First Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA

Background: Combined blockade of T-cell checkpoints by NIVO and IPI demonstrated a high objective response rate (ORR), promising overall survival (OS), and a manageable safety profile in pts with advanced MEL in a phase I study, based on which an appropriate dose was selected for registrational trials. We report efficacy and safety of the NIVO/IPI combination vs IPI alone in treatment-naïve pts with advanced MEL, including pts with poor prognostic factors, in a phase II study. Methods: Pts (N = 142) with metastatic or unresectable MEL were randomized 2:1 to receive NIVO 3 mg/kg combined with either IPI 1 mg/kg or placebo Q2W × 4, followed by NIVO 3 mg/kg or placebo Q2W until disease progression or unacceptable toxicity. The primary endpoint was ORR in BRAF wild-type (WT) pts. Secondary and exploratory objectives included PFS in BRAF WT pts, ORR and PFS in BRAF V600 mutation-positive (MT) pts, and safety. Results: In BRAF WT pts (n = 109), ORR was 60% (43/72) for NIVO + IPI; 11% (4/37) for IPI alone (P < 0.0001); complete responses were reported in 12 (17%) and 0 pts, respectively. Median PFS was 8.9 months for the combination vs 4.7 months for IPI alone (P = 0.0012). Higher ORR was observed for NIVO + IPI vs IPI in predefined pt subgroups with poor prognostic factors, such as elevated baseline LDH (53% vs 0%) and M1c stage disease (62% vs 25%). Similar ORR and PFS results were observed in 33 BRAF MT pts. Grade 3–4 drug-related adverse events (AEs) were reported in 51% of pts receiving NIVO + IPI vs 20% for IPI alone. The safety profile of NIVO + IPI was similar across pt subgroups, including age. Select AEs related to the combination regimen were consistent with phase I reports and most resolved with immunosuppressive medication ( > 83% across organ categories) with the exception of endocrinopathies. Updated results from a planned data analysis in March 2015 will be presented. Conclusions: NIVO + IPI significantly improved ORR and PFS compared with IPI alone and had a manageable safety profile. The efficacy and safety of the combination was similar across pt subgroups and provided a favorable risk-benefit ratio in treatment-naïve pts with advanced MEL. Clinical trial information: NCT01927419.

A phase Ib/I study of BRAF inhibitor (BRAFi) encorafenib (ENCO) plus MEK inhibitor (MEKi) binimetinib (BINI) in cutaneous melanoma patients naïve to BRAF/MEK therapy. First Author: Ryan J. Sullivan, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: MEKi addition to BRAF therapy has been reported to increase response rate (RR) and duration of response. The BRAFi ENCO (LGX818) and MEKi BINI (MEK162) have each shown promising single-agent activity in BRAFV600–mutant melanoma. Methods: Combined ENCO and BINI are being evaluated in this phase (Ph) Ib/I open-label study of patients (pts) with advanced metastatic melanoma (MEL). Pts entered the Ph Ib/I study at ENCO starting at 600 mg daily (1 in Ph Ib, 38 in Ph II), all with BINI. Of the 55 BRAFi-naive pts enrolled in Ph Ib (n = 21) and Ph II (n = 34), 24 received ENCO 400 mg or 450 mg daily (5 in Ph Ib, 4 in Ph II), and 39 received ENCO starting at 600 mg daily (1 in Ph Ib, 38 in Ph II), all with BINI. Among all pts starting at ENCO 600 mg, common adverse events (AEs; all grades > 30%) were nausea (54%), diarrhea (44%), fatigue, and arthralgia (33%) each, and vomiting, pyrexia, and increased AST (31% each). ENCO 400/450 mg, rates of grade 3-4 AEs were nausea and fatigue (44% each), diarrhea, vomiting, and increased AST (33% each), and arthralgia and pyrexia (11% each). Gr 3/4 AEs occurred in 64% of pts treated with 600 mg, commonly including increased ALT (18%), lipase (15%), AST (13%), and creatinine phosphokinase (13%). At 400/450 mg, Gr 3/4 AEs occurred in 22% of pts only event occurring in > 1 pt. Phototoxicity (n = 1, 400 mg, n = 1, 600 mg) and Gr 3/4 pyrexia (n = 2, 600 mg) were rare. The confirmed RR among pts treated at ENCO 400/450 mg was 78% (1 CR + 6 PRs) and at ENCO 600 mg was 72% (3 CRs + 25 PRs). Ph Ib and Ph II combined (all doses) median progression-free survival (95% CI) was 11.3 (7.4–14.6) mo, in pts with baseline lactate dehydrogenase (LDH) > upper limit of normal (ULN; n = 21) and ≤ ULN (n = 32), was 6.8 (5.0–11.3) mo and 20.0 (11.0–not reached) mo, respectively. Conclusions: These data suggest that ENCO + BINI is well tolerated at multiple doses, with promising activity in BRAF-naïve pts with BRAF-mutant melanoma. A Ph III trial (OLUMIANCE) is underway using ENCO 450 mg daily with BINI. Clinical trial information: NCT01543698.
Background: Acquired resistance (AR) to BRAF inhibitors (BRAFi) in melanoma is a near-universal phenomenon driven by numerous genetic and non-genetic alterations. Clinical implications of these AR mechanisms have not been described in a large cohort. We assessed the spectrum of BRAF AR mechanisms and their associated timing of onset, pattern of disease progression (DP), and clinical outcomes. Methods: We compiled clinical and genetic data from 100 patients (pts) with 132 melanoma samples obtained at BRAFi DP from three previously published studies of BRAFi resistance. Whole exome sequencing and/or PCR-based genetic testing were performed on all samples. Associations between AR mechanis and clinical features/outcomes were assessed with multivariate analysis. Results: In 132 DP samples, putative AR mechanisms were identified in 58%, including NRAS or KRAS mutations (20%), BRAF splice variants (16%), BRAF/exon8 amplifications (13%), MEK1/2 mutations (7%), and non-MAPK pathway alterations (11%). Marked heterogeneity was observed within tumors and patients. BRAF/exon8 amplifications and non-MAPK alterations often co-occurred with other genetic changes, whereas NRAS mutations, MEK1/2 mutations, and BRAF splice variants largely arose in isolation (p = 0.02). Of 19 pts with ≥ 2 DP biopsies, identified AR mechanisms were concordant in only 1 pt (5%). NRAS mutations were associated with vemurafenib use (p = 0.045) and baseline intracranial metastases (p = 0.036). Progression-free survival and patterns of DP were similar across AR mechanisms. The median survival after DP was 6.9 months, and subsequent responses to combined BRAF/MEK inhibition were uncommon (2/15; 13%); no patients responded to ipilimumab (0/24). Post-progression outcomes did not correlate with specific BRAF AR mechanisms. Conclusions: This is the largest study of BRAF progression to date. Marked heterogeneity was acquired BRAFI resistance in pts with BRAF mutant melanoma. Despite marked heterogeneity of AR mechanisms within pts and tumors, NRAS mutations were associated with vemurafenib use and intracranial disease. Further investigation into non-genetic AR mechanisms and immune features of BRAF progression is warranted.

Background: Uveal melanomas are a rare type of melanoma with only 5-7 cases per 1 million persons diagnosed each year. Patients with metastatic melanoma of uveal origin, tend to have lower response rates on traditional therapies, as well as are usually excluded from clinical trials. Herein we report our experience with 7 patients with metastatic uveal melanoma who received pembrolizumab as part Merck’s expanded access program. Methods: Patients were considered eligible for treatment on this protocol, if they were 12 years old, diagnosed with unresectable metastatic melanoma, had liver function abnormalities (1 pt). Two pts had seizures, 1 from peri- sional edema, 1 from tumor growth, treated with anti-convulsants and a brief course of steroids. Conclusions: Early results from this ongoing trial suggest that pembro has promising activity in untreated melanoma BrMs. Concomitant brain tumors were controllable with anti-convulsants and peri- sional steroids. Accrual is ongoing and correlative studies from pre-treatment brain and extra-cranial tumor samples are being conducted. Clinical trial information: NCT02085070.

Background: Brain metastases (BrMs) develop in 40% of metastatic melanoma (MM) patients (pts). Untreated BrMs exclude from most clinical trials. In prior trials, treatment of MM with pembrolizumab (pembro), an IgG4-antagonist of the immune checkpoint PD-1, produced response rates of 0/24. A phase 2 study (NCT02085070) was initiated to assess safety and activity of pembro in pts with previously untreated or progressing BrMs. Methods: Pts with BrMs from melanoma (reported here) or lung cancer are eligible if at least 1 asymptomatic 5-20mm BrM not requiring immediate local therapy or systemic steroids is present, and at least 1 BrM is amenable to biopsy or resection. Prior PD/PD-L1 inhibitors are excluded. Pembro 10mg/kg is administered every 2 weeks (wks). Brain MRI is repeated at 4 wks to assess safety and restaging is done every 8 wks. Primary endpoint is BrM response by modified RECIST (lesions ≥ 5mm are measurable on MRIs with 1mm slices; up to 5 BrMs are used to determine response). Results: Between April and December 2014, 17 pts were accrued, 6 with BRAF mutations, 10 previously received ipilimumab. Activity at interim analysis was sufficient to continue. Four were unevaluable for BrM response (3 due to rapid extracranial disease progression (PD), 1 due to inhaled cessation, and 1 was too early. Among 12 evaluable pts, BrM partial responses (PRs) were observed in 2 pts (one with prior ipilimumab), stable disease in 2, PD in 7 (2 with a mixed response and 1 with PD by imaging but pseudoprogression on histology). BrM responses are ongoing at 7+; 6+ and 3+ months. One CR and 3 PRs were observed in extra-cranial metastatic disease, 3 of these 4 with concurrent BrM response. The only grade 3 adverse event clearly related to pembrolizumab was transaminitis. Conclusions: First results from NCT02085070 of 12 patients with metastatic melanoma show promising radiographic activity with pembrolizumab. Activity was seen in all BRAF/MEK positive pts, and in BRAF wild-type pts who had significant disease burden. These results support further investigation of pembrolizumab in this patient population.
Deep profiling of tumor immune microenvironment (TME) with fluorescence activated cell sorting (FACS) in advanced melanoma. First Author: Kimberly Loo, UC San Francisco, San Francisco, CA

Background: Tumor PD-L1 expression by immunohistochemistry has limitations in describing the tumor immune microenvironment as it relates to treatment with PD-1/PD-L1-antibodies. We developed a new FACS based method to study the tumor immune microenvironment and used it in patients undergoing PD-1/PD-L1 antibody treatment. Methods: Multi-parameter flow cytometry was performed on freshly harvested metastatic melanoma tumor tissue following overnight enzymatic digestion (n = 161). The gating strategy sorted tumor cells, CD4+ , CD8+ and myeloid/stromal cells. CD8+ cells were further sorted for PD-1, PD-L1, CTLA-4, and HLA-DR, while CD4+ cells were sorted for Foxp3 in addition to these markers. Tumor associated macrophage and dendritic cell activation markers were also determined in samples. Overall responses were derived from investigator reported data by Response Evaluation Criteria in Solid Tumors (RECIST). Descriptive statistics for responders vs. non-responders to anti-PD-1 therapy were constructed to assess the prognostic utility of these markers. Results: TME-FACS was evaluative on 32 unique patients who were evaluable for response. A high percentage (> 35% of total CD8+ cells) of PD-1 and CTLA-4 expressing CD8+ TILs is associated with an increased response to anti-PD-1 therapy. Increased mean fluorescence intensity (MFI) of PD-1/CTLA-4 dual expression on CD8+ cells is also associated with response. Myeloid cell markers clearly stratified responders vs. non-responders to anti-PD-1 therapy. Conclusions: TME-FACS is a novel method to functionally define the immune microenvironment in melanoma. TME-FACS immunoprofiling revealed that an increased percent of PD-1/CTLA-4+ CD8+ TIL populations in metastatic lesions correlates with responsiveness to anti-PD-1 therapies. Defined myeloid subsets can also be uncovered by TME-FACS.

Response Assessment Median PD1 / CTLA4 MFI Median % PD1+ / CTLA4+ CD8 TILs
Complete Response (CR) 238 49 %
Partial Response (PR) 217.5 37.5 %
Stable Disease (SD) 199.5 32.05 %
Progressive Disease (PD) 163 26.1 %
Circulating melanoma cells and recurrence in stage III melanoma patients. First Author: Anthony Lucci, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: There is a need for more sensitive and specific prognostic markers for advanced stage melanoma patients to help improve the risk-benefit ratio of systemic adjuvant therapies. While it has been demonstrated that circulating melanoma cells (CMCs) can be detected in melanoma patients, there is limited data regarding the prognostic significance of CMCs. The aim of this prospective study was to determine if CMCs predicted relapse in stage III melanoma patients. Methods: Serial CMC assessments (7.5ml blood) were performed in 101 patients with stage III cutaneous melanoma patients using the CellSearch system (Janssen). CD45 +/−, CD34 +/−, CD146 +/−, CD45−/−, and CD34−/− nucleated cells were considered CMCs. Relapse-free survival was compared between patients with ≥1 CMC detected at baseline (first presentation to our clinic) or at second blood draw (6 months after baseline), versus those with no CMCs at baseline and at the second blood draw. Log-rank test and Cox regression analysis were applied to establish the association of CMCs with relapse-free survival. Results: CMCs were identified in 44 of 101 (44%) patients at either baseline or at second blood draw. Median follow up was 10 months. We observed no significant association between CMC presence and primary tumor factors including Breslow thickness, number of mitotic figures, or ulceration. Relapse was observed in 10 of 44 (23%) patients with ≥1 CMC, versus 4 of 57 (7%) of patients with no CMCs at baseline and at second blood draw (log-rank P = 0.04, HR 3.25, 95% CI 1.01 to 10.37; P = 0.04). Conclusions: CMCs at baseline or at a six month follow up blood draw were predictive of relapse in stage III melanoma patients. This data supports larger studies to confirm that presence of CMCs could be used to identify patients at risk for relapse, with an ultimate goal of early systemic intervention.

Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): A pooled analysis. First Author: Jeffrey S. Weber, Moffitt Cancer Center, Tampa, FL

Background: NIVO is a programmed death-1 (PD-1) immune checkpoint inhibitor which has shown durable tumor responses in multiple cancer types and prolongs overall survival in pts with MEL. The objective of the current analysis is to describe the safety profile of NIVO across recent MEL studies, including 4 studies in which guidelines for the management of adverse events (AEs) were utilized. Methods: A retrospective safety review was conducted for 4 ongoing phase I–II trials, in which MEL pts received NIVO 3 mg/kg Q2W until disease progression or unacceptable toxicity. Data were included from pts who received at least 1 dose of NIVO, and included assessments of AEs, select AEs (immune-related etiology), time to onset and resolution, and the use as well as impact of immune modulating agents (IMs). Results: A total of 576 patients received NIVO for a median of 3.7 months; 312 (54%) had received prior ipilimumab (Ipi). The most frequent drug-related AEs of any grade were fatigue (25%), pruritus (17%), diarrhea (13%), rash (12%), and nausea (12%); grade 3–4 drug-related AEs were observed in 5% of all pts, and in 8% of pts with prior Ipi. No drug-related deaths were reported. Drug-related select AEs of any grade were most frequent in the skin (34%), GI tract (13%), endocrine glands (8%) and liver (4%); grade 3–4 select AEs occurred in 4% of pts. Median time to onset of drug-related select AEs ranged from 5 wks for skin AEs to 15 wks for renal AEs. IMs were administered to 166/474 pts (35%) in phase III studies to manage AEs; 211/474 pts (45%) had help match patients to targeted therapies. Conclusions: From this pooled analysis, drug-related AEs with NIVO monotherapy were primarily low grade and the incidence of grade 3–4 drug-related AEs was not affected by prior Ipi. Nearly all drug-related grade 3–4 select AEs resolved with use of IMs, which did not appear to impact on tumor response.

Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. First Author: Douglas Buckner Johnson, Vanderbilt Univ, Nashville, TN

Background: Ipilimumab (Ipi) is a cornerstone of metastatic melanoma therapeutics. Since Ipi toxicities are largely immune-related, clinicians may withstand therapy in patients (pts) with pre-existing autoimmune disorders (AD). We assessed whether pts with AD treated with Ipi experienced exacerbation of their AD, excessive immune-related adverse events (irAEs), and optimal clinical activity. Methods: We retrospectively reviewed records from 12 pts with metastatic melanoma and pre-existing AD treated with Ipi from 4 centers. We characterized baseline AD symptoms, prior management, and disease course on therapy. We also assessed rates of classical Ipi-related irAEs, and subsequent clinical outcomes, including objective response rate (ORR), overall survival (OS), and progression-free survival (PFS). Results: Of 12 pts, 5 had baseline rheumatoid arthritis, 3 had psoriasis/psoriatic arthritis, 1 had systemic lupus erythematosus, 1 had Crohn’s disease, 1 had transverse myelitis, and 1 had sarcoidosis. Ten (83%) had previously received corticosteroids or other systemic therapy for their AD, including 5 ongoing at the time of Ipi initiation (low-dose prednisone in 2 pts and hydroxychloroquine in 3). Following Ipi, 6 pts (50%) had symptomatic worsening or flares of their AD; all resolved with short courses of corticosteroids and none required additional immune suppression. Grade 3 irAEs were observed in 5 pts (42%) including colitis (n = 2), hypophysitis (n = 2), and acute angle glaucoma (n = 1). One treatment-related death occurred, presumably from colitis and possibly hypophysitis (no laboratory confirmation) following dose 3 of Ipi. ORR was 17% (2/12 pts); median OS and PFS were 22.0 and 3.0 months, respectively. One pt experienced a durable complete response. Conclusions: This is the largest study of Ipi in pts with autoimmune disorders. Ipi was associated with moderate tolerability and clinical activity in this cohort of pts with mild to moderate pre-existing AD. Clinicians should monitor pts closely for irAEs and AD flares. Larger retrospective and prospective studies are ongoing to characterize this cohort further.
9020 Poster Session (Board #263), Mon, 1:15 PM-4:45 PM

Extended follow-up results of phase Iib study (BRIM7) of vemurafenib (VEB) with cobimetinib (COB) in BRAF-mutant melanoma. First Author: Anna C. Pavlick, New York University, Weill Cornell Medical College, New York, NY

Background: BRIM7 formed the basis for development of the VEM + COBI regimen, which, in a randomized phase III trial, confirmed the statistically significant and clinically meaningful progression-free survival (PFS) improvement of VEM + COBI over VEM. Results of BRIM7 with extended follow-up are presented. Methods: Eligible patients (pts) had advanced VEB (or VEM)-treated, metastatic melanoma, ECOG PS 0-1, and could either have progressed on VEM (or VEM-PC) or be BRAF inhibitor (BRAFI)-naive. Disease burden received VEM 720 mg or 960 mg twice daily (BID) continuously + COBI 60 mg, 80 mg, or 100 mg once daily (QD) 14 days on/14 days off (14/14); 21 days on/7 days off (21/7); or continuously. Two dose levels were expanded: VEM (720 mg and 960 mg) + COBI 60 mg QD 21/7. Results: Previously, we reported the 129 VEM + COBI treated pts with the following characteristics: BRAFI-naive: 49%; stage M1c: 70% and 82%; LDH > ULN: 46% and 62%; and median follow-up: 13 months and 6 months, for BRAFI-naive and VEM-PC pts, respectively. Adverse event (AE) frequency and severity remained stable with extended follow-up. The frequencies of symptomatic MEK inhibitor AEs (serous retinopathy and cardiomyopathy) and BRAFI AEs (skin squamous carcinoma) were also unchanged. Confirmed response rate in BRAFI-naive pts remained at 87%. Four additional pts attained complete response (CR) at Cycles 16-25, increasing CR rate from 10% (6 pts) to 15% (10 pts). Median PFS was unchanged at 13.8 months. With extended follow-up, median overall survival (OS) was reached at 28.5 months and 2-year OS was 61%. Confirmed response rate in VEM-PC pts remained at 15%, 1 pt attained CR at Cycle 22, CR was not according to clinician's standard of care. Median PFS and OS were unchanged at 2.8 months and 8.4 months, respectively. The 2-year OS was 15% with extended follow-up. Conclusions: VEM + COBI continues to show robust efficacy in BRAFI-naive pts, with a manageable and tolerable safety profile without new safety signals. Median OS in BRAFI-naive pts was >2 years. Late CR conversions indicate persistent activity with continued therapy. Clinical trial information: NCT01271803.

9022 Poster Session (Board #265), Mon, 1:15 PM-4:45 PM

Determination of locally advanced basal cell carcinoma (BCC) in the first 285 patients enrolled in the RegiSONIC disease registry study. First Author: Simon S. Yoo, Northwestern University, Chicago, IL

Background: Advanced BCC (aBCC), including metastatic (mBCC) or locally advanced BCC (laBCC), is rare, and a broadly accepted diagnostic definition of aBCC is lacking. The RegiSONIC disease registry (ClinicalTrials.gov identifier: NCT01604252) is designed to evaluate how clinicians diagnose and treat aBCC in real-world practice. Methods: RegiSONIC is an ongoing, multicenter, prospective observational cohort study in 3 BCC patient (pts) populations, treated according to clinician's standard of care: newly diagnosed pts with aBCC and/or BCC nevus syndrome (BCCNS) treated with VISMO. Here we present preliminary effectiveness and safety results in the first 66 non-BCCNS newly diagnosed laBCC pts treated with VISMO. Results: Pts are enrolling into 3 cohorts (C): newly diagnosed (VISMO-naive) aBCC pts (C1), aBCC pts who previously received VISMO in a Genentech-sponsored study (C2), or pts with BCCNS who have aBCC or multiple BCCs of any stage (C3). Determination of aBCC was at the clinician's discretion and not dictated by the protocol. This summary describes determination of laBCC in the first 285 pts enrolled to cohort 1 as of September 12, 2014. Results: Median time from initial diagnosis of the current BCC lesion to enrollment was 0.43 months. The median time from initial diagnosis of the current BCC lesion to enrollment was 1.64 months and from determination of laBCC to enrollment was 0.43 months. Determination of laBCC was based on the following sums to >100%: lesion size (78%), histopathology (55%), location (53%), extent of disease (51%), recurrence (30%), cutaneous lesion (29%), radiography (21%), surgery (16%), and other (8%). All pts had clinically visible locally advanced lesions; 72% had a single lesion, and 28% had multiple lesions (median, 3.0 lesions). The median size of target lesions was 20 mm among 220 pts diagnosed on the basis of lesion size, 65% had lesions measuring ≥20 mm. Among 84 pts diagnosed on the basis of recurrence, 40% had ≥2 recurrences, Clinical/histopathologic subtype of the target lesion (sums to >100%) was nodular (64%), morphoeiform/infiltrative (29%), superficial (13%), micronodular (3%), basocellular (3%), and other (11%). Target lesions were predominantly located on the head, including the nose (22.4%), forehead (12.6%), ear (8.3%), cheek (8.3%), and scalp (7.6%). Conclusions: Data from RegiSONIC will provide real-world clinical practice insight to help improve the diagnosis and care of pts with aBCC. Clinical trial information: NCT01604252.

9021 Poster Session (Board #264), Mon, 1:15 PM-4:45 PM

Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). First Author: Brigitte D'Incalci, Nantes University, Nantes, France

Background: The phase 3 coBRIM study showed significant improvement in progression-free survival in pts with metastatic melanoma on V + C compared with those on V and placebo (P) (HR, 0.51; 95% CI, 0.39-0.68, P < 0.001 (Larkin et al. N Engl J Med 2014;371:1867-1876). We report the evaluation of health-related QOL in coBRIM for V + C versus V + P, as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-BR21 and QLQ-C24 quality of life (QOL) Questionnaire (QLQ-C30). Methods: The EORTC QLQ-C30 was evaluated in pts with baseline (BL) and ≥1 post-BL assessment. Assessments were conducted on Days (D) 1 and 15 in cycles (C) 1 and 2 (each C = 28 days), and every other cycle thereafter until pt withdrawal or end of study. The analysis includes assessments up to CBO1. Each domain score, assessing global health status and QOL, and symptom scales were examined at BL and for each time point (change from BL) by treatment arm descriptively; formal statistical comparisons were not conducted. Clinically meaningful (CM) change was defined as a ≥10-point increase or decrease from BL. Results: The completion rate at BL for both treatment arms was 96.7% and was consistently high (>88%). Across all functioning domains (cognitive, emotional, social, role, and physical) and symptoms (appetite loss, constipation, nausea and vomiting, dyspnea, pain, and fatigue), pts in the V + C arm reported better scores at 1 or more post-BL time points evaluated versus those in the V + P arm, but mean score change did not reach CM criteria. However, pts in the V + C arm experienced CM or marginal improvement in insomnia (C2D15, C4D1, C6D1, C8D1), while no V + P pts showed CM change from BL in insomnia. The V + C arm experienced CM worsening of diarrhea from BL only at C1D15 and C2D15; no CM change from BL for diarrhea was observed in the V + P arm. Results of this analysis showed that a higher percentage of pts in the V + C arm had CM score improvements from BL for all EORTC domains; the greatest differences were observed in insomnia (16%), social functioning (11%), fatigue (9%), and pain (7%). Conclusions: In pts with metastatic melanoma, V + C provided superior efficacy compared with V + P and symptom improvement for insomnia, social functioning, fatigue, and pain with similar QOL. Clinical trial information: NCT01689519.

9023 Poster Session (Board #266), Mon, 1:15 PM-4:45 PM

The RegiSONIC disease registry: Preliminary effectiveness and safety in the first 66 newly diagnosed locally advanced basal cell carcinoma (BCC) patients treated with vismodegib. First Author: Marie E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Treatment of advanced BCC (aBCC), including metastatic or locally advanced (la) BCC, is challenging, with approaches ranging from surgery to recently approved targeted Hedgehog pathway inhibitor vismodegib (VSMO). RegiSONIC (NCT1604252) is an ongoing, multicenter, prospective observational cohort study designed to collect real-world data on the diagnosis and treatment of patients (pts) with aBCC and/or BCC nevus syndrome (BCCNS). Here we present preliminary effectiveness and safety results in the first 66 non-BCCNS newly diagnosed laBCC pts treated with VSMO. Methods: Pts are enrolling into 3 cohorts (C): newly diagnosed (VSMO-naive) aBCC pts (C1), aBCC pts who previously received VSMO in a Genentech-sponsored study (C2), or pts with BCCNS who have aBCC or multiple BCCs of any stage (C3). Determinations of disease response were investigator assessed. Pt discontinuation was every 3-4 months. Results: By Sept 12, 2014, 285 non-BCCNS newly diagnosed laBCC pts had been enrolled: median age, 68 years; male, 63%; 66 (23%) pts were treated with VSMO received VSMO within 90 days of determination of laBCC. Median (range) of follow-up: 15.2 (0.16-26.8) months. Results are in the Table. All AEs leading to treatment discontinuation and 1 SAE (acute renal failure) were considered related to VSMO; the 4 deaths (6%) were not. Conclusions: Preliminary data from the RegiSONIC study demonstrate effectiveness and safety of VSMO in non-BCCNS newly diagnosed laBCC pts, with a safety profile consistent with previous studies. Real-world data may provide clinical insights to the treatment of aBCC. Clinical trial information: NCT01604252.

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Impact of treatment breaks on vismodegib patient outcomes: Exploratory analysis of the STEVIE study. First Author: Reinhard Dummer, University Hospital Zurich, Zurich, Switzerland.

Background: Vismodegib (VSMO) is the first Hh pathway inhibitor approved for use in adults with advanced BCC (aBCC) that is inappropriate for surgery or radiotherapy. While most VSMO-related adverse events (AEs) are mild to moderate, the presence of monthly treatment breaks due to treatment failure, non-compliance or discontinuation. Treatment breaks are allowed in the STEVIE study (NCT01367665) for the management of toxicity, among other reasons. Herein we present an exploratory analysis assessing the safety and efficacy profile in patients (pts) with treatment breaks on study. Methods: STEVIE is an ongoing study focusing on efficacy of VSMO in pts with aBCC. Pts receive VSMO 150 mg once daily until progressive disease, unacceptable toxicity, or withdrawal from the study. The primary objective is safety; efficacy is a secondary end point. Tumor response assessments are performed using RECIST 1.1 as assessed by the investigator. Exploratory analyses were performed using data from a planned interim analysis (data cutoff Nov 6, 2013). Results: 499 pts were included in the safety population and analyzed according to number of treatment breaks received. The median duration of treatment was 223.5, 299.0, 399.0, and 454.0 days in pts with 0, 1, 2, or ≥ 3 treatment breaks, respectively. Median dose intensity was 97%, 89%, 86%, and 81%, respectively. Median treatment break duration was 22 days (SD 13.92). Safety and efficacy results are presented in the Table. Patients with more treatment-emergent AEs (TEAEs) including those experiencing more grade ≥ 3 TEAEs had more treatment breaks. These were AEs known to be commonly associated with VSMO use. The most common grade ≥ 3 TEAE was muscle spasm.

Conclusions: Increased number of treatment breaks was associated with longer median duration of VSMO treatment and did not appear to compromise efficacy. Clinical trial information: NCT01367665.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: In metastatic melanoma, immune checkpoint blockade has generated excellent response rates and prolonged survival. As the depth of immune activation may correlate with occurrence of immune related adverse events (irAEs), an association between irAEs and disease outcomes might also exist. We describe herein the irAE toxicity profile of 148 patients with resected and unresectable melanoma treated with nivolumab at our institution, and the association of irAEs with progression-free survival (PFS) and overall survival (OS). Methods: Data was pooled from 148 patients (33 resected, 115 unresectable) treated at 1-, 3-, or 10mg/kg doses (with or without peptide vaccine) every 2 weeks for 12 weeks, then an additional 12 weeks if stable or better, and up to 2 additional years if stable or better. Frequency, grade, and characteristics were analyzed, including kinetics of onset, resolution, and need for steroid therapy. We conducted a 12-week landmark OS analysis, with a multivariate time-dependent Cox proportional hazard model to assess differences in PFS (for 115 unresectable patients) and OS (all 148 patients) in the presence or absence of irAEs. Results: RAEs of any grade were observed in 69.2% of patients (101/148). Grade III/IV irAEs were infrequent: 3 patients (2%) had Grade III rash, 2 (1.4%) had asymptomatic Grade III amylase/lipase elevation, and 2 (1.4%) had Grade III colitis. Of the irAEs, colitis and pneumonitis required steroids (median duration = 5 wks). Statistically significant PFS and OS differences were seen in patients who experienced an irAE (HR=0.548, 95% CI 0.320 to 0.928) and in patients who did not (HR=1.835, 95% CI 1.106 to 3.034) at 18 mos follow-up. Improved PFS was associated with rash (p = 0.001 [HR 0.121, 95% CI 0.024 to 0.62]) and vitiligo (p = 0.005 [HR 0.121, 95% CI 0.024 to 0.62]). Rash was associated with improved OS (p = 0.005 [HR 0.098, 95% CI 0.006 to 1.71]), with no significant association between vitiligo and OS (p = 0.081 [HR 0.146, 95% CI 0.009 to 2.488]). No survival differences were seen with other irAEs (endocrinopathies, diarrhea, or pneumonitis). Conclusions: Rash and vitiligo are associated with prolonged PFS and OS in melanoma patients treated with nivolumab, which should be validated in subsequent prospective trials.

9030 Poster Session (Board #273), Mon, 1:15 PM-4:45 PM Final data from CALM: A Phase II study of Coxackievirus A21 (CVA21) oncolytic virus immunotherapy in patients with advanced melanoma. First Author: Robert Hans (Ingeram Andtbacka, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: CVA21 (CAVATAK) is a novel bio-selected oncolytic and immunotherapeutic strain of Coxackievirus A21. Intratumoral (i.t) CVA21 injection initiates preferential tumor cell infection, cell lysis and enhancement of a systemic anti-tumor immune response. Present are the final results of the open-label, multicenter Phase II CALM (CAVATAK in Late stage Melanoma) study. Methods: The CALM study investigated the efficacy and safety of i.t CVA21 in 57 patients with treated or untreated unresectable Stage IIIC-IVM1c melanoma. Pts received up to 3 × 10⁶ TCID₅₀ CVA21 i.t on study days 1,3,5, 8 and 22, and then every three weeks for a further 6 injections. Pts displaying immune-related progression-free survival (irPFS) or better at 6 mos were eligible for 9 additional injections. Key eligibility criteria were ≥ 18 yrs old, ECOG PS 0-1, and at least 1 injectable lesion. The primary endpoint was to achieve ≥ 9 of 54 evaluable pts with irPFS at 6 mos. Secondary endpoints included irRECIST overall response rate, duration of response, safety, and QoL. Methods: The median time to response and 1-year survival. Results: The primary endpoint of the study was achieved with 21 of 57 (36.8%) evaluable pts displaying irPFS at 6 mos with a median irPFS of 4.2 mos. The overall response rate (irRECIST) was 28.1% (16 of 57 evaluable pts) with a median time to response of 2.8 mos and 1-year survival rate 75.4% (43 of 57 pts). After a median follow-up of ~16.5 mos, median duration of response in responders and median OS for all pts was not reached. The most common AE’s were Grade 1 fatigue, chills, local injection site reactions and fever. No Grade 3 or 4 product-related AE’s were observed. Conclusions: Intratumoral CVA21 is a promising novel oncolytic immunotherapeutic agent for the treatment of unresectable Stage IIIC-IVM1c melanoma and the CALM study met its primary endpoint of irPFS at 6 mos. CVA21 was well tolerated and exhibited both local and distant durable tumor responses. Further clinical studies using CVA21 in combination with other immunotherapies are underway. Clinical trial information: NCT01277561.

9031 Poster Session (Board #274), Mon, 1:15 PM-4:45 PM Clinical characteristics predictive of response to pembrolizumab in advanced melanoma. First Author: Katy K. Tsai, UC San Francisco, San Francisco, CA

Background: Anti-PD-1 therapy has shown significant clinical activity in advanced melanoma and in other cancers. Factors predictive of response remain vaguely defined. We report on clinical characteristics correlated with higher response rates to therapy in our phase I trial of pembrolizumab in treatment-naïve advanced melanoma patients (n = 110, enrolled Dec 2011 to Oct 2013, data analysis July 2014) received pembrolizumab in 1 of 3 dosing regimens: 2Q3W, 10Q3W, or 16Q3W. PFS and OS were assessed using the 1.1 criteria. Sites of metastases were determined based on CT imaging, and this analysis was not limited to RECIST target lesions. The overall response rate (ORR) and exact treatment-free survival (TFS) were compared between responders and progressors. Results: In this cohort, ORR to pembrolizumab was 40%. Factors correlated with significantly higher ORR were: LDH ≤ normal (ORR 52.2%), no previous ipilimumab (ORR 48.3%), and presence of lung metastasis (ORR 52.8%). Patients with liver metastasis had worse response (ORR 18.4%), as did those with liver and lung metastases (ORR 31.3%, 95% CI 18.1-49.8%). Data for associations of subtypes with ORR in different patient populations are shown (Table). Conclusions: Normal LDH, no previous ipilimumab, and presence of lung metastasis are correlated with better response to pembrolizumab in advanced melanoma patients. The presence of liver metastasis is correlated with lower response to pembrolizumab, both in the presence and absence of lung metastasis. These correlations were observed regardless of BRAF status, presence of metastasis on baseline CT and previous ipilimumab (cutaneous vs. uveal). Clinical trial information: NCT01295827.
Prognostic relevance of baseline neutrophils and derived neutrophil to lymphocyte ratio for ipilimumab-treated advanced melanoma patients. First Author: Pier Francesco Ferrucci, European Institute of Oncology, Milan, Italy

Background: Clinical responses to ipilimumab are variable in terms of onset, magnitude and duration. Upfront identification of patients who are more likely to benefit from treatment is a major need. The prognostic value of baseline neutrophils and derived neutrophil to lymphocyte ratio (dNLR) has been addressed in different malignancies with interesting but contrasting data. 

Methods: Data from 720 metastatic melanoma patients treated with ipilimumab 3 mg/kg within the Italian expanded access programme were analyzed. Patients were stratified according to baseline neutrophilia (ANC ≥ 7500) and derived neutrophil to lymphocyte ratio (dNLR). The optimal cut-off value of baseline dNLR for survival was determined by the receiver operating characteristics curve analysis. Overall survival and progression free survival were estimated using the Kaplan-Meier method. The prognostic values of ANC and dNLR were assessed using multivariate Cox proportional hazard models. Results: The median follow-up was 16.5 months. Both baseline neutrophilia and dNLR were significantly associated with the outcome of melanoma patients treated with ipilimumab, in terms of disease progression and death (P < 0.0001 for all). When the two indexes were combined, we found that patients with both elevated ANC and dNLR had a significantly increased risk of death (HR = 6.25; 95%CI: 4.73-8.25) and of progression (HR = 4.60; 95%CI: 3.51-6.03) when compared to patients with both low ANC and dNLR. The 1-year and 2-year survival rates were 2% and 0%, respectively, for patients with both elevated ANC and dNLR, and 43% and 24%, respectively, for patients with both low ANC and dNLR.

Conclusions: By analyzing a large cohort of ipilimumab treated advanced melanoma patients, we identified a subpopulation of patients that is very unlikely to benefit from this treatment. Based on these data responders could be easily selected from general population, allowing for an upfront screening that could spare toxicity to non responder ones.
9036 Poster Session (Board #279), Mon, 1:15 PM-4:45 PM
Updated overall survival (OS) results for BRF113220, a phase I–II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with BRAF V600 melanoma (MM). First Author: Adil Daud, UC San Francisco, San Francisco, CA

Background: This Phase I–II study evaluated the safety and efficacy of the combination of dabrafenib and trametinib (the combination) compared with dabrafenib alone (monotherapy) in patients (pts) with BRAF V600 MM. Methods: BRAF V600E/K MM pts naive to BRAF and MEK inhibitors were enrolled. Part B (Ph I, n = 77, BRAF-naive) pts enrolled into escalating dose (mg) cohorts of dabrafenib twice daily (B) +trametinib once daily (QD) as follows: 75/1, 150/1, 150/1.5 and 150/2. Part C (Ph II, n = 162) pts were randomized 1:1:1 to dabrafenib 150 mg monotherapy, 150/1 and 150/2. Crossover from monotherapy to 150/2 combination was allowed post-progression of disease. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints were OS and pharmacokinetics. Results: Previously reported landmark 2-year OS results for pts in Parts B and C with median follow-up of 35 and 34 mo is presented in Table 1. In Part C, median OS rate for 150/2 combination pts was 25 mo (HR = 0.79 vs monotherapy, p = 0.3341). OS rate for monotherapy was confounded by crossover to the 150/2 arm; 45 (83%) pts crossed over at time of analysis. In the 150/2 arm, 16 (30%) pts continued to receive combination beyond progressive disease. Subsequent systemic therapies were similar across arms; 39 (24%) pts received ipilimumab, 17 (10%) received anti-PD-1/PD-L1 therapies, and 21 (13%) received vemurafenib.

Conclusions: Landmark 2-year OS rate was 51% for Part C 150/2. Further follow-up is ongoing. Landmark 3-year OS rate and safety data with 12 mo additional follow-up will be presented. NCT0172175 Clinical trial information: NCT0172175.

9038 Poster Session (Board #281), Mon, 1:15 PM-4:45 PM
XPC, XPF, TP53 and GSTP1 polymorphisms in prognosis of cutaneous melanoma patients. First Author: Carmen Silvia Passos Lima, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil

Background: XPC, XPF, TP53 and GSTP1 genes act on repair and detoxification of ultraviolet (UV) radiation-induced DNA damage, which are related to cutaneous melanoma (CM) development and progression. The DNA repair ability is variable in humans, since the genes enrolled in the detoxification of ultraviolet (UV) radiation-induced DNA damage, which are related to cutaneous melanoma (CM) development and progression. The DNA repair ability is variable in humans, since the genes enrolled in the DNA repair pathway related to XPC and XPF polymorphisms influence prognosis of CM patients. These findings, once validated in additional studies, will contribute to individualize high-risk patients, who deserve to receive a close follow-up and adjuvant therapy.

Conclusions: The data suggest, for the first time, that inherited abnormality in DNA repair pathway related to XPC and XPF polymorphisms influence prognosis of CM patients. These findings, once validated in additional studies, will contribute to individualize high-risk patients, who deserve to receive a close follow-up and adjuvant therapy.

9037 Poster Session (Board #280), Mon, 1:15 PM-4:45 PM
Prognostic value of BRAFV600E mutations in American Joint Committee on Cancer (AJCC) stage 3 cutaneous melanoma patients in the MelanCohort prospective cohort. First Author: Philippe Saigly, Hospital Ambroise Pare, Boulogne-Billancourt, France

Background: Prognosis of AJCC stage 3 melanoma pts is heterogeneous. The prognostic value of BRAFV600E mutations in melanoma is debated. In a retrospective study of 105 stage 3 pts with a nodal deposit of > 2 mm, we showed that BRAFV600E mutation was an independent factor of decreased both overall and distant metastasis free survivals (DMFS). We aimed to validate this finding in an independent prospective data set and to expand it to the entire AJCC stage 3 spectrum. Methods: We selected all pts with AJCC stage 3 cutaneous melanoma at inclusion or during follow-up that were included in MelanCohort (NCT00839410), which recruited prospectively during 2003-8. BRAFV600E mutations were detected by pyrosequencing of DNA in nodal or in transit met samples with > 60 % melanoma cells. Melanoma was considered mutated when > 10% of DNA was mutated. Endpoints were melanoma-specific survival (MSS) and DMFS. Kaplan-Meier curves and multivariate Cox PH regression model were used. 9 pts receiving targeted therapy were censored at first dose given. A sample of 155 pts gave 89% power to detect an HR of 2 for survival, with a risk set at 0.05. Results: Median follow-up of stage 3 pts was 56 months. BRAFV600E status was assessed in 158 melanomas. BRAFV600E (V600E & V600K) in 89 and 9% of cases, respectively) were detected in 50.6% of melanomas. The only significant differences according to BRAF status in AJCC stage 3 were histological subtypes and age (younger for BRAFV600E). The only characteristics associated with worst MSS in multivariate model were higher AJCC stage (P = 10-4, HR: 2.74, 95%CI: 1.69-4.43), age > 50 (P = 0.02, HR: 1.86, 95%CI: 1.1-3.14), BRAFV600E (P = 0.02, HR: 1.9, 95%CI: 1.1-2.78), male sex (P = 0.02, HR 1.91, 95%CI 1.06-2.75), and mutation in primary melanoma (P = 0.04, HR: 1.9, 95%CI 1.01-2.54). Worst DMFS was associated with higher AJCC stage (P = 0.003, HR: 1.9, 95%CI: 1.27-2.85), age > 50 (P = 0.0007, HR: 2.11, 95%CI: 1.34-3.33), and BRAFV600E (P = 0.02, HR: 1.59, 95%CI: 1.05-2.38). Conclusions: BRAFV600E was an independent prognostic criteria in stage 3 pts. This may help to better characterize this stage. Results of adjuvant trials in BRAFV600E stage 3 pts are urgently needed. Clinical trial information: NCT00839410.
**498s**

**Melanoma/Skin Cancers**

**Poster Session (Board #284), Mon, 1:15 PM-4:45 PM**

**Melanoma-specific MHC-II expression to predict response to α- PD-1 therapy. First Author: Justin M. Baiko, Vanderbilt Univ Med Ctr, Nashville, TN**

**Background:** α-PD-1 therapy yields objective clinical responses in 30-40% of advanced melanoma (MEL) patients (pts). While promising, many pts do not benefit clinically. Predictive biomarkers to guide pt selection are needed. We hypothesized that tumor antigen presentation (MHC-I or MHC-II expression) is a requirement of α-PD-1 benefit, and presence of these cell surface markers would predict benefit. **Methods:** We profiled MHC-I and MHC-II mRNA across 60 MEL cell lines. The transcriptional characteristics of MHC-II+ cell lines were analyzed by Gene Set Analysis. Cell surface expression of MHC-I and MHC-II was confirmed by flow cytometry (FC) in a subset of cell lines under basal and stimulated (IFNγ) conditions. In 26 tumor samples from α-PD-1 treated MEL pts, immunohistochemistry (IHC) was performed for HLA-DR (MHC-II) or HLA-A (MHC-I), SOX10, CD4 and CD8. IHC results were correlated with response and progression-free survival (PFS). **Results:** MHC-I mRNA was expressed in all cell lines while MHC-II expression was bimodal (60% positive). MHC-II+ cell lines had transcriptional signatures of the PD-1 signaling, allograft rejection, and T-cell receptor signaling. By FC, MHC-II+ (mRNA) cell lines were constitutive and inducible (IFNγ stimulation) for HLA-DR while MHC-II- cells did not express or induce HLA-DR. In contrast, all tested cell lines significantly upregulated PD-L1 with IFNγ stimulation. Of 26 pts treated with α-PD-1, 10 were MHC-II+. All 10 MHC-II+ (100%) pts had partial, complete, or mixed responses (MR), while only 7/16 (44%) of MHC-II- pts benefited (Fisher’s exact p = 0.004). Excluding MR pts (n = 2), median PFS for MHC-II+ was 728 days (d), while the median PFS for MHC-II- tumors was 98d (log-rank p = 0.01). MHC-II+ tumors had enhanced CD4 and CD8 infiltration (Pearson’s correlation p = 0.000002 and p = 0.03, respectively). MHC-I positivity was ubiquitous and not associated with response. **Conclusions:** A subset of MEL demonstrates an MHC-II signature that correlates with α-PD-1 response and enhanced CD4/CD8 T-cell infiltrate. MHC-II+ tumors can be robustly identified by routine melanoma-specific IHC for HLA-DR to guide pt selection. Combining HLA-DR IHC with other biomarkers, including PD-L1 expression may further improve pt selection.
**Association of PD-L1 expression in melanoma with response and prognosis to ipilimumab.** First Author: Caroline Brueggemann, Department of Dermatology, University Hospital Erlangen, Erlangen, Germany

**Background:** Immunotherapy with ipilimumab demonstrated a statistically significant survival benefit. In two large phase III trials responses were observed in 10-15% of patients. However, 64% of patients exhibited significant and 20% of the patients severe grade 3 and 4 side effects. Identifying predictive biomarker profiles could enable better treatment allocation. **Methods:** In this multicenter study 176 tumor samples from 125 patients with metastatic melanoma were analyzed for PD-L1 gene expression, thereof 78 patients had received ipilimumab (30 responders and 48 non-responders). mRNA was extracted from formalin-fixed paraffin embedded (FFPE) tumor tissue by a fully automated method and measured by quantitative RT-PCR. Differences of survival and PD-L1 expression between patient groups were assessed using the Mann-Whitney U test, the logrank test and the Kaplan-Meier technique. **Results:** Patients with low PD-L1 expression showed a significantly better survival than those with high expression of PD-L1 (p = 0.002) not considering the subsequent therapy. No statistical difference in PD-L1 expression between responders (n = 30) and non-responders (n = 48; p = 0.458) to ipilimumab was observed. **Conclusions:** Our results suggest that PD-L1 expression is not predictive for response to therapy with ipilimumab but is a positive prognostic marker for survival of melanoma patients.

**Evaluation of the impact of infliximab use for the treatment of ipilimumab related diarrhea in the outcome of patients with advanced melanoma.** First Author: Edurne Arriola, University of Southampton, Southampton, United Kingdom

**Background:** The use of immunosuppressants for the treatment of immune related (IR) toxicities from immunoregulatory antibodies, such as ipilimumab is intended to dampen harmful adaptive immune responses. It is uncertain whether this also results in reduction of anti-tumour immunity and adversely affects disease specific outcome. The aim of our study was to evaluate the impact of overall survival (OS) of infliximab use for the treatment of immune related diarrhea from ipilimumab in patients with metastatic melanoma. **Methods:** We retrospectively evaluated 90 patients with advanced melanoma treated with ipilimumab (3mg/kg) with assessment of response during and following treatment. We recorded clinical characteristics, toxicity data and outcome. Kaplan Meier and Log rank tests were used to assess outcome differences. **Results:** Fifty-one percent of patients were male, the median age was 64 years; sixty-nine (77%) patients have cutaneous primaries, 11(12%) uveal and 2(2%) mucosal. Sixty-five patients (72%) had M1c disease. BRAFAssessment was available in 77% of tumours and 32% cases harboured a V600E mutation. Infliximab was administered as second line treatment and 60% completed four cycles. Thirty percent (n = 27) of patients developed ipilimumab-related diarrhea of any grade. Twenty-one (80%) required oral steroids for management, escalated to iv methylprednisolone (1-2mg/kg/24hrs) in 12 cases. In seven patients (26%) infliximab was required to control G3/4 colitis. Median follow up was 8 months for the whole population. M1c disease, poor performance status at treatment initiation and progression at the week 12 response assessment were associated with shorter survival (all p-values < 0.05). Patients who developed diarrhea had improved OS when compared to those who did not (8.8m vs 5.4m; p = 0.16). Within patients with diarrhea, the median OS of those treated with infliximab compared to those without was 8.8m vs 6.8 (p = 0.16), respectively. **Conclusions:** In our series infliximab does not negatively affect the outcome of patients with advanced melanoma treated with ipilimumab and early switch in order to spare steroid toxicity appears warranted and safe.
Association of immune-related thyroid disorders with pembrozumab (pembro, MK-3475) in patients (pts) with advanced melanoma treated in KEYNOTE-001. First Author: Caroline Robert, Gustave Roussy, Villejuif, France

Background: The anti–PD-1 antibody pembrolizumab is approved in the US for treating advanced melanoma that progressed following ipilimumab and nivolumab, and is being investigated in combination with other immune checkpoint inhibitors. In KEYNOTE-001, 697 patients with advanced melanoma received pembrolizumab. Here we report the incidence and treatment of thyroid disorders.

Methods: Thyroid disorders were monitored during pembrolizumab treatment. Patients were divided in two groups: 289 pts received pembrolizumab monotherapy and 408 pts received pembrolizumab in combination with any chemotherapy other than ipilimumab.

Results: 111 (43%) pts had at least one thyroid disorder including: subclinical hypothyroidism in 110 (40%), subclinical hyperthyroidism in 71 (24%), and thyroiditis in 55 (20%). Hyperthyroidism was more common in pts treated with pembrolizumab in combination with chemotherapy (31%) compared to those treated with pembrolizumab monotherapy (13%). No cases of thyroiditis were identified in pts treated with pembrolizumab monotherapy.

Conclusions: Subclinical thyroid disorders are common during pembrolizumab treatment. Clinical evaluation and periodic screening may be useful in pts treated with pembrolizumab.
Identification of a predictive signature based on immunohistochemical (IHC), RNA-seq and epigenetic profiling of melanoma metastases for response to ipilimumab

First Author: Teotila Seremet, Universitair Ziekenhuis Brussel, Brussels, Belgium

Background: Ipilimumab (Ipi) improves the survival of patients (pts) with advanced melanoma. Combination of Ipi with an autologous monocyte-derived DC therapy (TriMixDC-MEL) may further improve patient outcome (Neyns et al., 2014 ASCO AM). A predictive melanoma tissue signature for the clinical efficacy of Ipi and TriMixDC is needed to optimize individualized treatment strategies.

Methods: Between 01/2011 and 05/2013 freshly frozen melanoma metastases were collected from pts treated with Ipi (n = 9), TriMixDC-MEL (n = 2), or TriMixDC-MEL plus Ipi (n = 14). Samples were profiled by IHC (incl. CD3, CD8, PanMel, MCSP, CD20, CD163, DC-LAMP, Casp-3, Ki-67, PHH3, HLA class I, WIF), RNA-seq and MBD-seq (genome-wide DNA methylation profiles). Tumors were classified according to the irRC. Results: Five pts obtained a complete response (CR), 6 obtained a mixed response (MR), and there was no evidence of tumor response in 14 pts (NR). A total of 26 metastases (15 obtained prior to and 11 post therapy) were profiled by IHC and 18 were additionally profiled by RNA and MBD-seq. Intra-tumor CD3 and CD8 T cell infiltration was observed in 23/26 samples, with variable pattern and extent of infiltration. None of the 3 pts with absent CD3/CD8 infiltration in their tumor core regions responded to Ipi-based immunotherapy. The differential analysis of the RNA-seq data resulted in a list of 195 genes with a statistically significant difference in expression between CR and NR (false discovery rate < 0.05). A gene ontology enrichment analysis revealed that the differentially expressed genes were enriched for immune-related ontologies. The MR expression profiles clustered together with the NR group. MBD-seq revealed differences in methylation status between CR and NR. These differences in methylation status were not linked to the observed response differences in RNA expression. Conclusions: Comprehensive analysis of melanoma metastases with gene expression and methylation status provides a distinct profile that identifies long-term responders to Ipi-based immunotherapy. Prospective validation is warranted.

9054 Triple wild type melanoma profiling in the Caris Molecular Intelligence registry

First Author: Kristian Homicsco, University Hospital Lausanne, CHUV, Lausanne, Switzerland

Background: Malignant melanoma is a genetically diverse disease. The most frequent mutation is BRAF, followed by NRAS and cKIT mutations. While BRAF, NRAS and cKIT mutations represent the largest fraction of patients, frequent mutation is BRAF, followed by NRAS and cKIT mutations. While BRAF, NRAS and cKIT mutations represent the largest fraction of patients, frequent mutation is BRAF, followed by NRAS and cKIT mutations. While BRAF, NRAS and cKIT mutations represent the largest fraction of patients, frequent mutation is BRAF, followed by NRAS and cKIT mutations. While BRAF, NRAS and cKIT mutations represent the largest fraction of patients, frequent mutation is BRAF, followed by NRAS and cKIT mutations.

Methods: We analyzed 541 patient samples for immunohistochemistry (IHC) and next generation sequencing (NGS) data available from the Caris database. Out of the 541 samples 89 samples also had PD-L1 expression data available. Samples were grouped in 4 subtypes: BRAFmut (n = 169), NRASmut (n = 151), cKITmut (n = 25) and 3xWT (n = 197).

Results: The database is skewed with an underrepresentation of BRAFmut patients and enrichment of 3xWT tumors. BRAFmut, NRASmut, cKITmut, and 3xWT patients were 30%, 26%, 3.7% and 40% of the total population, respectively. BRAFmut and 3xWT subgroups have more frequent cMET expression (p = 0.002). While NRASmut tumors show lack of ERCC1 expression, cMET is overexpressed. Tumor expression of mut mutation subtypes present equally frequent expression of MGMT, SPARC, TOP2A, TOP1, TS, TUBB3 and RRM1 suggestive of multiple chemoresistance pathways. TP53 mutations are recurrent (~15%) in all mutation subgroups. In 3xWT tumors a different spectrum of mutations arise with low frequency (< 1%). Most frequent KRAS, NRAS, cKIT, GNA11, GNAQ, GNAS, Notch1, Smo, STK11, VHL, MLH1, MPL, MPM1 A 3xWT Subanalyses showed an overall 75% positivity. 3xWT tumors were more frequently PD-L1 negative as compared to BRAFmut (p = 0.077).

Conclusions: To our knowledge, the Caris database provides one of the largest profiling of 3xWT. In contrast to BRAFmut, NRASmut and cKITmut tumors, 3xWT melanoma harbor a more complex mutational landscape. Low frequency mutations can identify targets in up to 40% of these patients. 3xWT are less frequently PD-L1 positive. Overall 3xWT patients should be tested for multiple markers in order to identify low frequency mutations.
A phase I study of vemurafenib and decitabine in metastatic melanoma.

First Author: Sneha Deepak Phadke, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Targeted therapy in metastatic melanoma has shown unprecedented response rates. However, this effect is usually short lived, with a median progression free survival of 5.3 months with the use of vemurafenib. This phase I study explored the novel combination of vemurafenib and decitabine. Methods: Patients with BRAF V600E mutated metastatic melanoma were eligible for participation. Dosing of decitabine was modified for each cohort, which is detailed in the Table. The primary objective was safety while the secondary objective was response rate. Results: There were 4 patients were enrolled in cohort 1, 3 in cohort 2, 4 in cohort 3, and 3 in cohort 4. Seven patients had previously been exposed to vemurafenib. The most common adverse events included hyperbilirubinemia, hypophosphatemia, leukopenia, arthralgia, and rash. Most grade 1–2. Ten patients required a dose reduction of vemurafenib. Maximum tolerated dose of decitabine was not reached, and there were no dose limiting toxicities. Six patients (43%) had a response to therapy with 3 (21%) achieving a complete response (CR). Five patients (36%) achieved stable disease while 3 (21%) had progressive disease. Two of the 3 patients with partial response had previously progressed on single agent vemurafenib. Of the 6 patients that had a response, 3 were in cohort 1. Conclusions: This study demonstrated that the combination of vemurafenib and decitabine in BRAF V600E mutated metastatic melanoma is safe and resulted in an overall response rate of 43%. In comparison to the BRIM-3 trial, this trial had a significantly higher rate of patients achieving CR with the combined treatment (21% vs < 1%, p < 0.01). As half the patients that responded were enrolled in cohort 1, a similar phase I trial is planned which will explore the effect of decitabine given at a low dose for a longer duration to ensure maximal depletion of DNA methyltransferase, the enzyme to which decitabine binds. Table. Clinical trial information: NCT01876641.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose of decitabine</th>
<th>Duration of decitabine treatment</th>
<th>Dose of vemurafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 mg/kg SQ three times weekly</td>
<td>2 weeks</td>
<td>960 mg BID continuous</td>
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<tr>
<td>2</td>
<td>0.2 mg/kg SQ three times weekly</td>
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<td>3</td>
<td>0.3 mg/kg SQ three times weekly</td>
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<td>4</td>
<td>0.3 mg/kg SQ three times weekly</td>
<td>2 weeks</td>
<td>960 mg BID continuous</td>
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Adoptive Cell Therapy for metastatic melanoma: A UK centre experience. First Author: Manan Rhys Pillai, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Adoptive cell therapy (ACT) with tumour infiltrating lymphocytes (TIL) has consistently demonstrated impressive clinical results in several international studies in the management of metastatic melanoma. We describe our experience as the only UK cancer centre providing TIL therapy. Methods: TIL are cultured from resected tumour samples as previously described. Infusion is preceded by non-myeloablative lymphodepleting chemotherapy (high dose cyclophosphamide and fludarabine) and followed by intravenous high dose interleukin 2 (HD-IIL2). Results: Eleven patients have been treated to date: eight with cutaneous melanoma, two with ocular melanoma and one patient with mucosal melanoma. All patients had metastatic disease and were heavily pre-treated with a combination of targeted agents and immunotherapies (anti-CTLA4 and anti-PD1 antibodies). In the ten patients currently evaluable, 60% achieved an objective clinical response according to the response evaluation criteria in solid tumours. Five of eight patients with cutaneous melanoma achieved a response, including one ongoing complete response (30+ months) and four partial responses. All other patients showed disease stabilisation. One patient with ocular melanoma achieved a short lived partial response. Of eight patients with significant symptomatic progressive disease, six obtained clear symptomatic benefit. Treatment is well tolerated. All patients experienced anticipated toxicities associated with pre-conditioning chemotherapy and HD-IIL2, which were short lived and manageable on the medical ward. Conclusions: We show that at our centre lympho-depleting chemotherapy followed by transfer of TIL and HD-IIL2 is feasible and clinically effective, demonstrating tumour regression in over 60% of patients with metastatic cutaneous melanoma. Short lived responses were additionally seen in patients with ocular melanoma, with ocular tumours and options limited, suggesting a potential role for TIL therapy in this group of patients also. Significant toxicities are attributable to HD-IIL2 and further evaluation of TIL follow by low dose IL2 should be conducted to decrease treatment related complications and expand clinical participation in ACT.

One-year overall survival (OS) and biomarker correlates from a phase II study of ipilimumab (IPI) with carboplatin and paclitaxel (CP) in patients with unresectable stage III or IV metastatic melanoma (MM). First Author: Rahima Jamal, Hopital Notre-Dame, Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada

Background: Pivotal trials. Patients whose tumors were wild type for BRAF/NRAS had a more favorable clinical outcome. Lower levels of PD-1 on CD4 and CD8 T cells were observed in responders compared to non-responders. Conclusions: Median OS and 1-year OS compared favorably to previous pivotal trials. Patients whose tumors were wild type for BRAF/NRAS had a higher rate of objective response. High baseline level of CD3 infiltrate was associated with a positive clinical response to IPI/CP. A low activation state (ICOS) before treatment and maintenance of low levels of PD-1 on T cells during treatment correlated to a favorable clinical response to IPI. Clinical trial information: NCT01676649.

Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIB-IV melanoma. First Author: Igor Puzanov, Vanderbilt University Medical Center, Nashville, TN

Background: T-VEC is an HSV-derived oncolytic immunotherapy designed to induce systemic antitumor immunity. In a phase 3 melanoma study, T-VEC monotherapy significantly improved durable response rate (DRR, ≥ 6 month response) vs GM-CSF (16% vs 2%, P < 0.0001; Andtbacka et al. ASCO 2013), and median OS was 4.4 months longer for T-VEC vs GM-CSF (23.3 vs 18.9 months; HR = 0.79, 95% CI: 0.62-1.00; P = 0.051; Kaufman et al, ASCO 2014). Combining T-VEC to promote tumor-derived antigen release with an immune checkpoint inhibitor may enhance efficacy compared to either agent alone. The phase 1b portion of this phase 1b/2 combination study (NCT01740297) completed enrollment and met its primary objective with no dose-limiting toxicities (DLTs) and an objective response rate (ORR) of 56% (Puzanov et al. ASCO 2014). Methods: Key inclusion criteria included stage IIB-IIIA melanoma; no prior systemic treatment; measurable disease; and ≥ 1 injectable cutaneous, subcutaneous, or nodal lesion. T-VEC was given intrathecally at ≤ 4 mL of 10^6 PFU/mL at week 1, then 10^7 PFU/mL at week 4, and then Q2W. Ipi 3 mg/kg Q3W was given as 4 infusions starting week 6. T-VEC continued until DLT, intolerance, all injectable tumors disappeared, or disease progression (PD) per immune-related response criteria (irRC). Results: The data cutoff was Dec 22, 2014 with all patients at least 17 months from start of treatment. 17 patients received different dose levels. Grade 3/4 treatment-emergent AEs occurred in 32% and grade 3/4 immune-related AEs occurred in 2 patients with no treatment-related deaths. Per irRC, ORR was 56% (33% CR) and DRR was 44%. Median time to response was 5.3 months (range 2.6-5.7). Median progression-free survival (PFS) was 10.6 months (2.6-19.3+). Median overall survival (OS) was not reached; 12-month and 18-month survival were 72.2% and 67%. On a lesion level, 24 and 11 of 35 injected index lesions and 8 and 5 of 16 uninjected index lesions regressed ≥ 50% and 100%, respectively. Conclusions: At ≥ 17 months, T-VEC+ipi continued to demonstrate durable responses with 2/3 of patients alive at 18 months and no new safety signals. Phase 2 (ipi vs T-VEC+ipi) is ongoing. Clinical trial information: NCT01740297.

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9064 Poster Session (Board #307), Mon, 1:15 PM-4:45 PM
Identification of potentially actionable mutations in RTKs in melanoma detected by next generation sequencing (NGS).
First Author: Jan Kemnade, Baylor College of Medicine, Houston, TX
Background: The success of personalized cancer therapies targeting patients with specific actionable mutations underscores the need to expand the search for relevant mutations with functional and/or clinical consequences. Cutaneous melanomas have a high mutation burden due to ultraviolet radiation exposure, thus necessitating approaches to distinguish driver versus passenger mutations. Here we report the analysis of the nature and location of somatic mutations in 16 receptor tyrosine kinases (RTKs) and a cutaneous melanoma cohort analyzed by next generation sequencing (NGS).
Methods: NGS for all exons of 201 cancer-related genes was performed on tumor and germline DNA from pts with non-acral cutaneous melanoma (n = 108). Somatic mutations in RTKs (MET, FLT3, PDGFRB, KIT, EGFR, ERBB2, ERBB3, RET, IGF1R, EPHA3, DDR1, DDR2, ALK, JAK1, JAK2, JAK3) were mapped to the tyrosine kinase domain (TKD), other functional regions (i.e. transmembrane domains, binding domains) or conserved protein domains (ORD), or regions of unknown significance (RUS) in each gene. The COSMIC database was analyzed for presence of the same mutations in other tumors. Results: Missense mutations were detected in all 16 RTKs. The number of mutations identified in each RTK ranged from 2 (IGF1R) to 24 (EPHA3), with a median of 7.5 mutations per RTK. The average incidence of mutations found in the TKD region for each RTK was 29% and ranged from 0% (ERBB2, ERBB3) to 80% (JAK2). For the ORD regions the average was 34%, ranging from 0% (ERBB2, ERBB3, RET, DDR2) to 61.5% (MET). For the RUS regions the average was 37%, ranging from 0% (PDGFRB, DDR1) to 100% (ERBB2, ERBB3). Mutations detected in 11 of the RTKs were also identified in cancer sequencing datasets available on COSMIC.
Conclusions: The prevalence of mutations in the TKD, ORD, and RUS regions varied significantly among the 16 RTKs in the cutaneous melanoma cohort. Overall ~62% of the mutations mapped to regions with potential functional significance, and ~16% have been reported previously in other cancers. Integration of these analyses with predicted structural and functional consequences may be used to prioritize candidate actionable mutations for in-depth characterization.

9065 Poster Session (Board #308), Mon, 1:15 PM-4:45 PM
The effect of ipilimumab on natural killer cells identifies the subset of advanced melanoma patients with clinical response.
First Author: Ines Domingues Firas Da Silva, New York Univ Langone Medcct, New York, NY
Background: The concept of immune cell exhaustion in the context of metastatic melanoma has been reinforced by the success of immunotherapies targeting the exhaustion markers CTLA-4 and PD-1. Natural Killer (NK) cell exhaustion, characterized by an up-regulation of inhibitory receptors and loss of function, was described in the context of melanoma. Ipilimumab (ipi) (anti-CTLA-4) improves the anti-tumor T cell activity and achieves response rates of 15–20%, however the effect of ipi on NK cells is unknown. In this project, we studied the effect of ipi on the phenotype of NK cells from melanoma patients and how it relates with clinical response.
Methods: NK cells were purified from the peripheral blood of 10 advanced melanoma patients before and after ipi. Blood samples were collected at baseline, after the 2nd and 4th cycles of ipi. NK cells were characterized according to the expression of (NGK2D2) and inhibitory (KIRB1) receptors, function (cytotoxicity, IFN-γ production), levels of the IL-2R α chain and response to IL-2 stimulation. We analyzed the effect of ipi on NK cells as it relates to clinical response. Results: IPI induces an upregulation of 50% in the IL-2R α chain levels on NK cells (p = 0.03). There was no significant difference in other receptors or function (p > 0.05). We then checked the phenotype and function of these NK cells after 48 hours of IL-2 stimulation and in 4 patients out of 10 there was an improvement of cytotoxicity and higher levels of IL-2R chain. Remarkably, this positive response to IL-2 was observed in patients with clinical response to ipi (partial/complete response) compared with non-responders, with higher cytotoxicity (p = 0.05) and levels of IL-2R α chain (p = 0.02).
Conclusions: CTLA-4 is expressed mainly on T cells, including regulatory T cells, with no expression in NK cells. On the other hand, ipi increases expression of the phenotype of NK cells, with an increase of IL-2R expression. More importantly, the effect of ipi on NK cells (better response to IL-2 stimulation and cytotoxicity) is associated with a good clinical response. The mechanism behind this effect is not clear yet, however this may be indirect through the action of ipi on other immune cells.

9066 Poster Session (Board #309), Mon, 1:15 PM-4:45 PM
Continued evaluation of a 31-gene expression profile test (GEP) for prediction of distant metastasis (DM) in cutaneous melanoma (CM).
First Author: David H. Lawson, Winship Cancer Institute of Emory University, Atlanta, GA
Background: A GEP has been validated as an independent predictor of DM, distant metastasis free survival (DMFS) and overall survival (OS) (Gerami, CCR 2015; Gerami JAAD, 2015). This abstract combines the third validation cohort of the GEP with the first 2 validation cohorts. Patients (pts) patients were enrolled in a multi-center IRB approved archival tissue study with a primary endpoint of DMFS. 492 CMs had T-factors available for analysis. Quantitative RT-PCR and Basal OASIS (OASIS) classifier classified CM tumors as low risk Class 1 vs. high risk Class 2. Results are reported for thin (T1), intermediate (T2/T3) and thick (T4) lesions. Most patients were node negative clinically or by sentinel node biopsy (SNB). Results: GEP was a significant predictor of DMFS and OS (log-Rank p < 0.0001), and GEP, Breslow’s thickness, and ulceration were independent predictors in Cox multivariate analysis (DMFS HR = 2.7, p = 0.0003; 2.2, p = 0.033; 3.3, p < 0.0001, respectively and OS HR = 2.8, p = 0.0002, 2.5, p = 0.01, 1.7, p = 0.01, respectively). In the T2/T3 NO cohort (n = 180) frequent Class 2 signature increases with depth (T2; 35/78 (45%) Class 2; T3; 75/102 (74%) Class 2) and ulceration (nonulcerated; 54/108 (50%) Class 2; ulcerated; 53/63 (84%) Class 2). The table reflects survival analysis in this cohort. In the T1 group (median follow-up for non-DM group ~ 7.4 yrs) 14/173 (8%) reported DM. For T4 group, 42/80 (53%) developed DM. Data not considered adequate for further analysis of either group. Conclusions: GEP offers prognostic information that complements conventional staging at least in patients with T2/T3 CM. Ongoing studies will further define the role of GEP in evaluating these patients.

9067 Poster Session (Board #310), Mon, 1:15 PM-4:45 PM
Long-term results of ultrasound (US)-guided fine needle aspiration cytology (FNAC) in conjunction with sentinel node biopsy (SNB) to support step-wise approach in melanoma.
First Author: Alexander Christoph Jonathan Van Akkooi, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands
Background: Ultrasound (US) guided Fine Needle Aspiration Cytology (FNAC) in conjunction with sentinel node biopsy (SNB) to support step-wise approach in melanoma.

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9068 Poster Session (Board #311), Mon, 1:15 PM-4:45 PM
Phase II trial of trametinib in combination with the AKT inhibitor GSK 2141795 in BRAF wild-type melanoma. First Author: Alain Patrick Algazi, University of California, San Francisco, CA

Background: There is currently a lack of effective targeted therapies for BRAF wild type (WT) melanoma. We explored the combination of the MEK inhibitor trametinib with the AKT inhibitor GSK2141795 in BRAF/NRAS WT and BRAF WT/NRAS mutant (MT) melanoma. Methods: Study accrual goal was 24 patients (pts) with metastatic BRAF WT/NRAS WT melanoma and 24 pts with BRAF WT/NRAS MT melanoma. Eligibility criteria included: unresectable stage III or IV disease, ECOG status 0-2, stable CNS disease, and adequate cardiac function (LVEF ≥ 50%, QTc > 480). For each cohort, an interim analysis was pre-specified after 10 pts. If no responses were seen, the cohort would be closed. If one or more responses were seen, an additional 14 pts would be accrued. Pts received trametinib (1.5 mg) and GSK 2141795 (50 mg) orally, once daily for each cycle lasting 28 days. ORR was assessed by RECIST 1.1 with restaging performed every 8 weeks (2 cycles). Results: Twenty pts were enrolled from October 2013 to October 2014: 10 pts in each NRAS cohort. Rash (70%) and diarrhea (50%) were the most common drug-related adverse events (AEs) for all grades; mucositis occurred in 40% of pts. The best overall response was stable disease in 65%; 80% of BRAF WT/NRAS WT patients and 50% of BRAF WT/NRAS MT patients. No RECIST-confirmed partial or complete responses were observed. As a result, both cohorts were closed to further accrual. Median progression-free survival was 2.75 months (IGR: 1.7 to 3.7 mos), with no difference between the NRAS cohorts (p = 0.46).

Conclusions: The combination of trametinib and GSK2141795 is safe, but at these doses and schedules, is ineffective in the BRAF WT population, regardless of NRAS status. Clinically significant adverse events were common at the doses tested. Pharmacodynamic studies are ongoing to determine the extent of pathway inhibition achieved. Clinical trial information: NCT01941927.

9070 Poster Session (Board #313), Mon, 1:15 PM-4:45 PM
Immunologic profile of melanoma brain metastases (MBM) in patients (pts) with prolonged survival. First Author: Kevin P. Lui, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY

Background: Median survival of MBM pts is significantly shorter than pts with extra-cranial metastases. However, a subset of MBM pts exhibit extended survival. Radiation therapy (RT - radiosurgery and whole-brain radiation) is used to treat MBM pts and recent data by several groups including ours demonstrate that RT may potentiate response to immunotherapies by inducing an immunological tumor cell death. In this study, we investigate the immunomodulator effect of RT on MBM tissue and attempt to identify an immunological profile associated with improved post-MBM survival. Methods: Expression of 560 immunoregulatory genes was assessed in 32 MBM tissues (10 post radiation and 22 no radiation) using a customized NCancer Gx Human Immunology Kit (Nanostring) comprising of 24 immunology-related gene networks compiled from the Genomics Consortium List of immunologically important genes. We also compared expression of the immunoregulatory genes in long term survivors (> 1 year) compared to short term survivors (< 1 year). We then verified the data using RT-PCR and IHC in an expanded cohort of 47 MBM tissues. Results: Irradiated MBM had high expression of genes involved in: (1) autophagy/ apoptosis (ATG12, BCL2L11 and CASP8); (2) adhesion (CD209, ICAM2; ITG4A , ITGB1 and PECAM-1); (3) immune cell development and activation (IFNAR2, IKZF2, MAP4K5, NFATC3, POU2F2 and TFCD) (p < 0.05). In addition, RT induced upregulation of PD-L1 (transmembrane protein involved in immunoinhibitory signals) and TGF-β (immunosuppressive cytokine and cell cycle regulator) at the gene expression level, as determined by Nanostring and confirmed by RT-PCR, and protein level of PD-L1 by IHC. Genes involved in lymphocyte activation such as CD44, CD81 and IL16 were significantly overexpressed in long term survivors (p < 0.05).

Conclusions: Our data demonstrate that RT induces both lymphocyte activation and upregulation of immunosuppressive signals. Our data also suggest that MBM pts with prolonged survival host an immunologically distinct subset of tumors with upregulated lymphocyte activating genes. Identification of MBM pts with enhanced immunogenicity may aid in prognostication and prediction of response to immunotherapy.

9069 Poster Session (Board #312), Mon, 1:15 PM-4:45 PM
Changes in blood eosinophilia during anti-PD1 therapy as a predictor of long term disease control in metastatic melanoma. First Author: Lydia Gao, Hospital Clinic de Barcelona, Barcelona, Spain

Background: The anti-PD1 antibody (Ab) Nivolumab (Nivo) has demonstrated to improve the overall survival (OS) in patients (pts) with metastatic melanoma (MM) compared to DTIC. Pembrolizumab (Pembro), another anti-PD1, showed durable antitumor activity in pts with MM and has been approved in the US for the treatment (tmt) of MM that progressed on ipilimumab and, if BRAFV600 mutant, a BRAF inhibitor. To date, no lab test has been identified to predict clinical benefit (CB) to anti-PD1 Abs. Methods: This retrospective observational study included pts with MM who received anti-PD1 tmt in a single institution. The objective was to identify whether an increase of at least 100/mm3 at 3 weeks over the baseline or increase > 400/mm3 at 12 weeks in the absolute eosinophil counts (AEC) could predict CB. Blood tests were performed before every administration. Response to tmt according immune-related response criteria, progression free survival (PFS) and OS were evaluated. Descriptive statistics were used to analyze patient baseline characteristics. Response rates (RR) were compared by exact Fisher test. PFS and OS were estimated by the Kaplan-Meier method. Results: From March 2013 to December 2014, 29 pts were treated with anti-PD1 Abs (3 pts with Nivo and 26 pts with Pembro). Median age was 57 years (range 30-83) with 10.3% stage M1a, 24.1% M1b and 65.5% M1c, and 51.7% had elevated LDH. Pts who experienced an increase in AEC over the baseline > 100/mm3 at 3 weeks demonstrated better outcomes in terms of RR (55.6% vs 9.1%, p = 0.190), PFS (9.9% [95% CI: 5.8-14.0]) vs 2.6% [95% CI: 1.0-4.2] months, p = 0.008) and OS (18.8% [95% CI: 15.5-22.1] vs 6.9% [95% CI: 3.5-10.3] months, p = 0.001) compared with those who did not. Moreover, pts with an AEC > 400/mm3 at 12 weeks responded to tmt (100% vs 18.2%, p = 0.08) and showed more benefit regarding PFS (18.6 vs 2.1 months, p < 0.0001) and OS (not reached vs 11.4 months, p = 0.171) compared to those who did not. Conclusions: An increase in AEC of 100/mm3 over baseline at week 3 and an absolute AEC > 400/mm3 at week 12 during anti-PD1 tmt might identify pts with MM most likely to experience long-term disease control with anti-PD1 Abs.

9071 Poster Session (Board #314), Mon, 1:15 PM-4:45 PM
A novel algorithm applicable to cancer next-generation sequencing panels to predict total tumor mutation load and correlation with clinical outcomes in melanoma. First Author: Jason Roszik, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Next-generation sequencing (NGS) panels of cancer-related genes are increasingly utilized in oncology. We developed an algorithm to estimate total tumor mutation burden in melanoma using genes present in local and commercial NGS panels. The algorithm was validated using independent datasets and analyzed for clinical significance in two cohorts of advanced melanoma patients (pts). Methods: Overlapping genes (n = 170) from two NGS panels were used for algorithm development. Publicly available whole exome sequencing (WES) data (n = 345) from the cutaneous melanoma TCGA was employed to develop a mutation score for each gene in the panel. The summation of the mutation scores yields the Predicted Total Mutation Load (PTML) of the tumor. The algorithm was applied to 3 independent melanoma WES datasets to test the correlation of predicted with actual mutation burden. The PTML was then determined for cohorts of melanoma pts treated with immune-therapy regimens (e.g., adoptive cell transfer (ACT)), and associations with clinical outcomes were determined. Results: PTML correlated strongly with the actual WES mutation load of each tumor in all 3 tested melanoma WES datasets (Set 1, n = 121, r2 = 0.58; Set 2, n = 64, r2 = 0.84; Set 3, n = 127, r2 = 0.93). For subsequent analyses low PTML was defined as ≤ 100, and high as > 100 based on observed distributions. High PTML predicted both increased PFS (HR = 3.6, p < 0.001) and improved OS (HR = 5.6, p < 0.001) compared with low PTML treated with ACT. Pts with high PTML also had a longer interval from stage III to stage IV (HR = 55, p < 0.05) and improved OS from stage IV (n = 62, p < 0.01) in a large cohort of MDACC patients with NGS data. Further testing demonstrated that accurate disease-specific PTML algorithms for other cancers (e.g., lung) are feasible. Conclusions: In this proof of concept study, a novel algorithm applied to NGS panels accurately predicted total mutation burden in cutaneous melanoma pts. High PTML (> 100 mutations) correlated with improved OS in two cohorts of melanoma pts, including pts treated with immunotherapy. These results support further testing of the PTML algorithm in risk assessment and management of melanoma pts.

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Low vemurafenib plasma exposure as a short-term predictive parameter of progression disease in metastatic BRAFV600mut melanoma. First Author: Lauren Goldwirt, AP-HP, Hôpital Saint-Louis, Department of Pharmacology, Paris, France

**Background:** The BRAF inhibitor Vemurafenib (V) improves survival in BRAFV600mut metastatic melanoma patients, with a 59% response rate (BRIM-3). The aim of this retrospective study is to explore the potential relationship between V plasma concentration (\(V_C\)) and progression disease (PD).

**Methods:** Patients with AJCC stage IIIb/c (9 or IV) or IV (39) BRAFV600mut melanoma treated with V in monotherapy were retrospectively included according a signed informed consent. Blood samples were collected monthly. Response evaluation (RECIST 1.1) and toxicity evaluation were performed monthly after V initiation. \(V_C\) were quantified using a routine HPLC-UV method. All samples were included in the response, control, and monitoring analysis. Statistical analyses were performed with R-software. \(V_C\) cut-off to predict progression was determined with ROC curve analysis (pROC R Package). Progression-free survival (PFS) was assessed with multivariate Cox analysis (survival R package).

**Results:** \(V_C\) obtained in 48 patients (148 blood collections) displayed a wide inter- and intra-individual variability (5.3 to 132.5 \(\mu\)g/mL, median 66.6). All patients declared high compliance to treatment. Eleven patients (23%) experienced PD during V treatment. With a median follow-up of 12 months (1 to 50), progression on V occurred after a median 5 months treatment duration (14±9). Median \(V_C\) tended to be lower in patients experiencing PD (51.2±22.9 \(\mu\)g/mL) compared to complete, partial or stable responders (67.5±24.4 \(\mu\)g/mL, \(p=0.06\)). Maximal concentrations were higher in responding patients (67 vs 51 \(\mu\)g/mL, \(p=0.01\)). Patients with at least one value reaching 65 \(\mu\)g/mL tended to have a lower risk of disease progression than other patients (\(p=0.11\)). This threshold value of 65 \(\mu\)g/mL predicted progression with 78% specificity and 82% sensitivity. Interestingly, this effect appeared to be more significant before 6 months (PFSG).

**Conclusions:** \(V_C\) was confirmed highly variable at steady state. As low exposure was associated to higher progression risk and lower PFS, therapeutic drug monitoring should be performed at least for 6 months from treatment initiation of V that is now used in combination to the MEK inhibitor cobimetinib.

Tumor size and clinical outcomes in melanoma patients (MEL pts) treated with talimogene laherparepvec (T-VEC). First Author: Howard Kaufman, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

**Background:** T-VEC is an HSV-1 derived oncolytic immunotherapy designed to selectively replicate in tumors, produce GM-CSF, and enhance systemic antitumor immune responses. We describe factors associated with clinical outcomes in 436 pts with previously treated or untreated, unresected stage IIIB-IV MEL in OPTiM, a randomized (2:1) phase 3 trial of intralesional T-VEC vs subcutaneous GM-CSF.

**Methods:** All OPTiM pts were included in the analysis. Demographics, clinical characteristics, and treatment outcomes were collected monthly. Response evaluation (RECIST 1.1) and toxicity evaluation were performed in duplicate. TCR repertoire quantification was performed using high-throughput sequencing of the rearranged TCR \(\beta\)-chain genes; these were amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method using primers to TCR \(\beta\) and \(\gamma\) gene segments. Productive TCR sequences were used to obtain a clonality metric, and frequency of each T cell clone was obtained by comparing the number of reads generated by each unique CDR3 sequence. The proportion of TIL was determined using quantitative immunohistochemistry. Variations in proportion of TIL and clonality between samples were analyzed using ANOVA test. Tests were performed in duplicate.

**Results:** Eight tumors from two pts receiving pembrolizumab (Four from pt A and four from pt B, obtained 2 and 4 months after treatment initiation, respectively) were analyzed. Significant intrapatient intertumoral heterogeneity in TCR repertoire was observed (pt A: \(p=0.000153\) and \(p=0.0132\) pt B: \(p=0.00083\) and \(p=0.901E-07\) for differences in proportion of TIL and clonality, respectively). There was a high correlation between duplicates (\(r^2 = 0.86-0.99\)), suggesting the findings were not the result of experimental variation. **Conclusions:** Our data suggest significant intrapatient intertumoral heterogeneity in the proportion of TIL and clonality of the TCR repertoire at the same post-treatment timepoint. Caution should be exercised in interpreting the results of TCR analyses from single tumor biopsies in patients treated with checkpoint blockade.
Background: P1446A-05 is a CDK 4/6 inhibitor that targets both CDK 4 and 6, and is being developed in combination with Vemurafenib (GSK-1120212) to treat BRAF-mutant melanoma. Both BRAF and CDK 4/6 are over-activated in BRAF-mutant melanoma. The CDK 4/6 inhibitor, P1446A-05, is being evaluated in a Phase I trial (NCT01841463) in combination with Vemurafenib in patients with metastatic melanoma.

Methods: The Phase I trial of the CDK 4/6 inhibitor, P1446A-05 has been conducted in 30 patients with advanced metastatic melanoma. This Phase I trial was conducted to determine the safety, maximum tolerated dose (MTD) and dose limiting toxicity of P1446A-05 in combination with Vemurafenib. The Phase I, "dose escalation" part of the trial is reported here. A total of 4 cohorts were planned in the Vemurafenib-arm of this phase in the trial. Vemurafenib was escalated from 720 mg PO BID to 960 mg PO BID and P1446A-05 was planned to be escalated from 150 mg up to 350 mg PO QD. In each cohort, 3 to 6 patients were planned to be enrolled. Extensive PK analysis was conducted. Eligible patients could be BRAF-naive or resistant, ECOG PS 0-1, and QTc at baseline.

Results: The trial was conducted at 5 centers. A total of 26 patients were enrolled in the Phase I trial. The MTD was not reached in the trial. Based on the available data, the recommended dose for further testing of this combination is Vemurafenib 960 mg PO BID with 150 mg PO QD of P1446A-05. No drug-drug interactions were observed and the PK parameters for the combination were acceptable. Preliminary evidence of efficacy in the treatment-naive patient was seen. Clinical trial information: NCT01841463.

Conclusion: The combination of P1446A-05 and Vemurafenib in patients with advanced melanoma is safe and well-tolerated. The combination has demonstrated activity in those patients who have progressed on prior treatment with BRAF inhibitors. Further trials are planned to further evaluate this combination.

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A multi-center phase II open-label study (CheckMate 204) to evaluate safety and efficacy of nivolumab (NIVO) in combination with ipilimumab (IPI) followed by NIVO monotherapy in patients with melanoma metastatic to the brain. First Author: Kim Alyson Margolin, Stanford University Medical Center and the Cytokine Working Group (CWG), Stanford, CA

Background: Brain metastasis develops in approximately 50% of pts with metastatic MEL. In these pts, progressive brain disease is the major cause of tumor-related death (median overall survival [OS] after diagnosis, 4 months). NIVO (a fully human IgG4 PD-1 immune checkpoint inhibitor antibody) and IPI (a fully human IgG1 CTLA-4 immune checkpoint inhibitor antibody) are each approved as monotherapy for advanced MEL. In a phase II study, IPI showed activity in some pts with advanced MEL and brain metastases. Building upon the success of that study, this open-label, multi-site, US, phase II study is the first to evaluate NIVO combined with IPI followed by NIVO monotherapy for pts with MEL metastatic to the brain. It is anticipated that approximately 50% of enrolled pts will have had prior stereotactic radiotherapy (SRT). Methods: Pts ≥ 18 years of age with MEL measurable in extracranial sites and with asymptomatic brain metastases are eligible. Pts with a history of leptomeningeal involvement, a history of whole brain irradiation, autoimmune disease or corticosteroid use will be excluded. Pts will receive NIVO 1 mg/kg combined with IPI 3 mg/kg every three weeks (Q3W; 4 doses), followed by NIVO monotherapy 3 mg/kg Q2W until progression or unacceptable toxicity. SRT for progression of a central nervous system (CNS) lesion will be permitted. The primary objective is to assess the CNS clinical benefit rate (CBR; complete response + partial response + stable disease [SD] ≥ 6 months) per protocol-defined response criteria; this endpoint was selected based on its relevance in this population and ability to capture both objective response and durable SD. Secondary objectives are to assess exploratory markers of efficacy, including PFS, OS and safety. Exploratory correlates are also planned. An estimated 110 pts will be enrolled. Clinical trial registration number: NCT02320058.

Clinical trial information: NCT02320058.

TPS9081 Poster Session (Board #323a), Mon, 1:15 PM-4:45 PM
A multi-center, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresectable, stage IIIIB-IV melanoma. First Author: Antohoo Ribas, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA

Background: T-VEC is a herpes simplex virus-1-based oncolytic immunotherapy designed to preferentially replicate in tumors, produce GM-CSF and stimulate an anti-tumor immune response. OPTiM, a phase III trial of T-VEC vs GM-CSF in unresected stage IIIB-IV melanoma (n = 436), met its primary endpoint of improved durable response rate (DRR) in the T-VEC arm (16 vs 2%; Andtbacka et al ASCO 2013). Pembrolizumab is a human programmed death receptor-1 (PD-1)-blocking antibody indicated in the U.S. for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Combining T-VEC with pembrolizumab may enhance the anti-tumor immune response vs either therapy alone. Here, we describe a study (NCT02263508) assessing safety and efficacy of T-VEC + pembrolizumab in previously untreated, unresected stage IIIB-IV melanoma. Phase 1b enrolment began 12/2014. Methods: 1o objectives: Phase 1b: assess dose-limiting toxicities of T-VEC + pembrolizumab. Phase 2: compare confirmed ORR by immune-related response criteria (irRC) at Wk 24 for T-VEC + pembrolizumab vs pembrolizumab alone 2o objectives: Best OR, DRR, duration of response (DOR), PFS, OS, treatment-emergent/relation AEs Treatment: T-VEC is injected into cutaneous, subcuta neous or nodal lesions at up to 4 mL of 10^6 plaque forming units (PFU)/mL Day 1, then at up to 4 mL of 10^8 PFU/mL Day 22 and Q2W (phases 1b and 2). Pembrolizumab is given at 200 mg IV Q2W from Day 36 in phase 1b (n = 20) and Day 1 in phase 2 (n = 90). Treatment with both therapies will continue until (whichever comes first): CR or PD per irRC, intolerance, for up to 2 yrs or, for T-VEC only, when there are no longer injectable lesions. Pts in phase 2 will be randomized 1:1 to T-VEC + pembrolizumab vs pembrolizumab alone. Key eligibility: Stage IIIB-IV melanoma naive to systemic treatment (except adjuvant), injectable lesions, ECOG PS 0-1, no active cerebral metastases, no autoimmunity/immunosuppression, no active herpetic infection. Clinical trial information: NCT02263508.

TPS9083 Poster Session (Board #324a), Mon, 1:15 PM-4:45 PM
A single-arm, open-label, multicenter phase II trial (CheckMate 172) of nivolumab (NIVO) safety in European patients (pts) with advanced melanoma (MEL) who have progressed after ipilimumab therapy (IPI). First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany

Background: In recent years, the treatment landscape for advanced MEL has evolved with approval of an anti-CTLA-4 antibody (IPI), BRAF/MEK inhibitors and anti-programmed death-1 (PD-1) antibodies (NIVO and pembrolizumab). In a phase III study with pts previously treated with IPI, NIVO had an objective response rate of 32% (vs 11% with chemotherapy) and improved manageable safety profile. Anti-PD-1 antibodies have been associated with select adverse events (AEs; i.e., those with a potential immunologic etiology), most of which resolve using established safety management guidelines. However, further safety information would be desirable in pts who progressed after prior IPI, particularly in pt subgroups that were under-represented in previous studies. Consequently, this phase II trial will assess the safety of NIVO in a large population of European pts with stage III or IV MEL progressing after prior IPI treatment, including a separate prospective cohort of pts with ECOG performance status (PS) 2. Methods: Eligible pts are ≥ 18 years of age, have histologically confirmed malignant stage III (unresectable) or stage IV MEL, have ECOG PS 0–1 (Cohort 1) or 2 (Cohort 2), were previously treated regardless of BRAF mutation status and have evaluable RECIST v1.1-defined disease progression. Pts will be treated with NIVO 3 mg/kg every 2 weeks (Q2W) until progression or unacceptable toxicities for a maximum of 24 months. Safety assessments will be performed at month 1 and every 3 months thereafter. Efficacy assessments will begin at week 12. The primary objectives are to determine the rate and frequency of high-grade (CTCAE v4.0 grade 3 or higher), treatment-related, select AEs. Secondary objectives are to characterize the outcome (grade of resolution; duration of AE-specific treatment) of high-grade, select AEs and to estimate overall survival and investigator-assessed best overall response. Approximately 1,800 pts will be enrolled across Europe, including a maximum of 300 pts with ECOG PS 2. Clinical trial registration number: NCT02156804.

Clinical trial information: NCT02156804.

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Phase 1 dose escalation and expansion safety study of BLZ-100 in subjects with skin cancer. First Author: Dennis Michael Miller, Blaze Bioscience Inc, Seattle WA

Background: BLZ-100 is an intraoperative, fluorescent imaging agent designed to specifically label malignant tissue and enable more complete surgical resection of tumor tissue. BLZ-100 achieves tumor targeting through the peptide portion of the molecule, a modified chlorotoxin (CTX) peptide, and its imaging properties from the coupled near-infrared fluorescent dye, indocyanine green. Tumor-specific uptake of BLZ-100 has been shown in multiple mouse tumor models and in dogs with spontaneous cancers. Methods: In order to characterize the safety of BLZ-100, a first-in-human, phase 1 dose escalation and expansion study in subjects with suspected skin cancer is being conducted. BLZ-100 is administered via a 15-minute IV infusion to subjects approximately 2 days before planned excision of their skin tumor. Subjects with known or suspected non-melanotic skin cancer (e.g., basal cell carcinoma) are included in the dose escalation. Subjects with known or suspected melanoma are included in the dose expansion. Subjects must have adequate bone marrow, liver and kidney function to participate. Dose escalation is being conducted according to a traditional 3+3 design. Dose limiting toxicity is defined as any related adverse event (AE) of ≥ Grade 3 severity occurring within 7 days of BLZ-100 administration. Measures of safety include patient or physician reported adverse events, laboratory measures of hematology, liver and kidney function, and coagulation parameters and changes in vital signs and electrocardiograms (ECG). Blood samples are collected over the 7-day DLT period to measure BLZ-100 serum concentrations via a LC/MS method. Serial fluorescence imaging of suspected skin tumors in situ is conducted over 48 hours using the Fluobeam 800 device. Portions of the excised skin specimens from the dose escalation were also subjected to fluorescent imaging analysis using an Odyssey scanner and immunohistochemistry analysis for the presence of Annexin A2 (presumed target of BLZ-100).

Dose escalation in the 5 pre-specified dose levels has been completed without DLT. Enrollment of the expansion cohorts is ongoing as of December 16, 2014. Clinical trial information: NCT02097875.

Randomized phase II study comparing the MET inhibitor cabozantinib to temozolomide (TMZ) or dacarbazine (DTIC) in ocular melanoma: A091201. First Author: Jason John Luke, University of Chicago, Chicago, IL

Background: Ocular melanoma has been described to express the receptor tyrosine kinase MET in up to 80% of specimens and preclinical data suggests that MET inhibitors reduce proliferation and metastatic potential in cell lines and murine xenografts. Cabozantinib is a receptor tyrosine kinase inhibitor with significant inhibitory activity against MET and VEGFR2 (among other targets). Cabozantinib was associated with a median progression-free survival (mPFS) of 4.8 months in final follow up of the ocular melanoma cohort of the cabozantinib randomized discontinuation clinical trial. Notably, the MEK inhibitor selumetinib was determined to deliver mPFS of 3.9 months in a randomized phase II study. Methods: This is a national (Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group, NCIC Clinical Trials Group) open-label phase II study comparing cabozantinib with TMZ/DTIC in advanced ocular melanoma (clinicaltrials.gov: NCT01835145). The study randomizes patients 2:1 to cabozantinib and facilitates cross-over from the chemotherapy arm to cabozantinib at progression of disease. Eligibility is for any line of therapy and allows for prior treatment with MEX inhibitor or immunotherapy. Other eligibility includes biopsy proven metastatic ocular melanoma, ECOG 0-1 and adequate organ function (modified for elevated liver function tests related to hepatic metastases). The primary endpoint is PFS at 50% OS information. Safety, pharmacokinetics, and quality of life data will also be studied.
TPS9088 Poster Session (Board #326b), Mon, 1:15 PM-4:45 PM

Phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRAIN-B).
First Author: Melissa K. Yee, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Significant advances in the management of melanoma have improved the diagnosis and overall survival of patients (pts) with metastatic disease. However, pts with active melanoma brain metastases (MBM) have been excluded from large Phase III trials and overall prognosis remains poor. Resistance to BRAF inhibitors (BRAFi) has been associated with reactivation of MAPK pathway and combination with MEK inhibitors (MEKi) has shown synergy and delay resistance. Cobimetinib is a potent MEK 1/2 inhibitor. In pts without MBM, the combination of vemurafenib + cobimetinib has improved response rates and PFS as compared to vemurafenib. Single agents BRAFi are safe to administer in pts with MBM resulting in objective intracranial responses. We aim to improve the outcomes of pts with MBM by assessing the clinical benefit of combination BRAFi/MEKi (vemurafenib + cobimetinib) in this population.

Methods: This is a multi-center single arm, open label, Simon 2-stage Phase 2 study to determine the safety and efficacy of the combination of cobimetinib and vemurafenib in patients with BRAF-mutated melanoma with active MBM. Pts must have histologically confirmed BRAF V600-mutated metastatic melanoma and > 1 measurable intracranial target lesion. Prior BRAFi or MEKi is not allowed. Subjects will be given vemurafenib 960 mg PO BID and cobimetinib 60 mg PO QD for 21 days (28-day cycle). The primary objective is to determine the investigator-assessed objective intracranial response rate (ORiRR) as measured by modified RECIST. The primary efficacy analysis is based on pts with BRAF V600E mutations and the study will accrue 29 pts in the 1st stage. If > 6 pts experience an ORiRR, accrual to the 2nd stage will proceed to a total of 72 pts. Pts with non-V600E mutation are allowed but will not enter into the primary efficacy analysis. Secondary objectives include safety/tolerability (intracranial + extracranial), PFS, OS, duration of response, changes in relative apparent diffusion coefficient by MRI, volumetric response using 3D-MRI in a subset of pts, immune modulation and early markers of progression in peripheral blood, and health-related quality of life (by FACT-Br). The trial is open for enrollment. NCT02230306 Clinical trial information: NCT02230306.

TPS9090 Poster Session (Board #327b), Mon, 1:15 PM-4:45 PM

A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis: the NIBIT-M2 trial.
First Author: Anna Maria Di Giacomo, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy

Background: The anti-CTLA-4 monoclonal antibody (mAb), ipilimumab (Ipi) and Immunotherapy, University Hospital of Siena, Siena, Italy is being investigated as adjuvant therapy in patients with resectable stage III melanoma through the use of mitogen -activated protein kinase pathway (MAPK)-targeted therapies, with several agents now FDA-approved for patients (pts) with BRAF V600 mutations with stage IV or unresectable stage III disease. Based on the efficacy of BRAF inhibitors and combined BRAF/MEKi inhibitors in patients with stage IV melanoma, these agents are being investigated as adjuvant therapies in patients with resectable stage III melanoma as part of multi-national phase 3 trials, where the current standard of care is upfront surgery. Natural results from these trials, however, will not be available for some time. A critical question to consider is whether neoadjuvant treatment with MAPK-targeted therapy will improve outcomes in a subset of these patients with significant burden of disease.

Methods: Here we report 2 current phase II trials - at MD Anderson Cancer Center (MD Anderson) and Melanoma Institute Australia (MIA) - of neoadjuvant combined BRAF inhibition (dabrafenib, at 150 mg by mouth twice a day) and MEK inhibition (trametinib, at 2 mg by mouth once a day) for high risk resectable metastatic melanoma (stage IIB-C; MIA and MD Anderson) and oligometastatic stage IV (MD Anderson)). Both trials incorporate serial biopsies during the course of treatment for translational research on molecular and immune biomarkers. At MD Anderson, eligible patients are randomized in a 2:1 fashion to neoadjuvant BRAF/MEK x 8 weeks followed by 104 weeks of SOC adjuvant therapy (target accrual 84 patients). Endpoints include RECIST response (RR), relapse-free survival (RFS), overall survival (OS), pathologic CR rate, and toxicity. At MIA, all patients receive neoadjuvant BRAF/MEK x 12 weeks, followed by adjuvant BRAF/MEK for 40 weeks (target accrual 35 patients). The primary endpoint is pathologic CR rate, secondary endpoints include RFS, OS, toxicity, and translational endpoints correlated with outcome. This neoadjuvant approach has the potential to establish a new treatment paradigm for patients with high-risk resectable metastatic melanoma harboring a BRAF mutation. Clinical trial information: NCT01972347, NCT02231775.

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A pilot study of neoadjuvant cetuximab in locally advanced squamous cell carcinomas of skin (SCCS). First Author: Kristen Renee Spencer, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

**Background:** The incidence of SCCS has increased over the past two decades, including a high risk subset with aggressive behavior. Due to a lack of high-quality clinical trials in this population, there is no standard systemic therapy for advanced SCCS. The epidermal growth factor receptor (EGFR), often highly expressed in SCCS, is implicated in UV-induced skin carcinogenesis and SCCS development. Cetuximab, a monoclonal antibody that competitively inhibits EGFR, improved disease control as first line therapy in unresectable SCCS in a single arm phase II trial. Despite impressive responses with cetuximab in some, most treated SCCS patients do not respond, and there is a need for predictive biomarkers. We hypothesize that the use of cetuximab will improve clinical outcomes in patients vs advanced SCCS in the neoadjuvant setting, and that measures of antibody dependent cytotoxicity (ADCC) in tumor and/or specific genomic features of the tumor may predict response to therapy. **Methods:** In this pilot trial (NCT 02324608), we will enroll 20 patients with resected locally advanced SCCS or SCCS unamenable to definitive local therapy. The primary endpoint will measure response rate to cetuximab by RECIST criteria with secondary endpoints of progression free survival and overall survival, and conversion to resectability. Molecular tumor correlates include analyzing DNA mutations and measuring downstream activation of EGFR signaling and ADCC, correlating these with clinical benefit. Patients will receive cetuximab at 400mg/m² Q2w as follows by weekly doses of 250mg/m² for 8 weeks prior to surgery. Patients will be evaluated for subsequent definitive surgical resection, or definitive radiotherapy if surgical resection is not possible. Postoperative adjuvant radiotherapy will be permitted. Patients will undergo pretreatment biopsies, and post-treatment tissue will be harvested at surgery or through a biopsy at the conclusion of cetuximab. Paired skin and tumor samples will be evaluated through partial DNA sequencing, IHC analysis of EGFR signaling components, and measurement of ADCC. The trial is currently screening eligible subjects. Clinical trial information: NCT02324608.
Phase III trials of anamorelin in patients with advanced non-small cell lung cancer (NSCLC) and cachexia (ROMANA 1 and 2). First Author: Jennifer S. Teitell, Massachusetts General Hospital, Boston, MA

Background: Patients with advanced cancers frequently experience anorexia and cachexia, which is associated with decreased functional status and poor tolerance of chemotherapy. ROMANA 1 and 2 were two randomized, double blind trials evaluating the effect of anamorelin, a ghrelin receptor agonist, on cachexia in patients with advanced NSCLC. Methods: We randomly assigned 484 patients (ROMANA 1) and 495 patients (ROMANA 2) with inoperable stage III or stage IV NSCLC and cachexia, with 5% weight loss within prior 6 months or BMI < 20 kg/m² to placebo or anamorelin 100 mg orally once daily. Co-primary efficacy endpoints were the change in lean body mass and handgrip strength from baseline over 12 weeks. Secondary endpoints included change in body weight and fat mass burden over 12 weeks and pooled survival from ROMANA 1 and ROMANA 2. Exploratory analyses evaluated change in total body mass and fat mass from baseline to 12 weeks. Results: Patients assigned to anamorelin experienced an increase in lean body mass compared to those assigned to placebo in ROMANA 1 (1.10 vs -0.44 kg, p < 0.001) and ROMANA 2 (0.75 vs -0.96 kg, p < 0.0001), but no difference in handgrip strength. Patients assigned to anamorelin also had a significant increase in body weight (2.2 vs 0.14 kg, p < 0.001) and (0.95 vs -0.57 kg, p < 0.001) and improvement in their anorexia/cachexia symptoms (4.12 vs 1.92, p = 0.001) and (3.48 vs 1.34, p = 0.002) in ROMANA 1 and 2, respectively. Exploratory analysis demonstrated an increase in total body mass (2.87 vs 0.07 kg, p < 0.001) and (2.04 vs -0.59 kg, p < 0.001), and fat mass (1.21 vs -0.13 kg, p < 0.001) and (0.77 vs 0.09 kg, p = 0.012) for anamorelin versus placebo in the two studies, respectively. Anamorelin was well tolerated, with similar pooled incidence of AEs of grade 3-4 and serious AEs compared to placebo. Conclusions: Anamorelin increased lean body mass, body weight, total body mass and fat mass indicating anabolic activity and restoration of energy balance in patients with advanced NSCLC. Patients also experienced significant improvement in anorexia/cachexia symptoms. Anamorelin was well tolerated, with similar pooled survival between study arms. Clinical trial information: NCT01387269 and NCT01387282.

Olanzapine versus fosaprepitant for the prevention of nausea and vomiting in patients receiving concurrent chemoradiation treatment. First Author: Rudolph M. Navari, Indiana Univ School of Medcyn South Bend, Mishawaka, IN

Background: The purpose of the study was to compare the effectiveness of olanzapine (OLN) and fosaprepitant (FOS) for the prevention of nausea and vomiting in patients receiving concurrent highly emetogenic chemotherapy (HEC) and radiation therapy for head and neck and esophageal cancer. Methods: A randomized, double-blind, phase III trial was performed in chemotherapy and radiation therapy naive patients receiving concurrent loco radiation and cisplatin, > 70 mg/m², based chemotherapy comparing OLN to FOS in combination with palonosetron (PAL) and dexamethasone (DEX). The OLN, PAL, DEX (OPD) regimen was 10 mg of oral OLN, 0.25 mg of intravenous PAL, and DEX 20 mg intravenous pre-chemotherapy, day 1, and 10 mg/day of oral OLN alone on days 2-4 post-chemotherapy. The FOS, PAL, DEX (FPD) regimen was 150 mg of intravenous FOS, 0.25 mg intravenous PAL, and 12 mg intravenous DEX, day 1, and 4 mg DEX twice a day, days 2 and 3. Distribution of patients to different groups were similar in gender, types of cancer, and radiotherapy regimens. Results: One hundred and nine patients consented to the protocol and were randomized. One hundred and nine patients were evaluable. Complete response (CR) (no emesis, no rescue) was 88% for the acute period (24 hours post-chemotherapy), 76% for the delayed period (days 2-5 post-chemotherapy), and 76% for the overall period (0-120 hours) for 51 patients receiving the OPD regimen. CR was 73% for the acute period, 73% for the delayed period, and 73% for the overall period in 49 patients receiving the FPD regimen. Patients without nausea (0, scale 0-10, visual analogue scale) were: OPD: 86%, acute; 71%, delayed; and 71%, overall; FPD: 77%, acute; 41%, delayed; and 41%, overall. There were no grade 3 or 4 toxicities. CR and control of nausea in subsequent chemotherapy cycles were equal to or greater than cycle one for both regimens. Conclusions: For the overall period, OPD was comparable in FPD in the control of emesis; nausea was significantly (p < 0.01) improved with OPD compared to FPD.
EXCAP exercise effects on cognitive impairment and inflammation: A URCC NCORP RCT in 479 cancer patients. First Author: Karen Michelle Mcmanus, University of Rochester Medical Center, Rochester, NY

**Background:** Cognitive impairment (CI) is one of the most troublesome side effects experienced by patients, arises due to chronic inflammation, and impairs quality of life (QOL). We conducted a nationwide, multi-site, phase III RCT examining the efficacy of exercise for improving CI and inflammation through the URCC NCORP Research Base. **Methods:** Non-metastatic cancer patients receiving chemotherapy were randomized into 2 arms: 1) chemotherapy and 2) chemotherapy plus a 6-week (wk) exercise intervention—Exercise for Cancer Patients (EXCAP): a home-based, personalized prescription of aerobic walking and anaerobic resistance band training. CI and inflammation were assessed via the FACT-Cog and standard serum Luminex assays, respectively, at pre- and post-intervention. **Results:** 479 patients beginning chemotherapy were accrued (94% female, 84% breast cancer, mean age = 54). ANCOVAs controlling for baseline CI and chemotherapy cycle (1 wk, 2 wk, 3 wk) revealed significant differences in CI total score, perceived CI, impact of CI on QOL, and perceived CI by others (all p < 0.05) with a trend for differences in perceived cognitive ability (p < 0.10) between groups at post-intervention. Follow-up analyses showed exercise participants receiving 2 wk cycles of chemotherapy demonstrated less CI overall and across all domains (all p < 0.05) except perceived cognitive ability (p < 0.10) than controls at post-intervention. T-tests revealed an exercise-induced anti-inflammatory response with down-regulation of pro-inflammatory cytokines (IFNγ, IL-8, IL-1β) and up-regulation of anti-inflammatory cytokines (IL-6, IL-10, sTNFα) in exercisers (all p < 0.05). Conversely, T-tests revealed down-regulation of IL-10 and less up-regulation of sTNFα in controls (all p < 0.05). Canonical correlations revealed a trend where changes in inflammation predicted changes in CI (r = 0.33; p = 0.06), but not controls. **Conclusions:** EXCAP exercise improves CI and inflammation in patients receiving chemotherapy, and exercise-induced anti-inflammatory responses may elicit improvements in CI. Clinicians should consider prescribing EXCAP to reduce CI and inflammation. NC1 UGCA189961 & K07CA120025. Clinical trial information: NCT00924651.

Randomized trial of exercise on quality of life and fatigue in women diagnosed with ovarian cancer: The Women’s Activity and Lifestyle Study in Connecticut (WALC). First Author: Yang Zhou, Yale Cancer Center, New Haven, CT

**Background:** Ovarian cancer survivors experience a wide range of treatment side effects that can affect health-related quality of life (HRQOL). Physical activity has been shown to improve HRQOL for other cancer survivors; however, prior to our study, no large randomized exercise trial (RCT) has been conducted in ovarian cancer. We examined the effect of exercise vs. attention control on HRQOL and fatigue in ovarian cancer survivors. **Methods:** We randomized 144 physically inactive ovarian cancer survivors who had completed initial chemotherapy into a 6 month RCT of exercise vs. attention control. Women in the exercise arm received weekly phone calls from a certified exercise trainer and were counseled on increasing their physical activity to 150 min/wk of aerobic exercise. Women in the attention control arm also received weekly phone calls to discuss a relevant health topic. HRQOL and fatigue were measured via SF-36 and FACT-F questionnaires. Generalized linear models were used to compare baseline to 6-month changes in HRQOL and fatigue between the two arms. **Results:** At baseline, participants were, on average (mean ± SD), 1.7 ± 1.0 years post-diagnosis, 54% stage III-IV, 53 ± 8.6 years of age, and exercised 31.0 ± 45.8 mins/wk. Baseline physical HRQOL (Physical component summary (PCS) score of the SF-36) (mean = 46.0 ± 9.0) and fatigue scores (mean = 36.3 ± 10.9) were similar for both arms. At 6 months, women in the exercise arm improved physical HRQOL compared to a decreased physical HRQOL in women in the attention control arm (SF-36 PCS change score of 1.7 ± 1.1 vs. −1.9 ± 1.2, mean ± SE, P = 0.02). Borderline significant improvements in fatigue were observed for women randomized to exercise (FACT-F change score of 4.0 ± 1.1) vs. a 1.2 ± 1.2 increase for controls at six months, P = 0.06. **Conclusions:** Our results show that ovarian cancer survivors are interested in and able to exercise at recommended levels, with exercise improving physical HRQOL. Exercise programs for ovarian cancer survivors should be implemented in an effort to improve HRQOL. Clinical trial information: NCT02107066.

The impact of physical activity on fatigue and quality of life in lung cancer patients: A randomised controlled trial (RCT). First Author: Janette L. Vardy, Concord Cancer Centre, University of Sydney, Sydney, Australia

**Background:** Physical activity (PA) has been shown to improve fatigue and quality of life (QOL) in a range of cancer populations. Little research has been done in the advanced lung cancer setting. This RCT evaluated a 2-month PA intervention in patients with unresectable lung cancer. **Methods:** Eligible patients (Performance Status ≥ 2) randomized to control (TARGET-2 study) or a home-based PA (30 min, 5 days a week) intervention from a certified exercise trainer and were counseled on increasing their physical activity to 150-200 mins/wk of aerobic exercise and 2 days of anaerobic exercise. **Results:** 111 patients were randomized: male 55%, median age 62 (35-80); 95% NSCLC, 5% SCLC; 95% Stage IV. At baseline, 77% were on active treatment. Baseline characteristics, including PA levels, comorbidities and QOL, were similar between groups. **Conclusions:** Adherence to the 8-week intervention was high (99% exercise group). Adherence to PA guidelines was increased from 36.6 min/wk at baseline in the attention control arm (P = 0.01). Women in the exercise arm improved physical HRQOL compared to the decreased physical HRQOL in patients in the attention control arm (SF-36 PCS change score of 1.7 ± 1.1 vs. −1.9 ± 1.2, mean ± SE, P = 0.02). Differences in QOL were also observed, with mortality and fatigue scores being lower in the intervention group (P = 0.001). Our results show that physical activity can improve QOL and symptoms for lung cancer patients and should be implemented in an effort to improve HRQOL. Clinical trial information: NCT01112839.

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Impact of the LIVESTRONG at the YMCA Program on physical activity, fitness, and quality of life in cancer survivors. First Author: Melinda L Irwin, Yale School of Public Health, New Haven, CT

Background: Physical activity (PA) has been linked to cancer risk and outcomes, yet many survivors are inactive. We evaluated the impact of the LIVESTRONG at the YMCA program, an exercise program available for cancer survivors at YMCA’s across the USA, on PA, fitness, and quality of life (QOL). Methods: Participants were recruited through Yale Cancer Center/Smilow Cancer Hospital and Dana-Farber Cancer Institute. Key eligibility criteria included having a cancer diagnosis and being able to walk. Participants were randomized to immediate participation in a 12-week LIVESTRONG at the YMCA program and 91 to control. The majority of patients had stage I-II disease and 50% had breast cancer. A majority of participants were inactive at baseline, with only 34% reporting 150+ min/wk of PA. Participants randomized to the LIVESTRONG Program attended on average 83% of scheduled sessions over the 3-month program and experienced significant increases in physical activity (75% exercising at 150+ min/wk vs. 25% of controls, p < .05) and improvements in fitness and QOL compared to controls (Table). Conclusions: The LIVESTRONG program was effective in increasing PA, fitness and QOL in cancer survivors. Additional work is needed to evaluate sustainability of these effects, but this program could provide a platform to increase physical activity in thousands of cancer survivors across the USA. Clinical trial information: NCT02112149.

Baseline to 12-week changes in PA, fitness, and QOL means (SD). Table 1

<table>
<thead>
<tr>
<th>Physical Activity (min/wk)</th>
<th>Exercisers</th>
<th>Control</th>
<th>p-value</th>
<th>Exercisers</th>
<th>Control</th>
<th>p-value</th>
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<tr>
<td>158.5 (25.0)</td>
<td>15.9 (15.9)</td>
<td>0.18</td>
<td>71.0 (24.3)</td>
<td>-23.6 (18.2)</td>
<td>0.004</td>
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</tr>
<tr>
<td>5-Min Walk Test</td>
<td>1502 (154)</td>
<td>1578 (335)</td>
<td>0.50</td>
<td>111 (204)</td>
<td>15 (220)</td>
<td>0.007</td>
</tr>
<tr>
<td>FACT-G</td>
<td>90.5 (14.4)</td>
<td>88.7 (12.3)</td>
<td>0.35</td>
<td>2.5 (1.1)</td>
<td>-0.3 (1.1)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

9509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Association between renal function and chemotherapy-related toxicity in older adults with cancer. First Author: Lindsay Leuthen Peterson, Med Univ of South Carolina, Charleston, SC

Background: Older adults with cancer are at increased risk for chemotherapy-related toxicity (CRT). Tools are needed to better define their risk and aid in treatment planning. Renal function declines with age and can be calculated with various formulas, although the ideal formula for such calculations is unclear. We therefore evaluated the association between renal function and CRT in older adults and compared the effect of different renal function formulas and body weight measurements on this association.

Methods: This is a secondary analysis of data from a prospective multicenter study of 500 patients age 65 and older who were starting a new chemotherapy regimen. Renal function was estimated with four formulas (modified Jelliffe [Jelliffe], Cockcroft-Gault [CG], Wright, and Modification of Diet in Renal Disease [MDRD]), using actual, ideal and adjusted body weights. The association between baseline renal function and grade 3-5 CRT was evaluated by unconditional logistic regression. Results: Mean age of the 492 evaluable patients was 73 (range 65-91); 40% were aged ≥ 75 years (18% age 80-91); 61% had stage IV disease; 56% were female. Mean estimated renal function ranged from 56 to 78 mL/min, depending on the formula. One or more grade 3-5 toxicities occurred in 53% of patients (26% hematoic; 43% non-hematoic). Decreased creatinine clearance [CrCl] calculated by CG (actual body weight) was associated with increased odds of CRT (OR 1.12, P < 0.01; OR 1.7, 2 points for metastatic cancers, 1 point for breast cancer, 5% colorectal cancer. There were no significant differences between decreased renal function with non-CG formulas (Jelliffe, Wright and MDRD) and odds for CRT. Serum creatinine alone was not associated with toxicity risk (OR 0.67, P = 0.15 95% CI 0.37-1.14).

Conclusions: Decreased CrCl (as measured by CG with actual body weight) is associated with increased odds of chemotherapy-related toxicity and should be considered when treating older adults with cancer. Serum creatinine alone is not adequate for risk assessment.

9510 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Evaluation of a web-based cognitive rehabilitation programme (CRP) in cancer survivors reporting cognitive symptoms following chemotherapy. First Author: Victoria J Bray, Liverpool Cancer Centre, Liverpool, Australia

Background: Self-reported cognitive impairment is frequently seen in cancer survivors. We evaluated a CRP in cancer patients with cognitive symptoms. Methods: 243 adult cancer patients who had completed adjuvant chemotherapy within 6-12 months and reported changes in memory and/or concentration were eligible for the study. The CRP was delivered online and consisted of neuro-psychological assessment (CogState), quality of life (QOL) and fatigue (FACT-F), anxiety/depression (GHQ), and stress (PSS). Primarily used linear mixed models comparing the difference in FACT-COG PCI between the 2 arms at each post baseline timepoint: post intervention (T2) and 6 months later (T3). Results: A total of 243 patients were randomized: median age 53 (range 23-74); 95% female; 89% breast cancer, 5% colorectal cancer. There were no significant differences between the groups at baseline. The CRP group had improvement in all FACT-COG domains including PCI at T2, which were sustained at T3. Individual NP test results were not significantly different at T2 or T3. Anxiety/depression was improved at T2 and T3, and stress in the CRP group. There were no changes between the groups in fatigue or QOL (global or in domains) at any timepoint. Conclusion: This is a multicentric CRP that significantly improved in cognitive symptoms that were sustained at 6 months compared to phone consultation alone. Clinical trial information: ACTRN12609000683235.

9511 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

A clinical score to predict early death at 100 days after a comprehensive geriatric assessment (CGA) in elderly cancer patients: A prospective study with 815 patients. First Author: Rabia Boulahsahss, UC CCOG PAST CHU de Nice, Nice, France

Background: Trying to predict very early death after a CGA is very difficult in clinical practice. Last year, we presented predictors of early death (Boulahsahss et al, 9511, ASCO 2014). The aim of this new study was the next step by developing a score to estimate the risk of death at 100 days in order to illuminate the clinical decision-making. Methods: This is a multicentric and prospective cohort study approved by an ethics committee. A standardized CGA has been done before the treatment decision at the baseline (MMSE, MNA, Grip strength, ADL, IADL, CIRSg, Charlson, Lee, PS, Gait speed, QLSc0, GB, Baulducci score). During the follow-up of 100 days, the events (death), the treatments made, and the targeted geriatric interventions were collected. A multivariate logistic regression permits the selection of risk factors. The calibration was assessed with the Hosmer-Lemeshow goodness of fit test. The internal validation of the model was performed by a bootstrap method with 1000 randomized samples. Score points were assigned to each risk factors by using the β coefficient. The accuracy of the score was assessed with the mean c-statistic (0.813). Results: 815 patients with a mean age of 82 years joined the study. The predictors were: metastatic cancer (OR 2.5 CI 1.6-3.6 p < 0.0001), gait speed < 0.8m/s (OR 1.7 CI 1.2-2.9 p = 0.025), MNA ≤ 17 (OR 8.8 CI 3.5-22.9 p < 0.0001), MNA ≤ 23.5 and ≤ 17 (OR 5.1 CI 2.1-12.2 p < 0.0001), PSA > 20ng/ml (OR 1.1-3.2 p = 0.01), cancers other than breast (OR 2.1 CI 1.3-3.2 P = 0.001). We assigned in the score 5 points for MNA < 17, 3 points for MNA ≤ 23.5 and ≥ 17, 2 points for metastatic cancers, 1 point for: lower gait speed, PS > 2, and for cancers other than breast cancers. The risk of death at 100 days after a CGA was 5% for 0 to 5 points, 20% for 6 to 7 points, 40% for 8 to 9 points and 60% for 10 points. Conclusions: This is the first score that estimates very early death in elderly cancer patients. This score could be useful in treatment decisions in clinical practice in order to choose the best treatment for the patient.

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9512 Poster Discussion Session; Displayed in Poster Session (Board #171), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Pilot study of family caregiver burden in home hospice: Stress-induced immune changes. First Author: Abdullah Ladha, Mayo Clinic Health System Eau Claire, Eau Claire, WI
Background: In 2012, 1.5-1.6 million patients received hospice care in United States. The majority received care at home. Unfortunately caregiving has been reported as an independent risk factor for mortality. Caregivers of hospice patients comprise a special group, as most patients die within short time span and have diverse trajectories. Therefore, this group deserves study to confirm or negate immune dysregulation as seen in dementia caregivers. Methods: Family caregivers were enrolled after providing informed consent. Caregivers were included if they provided minimum of eight hours cares each day, for at least two weeks and had no acute health conditions. Participants filled a questionnaire and provided a blood sample. Samples from age and sex matched healthy control subjects were acquired from the Mayo Clinic Biobank. ELISA and flow cytometry were used to test samples. Results: Blood samples from 39 caregivers were compared with controls. The following markers were significantly higher in caregivers: IL-1 beta, IL-2, IL-12, CRP, IL-8, CXCL1, CXCL2 and CXCL3. Cell markers with higher values in caregivers were: CD4+, CD8+, CD56+16+, CD69 and CD62L. Regulatory markers like regulatory T cells and TIM-3 were also higher in caregivers. Cytokines and chemokines significantly lower in caregivers were: CCL-26, CX3CL1 and CXCL10.

9514 Poster Discussion Session; Displayed in Poster Session (Board #173), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Depression and anxiety among family caregivers of patients with advanced cancer. First Author: Joel Nathan Fishbein, Massachusetts General Hospital, Boston, MA
Background: Despite the important role family caregivers (CGs) play in the care of patients with cancer, little is known about their psychological distress. We sought to describe rates and correlates of depression and anxiety in CGs of patients with advanced cancer to determine those at highest risk for psychological distress. Methods: As part of an ongoing trial of early palliative care, we are assessing baseline depression and anxiety in patients within 8 weeks of advanced lung, lung or gastrointestinal cancer diagnosis and their CGs. We are administering the Hospital Anxiety and Depression Scale (HADS), subscale scores >7 denoting clinically significant depression or anxiety. We are assessing patient coping styles with the Brief COPE. We used multiple logistic regression with purposes: the selection of covariates to identify correlates of CG depression and anxiety. Results: Of 240 CGs (mean age = 57 years), 156 (65%) were spouses/partners, 167 (70%) were female, and 131 (55%) were younger than 50. 15% of CGs reported significant depression and anxiety, respectively, age, gender, marital status and education level, as well as patients’ anxiety and presence of brain metastases were associated with higher rates of CG depression and anxiety. Conclusions: Younger, female CGs were at greatest risk of both depression and anxiety. Thus, this CG population should be monitored closely and referred for cancer center support services for distress management. We also found that patients’ anxiety was associated with higher rates of CG depression and anxiety. Our findings implicate the importance of interventions that address both patient and CG psychological distress.

9513 Poster Discussion Session; Displayed in Poster Session (Board #172), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Quality of life and satisfaction with care in caregivers of patients with advanced cancer: Results from a trial of early palliative care. First Author: Julie Clare McDonald, Department of Psychosocial Oncology and Palliative Care, Princess Margaret Cancer Centre, Toronto, ON, Canada
Background: Early palliative care has been shown to improve the quality of life (QOL) and satisfaction with care of patients with advanced cancer, but little is known about its effects on family caregivers. Here we report associations of caregiver QOL and satisfaction with care from a cluster-randomized controlled trial of early palliative care. Methods: 461 patients with advanced cancer were recruited from 24 medical oncology clinics at Princess Margaret Cancer Center between December 2006 and February 2011 to participate in a cluster-RCT of early palliative care versus standard care (2:1). CGs were asked to complete surveys at baseline and 2 months after randomization. 451 CGs completed at least one follow-up assessment. Over the 4-month period of the study, there was no significant improvement in QOL scores in the intervention group compared to the control group for the CQOLC (p = 0.53), SF-36 physical component summary (p = 0.27), or SF-36 mental component summary (p = 0.49). Early palliative care improved significantly in the intervention compared to the control group (p = 0.01). Conclusions: In this study, early palliative care involvement increased caregivers’ satisfaction with care but not their QOL. An intervention tailored specifically for caregivers may be required to have a substantial impact on caregiver QOL. Clinical trial information: NCT01248624.

9515 Poster Discussion Session; Displayed in Poster Session (Board #174), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Intended and unintended consequences: Ethics, communication, and prognostic disclosure in pediatric oncology. First Author: Jonathan Michael Marron, Dana-Farber/Boston Children’s Cancer and Blood Disorder Center, Boston, MA
Background: Most patients wish for all available information about their prognosis, but physicians can be hesitant to discuss prognostic information with patients, particularly those with poor prognoses. For some, concerns that this will cause anxiety, depression, or decreased hope outweigh the ethical obligation to provide such information. Methods: We surveyed 353 parents of children with newly diagnosed cancer at the Dana-Farber/Boston Children’s Cancer and Blood Disorders Center and the Children’s Hospital of Philadelphia. We used multivariable logistic regression to assess associations between parental report of elements of discussions of prognosis with the child’s oncologist (quality of information, quality of communication, prognostic disclosure) and the intended/unintended outcomes of these discussions (trust, hope, peace of mind, depression, anxiety). Analyses were stratified by the child’s prognosis: favorable (≥ 75% likelihood of cure) or less favorable (< 75% likelihood of cure) and the intended/unintended outcomes of these discussions (trust, hope, peace of mind, depression, anxiety). Results: Among parents of children with less favorable prognoses (n = 140), those who reported receiving high quality information from the oncologist expressed greater peace of mind (odds ratio [OR] 4.44, 95% confidence interval [1.53, 12.90], p < 0.01), and those who reported their oncologist to have provided high quality information expressed greater trust in the oncologist (OR 3.25 [1.22, 8.70], p = 0.02) and feelings of hope (OR 2.96 [1.24, 7.03], p = 0.01). Parents who received more information about prognosis were not significantly more anxious (p = 0.82), depressed (p = 0.55) or less hopeful (p = 0.86) than those who received less prognostic information. Similar findings were seen in the more favorable prognosis subset and the overall cohort. Conclusions: We find no evidence that greater prognostic disclosure leads to the unintended consequences of increased anxiety, depression, or decreased hope, even in parents of children with less favorable prognoses. Rather, communication processes may increase the intended consequences of peace of mind, trust, and hope, supporting the discussion of prognosis with all parents, even those of children with a lower likelihood of cure.
9516 Poster Discussion Session; Displayed in Poster Session (Board #175), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A randomized, controlled trial of a cardiopulmonary resuscitation (CPR) video decision support tool for seriously ill hospitalized patients with advanced cancer. First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA

Background: Discussing CPR preferences with patients with advanced cancer who are hospitalized is a critical component of end-of-life decision making. However, these discussions are challenging and often avoided by clinicians. We examined the impact of a CPR video decision tool on patients’ choices and knowledge about CPR, and their comfort with watching the video. Methods: We conducted a multi-center randomized controlled trial of 116 patients with advanced cancer hospitalized at two academic oncology centers. We randomized patients to either a 3-minute video describing CPR (n = 58) or a standard procedure (n = 58) group. The primary outcome was participants’ preferences for CPR (immediately after viewing the video in the intervention arm). Secondary outcomes included patients’ knowledge (using 5-item questionnaire with higher score reflecting greater knowledge), and intervention participants’ comfort with watching the video. Results: The mean age was 66 years (SD = 12); 50% were women, 84% were white, and 48% had lung or gastrointestinal cancer. Only 47% of study participants reported having a discussion about their CPR preferences at the time of admission to the hospital. At baseline, there were no differences in patients’ preferences for not wanting CPR between the intervention and control arms (63% vs. 58%, P = 0.79). After intervention, participants randomized to the video were more likely not to want CPR (81% vs. 58%, P = 0.03) and were more knowledgeable (mean knowledge score 4.3 vs. 3.2, P < 0.0001) versus control participants. In the intervention arm, 81% of patients found the video helpful, and 94% felt comfortable watching it and discussing it with their families. Conclusions: Seriously ill hospitalized patients with advanced cancer who watched a CPR video decision support tool were more likely not to want CPR and were better informed about their options. Participants reported feeling comfortable watching the video and would recommend it to others facing similar decisions. Video decision support tools can facilitate end-of-life decision-making for hospitalized patients with advanced cancer. Clinical trial information: NCT01527331.

9517 Poster Discussion Session; Displayed in Poster Session (Board #176), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Quality of life and mood in patients with advanced cancer: Associations with prognostic understanding and coping style. First Author: Ryan David Nipp, Dana-Farber / Harvard Cancer Center, Boston, MA

Background: Patients’ prognostic understanding and coping styles influence their treatment decisions, but how these factors relate to their quality of life (QOL) and mood has not been well studied. We sought to examine the relationship of patients’ prognostic understanding and coping style with their QOL and mood. Methods: As part of an ongoing trial of early palliative care, we are assessing baseline (Functional Assessment of Cancer Therapy-General, Hospital Anxiety and Depression Scale), coping (Brief COPE), and prognostic understanding in patients within 8 weeks of diagnosis of advanced lung or gastrointestinal (GI) cancer. To determine associations, we used linear and logistic regression, adjusting for patients’ age, sex, cancer type, and marital status. Results: Of 300 participants (mean age = 64.7 years; 138 (46%) female), 132 (44%) had GI cancer and 168 (56%) had lung cancer. More than 74% had PN and 21% (48%) had depression. 138 (49%) reported their prognosis as terminal. A terminal perception of prognosis was associated with lower QOL and higher rates of anxiety. Emotional support, acceptance, and active coping styles were associated with better QOL and mood. Conclusions: These data demonstrate that acknowledging a terminal prognosis may be associated with greater physical and psychological distress, or conversely, patients with worse QOL and mood may better appreciate the gravity of their illness. Certain coping styles (self-blame and denial) are associated with lower QOL and higher distress. Understanding the relationships among patients’ prognostic awareness, coping styles, QOL, and mood will allow us to develop more effective supportive care interventions.

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Comparison between clinician- and patient-reporting of baseline (BL) and post-BL symptomatic toxicities in cancer cooperative group trials (NCCTG N0591 [Alliance]). First Author: Thomas Michael Atkinson, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Reporting of clinician-based toxicity assessment via the Common Terminology Criteria for Adverse Events (CTCAE) commonly does not distinguish between symptoms already present at BL versus those that developed during a trial. Therefore, current estimation of toxicities may include symptoms that predate trial entry. We hypothesize that patient (pts) provide more complete BL symptom reports than clinicians, and that these BL symptoms can be “subtracted” from those reported during a trial at the pt level to better understand which toxicities actually developed during the trial.

Methods: Data were triennially collected on BL and throughout the trial, (1) clinician-reported symptomatic toxicities were documented with the CTCAE and (2) analogous pt self-reported symptoms were documented via a questionnaire. McNemar’s test was used to compare between clinician- and pt-reporting of: 1) BL prevalence, 2) maximum post-BL, and 3) worsening (i.e., BL subtracted) scores. Results: Across 26 trials, 24 clinician- and analogous pt-reported symptoms were captured for 2608 pts (median age 60, 62% female, 93% Caucasian, 97% non-Hispanic). For 20/24 (83%) symptoms at BL, pts reported a significantly higher prevalence (grade or score ≥ 1) than did clinicians. Prevalence using maximum post-BL was significantly higher among clinicians and pts for 21 (88%) symptoms with 16/21 (76%) having a higher prevalence by the pt report. When subtracting BL, a significant difference between clinicians and pts was observed in 16/24 (67%) symptoms, with a lesser number (9/16, 56%) having a higher incidence by pt report. Clinicians consistently underestimated prevalence of BL symptoms compared to pts. Change from pt-reported BL assessment appears to more closely match clinician-graded AEs. This method should be considered for future pt-based toxicity assessments in clinical trials as a more accurate appraisal of symptoms attributable to study treatments rather than pre-existing etiologies.

Long-term safety of fertility preservation by ovarian stimulation and concurrent aromatase inhibitor treatment in women with breast cancer. First Author: Kutlu K Oktay, Institute for Fertility Preservation and New York Medical College, New York, NY

Background: Cryopreservation of embryos and oocytes after ovarian stimulation (OS) is an established method of fertility preservation (FP). To minimize the elevation of serum estrogen levels, an aromatase inhibitor, letrozole, has been used concurrently with OS. However, long-term safety of this approach is unknown. The objective of this trial was to determine the long-term safety of controlled OS with letrozole supplementation (COSTLES) in women with breast cancer. The impact of BRCA mutations, estrogen-receptor (ER) and operative status on recurrence after COSTLES were also evaluated. Methods: A total of 337 women aged 24-43 with a diagnosis of stage ≤ 3 breast cancer were enrolled during FP consultations. Of those, 120 elected to undergo COSTLES for FP prior to chemotherapy; the remaining 217 served as controls. Results: The baseline characteristics were similar between FP and control groups except for the younger age (P = 0.03) and less frequent lymph node involvement (P = 0.02) in the former. The mean follow-up after diagnosis was 4.9 years (range 1-13) in the FP and 6.2 years (1-14) in the control group. In the FP group, the hazard ratio for recurrence was 0.77 (95% CI: 0.28, 2.13) and the survival was not compromised compared with controls (P = 0.61). Neither BRCA gene mutation status (P = 0.28), nor undergoing FP before breast cancer diagnosis (P = 0.56) affected survival . Likewise, none of the tumor characteristics including the receptor status affected the survival following COSTLES. Thirty-three women attempted pregnancy with frozen embryos; 15 using a gestational carrier. Seventeen of those 33 had at least one child (FP rate: 51.5%; live birth rate: 45.0%). The live birth rate was similar to an age-matched control group from a national IVF database. There were no recurrences among women who conceived. Conclusions: COSTLES is unlikely to cause substantially increased recurrence risk in breast cancer even in the presence of BRCA gene mutations, and it results in fertility preservation in a majority of women. Our data strongly support that FP via COSTLES should be made more widely available for young women with breast cancer even before undergoing breast surgery. Clinical trial information: NCT00504699.

The impact of adjuvant breast cancer (BC) chemotherapy on ovarian reserve and menses. First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In prior studies, menses was used as a surrogate for fertility. But, anti-mullerian hormone (AMH) may be a better surrogate for ovarian reserve. The goal of this study is to delineate the extent of ovarian damage resulting from adjuvant breast cancer chemotherapy in young women. AMH levels were measured in frozen sera with an ELISA kit. AMH levels were captured for 2608 pts (median age 60, 62% female, 93% Caucasian, 97% non-Hispanic). For 20/24 (83%) symptoms at BL, pts reported a significantly higher prevalence (grade or score ≥ 1) than did clinicians. Prevalence using maximum post-BL was significantly higher among clinicians and pts for 21 (88%) symptoms with 16/21 (76%) having a higher prevalence by the pt report. When subtracting BL, a significant difference between clinicians and pts was observed in 16/24 (67%) symptoms, with a lesser number (9/16, 56%) having a higher incidence by pt report. Clinicians consistently underestimated prevalence of BL symptoms compared to pts. Change from pt-reported BL assessment appears to more closely match clinician-graded AEs. This method should be considered for future pt-based toxicity assessments in clinical trials as a more accurate appraisal of symptoms attributable to study treatments rather than pre-existing etiologies.

Treatment-related amenorrhea among young women one year following diagnosis of early-stage breast cancer. First Author: Philip Daniel Poovu, Dana-Farber Cancer Institute, Boston, MA

Background: Treatment-related amenorrhea (TRA) is common among premenopausal women treated for early-stage breast cancer and is associated with increased risk of metabolic and oncologic dysfunction. Several studies have prospectively evaluated factors associated with TRA among young women receiving modern treatment regimens. Methods: As part of a prospective cohort study, we surveyed women ≤ 40 diagnosed with breast cancer, participated in women were surveyed at enrollment and one year following diagnosis (dx) regarding sociodemographic, medical history, menstrual status, and treatment. TRA at one year was defined as the absence of menses within the six months prior. Participants with stage IV disease or on ovarian suppression were excluded from this analysis. Univariable and multivariable modeling were used to determine demographic and treatment factors associated with TRA. Results: Among the 504 women included, 38% were age ≤ 35. Overall, 31% experienced TRA (Table 1). Univariable analysis revealed that TRA was associated with age, tamoxifen (TAM) use, and chemotherapy, but not race, BMI, smoking, comorbidity (Charlson), or weight change since dx. Multivariable modeling revealed that relative to women age 36-40, women age 21-30 experienced significantly less TRA (OR 0.18, p < 0.001). This difference was not observed between women age 31-35 and women age 36-40 (OR 0.67, p = 0.09). TAM use (OR 1.97, p = 0.0002) and chemotherapy (OR 3.89, p < 0.0001) were also independent predictors of TRA. Effects of different modern regimens on TRA in this young cohort will be presented. Conclusions: This analysis represents the largest evaluation to date of very young women and confirms that older age and treatment with TAM and chemotherapy are predictors of TRA. Further research is needed to identify differences in short and long-term risk of TRA with modern treatment, including specific chemotherapeutic regimens, is warranted.

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Differences in attitudes and beliefs toward end-of-life treatments between hematologic (Heme) and solid tumor (ST) oncology specialists. First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with Heme malignancies often receive intensive care at the end of life. To better understand the end of life decision making process among oncology specialists, we compared the cancer treatment recommendations, and attitudes and beliefs toward palliative care between Heme and ST specialists. Methods: We randomly surveyed 120 Heme and 120 ST oncology specialists at our institution. Respondents completed a survey examining two aspects of end of life care: palliative systemic therapy using standardized case vignettes and palliative care profiticiency. We compared the two groups using the Wilcoxon rank sum tests and Chi-square tests, and conducted multivariate logistic regression to identify predictors of treatment preferences. Results: 182/240 (76%) clinicians responded. Compared to ST specialists, Heme specialists were significantly more likely to favor prescribing systemic therapy with moderate toxicity and no survival benefit for patients with ECOG performance status (PS) 4 and an expected survival of 1 month (P<0.0001, Table). This decision was highly polarized. Heme specialists felt less comfortable discussing death and dying (72% vs. 88%, P=0.007) and hospice referrals (81% vs. 93%, P=0.02), and were more likely to feel a sense of failure with disease progression (46% vs. 31%, P=0.04). They were also less likely to refer patients with newly diagnosed cancer (21% vs. 43%, P=0.02) to palliative care. On multivariate analysis, Heme specialty (odds ratio 2.77, P=0.02) and comfort level with prescribing treatment to ECOG 4 patients (odds ratio 3.79, P=0.02) were associated with the decision to treat in the last month of life. Conclusions: We found significant differences in the attitudes and beliefs toward end-of-life care between Heme and ST specialists, and identified opportunities to standardize end-of-life care.

Treatment recommendations for case vignettes.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heme</th>
<th>ST</th>
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<td>Expected survival 3 months, PS 3</td>
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<td>Expected survival 6 months, PS 2</td>
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</table>

*Median (IQR), where 1 = strongly against treatment, 7 = strongly favors treatment.

9526 Poster Session (Board #185), Sat, 1:15 PM-4:45 PM

Trends and regional variation of end-of-life cancer care in the Medicare program. First Author: Shi-Yi Wang, Yale School of Public Health, New Haven, CT

Background: Although there has been substantial concern of aggressiveness of cancer care near the end-of-life (EOL) in the United States, little is known about recent trends in EOL cancer care and associated regional variation in the Medicare program. Methods: Using the Surveillance, Epidemiology, and End Results–Medicare data, we identified 82,245 beneficiaries who had breast, prostate, lung, colorectal, pancreas, liver, kidney, and melanoma, or hematological cancer diagnosis from 2004-2009 and died within 2 years as a result of cancer by December 2009. Aggressiveness of EOL care was measured by 1) chemotherapy received within 14 days of death; 2) ≥ 1 emergency department (ED) visit within 30 days of death; 3) ≥1 hospitalization within 30 days of death; 4) ≥ 1 intensive care unit (ICU) admission within 30 days of death; 5) hospital death; and 6) hospice enrollment ≥3 days before death. Using hierarchical generalized linear models, we assessed regional variation of EOL care adjusting for patient demographics, tumor characteristics and hospital referral region (HRR)-level market factors. Results: Proportions of receipt of at least one potentially aggressive EOL care increased from 48.3% in 2005 to 48.7% in 2009 (P<.001). From 2005 to 2009, increasing proportions of patients had repeatedly hospitalization (14.0% vs. 14.8%; P=0.113) or ICU admission (15.2% vs. 19.5%; P<0.001), whereas in-hospital death declined (24.1% vs. 22.0%; P=0.001). Proportions of receiving chemotherapy increased (5.3% vs. 6.6%), ED visits increased ED (3.2% to 3.9%, P=0.02), short hospice enrollment (7.2% vs. 8.3%) did not change significantly over time. The proportions of decedents who experienced aggressive EOL care varied substantially across HRRs. After adjusting for patient and HRR-level factors, the difference in the proportion of patients receiving potentially aggressive EOL care between HRRs in the lowest and the highest quintiles was 16.9 percentage point (57.2% vs. 40.3%). Conclusions: Despite growing focus on providing appropriate EOL care, nearly 50% of cancer decedents in the Medicare Program received aggressive EOL care with no evidence of demonstrable improvement in reducing aggressive EOL cancer care.
Frailty and outcomes in older adults undergoing pancreaticoduodenectomy.

Methods: A sectional anonymous questionnaire was administered to advanced cancer pts and caregivers (PCU pts and OC) between August 2012 and September 2014. PCU pts responded when there was no delirium and the primary caregiver responded when the patient (pt) was unable to respond. In the case of outpatients dyads were assessed. Results: Overall 141/266 (65%) preferred home death. PCU pts preferred home death less than outpatients (table). Patient and caregiver agreement regarding preferred place of death was 86% (p < 0.001). The preferred POd was the same as one month ago for 82/99 (83%) PCU pts and 111/116 (96%) outpatients, with significant difference between groups (p = 0.002). Conclusions: Although home is the preferred POd in advanced cancer pts, a substantial minority prefer hospital death or no difference. Pts admitted to the PCU have a higher preference for hospital death in comparison to the outpatients, likely reflecting more severe distress because they already tried home care. Pts and caregivers agree on POd in most cases. Personalized assessment of POd preference for both patient and caregiver is needed.

Frailty and outcomes in older adults undergoing pancreaticoduodenectomy. First Author: Manoletua Vidal, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Understanding the preferred place of death (POD) for advanced cancer patients (pts) is very important when they are approaching the end of life. Meeting the preferences of pts is considered an important palliative care outcome. Prior studies have shown that more than half of pts with terminally ill cancer prefer to die at home. In many countries such as the UK, Italy, Greece, South Korea and Japan home deaths have been falling, but in some states of the US/Canada there are indications of a reversal of trends. Dying at home may be more difficult for pts in severe physical and psychosocial distress, or when there are social or financial difficulties. The purpose of this study was to determine POD preference among palliative care pts in the outpatient center (OC) and the palliative care unit (PCU). Methods: A section anonymous questionnaire was administered to advanced cancer pts and caregivers (PCU pts and OC) between August 2012 and September 2014. PCU pts responded when there was no delirium and the primary caregiver responded when the patient (pt) was unable to respond. In the case of outpatients dyads were assessed. Results: Overall 141/266 (65%) preferred home death. PCU pts preferred home death less than outpatients (table). Patient and caregiver agreement regarding preferred place of death was 86% (p < 0.001). The preferred POD was the same as one month ago for 82/99 (83%) PCU pts and 111/116 (96%) outpatients, with significant difference between groups (p = 0.002). Conclusions: Although home is the preferred POD in advanced cancer pts, a substantial minority prefer hospital death or no difference. Pts admitted to the PCU have a higher preference for hospital death in comparison to the outpatients, likely reflecting more severe distress because they already tried home care. Pts and caregivers agree on POD in most cases. Personalized assessment of POD preference for both patient and caregiver is needed.

Prefered POD per location.

<table>
<thead>
<tr>
<th>Preference</th>
<th>Total</th>
<th>PCU</th>
<th>OC**</th>
<th>p</th>
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P-values are from Fisher's exact test comparing preference of POD between PCU & OC; *PCU (N = 27); OC (N = 176); ** Patients (N = 1165).

Frailty and outcomes in older adults undergoing pancreaticoduodenectomy.

Methods: A sectional anonymous questionnaire was administered to advanced cancer pts and caregivers (PCU pts and OC) between August 2012 and September 2014. PCU pts responded when there was no delirium and the primary caregiver responded when the patient (pt) was unable to respond. In the case of outpatients dyads were assessed. Results: Overall 141/266 (65%) preferred home death. PCU pts preferred home death less than outpatients (table). Patient and caregiver agreement regarding preferred place of death was 86% (p < 0.001). The preferred POD was the same as one month ago for 82/99 (83%) PCU pts and 111/116 (96%) outpatients, with significant difference between groups (p = 0.002). Conclusions: Although home is the preferred POD in advanced cancer pts, a substantial minority prefer hospital death or no difference. Pts admitted to the PCU have a higher preference for hospital death in comparison to the outpatients, likely reflecting more severe distress because they already tried home care. Pts and caregivers agree on POD in most cases. Personalized assessment of POD preference for both patient and caregiver is needed.

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P-values are from Fisher's exact test comparing preference of POD between PCU & OC; *PCU (N = 27); OC (N = 176); ** Patients (N = 1165).
**Background:** Standard prognostic methods do not optimally stratify patients according to the risk of death due to competing events. In contrast, competing event (CE) models (ref: PMID 24969798) have the potential to better inform practitioners regarding when to treat elderly patients with localized prostate cancer (PC).

**Methods:** Using SEER-Medicare data, we identified 68,259 patients with localized PC treated with either radical prostatectomy (RP) or radiotherapy (RT) alone, splitting each group into 60% training and 40% test sets. Using patients’ demographic, tumor, and clinical characteristics, we trained risk scores based on CE models vs. standard Cox models for cancer-specific and all-cause mortality (ACM). In test sets, we compared how well models stratified subpopulations according to the ratio of the hazard for prostate cancer mortality (PCM) to the hazard for ACM. We tested the predictive ability for the cause-specific events, using the area under the curve (AUC).

**Results:** For patients treated with RP, the CE risk score was associated with increased risk of PCM (HR 1.93, P<.001). Similar findings were observed for the cancer-specific and ACM risk scores. However, unlike standard models, increasing CE risk score was not associated with second cancer mortality (HR 0.90, P=.19) or non-cancer mortality (HR 0.96, P=.56). For patients treated with RT, the CE risk score was associated with increased risk of PCM (HR 2.13, P<.001), but was not associated with second cancer mortality (HR 0.90, P=.19), and was associated with decreased risk of non-cancer mortality (HR 0.84, P<.001). For patients treated with RP, the AIC was superior for CE models, relative to the cancer-specific and ACM models (AIC, 50.1 vs. 54.6 vs. 53.8, respectively). Similar findings were observed for RT patients (AIC, 43.4 vs. 45.2 vs. 54.4). The CE models also created greater separation in AUC for cancer mortality vs. non-cancer mortality, compared to the cancer-specific and ACM models (P<.001).

**Conclusions:** Compared to standard methods, CE models more efficiently stratify elderly PC patients according to likelihood to benefit from therapy.

**Poster Session (Board #191), Sat, 1:15 PM-4:45 PM**

**Novel method to stratify elderly patients with prostate cancer.**

*First Author: Ruben Carmona, UC San Diego, La Jolla, CA*

**Background:** Older adults with cancer often value maintaining or recovering their HRQOL over overall survival. This study aims to (1) describe patient reported global measures of physical and mental HRQOL in a large sample of older adults with cancer and (2) to evaluate associations with demographic and other measures of health status to better screen and identify populations at-risk of poor HRQOL.

**Methods:** The Health Registry/Cancer Survivorship Cohort is an institutional database at University of North Carolina designed to aid in cancer survivorship research (http://unchealthregistry.org). Outcome measures of patient-reported HRQOL included FACT-G (range 0-108), PROMIS Physical and Mental health (mean = 50, SD = 10 in general US population). Higher scores indicate better HRQOL.

**Results:** Other measures of health status: the single item Patient-Generated Subjective Global Assessment Performance Assessment (PG-SGA-PA), number of co-morbidities, FACT Cognitive Function, PROMIS Sexual Function, and global physical activity. **Results:** Of the 807 older adults (65y+) with cancer, mean age was 72y, 60% female, and 88% Caucasian. The cohort was comprised of 25% genitourinary, 24% breast, 22% gastrointestinal, and 15% gynecologic malignancies. Only 37% reported a high level of physical activity, 24% had ≥ 4 co-morbid conditions, and 25% reported that they lived alone. Mean scores for HRQOL were: FACT-G (85, range: 25-108), PROMIS-Physical (48, range: 16-67) and PROMIS-Mental (51, range: 21-67). In the multivariable models including demographies and health status measures, ≥ 4 comorbidities, poor PG-SGA-PA and lower levels of cognition were associated with poor HRQOL for each outcome measure (all p<.0001). **Conclusions:** Older adults with cancer with a high comorbidity burden, reduced cognition, and poorer scores on the PG-SGA-PA have poorer HRQOL. This study found that the single item PG-SGA-PA was independently associated with complex measures of global physical and mental health and with further validation could be a useful tool for oncologists to quickly identify older adults with poor HRQOL.

**Poster Session (Board #192), Sat, 1:15 PM-4:45 PM**

**Health related quality of life (HRQOL) in older adults with cancer: The potential of a single-item screen.**

*First Author: Mackenzie Pergolotti, UNC Chapel Hill, Chapel Hill, NC*

**Background:** Frailty is a state of increased vulnerability to adverse outcomes and can be defined by counting the number of health deficits an individual acquires. This study constructs a frailty index from a geriatric assessment (GA), defines the prevalence of frailty in older adults (65+) with cancer, and evaluates associations of frailty with sociodemographic and GA variables. **Methods:** The Carolina Senior Registry (CSR) is an institutional database (NCT01137825) that contains GA data on older adults with cancer. From the CSR, a 32-item frailty index (range 0-1) was developed by deficit counting as previously reported [Searle et al. BMC Geriatrics 2008] and categorized as robust (0-0.2), pre-frail (0.2-0.35), and frail (> 0.35) based on prior studies. Fisher’s exact tests and linear regression were used to evaluate associations. **Results:** Of the 1179 total patients, the mean age was 72y, 87.7% Caucasian, 69.6% female, and 90.7% had at least a high school education, 58.7% married, and 44.3% had a breast cancer diagnosis. Overall 59% were robust, 25.3% were pre-frail, and 15.7% were frail. Frailty and pre-frailty were more prevalent among lung cancer patients (54.6%) compared to patients with hematologic malignancies (46.5%) and breast cancer (34.1%). In a multivariable model, increasing age, African American race, lower education, increasing number of daily medications, and decreasing Karnofsky Performance Status were significantly associated with increased frailty (all p<.001). Gender, marital status, cancer type, and differences (in frailty) among GA subgroups were not significant. **Conclusions:** We created a 32-item frailty index using GA data from a cohort of older adults with cancer. Frailty was prevalent and significantly associated with sociodemographic variables. Additional work will be focused on validating our frailty index by using outcomes data. Because frail older adults with cancer are at an increased risk for adverse outcomes, a frailty index constructed from a cancer-specific GA may provide a straightforward way to identify frail patients who should be targeted for further intervention.
Feasibility of administering a geriatric assessment to older adults with cancer using web-based and touchscreen platforms. First Author: Jerome G. Zalcberg, City of Hope, Duarte, CA

Background: A geriatric assessment (GA) can help identify factors that increase the risk for chemotherapy-related toxicity in older patients with cancer. A GA has been developed which is primarily self-completed by patients using a paper and pencil questionnaire. With the shift to electronic medical records and the prospects of Big Data, a transition to an electronic GA is imperative to allow convenient deployment of this tool. The goal of this study was to 1) evaluate the feasibility of capturing patient reported GA data using 2 separate computer-based applications: web-based (REDCap [RC]) and a touchscreen (Support Screen [SS]), and 2) compare the computer responses to those obtained via paper-pencil. Methods: Patients (pts) aged > 65 yrs with cancer were eligible. Pts were randomized to 1 of 4 arms: (a) Paper; (b) RC / SS; (c) RC / Paper; (d) SS/Paper; SS/SS. The feasibility of each computer methodology was determined by the % of pts who could complete the GA independently, time to complete the GA (first time), and pt satisfaction with the survey platform. Correlations between the paper version and electronic version responses were evaluated. Results: 100 pts were accrued: median age 72 yrs (65-92 yrs), 51% female, and 63% stage IV disease. Primary cancers included lung (22%), breast (21%), GU (20%), GI (17%), and leukemia (9%). Pts' self-reported computer skills were None + Beginner (N+B, 42%) or Intermediate + Advanced (57%). The mean (SD) time to completion using RC, SS, and Paper were 23 (8), 17 (7), and 16 (5) mins. Pts with limited computer skills (N+B) were able to complete the electronic assessment independently: RC (75%), SS (100%), and preferred the computer version over the paper survey (RC 67%, SS 76%). The correlations between the paper version and the electronic versions (SS, RC) were 0.91, 0.96 for Instrumental Activities of Daily Living (IADL), 0.92 and 0.96 for Medical Outcomes Survey-Physical Health scales, respectively. Conclusions: The majority of patients in this cohort could complete an electronic GA using either a web-based or touchscreen platform independently. A higher proportion of patients preferred the touchscreen methodology. The electronic versions have high reproducibility compared to the paper GA.

Feasibility during first-line chemotherapy in elderly patients can be predicted by abnormal G8 score and performance status. First Author: Camille Chakiba, Department of Medical Oncology, Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France

Background: Predicting major adverse events such as functional decline during chemotherapy is an important issue in geriatric oncology. Recent studies have shown that different parts of comprehensive geriatric assessment (CGA) (Geriatric Depression Scale and Instrumental Activities of Daily Living) were predictive of functional decline. However CGA is time-consuming and has to be performed by trained geriatricians who are not in sufficient number to face the increasing demand of elderly cancer patients. Thus screening tools, such as G8-score validated on 1435 patients, have been developed to identify patients who may benefit from CGA. In addition to its value as a screening tool, the value of the G8 as a predictive tool of survival has been suggested and we here investigate whether it can be used to predict functional decline during chemotherapy. Methods: We tested on a cohort of 364 patients over 70 year-old treated with first-line chemotherapy the value of clinical (G8, age, sex, performance status –PS-, disease localization, extension) and biological factors (platelets, creatinine clearance, albumin, CRP, neutrophils) in predicting early functional decline, defined as a decrease of 0.5 points on the Activities of Daily Living (ADL) scale between the beginning of chemotherapy and the second cycle. We performed a multivariate analysis using logistic regression model. Results: Of the 364 patients, 312 were assessable for functional status and 68 express wild-type EGFR. On univariate analysis, PS 2 to 4, low platelets, metastatic disease and abnormal G8 (≤ 14 score) were associated with functional decline. On multivariate analysis, abnormal G8 score (OR, 3.56; 95% CI 1.22; 10.34; p = 0.02) and PS 2 to 4 (OR, 2.0; 95% CI 1.1; 3.6; p = 0.04) were significantly associated with increased likelihood of early functional decline. Conclusions: G8 has been developed as a screening tool to predict abnormal geriatric assessment. We have shown here that it could also be used together with performance status to select elderly patients more likely to develop functional decline during chemotherapy. These data reinforce the routine use of G8 in all elderly patients treated for cancer.

Is standard dose appropriate in elderly non-small cell lung carcinoma (NSCLC) patients treated with erlotinib? First Author: Frederic Bigot, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France

Background: Given the median age of 70 years in patients (pts) presenting NSCLC, the impact of age on outcomes including efficacy and toxicity of erlotinib remains unclear. In the BR21 study, analysis of subgroup based on age have reported similar survival benefits of erlotinib compared with placebo; however, elderly pts (> 70 years) had significantly more toxicity, and were more likely to discontinue treatment (Pazdur et al., 2008). Thus we hypothesized that elderly were more exposed than younger pts. Methods: All consecutive pts with advanced or metastatic NSCLC treated with erlotinib between 2010 and 2014 were eligible in this prospective cohort. Erlotinib concentrations in plasma were determined using high-performance liquid chromatography at Day 15 after treatment initiation. We compared dose-normalized concentrations between pts < or ≥ 75 years old using the Mann-Whitney U test and the occurrence of acute grade ≥ 2 adverse events (AE) or treatment modifications by Fisher’s test. AE reports were graded using the National Cancer Institute Common Terminology Criteria V4. Lean body mass was estimated using Jamhahasa’s equation. Results: Out of 55 pts, erlotinib plasma concentration was analyzed in 45 pts. Median age was 65.6 (range 25-83), and 14 pts were over 75 years old. Among these 45 pts, 58% were female, 93% had an adenocarcinoma subtype; 44% were never smoker. Eighty-six percent of the pts received a performances status at baseline ≤ 2. Elderly pts significantly lower estimated lean body mass (36.6 kg vs 47.7 kg; p = 0.0038). Within 2 weeks, grade ≥ 2 AE occurred in 20% of pts, and 28% in elderly. In the subgroup of pts over 75 years old, there was a trend for higher dose-normalized concentration at day 15 (1923.3 mg/L vs 1380.9 mg/L, p = 0.07), and the difference was significant in pts older than 80 (7 pts; 2484.6 mg/L vs 1377.4 mg/L; p = 0.0074). Four pts > 75 years old had dose reduction or discontinuation versus 0 in younger pts (p = 0.014, CI95% [1.253; infinite]). Conclusions: Elderly patients are susceptible to be overexposed to erlotinib at 150mg/day, resulting in increased acute toxicity and treatment discontinuation.

Association of baseline pro-inflammatory (IL-6, CRP) and coagulation (D-dimer) markers with relative dose intensity (RDI) in women with breast cancer (BC) undergoing (neo) adjuvant chemotherapy (chemo). First Author: Yuan Yuan, City of Hope, Duarte, CA

Background: Chemo decreases the risk of relapse and mortality from BC. Chemo efficacy depends on RDI, and patients (pts) who receive <85% RDI have poorer overall survival. Pro-inflammatory and coagulation factors such as IL-6, CRP and D-dimer serve as biomarkers for aging. The utility of these markers as biologic correlates of the ability to deliver chemo (i.e. RDI) in pts with BC is unknown. This study was performed to determine if prechemo IL-6, CRP and D-dimer correlate with RDI in BC women. Methods: This is a prospective longitudinal study that enrolled 153 women with BC who had pre-chemo peripheral blood assayed for IL-6, CRP, and D-dimer. (Neo)adjuvant chemo regimens were prescribed at the physician’s discretion. Univariate analyses evaluated the association of these 3 markers with <85% RDI and clinical factors (patient age, physician rated Karnofsky performance status (KPS) and number of comorbidities). Multivariate analyses were performed to evaluate the association of each biomarker and clinical factor with RDI. Results: 119 pts (mean age of 56 y, range 30-81 y) with stage I-III BC (Stages I-II [23%], II [54%], III [24%]) were enrolled. Chemo regimens include: doxorubicin + cyclophosphamide /paclitaxel (AC-T; 44%); docetaxel + cyclophosphamide (TC; 35%); docetaxel/carboplatin/trastuzumab (TCT; 7%) and other regimen (14%); RDI was less than 85% for 26% of pts. There were associations between RDI <85% and higher D-dimer (p<0.01) and IL-6 (p<0.02) levels pre-chemo (Table 1). There was a significant association between RDI <85% and CRP or above clinical factors. Conclusions: Higher pre-chemo levels of IL-6 and D-dimer correlate with reduced RDI (<85%). Future studies are underway to validate these findings. Table 1. Association of pre-chemo biomarkers, clinical factors and RDI <85%. Clinical trial information: NCT0130250.

512s Patient and Survivor Care
9540 Poster Session (Board #199), Sat, 1:15 PM-4:45 PM
Combination of eribulin (E) and capetibabine (C) in elderly metastatic breast cancer (MBC): Update of a new option suitable in older elderly. First Author: Ignazio Ugo Carreca, University of Palermo, Palermo, Italy

Background: E mesylate, a nontaxane microtubule dynamics inhibitor is widely prescribed for MBC pts pretreated with at least 1-2 lines of chemotherapy, including anthracyclines and taxanes (A&T). Elderly Patients (EP) develop rapid and sometimes fatal toxicity during standard treatments because of their pharmacokinetic features. We designed a new combination schedule (E+C) to evaluate its suitability for elderly MBC patients. Methods: Treatment plan: E 0.96 mg/sqm IV on d1 every 21d - C 900 mg/sqm bid d1-14 every 28d (Dose-adjustment if necessary was according to Kintzel-Dorr’s formula for EP), schedule was to be continued until progression or intolerable toxicity. Eligibility criteria: histologically confirmed diagnosis of MBC, written informed consent, at least 1 measurable lesion, at least 1 site of visceral pts (not brain mts), age > 70 years, previous treatment with A&T, Comprehensive Geriatric Assessment evaluation (CGA) permissive for chemotherapy, adequate renal, bone marrow and liver function. Charlson’s Score Comorbidity Scale was also considered. Evaluations tools: Clinical Benefit (CB) as Stable Disease + Objective Response Rates according to WHO criteria, toxicity profile using NCI-CTC v2.0 and Quality of Life (QoL) score through EORTC QLQ-C30 questionnaires. Results: From 2013 jan to 2014 dec 39 metastatic EP, mean age 80.5 (range 71 - 90) were treated and 37 are still under maintenance therapy (2 pts discontinued treatment for personal reasons). A total of 599 cycles were delivered to the 37 pts without G4 toxicity. No delay in therapy delivery was needed. QoL score shows no worsening with improvement in about 55% (72-78 y/o group) after treatment in comparison with baseline. Total CB was 80%. Conclusions: A further period of monitoring allowed to confirm our previous report in this setting with this combination schedule. It performs more fit with comorbidly or frailty than other standard chemotherapy regimens for MBC. In this updated analysis this schedule has showed non-inferiority vs standard treatments and more suitability for older EP. This study will be extended to confirm these outcomes in order to validate a schedule devoted to EP.

9542 Poster Session (Board #201), Sat, 1:15 PM-4:45 PM
Association of geriatric assessment factors with falls in older adults initiating chemotherapy. First Author: Tanya Marya Wildes, Washington Univ School of Medicine, St. Louis, MO

Background: In older adults with cancer, falls are common and associated with injury, functional decline, and poorer quality of life and survival. Prior oncology studies have been inconsistent in identifying factors associated with or predictive of fall risk. Identifying individuals with cancer at greater risk for falls is essential to allow targeted intervention to prevent falls. Methods: In a previously reported prospective study (Hurria et al, JCO 2011), 500 older adults with cancer underwent geriatric assessment (GA) prior to initiation of a new course of chemotherapy. In this analysis, we examined cross-sectional demographic, cancer and GA factors associated with falls in the 6 months before GA using logistic regression with bidirectional stepwise selection (p<0.15 for factor retention). Results: We analyzed 401 evaluable patients. The median age was 73 (range 65-91); 58% were female; 87% were white race, and just over half (59%) had stage IV disease. The most common cancers included lung (28%), gastrointestinal (19%), and gynecologic (19%). The median MD-rated Karnofsky performance status was 90 (range 50-100). About 18% (73 patients) reported one or more falls in the previous 6 months; of these, 62%, 15%, and 23% reported 1, 2, and 3+ falls respectively. On multivariate analysis, antidepressant use, benzodiazepine use and dependence in instrumental activities of daily living (IADLs) were associated with increased odds of falls (Table). The area under the curve of our model is 0.71, with positive and negative predictive values of 58% and 94% respectively. Conclusions: In older adults with cancer, falls are associated with antidepressant use, benzodiazepine use and dependence in IADLs. Prospective study of incident falls will be required to confirm if the presence of these factors at baseline increases the risk of subsequent falls.

Predictor   Adjusted Odds Ratio   95% Confidence Intervals   p
Antidepressant use   2.96   (1.40, 6.16)   0.004
Hospital Anxiety and Depression Scale Anxiety score ≥ 8   1.72   (0.81, 3.52)   0.15
Benzodiazepine use   2.17   (1.00, 4.65)   0.05
Proton Pump Inhibitor use   0.73   (0.98, 3.04)   0.06
Age ≥ 70   1.30   (0.98, 2.97)   0.25
IADL dependence   1.77   (1.01, 3.11)   0.05
Timed Up & Go ≥ 13.5 sec   1.66   (0.90, 3.01)   0.10

9544 Poster Session (Board #202), Sat, 1:15 PM-4:45 PM
Feasibility of a home-based walking program in female breast cancer patients aged 60+ during chemotherapy. First Author: Kirsten A Nyrop, UNC Chapel Hill, Chapel Hill, NC

Background: National guidelines recommend 150 minutes a week of moderate-intensity physical activity for adults with a cancer diagnosis. Our study investigated the feasibility of a self-directed walking in women age 60 or older undergoing cytotoxic chemotherapy treatment for breast cancer. Feasibility was defined as at least 50% of study participants reporting an average of 150 minutes or more of walking/week for exercise or pleasure during the first 6 weeks of chemotherapy. Methods: Eligibility: Female, age 60 +; Stage I-III breast cancer; scheduled for chemotherapy; physician permission to engage in physical activity; English speaking. Intervention: Evidence-based physical activity program for adults with arthritis: “Walk With Ease”. Measures: Patients self-reported the average number of days and number of minutes per day of walking for exercise or pleasure during chemotherapy. Study participants also maintained a daily walking diary throughout the first 6 weeks of chemotherapy. Data analysis: Descriptive statistics. Results: Study sample (N = 22): mean age 68 (60-79), 95% Caucasian, 41% high school degree or less, mean Body Mass Index/BMI 31 (20-50), 50% two or more comorbidities. At baseline (pre-chemotherapy), 29% of participants reported walking at least 150 minutes/week. During chemotherapy, the proportion walking > 150 minutes/week: 41% Week 1, 54% Week 2, 32% Week 3, 45% Week 4, 50% Week 5, 45% Week 6. During chemotherapy, the proportion walking > 100 minutes/week: 68% Week 1, 73% Week 2, 73% Week 3, 64% Week 4, 68% Week 5, 65% Week 6. Conclusions: A home-based, self-directed walking program can encourage older female breast cancer to engage in regular exercise during chemotherapy at a level that is higher than pre-chemotherapy. Achievement of the goal of 150 minutes per week is challenging, and more feasible at a level of 100 minutes per week. This pragmatic physical activity intervention is now being tested in a 4-year efficacy trial with a large sample of female breast cancer patients age 65 or older during chemotherapy treatment, to evaluate the impact of exercise on p16ink4a (biomarker of aging), fatigue and other patient-reported outcomes. Clinical trial information: NCT01754235.
9544  Poster Session (Board #203), Sat, 1:15 PM-4:45 PM
Do quality of life, physical function, or the Wheatley Index at diagnosis predict 1-year survival with intensive chemotherapy in older and younger acute myeloid leukemia patients? First Author: Nathar Timilsina, University of Toronto, Brampton, ON, Canada

Background: Treatment decision-making is complicated in older adults with acute myeloid leukemia (AML) because of poor prognosis and significant treatment toxicities. Improved prognostication at the time of diagnosis, such as with the Wheatley Index, may aid clinical decision-making. However, the Wheatley Index has not been validated outside clinical trials. Additionally, quality of life (QOL) or objective physical performance measures (PPM) may predict outcomes such as survival in oncology. We investigated the predictive value of baseline QOL, physical function, and the Wheatley Index at diagnosis on 1-year survival during IC in younger (<60 years) and older (60+ years) AML patients. Methods: AML patients undergoing intensive chemotherapy (IC) at the Princess Margaret Cancer Centre were enrolled in a prospective study. At the baseline assessment (pre-IC), patients completed the EORTC QLQ-30 questionnaire in addition to 3 PPMs (grip strength, 2-minute walk test, and timed chair stands). The prognostic risk category (good, standard, and poor) was categorized according to the index defined by Wheatley et al. for older adults and modified for younger adults. Predictive value for 1-year survival was analyzed with multivariable Cox proportional hazards regression. Results: 140 younger and 97 older patients were recruited. Overall 1-year mortality was 22.1% in younger and 37.1% in older patients. One-year mortality was significantly higher among the poor Wheatley risk category than the other 2 risk categories in both younger and older groups (40.0% and 63.3%, P < 0.05, respectively). Global health and PPMs were not predictive of 1-year survival. Poor Wheatley risk category was the most significant predictor in both univariate and multivariate survival models (p < 0.001) in both older and younger groups. Conclusions: Although QOL and PPMs at diagnosis were not good predictors of 1-year survival among younger and older AML patients, the Wheatley index may help inform clinicians and patients about up-front therapy in AML.

9545  Poster Session (Board #204), Sat, 1:15 PM-4:45 PM
Differences between patient and caregiver burden in caregivers of older adults with cancer. First Author: Tina Hsu, University of British Columbia, Kelowna, Canada

Background: Caregivers are a valuable support for patients and an important source of information about patient health, particularly in older adults who are more likely to be frail or have cognitive impairment. We sought to determine whether a) differences exist between patient and caregiver assessments and b) these differences were associated with increased caregiver burden. Methods: 100 cancer patients, age ≥65, and their caregivers independently assessed patient function, comorbidities, nutrition, psychological status, social activity and social support. Caregiver Strain Index (CSI) was used to assess caregiver burden. Patient-caregiver assessments were compared using the Wilcoxon signed rank test. The relationship between caregiver burden and variables in which patient-caregiver assessments differed was determined using linear regression. The final model and adjustment for confounders was done. Results: Median patient age was 70, 70% had advanced disease, 62% were on chemotherapy. Patients reported a median of 2 comorbidity conditions, no falls within 6 months, and 39% reported >5% weight loss. Patients reported good function (median KPS 90 and Medical Outcomes Study (MOS)-physical function 67), independence with most instrumental activities of daily living (IADL) (median OARS-IADL 13), and good social health (median Mental Health Index 85). 75% of caregivers experienced some caregiver burden (mean CSI 3.1±3.2, 15% had high burden). Caregivers were more likely than patients themselves to rate patients as having poorer function (meaning more help with IADLs (p = 0.008), lower KPS (p = 0.02), and lower MOS-physical function (p < 0.0001)), poorer mental health (p = 0.0002), but more social supports (p = 0.03). Only a difference in patient-caregiver assessment of a patient’s need for help with IADLs was associated with increased caregiver burden (p = 0.002). Conclusions: Patients and caregivers differ in their assessment of patient function, mental health, and social support. However, only differences in patient-caregiver reported need for help with IADLs were associated with increased caregiver burden.

9546  Poster Session (Board #205), Sat, 1:15 PM-4:45 PM
Advanced cancer patients’ reported priorities regarding wishes at the end of life: A randomized controlled study. First Author: Marvin Omar Delgado-Guay, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Conversations about wishes around the end-of-life (EOL) are challenging and difficult for all clinicians. There is limited literature about the type and stability of patient’s reported EOL priorities. We compared a set of 36 cards (“Go-wish-Game”: GWG) v. a paper list to assist patients in identifying which patients are at the highest risk of dying in hospital. The likelihood of mortality, but tools are needed to assist clinicians in establishing priorities. Methods: Randomized controlled study. Patients were randomized to GWG or to a list of 36 Wishes/Statements (LOS) and were asked to categorize them as very, somewhat, or not important; Group A received LOS followed by LOS 4-24 hours later; Group B: GWG-GWG; group C: GWG-LOS, and group D: LOS-GWG. The State-Trait Anxiety inventory for patients and caregivers independently assessed patients’ need for help with IADLs was associated with increased caregiver burden (p = 0.002). Conclusions: Patients and caregivers differ in their assessment of patient function, mental health, and social support. However, only differences in patient-caregiver reported need for help with IADLs were associated with increased caregiver burden.

9547  Poster Session (Board #206), Sat, 1:15 PM-4:45 PM
Evaluation of the MPM2 score versus clinical predictions of mortality in a tertiary cancer center. First Author: Alison Wiesenthal, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Prognostication is an essential yet challenging clinical skill for oncologists, even as patients approach death. Goals-of-care discussions may be improved by giving patients and families objective reference for likelihood of mortality, but tools are needed to assist clinicians in identifying which patients are at the highest risk of dying in hospital. The aim of this study was to evaluate the transferability of the ICU-derived Mortality Probability Models Version 2 (MPM2) score to the general wards at a comprehensive cancer center, and to compare it to clinical predictions of dying in hospital (CPDH). Methods: Prospective case series of inpatients receiving palliative medicine consultations over a 3 month period. Prior to calculating MPM2 score, the CPDH was estimated in categories: unlikely (<10%), less likely (25%), possible (50%), probable (75%), consistent with (90%). Overall survival was determined 6 months after end of enrollment. Calibration of MPM2 in these patients was evaluated by logistic regression. For survival analysis, MPM2 scores were grouped as <10, 10-50, >50. Results: Of 79 patients consecutively evaluated, 18 (23%) died in hospital. Among 41 (52%) died after discharge, MPM2 score and CPDH were each significantly predictive of dying in hospital (p<0.001). Agreement between CPDH categories and corresponding MPM2 categories was fair (weighted kappa 0.37), CPDH being more pessimistic overall and avoiding use of the middle category (see Table). Overall survival was different between Caregiver and MPM2 (median 131.5, 36 and 6 days respectively; log rank test of 2, χ²=42.6, p<0.001). Conclusions: The MPM2 score shows promise as a clinical tool for determining in-hospital mortality outside of the ICU. It was most helpful for identifying and correctly classifying patients with intermediate likelihoods of surviving. Larger studies in this and other settings are needed.
9548 Poster Session (Board #207), Sat, 1:15 PM-4:45 PM
Distress in older adult cancer patients approaching end of life. First Author: Elizabeth Ann Kvale, Birmingham VA Medical Center, Birmingham, AL

Background: Lay health navigators are able to address various issues that cause distress in older cancer survivors by administering and responding to distress thermometers (DT). Methods: Lay navigators in the UAB Patient Care Connect Program assist cancer patients ≥ 65 years old with traditional Medicare insurance at 12 cancer centers in Alabama, Mississippi, Georgia, Florida, and Tennessee. Navigators documented distress levels, causes of distress, and requests for intervention. Distress screening data from the final DT administered prior to death were used to describe care gaps for older adults with advanced cancer. Results: DTs were collected on a representative sample of 1060 patients who were evenly divided with respect to gender and 18% minority. Median number of days from date of last DT to date of death was 42(1-544). Distress score 4 were observed in 43% of patients; 10% reported scores ≥ 8. Forty four percent of patients attributed distress to physical symptoms such as pain and fatigue. Twenty percent indicated mobility issues contributed while 15% indicated informational needs related to their illness or treatment. Patients were more likely to ask for help from navigators with informational issues related to their illness (63%) or hospice (75%) than mobility (35%) or physical symptoms (33%). Conclusions: Through distress screening lay navigators are able to help older adults with advanced cancer with informational or logistical needs and advocate for proactive assistance with issues related to symptom burden. The project described was supported by Grant Number 1D1CMS3311023 from the Department of Health and Human Services, Centers for Medicare & Medicaid Services. The contents of this abstract are solely the responsibility of the authors and do not necessarily represent the official views of the U.S. Department of Health and Human Services or any of its agencies.

9549 Poster Session (Board #208), Sat, 1:15 PM-4:45 PM
“Months, Not Years”: Impact of Clinical Discussions of Advanced Cancer Life-Expectancy on Patient Illness Understanding. First Author: Andrew S. Epstein, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients’ understanding of their illness often guides best practice, and this is no less true at the end of life. Data showing the influence of patients’ acknowledgment of prognostic discussions on the accuracy of patients’ illness understanding could inform the debate regarding how to engage in these difficult discussions. Methods: To evaluate the effects of recent and past oncologist-patient discussions about prognosis/life-expectancy (P/L/E) on changes in advanced cancer patients’ illness understanding (acknowledgement of their illness as 1 terminal; 2 incurable; 3 advanced stage; and 4 associated with an estimated life-expectancy in months, not years), 208 patients (with advanced lung or upper gastrointestinal cancers that progressed on 1 chemotherapy regimens, or advanced colorectal cancers that progressed on 2) from Coping with Cancer II, a prospective observational cohort study, were interviewed before and after a visit with their oncologists who discussed scan results regarding potential additional progression. Results: Median time between pre- and post-scan interviews was 38 days. Controlling for potential confounds (i.e., patients’ race) and adjusting for patients’ pre-scan illness understanding, patients who acknowledged ever having discussions of P/L/E with their oncologists were more likely to recognize that their disease was incurable (Adjusted Odds Ratio [AOR] = 2.97, p = 0.009) than those who did not. Compared to patients who denied ever having a discussion of P/L/E, those who reported having both recent and past discussions of P/L/E were more likely to recognize that their disease was at an advanced stage (AOR = 4.88, p = 0.012), and those who reported having only recent discussions, or both recent and past discussions, of P/L/E were more likely estimate their life-expectancy in terms of months as opposed to years (AOR = 10.1, p = 0.005, and AOR = 17.5, p = 0.006, respectively). Conclusions: Advanced cancer patients who acknowledge having discussions of P/L/E with their oncologists have a better understanding of the terminal nature of their illnesses as compared to those who do not, and thus may be better prepared to make informed end-of-life care decisions.

9550 Poster Session (Board #209), Sat, 1:15 PM-4:45 PM
Standardization of measurement of tobacco use in cancer clinical trials. First Author: Stephanie R Land, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD

Background: ASCO and AACR recommend assessment of tobacco use (TU) for all cancer patients, but there is little consensus regarding approaches for reliable, valid, and clinically meaningful TU measurement. Our aim was to develop clinically efficient evidence-based assessments that can be applied across research settings, and to provide expert recommendations for the timing of assessment. Methods: In 2013-2014, an expert Task Force developed candidate TU measurement items via consensus dialog and systematic evaluation of existing tools. From 9/2014-1/2015, in-depth, semi-structured cognitive interviews were conducted with three rounds of cancer patients to evaluate patient comprehension, memory retrieval, and judgment of draft versions of the instrument. Interviews were abstracted into structured reports tabulating cognitive difficulties. A subcommittee convened to recommend modifications. Results: Two tiers of TU measurement items were developed: a core set for all cancer studies, and a longer menu of curated items for use when comprehensive assessment is feasible. Domains include TU history, status and intensity relative to cancer diagnosis and treatment, other tobacco products; cessation approaches; and second hand smoke. We interviewed 22 participants (mean age 64; 68% male; 50% college educated; with cancers of the prostate (n = 8), bladder (3), colon & rectum (1), lung (7), pancreas (1), testis (1), thymus (1)). Numerous instrument improvements addressed patients’ understanding of different, response options, and recall periods. The final version was performed well. Task Force recommendations also include a protocol for assessments at baseline and follow-up. Conclusions: These results provide preliminary support for content validity of the TU assessment instrument. Standardized TU assessment implemented in research across a range of disease sites and treatment modalities will permit data pooling and comparisons between populations. Recommendations facilitate TU assessment in clinical trials and will enable researchers to identify novel clinical interactions, better understand the effects of TU on cancer treatment efficacy and toxicity, address cessation, and ultimately improve clinical outcomes.

9551 Poster Session (Board #210), Sat, 1:15 PM-4:45 PM
Dissonance reduction as prominent coping strategy in phase I study participants. First Author: Diane A.J. van der Biessen, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: Phase I trials are essential for progress in cancer treatment but the reasons for patients to participate in these trials remain relatively ill-explored (Van der Biessen et al, 2013). This study aims to understand how psychological factors like coping strategies, locus of control, and hope affect the motivation to participate in these trials. Methods: In this prospective study we asked patients to complete a survey before initial informed consent for the phase I study was obtained for the first time. We used questionnaires regarding treatment motivation (TM, Van der Helm et al, 2012), hope (Herth Hope Index, coping (assimilation and accommodation coping-scale of Brandstädter and Renner), locus of control (Rotter locus of control scale) and Quality of Life (QoL, EQRCT QLQ-C30). To investigate relationships between the scales a structural equation model (SEM) was fitted to the data. Results: During 18 months 135 patients enrolled in the questionnaire survey. 65 (48%) of the patients were male, with a mean age of 62 (range 30-83). The SEM-analysis showed ‘hope’ was significantly predicting treatment motivation $X^2 (5) = 5.119$. Fit indices showed a close fit: NFI = 0.996; CFI = 0.999; TLI = 0.996; RMSEA = 0.013. An unique combination of flexible (p < 0.01) and tenacious (p < 0.01) coping, together with internal locus of control (p < 0.01) was predicting for ‘hope’. Conclusions: Patients entering phase I studies seem to combine seemingly contradictory coping strategies:tenacity and flexibility. Also locus of control contributes towards hope. These data suggest a specific psychological adaptation, called dissonance reduction. This process that unconsciousely discounts threatening information (i.e. about fatal prognosis of the disease) predicts for the motivation to participate in oncology phase I trials. Clinical trial information: NTR3354.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Many studies have shown high levels of emotional and psychosocial distress in cancer patients. However, it is not well known yet to what extent psychological problems meet the criteria of a mental disorder according to clinical diagnosis classification systems (ICD-10, DSM-IV). We investigated the 12-month prevalence of mental disorders in a representative sample of cancer patients treated in different care settings in order to provide epidemiological data for evidence-based psycho-oncological service care planning. Methods: We interviewed a representative sample of patients with different tumour entities (N = 2,141) in outpatient, inpatient and rehabilitation settings using the standardized computer-assisted Composite International Diagnostic Interview for mental disorders adapted for cancer patients (CIDI-O). Results: The overall 12-month prevalence for any mental disorder was 39.4% (95%CI: 37.3-41.5%). The following prevalence rates were diagnosed: 15.8% (95%CI: 14.3-17.4%) for anxiety disorders, 12.6% (95%CI: 11.2-13.9%) for mood disorders, 9.5% (95%CI: 8.3-10.8%) for somatoform disorders, 7.3% (95%CI: 6.2-8.4%) for nicotine abuse, 3.7% (95%CI: 3.0-4.5%) for disorders resulting from a general medical condition, 1.1% (95%CI: 0.6-1.5%) alcohol abuse or dependence and 0% eating disorders. Highest prevalence of mental disorders was found in patients with head and neck cancer, breast cancer, malignant melanoma and kidney/urinary tract cancers. Conclusions: Mental disorders are highly prevalent in cancer patients. Having shown differences regarding type and amount of mental disorders across different tumour entities, our results emphasize a different need for psycho-oncological and psychotherapeutic support leading to an appropriate allocation of direct personnel and other resources.

Background: Retrospective data show that the rate of contralateral prophylactic mastectomies (CPMs) is increasing; meanwhile, parallel information informing impact of CPM on quality of life (QOL) is lacking. We undertook this study to ascertain whether patient-reported outcomes (PRO), and more specifically QOL, differed between women who did or did not elect CPM. Methods: Women recruited from the Army of Women (AOW) with a history of breast cancer surgery took electronically-administered surveys including a background survey to collect patient, disease, and procedure specific factors, as well as the BREAST-Q, a well-validated breast surgery outcomes patient reporting tool. Descriptive statistics, univariate hypothesis testing, and regression analysis were used to evaluate the association of CPM with PRO scores in 4 QOL domains incorporated in the BREAST-Q (satisfaction with breasts, and psychosocial, physical and sexual well-being). Results: 7628 women completed questionnaires; of these, 4152 had mastectomy and 1519 (37%) reported receipt of CPM. Women undergoing CPM were younger (median age 53.7 y vs. 59.3 y, p < 0.0001) and reported earlier breast cancer stage at presentation than those who did not choose CPM. In univariate analysis, mean breast satisfaction was significantly higher among the CPM group (60.4 vs. 58.1, p = 0.0005) and mean physical well-being was significantly higher among those who did not have a CPM (76.6 vs. 74.6, p = 0.0002). The groups did not differ with respect to psychosocial or sexual well-being. On logistic regression, the CPM group continued to report higher breast satisfaction (p = 0.0019) but reported no difference from the non-CPM group in the other QOL domains. Psychosocial well-being improved over time for both CPM and non-CPM groups (p < 0.0001), but did not differ significantly within time interval since surgery. Conclusions: Choice for CPM was only associated with improved QOL in the breast satisfaction domain and did not impact psychosocial, physical and sexual well-being after adjustment for other factors known to influence QOL. Such PRO data are important to consider when counseling women contemplating CPM as part of their breast cancer treatment.

Background: Primary breast tumor patients experience a high level of psychosocial distress, not only due to their diminished functional and neurocognitive capacities, but also due to the psychosocial stigma of being a primary brain cancer patient. The purpose of this study is to evaluate the level of psychosocial distress, the different sources of this stress, and its effect on health-related quality of life (HRQoL) in primary brain tumor patients. Methods: Demographic and clinical information in the PRODRESS registry at Duke’s Preston Robert Tisch Brain Tumor Center was queried retrospectively for December 2013 through February 2014. Data was also obtained from patient-reported outcome questionnaires including the National Comprehensive Cancer Network’s Distress Thermometer (NCCN-DT), Functional Assessment of Cancer Therapy-Brain Cancer (FACT-BR), and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACT-F). Results: Among the 845 subjects completing the NCCN-DT, 385 (46%) were female and 460 (54%) were male. 98% reported physical problems with the most frequent being memory/concentration (40%) and fatigue (42%), and 41% complained of an emotional problem with nervousness (22%) and worry (29%) being the most reported concerns. 12% reported insurance/financial concerns. 94% of the subjects completed the distress thermometer with a mean score of 2.68 (SD = 2.70). There was no difference in distress between tumor grades (low grade: mean = 2.73, SD = 2.89; high grade: mean = 2.67, SD = 2.62; p = 0.8297). Females (mean = 3.05, SD = 2.81) experienced significantly more distress than males (mean = 2.39, SD = 2.57; p = 0.0007), as well as a higher rate of practical (p = 0.0026), family (p = 0.0209) and emotional (p < 0.0001) problems. Patients who reported at least one practical, family, or emotional problem had significantly lower HRQoL (p < 0.0001). Conclusions: Primary brain tumor patients experience memory dysfunction, fatigue, nervousness, worry, and financial concerns which have a negative effect on the patient’s HRQoL. By identifying and addressing these stressors during a clinic visit, it may be possible to improve patient HRQoL.
9556 Poster Session (Board #215), Sat, 1:15 PM-4:45 PM

Change in second-hand smoke exposure after a lung and head and neck cancer diagnosis and subsequent patient smoking cessation. First Author: Lauren Eng, Division Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Exposure to second-hand smoke (SHS) after a cancer diagnosis is associated with continued smoking in lung and head and neck (HN) cancer patients (PMID: 24419133, 23765604). We evaluated whether complete reduction/cessation of SHS exposure around and after a diagnosis of lung or HN cancer is associated with smoking cessation in the cancer patient.

Methods: Lung and HN cancer patients from Princess Margaret Cancer Centre (2006-12) completed questionnaires at diagnosis and follow-up (median 2 years apart) that assessed smoking history and SHS exposures (cohort design). These cancers were chosen because these patient groups had the highest rates of smoking at the time of diagnosis. Multivariate logistic regression analysis evaluated the association of cessation of SHS exposure after a diagnosis of cancer with subsequent smoking cessation, adjusted for significant covariates. A cross-sectional study (2014) of 90 lung and HNC smoking patients assessed consistency in quitting of SHS exposure after a diagnosis of cancer with subsequent smoking exposures (cohort design). These cancers were chosen because these patient groups had the highest rates of smoking at the time of diagnosis. Multivariate logistic regression analysis evaluated the association of cessation of SHS exposure after a diagnosis of cancer with subsequent smoking cessation, adjusted for significant covariates.

Results: For the cohort, 261/731 lung and 145/450 HN cancer patients smoked at diagnosis; subsequent overall quit rates were 69% and 50% respectively. 91% of lung and 94% of HN cancer patients were exposed to SHS at diagnosis while only 40% (lung) and 62% (HN) were exposed at follow-up. Cessation of SHS exposure was associated with smoking cessation in lung (OR = 4.76, 95% CI [2.56-9.09], P < 0.001), HN (OR = 5.00 [1.61-14.29], P < 0.001), and in both cancers combined (OR = 5.00 [3.03-8.33], P < 0.001). The cross-sectional study had a similar trend for cessation of SHS with smoking cessation, but a lower magnitude of association (OR = 2.73, P = 0.09). However, when asked directly, only 13% of patients quit smoking with another individual.

Conclusion: Cessation of SHS exposure around and after cancer diagnosis is associated with continued smoking in lung and HN cancer patients. This cessation of SHS exposure is significantly associated with smoking cessation in lung and HN cancer patients. However, few patients quit smoking at the same time as their friends, family or household. Changing the environment around cancer survivors to reduce SHS exposure and encouraging households/friends to quit smoking may both improve cessation rates in cancer patients.

9557 Poster Session (Board #216), Sat, 1:15 PM-4:45 PM

Psychological distress during hospitalization for hematopoietic stem cell transplantation to predict lower quality of life and high post-traumatic stress disorder symptom months post-transplant. First Author: Harry VanDusen, Massachusetts General Hospital, Boston, MA

Background: Patients undergoing hematopoietic stem cell transplantation (HCT) experience a steep deterioration in quality of life (QOL) and mood during hospitalization for HCT. The impact of this deterioration on patients’ long-term QOL and post-traumatic stress disorder (PTSD) symptoms is unknown.

Methods: We conducted a prospective longitudinal study of patients hospitalized for HCT. At baseline (day-6), day+1, day+8, and 6 months post-HCT, we assessed QOL (Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT)) and mood (Hospital Anxiety and Depression Scale (HADS)). We used the PTSD Checklist to assess for PTSD symptoms at 6 months. We used multivariable linear regression models to identify predictors of QOL and PTSD symptoms at 6 months post-HCT.

Results: We enrolled 97% (90/93) of consecutively eligible patients undergoing autologous (n = 30), myeloablative allogeneic (n = 30), or reduced intensity allogeneic (n = 30) HCT. Overall, patients’ QOL at 6 months (mean FACT-BMT: 110, 95% CI [104-116]) recovered to baseline pre-transplant values (mean FACT-BMT: 110, 95% CI [107-115]). At 6 months, 28.4% of participants met provisional diagnostic criteria for PTSD. In multivariable regression analyses, depression and anxiety symptoms during hospitalization for HCT predicted impaired QOL (HADS-depression β = −1.8, P < 0.04; HADS-anxiety β = −1.7, P = 0.06) and PTSD symptoms (HADS-depression β = 1.0, P < 0.005; HADS-anxiety 1.2, P = 0.01) at 6 months post-HCT.

Conclusions: While patients’ overall QOL at 6 months post-HCT returned to baseline values, a significant proportion met provisional diagnostic criteria for PTSD. Psychological distress during hospitalization for HCT was the most important predictor of long-term QOL impairment and PTSD symptoms. Future studies should evaluate whether interventions to reduce psychological distress during HCT may improve long-term QOL and reduce the risk of PTSD symptoms.

9558 Poster Session (Board #217), Sat, 1:15 PM-4:45 PM

Treatment-adherence beliefs and behaviors in patients with chronic myeloid leukemia (CML). First Author: Joanne S. Buzaglo, Cancer Support Community, Research and Training Institute, Philadelphia, PA

Background: Tyrosine kinase inhibitors (TKIs) are effective yet chronic indefinite therapy for CML. Strong links exist between TKI adherence and optimal outcomes. Suboptimal adherence is common, affecting clinical outcomes and healthcare costs. Nonadherent patients underrecognize missed-dose impact on response. This study explored the link between belief and behavior vis-à-vis adherence.

Methods: With outreach to online, national and community networks from 10/13 to 7/14, 484 CML patients enrolled in the Cancer Experience Registry: CML, an online project to advance CML knowledge and patient engagement. 393 (81%) completed a web-based survey including questions assessing accord with 2 statements (1) It is okay to miss a dose of my CML medicine every now and then, and (2) I need to take every dose of my CML medicine or it might not work; as well, participants reported missed TKI-dose frequency. Logistic regression model 2, 6% strongly disagreed they needed to take every dose, 17% disagreed, 28% agreed, 24% disagreed, 43% strongly disagreed. For statement 1, 5% strongly disagreed they needed to take every dose, 17% disagreed, 28% agreed, 24% disagreed, 43% strongly disagreed. For the cohort, 50.6 of patients reported missed-dose frequency. Logistic regression was used to study the beliefs-behavior link among US patients taking TKIs (n = 318). Regression models were adjusted for age, gender, time since diagnosis, and TKI cost/month.

Results: Responders averaged 56.6 of age and 5.2 y from diagnosis; the majority was female (68%) and white (90%). 23% reported TKI spending of ≤ $50. Regarding statement 1 and missed TKI dose, 5% strongly agreed, 28% agreed, 24% disagreed, 43% strongly disagreed. For statement 2, 6% strongly disagreed they needed to take every dose, 17% disagreed, 28% agreed, 24% disagreed, 43% strongly disagreed. For the cohort, 26% reported missed TKI dose at least monthly. Compared to those who disagreed/strongly disagreed, those who agreed/strongly agreed with statement 1 were significantly more likely to have reported missing doses monthly (OR = 7.04; 95% CI = 3.65, 13.57). Also, those who disagreed/strongly disagree with statement 2 vs. those who agreed/strongly agreed were significantly more likely to have reported missing doses at least once monthly (OR = 5.36; 95% CI = 2.81, 10.2).

Conclusions: CML patients’ medication beliefs were strongly associated with suboptimal adherence. The results suggest multifaceted patient education would impact adherence, outcome and survival. The relationship between beliefs and drug adherence merits further study.

9559 Poster Session (Board #218), Sat, 1:15 PM-4:45 PM

Association between oncologists’ dispositional affect and depressive symptoms in their patients with metastatic cancer. First Author: William F. Pirl, Massachusetts General Hospital, Brookline, MA

Background: While caring for patients with metastatic cancer can be emotional, relationships between the emotions of oncologists and their patients have not been examined. As patients and oncologists read emotional cues in encounters, emotions of one or both may impact the other. We explored associations between dispositional affect, tendencies to emotionally respond to situations in certain ways, in oncologists and depressive symptoms in their patients with newly diagnosed metastatic lung and gastrointestinal (GI) cancers. Methods: As part of an ongoing trial of early palliative care, participants were assessed at baseline for depressive symptoms (Patient Health Questionnaire-9, PHQ9) within 8 weeks of diagnosis with metastatic lung and GI cancers. Oncologists providing care for these patients completed the Positive and Negative Affect Scale (PANAS), a validated measure of dispositional affect with positive and negative dimensions. Associations between patient depressive symptoms and positive and negative dispositional affect were tested with rank sum tests and multivariate linear regressions. Results: Sixteen of the 18 oncologists with patients in the trial completed the PANAS. Among 323 participants with baseline assessments, 277 (86%) had oncologists who completed the PANAS. Mean age was 64.6, 129 (46%) were female, 159 (57%) had GI and 118 (43%) lung cancer, and mean PHQ9 score was 6.5. Positive and negative dispositional affect were not associated with oncologists’ depressive symptoms in their patients. Patient depressive symptoms were significantly higher if their oncologists reported greater negative dispositional affect (p = .04). The relationship remained significant adjusting for patient age, sex, cancer type, ECOG PS, smoking, and number of oncology visits (β = .13, t = 2.1, p = .04). PHQ9 scores were not associated with oncologists’ positive dispositional affect.

Conclusions: Depressive symptoms in patients with metastatic lung and GI cancers appear to be associated with their oncologists’ negative dispositional affect. Determining the direction of the association may lead to new ways of improving patients and/or oncologists mood.
Mild cognitive impairment (MCI) in chemotherapy-treated breast cancer survivors.

First Author: Abigail Gifford, Wake Forest University, School of Medicine, Winston-Salem, NC

Background: Infertility and sexual dysfunction resulting from cancer therapy are often inadequately addressed by physicians, even though these issues cause significant distress for young adult cancer patients. In this study, we examined survivors’ expectations of their physicians regarding reproductive and sexual healthcare, and identified factors associated with these expectations. Methods: We surveyed patients aged 20 to 39 years who were diagnosed with solid tumors, evaluated at any of 1 of 5 regional cancer centers in British Columbia, and alive at 2 or more years after their original diagnosis. Using multivariate regression models, we explored the relationships between patient expectations of their care and the factors associated with these expectations, while controlling for potential confounders. Results: With a survey response rate of 56%, a total of 447 participants were analyzed: median age was 35 years (IQR 31-38), 30% were men, 89% had ECOG 0, and 75% reported being in a relationship. Tumor sites included breast (222; 50%), testicular (126; 28%), gynecological (76; 17%), and colorectal (23; 5%). A significant proportion of patients received chemotherapy (65%) and radiation (47%) that posed the potential for infertility or sexual dysfunction. While the majority of patients expected their primary care providers (PCPs) and cancer specialists (CS) to share responsibility in addressing fertility and sexual health concerns (85% and 74%, respectively), a fair number of patients preferred that reproductive health be fully managed by CS (16% vs. 10%, p = 0.004) and that sexual health be mainly addressed by PCPs (31% vs. 21%, p < 0.0001). In regression analyses, prior discussions about infertility or sexual dysfunction conducted by oncologists increased the patient’s expectations of their ongoing involvement in these areas (p = 0.047 and p = 0.006, respectively). Conclusions: Young adult cancer survivors have specific expectations about physician roles in addressing reproductive and sexual health. As discussions can modify patient expectations, early and appropriate engagement of both CS and PCPs in such conversations can facilitate the development of effective shared-care models of follow-up.

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A comparison of the natural history of oxaliplatin- and paclitaxel-induced neuropathy (NCT08 N08BC/Aliance). First Author: Kathryn Jean Ruddy, Mayo Clinic, Rochester, MN

Background: We examined the similarities and differences of paclitaxel and oxaliplatin neuropathy symptoms. Methods: Acute and chronic neuropathy data were pooled from pts receiving 1) adjuvant oxaliplatin (FOLFOX) in protocol N08BC (346 pts) and 2) weekly paclitaxel or every 3 week paclitaxel/carboplatin in protocol N08C1 (179 pts). In both trials, pts completed daily questionnaires for several days after each chemotherapy dose (to evaluate acute neuropathy) and the EORTC CIPN20 tool before each chemotherapy dose and at 1, 3, 6, and 12 months post treatment (to assess chronic neuropathy). Results: The acute neuropathy symptoms from both drugs peaked on day 3, with acute symptoms experienced in cycle 1 predicting occurrence in the subsequent cycles. Paclitaxel-induced acute symptoms were similar in intensity in each cycle and largely resolved between cycles. Oxaliplatin-induced acute symptoms were about half as severe in the first cycle, as in later cycles, and did not resolve completely between cycles. For chronic neuropathy, both drugs caused a predominately sensory neuropathy (numbness and tingling much more common than pain). Oxaliplatin-induced chronic neuropathy worsened after the completion of treatment (coasting phenomenon) and began to improve 3 months post-treatment. In contrast, paclitaxel-induced chronic neuropathy typically began improving immediately after chemotherapy cessation. During treatment, paclitaxel numbness/tingling symptoms were similar in hands and feet; with oxaliplatin, hands were affected more than feet. After treatment completion, hand symptoms improved faster than foot symptoms, for both drugs, so that foot symptoms were more problematic one year later. Both paclitaxel- and oxaliplatin-induced acute neuropathy appeared to predict the severity of chronic neuropathy (more prominently with oxaliplatin). Conclusions: Patients receiving paclitaxel or oxaliplatin should be counseled regarding these patterns of neuropathy symptoms and recovery. Understanding the similarities and differences between these neuropathy syndromes should provide insight into the underlying pathophysiology and help find preventative treatment approaches. Clinical trial information: N08C1/N08BC.

Effects of strength training intervention in breast cancer survivors. First Author: Joanne Monterosso, University of Vermont Medical Center, Burlington, VT

Background: Oncology rehabilitation programs provide a potential avenue for improving fitness, function and quality of life. Few studies evaluate how cancer survivors respond to such interventions. Objectives: 1. Compare upper and lower body strength of breast cancer survivors (BCS) to normative data. 2. Evaluate changes in strength after 12 weeks of resistance training. Methods: Participants received a 12 week, 2x per week aerobic and resistance training intervention as part of the University of Vermont Medical Center oncology rehabilitation program. One repetition maximum strength testing of upper and lower body strength was completed before and after the intervention. Strength was compared to American College of Sports Medicine normative values. Pre/post comparisons were completed for participants attending ≥ 25% of sessions. Breast cancer survivors were included in the analysis. Results: Baseline assessments were obtained on 130 participants, 91 completed at least 25% of exercise sessions. 90% completed ≥ 66% of training sessions. Over 90% of BCS had upper extremity strength at < 25th percentile and over 74% had lower extremity strength at < 20th percentile. Upper and lower extremity strength remained < 25th percentile for the majority of participants after the intervention but percentiles improved 8 and 16 points respectively. For participants completing the intervention, upper extremity strength increased from 57 ± 31lbs to 70 ± 31lbs (p < 0.001). Lower extremity strength increased from 125 ± 45 to 154 ± 42lbs (p < 0.001). There were no significant differences in strength improvement between BCS who did and did not receive chemotherapy. The upper extremity strength of women age ≥ 55 improved to a greater degree than women over age 55 (p = 0.01). Conclusions: Breast cancer survivors entering an oncology rehabilitation program have markedly lower upper and lower body strength compared to normative data. Strength training intervention results in improved strength in this population but strength remains below expected. The benefit of resistance training was seen regardless of age or previous exposure to chemotherapy. Opportunities for breast cancer survivors to participate in resistance training interventions should be encouraged.

A randomized controlled trial (RCT) of a supportive care package (SurvivorCare, SC) for survivors of colorectal cancer (CRC). First Author: Michael Jefford, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia

Background: Colorectal cancer (CRC) and its treatments can cause distressing short and long-term side effects as well as significant functional consequences. Current models of follow-up do not adequately address these issues. We conducted a multi-center RCT of an innovative program (SurvivorCare (SC)); designed to have a beneficial effect on psychological distress, supportive care needs (SCN) and quality of life (QOL). Methods: At the end of active treatment for stage I-III CRC, eligible patients (> 18 years, adequate English) were randomized 1:1 to usual care (UC) or to UC + SC. SC comprised educational materials, needs assessment, an individualized survivorship care plan, nurse-led end-of-treatment session and three follow up (FU) phone calls. Distress (BSI-18), SCN (CaSUN) and QOL (EORTC QLQ-C30, CR29) were assessed at baseline, 2 (FU1) and 6 (FU2) months. Primary hypothesis: SC would have a beneficial effect on distress at FU1. Secondary hypotheses: SC would have a beneficial effect on (1) SCN and QOL at FU1; and (2) distress, SCN and QOL at FU2. 15 items assessed satisfaction with survivorship care. Sample size of 180 (90/arm) was based on 80% power, 2-sided alpha of 0.05, to detect a between groups difference of 3.6 on BSI-18 at FU1. Outcome analysis was ITT. Results: Of 221 patients randomized (111 UC, 110 SC), 4 were ineligible and 1 lost to FU, leaving 110 UC, 106 SC. Groups appeared well balanced. Median age was 64, 52% male, 56% colon, 35% rectal cancer, 105 CRC. SC: Stage IV 22%, II 71%. Intervention fidelity was acceptable. Baseline distress and QOL were similar to population norms. Between groups differences in distress at FU1 (primary outcome), distress at FU2 and SCN and QOL at FU1 and FU2 were small and non-significant. SC patients were more satisfied with survivorship care than UC patients (significant differences on 10 of 15 items). Conclusions: The addition of SC to UC did not have a beneficial effect on distress, SCN or QOL outcomes but SC patients were more satisfied with survivorship care. Clinical trial information: ACTRN1261000207011.
Comprehensive characterization of cisplatin-related hearing loss in U.S. and Canadian Testicular Cancer Survivors (TCS). First Author: Heather E. Wheeler, Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: Cisplatin is one of the most ototoxic drugs in use, causing multi-sensory hearing loss. Our aim was to characterize cisplatin-related hearing loss in testicular cancer survivors.

Methods: We performed detailed audiometry for 359 patients enrolled in an ongoing multi-center clinical study of cisplatin-based chemotherapy in centers across North America (NCI R01CA157823). Air conduction thresholds were measured at frequencies ranging from 0.25-12 kHz. Tinnitus and hyperacusis were also assessed.

Results: Median age at evaluation was 39 years (range 20-63 years) with approximately 43% previously having seminomas and 57% non-seminomas. Among those exposed to cisplatin, 90% had at least one ear with hearing loss (≥ 20 dB) at any frequency. Approximately 40% had hearing loss (≥ 40 dB) at any frequency. Tinnitus and hyperacusis were reported by 40% and 10% of patients, respectively.

Conclusions: Cisplatin-induced ototoxic phenotypes affect 29-40% of TCS in this North American study. Future analytic investigations will focus on genetic and mechanistic investigations to facilitate the development of predictive, management, and preventive efforts for ototoxicity in high-risk patients.
Background: Weight loss among overweight and obese breast and colorectal cancer survivors is hypothesized to be associated with improved disease-free survival. Phase III trials are needed to test effective and implementable weight loss interventions in breast and colorectal cancer survivors. Methods: We conducted a feasibility study of a 12-month community-situated physical activity and telephone-based dietary change weight loss intervention in female breast and colorectal cancer survivors. We report the primary outcomes for the breast cancer (BC) cohort. Sedentary postmenopausal women with prior Stage I-III BC and BMI ≥ 25 kg/m² were eligible. Primary objectives were to assess feasibility and weight loss at 12 months. Target accrual was 25 BC participants (ppts). Ppts were assigned a telephone counselor and given a 12-month membership to a local Curves fitness center, which offers a 30-minute circuit-based exercise program. Ppts were counseled 14 times over 12 months and were instructed to exercise 150 minutes/week, walk 10,000 steps/day, and decrease caloric intake by 500 kcal/day. The intervention would be considered feasible if full accrual was met within 10 months, ≥ 68% of ppts met minimum goals for exercise (attend ≥ 2 exercise sessions/week for ≥ 36 weeks) and diet (reduce caloric intake by ≥ 100 kcal/day and/or increase fruit/vegetable intake by ≥ 1 serving/day) (adherence), and ≥ 68% of ppts provided anthropometric measures at 12 months (retention). Results: Among 25 evaluable ppts, median age was 57.3 years with median BMI 37.5 kg/m² (range 27.7-54.6), 64% Stage I, and median 2.1 years from diagnosis. Accrual occurred in 10 months, 80% of ppts provided anthropometric measures at 12 months, 96% of ppts met the diet goal, and 28% of ppts met the exercise goal. Thus, feasibility goals were met, with the exception of exercise adherence as defined a priori. At 12 months, average weight loss was 7.6% (95% CI -3.9%, 19.2%) with median weight loss of 7.1%. Conclusions: It is feasible to recruit and retain BC survivors in a multicenter weight loss trial using dietary change plus physical activity to achieve clinically meaningful weight loss over 12 months. Clinical trial information: NCT01453452.
Prevalence of hypogonadism in patients with previously treated germ cell tumors. **First Author:** Trent James Miller, Indiana Univ, Indianapolis, IN

**Background:** The vast majority of men with germ cell tumors (GCT) will be cured of their disease and may face long-term risks associated with survivorship. This may include hypogonadism (HG), which can be associated with depression, fatigue, and a lower quality of life (QOL). It is thus important to identify the prevalence of HG and correlation with symptoms in survivors of GCT, both in patients treated with platinum combination chemotherapy (PCC) as well as chemo-naïve patients. **Methods:** Patients treated with chemotherapy (Group 1) or with orchidectomy and/or surgery or radiotherapy for GCT (Group 2), were 18-50 yrs of age, and not receiving supplemental testosterone at baseline were eligible. Total testosterone was measured at baseline and at 3, 6, and 12 mos. Either A.M. and P.M. lab draws were done depending upon time of patient follow-up. HG was defined as a serum testosterone < 300 ng/dl. Cancer diagnosis and treatment variables were obtained from medical records. Patients completed a validated health questionnaire at baseline, 3, and 6 mos.

**Results:** We evaluated 172 patients treated for GCT. The overall prevalence of HG at baseline was 49.4% (95% CI 41.9-57.0). In Group 1 (N = 103), prevalence was 51.5% (95% CI 41.7-61.2). In Group 2 (N = 69), prevalence was 46.4% (95% CI 34.5-58.3). Overall prevalence of HG was not statistically different between the two groups (p = 0.5371). Within Group 1, there was no difference in prevalence of HG when patients were divided into those who received < 3 cycles of PCC, 3 cycles of PCC, > 3 cycles of PCC, or salvage chemotherapy (p = 0.8131). Overall, compared to patients with testosterone ≥ 300, patients with baseline testosterone < 300 reported worse perceived general health (p = 0.0003) and worse sleep quality (p = 0.0344), but no statistically significant difference in depression (p = 0.3131) or fatigue (p = 0.0622).

**Conclusions:** The overall prevalence of HG is higher than would be expected in the general population. Testosterone levels are lower in the P.M., so the prevalence may have been artificially high due to P.M. as well as A.M. lab draws. There was no difference between the prevalence of HG between the two groups. HG can be a potential cause of medical and psychological distress if not recognized and treated.

Cardiac care after myocardial infarction in cancer survivors: A population-based study. **First Author:** Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

**Background:** Cancer survivors (CS) may receive suboptimal non-cancer related care, such as lower rates of bypass surgery after myocardial infarction (MI) when compared to non-cancer patients (NCP). **Methods:** All acute MI patients (pts) hospitalized in Ontario between 1999 and 2012 were identified from the Canadian Institute of Health Information databases, and linked to the Ontario Cancer Registry to determine whether they were CS or NCP. Those who were diagnosed with cancer < 1 year before their MI were excluded. The cohort was linked to other administrative databases to determine demographics, comorbidities, cancer risk factors, hospital-based interventions and, for those age 65, outpatient-based medication use. Propensity scores derived from baseline characteristics were used to create a 1:4 (CS:NCP) matched cohort. The use of medications and interventions within the first 90 days of MI, and medication adherence (measured by proportion of days covered [PDC]) within the first year of MI were compared between CS and NCP using matched analyses. **Results:** We identified 102,415 MI pts (CS = 20,483; NCP = 81,932) with 57% male and 86% > age 65. Slightly fewer CS vs. NCP received angiograms (37.4% vs. 38.6%; p = 0.003) and percutaneous coronary interventions (17.0% vs. 17.8%; p = 0.01), but similar CS and NCP received bypass surgery (2.5% vs. 2.6%) and CABG. Pts who were ≥ 65 and active users of the public drug programs with MI < 5 years after cancer diagnosis, fewer CS vs. NCP received ACEi/ARB (67.0% vs. 70.6%; p < 0.001), statins (54.9% vs. 60.0%; p < 0.001), and clopidogrel (27.8% vs. 33.8%; p < 0.001), but the differences for those with MI > 5 years after cancer diagnosis were much smaller (p < 0.01). Similar CS and NCP received beta-blockers and nitrates. Both groups had similar degree of medication adherence, except for ACEi/ARB (PDC: 76.0% [CS] vs. 76.9% [NCP], p = 0.03). **Conclusions:** Slightly fewer CS than NCP received SP after MI, especially for those occurred within 5 years after cancer diagnosis. Further studies are needed to examine the outcome implications of this finding.

**Self-efficacy through survivorship: Results from the LIVESTRONG Cancer Navigation Study.** **First Author:** Bree Hemingway, LIVESTRONG Foundation, Austin, TX

**Background:** With more than 13.7 million cancer survivors in the U.S., two-thirds of whom will live beyond five years post-treatment, creating programs to support survivors can be challenging as their needs evolve through each stage of survivorship. LIVESTRONG Cancer Navigation (LCN) offers services designed to address survivors’ needs at all stages of the cancer experience. Survivors experience new challenges and concerns when they transition from treatment to post-treatment care. We present the results of a LCN research study to describe how clients’ self-efficacy (SE) and needs vary depending on their stage of survivorship. **Methods:** In 2012, researchers studied LCN to determine how well the program enables cancer survivors to manage their health and practical concerns. Participants (n = 1388) completed surveys at intake, two, and six weeks post-intake to measure quality of life outcomes including cancer-related concerns, SE and distress. The SE score is based on three items that assess the individual’s confidence related to: emotional support; communication with their doctor; and making themselves feel better. Participants’ needs were documented at intake and those who completed two or more surveys (63%) were included in the analytical sample (n = 874) and were categorized into three groups: in treatment (60.9%), < 5 years post-treatment (24%) and 5+ years post-treatment (4.5%). **Results:** At all three time points, SE was lowest among individuals who had finished treatment 5+ years ago. Significant differences in the needs of need categories were observed between participants at different stages of survivorship (<p < .0003). Participants in treatment reported the most needs (6.6), followed by participants 5+ years post-treatment (6.3). Participants 5+ years post-treatment reported significantly higher cancer concern scores than participants who had completed treatment < 5 years and had substantial outcome differences in all three groups. **Conclusions:** Findings suggest that SE decreases post-treatment. Understanding the various challenges and type of support survivors need at all stages of survivorship can inform service design in clinical and community-based settings that can continue to support clients into survivorship.

Healthcare plan and provider ratings among cancer survivors. **First Author:** Michael T. Halpern, University of Arizona Coll of Public Health, Tucson, AZ

**Background:** Providing optimal healthcare for cancer survivors is important to address symptoms from cancer and cancer treatment, reduce risks of subsequent cancers, and improve quality of life. However, little is known about patient-level factors influencing ratings of healthcare plans or providers by survivors of cancer. **Methods:** This study uses ratings provided by cancer survivors in the Consumer Assessment of Healthcare Providers and Systems (CAHPS) Medicare Survey linked to data from NCI’s Surveillance, Epidemiology, and End Results (SEER) Program (SEER-CAHPS). CAHPS data on self-reported general and mental health status and three rating categories (overall care, physician [MD], and healthcare plan [HP]) were linked to SEER data on patient sociodemographic and cancer characteristics. **Results:** We identified 23,969 cancer survivors with linked SEER-CAHPS data. Higher self-rated general health was associated with higher ratings for OC, MD, and HP for all included cancer types. However, other factors significantly associated with ratings tended to differ by both rating category and cancer type (see table). Time since diagnosis and type of Medicare plan (FFS vs. HMO) were not significantly associated with any ratings. **Conclusions:** Beyond self-rated general health, survivor characteristics predicting higher ratings varied substantially by cancer and rating type. These results suggest that the experience of care among cancer survivors is diverse and is significantly influenced by their cancer type. Efforts to improve care for cancer survivors will need to be tailored for each survivor group.

**Significant (p < 0.01) predictors of higher (+) or lower (-) CAHPS ratings.**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Overall Care</th>
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<th>Healthcare Plan</th>
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<tbody>
<tr>
<td>OC MD HP</td>
<td>+</td>
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<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>+</td>
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<td>Colorectal</td>
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<td>Prostate</td>
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| Significant (p < 0.01) predictors of higher (+) or lower (-) CAHPS ratings.**

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Using survivorship care plans (SCP) to improve cancer communication and care coordination. First Author: Deborah Mayer, UNC Chapel Hill Lineberger Comprehensive Cancer Center, Chapel Hill, NC.

Background: There is a need for closer collaboration between oncologists and primary care providers (PCP) to improve survivorship care. However, PCPs often feel unprepared to manage survivor care needs. We conducted a pilot study to evaluate SCP +/- a coordinated PCP visit effect on confidence in survivorship care for patients (pt) and PCP. Methods: Pts completed baseline measures and then received a SCP after completing curative treatment during a scheduled post-treatment visit; half were randomized to attend a PCP visit within 30 days to review the SCP. Pre-Post measures for pts and PCPs included Confidence in Survivorship Information (CSI), Assessment of Survivor Concerns (general and cancer worries), Expectations for Care, and Patient Activation Measure. Wilcoxon signed-rank and rank sum tests were used for comparisons. Results: Pts (n = 34) were male (65%), age 57 (29-73), Caucasian (82%), and married (79%). PCPs (N = 30) were male (50%), age 48 (26-67), Caucasian (83%) with 19.5 years in practice (range 2-39); 52% were in family medicine. Patient: After receipt of the SCP, all pts had improved knowledge about next steps (p = 0.06) and less confidence about cancer care; survivors who had a PCP visit after receiving the SCP had fewer worries than controls. PCP also had improved confidence in survivorship care after SCP receipt. Clinical trial information: UNC HENC LCCC 1325.

9582 Poster Session (Board #241), Sat, 1:15 PM-4:45 PM

Degradation of extracellular matrix measured in serum for predicting mortality risk in women diagnosed with cancer: The Prospective Epidemiology, Comorbidity, Risk Factor (PERF) I study. First Author: Nicholas Willumsen, University of Southern Denmark, Odense, Denmark.

Background: Extracellular matrix (ECM) turnover mediated by matrix metalloproteinase (MMP) has been speculated to be associated with cancer diagnosis and mortality. No tools have so far been able to quantify this. Degradation of ECM is part of the malignant changes that drives cancer. The most abundant ECM protein is type I collagen. MMP mediated degradation of type I collagen in serum protein is type I collagen. MMP mediated degradation of type I collagen in serum is associated with cancer diagnosis and mortality risk in women diagnosed with cancer: The Prospective Epidemiology, Comorbidity, Risk Factor (PERF) I study. Demographics and serum samples were collected at time of enrollment. Cancer diagnoses, cause and time of death were collected from Danish registries until 2014. Serum C1M levels were assessed by ELISA and divided into quartiles (Q1-Q4). Hazard ratios (HR) for all-cause and cancer-specific mortality were determined by Cox-regression analysis and adjusted for common risk factors: age, smoking, alcohol intake, exercise and BMI. Women deceased +3 years after enrollment was excluded from analysis. Results: Within 3 years from PERF I enrollment subjects with high serum C1M levels at baseline showed significant increased mortality (see Table). The 3-year HR for all-cause mortality and cancer-specific mortality was >2 when comparing Q1 to Q4 for all women. Women diagnosed with cancer (n = 1280) had an HR for all-cause mortality of >2.5 compared to intervention women. Adjusting for smoking and confounders did not change this significance. Conclusions: MMP-mediated degradation of the ECM was predictive of cancer mortality by 2.3 fold, and predicted for mortality for cancer patients with >2.5 fold within 3 years of follow-up.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All</th>
<th>With cancer diagnosis</th>
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<tbody>
<tr>
<td>Mortality n, total</td>
<td>4010</td>
<td>4010</td>
</tr>
<tr>
<td>n, death within 3 years from enrollment</td>
<td>1320</td>
<td>1260</td>
</tr>
<tr>
<td>HR (95% CI), C1M Q4 relative to Q1, p-value</td>
<td>2.08 (1.30-3.33), 2.31 (1.27-4.19), 2.59 (1.45-4.63), p = 0.0024, p = 0.0064, p = 0.0014</td>
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9583 Poster Session (Board #242), Sat, 1:15 PM-4:45 PM

Outcomes and predictors of hospital mortality in metastatic cancer patients receiving life sustaining treatments (LSTs). First Author: Kah Polh Loh, Baystate Med Ctr, Springfield, MA.

Background: Hospital mortality for patients with metastatic cancer is high, especially for those who receive LSTs. Information on predicting the probability of surviving the hospitalization will help patients and clinicians make an informed decision. Methods: We used the 2010 California Healthcare Cost and Utilization Project - State Inpatient Database to identify metastatic cancer patients (≥18 years). Using ICD-9-CM diagnosis codes, we limited the dataset to patients receiving LSTs (mechanical ventilation, tracheostomy, PEG tube, TPN and acute use of dialysis). We described characteristics and outcomes in patients who survived hospitalization and who did not. We used multivariate logistic regression models to identify predictors for hospital mortality. Results: We identified 9,438 admissions among metastatic cancer patients who received LSTs. Mean age (65 years) and gender distribution were similar in both groups. Hospital mortality was 33%. Of those who survived, 31% were discharged to acute or post-acute facilities. Other outcomes are listed below. Predictors of hospital mortality included non-white race, unscheduled admissions, infectious; cardiovascular and circulatory or pulmonary diagnosis (vs. cancer-related) and greater burden of comorbidities. Comorbidities including ESRD (OR 2.03, 95% CI 1.12-2.94) and liver disease (OR 1.94 95% CI 1.55-2.33) were significantly associated with hospital mortality. Compared to lung cancer, colorectal (OR 0.32, 95% CI 0.26-0.38) and GU (OR 0.39, 95% CI 0.24-0.58) cancers were less likely to die in the hospital. Admissions with DNR status were strongly associated with hospital mortality (OR 2.32, 95% CI 2.01-2.63). Conclusions: Patients with metastatic cancer who survived in the hospital had longer LOS and one-third of them were discharged to facilities. Hospital mortality outcomes predict LST, ESRD, liver disease, DNR status, higher co-morbidity score and an unscheduled admission.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Died (n = 3055) Alive (n = 6273)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Comorbidity score*</td>
<td>3.1 (2.3) 2.5 (2.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total charge per patient (in $100,000)</td>
<td>1.5 (2.1) 1.5 (1.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of stay* (days)</td>
<td>13.4 (17.0) 15.5 (14.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a Mean (SD), b Median (IQR).
Supradiaphragmatic RT most strongly increased this risk. SMN and/or CVD rising to 73% after 40 years from initial treatment. High disease burden during follow-up, with the cumulative incidence of RT was associated with a strongly increased (HR: 4.4, 95%CI: 2.6-7.7) risk events. Both supradiaphragmatic RT (Hazard Ratio [HR]: 2.6, 95%CI: 3.2-3.9 and 6.8-8.8), resulting in 83 and 60 excess cases/10,000 person-years. After 40 years, at a median attained age of 60 years, the SIRs of CHD and HF were 3.5 and 7.8, respectively (95%CI: 2.9-3.2-3.9 and 6.8-8.8), resulting in 83 and 60 excess cases/10,000 person-years. The SIRs of CHD and HF were 3.5 and 7.8, respectively (95%CI: 2.9-3.2 and 6.8-8.8), resulting in 83 and 60 excess cases/10,000 person-years.

Background: Hodgkin lymphoma (HL) survivors are at increased risk to develop late treatment-related complications, including second malignant neoplasms (SMNs) and cardiovascular disease (CVD). Research to date has focused on separate risk estimates and therefore, we aimed to assess the combined risk of developing SMN and/or CVD. Methods: Our multicenter cohort comprised 2,450 5-year HL survivors, treated between 1965 and 1995. CVD endpoints (coronary heart disease (CHD), cardiomyopathy and congestive heart failure (HF), and valvular heart disease) were assessed through general practitioners. Data on SMN were derived from linkage with the Netherlands Cancer Registry. Standardized incidence ratios (SIRs) were estimated to compare SMN and CVD risk with the general population. Cumulative incidences of SMN and/or CVD were calculated with death from other causes as competing risk. Treatment-specific risks of developing SMN and/or CVD were quantified using Cox regression analysis. Results: After a median follow-up of 22 years, we identified 874 SMNs and 1368 CVDs. 1246 patients developed ≥1 major event, of whom 276 developed both SMN and CVD. HL survivors had a 5.2-fold increased SIR of any SMN (95%CI: 4.8-5.6), compared to the general population, corresponding to 141 excess cases/10,000 person-years. The SIRs of CHD and HF were 3.5 and 7.8, respectively (95%CI: 3.2-3.9 and 6.8-8.8), resulting in 83 and 60 excess cases/10,000 person-years. After 40 years, at a median attained age of 60 years, the cumulative incidence of SMN or CVD was 73.3% (95%CI: 70.6-75.7), whereas 22.5% (95%CI: 19.8-25.3) of patients had developed both events. Both supradiaphragmatic RT (Hazard Ratio [HR]: 2.6, 95%CI: 2.1-3.1) and age at diagnosis (HR: 1.5, 95%CI: 1.3-1.7) independently increased the risk of SMN and/or CVD. Supradiaphragmatic RT was associated with a strongly increased (HR: 4.4, 95%CI: 2.6-7.7) risk of developing both SMN and CVD. Conclusions: HL survivors experience a high disease burden during follow-up, with the cumulative incidence of SMN and/or CVD rising to 73% after 40 years from initial treatment. Supradiaphragmatic RT most strongly increased this risk.

QOL at 3 years after diagnosis in aggressive lymphoma survivors. First Author: Carrie A. Thompson, Mayo Clinic Rochester, Rochester, MN

Background: Patients with aggressive lymphoma are potentially curable, but longer-term effects of treatment may adversely impact quality of life (QOL). We examined QOL scores at baseline enrollment and 3 year follow-up in survivors of aggressive lymphoma. Methods: Newly diagnosed lymphoma patients were prospectively enrolled within 9 months of diagnosis in the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource (MER) and systematically followed. We measured baseline QOL at time of enrollment and at 3 years after diagnosis with the Functional Assessment of Cancer Therapy-General (FACT-G) scale. This scale measures well-being (WB) in 4 QOL domains—physical (PWB), social/family (SWB), emotional (EWB), functional (FWB)—along with a total FACT-G score (TOT). For this study, we defined “survivor” as alive at 3 year follow-up with no active treatment or treatment within the previous year. Results: From 2002-2005, 1902 patients with aggressive lymphoma were prospectively enrolled. Of these, 477 completed QOL questionnaires at both baseline and 3 years and met the study definition of survivor. Median age at diagnosis was 62 years (range 18-87) and 58% were male. Distribution of NHL subtypes were 61% DLBCL, 12% mantle cell, 10% FL grade III, 9% T cell, and 8% other. Each FACT-G subscale was significantly higher than assessment at diagnosis with the exception of SWB, which was significantly lower (all p<0.0001), with mean changes ranging from -1.8 (SWB) to 7.0 (TOT) points. After adjusting for baseline QOL, there was a modest association between older age and a smaller change from baseline in PWB (p=0.012), and FWB (p=0.001); otherwise there were no other clinical associations between change in TOT from diagnosis to 3 years (all p>0.11). Compared to the US general population, 3-year survivors have significantly higher QOL (EWP p=0.039, all other p<0.0001), while their QOL at baseline was similar to the general population for PWB (p=0.59), higher for SWB (p<0.0001) and TOT (p=0.0033), and lower for FWB (p=0.0003) and EWB (p<0.0001). Conclusions: In survivors of aggressive lymphoma, QOL improves over time and is higher than the QOL for the US general population at 3 years post-diagnosis.

QOL at 3 years after diagnosis in aggressive lymphoma survivors. First Author: Carrie A. Thompson, Mayo Clinic Rochester, Rochester, MN

Employment and quality of life (QOL) in human papillomavirus-related (HPV+) oropharynx cancer treated with definitive chemohormonal therapy (CRT). First Author: Shrija S. Baxi, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HPV+ oropharynx cancer affects younger patients and is often treated with CRT. We aimed to assess the impact of CRT on employment and QOL in these patients. Methods: We completed a cross-sectional survey of clinically cancer-free patients with advanced, M0, HPV+ oropharynx cancer ≥1 year from primary CRT. We assessed employment status using standardized specific items. QOL was measured using the EQ5D and EQV2-D and EORTC QLQ-HN35. We examined the association between sociodemographic and clinical factors on employment outcomes and QOL at time of survey. Results: 129 patients (mean 23 months, post-CRT) completed the survey. Median age was 57 years (range 25-76); 91% were male, 56% had an ECOG functional status score of 0 (61/2); 83% had stage IVA disease. High-dose cisplatin was the most common chemotherapy (63%), 53% reported at least one problem on the EQ5D, most commonly pain (29%) and anxiety (24%). Despite high rates of dry mouth (88%), thick saliva (69%), coughing (54%) patients reported high overall QOL, as measured by EQ-5D. At diagnosis, 107 (83%) patients were employed including 23/23, 58/65 and 26/41 of patients ages < 50, 50-59, and > 60 years, respectively (p<0.001); 80% were professionals or managers. Employment at diagnosis did not vary by pretreatment functional status. During CRT, 10 (9%) stopped working and did not return, 74 (69%) took time off but were able to return to work, 15 (13%) were unable to return to work, and 3 (3%) continued working. Of the 74 patients who took time off, median time to return to work was 14 weeks (interquartile range 8-24 weeks). There was no significant difference in time off by chemotherapy type, ECOG status, or age. At time of survey, 75% were employed. Current employment status did not vary by overall QOL at the time of survey. Conclusions: Despite persistent effects of CRT, survivors of HPV+ oropharynx cancer reported good QOL. CRT interrupted employment in the majority of these patients, but most returned to work. More efforts are needed to evaluate the determinants of employment, return to work and the socioeconomic burden of CRT in this working-age population.
Young and strong: A randomized study to improve care for young women with breast cancer. First Author: Ann H. Partridge, Dana-Farber Cancer Institute, Boston, MA

Background: Research has revealed that needs of young women with breast cancer are not being met, particularly fertility concerns. A QOP audit found rates of attention to fertility of < 30% in practices. We conducted a cluster-randomized study to determine the effect of an exportable education and support intervention for young women with breast cancer (YW1) and their oncologists. Methods: Sites were randomized 1:1 to YWI or a physical activity intervention (PAI) stratified by academic or community. Up to 15 women aged 45 with newly diagnosed breast cancer were enrolled at each academic site, 10 at community sites. The primary endpoint was attention to fertility prior to systemic treatment by medical record review. Pts were surveyed at 3, 6, and 12 mos; physicians surveyed after enrolling their first patient. The study was designed to have 80% power to detect an improvement in attention from 10% with PAI to 38% with YWI using General Estimating Equations, two-sided alpha = 0.05. Results: 467 patients across 54 sites (14 academic, 40 community) enrolled between 7/2012 - 12/2013. Median age at dx was 40yrs (range 22-45); patient characteristics did not vary by arm. Attention to fertility by 3 mos after enrollment was observed in 55% YWI pts and 58% on PAI (p = 0.88). Rates were strongly correlated with age (p < 0.0001), highest in pts < 30 (100% YWI, 94% PAI) vs. 30-40 (68% YWI, 59% PAI) vs. 40-45 (42% YWI, 52% PAI) although interaction testing age x intervention was not significant (p = 0.12). At 3 mos, pts rated YW1PAI as valuable in educating them (64% YWI, 63% PAI). Of responding providers (145/171, 85%), most reported YW1/PAI educated providers (55% YWI/51% PAI) and pts (79% YWI, 77% PAI), and improved care (79% YWI, 60% PAI). Conclusions: This study failed to show improvement in attention to fertility with YWI vs. PAI. Rates were high in both arms, especially in women < 40, and the study had limited power to detect an age-dependent effect. Pts and providers valued both interventions. This work serves as a novel model to educate and support patients and providers to improve care. Clinical trial information: NCT01647607.

A feasibility study of an electronic interface between Internet-based survivorship care plans and electronic medical records (EMR)/tumor registries. First Author: Christine Hill-Kayser, University of Pennsylvania, Philadelphia, PA

Background: SCP are recommended for all cancer survivors by the Institute of Medicine and Commission on Cancer (CoC). Barriers to implementation include time/ resource limitations, survivor access, and concerns about accurate treatment summary information. This study was performed to evaluate the feasibility of interface development between an SCP and an EMR and cancer registry. Methods: An information technology (IT) application was developed to extract data from the EMR in use at Penn Medicine (EPIC), as well as from the registry at Baptist Memorial Hospital in Memphis, a community hospital utilizing the CoC Rapid Quality Reporting System (RQRS). Data were transferred via XML tunnel to auto-populate an Internet-based tool for creation of SCP (LIVESTRONG Care Plan) that had been previously used for creation of more than 35,000 plans and available at www.oncolink.org / www.livestrongcareplan.org. Results: Design phase involved IT staff at Penn Medicine, RQRS, and OncoLink. Data (demographics, surgeries, chemotherapy drugs, radiation site) were extracted from EMR/RQRS, de-identified, and tunneled to the OncoLink platform, without transfer of PHI. Care plans were created and linked to EMR/registry via global unique identifiers; after auto-population and creation, SCP were tunnelled back to the EMR to become part of the medical record, with the entire process occurring less than one minute. During clinical testing at the EMR site, SCP were created by nurse practitioners during scheduled clinic visits. Overall, 147 survivors were screened, 146 eligible, and 89 received SCP. Of these, 60 received breast cancer SCP, 27 colorectal SCP, and 2 both. Survivors were 85% women, 58% Caucasian, median age 56y (24-81y). Conclusions: This is a feasible and rapid solution for the auto-population of SCP with EMR and/or registries, taking less than 1 minute to complete. It represents a future methodology through which widespread implementation of SCP may be undertaken. Future directions include further clinical testing, as well as assessment of provider perceived usefulness, ease of use, and integration into routine clinical care.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Sexual dysfunction is a serious issue for women with gynecologic cancer. This study examines sexual function following cancer treatment and its impact on marital relationships. Methods: A multi-institutional study of women with gynecologic cancer was conducted with a 181-item survey of instruments to assess sexual/marital dysfunction. Sexual dysfunction was measured by change in the Female Sexual Function Index (FSFI). A significant decline in sexual function was determined to be a 5-point decrease using a Reliable Change Index Statistic (RCIS). Marital relationships were assessed using Intimate Bond Measure (IBM). Standard statistical analyses were used. Results: A total of 290 women were enrolled. Cancer diagnoses included uterine/endometrial (41%), ovarian (37%) cancers. Treatment included surgery (92%), chemotherapy (62%), and radiation (30%). Among all women, sexual function declined from a score of 23.2 ± 11.2 prior to diagnosis to 15.2 ± 10.2 after treatment (P < 0.001) and sexual activity decreased from 6.1 ± 6.8 to 2.6 ± 4.9 times/month following treatment (P < 0.001). Sexual dysfunction after treatment was associated with younger age (51.8 ± 12.2 to 97.3 ± 12.1; P = 0.004), being premenopausal (27% vs 13.5%, OR 2.38, 95% CI 1.23-4.71), chemotherapy (69.8% v 51.9%, OR 2.05, 95% CI 1.10-3.84), and being in a committed relationship (97.3% vs 82.7%, OR 7.43, 95% CI 1.67-33.11). IBM scores, relationship length, surgery and radiation therapies, cancer site diagnosis/stage and race were not associated with sexual dysfunction. Women with sexual dysfunction reported decreased sexual activity (ΔS = 4.8 vs ΔS = 3.8; P < 0.001) and increased relationship counseling, 13.7% vs 4.9%, (OR 3.11, 95% CI 1.02-9.53) compared to those with no impairment. Conclusions: Women with gynecologic cancer are at significant risk for sexual dysfunction. Young, premenopausal women, chemotherapy, and women in committed relationships are at particularly risk for these issues. Patients with sexual dysfunction reported greater decline in sexual activity and sought counseling following treatment. Practitioners should address these issues and engage patients during treatment.

A phase II randomized, double-blind, placebo-controlled trial to evaluate naldemedine for the treatment of opioid-induced constipation (OIC) in patients with cancer pain. First Author: Narikazu Boku, St Marrianna University School of Medicine, Kawasaki, Japan

Background: While opioid analgesics play a central role in managing cancer pain, opioid-induced constipation (OIC) is one of the most common side effects. Opioid analgesics are typically given to patients with cancer pain, and they can cause constipation. This study evaluated naldemedine, a medication that can help relieve constipation, in patients with cancer pain. Methods: This study assessed naldemedine doses of 0.1, 0.2, or 0.4 mg once-daily (QD) for 2 weeks in cancer patients with OIC. Eligibility criteria included: regular opioid use for ≥ 2 weeks, ≤ 5 spontaneous bowel movements (SBMs) during a 14-day screening period despite laxative use. The primary endpoint was the change from baseline in frequency of SBM/week during the 2-week treatment period. The SBM responder rate was defined as ≥ 3 SBM/week and an increase from baseline of ≥ 1 SBM/week, was a secondary endpoint. Safety assessments included adverse events (AEs), Clinical Opiate Withdrawal Scale (COWS) questionnaire, and 11-point Numerical Rating Scale (NRS) pain questionnaire. Patients scored bowel movement (BM) consistency using the Bristol Stool Scale; BMs with a score of 2 were to be recorded. The primary analysis was conducted using ANCOVA with frequency of SBM/week at baseline as a covariate. The planned total sample size was 212 (53 per group) to ensure at least 80% power in the two-sample t-test with a level of significance of 0.05 (two-sided). Results: A total of 227 patients were randomized to one of three naldemedine doses or placebo (N = 227). The change from baseline in frequency of SBM/week was 1.50 for PBO, 3.43 for 0.1 mg (P = 0.0465), 4.75 for 0.2 mg (P = 0.0007), and 7.29 for 0.4 mg (P < 0.0001). All three groups demonstrated a significantly higher SBM responder rate vs. PBO. The most common AE was diarrhea (25.0%, 26.8%, 39.7% and 51.8% in PBO, 0.1%, 0.2%, 0.4 mg groups, respectively). Most AEs of diarrhea were mild. No clinically meaningful changes in NRS scores or COWS scores were observed. Conclusions: In this study nalde medine was effective and generally well tolerated in patients with cancer pain with OIC. Based on its efficacy and safety profile, 0.2 mg QD was selected as the dose for phase 3 studies. (Clinical trial information: JapicCTI-111510) Clinical trial information: JapicCTI-111510.

Can pregabalin prevent paclitaxel-associated neuropathy?: A pilot trial. First Author: Shivani S. Shinde, Mayo Clinic, Rochester, MN

Background: Paclitaxel, a commonly used chemotherapeutic drug, can cause an acute pain syndrome (P-APS), considered to be an acute form of neuropathy, and chronic chemotherapy-induced peripheral neuropathy (CIPN). There are no good means to prevent and/or treat these prominent clinical problems. The purpose of this randomized, placebo-controlled, double-blinded pilot study was to obtain pilot data to support or refute the utility of pregabalin for the prevention of P-APS and CIPN, based on anecdotal reports suggesting that gabapentinoids were helpful in this setting. Methods: Patients scheduled to receive adjuvant weekly paclitaxel (80 mg/m²/dose) were randomized to receive pregabalin 75mg or a placebo, twice daily, starting on the first night of chemotherapy and continuing during the 12 weeks of chemotherapy. Patients completed the EORTC OLCIPN20 questionnaire at baseline, prior to each dose of paclitaxel, and monthly for 6 months post treatment. Patients completed an acute pain syndrome questionnaire daily, for 6 days after each dose of paclitaxel. The primary endpoint was to determine the effect of pregabalin on the maximum of the worst acute pain scores for the week following paclitaxel administration for cycle 1. Secondary endpoints included the effect of pregabalin on paclitaxel-induced peripheral neuropathy and pregabalin-associated toxicities. Results: 46 patients were randomized; data regarding the acute pain syndrome and CIPN are presented in the Table. There were no differences in pain score or evidence of toxicity between the two study arms. Conclusions: The results of this pilot trial do not support that pregabalin is helpful for preventing P-APS or paclitaxel CIPN. Clinical trial information: NCT01637077.

P-APS (Pain score over 6 days following initiation of paclitaxel; higher scores are worse)

<table>
<thead>
<tr>
<th>Placebo (N = 22)</th>
<th>Pregabalin (N = 19)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Pregabalin</td>
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<tr>
<td>Worse pain: Mean (SD)</td>
<td>2.9 (3.2)</td>
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<tr>
<td>Average pain: Mean (SD)</td>
<td>2.2 (2.6)</td>
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<tr>
<td>EORTC CIPN20 Sensory Neuropathy (higher scores represent fewer symptoms)</td>
<td>Placebo</td>
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<td>Pregabalin</td>
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<tr>
<td>Mean (SD)</td>
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<td>Median (Range)</td>
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526s Patient and Survivor Care
9596 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM

Predictors of hand-foot syndrome (HFS) in randomized double-blind, placebo-controlled trial of pyridoxine for prevention of capcitabine-induced HFS. First Author: Sun Yan, National Cancer Centre Singapore, Division of Medical Oncology, Singapore, Singapore

Background: Hand-foot syndrome (HFS) is a common side effect of capcitabine, although East Asian patients appear to have better tolerability. Methods: This study aimed to evaluate the incidence of grade ≥ 2 HFS in patients receiving pyridoxine versus placebo (primary objective), compare the time to onset of grade ≥ 2 HFS, and identify biomarkers predictive of HFS, including baseline folate and vitamin B12 levels, plus genetic polymorphisms (secondary objectives). Patients starting capcitabine single-agent chemotherapy for breast, colorectal and other cancers in National Cancer Centre Singapore were randomized to receive concurrent pyridoxine (200mg) or placebo daily for a maximum of 8 cycles of capcitabine, with stratification by gender and use in adjuvant/neoadjuvant versus palliative setting. Patients were withdrawn from the study upon development of grade ≥ 2 HFS or cessation of capcitabine. Results: The trial was terminated before reaching the original target of 296 patients due to slow accrual. Grade ≥ 2 HFS occurred in 33 of 105 patients (31.4%, 95% CI: 22.6% - 40.3%) receiving pyridoxine compared to 39 of 103 patients (37.9%, 95% CI: 28.5% - 47.2%) receiving placebo (p = 0.329). The median starting dose of capcitabine was 1000mg/m² (range 793-1250 mg/m²) bid in the pyridoxine arm, and 1011mg/m² (range 845-1250 mg/m²) bid in the placebo arm (p = 0.667). The median time to onset of grade ≥ 2 HFS was not reached in patients on pyridoxine, compared to 174 days in patients on placebo (p = 0.677). On multivariate analysis, baseline serum folate (odds ratio 1.27 for every increase of 5nmol/l; 95% CI: 1.10-1.47; p = 0.001) was associated with increased risk of grade ≥ 2 HFS. Pyridoxine did not significantly decrease the risk compared to placebo (odds ratio 0.50; 95% CI: 0.17-1.63; p = 0.329). Initial dose intensity and baseline red cell folate were associated with increased risk of grade ≥ 2 HFS on univariate, not multivariate analysis. Genotyping with Zhonghua SNP arrays is in progress. Conclusions: Pyridoxine did not significantly prevent or delay the onset of grade ≥ 2 HFS. Serum folate was a significant predictor of HFS. Clinical trial information: NCT00486213.

9599 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM

Palonosetron or granisetron for prevention of CINV in patients with breast cancer receiving dexamethasone and fosaprepitant following anthracycline plus cyclophosphamide (AC) regimen. First Author: Koji Matsumoto, Hyogo Cancer Center, Akashi-shi, Japan

Background: Superiority of palonosetron to granisetron is uncertain, for patients with breast cancer receiving both steroid and NK1 inhibitor against CINV caused by AC regimen. Methods: This double-blind active-controlled study. 341 chemo-naïve patients treated during H11001 chemotherapy-naïve pts randomized to NEPA (palonosetron 0.025mg; placebo 0.01mg daily for a maximum of 8 cycles of capecitabine, with stratification by gender and use in adjuvant/neoadjuvant versus palliative setting. Patients were withdrawn from the study upon development of grade ≥ 2 HFS or cessation of capcitabine. Results: The trial was terminated before reaching the original target of 296 patients due to slow accrual. Grade ≥ 2 HFS occurred in 33 of 105 patients (31.4%, 95% CI: 22.6% - 40.3%) receiving pyridoxine compared to 39 of 103 patients (37.9%, 95% CI: 28.5% - 47.2%) receiving placebo (p = 0.329). The median starting dose of capcitabine was 1000mg/m² (range 793-1250 mg/m²) bid in the pyridoxine arm, and 1011mg/m² (range 845-1250 mg/m²) bid in the placebo arm (p = 0.667). The median time to onset of grade ≥ 2 HFS was not reached in patients on pyridoxine, compared to 174 days in patients on placebo (p = 0.677). On multivariate analysis, baseline serum folate (odds ratio 1.27 for every increase of 5nmol/l; 95% CI: 1.10-1.47; p = 0.001) was associated with increased risk of grade ≥ 2 HFS. Pyridoxine did not significantly decrease the risk compared to placebo (odds ratio 0.50; 95% CI: 0.17-1.63; p = 0.329). Initial dose intensity and baseline red cell folate were associated with increased risk of grade ≥ 2 HFS on univariate, not multivariate analysis. Genotyping with Zhonghua SNP arrays is in progress. Conclusions: Pyridoxine did not significantly prevent or delay the onset of grade ≥ 2 HFS. Serum folate was a significant predictor of HFS. Clinical trial information: NCT00486213.

9597 Poster Session (Board #256), Sat, 1:15 PM-4:45 PM

Should all antiemetic guidelines recommend adding a NK1 receptor antagonist (NK1 RA) in patients (pts) receiving carboplatin (carbo)? Efficacy evaluation of NEPA, a fixed combination of the NK-RA, netupitant, and palonosetron. First Author: Karin Jordan, University of Halle, Halle, Germany

Background: Controversy continues whether a NK1RA should be added to a 5HT3RA + dexamethasone (DEX) in pts receiving carbo, with inconsistent guideline recommendations by NCCN, ASCO, and MASCC/ESMO. It is routinely to use a NK1RA for pts receiving cisplatin where a 12%-20% benefit is seen. A subset analysis in 192 pts receiving carbo in a 2009 randomized trial (Rapopt, Singapore) indicated a 14% benefit in pts receiving a NK1RA as part of triple antiemetic therapy (no emesis rate: 84%; 95% CI 77-91% versus 70%, 95% CI 59-79% with 2 drugs, p < 0.02). Similar results were seen in other trials. We undertook this post-hoc subset analysis of pts receiving carbo as part of a NEPA Phase 3 trial to determine if NEPA would show a consistent complete response (CR: no emesis/rescue) rate and to examine nausea control. Methods: 192 patients (pts) randomized to NEPA + DEX (n = 92) or aprepitant (APR) + PALO + DEX (n = 51) received carbo in cycle 1. CR and no significant nausea (NSN: score ≤25 on 100mm visual analog scale) rates were calculated for all pts and by gender/age for NEPA pts over multiple cycles. Results: The overall (0-120h) CR rates for cycles 1-4 were similar for NEPA (80%, 91%, 92%, and 93%) and APR (82%, 88%, 88%, and 90%). Cycle 1-4 NSN rates were also similar (NEPA 84-96%; APR 82-90%). In the NEPA pts, 54% had lung cancer and 21% ovarian; cycle 1 overall CR rates were 77% / 77%, respectively. NEPA results by risk groups are in the Table. Conclusions: This subset analysis of pts receiving carbo shows consistent 5-12 CR rates with an added NK1RA in this and historical studies; additionally, it documents high control rates of nausea with NEPA even in women and younger pts. Given the consistency of the control rates for added NK1RAs, as seen for NEPA and APR, guideline groups and practitioners should consider giving a NK1RA antiemetic in pts receiving carbo. Clinical trial information: NCT01376297.

9598 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM

Use of mobile device technology to collect patient-reported symptoms during radiotherapy for head and neck cancer: A prospective feasibility study. First Author: Aaron David Falchuck, NC Cancer Hospital, Chapel Hill, NC

Background: Accurate assessment of toxicity allows for timely delivery of necessary supportive measures during radiotherapy (RT) treatment for head and neck cancer. The purpose of this prospective trial is to evaluate the feasibility of using mobile device technology to collect daily patient reported symptoms. Methods: A HIPAA-secure mobile application was developed to allow patients receiving RT for head and neck cancer to report symptom severity in five domains (fatigue, pain, nausea/vomiting, decreased appetite, anxiety) using the Patient Reported Symptom Monitoring System questionnaire. Patients were asked to report symptoms using a smartphone and/or tablet at least once daily during treatment or more often as needed. Patient surveys regarding use of mobile devices were obtained after completion of RT. Descriptive statistics, linear regression, and Fisher’s exact test were used to examine factors associated with symptom reporting. Results: 22 patients enrolled and 1 withdrew consent. A total of 921 symptom reports were collected during treatment. Median treatment duration was 45.5 days (interquartile range [IQR] 42-49). The median number of reports submitted per patient was 33.5 [IQR 21-54]. Median reporting compliance (defined as number of days with report / duration between enrollment and end of RT) was 71% [IQR 44-81]. There were no significant associations between reporting compliance and patient characteristics or symptom severity. Timing of symptom reporting is summarized (Table). Patients reported high levels of satisfaction with use of mobile devices to report symptoms. Conclusions: It is feasible and convenient for patients to use mobile devices to continuously report symptoms throughout an entire course of RT for head and neck cancer, including nights and weekends. Future studies will evaluate the impact of mobile device symptom reporting on improving patient outcomes.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Association of severe pain with poor response to opioids, psychological distress, and aberrant drug taking behaviors in a large cohort of cancer patients. First Author: Vinnydhy Dave, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pain is one of the most feared consequences of cancer. Systematic reviews indicate opioids are effective for cancer pain, but are often underutilized. At the same time, there is increased societal concern about opioid abuse. Identifying patients with a history of cancer who are at risk for poor pain outcomes is important when considering opioid therapy. The aim of this study was to evaluate associations between pain intensity, analgesic effectiveness, disability, distress and aberrant drug taking in the subpopulation from Memorial Sloan Kettering Cancer Center of a pain clinic registry. Methods: At each outpatient encounter, patients completed the Brief Pain Inventory, Condensed Measure (COMM) was also completed and Current Opioid Misuse Measure (COMM). Though not yet validated in patients with cancer, in other chronic pain populations a COMM score greater than 9 has a positive likelihood ratio for diagnosing opioid misuse/abuse of 3.5. Data analysis performed by International Severity Information Systems, Salt Lake City, UT. Results: From 6/1/2011 to 12/10/2014, 1593 of 2085 (76.4%) patients completing 5995 surveys reported continuing pain despite taking opioids. Average pain score was mild (1-4) in 25%, moderate (5-6) in 41%, severe (7-10) in 34%. Those with severe pain reported less relief from their pain medication, were more disabled (higher pain interference), and had more physical and psychological distress and higher COMM scores (see Table, all p values < 0.001). Conclusions: Ambulatory patients with a cancer history who report severe pain despite taking opioids are a challenging management problem. These data suggest they have concomitant disability, physical, and psychological distress, and behaviors suggestive of opioid misuse/abuse. To improve their outcomes, more research is needed to understand the causal links between these associations.

Safety and efficacy of eltrombopag (EPAG) vs placebo (PBO) for treatment of chemotherapy (CTx)-induced thrombocytopenia (TCP) in patients (Pts) with hematologic or solid tumors receiving gemcitabine (GEM)-based CTx: A phase 2 study. First Author: Eric S. Winer, Rhode Island Hospital, Providence, RI

Background: A phase 1 EPAG study showed favorable results for the treatment of CTx-induced TCP in pts receiving GEM-based CTx. Methods: This was a phase 2, blinded, PBO-controlled, multicenter study in adults with solid tumors and TCP receiving 4-6 cycles of CTx. Pts received GEM on days 1 and 8 (every 21 days) and cisplatin on day 1 (or divided dose on days 1 and 8) or carboplatin on day 1, or received GEM alone on days 1, 8, and 15 (every 28 days). Pts were randomized (2:1) to EPAG 100 mg or PBO, daily, starting day 1 before and after each course of CTx. Results: We report early results of 44 pts randomized to EPAG (n = 31) or PBO (n = 13). Data review with an external, independent physician after 2 cycles showed no safety concerns. Myelosuppression was the most common adverse event (AE), with lower rates of anemia, neutropenia, and TCP seen with EPAG versus PBO (Table). In the EPAG arm, 23% of patients developed TCP (all grade 3/4) vs 46% (31% grade 3/4) of PBO patients. Proportionately fewer serious AEs (SAEs)/deaths occurred with EPAG than with PBO, CTx dose delays/reductions were lower for any reason, specifically for TCP, were lower for EPAG pts than PBO pts, with a greater difference shown in later treatment cycles. Conclusions: These early safety and efficacy results are encouraging, with a potential trilineage benefit as seen in other EPAG studies. Enrollment was completed in 2014, with a total of 75 pts. Study NCT01147809 was funded by GlaxoSmithKline. Clinical trial information: NCT01147809.

Febrile neutropenia risk factors: A subanalysis of the NEXT study. First Author: Nicolas Jovenin, Institut Jean Godinot, Reims, France

Background: Biosimilar filgrastim is a Granulocyte-Colony Stimulating Factor (G-CSF) licensed for the treatment of neutropenia and febrile neutropenia (FN) induced by myelosuppressive chemotherapy (CT). This subanalysis of the NEXT study attempts to assess the impact of each of the FN risk factors defined in the EORTC guidelines for the use of G-CSF. Methods: NEXT was a prospective, post-marketing, non-interventional, longitudinal, national multicenter study aimed to assess the safety of biosimilar filgrastim in patients (pts) undergoing CT for malignancies (excluding chronic myeloproliferative and myelodysplastic syndrome). FN risk factors defined in the EORTC guidelines were tested by univariate analyses and were also included in a logistic regression model. A search of the age at which pts in the NEXT study were significantly more likely to have a FN was also conducted. Results: Overall, the NEXT study analyzed 2102 pts but only 1838 pts who received primary prophylaxis (PP) with biosimilar filgrastim were included in this subanalysis. Apart from CT-related FN risk, other factors that may increase the FN risk are in order of importance: age ≥ 65 years, advanced disease, history of prior FN, no antibiotic prophylaxis, no G-CSF use, poor performance and/or nutritional status, female gender, Hemoglobin < 12 g/dl, liver, renal or cardiovascular disease. The analysis of age distribution of pts with FN, who received PP in NEXT study, shows a threshold at 62 years. The only factor statistically significantly associated with FN occurrence among those included in the logistic regression is age at ≥ 62 years, conferring age-related high risk of FN. Indeed, patients older than 62 years are more likely to have a FN than younger patients (OR [95% CI]: 2.1 [1.1 - 4.0]). The limit to 65 years stated by EORTC guidelines is not significantly associated with FN occurrence among those included in the logistic regression. Caution is required even before the 65 years stated in these guidelines. Indeed, we might wonder about the need for G-CSF prophylactic use in >62-years patients with a CT-related FN risk 10-20%. Clinical trial information: NCT01574235.
Pilot trial assessing the efficacy and safety of a supplemental B vitamin complex to reduce the onset and severity of chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating side effect resulting from the administration of neurotoxic chemotherapy agents. It is estimated that a third of all patients undergoing chemotherapy experience CIPN, with a third of those progressing to a debilitating side effect resulting from the administration of neurotoxic chemotherapy. Chemotherapy-induced peripheral neuropathy [CIPN] is a complex to reduce the onset and severity of chemotherapy-induced peripheral neuropathy with B vitamin supplementation over placebo was statistically significant. Multivariate analysis revealed that the incidence of adenral suppression was significantly associated with the duration of megestrol acetate use (P < 0.001). Adrenal suppression did not correlate with age, sex, performance status, primary tumor site, tumor stage, intent of first chemotherapy, anesthetic risk of first chemotherapy, chemotherapeutic agents used, or the dose and duration of dexamethasone. Conclusions: This large prospective study indicates that approximately 15% of cancer patients with a normal adrenal response showed suppressed adrenal response after antianemic dexamethasone therapy; this was particularly significant for patients co-treated with megestrol acetate.

Identifying predictors of taxane-induced peripheral neuropathy using shotgun proteomics technology. First Author: Meghna S. Trivedi, Columbia University Medical Center, New York, NY

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of taxanes. Advances in proteomic technologies incorporating mass spectrometry (MS) for biomarker discovery show great promise in providing molecular profiles from complex biological samples. We evaluated the association between protein cargos in serum exosomes and severity of CIPN. Methods: We conducted a nested case-control study within a prospective cohort of women with early stage breast cancer receiving adjuvant taxane chemotherapy. Neupropathy was assessed at baseline, completion of taxane, and 6 months after taxane completion using the Functional Assessment of Cancer Therapy-GOG-Neurotoxicity (FACT-Ntx) score (range 0–44). Blood samples were collected at baseline, completion of taxane, and 12 months. The change in FACT-Ntx score from baseline to follow-up time points were used to identify 2 groups of subjects: those with no change in FACT-Ntx score (N=8) and those with a ≥20% worsening in FACT-Ntx score (N=8). MS-based proteomics technology was used to identify proteins present in serum exosomes and potential biomarkers for CIPN. One-way ANOVA analysis with p < 0.05 as the threshold cutoff for statistical significance was applied using the Quilcore Omics Explorer to identify biomarkers predictive of developing CIPN. Results: From the serum exosomes derived from this cohort, MS-based proteomics technology identified over 700 proteins known to be in different subcellular compartments (e.g., 3% cytoplasm, 19% nucleus) and have different functions (e.g., 15% enzymes, 6.8% transcription regulators, and 5% kinases). We found a 12-protein signature from the baseline serum samples that can be used to distinguish between patients with or without CIPN after taxane treatment (p < 0.05) suggesting that the baseline samples can predict subsequent neurotoxicity. Conclusions: We were able to identify a serum exosomal profile that is associated with taxane-induced peripheral neuropathy. We believe that this new panel of biomarkers could be used to identify patients at high risk of developing severe CIPN. We plan to validate the 12-protein profile in a larger cohort of patients who have received taxane therapy.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A randomized trial of vitamin D₃ in aromatase inhibitor-associated musculoskeletal symptoms. First Author: Alice C. Shapiro, Frauenhhofer Cancer Center and Park Nicollet Institute, Minneapolis, Minnesota, USA

Background: Vitamin D₃ supplementation (D₃) has been suggested as a treatment for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS), but efficacy and safety are unclear. Methods: We randomly assigned 113 post-menopausal women (≥ 18 years; stage I-III breast cancer; taking an AI and experiencing AIMSS), to either 600 IU D₃ (control: n = 56) or 4,000 IU D₃ (experimental: n = 57), daily for 6 months (6 mos). The primary study endpoint was change in musculoskeletal symptoms (AIMSS) from baseline to 6 mos, measured by: The Breast Cancer Prevention Trial Symptom Scales-MS subscale (BCPT-MS), the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), the Western Ontario and McMaster Osteoarthritis Index (WOMAC) and hand grip strength (Dynamometer). Plasma 25(OH)D levels (AI-PK) were estimated using non-linear mixed-effects modeling. Effects of D₃ on AI-PK were tested by likelihood ratio test. Serum 25(OH)D was quantified by chemiluminescent immunoassay (DiaSorin, Stillwater, MN). Sample size was calculated on a change of 0.62 in BCPT-MS score. Assuming a two-tailed test with a = 0.05 and power = 80%, adequate sample size was 116 (58 per group). Primary endpoint analyses were based on intent-to-treat and determined using a General Linear Model controlling for possible effect modifiers. Results: The groups did not differ on demographic or clinical characteristics nor on AIMSS measures. After 6 mos, serum 25(OH)D was 33±8 ng/mL vs. 46±11 (mean ±sd; control vs experimental; p < 0.001). There were no statistically significant differences between groups (control vs exp) in mean change in AIMSS scores from baseline to 6 mos: BCPT-MS: -0.45 vs. -0.24; WOMAC function: -1.23 vs -3.96; WOMAC pain: -0.56 vs. -1.18; WOMAC stiffness: -0.47 vs -0.54; AUSCAN function: -0.75 vs -1.12; AUSCAN pain: -0.24 vs -0.90; AUSCAN stiffness: -0.08 vs 0.1; hand grip: 1.06 vs 1.78 (all p < 0.1). AI clearance did not differ significantly between groups (baseline vs 6 mos; p > 0.5). Conclusions: Women randomly assigned to higher dose D₃ (4,000 IU) showed no improvement in AIMSS over usual dose D₃ (600 IU). While D₃ does not appear to adversely affect AI drug metabolism, it may have other health effects in this population. Clinical trial information: NCT01509079.

Phase II study of preventive effect of topical menthol for chemotherapy-induced peripheral neuropathy. First Author: Kumi Nakamura, Aizawa Hospital, Matsumoto, Japan

Background: Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a major dose-limiting toxicity of many commonly used chemotherapy agents that not only negatively affects quality of life, but also can limit successful disease control in cancer care. Menthol is a compound derived from mint leaves that functions as an agonist of Transient Receptor Potential Melastatin-8 (TRPM-8). TRPM-8 is distributed in peripheral nerves and has been shown to be associated with cold hypersensitivity, which is related to concurrent chemoradiation therapy (CXRT) are lacking. We therefore studied that quantify symptom development and major toxicity levels related to concurrent chemoradiation therapy (CXRT) are lacking. We therefore longitudinally examined the relationship between PROs and clinician-rated toxicities in patients with locally advanced non-small cell lung cancer (NSCLC) treated with CXRT. Methods: 155 patients repeatedly reported symptoms on a 0-10 scale via the MD Anderson Symptom Inventory (MDASI-Lung Cancer), from pre-CXRT for up to 6 months. Clinicians rated toxicity using the CTCAE 4.0. Patient factors (age, sex, comorbidities), worst CTCAE score of each toxicity during the study, radiation dose/volume variables, and days from start of CXRT were included in the longitudinal mixed modeling. Results: We observed a significant linear increase in coughing and shortness of breath over time during the study (both P < 0.0001), whereas the most-severe symptoms overall (fatigue, lack of appetite, disturbed sleep) exhibited a decrease by the end of treatment. Post-CXRT, patients with grade 2+ radiation pneumonitis (RP) had significantly more-severe cough and shortness of breath, compared with those with grade 0-1 (P < 0.0001). Moreover, patients with grade 2+ RP (OR, 1.27 (1.09-1.49), P = .0023). Gross tumor volume was significantly related to increased cough severity (P < .01). Pain, sore throat, and difficulty swallowing peaked by the end of CXRT, and all were significantly worse for patients with grade 2+ esophagitis vs. grade 0-1 (all P < .0001). There was no difference in symptom severity pre-CXRT by toxicity group. Conclusions: Longitudinal analysis identified temporal associations between clinician-rated toxicity and emerging patient-reported symptom burden from CXRT for NSCLC. Further investigation of the benefits of routine symptom assessment for clinical management and early prevention of RP and esophagitis is warranted.
9612 Poster Session (Board #271), Sat, 1:15 PM-4:45 PM
The conversion ratio (CR) for opioid rotation (OR) from strong opioids to transdermal fentanyl (TDF) in cancer patients. First Author: Akhila Sunkepudi Reddy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cancer patients frequently undergo OR for uncontrolled pain or opioid induced neurotoxicity (OIN). TDF is one of the most common opioids prescribed to cancer patients. However, the accurate CR for OR from other opioids to TDF is unknown and various cut-off values have been used. We used a method recently reported in a wide variation of CRs. Our aim was to determine the CR of morphine equivalent daily dose (MEDD) to TDF when correcting for MEDD of breakthrough opioids (not TDF) in a cancer outpatient population. We reviewed records of 22,532 consecutive patient visits at our Supportive Care Center in 2010-13 for OR from other opioids to TDF. Data regarding Edmonton Symptom Assessment Scale (ESAS) and MEDD were collected in patients who returned for follow up within 5 weeks. Linear regression analysis was used to estimate the CR between TDF dose and net MEDD (MEDD prior to OR minus MEDD of breakthrough opioid used along with TDF after OR). Successful OR was defined as ≥2 point or 30% reduction in pain score and continuation of the new opioid at follow up. Results: 129 patients underwent OR from other opioids to TDF. The mean age was 56 years, 59% male, and 88% had advanced cancer. The median time between OR and follow up was 14 days. Uncontrolled pain (80%) was the most frequent reason for CR and 59% had a successful OR with significant improvement in ESAS pain, constipation, and symptom distress scores. In 101 patients with OR and follow up was missing, the median CR (range) from net MEDD to TDF mg/day was 0.1 (0.02-0.06) and correlation of TDF dose to net MEDD was 7.7 (P < .0001). The CR was not significantly impacted by variables such as cachexia, serum albumin, and body mass index (BMI). The CR of 0.1 suggests that MEDD of 100 mg could be equivalent to 1mg TDF per day or 40mcg/hour TDF patch (1000mcg/24hours). Conclusions: The median CR from MEDD to TDF mg/day is 0.1 and the CR from MEDD to TDF mg/hour patch is 0.4. Further validation studies are required.

9613 Poster Session (Board #272), Sat, 1:15 PM-4:45 PM
Association of high symptom burden with oral oncolytic agents. First Author: Jane Alecy Severson, University of Michigan Health System, Ann Arbor, MI

Background: Increasing numbers of cancer patients are being treated with oral oncolytics. This change represents a shift from frequent direct observation during intravenous therapy to periodic observation and self-management. During this shift, patients are at risk for many of the same chemotherapy-associated symptoms and toxicities. We sought to characterize the symptom burden experienced by patients prescribed oral oncolytics. Methods: Michigan Oncology Quality Consortium (MOQC) sponsored a collaborative focused on improving oral oncolytic care. Eight oncology practices participated. Patient symptoms were assessed with a modified Edmonton Symptom Assessment Scale (ESAS) prior to each outpatient visit. 13 symptoms were categorized as mild (0 to 3), moderate (4 to 6), and severe (7 to 10). A total of 1196 surveys were analyzed. Results: Overall, the average ESAS symptom score was mild in 83% of patients, moderate in 12% of patients, and severe in 5% of patients. These composite scores, however, obscure the significant symptom burden in select ESAS domains. For example, 34% of patients categorized their overall well-being as being moderate/severely affected; 35% of patients felt they were moderate/severely fatigued, and 20% indicated moderate/severe pain symptoms. Notably, 271/1196 (23%) of the assessments had 4 or more symptoms reported moderate to severe. (See table). Conclusions: Whether due to underlying disease or medication side effects, patients taking oral oncolytics experience significant symptom burden that impacts quality of life. Intolerance of oral oncolytics may lead to adherence issues, potentially affecting expected outcomes. Given the prevalence of symptoms and potential for toxicity, self-management strategies to improve early recognition and treatment are critical to managing oral oncolytic therapy.

Oral oncolytic symptom burden profile.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild (0-3)</th>
<th>Moderate (4-6)</th>
<th>Severe (7-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>80%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Tiredness</td>
<td>65%</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Nausea</td>
<td>78%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>95%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>73%</td>
<td>9%</td>
<td>18%</td>
</tr>
<tr>
<td>Numbness</td>
<td>89%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>52%</td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>Tingling/ numbness</td>
<td>92%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>96%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Overall Symptom Burden (n = 1196)</td>
<td>83%</td>
<td>12%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*ANCOVA with study and gender as covariates; **FLIE total score

9614 Poster Session (Board #273), Sat, 1:15 PM-4:45 PM
Randomized pilot study comparing high-dose (HD) influenza vaccine to standard-dose (SD) influenza vaccine in adult oncology patients younger than 65 receiving chemotherapy. First Author: Saad Jamshed, Rochester General Hospital, Rochester, NY

Background:Pts on chemotherapy often fail to develop a robust response to influenza vaccine. Compared to SD influenza vaccine, HD vaccine has shown improved immunogenicity & protection against influenza illness in adults ≥65 yrs. This study compared the immunogenicity & tolerability of SD and HD influenza vaccine in pts < 65 yrs receiving chemotherapy. Methods: 105 pts were randomized to receive SD or HD influenza vaccine on day 1 of chemotherapy during 2012-2013 & 2013-2014 seasons. HAI titers were measured prior to & 4-wks after vaccination. HAI were summarized as GMT, seroconversion & seroprotection rates. Sample size calculation was based on 5 pts were excluded, 1 received the vaccine twice. 4 pts who enrolled both seroconversion & seroprotection rates. Sample size calculation was based on 58 vs 50% were receiving curative therapy in SD vs HD arms, respectively. Mean age (52.9 vs 53.9 yrs) and BMI (20-30 62 .01 -0.02-0.04 .67 20 13 .01 0-0.02 .43 220-30 62 .01 -0.02-0.04 .43 220-30 62 .01 -0.02-0.04 .43

9615 Poster Session (Board #274), Sat, 1:15 PM-4:45 PM
Impact of rolapitant on quality of life (QoL) in patients (pts) receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). First Author: Martin Chasen, Palliative Care, At the Ottawa Hospital Cancer Centre and the Medical Director of the Palliative Rehabilitation Program at the Elisabeth Bruyère Hospital, Ottawa, Ottawa, ON, Canada

Background: Rolapitant is a novel NK-1 receptor antagonist with a half-life of 180h, and does not inhibit CYP3A4 as other drugs do in the class, and therefore requires no dose modifications for concomitant steroids. Rolapitant demonstrated efficacy for prevention of CINV in phase 3 trials (HEC1, HEC2, and MEC). The pooled analysis examined the effect of rolapitant vs. QOL. Methods: In 3 double-blind, active-controlled studies, pts were randomized to oral rolapitant 200 mg or placebo 1–2 h before chemotherapy. All pts received active control: granisetron 2 mg oral or 10 mcg/kg IV and oral dexamethasone 20 mg. In the MEC study, granisetron was continued on Days 2 and 3. QoL was assessed on Day 6 using the Functional Living Index-Emesis (FLIE) Questionnaire, and reported as a total score and by nausea and vomiting domains. Pts with a valid questionnaire from the MITT population (all randomized pts who received at least 1 dose of study drug) in the 2 pooled HEC studies and one MEC study were analyzed. Results: Baseline characteristics were comparable across treatment groups. Most common cancers were breast for MEC and lung for HEC studies. At Day 6, significant improvements (P < 0.05) were observed with rolapitant vs. active control for FLIE total score, nausea, and vomiting domain scores (Table). Conclusions: Rolapitant improved QoL pts receiving both HEC and MEC compared with active control, in addition to providing significant protection from CINV. Clinical trial information: NCT01500226; NCT01499849; NCT01500226.
Evaluation of brain-derived neurotrophic factor (BDNF) genetic polymorphism (rs6265) on chemotherapy-associated cognitive impairment in early-stage breast cancer (ESBC) patients. First Author: Terence NG, National University of Singapore, Singapore, Singapore

Background: BDNF is a neurotrophin that regulates neuronal function and development, which is implicated in several neurodegenerative conditions. There is preliminary data to suggest that the reduction of BDNF concentrations may lead to post-chemotherapy cognitive impairment. We hypothesized that a single nucleotide polymorphism (rs6265) of the BDNF gene may play a role in the manifestation of serious complications associated with chemotherapy-induced cognitive impairment. This study was designed to evaluate the impact of BDNF gene polymorphism on chemotherapy-associated cognitive impairment.

Methods: Overall, 145 chemotherapy receiving ESBC patients (mean age: 50.8 ± 8.8 years; 82.1% Chinese) were recruited between 2011 and 2014. Patients' self-perceived cognitive function was assessed longitudinally over three time points, using the validated FACT-Cog (v.3) to examine treatment arm. A significantly greater proportion of patients on rolapitant (73.0%) vs. active control (60.2%) had no emesis during the overall phase (p < 0.001).

Conclusions: This is the first study to provide evidence that carriers of the BDNF Met allele are protective against chemotherapy-associated cognitive impairment. Further validation studies are required to confirm the findings.

Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients (pts) receiving anthracycline-cyclophosphamide (AC)-based chemotherapy. First Author: Ian D. Schnadig, Compass Onc, Tulsa, OK

Background: Rolapitant, a novel NK-1 receptor antagonist, demonstrated efficacy in the prevention of CINV in pts receiving moderately- or highly emetogenic chemotherapy (MEC, HEC). In this post-hoc analysis, we evaluated safety and efficacy of rolapitant 200 mg plus granisetron 2 mg and dexamethasone 20 mg or placebo in pts receiving AC-based therapy, now considered HEC. Methods: This double-blind, active-controlled study randomized pts to oral rolapitant 200 mg plus granisetron 2 mg and dexamethasone 20 mg or placebo. CR (no emesis and no use of rescue medication), no emesis, no significant nausea, and time to emesis or rescue medication during overall, acute, and delayed phases and treatment-emergent adverse events (AEs) were assessed. Results: 703 pts received AC-based therapy, of which 97% had breast cancer. CR was significantly higher for rolapitant vs. active control for delayed and overall phases in pts receiving AC-based therapy (Table). Time to first emesis or use of rescue medication was significantly longer with rolapitant vs. active control (between-group comparison, p = 0.032); median was not reached in either treatment arm. A significantly greater proportion of pts on rolapitant (73.0%) vs. active control (60.2%) had no emesis during the overall phase (p < 0.001).

Conclusions: Rolapitant was superior to active control in preventing CINV during delayed and overall phases after AC-based chemotherapy. There were significant differences in the safety profile of rolapitant in the pt groups. These results are consistent with the overall pt population in this study. Clinical trial information: NCT01500213; NCT01499849; NCT01500226.

Evaluating the effect of neutropenic diet on infection and mortality rate in cancer patients: A meta-analysis. First Author: Mohanad Bassam Sonbol, Georgia Regents University, Augusta, GA

Background: Dietary manipulation for patients undergoing chemotherapy has been proposed as a method to reduce the risk of infection. These diets, referred to as “neutropenic diets (ND)” usually restrict fresh raw fruits, raw vegetables, raw meat or soft cheeses. Regular diets (RD) generally include foods restricted in ND and are prepared within standardized FDA food safety guidelines. ND are used in transplant centers and hospital wards where cancer patients are being treated. The goal of this meta-analysis was to determine the effectiveness of ND over RD at preventing infection. Methods: We searched the medical literature to identify studies comparing ND with RD in patients with cancer. Primary outcomes were mortality of any cause, major infections (pneumonia, bacteremia, or fungemia), and the composite outcome of neutropenic fever or infection (major infections as defined above, minor infections, or fever). The overall effect was calculated by use of a random effects model. A sensitivity analysis was conducted to evaluate influence of the included observational trials on outcomes. Results: Four studies were identified, 3 randomized trials and 1 observational study, encompassing 918 patients with cancer or stem cell transplant. Patients randomized to ND had no difference in major infection rate compared to the RD group (RR = 1.08, CI 0.72 to 1.61). ND patients also had a comparable mortality rate to the RD group (RR = 1.08, CI 0.78 to 1.50). These results persisted after including the observational study from analysis. When analyzing for the overall composite outcome of any infection or fever, the hazard was significantly higher in ND arm compared to RD arm (RR 1.18, CI 1.05 to 1.34). Conclusions: This study shows no superiority or advantage with respect to mortality or infection of using neutropenic diet over a regular diet in neutropenic cancer patients. Larger randomized controlled studies are needed to further study this important dietary issue for patients. In the meantime, it may be time to relax the restrictions of ND in order to attain better nutrition.
Efficacy and safety of rolapitant for prevention of chemotherapy-induced early acute toxicity. The measurement of resting energy expenditure might predict EAT.

### Background:
- alterations of nutritional status and the development of cachexia are major determinants for the alteration of nutritional status and the development of cachexia and cachexia. We investigated whether abnormal metabolic profiles could predict early acute toxicity (EAT).
- The study was a prospective observational monocentric study. REE was measured by indirect calorimetry before anticancer treatment initiation. C-Reactive Protein (CRP), albumin, transthyretin and PS were collected. Measured REE was compared with predicted REE as defined by the Harris-Benedict formula. Patients were classified as hypometabolic (REE < 90%), normo-metabolic (90-110%) or hypermetabolic (> 110%). Toxicity was assessed after the first cycle of treatment. An EAT was defined as any event leading to unplanned hospital admission, dose reduction, treatment delay (> 7 days) or discontinuation.

### Results:
- A total of 277 patients (pts) with solid tumors (gastro-intestinal 25%, genitourinary 23%, thoracic 22%) were included. Sex ratio: 1.25; median age: 63 years (20-91). Most of the pts (71%; 217) had locally advanced or metastatic disease and were treated with chemotherapy (246; 89%) or tyrosine-kinase inhibitor (30; 11%). Calorimetry revealed pts with either normo- (29%), hyper- (51%) or hypometabolism (20%). A subset of 59 pts (21%) exhibited early acute toxicity (EAT). The measurement of resting energy expenditure (REE) is often increased in cancer patients and may be a major determinant for the alteration of nutritional status and the development of cachexia and cachexia. We investigated whether abnormal metabolic profiles could predict early acute toxicity (EAT). The measurement of resting energy expenditure (REE) might predict EAT.

### Conclusions:
- Pts with abnormal metabolism experience more early acute toxicity. The measurement of resting energy expenditure might improve the detection of patients at risk for toxicity and missed with the standard clinical evaluation.

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**Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) in moderately emetogenic therapy (MEC).** First Author: Paul Joseph Hesketh, Lahey Hosp and Med Ctr, Burlington, MA

### Background:
- Rolapitant, a novel NK-1 receptor antagonist, showed efficacy for prevention of CINV in patients (pts) receiving MEC (anthracycline/cyclophosphamide (AC) and other regimens) in a global phase 3 trial. Recent anti-emetic guidelines consider AC regimens to be moderately emetogenic. In the current analysis, the efficacy and safety of rolapitant was assessed during Cycle 1 in pts receiving non-AC MEC.

### Methods:
- In a double-blind, active-controlled study, pts were randomized to oral rolapitant 200 mg or placebo 1–2 hours before MEC. All pts received granisetron 2 mg oral on days 1–3 and oral dexamethasone 20 mg on day 1. Pt subgroups were carboplatin-based MEC and Other MEC (OM; non-AC, non-NK1). Completeness of data, use of rescue medication, no emesis, and no nausea were assessed during overall (≥ 12 h), acute (0–24 h), and delayed (>24–120 h) phases. EAT was associated with poor PS (2–3 vs 0–1: OR 9.29 vs 0.01; p < 0.001) and diagnosis of hepatobiliary cancer (HR 2.91; 95% CI 1.2–7.02; p = 0.018).

### Results:
- In multivariate analysis, risk factors associated with recurrent VTE included venous compression (HR 2.96; 95% CI 1.8–4.86; P = 0.001) and diagnosis of hepatobiliary cancer (HR 2.91; 95% CI 1.2–7.02; P = 0.018). Ottawa score did not predict for recurrence risk, with recurrent VTE rates of 3.4, 9.7 and 8.2% in low-, intermediate- and high-risk groups, respectively.

### Conclusions:
- Cancer patients with acute VTE are at significant risk for recurrent events, despite anticoagulation. More intensive treatment strategies for higher-risk patients should be considered. Clinical trial information: NCT01130025.
Sleep quality and its association with fatigue, symptom burden, and mood in patients with advanced cancer in a phase 1 clinical trial. First Author: Golden G. Genauer, Department of Therapeutics, MD Anderson Cancer Center, Houston, TX

**Background:** Limited data exist about sleep quality (SQ) in patients (pts) on phase 1 clinical trials. Poor SQ is often not captured as an adverse event (AE) and its association with fatigue, one of the most frequently reported AEs, is not documented routinely. Here, we describe SQ and the relation between SQ and fatigue, symptoms, and mood in pts in the MD Anderson phase 1 clinical trials clinic. **Methods:** Sleep, fatigue, symptom severity/interference and mood were assessed using the validated Pittsburgh Sleep Quality Index (PSQI), Brief Fatigue Inventory, MD Anderson Symptom Inventory, and Profile of Mood States, respectively, ECOG was from medical records. **Statistics:** Included multivariable regression models. **Results:** The sample (N = 262) was 52% female, 80% ECOG 0-1, mean age 58.4 ± 0.7y. The % of “poor” sleepers (global PSQI score > 5) was 64%. In contrast, pts’ subjective self-assessment of SQ was: 27% as “bad” or “fairly bad”, 59% as “fairly good” and 14% as “very good”. Among pts, 28% took medicines for sleep; 15% slept < 6 hours at night; 20% had sleep latency > 30 minutes for ≥ 3 nights per week; and 42% reported poor sleep efficiency (< 85% time in bed spent sleeping). The % of pts reporting fatigue were 35% as “severe”, 14% as “moderate”, 39% as “mild”, and 12% “none”. In an adjusted multivariable regression model, poor overall SQ was associated with greater fatigue (P < 0.01). Interestingly, SQ (PSQI) sub-components associated with greater fatigue were sleep disturbance (OR = 2.6, 95% CI = 1.3, 5.1, P < 0.007) and daytime dysfunction (OR = 4.1, 95% CI = 2.3, 7.6, P < 0.001), but sleep latency, and sleep efficiency were not related to fatigue. Poor overall SQ was also associated with greater symptom severity (Pearson’s r = 0.6, P < 0.001) and mood disturbance (Pearson’s r = 0.5, P < 0.001) and greater fatigue (Pearson’s r = 0.4, P < 0.001) and symptom-related interference (Pearson’s r = 0.5, P < 0.001) with activity, walking, relationships with others, and enjoyment of life. **Conclusions:** Poor SQ is a significant problem across all pts and associated with increased fatigue, symptom severity, symptom interference, and greater mood disturbance. Deciphering SQ should be routine practice in phase 1 clinical assessments.

Can a homeopathic medicine complex reduce hot flashes induced by adjuvant endocrine therapy in localized breast cancer patients? Results of a randomized placebo-controlled phase III trial. First Author: Pierre-Etienne Heudel, CENTRE LEON BERARD, Lyon, France

**Background:** Homeopathy is already used for the management of menopausal hot flashes (HF) and could reduce this frequent endocrine therapy’s (ET) side effect. **Methods:** Localized breast cancer patients (pts), treated for at least one month with adjuvant ET and complaining of HF were included in a multicentric randomized double-blind phase III study. Primary endpoint, analyzed in an intent-to-treat basis, was the variation of HF score (HFS) between pre and 4 weeks (w) post randomization. HFS was calculated (over 1 w) as the mean of HF frequency, weighted by a 4-level intensity scale. After a run-in period of placebo (2-4 w to exclude pts with strong placebo effect), only pts maintaining a HFS ≥ 10 were randomized to receive Arthene (a homeopathic medicine complex SRN-01) (A) vs Placebo (P) during 2 months. The trial was powered (90% power, two-sided alpha of 5%) to detect a 5-point (≥ 8.6) difference of HFS variation between arms; 138 randomized pts were needed. Secondary endpoints were HFS variation after 8 w of treatment, compliance, tolerance, quality of life (QoL) and satisfaction. **Results:** On February 28th to April 2014, 299 pts were included and 138 (46.2%) randomized (65 to A and 73 to P). Patients’ characteristics were well balanced between groups. Median age was 51 years (range 36-72), 82 pts were postmenopausal, 79 were treated by tamoxifen and 59 by aromatase inhibitor. No statistical differences were observed between A and P in covariables at baseline for age, chemotherapy intent, chemotherapy regimen and accounted for random effects of study and chemotherapy regimen. This meant that a 13% FN rate in RCT would translate into 20% FN rate in OB study. The unadjusted FN rates were higher in taxane regimens than non-taxane regimens in both the OBs (16.5% vs. 6.4%) and RCT (10.0% vs. 4.7%) cohorts. **Conclusions:** FN rates in OBs are significantly higher than suggested by RCTs in many breast cancer-related chemotherapy regimens. A 13% FN rate in RCT appeared to correspond to the 20% FN rates in the real world. Large population-based studies are needed to confirm FN rates of different regimens in the real world to ensure optimal utilization of G-CSF.
A randomised, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent chemotherapy-induced peripheral neuropathy (CIPN) in patients undergoing chemotherapy. First Author: Stein Kaasa, Trondheim University Hospital, Trondheim, Norway

Background: The pathophysiology of cancer cachexia is multi-factorial consisting of muscle wasting, negative protein and energy balance, and systemic inflammation. There is no established treatment for cachexia, paradoxical to the importance of this condition in limiting oncology treatment. New approaches are needed to address the complex multi-factoriology and to challenge the accepted therapeutic nihilism. To treat cachexia optimally it has been argued that a multimodal intervention is necessary to enable the multi-factorial pathophysiology to be targeted. Integral to this is targeting inflammation as the main driver of cachexia.

Methods: An international, multicentre randomised phase II study was conducted. Eligible patients had advanced lung cancer or pancreatic cancer and were due to start palliative chemotherapy. Patients were randomised (1:1.1 ratio) to receive either a multimodal intervention (exercise, anti-inflammatory medicines, energy dense nutritional supplements combined with dietary advice) or standard cancer care. Primary outcome measures were feasibility of the intervention assessed by compliance and enrolment. Secondary outcomes examined weight, physical activity (using ActivPAL) and CT based muscle mass. Means and standard deviations (SD) are reported. Results: Forty-six patients were recruited from three regional cancer centers' clinic (London, UK) and Tew隰haim University Hospital, Tew隰haim, Norway. Overall compliance was >54% in all components of the intervention. Patients in the treatment arm weight increased (0.91% (SD 2.46)), whilst those in the control arm lost weight (0.07% (SD 2.27)). The majority were white, 50.6% women, and 77.3% aged ≤ 50 years. CR was achieved in 79.4% (81/104) in the FA group and 84.6% (89/105) in the control group (p = 0.15). Safety profiles were comparable between the two groups; drug-related adverse events occurred in 8.5% (FA) vs 9.1% (control) in the treatment group and 9.6% (FA) vs 10.4% (control) in the control group. No cases of severe infusion-site pain, erythema, or induration were reported. Conclusions: A multimodal intervention is feasible and improves weight in patients with incurable lung or pancreatic cancer undergoing chemotherapy. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

Conclusions: First Author: Berardo Leon Rapoport, The Medical Oncology Center of Rosebank, Johannesburg, South Africa

Background: This is the first study performed to directly evaluate the efficacy and safety of a single dose of intravenous fosaprepitant (FA), an NK1 receptor antagonist, used with a 5-HT3 antagonist and corticoste-roid in subjects receiving moderately emetogenic chemotherapy (MEC). Methods: This was a global, phase 3, randomized, double-blind, parallel group study in adult subjects naïve to MEC and highly emetogenic chemotherapy (HEC) scheduled to receive an IV dose of ≥ 1 MEC agents on treatment day 1. Subjects were randomly assigned 1:1 to a control or FA regimen. Those in the control regimen received 8 mg oral ondansetron, 20 mg dexamethasone, and IV saline as placebo before the first dose of MEC on day 1 and 8 mg oral ondansetron 8 hours after the first dose, followed by 8 mg oral ondansetron every 12 hours on days 2 and 3. Those in the FA regimen received the same dose of oral ondansetron on day 1, along with 12 mg dexamethasone and a single dose of 150 mg IV FA before the first dose of MEC on day 1, with no additional prophylactic antiemetic beyond day 1. Primary outcomes were the proportion of subjects with a complete response (CR: no vomiting and no rescue medication use) during the delayed phase (25 to 120 hours after MEC) and FA safety/tolerability. Results: Baseline characteristics were generally balanced among the 1000 subjects in the primary efficacy population (502 FA, 498 control). Over a thousand (1164/5341, 22%) of the subjects in the primary efficacy population (502 FA, 498 control). The majority were white, ≥ 50 years of age, and female. CR was achieved in 396 (78.9%) subjects in the FA group and 341 (68.5%) in the control group during the delayed phase (treatment difference of 10.4%, P < 0.001). Safety profiles were comparable between the two groups; drug-related adverse events occurred in 8.5% (FA) vs 9.1% (control). There were no cases of severe infusion-site pain, erythema, or induration reported; 3 cases of infusion-site thrombophlebitis were observed in the FA regimen compared with 0 in the control regimen. Conclusions: Single-dose 150 mg IV FA regimen is generally safe and well tolerated and provides significant control of chemotherapy-induced nausea associated with MEC as measured by the proportion of subjects with CR in the delayed phase. Clinical trial information: NCT01594749.

Effective complementary ASCO policy and day to day decision support strategies optimize anti-emetic choices. First Author: Anmol Banarwal, Oncology Analytics, Inc., Plantation, FL

Background: Emetogenicity is a common reason for patients forgoing effective chemotherapy. ASCO, in its 2013 Top Five list, recommends against overuse of antiemetics and for the use of cost-effective agents. Oncology Analytics (OA) is a cancer care decision-support entity comprised of oncologists, PharmDs and oncology RNs, interacting with some 5000 oncologists and promoting high quality cost-effective cancer treatment based on level I data and national guidelines. We hypothesize that on-patient antiemetics are overused in comparison to equally effective generics; that this misuse/overuse induces financial toxicity; and that these ill effects can be offset by ASCO policy initiatives and OA decision support activities. Methods: We analyzed antiemetic requests in 2013 & 2014 in Georgia and Florida. Linear regression and chi-squared were utilized to determine time trends for the ratio of palonosetron vs. generic antiemetic regimens (ondansetron and granisetron) across these 7 quarters. We contrasted prescribing behavior concurrent with ongoing OA interaction, before and after the release of ASCO recommendations against unnecessary expensive anti-emetics. Results: 12,116 antiemetic requests were assessed in a pre-approval setting. After the 2013 ASCO policy recommendation, there was an immediate increase in the likelihood of requests for cost-effective regimens compared to more expensive “on-patient” choices (chi-squared p = 0.004). Over a thousand (1164/5341, 22%) of the requests met the ASCO and/or NCCN guidelines, and discouraged by OA. Over this time span, there is a clear trend toward cost-effective generic choices, decreasing extrapolated costs by about $300,000 annually. Conclusions: The ASCO-defined overuse of expensive antiemetics in Florida and Georgia is substantial. ASCO national Policy, supported by daily OA interventions, diminishes the unnecessary use of expensive anti-emetics, increases the use of cost-effective antiemetic alternatives, and diminishes financial toxicity while enhancing cancer care quality. ASCO guidelines, when supported by a decision support program, result in significant cost savings.

Do cancer patients present with subclinical peripheral neuropathy prior to initiating neurotoxic chemotherapy? First Author: Sabrina Ramnarine, Edinburgh Cancer Research UK Centre, University of Edinburgh, Edinburgh, United Kingdom

Background: Chemotherapy-induced peripheral neuropathy (CIPN), is a common dose-limiting toxicity which may compromise patient survival, leaving many with chronic pain, disability and a negative impact on quality of life. The natural history and underlying pathophysiological mechanisms are unclear. Clinical management is challenging, therefore, early identification of subclinical and prediction of patients who will develop CIPN is critical. Using a translational approach, this study aims to investigate and characterise the presence of subclinical peripheral neuropathy in gynaecological, colorectal and lung cancer patients. Methods: Quantitative Sensory Testing (QST) was conducted on 21 patients with the above cancers prior to starting neurotoxic chemotherapy and compared with 21 age and gender matched healthy controls, to characterise somatosensory profile. Skin temperature, thresholds for thermal, mechanical and sharpness detection along with sensorimotor function (grooved pegboard test) were assessed. Resting heart rate was measured as a marker of autonomic function. Results: Heart rate differed significantly between the two groups (healthy, mean 72.3 vs 87.9 in patients; p < 0.0001). Detection of painful thermal thresholds (lower limb) were also significantly different in the healthy group compared to patients (hot: 47.4°C vs 45.4°C; p = 0.005; cold: 9.7°C vs 16.2°C; p = 0.04) with evidence of variance in the upper limb for hot (42.0°C vs 35.0°C; p = 0.03). Although not statistically significant, test-difference existed between the groups in the pegboard test: dominant hand 75.6secs vs 83.2secs (p = 0.15), non-dominant hand, 79.0secs vs 88.4secs (p = 0.06). Conclusions: This cohort of patients exhibited signs suggestive of subclinical autonomic and sensory nerve dysfunction prior to initiating chemotherapy manifested as: increased resting heart rate, hot and cold hyperalgesia and evidence of some sensorimotor impairment. This indicates a cancer-mediated process potentially contributing to CIPN and may provide insight into the complexities of the underlying pathophysiological mechanisms.

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**Background:** Care team-patient communication regarding costs has been suggested as a means of minimizing patients’ financial burden (FB) in oncology. However, it is unknown how cost communication preferences are related to FB or HRQoL.**Methods:** Patients with advanced cancer who had completed at least 3 months of chemotherapy were asked whether they agreed or disagreed with the following communication preference items: (1) willingness to discuss costs; (2) willingness to know the costs before treatment; (3) willingness to allow costs to be incorporated into shared-decision making (SDM); (4) wishing costs had been discussed in the past; and (5) whether costs were actually discussed. FB was assessed by the COST (Comprehensive Score for Financial Toxicity), as well as by the EORTC financial impact (FI). Demographics, resource utilization, and HRQoL, measured by the FACT-G and EORTC QLQ-C30, were collected. Linear regression and chi-square tests were performed. **Results:** 233 patients were assessed. Most of the patients (n = 190, 82%) had never discussed costs with their care team. There was no association between preferences and HRQoL. Patients with FB by either instrument were more likely to report item (4) (COST, p < .01; FI, p < .001). Out of the 43 (18%) patients who agreed with this item, 34 (79%) had FB by COST, and 37 (86%) by the FI. There was no significant association between items (1), (2), (3), (5) and FB. Factors associated with communication preferences included age (item 4), race (2 and 4), employment (4), income (4) and education (1), as listed in the table below. **Conclusions:** HRQoL is not significantly associated with cost communication preferences. An opportunity for intervention was identified, as most of the patients who wished to have discussed costs in the past were now experiencing FB. The knowledge of these preferences may indicate the best timing and population with whom costs should be discussed.

<table>
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<tr>
<th>Willingness to:</th>
<th>A %</th>
<th>D %</th>
<th>U %</th>
<th>Age</th>
<th>Race</th>
<th>Employment</th>
<th>Income</th>
<th>Education</th>
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<tbody>
<tr>
<td>(1) to discuss</td>
<td>45</td>
<td>29</td>
<td>17</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>(2) to know</td>
<td>68</td>
<td>15</td>
<td>17</td>
<td>NS</td>
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<td>(3) wish SDM</td>
<td>48</td>
<td>37</td>
<td>17</td>
<td>NS</td>
<td>NS</td>
<td>A</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>(4) wished had discussed</td>
<td>18</td>
<td>54</td>
<td>27</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>(5) Costs</td>
<td>18</td>
<td>82</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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A%, agree; D%, disagree; U%, unsure; NS, not significant; * p < .05; ** p < .005

**Background:** The majority of persons diagnosed with cancer are older adults. A comprehensive geriatric assessment (CGA) can identify current health care issues, start interventions to prevent/postpone adverse outcomes and maintain/improve the functional status and well-being of older adults. However, there is limited and conflicting evidence to support the effectiveness of CGA in oncology settings. Here, we explore the impact of a CGA and integrated care plans with advanced cancer patients with least 3 advanced breast (BC), gastrointestinal (GI) or genitourinary (GU) cancer **Methods:** A two-group parallel single-blind phase II RCT is enrolling 60 patients aged 70 years and over, diagnosed with GI, GU or BC, referred for first line chemotherapy or having received 6weeks ( < 6weeks) of chemotherapy at Princess Margaret Cancer Centre. Patients need to be fluent in English, have a life expectancy > 6 months, ECOG PS 0-2 and able to provide informed consent. Randomization to intervention and control group is 1:1 and stratified by treatment intent (adjuvant vs. palliative). The intervention includes a full CGA by a multidisciplinary geriatric team followed by an integrated care plan to address the issues identified. Based on the CGA and discussion with the patient, tailored evidence-based interventions will be carried out by the team using a standardized intervention protocol. Participants in the intervention group are seen by the intervention team at baseline for the CGA and development of the integrated care plan; and at 3 and 6 months to assess intervention fidelity and measure outcomes. The co-primary outcomes are: 1) Maintaining/improving quality of life (EORTC QLQ-C30); 2) Modification of the cancer treatment plan. The secondary outcomes are: 1) Functional status (OARS Instrumental Activities of Daily Living); and 2) Feasibility of the study, by tumor site, 15 of 0 planned patients have been enrolled to date. This will be one of the first RCTs of CGA in geriatric oncology to show feasibility and provide estimates of impact on relevant outcomes to inform the design of a phase 3 trial. Clinical trial information: NCT02222259.
Cancer-related cognitive dysfunction (CRCD) and psychosocial development in young adult cancer survivors. First Author: Kim Edelstein, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Chemotherapy is associated with long-lasting neurocognitive sequelae and structural and functional brain imaging changes in about 25% of older adults who do not receive central nervous system (CNS) directed treatment. This suggests that cancer or its treatment affects the brain regardless of primary tumor site. Because the brain continues to develop into the 3rd decade of life, younger adults (YA; age 18-39 yrs) may be vulnerable to CRCD. Cancer also disrupts acquisition of developmental milestones in YA. CRCD may exacerbate those disruptions, but this has never been studied. Study aims are to characterize CRCD in YA, explore its relation to psychosocial development, and identify subgroups at risk of adverse outcomes. Methods: In this prospective, inception-cohort study, we are recruiting YA who do not require CNS-directed therapy from ambulatory clinics at the Princess Margaret Cancer Centre (leukemia, lymphoma, breast, gynecology, gastrointestinal, genitourinary, sarcoma) and the YA Oncology clinic at the Jewish General Hospital: 200 YA with cancer who require chemotherapy, 100 YA with cancer who do not require it, and 100 healthy YA with no cancer history. As of Jan 30 2015, 113 participants were enrolled. Chemotherapy patients are assessed prior to treatment, and then 6 and 12 months later. The other groups are assessed at similar time intervals. The 2-hr test battery consists of standardized neurocognitive tests sensitive to CRCD and validated self-report psychosocial measures. Repeated measures mixed effects models will be used to examine longitudinal changes in each of the neurocognitive domains and each of the psychosocial development scores, using the predicted residual sum of squares method to avoid interpretation problems associated with repeated testing. Relationships between CRCD, psychosocial development, treatment, cancer type, and individual characteristics will be examined using regression. Exploratory analyses will investigate whether demographic, disease, or treatment factors contribute to longitudinal changes. Results will provide the basis for interventions that alleviate the psychosocial and cognitive sequelae in this underserved population.

TPS9638 A phase III randomized double-blind study of prophylactic topical dapsone 5% versus moisturizer for cetuximab-induced papulopustular (acneiform) rash. First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Epidermal growth factor receptor inhibitors (EGFRIs) such as cetuximab, are associated with an acneiform rash that can affect up to 90% of treated patients, and can lead to interruptions and discontinuation of treatment by 76% and 32% of oncologists, respectively. Affected patients experience significant impairment in their quality of life (QoL) and psychosocial well-being. Prophylactic therapies include topical corticosteroids in combination with oral antibiotics, or the latter as single agents. Nonsteroidal topical agent has hitherto been investigated for the prevention of rash. Dapsone, a sulfone anti-microbial agent with known anti-inflammatory properties, is approved for the topical treatment of acne vulgaris. It suppresses neutrophil recruitment (interferes with migration and β-2 integrin-mediated adherence), inhibits release of prostaglandins and leukotrienes, IL-8 (from keratinocytes), and generation of toxic, oxygen-derived free radicals. While the exact pathogenesis of the acneiform rash to EGFRIs is not known, neutrophil recruitment and activation appear to play a key role. Therefore, we hypothesized that topical dapsone may be a safe and effective preventative strategy. Methods: We designed a prospective, randomized double-blind controlled trial to measure the ability of twice daily split-face and chest application of topical dapsone 5% gel versus moisturizer, to reduce the total lesion count (of the acneiform rash) by 20% at day 28. Patients with metastatic colorectal cancer (80 sides) with metastatic colorectal cancer or head and neck squamous cell carcinoma will be randomized and monitored for 6 weeks. Secondary objectives include evaluation of the difference in dermatologic QoL between the side of the face/ chest treated with dapsone versus the contralateral side treated with moisturizer, using the Skinindex-16/FACIT-EFRI-18 questionnaires. The difference in global severity of rash between the two application sides will also be evaluated by measuring the agreement of blinded independent dermatologists’ review of day-28 standardized photography of both sides. ClinicalTrials.gov: NCT01931150. Clinical trial information: NCT01931150.

TPS9639 Efficacy and safety of olanzapine combined with aprepitant, palonosetron, and dexamethasone for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting (CINV). But its preventive efficacy in combination with standard antiemetic therapy (palonosetron, aprepitant, and dexamethasone) is unknown. The purpose of this study is to prove the preventive effect of olanzapine on CINV caused by highly emetogenic chemotherapy (HEC) when used with standard antiemetic therapy. We started a prospective multicenter phase II study at six facilities related to Kansai Clinical Oncology Group (KCOG) since September 2013. Methods: Chemo-naïve patients aged 20-79 years old is enrolled. They are gynecologic cancer patients who are treated with HEC regimen containing cisplatin (more than 50 mg/m2). Target sample size is 40. Since olanzapine is contraindicated in patients with diabetes mellitus, their blood sugar level and HbA1c are checked to confirm that they do not have glucose intolerance before treatment. All patients are informed of drug information and the consent of using olanzapine is obtained. Aprepitant is adminis- tered at a dose of 125 mg before chemotherapy on day 1 and at 80 mg on days 2 and 3. Palonosetron (0.75 mg) is given before chemotherapy on day 1. Dexamethasone is administered at a dose of 9.9 mg before chemo- therapy on day 1 and at 6.6 mg on days 2–4. 5mg oral olanzapine is administered during 6 days (before chemotherapy on day 2 and days 2–4). At 24 hours after chemotherapy, record the self-evaluation diary about their emesis every 24 h throughout the overall phase (0–120 h after cisplatin). The primary endpoint is the proportion of patients with a complete response (no vomiting and no rescue therapy) throughout the overall phase. The secondary endpoints are the proportion of patients with complete response in the acute phase (0–24 h after cisplatin) and in the delayed phase (24–120 h after cisplatin) of the study, as well as the proportion of patients with complete control (no vomiting, no rescue therapy, no significant nausea (numeric rating scale 0-2)) and total control (no vomiting, no rescue, no nausea) throughout the study and in the acute and delayed phases. Clinical trial information: UMIN0000118572.

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NCT01991691. with its daily reporting of PRO has the potential to change the current rapid reaction to the reported symptoms. Consequently the TabPRO trial patient compliance. Due to early intervention this type of outcome-related symptoms in terms of frequency, severity, both association with chemotherapy cycles or patient characteristics and course during chemotherapy on at least a daily basis. Moreover, we evaluate time of reaction between reporting of PRO by the patient and both assessment and contacting by the physician. We evaluate the frequency of intervention as well as satisfaction with such a system by both patients and physicians. Electronic tablet-based PRO might increase efficiency of data collection and transmission, the patient-physician communication and consecutively patient compliance. Due to early intervention this type of outcome-monitoring might help to minimize chemotherapy-induced side effects by a rapid reaction to the reported symptoms. Consequently the TabPRO trial with its daily reporting of PRO has the potential to change the current assessment of chemotherapy-related side effects and to optimize patient care during outpatient chemotherapy. Clinical trial information: NCT01916919.

TPS9640 Poster Session (Board #296a), Sat, 1:15 PM-4:45 PM
TabPRO trial: Tablet-based real-time detection of patient-reported outcomes during adjuvant outpatient chemotherapy for breast cancer. First Author: Michael R. Mallmann, Department of Obstetrics & Gynecology, University Hospital of Bonn, Bonn, Germany
Background: Current symptom inquiry during adjuvant chemotherapy is based on symptom reporting at regular intervals, usually at the start of the subsequent cycle of chemotherapy or by telephone interviews during chemotherapy cycles. Consequently there exists a time lag between occurrence of symptoms, reporting by the patient and initiation of side-effect-directed therapy. In contrast, a real-time reporting of symptoms might fasten reaction towards side effects and thus improve patient care. Methods: This prospective multicenter trial determines the feasibility of an App-based query system to collect patient-reported outcomes (PRO) during outpatient adjuvant chemotherapy for breast cancer and to treat side effects during chemotherapy in real-time. The system includes an App-based symptoms assessment software for patients and an either Tablet- or computer-based symptoms-control software for physicians and health-care professionals offering a daily checkup of symptoms using a visual and intuitive App-based symptom assessment. Thus far, all 57 anticipated patients that are treated with adjuvant therapy for breast cancer in the participating trial centers have been enrolled. We evaluate all chemotherapy-related symptoms in terms of frequency, severity, both association with chemotherapy cycles or patient characteristics and course during chemotherapy on at least a daily basis. Moreover, we evaluate time of reaction between reporting of PRO by the patient and both assessment and contacting by the physician. We evaluate the frequency of intervention as well as satisfaction with such a system by both patients and physicians. Electronic tablet-based PRO might increase efficiency of data collection and transmission, the patient-physician communication and consecutively patient compliance. Due to early intervention this type of outcome-monitoring might help to minimize chemotherapy-induced side effects by a rapid reaction to the reported symptoms. Consequently the TabPRO trial with its daily reporting of PRO has the potential to change the current assessment of chemotherapy-related side effects and to optimize patient care during outpatient chemotherapy. Clinical trial information: NCT01916919.

TPS9642 Poster Session (Board #297a), Sat, 1:15 PM-4:45 PM
Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism. First Author: Annie Young, University of Warwick, Coventry, United Kingdom
Background: Venous thromboembolism (VTE) in cancer patients is an important and increasingly frequent clinical problem. The impact of VTE on cancer patients can be considerable. Targeted patient selection by identifying patients with clinically relevant recurrent VTE may have wider health economic benefits whilst reducing patient risk through over-treatment. In the UK, dalteparin is the licensed anticoagulant for the extended treatment of VTE in cancer patients and thus the gold standard. Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability. Methods: Select-d is a prospective, randomised, open label, multicentre pilot trial comparing dalteparin (200 IU/kg daily subcutaneously for 1 month and 150 IU/kg months 2-6), and rivaroxaban (15 mg orally twice daily for 3 weeks and 20mg once daily for 6 months in total) for cancer patients with VTE, with a second placebo-controlled randomisation (rivaroxaban vs placebo) comparing the duration of therapy (6 vs 12 months) in residual vein thrombosis (RVT) positive patients. 70% of patients are estimated to be RVT positive after initial treatment. 530 patients are being recruited to provide reliable estimates of the primary outcome (VTE recurrence rates) to within the 95% confidence interval of 8% assuming VTE rates are 10% at six months. The secondary objectives include safety, acceptability, biomarker identification and health economics. The select-d trial is amongst the first randomised trials of the new oral anticoagulants in patients with cancer, following recommendations from the UK National Institute of Health and Care Excellence. The select-d trial will recruit for two years with a minimum of one year follow up. The results will support optimal treatment for this key patient group. The independent TSC and DSMC fully support this important trial. Clinical trial information: ISRCTN85671230.

TPS9643 Poster Session (Board #297b), Sat, 1:15 PM-4:45 PM
Phase 3 randomized double blind placebo controlled trial evaluating Omega-3 in the prevention of Taxane or Platinum Induced Peripheral Sensory Neuropathy. First Author: Ralph Maroun, Department of Oncology, McGill University Health Center, Montreal, QC, Canada
Background: Chemotherapy induced peripheral neurotoxicity (CIPN) is a common and feared side effect of taxanes and platinum based chemotherapy. CIPN often leads to a decrease in dose intensity and or premature discontinuation of chemotherapy. Omega-3 fatty acids (OMA) have beneficial effects on neurological disorders including diabetic neuropathy, primarily by inhibition of the formation of proinflammatory cytokines involved in peripheral neuropathy (PN). A small study by Ghereishi et al. has shown benefit of OMA in the prevention of taxane induced neuropathy. We hypothesize that the supplementation of OMA should diminish or delay platinum or taxane induced PN. Methods: Randomized double blind placebo controlled trial to investigate the efficacy of OMA in reducing incidence and severity of taxane or platinum-induced PN. Eligible patients with breast cancer randomly assigned to take mammalian OMA with Vit D3 (provided by Aum Inc) 5cc sublingual tid vs placebo tid for 6 months. Clinical and electrophysiological studies were performed before the onset of chemotherapy and one month after cessation of therapy to evaluate CIPN based on “reduced Total Neuropathy Score” (rTNS). Eligibility criteria: Age 18-75, ECOG < 2, receiving taxane or platinum based chemotherapy Endpoints: The primary endpoint was the incidence of grade 2+ CIPN (CTCAE v 3.0) in each treatment arm, analyzed by chi-square testing. Patients with sample size n=100 patients per arm to provide 80% power to detect a difference in incidence of grade 2+ CIPN from 25% in the placebo group to 10% in the OMA group. Secondary endpoints: 1: rTNS to evaluate the existence and severity of CIPN (rTNS consists of subjective sensory symptoms and objective measured by nerve conduction studies). The patients receive an rTNS score ranging from 0-120 (higher score indicates more severe CIPN). In the case of an rTNS score of 20 or greater in the placebo group the severity of CIPN is then graded as follows: 1.mild (total score 1–10); moderate (total score 11–19); and severe (total score 20–28). In the case of an rTNS score of 20 or greater in the placebo group the severity of CIPN is then graded as follows: 1. mild (total score 1–10); moderate (total score 11–19); and severe (total score 20–28). 2Brief pain inventory and 3.The 11-item FACT/GOG-Ntx, version 4 (questionnaires validated to assess neuropathy due to chemotherapy). Conduct to Date: Study activation: Dec 2014. Enrollment: 15 subjects. Clinical trial information: NCT02294149.

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Morbidity and mortality associated with subsequent meningiomas among childhood cancer survivors exposed to cranial radiotherapy: A report from the Childhood Cancer Survivor Study. First Author: Daniel C. Bowers, The University of Texas Southwestern Medical Center, Dallas, TX

Background: Survivors of childhood cancer who were exposed to cranial radiotherapy (CRT) are at increased risk of subsequent meningiomas. However, incidence rates, neurological sequelae and impact on mortality are not well defined. Methods: Among 4,221 survivors exposed to CRT, subsequent meningiomas were self-reported and confirmed by pathology, medical records or death certificate. Age of onset of specific neurologic conditions was self-reported and proxy-reported. Standardized incidence ratios (SIRs) and absolute excess risk (AER) were estimated using expected age-, gender-, and calendar-year specific rates from SEER. Hazard ratios (HRs) for neurological sequelae and mortality were estimated using Cox proportional regression. Results: 199 meningiomas were identified among 169 survivors. The median age at meningioma diagnosis was 28 years (range, 7 – 50 years); median age at last follow-up was 32 years of age (range, 9 – 56 years). Median interval from primary cancer to first meningioma diagnosis was 22 years (range, 5 – 37 years). The cumulative incidence of a subsequent meningioma by age 40 years was 5.6% (95% CI: 4.7% – 6.7%). The SIR for a subsequent meningioma was 619.4 (95% CI: 532.7 – 720.2) and the AER was 21.8 per 10,000 person-years (95% CI: 18.5 – 25.1). Within 12 months of diagnosis of a subsequent meningioma, 13.6% of participants reported new-onset seizures, 10.7% auditory-vestibular-visual deficits, 11.8% focal neurological dysfunction and 6.5% severe headaches. With a median follow-up of 72 months following subsequent meningioma diagnosis, 22 (13%) participants died (6 deaths attributed to meningioma). Adjusting for cranial radiotherapy dose, a diagnosis of subsequent meningioma was independently associated with increased all-cause mortality (HR: 2.3; 95% CI: 1.5 – 3.5; p = 0.015). Conclusions: CRT-exposed childhood cancer survivors with subsequent meningiomas experience considerable new-onset neurological morbidity and increased all-cause mortality. Effective screening methods for subsequent meningiomas may reduce neurological morbidity.

Neurocognitive function of children treated for high-risk B-acute lymphoblastic leukemia (HR-ALL) randomized to Capizzi (CMTX) versus high-dose methotrexate (HD-MTX): A report from the Children’s Oncology Group (COG). First Author: Naomi J. Winick, The University of Texas Southwestern Medical Center, Dallas, TX

Background: Survivors of childhood HR-ALL are at risk for neurocognitive deficits. The causes are multifactorial including treatment, host and environmental factors. This study evaluated the relative impact of two different approaches to methotrexate delivery while simultaneously examining associations with demographic and treatment factors, in the absence of cranial radiation, on neurocognitive functioning after completion of therapy. Methods: Patients with HR-ALL, treated on COG AALL0232, were randomized to receive HD-MTX with leucovorin rescue versus lower dose, escalated CMTX with asparaginase. Intellectual functioning (IQ), working memory, and processing speed (PS) of participants was evaluated 8-24 months following completion of therapy. Results: Two hundred thirty-seven participants were eligible and enrolled on study, with 195 (54% female) submitting valid data. Mean age at diagnosis was 8.9 years (SD = 5), with 46% (n = 90) under age 10 at diagnosis. Method of methotrexate delivery was unrelated to differences in neuropsychological outcomes. Survivors younger than 10 at diagnosis, however, had an 11.8 point decrement (SE = 2.1) in estimated IQ (p < .01), and a 5.3 (SE = 2.2) point estimated decrease in PS scores (p < .05), compared to older participants, after controlling for ethnicity, race, gender, insurance status and time off treatment (raw IQ: F(7, 231) = 107.2, p < .001; PS: F(7, 231) = 16.16). Additionally, participants covered by US public insurers had adjusted IQs that were 12.0 points lower (SE = 2.8, p < .01), than participants with private insurance (raw IQ: 93.1 ± 15 vs. 106.1 ± 15). Conclusions: Even in the absence of cranial radiation, young survivors of HR-ALL are at risk for deficits in global intellectual functioning and processing speed. Critically, insurance status was also strongly associated with neurocognitive outcomes. These data may serve as a basis for developing screening protocols and potential interventions to both identify children with deficits and to ameliorate the impact of therapy on their neurocognitive outcomes. Clinical trial information: NCT00437060.

Chemotherapy and brain function in long-term survivors of childhood acute lymphoblastic leukemia (ALL). First Author: Yin Ting Cheung, St. Jude Children’s Research Hospital, Memphis, TN

Background: Limited data are available on associations among chemotherapy treatment and brain function in long-term survivors of childhood ALL. This study evaluated associations between treatment exposure, neurocognitive testing, and functional magnetic resonance imaging (fMRI) in children treated on an institutional protocol, which featured chemotherapy without cranial irradiation. Methods: Long-term survivors of ALL (n = 213; 51.2% male; median[SD] age 14.8[4.8] 7[11.7] years post-diagnosis), completed neurocognitive testing and brain fMRI during an executive function/attention task. During chemotherapy, serum concentrations of high-dose intravenous methotrexate (HD-MTX), plasma homocysteine (HCY) following HD-MTX, and dexamethasone (DEX) were quantified as area under the curve (AUC). Serum cortisol level was also measured following oral DEX. These variables, along with number of triple intrathecal therapy doses, were analyzed with general linear modeling as predictors of neurocognitive and fMRI outcomes. fMRI analysis was performed using SPM8. Results: Survivors performed below normative data on two standard measures of executive function: cognitive flexibility (mean[SD] Z-score = -0.58[1.2]) and fluency (-0.38[0.9]), both p’s < 0.0001. After adjustment for demographic factors, poorer cognitive flexibility was associated with higher MTX AUC (Est. -0.024; p = 0.015) and higher HCY AUC (Est. -0.011; p = 0.049). Poorer fluency was also associated with higher MTX AUC (Est. -0.023; p = 0.007). Survivors diagnosed at younger ages performed poorly on fluency at any level of MTX AUC, while those diagnosed at older ages performed poorly only if exposed to high MTX AUC (p = 0.063). Brain activation was positively correlated with MTX AUC in bilateral frontal and caudate nuclei, and left putamen and anterior cingulate cortex. Of note, these brain regions are commonly associated with cognitive flexibility and fluency, as well as other executive functions. Conclusions: Higher serum concentrations of MTX and plasma HCY following HD-MTX for childhood ALL may predict those at greatest risk for neurocognitive problems, particularly executive dysfunction, and altered brain activity during long-term survivorship.
Phase 1 study of dabrafenib in pediatric patients (pts) with relapsed or refractory BRAF V600E high- and low-grade gliomas (HGG, LGG), Langerhan cell histiocytosis (LCH), and rhabdomyosarcoma (RMS) (OST); First Author: Mark W. Kieran, Dana-Farber Cancer Inst-PN, Boston, MA

Background: Dabrafenib is an orally available, selective ATP-competitive inhibitor of BRAF V600E kinase, approved in unresectable or metastatic melanoma pts with the V600E mutation. This international study was designed to determine the recommended phase 2 dose (RPD2) in pts < 18yrs based on maximum tolerated dose, or systemic exposure similar to that seen in adult pts (AUC, 4000–5500 ng*h/mL), whichever came first.

Methods: Dabrafenib was given orally twice daily, beginning at 3.0mg/kg/day. Toxicity, pharmacokinetics, and response were assessed by disease-appropriate criteria at each dose for pts > 12yrs and ≤ 12yrs. Doses of 3.0, 3.75, 4.5, and 5.25mg/kg/day were assessed by a rolling six design. When a dose-limiting toxicity (DLT) of ≥ grade 3 maculopapular rash (MR) at 4.5mg/kg/day, but is on study >9mts after restarting dabrafenib at 3.75mg/kg/day. Serious adverse events judged related to dabrafenib included MR (1 pt); hypotension, disseminated intravascular coagulation, fever (1 pt, outside DLT period); and arthralgia (1 pt). Duration on study ranged from 9wks to 19mo (ongoing); 20 pts remain on treatment. The RPD2 for pts > 12yrs is 4.5mg/kg/day (median AUC 5285) and 5.25mg/kg/day (median AUC 4384) for ≤ 12yrs. Investigator-assessed best radiographic responses included 3 complete response (CR), 3 partial response (PR) and 2 progressive disease (PD) in HGG; 8 PR, 6 stable disease (SD) and 1 PD in LCH; 2 CR in LCH; 1 SD and 1 PD in RMS (source data verification ongoing).

Conclusions: The RPD2 of dabrafenib for children ≤ 12yrs is 4.5mg/kg/day. For pts ≥ 12yrs, the safety, PK and efficacy of adding dabrafenib 60mg/m2 daily to AALL0031 chemotherapy was well tolerated with no toxic deaths. For the 51 evaluable subjects were enrolled from 7/2008 to 2/2012 (39 Cohort 1 and 21 Cohort 2); 33 completed protocol therapy; 12 pts had dose-limiting toxicity ≥ 560 mg/m2, 11 were assessed ALD ALCL and persistent G2 abdominal pain. PK at the RDE (AUC and CL/F) was comparable to that reported for adults at this dose. Early data shows responses in 2 of 2 pts with AALL and 4 of 7 pts with MT/IMT (2 CR: 1 in a crizotinib-pretreated pt). To date, one pt with ALK F1174L mutated NB had shrinkage of a retroperitoneal mass; disease progressed in the brain, where lower ceritinib exposure is expected. Dose escalation with food is ongoing. Conclusions: The RDE in children is 510 mg/m2/day without food. The toxicity profile is similar to that in adults. Food may reduce gastrointestinal symptoms and allow further dose escalation. Ceritinib shows efficacy in pediatric pts with ALCL and MT/IMT. Clinical trial information: NCT01742286.

Feasibility of intensive post-Induction therapy incorporating clofarabine (CLOF) in the very high risk (VHR) stratified of patients with newly diagnosed high-risk B-cell lymphoblastic leukemia (HR-B-ALL) on Children’s Oncology Group AALL1131. First Author: Michael Burke, Medical College of Wisconsin, Milwaukee, WI

Background: Four-year disease free survival (DFS) for patients with B-ALL classified as VHR is approximately 70%. Strategies to improve DFS with intensive post-Induction therapy using fractionated cyclophosphamide (CYT), etoposide (ETO) and CLOF were evaluated on AALL1131. Methods: AALL1131 enrolled patients 1-30 yrs old with newly diagnosed HR-B-ALL. The VHR subjects had isolated post-Induction cerebellar hyperplasia (CH); ALK-positive; +/− translocated non-small cell lung cancer. This report describes the results of a phase I study (NCT01742286) in pediatric pts with ALK-aberrant malignancies: anaplastic large cell lymphoma (ALCL); myeloidblastic tumor (MT)/inflammatory (IMT) rhabdomyosarcoma (RMS) and neuroblastoma (NBL). The phase I design of the dose finding phase established a RDE of 510 mg/m2/day without food. Common adverse events (% Any Grade) were diarrhea (84.6; 9.1); vomiting (81.8; 0); nausea (54.4; 0); elevated ALT (45.5; 18.2); abdominal pain (40.9; 9.1), decreased appetite (40.9; 0); elevated AST (36.4; 18.2); pyrexia (36.4; 0), and fatigue (31.8; 0). Two pts had dose-limiting toxicity ≥ 560 mg/m2, 33 were assessed ALD and persistent G2 abdominal pain. PK at the RDE (AUC and CL/F) was comparable to that reported for adults at this dose. Early data shows responses in 2 of 2 pts with AALL and 4 of 7 pts with MT/IMT (2 CR: 1 in a crizotinib-pretreated pt). To date, one pt with ALK F1174L mutated NB had shrinkage of a retroperitoneal mass; disease progressed in the brain, where lower ceritinib exposure is expected. Dose escalation with food is ongoing. Conclusions: The RDE in children is 510 mg/m2/day without food. The toxicity profile is similar to that in adults. Food may reduce gastrointestinal symptoms and allow further dose escalation. Ceritinib shows efficacy in pediatric pts with ALCL and MT/IMT. Clinical trial information: NCT01742286.

Toxicities: CON PART 2

CLOF (30 mg/m2 × 5 days)

<table>
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<th>Toxicity</th>
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CLOF (20 mg/m2 × 5 days)

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<td>Gr 1-2 Infection</td>
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<td>Gr 3/4 AKI</td>
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*Also listed as a Gr 4 infection.*
Augmentation of therapy for favorable-histology Wilms Tumor with combined loss of heterozygosity of chromosomes 1p and 16q: A report from the Children’s Oncology Group (COG) studies AREN0532 and AREN0533. First Author: David B. Dix, British Columbia Childrens Hosp, Vancouver, BC, Canada

Background: In National Wilms Tumor Study-5, tumor-specific combined loss of heterozygosity (LOH) of chromosomes 1p and 16q was associated with adverse outcome in patients with favorable histology Wilms Tumor (FWHT): stage II patients treated with Regimen EE4A (vincristine (VCR)/ doxorubicin (DOX))/dactinomycin (DACT) had 4-year EFS of 91.2% without LOH and 74.3% with LOH; stage III/IV patients treated with Regimen DD4A (VCR/ DACT/doxorubicin(DDX) and radiotherapy (RT)) had 4-year EFS of 83% without LOH and 65.9% with LOH. The AREN0533/AREN0532 studies assessed whether augmenting therapy would improve EFS for FWHT with combined 1p/16q LOH. Stage I/II patients treated with Regimen DD4A (Regimen DD4A) but no RT. Stage III/IV patients were treated with Regimen M (VCR/DACT/DDX alternating with cyclophosphamide/etoposide) and RT. Methods: Patients were enrolled through the AREN03B2 Biology and Classification study between 10/2006 and 7/2013. All patients underwent central review of pathology, surgical reports and diagnostic imaging. Tumor tissue was evaluated for LOH 1p and 16q by microsatellite testing. Descriptive statistics were used to compare the EFS/OS between NWT5-5 and the current studies. Results: Median follow up for 1,134 patients enrolled on AREN0532/0533 was 3.6 years (0.1 to 8.1 years). Combined LOH 1p and 16q was detected in 35 evaluable stage II/III patients and 52 stage III/IV patients. At analysis in December 2014 the number of events was 6 observed versus 9 expected for stage II/III, and 4 observed versus 18 expected for stage III/IV. The 4 year EFS for the stage I/II LOH patients and stage III/IV LOH patients was 83.9% (95%CI: 64.9%, 93.1%) and 91.5% (95%CI: 78.5%, 96.8%) respectively. Grade 3 or higher hematological toxicity was the most common toxicity observed with Regimen M, affecting 60% of patients. There were no unexpected toxicities. Conclusions: Regimen M therapy improved EFS for patients with stage III/IV FWHT with LOH at 1p/16q as compared to the historical controls. Group treated with Regimen M had 4 year EFS of 83% compared to 62% for patients treated with Regimen DD4A instead of Regimen EE4A for stage III/IV FWHT with LOH is less clear. Clinical trial information: NCT00379340; NCT00352534.

Omission of lung radiation in patients with stage IV favorable histology Wilms Tumor (FWHT) showing complete lung nodule response after chemotherapy: A report from Children’s Oncology Group study AREN0533. First Author: David B. Dix, British Columbia Childrens Hosp, Vancouver, BC, Canada

Background: In National Wilms Tumor Study-5, patients with stage IV FWHT with metastases limited to the lung had 5-year EFS of 74% in the setting of incomplete lung nodule response by Day 70 versus 85% with complete lung nodule response (CR). All patients were treated with Regimen DD4A (vincristine (VCR)/ doxorubicin (DOX)/dactinomycin (DACT) and chest radiation (RT)). To decrease the risk of long-term toxicities associated with RT, the AREN0533 study sought to determine whether patients with lung nodule CR after 6 weeks of chemotherapy would maintain excellent EFS without the use of lung RT. Methods: Patients were enrolled between February 2007 and February 2013 after undergoing central review of surgical reports, pathology slides and chest CT scans on the AREN03B2 Biology and Classification Study. Lung nodule response after 6 weeks of chemotherapy was determined by central radiology review. The null hypothesis was that 4-year EFS for CR when treated with DD4A therapy and prophylactic chest irradiation (RT) is 85%. The study was designed with the alternative hypothesis (p = 0.15) of the 2-sided chi-square test at 10% 1-sided to detect an increase in the risk of failure corresponding to 4-year EFS of 75%. Results: Among 391 patients enrolled, 296 had lung-only metastases, of which 105 (39%) had CR. At interim analysis in June 2014, 20 events were observed, compared to 14.5 expected under the null hypothesis (p = 0.01). Nineteen of the 20 events (95%) were due to lung failure. CR was a secondary malignancy. Among the 19 recurrences, there were 2 deaths with a median follow-up of 2.3 years from recurrence. Recurrences were in the lung only (17), lung and liver (1) and abdomen (1). The 4-year EFS and OS estimates for the CR patients were 78% (95% CI: 68%, 86%) and 95% (95% CI: 83%, 98%) respectively. Conclusions: Patients with FWHT with week 6 lung nodule CR treated without lung RT had EFS somewhat less than the historical standard treated with lung RT, though this difference was not statistically significant. The excellent OS suggests that omission of lung RT may provide an acceptable treatment approach for this patient subgroup. Clinicians should balance the benefit of avoidance of lung RT against the possibility of a modest increase in relapse risk. Clinical trial information: NCT00379340.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Synovial sarcoma (SS) is the second most common soft tissue sarcoma in children. ARST0332 evaluated a risk-based treatment strategy for young soft tissue sarcoma patients designed to limit therapy for low-risk disease and to test neoadjuvant chemoradiotherapy for unresected high-risk disease. Methods: Newly diagnosed SS patients < 30 years old were assigned to 4 treatment arms based on disease features including POG 50%, respectively. The outcome of Type II and III PPB after a relapse solid. Five-year survival rates for Types I/Ir, II and III PPB are 91%, 71% and 16%, respectively. Results: Of the 149 SS patients enrolled, 129 were eligible for analysis. LR (43), IR (66) and HR (20). Most (74%) were 10-19 years of age and 52% were female. Tumors were 79% extremity, 71% < 5 cm, 30% intermediate-grade, 70% high-grade, 63% invasive, 96% deep, and 16% metastatic. Thirty-nine patients (30%) did not receive RT. There were no toxic deaths and only 5 unexpected grade 4 adverse events. By risk group, at a median follow-up of 2.6 years, estimated 3-year event-free survival was: LR 97%, IR 93%, HR 29%. After accounting for risk category, none of the other patient or disease characteristics (age, gender, tumor site, neurovascular invasiveness, depth) were statistically significant. Conclusions: The novel risk-based treatment strategy used in ARST0332 was associated with favorable outcomes in non-metastatic SS patients relative to historical controls using RT less frequently and at lower doses. The outcome for metastatic SS remains unsatisfactory and new therapies are urgently needed. Besides risk group, no other factors predictive of outcome were identified. Clinical trial information: NCT00346164.

10014 Oral Abstract Session, Mon, 8:00 AM-11:00 AM
Association of recurrent or progressive p of form types II and III pleuropulmonary blastoma (PPB) with poor outcome: A report from the international PPB registry. First Author: Kris Ann Pinekenstein Schultz, Childrens Hosp and Clinics - Minnesota, Minneapolis, MN

Background: Pleuropulmonary blastoma (PPB) is a rare malignancy of the lung presenting in young children. PPB is the sentinel disease of the PPE-DICER1/familial syndrome. The International PPB Registry (IPPPR) has pathologic data on 425 cases of PPB. Three pathologic subtypes correlate with outcome: Type I/Ir, purely cystic; Type II, combined cystic solid; Type III, purely solid. Five-year survival rates for Types I/I, II and III PPB are 91%, 71% and 53%, respectively.

Methods: Yearly follow-up is requested for all patients by the IPPPR. All PPB was confirmed by central pathology review. Reports of relapse and second malignancies were obtained by the IPPBR from the local institution. In most cases, the pathology of relapse or second malignancy was available for additional central review. Results: A total of 107 PPB patients released, of them 35 (33%) were alive at a median of 14 months (range 0-61) and 72 (67%) had died at a median of 10 months (range 0-60). Twenty-nine (27%) relapsed with isolated CNS metastases, 51 (48%) with isolated chest relapse, and 27 (25%) with other relapse; of them 66%, 53% and 96% respectively have died. Of the survivors, 34/35 (97%) had isolated disease either in the chest or CNS. In addition to the patients with recurrence, 6 patients had secondary malignancies believed to be related to prior therapy and 5 had a metastatic DICER1-related tumor; of these 83% and 100% respectively, were alive. Conclusions: This cohort confirmed previous relapse of PPB in only one-third were alive at last follow-up. Patients with isolated CNS or chest metastases, but with bone metastases rarely survive. Novel treatment regimens for relapsed PPB are urgently needed.

10015 Oral Abstract Session, Mon, 8:00 AM-11:00 AM
Early results from Children’s Oncology Group (COG) ARST0881: Pilot studies of cixutumumab or temozolomide with intensive multiagent chemotherapy for patients with metastatic rhabdomyosarcoma (RMS). First Author: Suman Malempati, Oregon Health and Science University, Portland, OR

Background: Data from a previous COG study (ARST0431) showed an early FFS improvement but no long-term survival benefit with intensive interval-compressed chemotherapy in metastatic RMS. ARST0881 aimed to determine the feasibility of adding cixutumumab (inulin-like growth factor-1 receptor [IGF1R] monocolonal antibody) or temozolomide to an intensive chemotherapy backbone. Methods: A series of non-randomized single-arm pilot studies were conducted. After determining feasibility, pilots were expanded to assess efficacy. Eligible patients were <50 yrs with metastatic RMS. Backbone therapy consisted of blocks of vincristine/irinotecan (weeks 1-2, 20-25, 47-51), interval-compressed vincristine/irinotecan/ cyclophosphamide alternating with ifosfamide/etoposide (weeks 7-9 and 26-34), and vincristine/actinomycin-D/cyclophosphamide (weeks 38-46). In Pilot 1, patients received cixutumumab (3, 6, or 9 mg/kg) IV once weekly throughout therapy. In Pilot 2, patients received oral temozolomide (150 mg/m2) daily x 5 days each cycle. In Pilot 3, patients received irinotecan. Patients received therapy treatment (RT) at weeks 20-25. RT was also permitted at weeks 1-6 or 47-51. Results: 168 eligible patients were enrolled (1/2010 - 7/2013). 71 patients received temozolomide and 97 patients received cixutumumab (19 at 3 mg/kg, 18 at 6 mg/kg, and 60 at 9 mg/kg). Most patients were 10 years old (74%), with alveolar RMS (70%) and with metastases (59%). Two cases of Grade 4 and one grade 5 sinusoidal obstructive syndrome (SOS) occurred with cixutumumab at 9 mg/kg in combination with the chemotherapy backbone. Otherwise, toxicities were similar to ARST0431. With a median follow-up of 1.6 yrs, 16-month EFS was 68% with cixutumumab and 39% with temozolomide (log-rank p-value < 0.001). Conclusions: Addition of cixutumumab or temozolomide to intensive multi-agent chemotherapy for metastatic RMS was safe and feasible. SOS may be a concern with higher doses of cixutumumab combined with intensive chemotherapy. Early FFS was better with cixutumumab than temozolomide. Overall outcome for metastatic RMS remained poor. Clinical trial information: NCT01055314.
Banked EBV-specific T-cells from HLA-partially matched normal donors to induce durable remissions of rituximab refractory EBV+ B-cell lymphomas post hematopoietic and organ allografts. First Author: Susan Prockop, Memorial Sloan Kettering Cancer Center, New York, NY

Background: EBV-LPD complicating allogeneic hematopoietic cell transplant (alloHCT) most frequently present as malignant, high grade, diffuse large B cell lymphomas (DLBCL) that do not respond to reduction in immune suppression. Rituximab induces remissions in about 55% of those with radiographic evidence of disease. Survival of rituximab-refractory EBV-LPD patients (pts) is 16 – 56 days. There are few other treatment options. We evaluated the efficacy and safety of EBV-CTLs in 2 clinical trials in alloHCT recipients with EBV+ disease. Methods: As part of 2 ongoing clinical trials (95-024 and 11-130) 57 pts received EBV-CTLs derived from unrelated third-party donors (13 on 95-024 and 18 on 11-130) or primary stem cell donors (26 on 95-024). Fifty-one pts were treated for monomorphic DLBCL, 3 polyomiphic, 1 NKT cell lymphoma and 2 for viremia alone. On subjects 11-130 had all failed prior rituximab. On 95-024 28 of 39 pts had failed prior rituximab. Subjects in both studies received up to 5 cycles of EBV-CTL infusions; each cycle 1 or 2×10^6 cells/kg weekly for 3 weeks. Results: Of the 18 recipients of 3rd party EBV-CTLs on 11-130, 9 had complete response (CR), 3 partial response (PR) and 1 stable disease (SD) for a response rate of 67% and non-progression rate of 72%. The median duration of CR+PR was 318 days. Kaplan-Meier (KM) overall survival (OS) was 71.8% at 1 and 2y. KM progression-free survival was 66.7% at 1y. OS 95-024, 23 had CR, 1 PR, and 3 SD, for a response rate of 62%. Strikingly, the 1y OS for rituximab-refractory pts in both studies was 50% and 49% for pts treated with 3rd party and transplant donor-derived EBV-CTLs respectively. Four patients on 11-130 and 6 patients on 95-024 died soon after the first EBV-CTL infusion; no death was considered related to treatment. EBV-CTLs had low toxicity; no pts developed cytokine release syndrome or required therapy for EBV-CTL-related GVHD. Conclusions: EBV-CTLs produce high response rates that are durable; pts who achieved CR had no relapses of EBV LPD. The OS in both studies far exceeded the survival reported for this patient population. EBV-CTLs had a favorable safety profile and were well tolerated. Clinical trial information: NCT01498484.

Pulmonary function in adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort Study (SJLIFE). First Author: Daniel M. Green, St. Jude Children’s Research Hospital, Memphis, TN

Background: The relationship between treatment exposures and long-term pulmonary function of childhood cancer survivors (CCS) treated with pulmonary toxic therapies has not been well studied. SJLIFE (n=989) previously treated with pulmonary toxic therapies underwent assessment of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), single breath diffusing capacity for carbon monoxide corrected for hemoglobin (DLCOcorr) and total lung capacity (TLC) according to American Thoracic Society standards. Results were expressed as percent of age-, race-, and sex predicted values. Lung radiation dose was estimated using the patients’ actual treatment ports and a CT dosimetry phantom. Associations were assessed using logistic regression. Variables significant at p < 0.1 on univariate analysis were entered into the multivariable models. Results: Median age at evaluation was 34.2 years (interquartile range [IQR], 28.7 to 40.1) and median time from diagnosis 21.9 years (IQR 16.6 to 27.8). Among survivors, 50.7% had FEV1 < 80% of predicted, 47.2% FVC < 80%, 31.2% TLC < 75%, and 44.6% DLCOcorr < 75%. Only 0.8% of survivors had obstructive (FEV1/FVC < 0.7), but 31.2% had restrictive (TLC < 75%) lung defects. Risk factors are shown in the Table. Conclusions: These risk factors identified CCS who may benefit from interventions to improve pulmonary function.

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<tr>
<th>Risk factor</th>
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<tr>
<td>DLOcorr &lt; 75% predicted</td>
<td>BLD &lt; 80% predicted</td>
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<tr>
<td>Age at diagnosis (years)</td>
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<tr>
<td>10 – 14</td>
<td>0.88 (0.84, 0.92)</td>
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<tr>
<td>15 – 19</td>
<td>0.82 (0.78, 0.86)</td>
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<td>Diagnosed before age 2</td>
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<tr>
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<td>Other grade 3 and 4 non-hematologic toxicities</td>
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<td>Blomkran (per 40 mg/dL)</td>
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<td>Cytosine arabinoside (per 100 mg/m2)</td>
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<tr>
<td>V10 (per 10% increase)</td>
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* Did not satisfy criterion for inclusion in multivariable model.

Second malignancies in neuroblastoma patients: A report from the International Neuroblastoma Risk Group. First Author: Mark A. Applebaum, University of Chicago, Chicago, IL

Background: Exposures to radiation and chemotherapy are associated with increased risk of second malignant neoplasms (SMN) in neuroblastoma survivors. However, it remains unclear if modifications in risk-based treatment strategies during the past 25 years have changed SMN rates. Methods: The International Neuroblastoma Risk Group (INRG) Task Force created a database of neuroblastoma patients diagnosed from 1974-2013. SMN risk was measured by cumulative incidence, standardized incidence ratios (SIR) and absolute excess risk (AER) per 10,000 person-years relative to a matched United States population. Poisson regression compared rates of SMN between different groups. Results: Of the 16,520 patients in the INRG database, 9,261 enrolled on Children’s Oncology Group protocols had SMN data available. 79 (0.85%) patients developed SMN, including hematologic malignancies (n = 38), sarcomas (n = 19), carcinomas (n = 10), CNS tumors (n = 10), hepatoblastoma (n = 1), and nephroblastoma (n = 1). The incidence of SMN of the entire cohort was 0.56% at 10-years, p < 0.012). The cumulative incidence of SMN for two treatment eras (1: 1990-1996; 2: 1997-2009), corresponding to intensification of treatment regimens for high-risk disease, showed a higher frequency of SMN for those treated in Era 2 compared to Era 1 (1.4% vs. 0.39% at 10-years, p = 0.012). Conclusions: The incidence of SMN is higher than expected in high and intermediate-risk neuroblastoma survivors. The exposure to more intensive treatment likely contributes to the higher incidence of SMN in high-risk patients diagnosed after 1996. Genome-wide association studies (n = 5,188) to identify modifiers of SMN susceptibility are ongoing.
Temporal trends in health status among adults in the Childhood Cancer Survivor Study (CCSS). First Author: Kirsten K. Ness, St. Jude Children’s Research Hospital, Memphis, TN

Background: The impact of temporal changes in childhood cancer therapy on long-term health status has not been evaluated. With expansion of CCSS, information about health status is available for $b$ survivors diagnosed from 1970-1999. Methods: We estimated prevalence of poor general and mental health, functional impairment, activity limitation and cancer-related anxiety and pain at baseline evaluation among 15,830 survivors of childhood cancer. Results: Prevalence of poor general health (37.7 to 19.7%) dropped over three groups (standard, intermediate and high risk groups). Conclusions: The impact of temporal changes in childhood cancer therapy on long-term health status has not been evaluated. With expansion of CCSS, information about health status is available for $b$ survivors diagnosed from 1970-1999. Methods: We estimated prevalence of poor general and mental health, functional impairment, activity limitation and cancer-related anxiety and pain at baseline evaluation among 15,830 survivors of childhood cancer. Results: Prevalence of poor general health (37.7 to 19.7%) dropped over time. Survivors diagnosed more recently were more likely to report poorer general health, pain and anxiety, and less likely to report functional impairment. Diagnoses with large increases ($p < 0.001$) in prevalence of adverse outcomes from 1970-79 to 1990-99 were leukemia (9.8 to 12.6% poorer general health), bone tumor (23.2 to 30.7% pain) and Hodgkin lymphoma (15.7 to 19.2% anxiety). CNS survivors had the largest decrease in functional impairment prevalence (37.7 to 19.7%). Conclusions: While the proportion of childhood cancer survivors reporting functional impairment in the most recent era decreased, particularly among CNS survivors, proportions reporting poor general health, pain and anxiety increased slightly from 1970 to 1999.

10023 Poster Discussion Session; Displayed in Poster Discussion Session (Poster #93), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM
Clinical outcome and biological predictors of relapse following nephrec- tomy only for very low risk Wilms tumor (VLRT): A report from Children’s Oncology Group AREN0532. First Author: Conrad Vincent Fernandez, IWK Health Centre, Halifax, NS, Canada

Background: An earlier study of observation only for nephrectomy for VLRT defined as stage I, age < 2 years, favorable histology with a weight <550 grams was suspended for excess relapse. Follow-up revealed a higher salvage rate than originally predicted and suggested novel prognostic biomarkers. In this study, we sought to determine if 1) an observation alone strategy in centrally reviewed VLRT WT demonstrates an Event Free Survival (EFS) of > 85% and Overall Survival (OS) of > 95%, and 2) to validate prognostic biomarkers. Methods: From 10/30/2006-12/31/2013, 116 eligible patients were enrolled with VLRT WT, negative lymph node sampling was required and predilection syndromes were excluded. All cases had central review of pathology, diagnostic imaging and surgical reports on the AREN03B2 biology and classification study. Evaluable tumors were analyzed for mutation of WT1, 1p and 16q loss of heterozygosity (LOH) using microsatellite analysis, 1q gain, 1p and 16q loss by MLPA, and 11p15 loss or retention of imprinted LOH (ROI) using methylation restriction sites sites analysis. Results: Median follow up was 80 months (5-97). Median age was 11.5 months (0.1-23). 12 patients relapsed with no deaths. Estimated 4-year EFS was 99.7% (95% CI 84.1-100%), and 100%. 1 patient is alive with disease after 4 relapses. First site of relapse was lung (n=5), tumor bed (n=4), abdomen (n=2), partial visceral (n=2). Median time to relapse was 4.2 months (2.2-4.3). The presence of intralobar (p=0.46) or periblar rests (p=1.0) was not associated with relapse, nor was histological subtype (p=0.16). 1q gain, 1p loss and 16q loss did not predict relapse, nor did WT1 mutation (but 13/14 with WT1 mutations had 1p and 16q LOH). Conclusions: Most patients meeting VLRT criteria can be safely managed by nephrectomy alone. 11p15 LOH/ROI predicts relapse in future trials and ongoing exploration of an observation alone strategy for low risk WT should incorporate these biomarkers. Clinical trial information: NCT00352534.
Loss of STAG2 expression and prognosis in Ewing sarcoma family of tumors. First Author: Armita Bahrami, St. Jude Children’s Research Hospital, Memphis, TN

Background: The Ewing sarcoma family of tumors (ESFTs) is an aggressive primitive sarcoma of bone and soft tissue. Although several clinical factors are associated with patient outcomes, few biomarkers have prognostic relevance. Recurrent inactivating mutations or deletions in the cohesin complex subunit STAG2 have been recently described in 15-20% of ESFTs, but their prognostic significance is uncertain. We previously reported that concurrent STAG2 and TP53 mutations in ESFTs predict clinical aggressiveness. In this study of an independent cohort, we evaluated the prognostic significance of STAG2 deficiency on clinical outcomes in correlation with established clinical risk markers. Methods: Immunohistochemical (IHC) analysis for STAG2 was performed on 143 ESFT samples from 111 patients (90 osseous; 21 extraskeletal). The Cox regression model was used to study the association between overall survival (OS) and potential risk factors (age at diagnosis (< 15 vs. ≥ 15 years), gender, primary tumor site (axial vs. extremities), metastatic disease at diagnosis, and STAG2 status). IHC was performed on STAG2-deficient ESFTs to determine the frequency of coexisting TP53 missense mutations (TP53mut). Results: ESFTs occurred in 68 (66%) male and 43 (34%) female patients with a median age of 12.9 years (range, 5 months to 22 years). Tumors involved extremities in 47 (42%) patients and axial/pelvis in 64 (58%) patients. Metastatic disease at diagnosis was seen in 27 (24%) patients. Of the 111 patients, 38 were alive (median follow-up, 16.1 years), 64 died of disease, and 9 died of other causes (median time to death, 2.8 years). STAG2 was expressed in 95 (86%) tumors and not in 16 (14%) tumors. Of the 16 STAG2-negative tumors, 4(25%) harbored concurrent TP53mut. Cox regression analysis identified metastatic disease at diagnosis as the most significant adverse prognostic indicator for OS (P = 0.0005). Axial location and STAG2 deficiency were associated with a lower OS, but neither reached statistical significance (P = 0.053 and P = 0.059, respectively). Conclusions: Our findings do not support using STAG2 loss as a single predictor of outcome. The effects of STAG2 deficiency in ESFTs may be mediated by coexisting genetic modifiers such as TP53 alterations.

RNA helicase DDX3 is a novel therapeutic target for Ewing sarcoma. First Author: David Mark Loeb, Johns Hopkins Univ, Baltimore, MD

Background: There is growing interest in RNA and DNA helicases as therapeutic targets in a variety of sarcomas. We investigated the expression and function of RNA helicase DDX3 in Ewing sarcoma and have begun to explore the effect of a novel DDX3 inhibitor, RK-33. Methods: Immunohistochemical (IHC) analysis for DDX3 was performed on 143 ESFT samples from 111 patients (90 osseous; 21 extraskeletal). The Cox regression model was used to study the association between overall survival (OS) and potential risk factors (age at diagnosis (< 15 vs. ≥ 15 years), gender, primary tumor site (axial vs. extremities), metastatic disease at diagnosis, and DDX3 status). IHC was performed on DDX3-deficient ESFTs to determine the frequency of coexisting TP53 missense mutations (TP53mut). Results: ESFTs occurred in 68 (66%) male and 43 (34%) female patients with a median age of 12.9 years (range, 5 months to 22 years). Tumors involved extremities in 47 (42%) patients and axial/pelvis in 64 (58%) patients. Metastatic disease at diagnosis was seen in 27 (24%) patients. Of the 111 patients, 38 were alive (median follow-up, 16.1 years), 64 died of disease, and 9 died of other causes (median time to death, 2.8 years). STAG2 was expressed in 95 (86%) tumors and not in 16 (14%) tumors. Of the 16 STAG2-negative tumors, 4(25%) harbored concurrent TP53mut. Cox regression analysis identified metastatic disease at diagnosis as the most significant adverse prognostic indicator for OS (P = 0.0005). Axial location and STAG2 deficiency were associated with a lower OS, but neither reached statistical significance (P = 0.053 and P = 0.059, respectively). Conclusions: Our findings do not support using STAG2 loss as a single predictor of outcome. The effects of STAG2 deficiency in ESFTs may be mediated by coexisting genetic modifiers such as TP53 alterations.

Activity of Hsp90-inhibitor drug conjugate (HDC) STA-12-8666 in preclinical models of pediatric sarcoma. First Author: Christine Heske, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD

Background: Long-term survival in patients with metastatic relapsed or recurrent Ewing sarcoma (ES) and rhabdomyosarcoma (RMS) is poor. Early phase studies have shown encouraging responses in these patients using irinotecan. However, limitations of irinotecan, including a low conversion rate to active metabolite (SN38) and a high excetration rate of the inactive form, diminish delivery of this drug to tumors and hinder efficacy. In addition, systemic toxicity limits dose escalation in the clinical setting, especially in drug combinations. Hsp90 is widely expressed in cancer cells, and Hsp90 inhibitors display favorable pharmacokinetics for anticancer use as they remain in tumors for a prolonged period of time and at higher levels, compared to normal tissue. This property makes them ideal intracellular delivery vehicles for chemotherapeutic drugs, allowing for high tumor exposure and low systemic toxicity. STA-12-8666 (Synta Pharmaceuticals) is an HDC conjugated to SN38. The purpose of this study was to test this HDC in xenograft models of pediatric sarcoma. Methods: To test therapeutic efficacy of this HDC, female SCID mice underwent orthotopic injection of ES or RMS cells. When tumors reached between 100 and 500 mm3 (ES) or 50 and 90 mm3 (RMS), mice were randomized and then treated weekly with STA-12-8666, vehicle, irinotecan or ganetespib (an Hsp90 inhibitor). Tumors were measured twice per week with calipers, and mice were weighed weekly to determine drug tolerability. Tumors were harvested at midpoints and at study endpoint for biology studies. Results: In xenograft models of both ES and RMS, treatment with STA-12-8666 produced superior antitumor efficacy compared to controls. All tumors underwent significant regression on a single treatment, and some tumors showed greater than 11 weeks. Additional early data has shown regression of larger tumors to 1000 mm3. Studies are ongoing and will be reported. Tolerability was excellent with no toxicity-related deaths or significant weight loss in treated mice. Dose titration arms and pharmacodynamic studies on tumors are ongoing. Conclusions: Preclinical data suggest that STA-12-8666 may be a promising anticancer agent for ES and RMS patients.

The methylene of pediatric acute myeloid leukemia. First Author: Stanley Pounds, St. Jude Children’s Research Hospital, Memphis, TN

Background: DNA methylation can alter gene expression by either creating binding sites for methylation-dependent repressor proteins, or by disrupting the binding of transcription factors to their target sequences. DNA methylation has been studied extensively and associated with survival in adults with AML. However, a detailed genome-wide study of epigenetic regulation of gene expression and its pharmacological and clinical impact in pediatric AML patients has not been performed. Methods: In this study, we obtained Illumina 450K methylation array profiles for 175 pediatric patients and Affymetrix U133A gene expression arrays for 166 pediatric patients treated in the multicenter ALL02 clinical trial (NCT00136084). Results: We found a very significant canonical correlation of methylation with expression (FDR ≤ 0.01) in 1,978 genes with several of the top ranked genes having established roles in the biology and treatment of AML. An analysis adjusting for risk group found that the canonical correlation methylation and expression variables of 24 genes showed statistically significant evidence of a biologically meaningful association with in vitro sensitivity to cytarabine, minimal residual disease assessed by flow cytometry after the first course of chemotherapy, and event-free survival (p ≤ 0.001; FDR ≤ 0.32). Finally, we observed differential methylation according to clinical risk group at 36,667 markers scattered throughout the genome (FDR ≤ 0.01) with low composite scores, showing hypomethylation at 32,920 of those 36,667 (89.8%) markers. Conclusions: Given the methylation differences in clinical risk groups incorporation of demethylating agents might be a useful strategy to improve the outcome of high-risk AMLs by modifying the methylation to more closely resemble that of low-risk AMLs, which are most sensitive to cytarabine. Our results illustrate the power of combined profiling of methylation and expression to improve our understanding of the disease and the molecular level and identify potentially useful therapeutic targets.
Accuracy of adverse event reporting on a phase III clinical trial for pediatric acute myeloid leukemia: A report from the Children’s Oncology Group. 

First Author: Tamara P. Miller, Children’s Hosp of Philadelphia, Philadelphia, PA

Background: Adverse events (AE) on Children’s Oncology Group (COG) trials are reported by clinical research associates (CRA) on case report forms using the Common Terminology Criteria for Adverse Events (CTC). CTC has increased in complexity from initially 49 AEs to 789 currently. This complexity challenges CRAs to accurately identify AEs. This study sought to evaluate the accuracy of AE reporting on a COG clinical trial and to determine if Pediatric Health Information System (PHIS) billing or microbiology data can improve AE reporting. 

Methods: Two pediatric oncologists performed chart review to identify 12 Grade III-IV AEs (Table) for patients enrolled on AAML0531 at 11 hospitals across the United States and establish a gold standard. The sensitivity and PPV for COG AEs and AEs based on PHIS billing or microbiology data were calculated comparing to the gold standard.

Results: Chart abstraction was performed on 179 patients (661 courses). PHIS billing data were available on all patients and PHIS microbiology data were available on 53 patients (202 courses) at 3 hospitals. The sensitivity of COG AE reports is modest with a relatively good PPV. PHIS billing data are generally more sensitive but have a lower PPV. While nearly 25% of VGS episodes were missed by COG AE report, the sensitivity and PPV of PHIS microbiology data were greater than 92%. These data suggest that current COG AE reporting is not sensitive and that accuracy may be improved by using external laboratory data.

Sensitivity and PPV of 12 AEs.

<table>
<thead>
<tr>
<th>AE</th>
<th>COG AE Report</th>
<th>PHIS Billing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>23.3%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>34.8%</td>
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<td>Malignant NHL</td>
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<td>VGS</td>
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<td>96.9%</td>
</tr>
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<td>80.0%</td>
</tr>
<tr>
<td>Renal Failure</td>
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Accuracy of adverse event reporting on a phase III clinical trial for pediatric acute myeloid leukemia with inferior progression-free and overall survival: Association of higher lung dose received during total body irradiation for hematopoietic stem cell transplantation. A report from the Children’s Oncology Group.

First Author: Olanrewaju O Okusanya, U.S. Food and Drug Administration, Silver Spring, MD

Background: Lung shielding is not standardized during total body irradiation (TBI) preparative regimens for hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia (ALL) on Children’s Oncology Group trial ASC0431. 

Methods: The lung radiation dose received during TBI (1200 or 1320 cGy given bid in 6 or 8 fractions) was analyzed in relation to the following variables: total TBI dose, TBI dose per fraction, TBI dose rate, TBI fields, patient position during TBI, pulmonary toxicity, acute graft versus host disease (GVHD), veno-occlusive disease (VOD), TRM, donor type, minimal residual disease (MRD) levels, RFS and OS. 

Results: From a total of 143 enrolled, 109 patients had lung doses available for analysis. Patients treated with lateral fields were significantly more likely to receive lung doses ≥ 800 cGy (p < 0.001). Patients receiving lung dose ≥ 800 cGy had higher rates of relapse or TRM (p = 0.034), a trend for higher rates of death (p = 0.078), and a significantly lower association between lung dose and death and rates of reported pulmonary toxicity (p = 1.000). In univariate analysis, lung dose ≥ 800 cGy vs < 800 cGy was associated with lower toxicity, RFS, higher disease risk group and unmatched donor types were associated with significantly inferior RFS and OS. Multivariate analysis identified lung dose ≥ 800 cGy to be significantly associated with inferior RFS (HR 1.9; p = 0.031) and OS (HR 2.1; p = 0.023) while controlling for risk stratification and donor type. 

Conclusions: Data from ASC0431 demonstrate that lung irradiation dose ≥ 800 cGy as part of TBI was associated with inferior RFS and OS. While understanding the mechanisms underlying these results require more research, reducing the lung dose to 800cGy for TBI regimens administering ≥ 1200 cGy is recommended. Clinical trial information: NCT00382109.
Kidney Injury Molecule-1 and its association with delayed clearance and drug exposure in pediatric oncology patients treated with high dose methotrexate. First Author: Andrew J. Bukowinski, Cincinnati Children’s Medical Center, Cincinnati, OH

Background: High-dose methotrexate (HD-MTX) is a critical component of therapy for pediatric malignancies. The ability to identify patients at risk for delayed MTX clearance and acute kidney injury (AKI) is limited. Kidney Injury molecule-1 (KIM-1) is a urinary biomarker which is an early indicator of tubular injury. The current study evaluates associations between urinary KIM-1, delayed MTX clearance, and MTX exposure. The 192-13 study showed that a certain portion of ALL, including male, HHD required the standard duration of maintenance, whereas HEX group, female could be cured even with very short maintenance therapy. This result provides precise information of leukemia biology and highlights the role of maintenance therapy.

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10037 Poster Session (Board #107), Sun, 8:00 AM - 11:30 AM
Exploring Tenascin-C as a novel therapeutic target in pediatric brainstem glioma. First Author: Amanda Muits Sarabia, Ann & Robert H. Lurie Children’s Hospital of Chicago (Northwestern University Feinberg School of Medicine), Chicago, IL

Background: Diffuse intrinsic pontine glioma (DIPG) is the most deadly solid tumor of childhood. Histone 3 mutation occurs in up to 80% of DIPGs, causing global epigenetic aberration. Tenascin-C (TNC) is an extracellular matrix protein expressed during brain development by oligodendroglial progenitor cells (OPCs), the purported DIPG cell of origin. TNC is highly expressed in adult glioma, contributing to local invasion and poor survival. We report increased TNC in tumor tissue and cerebrospinal fluid (CSF) from children with high-grade glioma, including DIPG, and characterize TNC expression in relation to histone 3 mutation and DNA methylation.

Methods: Tissue collected intraoperatively or post-mortem from children with a histologic diagnosis of DIPG (N = 14), supratentorial (n = 7), and cerebellar astrocytoma (n = 2), and CSF from DIPG (n = 9) and supratentorial astrocytoma (n = 17), were subjected to MS/MS proteomic analysis. Tissue gene expression, DNA methylation, and H3F3A or HIST1H3B sequencing was performed. TNC expression was validated and correlated with tumor grade and H3K27M status via western blot and immunohistochemistry. Data integration was performed via Partek Genomics Suite and Ingenuity Pathway Analysis. Results: TNC protein expression was significantly increased in 75% of glioma tissue specimens compared to normal tissue, including all DIPG specimens tested (fold change > 2, p < 0.05). Secreted TNC was detected in 7/10 DIPG CSF specimens (77.8%). Tumor-specific TNC expression was confirmed with Western blot and tissue immunohistochemistry. Greater relative TNC expression correlated with tumor grade and was associated with Notch pathway activation, H3K27M mutation, and TNC promoter hypomethylation. Conclusions: We report increased TNC expression in tissue and CSF of DIPG. Newly diagnosed, including DIPGs, associated with promoter hypomethylation and H3K27M mutation. Given the effect of TNC on OPC proliferation, migration and differentiation, TNC could serve as a clinical biomarker of disease and rational therapeutic target for a substantial subgroup of DIPG patients. Further studies exploring the mechanism of TNC overexpression and effects of targeting TNC expression in DIPG are currently underway.

10038 Poster Session (Board #108), Sun, 8:00 AM - 11:30 AM
Diagnostic and prognostic role of circulating miR-206 in rhabdomyosarcoma patients. First Author: Mitsuru Miyachi, Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Background: miR-206 is a muscle-specific microRNA and is much more strongly expressed in rhabdomyosarcoma (RMS) tumors than in non-RMS tumors. Here, we analyzed the diagnostic and prognostic role of circulating miR-206 values in serum specimens of RMS patients. Methods: Total RNA was extracted from serum samples (200 µL) from 60 patients (28 RMS, 9 Ewing sarcoma, 4 rhabdomyosarcoma, 4 other tumors) and quantified by real-time quantitative RT-PCR. Receiver-operating characteristics (ROC) curves were established to evaluate the diagnostic value. Survival curves for RMS patients were calculated by the Kaplan-Meier method and were compared using the log-rank test. The median follow-up time was 30 months. Serum miR-206 expression level and prognostic factors were evaluated with a univariate analysis. The factors included analyzed, primary tumor size, regional lymph node involvement, distant metastasis, fusion gene status, histologic subtype and primary tumor site. A multivariate analysis was conducted using the Cox proportional hazards regression method. The variables correlated with progression-free survival (PFS) in the univariate analysis were included in the model. Results: Serum miR-206 expression levels were higher in RMS patients than in non-RMS patients (p < 0.001) with an area under the ROC curve of 0.8705 (95% confidence interval [CI], 0.7791-0.9626), sensitivity of 0.714 and specificity of 0.938. The cut-off value was 164.1 copies/µL serum. Serum miR-206 expression was an independent risk factor for shorter PFS (2.5-year PFS: 10.7% (n = 14) vs 77.9% (n = 14), p = 0.0019) and the presence of both distant metastasis and locoregional lymph node involvement (2.5-year PFS: 30.9% (n = 18) vs 80.0% (n = 10), p = 0.017) in univariate analysis. In the multivariate analysis, a high serum miR-206 expression level had an independent prognostic significance (hazard ratio: 3.50 [95% CI: 1.12-11.0], p = 0.031). Conclusions: miR-206 can be a novel biomarker for both diagnosis and treatment stratification of RMS. The limitations of our study include a retrospective design, small sample size and non-uniform treatment. The Japanese Rhabdomyosarcoma Study Group will prospectively validate its prognostic significance in a large cohort of newly-diagnosed patients.
Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics. First Author: Stephen Richard Grant, Baylor College of Medicine, Houston, TX

Background: Adjunct radiotherapy (RT) is often a component of treatment for high-risk salivary gland tumors. Minimizing irradiation of surrounding normal tissues is particularly important for pediatric patients. We compared acute toxicity profiles, clinical outcomes, and dosimetric data for children with parotid or submandibular tumors treated with adjuvant photon/electron-based RT (X/E RT) or proton RT (PRT). Methods: We retrospectively identified 24 pediatric patients who had received adjuvant RT at a single institution for salivary gland tumors (20 parotid, 4 submandibular). Demographic, disease control and survival data were extracted from the medical records and dosimetric data from the treatment planning systems. Toxicity was scored according to the Common Terminology Criteria for Adverse Effects 4.0. Results: Eleven patients received X/E RT and 13 PRT. The median prescribed dose was 60 Gy for each group. PRT was associated with significantly lower mean doses to the thyroid (1.5 vs. 22.5 Gy, Pc < 0.05), oral cavity (4.6 vs. 20.7 Gy, P < 0.05), and larynx (11.3 vs. 44.3 Gy, P < 0.05); and the contralateral parotid (0.0 vs. 4.6, P < 0.05), hemi-mandible (0.0 vs. 11.9 Gy, P < 0.05), and submandibular gland (0.0 vs. 13.5 Gy, P < 0.05). In the X/E RT group, 27% had acute grade 3 dermatitis, 18% grade 3 mucositis, and 9% grade 3 dysphagia, and the median weight loss was 5.3%. No patient in the PRT group experienced acute grade 3 toxicity, and a median weight gain of 1.2% was noted. At a median follow-up time of 35 months, no disease recurrence or deaths were observed in either group. Conclusions: Compared with X/E RT, PRT significantly reduced the radiation dose to many surrounding normal tissues, which translated to reductions in clinical acute toxicity. Continued follow-up is needed to identify any differences in long-term toxicity and disease control.

Outcome of recurrent osteosarcoma patients enrolled in seven phase II trials through CCG, POG, and COG: Learning from the past to move forward. First Author: Joanne P. Lagmay, University of Florida Shands Hospital for Children, Gainesville, FL

Background: The use of radiographic response as the primary endpoint in phase II osteosarcoma (OS) trials may limit optimal detection of treatment response due to the calcified tumor matrix. We assessed outcome data for children with recurrent/refractory OS enrolled on single arm Children’s Oncology Group phase II trial to establish this cohort’s baseline expected survival outcome. Methods: We performed a retrospective analysis of outcome for children with recurrent/refractory OS enrolled on one of seven phase II trials with an OS stratum conducted by COG and predecessor groups from 1997-2007. Trials included A09713 (topotecan), ADVL0122 (imatinib), ADVL0421 (oxaliplatin), ADVL0524 (ixabepilone), COG0962 (docetaxel), P9761 (irinotecan) and P9963 (rebeccamycin analog). All trials used RECIST or WHO with primary endpoint as response rate. Event Free Survival (EFS) was correlated with the following potential prognostic factors: age, trial, number of prior chemotherapy regimens, gender and race. To determine the historical disease control rate for patients with fully resected disease, we used the EFS in a Phase II study (AOST0221) of osteosarcoma patients given inhaled GMCSF with first pulmonary recurrence, which had a biological endpoint. Results: In each included trial the OS stratum failed to meet the primary endpoint. Radiographic responses were observed in only 3 trials. The highest response rate was 11% seen in ADVL0122. EFS for 96 subjects with OS and measurable disease was 12% at 3 months (95% CI: 6-19%). There was no impact of age, gender or race on EFS nor was there a significant difference in EFS across trials or by number of prior treatment regimens. The 12-month EFS for the 42 subjects enrolled in AOST0221 was 20% (95% CI: 10-34%). Conclusions: The aggregate outcome for children with recurrent/refractory OS is in line with previously conducted single arm phase II trials was disappointing. Given the poor EFS for children with recurrent/refractory OS it is unlikely that active agents were missed using traditional RECIST response. Nevertheless, we have now defined baseline EFS outcomes that can be incorporated into future phase II trial design for recurrent osteosarcoma.

Vesicular monoamine transporter protein expression in neuroblastoma: a report from the Children’s Oncology Group. First Author: Steven G. DuBois, University of California, San Francisco, San Francisco, CA

Background: Vesicular monoamine transporters 1 and 2 (VMAT1 and VMAT2) are thought to mediate MIBG uptake in adult neuroendocrine tumors. VMAT expression has not been comprehensively investigated in neuroblastoma. Methods: We evaluated VMAT1 and VMAT2 expression by immunohistochemistry (IHC) in neuroblastoma tumors from 76 patients with high-risk disease treated on COG protocol A3973. All patients had baseline MIBG diagnostic scans centrally reviewed. IHC results were scored as the product of intensity grading (0-3) and percent of tumor cells expressing the protein of interest. Association of VMAT1 and VMAT2 scores with clinical and biological features was tested using Wilcoxon rank sum tests. Results: Patient characteristics were typical of high-risk neuroblastoma, though the cohort was intentionally enriched for patients with MIBG non-avid tumors (n = 20). VMAT1 and VMAT2 were expressed in 62% and 75% of neuroblastoma tumors, respectively. VMAT1 and VMAT2 scores were both significantly lower in MYCN amplified tumors, non-adrenal primary tumors, and in tumors with high mitotic karyorrhectic index. MIBG avid tumors had significantly higher VMAT2 scores compared to MIBG non-avid tumors (median 216 vs. 45; p = 0.04). VMAT1 expression did not correlate with MIBG avidity. Conclusions: VMAT1 and VMAT2 are expressed in the majority of neuroblastomas. Expression correlates with clinical and biological features. Expression of VMAT2 but not VMAT1 correlates with avidity for MIBG.
10044 Poster Session (Board #114), Sun, 8:00 AM-11:30 AM
Meta-analysis of effects of demographic and treatment variables on outcome for localized paratesticular rhabdomyosarcoma (PT RMS) in North America and Europe. First Author: David Whitherhouse, Ann and Robert H Lurie Children’s Hosp of Chicago, Chicago, IL

Background: Treatment recommendations for localized PT RMS differ based on clinical trials conducted by cooperative groups in North America and Europe. We conducted a meta-analysis to identify effects of demographic features and treatment choices on outcome for patients with localized PT RMS. Methods: We analyzed demographic and treatment variables from 12 studies conducted by the Children’s Oncology Group (COG; n = 416), Cooperative Weichteilsarkom Studiengruppe (CWS; n = 106), European paediatric Soft Tissue Sarcoma Group (EpSSG; n = 99), Italian Cooperative Group (ICG; n = 64), and SIOP Malignant Mesenchymal Sarcoma Group (MMT; n = 159) that enrolled 844 eligible patients with localized PT RMS from 1988-2013. Categorical and continuous variables were checked for association. Event-free survival (EFS) and survival (S) were compared among groups using univariate and multivariate analyses. Results: Mean patient age at enrollment differed among the cooperative groups (7 yrs [MMT] – 11 yrs [EpSSG]; p < 0.05). Patients ≥ 10 yrs were more likely to have tumors > 5 cm (60%; p < 0.05), enlarged nodes (N1) (17%; p < 0.05), and pathologically involved nodes (33%; p < 0.05) than younger patients. 89% of N1 nodes and 19% of N0 nodes were pathologically involved in patients ≥ 10 yrs. With a median follow-up of 7 yrs, 87.5% of patients were event-free and 94.9% were alive. Variables that impacted EFS (p < 0.05) were cooperative group, era of enrollment, age, IRS group, T-stage, tumor size, and surgical assessment of nodes in patients ≥ 10 yrs with tumors > 5 cm. Using a stepwise variable selection procedure on a proportional hazards regression model starting with all demographic and treatment variables, the EFS model selected era, age, size, and surgical assessment of regional lymph nodes (p < 0.05) and the 5 model selected era, age, size, and histology (p < 0.05). Conclusions: Localized PT RMS has a favorable prognosis using approaches of North American and European cooperative groups. Surgical assessment of regional nodes is important in boys ≥ 10 yrs as this impacts EFS (but not S), and in younger boys with N1 disease. Clinical lymph node staging is otherwise sufficient to guide therapy.

10045 Poster Session (Board #115), Sun, 8:00 AM-11:30 AM
Treatment outcomes of pediatric and young adult sporadic desmoid tumors. First Author: Sara Heling, Cincinnati Children’s Hospital and Medical Center, Cincinnati, OH

Background: Desmoid tumor (DT) is a non-malignant soft-tissue neoplasm of children and adults that is often treated with surgery, radiation and/or chemotherapy. DTs may recur even after complete resection, and the benefit of medical therapy is unpredictable. Data driven DT therapy guidelines are lacking for children and young adults. Methods: A retrospective review of DT patients treated at a single institution between 2003 and 2014. Results: Twenty-three patients, aged 3 months to 25 years of age at diagnosis, were identified from a complex patient population that included 7 patients with congenital deformity or syndromes. Anatomic locations included extremity (15), head/neck tumors (2), and trunk/abdomen (6). Both head/neck and 6 of 7 trunk patients demonstrated no evidence of disease (NED) at last follow-up. Whereas overall 5 year event-free survival (EFS) was NED (p = 0.001), of the 23 patients, all but 2 patients had at least one surgical resection. Six patients required a single surgery only: R0 (n = 4), R1 (n = 1), and R2 (n = 1). Eight patients received vinblastine and methotrexate (VBL/MTX), 5 received sorafenib, and tamoxifen (TAM) with sulindac, hydroxyurea, and liposomal doxorubicin were each administered to 1 patient. One VBL/MTX patient experienced a partial response while the others experienced prolonged stabilization ( > 36 months). Two of four patients treated with sorafenib experienced stabilization ( > 24 months). The single patient treated with TAM/sulindac experienced prolonged stabilization. Five patients received radiation therapy, with one developing a secondary sarcoma and two others stabilizing without further sequela. There were no deaths related to DT. Conclusions: Our findings demonstrate that a subset of tumors can be adequately treated with a single surgery. Head/neck and trunk tumors were more likely to be rendered NED than extremity tumors. Another subset of unresectable/recurrent tumors treated with mild medical therapy stabilized without significant morbidity, although RECIST response was rare in this complex cohort. Given the unpredictable benefit of therapies for unresectable/recurrent disease, genre directed approaches and observation-only strategies merit further exploration in this age group.

10046 Poster Session (Board #116), Sun, 8:00 AM-11:30 AM
The prognostic significance of MIBG uptake in left supraclavicular lymph nodes in high risk neuroblastoma patients. First Author: Shifra Ash, Pediatric Hematology Oncology, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel

Background: Metastatic MIBG localization in the soft tissues of the left supraclavicular (LSC) region is occasionally seen in children with high risk (HR) neuroblastoma. The purpose of the study was to evaluate the prognostic significance of this uptake. Methods: We performed a retrospective analysis of MIBG studies and clinical data of 77 HR neuroblastoma patients treated at Schneider Children’s Medical Center of Israel between 1998 – 2015. The median age was 2.8 years (0.1-7.6) and the median follow up was 39 months (1-202). HR was defined as patients diagnosed as stage 3 with MYCN amplification and stage 4. Treatment consisted of induction chemotherapy, surgery, autologous bone marrow transplantation, local radiation and retinoic acid with or without immunotherapy. MIBG studies included whole body surveys, SPECT or SPECT/CT with the supraclavicular regions in the field of view. Results: LSC uptake was identified in 13/77 children (17%). All children with LSC MIBG uptake had abdominal primary tumors. Patients with LSC uptake had a 5y relapse free survival (RFS) of only 42% as opposed to 42% for 7 patients with no uptake (p = 0.021). Five year overall survival (OS) was 0% in children with LSC uptake and 57% in those without (p = 0.001). Within the group of 46/77 patients without MYCN amplification, 5y OS was 0% in 8 children with LSC uptake and 51% in 39 in 38 without (p = 0.014). On multivariate analysis for only LSC MIBG uptake, only LSC MIBG uptake was found to be a poor independent prognostic factor, with an increased risk of 3.69 fold (95% CI 1.6-8.3, p = 0.002). Conclusions: Avid metabolastes identified by MIBG in the LSC region can identify HR patients with worse prognosis. This phenomenon resembles metastatic spread to Virchow nodes from gastric cancer and can be used as a prognostic factor. Cross sectional imaging with MIBG (or other modalities) should always include the left supraclavicular region. The presence of left supraclavicular disease should be considered for therapy planning.

10047 Poster Session (Board #117), Sun, 8:00 AM-11:30 AM
Comparison of 18F-FDG-PET-CT and bone scintigraphy for evaluation of osseous metastases in newly diagnosed and recurrent osteosarcoma. First Author: Caitlin Hurley, St. Jude Children’s Research Hospital, Memphis, TN

Background: Bone scintigraphy (BS) is routinely used to detect osseous metastases in osteosarcoma. The use of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG-PET-CT) to assess tumor extent in pediatric sarcomas has increased recently. We compared the sensitivity, specificity, and diagnostic accuracy of PET-CT and BS for detection of osseous metastases in osteosarcoma. Methods: We retrospectively reviewed 39 patients with osteosarcoma who underwent paired PET-CT and BS studies. For all sites combined, sensitivity, specificity, and diagnostic accuracy were 77%, 76% and 76% for PET-CT, 41%, 64%, and 64% for BS, respectively. Conclusions: PET-CT is at least as sensitive as BS in detecting osseous metastases in osteosarcoma; combined use with BS further increases sensitivity. Our findings support the use of both 18F-FDG-PET-CT and BS for staging of osteosarcoma.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**Conclusions:** The 89Zr-labeled anti-CD99 Ab PET probe out-performed existing safety data for the imaging of adult solid tumors with 89Zr-labeled dous implications for the clinical care of patients with Ewing sarcoma. In light of specific detection and monitoring of metastatic disease may have tremen-

d-tumor-to-background ratio that was two-fold higher. The more sensitive and immunoPET data, but were not detected using [18F]FDG. Autoradiography post-injection with the maximum tumor-to-background ratio observed at 72 h (SUVmax = 12.5 for tumor and 4 for local normal tissues). Liver metastases of 2-3 mm diameter were identified on MR images guided by immunoPET data, but were not detected using [18F]FDG. Autoradiography demonstrated a 39Zr-labeled metastases-to-liver uptake ratio of 13:1.

**Conclusions:** The 39Zr-labeled anti-CD99 Ab PET probe out-performed [18F]FDG and MRI in the detection of Ewing sarcoma metastases, validating our prior work with a 64Cu-labeled anti-CD99 probe. The longer half-life of 39Zr allowed imaging at later time points (72 h) than 64Cu yielding a tumor-to-background ratio that was two-fold higher. The more sensitive and specific detection and monitoring of metastatic disease may have tremen-
dious implications for the clinical care of patients with Ewing sarcoma. In light of existing safety data for the imaging of adult solid tumors with 39Zr-labeled Abs, this study supports next steps for translation to pediatrics.

**Background:** Chemotherapy and surgery are the mainstay of osteosarcoma (OS) treatment. Using 2-4 drugs and short or long duration in chemo-


therapy protocols have been evaluated in various trials. A metaanalysis (Anning JK, 2011) has reported, 3-drug regimen is better than 2, but not inferior than 4-drug. Our study aims to evaluate the outcome of Osteosar-
mus (OS) patients treated with a nonmethotrexate 3-drug regimen and surgery. **Methods:** Children and adolescents with osteosarcoma treated between January, 1990- January, 2015 at Istanbul University, Oncology Institute were retrospectively evaluated in terms of demographic features and survival. The patients received 6 courses of a 3 drug regimen comprising of fosfamide 1.8 g/m2/d x 3 days, epirubicin 90 mg/m2/d and cisplatin 100mg/m2/d administered 3-pre and 3-postoperatively. Methotrexate was not in the protocol because drug levels could not be monitored in the 1990’s at our center. Since 2012, ifosfamide was added to the protocol postoperatively for nonmetastatic patients. **Results:** 189 children (105 boys, 84 girls) with a median age of 12 years (3-18yrs) were evaluated, 151 (80%) were non-metastatic and 38 metastatic. Median follow-up was 3,6 years (1mo-24 yrs). 91.5 % had limb salvage surgery. Relapse/progressive disease was observed in 69 patients at a median 15 months (1mo-63 mo). The 5 and 10-year overall survival and event free survival for the whole group (OS) was 60.5% and 61.9%, respectively. In non-metastatic and in metastatic patients, 5-year OS was 73.8 and 23.9%, 5-year EFS was 69.4% and 20.8%; respectively (p = 0.0001). In 25 nonmetastatic patients receiving chemotherapy and ifosfamide 2-year OS and EFS were 90.9% and 85.5% respectively at a median of 20 months/Neil. Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA

**Efficacy in six courses of nonmethotrexate three-drug chemotherapy and surgery in osteosarcoma: 25-year experience. First Author: Rejin Rebodi, Istanbul University, Oncology Institute and Cerrahpasa Medical Faculty, Pediatric Hematology-Oncology, Istanbul, Turkey**

**Background:** Chemotherapy and surgery are the mainstay of osteosarcoma (OS) treatment. Using 2-4 drugs and short or long duration in chemo-


therapy protocols have been evaluated in various trials. A metaanalysis (Anning JK, 2011) has reported, 3-drug regimen is better than 2, but not inferior than 4-drug. Our study aims to evaluate the outcome of Osteosar-
mus (OS) patients treated with a nonmethotrexate 3-drug regimen and surgery. **Methods:** Children and adolescents with osteosarcoma treated between January, 1990- January, 2015 at Istanbul University, Oncology Institute were retrospectively evaluated in terms of demographic features and survival. The patients received 6 courses of a 3 drug regimen comprising of fosfamide 1.8 g/m2/d x 3 days, epirubicin 90 mg/m2/d and cisplatin 100mg/m2/d administered 3-pre and 3-postoperatively. Methotrexate was not in the protocol because drug levels could not be monitored in the 1990’s at our center. Since 2012, ifosfamide was added to the protocol postoperatively for nonmetastatic patients. **Results:** 189 children (105 boys, 84 girls) with a median age of 12 years (3-18yrs) were evaluated, 151 (80%) were non-metastatic and 38 metastatic. Median follow-up was 3,6 years (1mo-24 yrs). 91.5 % had limb salvage surgery. Relapse/progressive disease was observed in 69 patients at a median 15 months (1mo-63 mo). The 5 and 10-year overall survival and event free survival for the whole group (OS) was 60.5% and 61.9%, respectively. In non-metastatic and in metastatic patients, 5-year OS was 73.8 and 23.9%, 5-year EFS was 69.4% and 20.8%; respectively (p = 0.0001). In 25 nonmetastatic patients receiving chemotherapy and ifosfamide 2-year OS and EFS were 90.9% and 85.5% respectively at a median of 20 months/Neil. Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA

**Conclusion:** The prognostic significance of having extraskeletal Ewing sarcoma (EES) using modern chemotherapy protocols is unknown. The purpose of this study was to compare the clinical characteristics and outcomes for patients with extraskeletal and skeletal Ewing sarcoma. **Methods:** Patients had localized Ewing sarcoma and were treated on two consecutive protocols using 5-drug chemotherapy (INT-0154 and AEW50031). Pa-


tients were analyzed based on having an extraskeletal (n = 213) or skeletal (n = 826) site of tumor origin. Patient characteristics were compared using Wilcoxon rank sum, Fisher exact, and chi-square tests. Event-free survival (EFS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Relapse, death, or second malignancy were considered events. **Results:** Age of diagnosis and sex did not differ according to tissue of origin. Patients with EES were less likely to be white (80.8% vs. 87.7%; p = 0.02), and were less likely to have tumors > 8cm (22.3% vs. 36.3%; p = 0.01) compared to patients with skeletal Ewing sarcoma. There was a trend to suggest superior EFS for patients with EES compared to skeletal tumors (hazard ratio 1.34; p = 0.022). Among patients with extraskeletal tumors, the EFS was inferior for those patients who were not white (p = 0.005) and who were > 18 years of age (p = 0.02). The distribution of event types experienced by each group did not differ. Conclusions: Clinical characteristics differ between patients with extraskeletal and skeletal Ewing sarcoma and outcomes may be superior for patients with EES. The origin of these differences requires further investigation.
Pharmacogenetic markers for efficacy and toxicity of chemotherapy in osteosarcoma patients.

**First Author:** Hanneke I. Vos, Radboud University Medical Center, Nijmegen, Netherlands.

**Background:** Despite multilagent chemotherapeutic treatment, osteosarcoma patients relapse frequently and survival has reached a plateau in the past decades. A poor response to chemotherapy is considered as risk factor for patient outcome. We have previously identified genetic markers predictive of treatment outcome in genes of cisplatin and doxorubicin metabolism and transport. Therefore we have performed large scale association studies to determine potential pharmacogenetic markers for efficacy and toxicity of chemotherapy in osteosarcoma treatment.

**Methods:** From two cohorts of osteosarcoma patients (n = 139 and n = 177), germline DNA was genotyped using the DMET Plus array. Associations between genetic variants and ototoxicity (SIOP grade 4-1), histological response (HR) to preoperative cisplatin and doxorubicin based chemotherapy, and 5-Year Disease Free Survival (DFS) were assessed by logistic regression models in PLINK and Cox proportional hazards models in GenABEL respectively.

**Results:** 689 markers and 136 patients (cohort 1), and 669 markers and 174 patients (cohort 2) passed quality control (call rates > 0.9, minor allele frequency > 0.01). Upon meta-analysis, 16 markers were significantly associated (P < 0.05) with ototoxicity, including AOX1 encoding a protein involved in homeostasis of reactive oxygen species. A total of 14 variants showed association with HR, and 10 markers with DFS, with association strength similar to those of previously detected variants.

**Conclusions:** The combination of sirolimus with metronomic chemotherapy is well tolerated in children. A phase II trial of this combination is planned. Clinical trial information: NCT01331135.
Background: Pediatric patients with relapsed metastatic neuroblastomas have a poor prognosis and additional therapeutic strategies are needed. We present results of a phase I/II-trial with subsequent immunotherapy with an anti-GD2 antibody for patients with refractory progressive disease in osteosarcoma patients. First Author: Emily Gustav Greengard, University of Minnesota, Eden Prairie, MN

Methods: In 5/7 investigated patients, effective ADCc and complement mediated (CDC) anti-tumor effects against neuroblastoma cells were detectable in vitro (85% specific lysis, E:T-ratio = 20:1, BATDA-release). 14/34 patients did not reach the end of the protocol (due to side effects, n = 2; TRM, n = 1; progression or relapse, n = 11). 8/34 patients could maintain a CR, 9/34 patients improved their partial remission and achieved CR. 3/34 patients had stable disease. Thus, success of treatment defined as stable disease or improvement was shown in 59%. Progression free survival at 2 and 3 years was 55% and 38% (median follow up: 550 days). Frequent side effects were pain, fever and CRP elevation; rare side effects comprised SIRS/capillary leak syndrome, seizures, and accommodation disturbances. Only 1 patient developed transient acute GvHD grade II. Conclusions: CH14.18/CHO infusions after haploidentical stem cell transplantation appear to be feasible without increased risk of inducing GvHD. Results of our study also suggest an anti-tumor effect of the new, donor-derived immune system in vitro and in vivo. Clinical trial information: NCT02295815.

Background: Despite treatment, some osteosarcoma patients have refractory/progressive disease and a very poor prognosis. We have previously identified genetic markers predictive for disease free survival. We hypothesize that osteosarcoma patients with refractory/progressive disease have a pharmacogenetic profile different from patients with recurrent disease. To investigate this, we have analyzed these subgroups of patients using a large scale screening including 1,936 genetic markers in 231 drug metabolism and transport genes. Methods: Germline DNA of Dutch osteosarcoma patients treated with cisplatin and doxorubicin-based chemotherapy (n = 316) was genotyped with the DMET Plus array. Patients with refractory/progressive disease (primary tumor growth/ growth or development of new metastases, up to 3 months post chemotherapy) were compared to control patients (without refractory/progressive disease or recurrence), as were patients with recurrent disease (local or distant relapse). Associations between genetic variants and refractory/progressive disease or recurrent disease were assessed by logistic regression models in PLINK. Results: 710 markers and 310 patients passed quality control. Of 280 eligible patients, 36 experienced progression and 76 recurrence. In multivariate association analyses of genetic variants and refractory/progressive disease or recurrent disease, adjusted for presence of primary metastases, sex and age at diagnosis, 25 genetic markers were significantly associated (P< 0.05) with refractory/progressive disease. Of these, 18 genetic variants in 13 genes were uniquely associated with refractory/progressive disease and not with recurrent disease in this cohort. Conclusions: This is the first pharmacogenetic analysis of osteosarcoma patients to distinguish between refractory/progressive disease and recurrent disease. In this exploratory study we have identified genetic variants specifically associated with refractory/progressive disease in osteosarcoma patients. This analysis represents the first step to identify patients for whom chemotherapeutic treatment is ineffective and should be further explored in future studies.

Methods: 34 patients with 1st or 2nd metastatic relapse were enrolled. During antibody infusions, endogenous secretion of IL2 was increased (928U/ml prior vs. 1690U/ml post, p < 0.001), which resulted in significantly increased numbers of activated CD69 + Natural Killer (NK) cells (3 vs. 13% p < 0.01). In 5/7 investigated patients, effective ADCc and complement mediated (CDC) anti-tumor effects against neuroblastoma cells were detectable in vitro (85% specific lysis, E:T-ratio = 20:1, BATDA-release). 14/34 patients did not reach the end of the protocol (due to side effects, n = 2; TRM, n = 1; progression or relapse, n = 11). 8/34 patients could maintain a CR, 9/34 patients improved their partial remission and achieved CR. 3/34 patients had stable disease. Thus, success of treatment defined as stable disease or improvement was shown in 59%. Progression free survival at 2 and 3 years was 55% and 38% (median follow up: 550 days). Frequent side effects were pain, fever and CRP elevation; rare side effects comprised SIRS/capillary leak syndrome, seizures, and accommodation disturbances. Only 1 patient developed transient acute GvHD grade II. Conclusions: CH14.18/CHO infusions after haploidentical stem cell transplantation appear to be feasible without increased risk of inducing GvHD. Results of our study also suggest an anti-tumor effect of the new, donor-derived immune system in vitro and in vivo. Clinical trial information: NCT02295815.

Background: Wild type and mutated TP53 are common in pediatric CNS tumors. p28 is a cell penetrating peptide that preferentially enters cancer cells and binds to wild type and mutant p53 protein inhibiting COP1 mediated ubiquitination and protein degradation. This results in an increase in levels of p53, which induces cell cycle arrest at G1/M. A Phase I trial in 15 TP53 positive, adult patients with stage IV tumors reported no AEs and 1CR and 3PR with 4 patients alive greater than 40 weeks. Regression analysis suggested that p28 has activity in patients whose tumors express both wild type and mutated TP53. Methods: Intravenous p28 was administered 3 times weekly for 4 consecutive weeks of a 6 week cycle at 4.16 mg/kg/dose (the adult MTD) using a rolling 6 study design. TP53 expression status was characterized by immunohistochemistry and serum pharmacokinetics were established on the second dose. Results: Of the 18 patients registered on the study, 12 patients (8 males, median age 11 years (range 3-19)) completed the DLT period and are evaluable for toxicity with malignant glioma (n = 4), choroid plexus carcinoma (n = 2), medulloblastoma (n = 2), pineoblastoma (n = 2), DIPG (n = 1) and AT/RT (n = 1). p28 was well tolerated; 7 patients received 2 or more courses and the most common adverse event attributed to drug was transient Grade I infusion site reaction. One patient with metastatic neuroblastoma with bone marrow involvement had 2 DLTs of Grade 4 neutropenia and thrombocytopenia. Pharmacokinetic analysis of 16 patients revealed an overall t½a and t½m similar to adults. An increased AUC was observed in pediatric patients, as a result of a higher Cmax and longer t½m, p28 expression in tumor cell nuclei. This study demonstrates that p28 is well tolerated in children with recurrent CNS malignancies at the adult MTD. Future combination studies are being explored. Clinical trial information: NCT01975116.
Transcriptome based individualized therapy of refractory pediatric cancer in adolescents and young adults. First Author: Bushra Weidenbusch, Technische Universität München, Munich, Germany

Background: Progress in pediatric oncology had little impact on adolescents and young adults (AYAs). Survival rates stagnated and are even worse than in younger and older age groups. Tumor biology in refractory patients is highly heterogeneous inter- and even intra-individually. New approaches are therefore urgently needed. Gene expression analysis may aid in medical decision making in this setting. Methods: We enrolled patients aged 10-40 years for whom standard of care and current clinical trials provided no further treatment options in a one arm open label prospective study to assess survival. Tumor samples obtained for diagnosis underwent transcriptome analysis with Affymetrix arrays. We focused on genes with > 1.5 fold expression vs. normal tissue, identified as drivers by TARGETgene. Targets ranked between 1-100 were considered for therapy. Drug selection criteria were: delivery, no previous use in the patient, citations related to disease, citations related to other cancers, side effects, drug interactions, oral application, approval by German authorities. Results: From 12/12-01/15, 18 biopsies were obtained after informed consent from 16 eligible patients at a single institution (TUM) with a mean age of 15.8 years. Diagnosis was: sarcoma in 14 (6 Ewing sarcomas, 4 soft tissue sarcomas, 4 osteosarcoma), and embryonal tumor in 2. Targeted therapy was administered in 10, while in 5 no druggable targets could be identified. One patient was noncompliant. Mean druggable targets per patient was 7.6, with 462 medications assessed. 18 different drugs were recommended with an average of 3 drugs per patient, including PkIs, Tki, TOP2is, nucleoside analogs, arsenic trioxide and ATRA. Therapy was well tolerated with no adverse reactions and no side effect-related discontinuation of treatment. In this pilot study survival was at least not inferior to best medical care. Conclusions: Targeted therapy is a feasible alternative to best medical care in refractory cancer in AYAs. In the majority of patients druggable targets can be identified and therapy typically does not cause side effects. Prospective studies to determine potential overall survival benefit are ongoing within the INFORM consortium.

Phase II study of nimotuzumab and radiotherapy in children and adolescents with newly diagnosed diffuse intrinsic pontine gliomas (DIPG). First Author: Sidnei Epelman, Santa Marcelina Hospital, Sao Paulo, Brazil

Background: DIPG are amongst the most challenging tumors to treat in childhood with no drug proven to be effective. Standard of care remains focal radiotherapy alone however, rapid disease progression usually occurred. Median overall survival is less than 1 year, and the 2-year survival is less than 10%. Methods: Patients with clinically and radiologically confirmed, centrally reviewed newly diagnosed DIPG were eligible for this multicenter phase II study. The anti-epidermal growth factor receptor antibody, nimotuzumab (150 mg/m2) was administered intravenously once weekly concomitant with focal radiotherapy (54 Gy) and every 2 weeks until tumor progression. Response evaluation was based on clinical and radiological assessments. Primary objective was to improve survival with a historic cohort that received radiation therapy alone. Results: 21 patients entered into this study (7/14, male/female; median age, 7.6 years; range 2-16 years). All received radiotherapy. Treatment was well tolerated. 40/502 cycles had adverse effects related to the drug and very mild. The majority of adverse effects were associated with progression of disease. Disease free survival at 7.3 months was 85.7% (91.9% - 70.7-100). Overall survival at 9 months was 71.4% and at one year, 57.1% (91.9% - 33.8-74) which demonstrated better results when compared with historic trials. Conclusions: This trial demonstrated some activity of nimotuzumab in DIPG. It was well tolerated and improved overall survival. A small subset of patients appeared to benefit from this anti-EGFR antibody and can be considered in future trials with synergistic drugs. An upfront biopsy can bring the prospect of a better understanding of DIPG biology and selection of better treatment. Clinical trial information: NCT01145170.
Background: Adult survivors of childhood NHL are at risk for chronic conditions likely underestimated by patient reported outcomes. Prevalence and severity based on direct clinical assessment are lacking. Methods: Clinical, laboratory, and performance-based evaluations were obtained on 200 adult survivors of pediatric NHL at St. Jude Children’s Research Hospital. Chronic conditions were graded per CTCAE criteria. Impaired physical function was defined as performance below the 10th percentile of normative data. Multivariable Poisson regression models were used to investigate associations (relative risk (RR), 95% confidence intervals (CI)) between patient characteristics, therapies, and clinical outcomes. Results: Survivors (66% male, 87% white) were a median age of 10 years (range 1-19) at diagnosis and 34 years (20-58) at evaluation. Forty-six (23%) received radiation to the brain, 69(35%) high dose methotrexate, and 161(81%) steroids. Most (93%) had ≥ 1 chronic condition, 77% ≥ 2 chronic conditions, and 50% a severe/life-threatening (grade 3-4) condition. Most prevalent were overweight/obesity (65%), cognitive impairment (46%), dyslipidemia (41%), and impaired fasting glucose (37%). Most prevalent grade 3-4 conditions were obesity (35%), hypertension (15%), and cognitive impairment (13%). Risk-based screening detected cardiomyopathy in 14(8.5%); 50% grades 3-4. There were 27 second cancers (61% grades 3-4) in 23(12%) survivors. Prevalence of abnormal body composition, measured by waist to height ratio and percent fat on dual-energy x-ray absorptiometry was 72%. Many had impaired aerobic (22%), strength (48%), muscular endurance (36%), flexibility (39%), and mobility (36%) assessments. Adjusting for ages at diagnosis and evaluation, race, and methotrexate, male sex (RR 1.2, CI 1.1-1.5), anthracycline ≥ 250mg/m² (RR 1.3, CI 1.1-1.6), and radiation (RR 1.3, CI 1.1-1.6) were associated with having ≥ 2 chronic conditions. Non-white race (RR 1.6, CI 1.2-2.1) was associated with a grade 3-4 condition. Conclusions: Prospective systematic evaluation identified significant chronic conditions and performance limitations in adult survivors of childhood NHL.

10065 Poster Session (Board #135), Sun, 8:00 AM-11:30 AM

Patterns and predictors of psychological distress in adult survivors of childhood cancer: A Childhood Cancer Survivor Study (CCSS). First Author: Norma Mammone D’Agostino, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Screening for psychological distress is an important part of comprehensive survivorship care. While elevated symptoms of depression and anxiety have been reported, patterns of emotional comorbidity have not been examined. The aims of this study are to identify clusters of distress symptoms and to examine disease, treatment and demographic predictors. Methods: Multinomial logistic regression was conducted using responses to the Distress Thermometer (depression, anxiety, somatization) from the Brief Symptom Inventory – 18 in siblings (N = 3085) and 5+ year survivors (N = 16032) from the CCSS. High distress was defined using t-score > 63. Bayesian information criterion and Lo-Mendell-Rubin adjusted certainty were used to select the optimal cluster number. Multinomial logistic regression was used among survivors to identify disease, treatment and demographic predictors of cluster membership stratified by sex. Results: Four latent clusters were identified: low distress on all 3 domains (well-adjusted); high distress on all 3 domains (global distress); high somatization relative to anxiety and depression (somatic distress); high anxiety and depression relative to somatization (affective distress). Compared to siblings, fewer survivors were well-adjusted (62% v. 74%) and more had global distress (11% v. 5%), both p’s < 0.0001. Diagnosis-specific patterns of distress were identified (leukemia and bone cancer: global distress, CNS: affective distress, Hodgkin lymphoma and neuroblastoma: somatic distress). More male (66%) than female (58%) survivors were well-adjusted, but more females reported somatic (17% vs 10%) and global (12% vs 9%) distress, all p’s < 0.0001. Among females, fair/poor perceived health (OR 30.9, 95% CI 19.4-49.1; compared to excellent health), headache (OR 2.69, 95% CI 2.24-3.24), and metabolic complications (OR 3.13, 95% CI 2.03-4.82) were associated with global distress. Perceived health and pain were associated with global distress in males. Conclusions: Results support the conceptual distinction between physical (somatic) versus affective (anxiety and depression) symptoms of distress and highlight sex differences and health-related predictors of distress.
Background: Retinoblastoma (RB) is the most common intraocular tumor in childhood. With current modalities, cure rates are high and hence number of survivors is increasing. However, data on quality of life (QOL) in this population are minimal. Methods: We analyzed QOL in 122 retinoblastoma survivors using the PedQLQ 4.0 generic core scale in local language, which has been validated in Indian population. The self-reported questionnaire was filled by children of more than 5 years of age who had completed treatment for more than 12 months. The questionnaire consists of 23 questions on physical, emotional, and school domains on a scale from 0 to 4. This was converted to a scale from 0 to 100, where higher values represented better QOL. The QOL was compared with 50 siblings using student’s t-test. Factors predicting the QOL were assessed. Results: The median age of RB survivors was 98 (range, 60-247) months and 68.4% were males. Seventy-nine percent were International Retinoblastoma Staging System (IRSS) stage 1 and 25% had bilateral disease. Seventy-four percent had extralocular involvement and 22% received radiotherapy. The overall QOL was significantly poorer in RB survivors as compared to controls (Table). The emotional health domains of QOL (fear, anger and sleeping) were significantly lower in RB survivors. Difficulties in maintaining friendships and competing were reported in the social health domain. In school health domain, there were significantly higher absenteeism due to sickness and hospital visits among RB survivors. However, the physical health domain including household work, exercise and self-care was similar in both the groups. Age, sex, IRSS stage and previous radiotherapy did not affect the QOL. Conclusions: QOL is often a neglected aspect in survivors of pediatric solid tumors. We found a significantly poorer QOL in RB survivors. However, no predicting factors for poor QOL were found in this group. Although a high survival rate has been achieved in early stage RB, efforts need to be made to improve QOL.

### Domain Rb Survivors (N = 122) Controls (N = 50) P value

| Physical | 79.1 ± 9.1 | 81.4 ± 10.1 | 0.14 |
| Social | 71.8 ± 13.1 | 83.5 ± 10.5 | <0.001 |
| Emotional | 78.2 ± 9.8 | 82.5 ± 12.5 | 0.02 |
| School | 79.9 ± 12.3 | 91.9 ± 4.7 | <0.001 |
| Overall | 77.3 ± 8.6 | 82.9 ± 5.9 | <0.001 |

**SNM:**

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<th>Late Mortality</th>
<th>RR (95% CI)*</th>
<th>P value</th>
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<td>MNMSC (irradiated cohort)</td>
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**Conclusions:** By and large, when adjusted for SES and treatment, morbidity/mortality did not differ by race/ethnicity. However, specific morbidities (H: endocrine, AA: cardiac) were more prevalent, and were partially explained by CVRFs. QOL of MNMSC was negligible (grade 3-5) compared to NHW. These findings inform targeted intervention opportunities.

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**Background:** Racial/ethnic differences in risk for long-term adverse outcomes in childhood cancer survivors are not well established. **Methods:** We analyzed QOL in childhood cancer survivors using the PedQLQ 4.0 generic core scale in local language, which has been validated in Indian population. The self-reported questionnaire was filled by children of more than 5 years of age who had completed treatment for more than 12 months. The questionnaire consists of 23 questions on physical, emotional, and school domains on a scale from 0 to 4. This was converted to a scale from 0 to 100, where higher values represented better QOL. The QOL was compared with 50 siblings using student’s t-test. Factors predicting the QOL were assessed. Results: The median age of RB survivors was 98 (range, 60-247) months and 68.4% were males. Seventy-nine percent were International Retinoblastoma Staging System (IRSS) stage 1 and 25% had bilateral disease. Seventy-four percent had extralocular involvement and 22% received radiotherapy. The overall QOL was significantly poorer in RB survivors as compared to controls (Table). The emotional health domains of QOL (fear, anger and sleeping) were significantly lower in RB survivors. Difficulties in maintaining friendships and competing were reported in the social health domain. In school health domain, there were significantly higher absenteeism due to sickness and hospital visits among RB survivors. However, the physical health domain including household work, exercise and self-care was similar in both the groups. Age, sex, IRSS stage and previous radiotherapy did not affect the QOL. Conclusions: QOL is often a neglected aspect in survivors of pediatric solid tumors. We found a significantly poorer QOL in RB survivors. However, no predicting factors for poor QOL were found in this group. Although a high survival rate has been achieved in early stage RB, efforts need to be made to improve QOL.

### Domain Rb Survivors (N = 122) Controls (N = 50) P value

| Physical | 79.1 ± 9.1 | 81.4 ± 10.1 | 0.14 |
| Social | 71.8 ± 13.1 | 83.5 ± 10.5 | <0.001 |
| Emotional | 78.2 ± 9.8 | 82.5 ± 12.5 | 0.02 |
| School | 79.9 ± 12.3 | 91.9 ± 4.7 | <0.001 |
| Overall | 77.3 ± 8.6 | 82.9 ± 5.9 | <0.001 |

**SNM:**

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**Conclusions:** By and large, when adjusted for SES and treatment, morbidity/mortality did not differ by race/ethnicity. However, specific morbidities (H: endocrine, AA: cardiac) were more prevalent, and were partially explained by CVRFs. QOL of MNMSC was negligible (grade 3-5) compared to NHW. These findings inform targeted intervention opportunities.

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**Background:** For adult survivors of childhood cancer, knowledge about the long-term risk of intestinal obstruction from surgery, chemotherapy, and radiotherapy is limited. **Methods:** Intestinal obstruction requiring surgery (IOS) occurring 5 or more years after cancer diagnosis was evaluated in 12,316 five-year survivors from the CCSS cohort (2,002 with and 10,314 without abdominopelvic tumors) and 4,023 sibling participants. Cumulative incidence of IOS was calculated with second malignant neoplasm, late recurrence, and death as competing risks. Piecewise-exponential models assessed the associations of clinical and demographic factors with rate of IOS. **Results:** IOS was reported by 165 survivors (median age at IOS = 19 years, range = 5-50 years; median time from diagnosis to IOS = 13 years) and 114 siblings. Cumulative incidence of IOS at 35 years was 5.8% (95% confidence interval [CI] = 4.4-7.3%) among survivors with primary abdominopelvic tumors, 1.0% (95% CI = 0.7-1.4%) among those without abdominopelvic tumors, and 0.1% (95% CI = 0.1-0.5%) among siblings. Survivors of abdominopelvic lymphoma had the highest 35 year cumulative incidence of IOS, 7.2% (95% CI = 2.8-12.5%). Among all survivors, abdominopelvic tumor (adjustd rate ratio [ARR] = 3.6, 95% CI = 1.9-6.8, P<0.001) and abdominal/pelvic radiotherapy within 5 years of diagnosis (ARR=2.4, 95% CI = 1.6-3.7, P<0.001) increased the rate of IOS, adjusting for year of diagnosis; sex; race/ethnicity; age at diagnosis; age at diagnosis-up (as measured using last cubic spline); primary cancer type; surgery, chemotherapy, radiotherapy, and surgery occurring within 5 years of diagnosis. Developing IOS increased the subsequent mortality among survivors (ARR=1.8, 95% CI =1.1-2.9, P=0.016), adjusting for the same clinical and demographic factors. **Conclusions:** In the decades following diagnosis and treatment, survivors of childhood cancer are at increased risk of developing late-onset IOS, with subsequent increased risk of mortality. These findings underscore the need to promote long-term awareness of these risks among patients and providers, especially for survivors with abdominal or pelvic tumors who have undergone treatment with surgery or radiotherapy.

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**Background:** Long term survivors of paediatric cancer have increased over time. Optimal models of long term care must be developed dependent on current and predicted morbidity, which is affected by tumour type and intensity of treatment. Currently, survivors are referred to the long term follow-up (LTFU) clinic 5 years post treatment and are followed indefinitely. The aim of this project was to assess use of risk-stratification to guide intensity of LTFU of survivors of childhood cancer. **Methods:** A retrospective review of the Royal Marsden Hospital Children’s Late Effects (LE) database was performed. Electronic records of survivors aged 13 to 24 seen in clinic between 2000 to 2012 were reviewed. Patients (pts) were divided into Wallace level 1 depending on tumour type and treatment given. New and grades of LEs of treatment were documented using NCI CTC version 4. **Results:** 316 survivors were divided into Wallace level 1 (n = 18, 6%), 2 (n = 163, 52%) and 3 (n = 135, 43%). At a median follow up of 10.9 years from end of treatment, there were a total of 21 groups of LEs identified. Total LEs were 7 for level 1 pts, 128 for level 2 and 373 for level 3. There were 0.39 LEs seen per pt in level 1, the majority of which were grade 1 or 2, in contrast to 2.7/pt in level 3. The relative risk of at least one grade 3 LE at level 3 compared to level 2 was 4.16. The number lost to follow up was 37, 70% of which were in level 2. **Conclusions:** All survivors of childhood cancer need a treatment summary and care plan at 5 years post treatment, when the risk of relapse is very small. Stratification using Wallace levels is feasible and helps define level of care required. Level 1 and 2 pts can be discharged to a primary care colleague informed by a treatment summary and personalised LTFU care plan. Level 3 pts with higher prevalence and grade LEs will need on-going specialist input from a LTFU service.
Neurocognitive, emotional, and quality of life outcomes in long-term survivors of rhabdomyosarcoma: A report from the Childhood Cancer Survivor Study (CCS). Methods: 482 survivors diagnosed 1970-1986 (mean age SD) 7.2 (5.4) years at diagnosis, 243 (4.8) years of follow-up and 353 siblings from the CCS rated their neurocognition, emotions, and QOL using the Neurocognitive Questionnaire (NCQ), Brief Symptom Inventory-18 (BSI-18), and Medical Outcomes Short Form-36 (SF-36). Based on normative data, impairment was defined as the bottom 10th percentile of performance on the NCQ, the top 10th percentile of symptom prevalence on the BSI-18, and the bottom 15th percentile on each SF-36 subscale. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression. Results: Survivors reported more impairment than siblings on NCQ task efficiency (p < 0.001), higher symptom prevalence on BSI-18 depression (13.3% vs. 8.1%, p < 0.020) and anxiety (7.9% vs. 4.4%, p = 0.038), and poorer QOL on all SF-36 subscales: physical (12.5% vs. 3.1%, p < 0.001), social (15.5% vs. 9.4%, p = 0.009), and emotional (19.2% vs. 13.5%, p = 0.030) functioning, pain (12.4% vs. 14.8%, p = 0.015), general health (26% vs. 11.5%, p < 0.001), vitality (27.6% vs. 20.6%, p = 0.022), and role limitations due to physical (17.4% vs. 9.9%, p = 0.002) and emotional (21.3% vs. 13%, p = 0.002) problems. Among survivors, women were more likely than men to report impaired vitality (OR 2.3, 1.3-3.5) and social functioning (OR 2.3, 1.3-4.3). Adjusting for age at diagnosis and sex, cranial radiation therapy was associated with poorer task efficiency (p = 0.004) and greater likelihood of depression (OR 2.3, 1.3-4.3). Survivors with recent use of antidepressants/antianxiety agents reported significantly worse task efficiency and poorer QOL on all SF-36 subscales than survivors not using these medications. Conclusions: Adult RMS survivors demonstrate substantial long-term impairment of neurocognitive function, emotional status, and QOL, warranting clinical assessment and appropriate interventions.

Temporal changes in treatment exposures in the Childhood Cancer Survivor Study (CCS). Methods: We analyzed cancer and treatment characteristics of 24,000 CCS participants. Treatment exposures were abstracted from medical records. Trends across 5 year intervals were evaluated using logistic regression models with weights to account for sampling probabilities. Results: Within the expanded CCS, the use of chemotherapy significantly increased over time (Table, T1-T6) for all diagnoses except leukemia which was always >100%. Exposure to radiation (RT) decreased overall and for all diagnoses except leukemia which was always 100%. Exposure to radiation (RT) decreased overall and for all diagnoses except leukemia which was always >100%. Radiotherapy (RT) to chest decreased overall (Table, T1-T6) for all diagnoses except leukemia which was always >100%. RT to neck* increased significantly, particularly for doses lower than 250 mg/m2. Conclusions: The expansion of the CCS cohort provides a unique resource to evaluate the impact of historical changes in primary cancer therapy, including reduction of therapeutic intensity for low- and standard-risk populations, as well as intensification of specific therapies for high-risk populations on health and psychosocial outcomes.

Longitudinal smoking patterns in survivors of childhood cancer: A Childhood Cancer Survivor Study (CCSS) update. Methods: We examined self-reported smoking status in 10,430 CCS participants (age ≥18 years) across 2 questionnaires, at a median time of 7.9 years (range 1.4-11.9) apart. Smoking prevalence was compared among survivors, siblings, and the U.S. general population (standardized by age, sex, race/ethnicity and calendar time). Among a subgroup of survivors who also completed an additional follow-up questionnaire (N=3908) a median of 12.5 years (range 4.3-16.3) after the first questionnaire, multivariable regression models evaluated characteristics associated with longitudinal smoking patterns. Results: At baseline, 19% of survivors were current smokers, compared with 24% of siblings and 29% in the standardized U.S. general population. At first follow-up, 17% of survivors were current smokers, compared to 21% of siblings and 24% of the U.S. population. Characteristics associated with consistent “never smoking” over all three questionnaires included higher household income (RR 1.17, 95% CI 1.08-1.25 for ≥$60,000 per year versus < $20,000 per year), higher education (RR 1.36, 95% CI 1.26-1.47 for > high school versus ≤ high school), and receipt of cranial radiation therapy (RR 1.10, 95% CI 1.05-1.16). “Ever smokers’” higher income (RR 1.22, 95% CI 1.09-1.38) and education (RR 1.26, 95% CI 1.13-1.40) were associated with quitting, whereas cranial radiation was associated with not having quit (RR 0.85, 95% CI 0.76-0.96). Development of an adverse health condition was not associated with smoking patterns. Conclusions: Although smoking prevalence may be declining, the substantial number of consistent, current smokers reinforces the need for continued development of effective smoking interventions for survivors.
Background: To investigate long-term survival in pediatric primary liver cancers, including hepatoblastoma & hepatocellular carcinoma (HCC) based on sociodemographic factors & therapy in a large-scale population study. Methods: The Surveillance, Epidemiology and End Results (SEER) database was queried for pediatric cancer patients with the liver as the primary site (C22.0), diagnosed 1973-2011. Overall survival (OS) was stratified by tumor & patient characteristics. Analysis of OS via therapy was further stratified based on socio-demographic factors. Kaplan-Meier & Cox proportional hazard models were used to assess independent predictors for OS. Results: Of 1145 newly diagnosed pediatric cancer patients with liver as primary site, 1012 had primary liver cancers, of whom 725 had hepatoblastoma and 287 had HCC, median age 2yrs, 60.47% male. Overall median OS was 210.7±6.4 mo. Median OS significantly correlated with younger age at diagnosis (< 2 vs. ≥ 2yrs, 240.7 vs. 159.7 mo, p < 0.001), ethnicity (white, black, other; 193.1, 81.6, 166.5 mo; p = 0.0316), geographic location (Alaska, East, Northern Plains, Southwest, Pacific Coast; 106.2, 91.6, 173.1, 112.0, 144.3; p = 0.0144), median family income (≥ $75k vs. < $75k/year, 194.1 vs. 184.5 months, p = 0.013), and regional education levels (% bachelor degree or above, ≥ 25% vs. < 25%, 198.5 vs. 191.5 months, p < 0.0247). Surgery was performed in 684 patients (67.6%), 40 patients received radiation (3.96%). 15 patients received both surgery and radiation (1.48%), and 274 patients received best supportive care (27.0%). OS was significantly lower in patients who received best supportive care (22.6 mo) compared to surgery (275.4 mo, p = 0.58). Favorable sociodemographic factors significantly correlated with higher therapy rates. Conclusions: In pediatric primary liver cancers, socio-demographic factors including younger age at diagnosis, white ethnicity, higher family income & higher regional education levels correlated with prolonged survival. Significantly higher survival with treatment was observed; favorable socio-demographic factors predicted higher treatment rates.

Risk assessment in children presenting with fever and chemotherapy-induced neutropenia. First Author: Kristen Schrutz, Department of Pediatrics, Columbia University Medical Center, New York, NY

Background: Febrile neutropenia (FN) is a common complication of cancer treatment and predisposes children to develop severe infections. The purpose of this study was to identify clinical and laboratory factors predictive of a serious infectious complication in pediatric cancer patients with FN. Methods: A retrospective cohort study was performed in 188 children admitted for management of 381 episodes of febrile neutropenia. The primary outcome was development of a severe infectious complication (SIC), which included an infection diagnosed by clinical exam, a proven bacterial infection of the blood, urine or other sterile site or a radiologically diagnosed infection. Twenty-five variables assessable at the time of presentation to the oncology clinic or emergency department were analyzed for significance, and included patient-specific, treatment-related and episode-specific variables, as well as complete blood count results. Results: The cohort’s mean age was 8.4 years. The underlying diagnosis was a solid tumor in 57.1%, and a hematologic malignancy in 42.9% of patients. The rate of SIC was 30.6% with the most prevalent complication being bacteremia in 49% of those. Of the episodes of bacteremia gram-negative bacilli were isolated in 58.6%. Factors identified in univariate analysis to be significant predictors were maximum temperature, leucocyte count, hemoglobin level, platelet count, baseline disease activity and hypotension. Multivariable regression analysis identified relapsed or advanced disease status, presence of hypotension and degree of leukopenia as significant predictors for a SIC. Conclusions: This study identifies several predictors of FN in pediatric patients with FN, which will enable the development of a prediction model to distinguish patients at low risk of developing SIC. Risk stratification will allow for the design of a prospective safe outpatient management for the low-risk group.

A multicentric study of interval compressed multiagent chemotherapy and metronomic chemotherapy for patients with Ewing sarcoma family of tumours. First Author: Lauro José Gregrian, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

Background: Large cooperative group studies have shown the efficacy of risk-adapted treatment for Ewing sarcoma (ES). However, validation and local adaptation by national cooperative groups is needed. A multicenter protocol to determine the efficacy and safety of adapted regimen was developed by the Latin American cooperative group for pediatric oncology (GALOP). The primary endpoint is to investigate the feasibility and progression free survival (PFS) of combined modality therapy that incorporates interval-compressed VDC/IE as shown by the AEWSS031 study, and metronomic chemotherapy (CT). Secondary endpoints include safety, overall survival and duration of response. Methods: Inclusion (Indct) CT consisted of alternating cycles of VDC (vincristine 1.5 mg/m2 d1, doxorubicin 37.5 mg/m2 d1 and d2, cyclophosphamide 1.2 g/m2 d1) and IE (ifosfamide 3 g/m2 d1, d2 and d3, and etoposide 165 mg/m2 d1, d2 and d3), followed by local control. Pts with localized disease received 6 cycles at Indct and 8 at consolidation (Cons), and pts with metastasis received 9 at Indct and 5 at Cons. The time interval between cycles at Indct and Cons are 14 and 21 days, respectively. After Cons, pts with metastasis received metronomic CT, which consisted in oral cyclophosphamide (25 mg/m2/day, continuously) and来临bin (3 mg/m2, weekly), for 1 year, while pts with localized disease were randomized (1:1) to receive or not metronomic CT according to the following risk factor: age above versus (vs) below 14-years-old, pelvic vs non-pelvic primary tumor, tumor size more vs less than 8 cm, and male vs female. Toxicity is assessed following cycles of CT according to the CTC criteria. Enrollment began in April 2010, and, as of January 2011, 234 pts (107 with metastasis) have been recruited across 37 hematology/oncology centers in Argentina, Brazil, Chile, and Uruguay. Statistical design: Target enrollment is 500 subjects; 200 pts with metastasis, and 300 pts with localized disease, of which 150 is randomized to the metronomic CT arm and 150 receive no further CT, in order to identify a difference in 5-years PFS of 15% (power 0.80, 2-tail type 1 error of 0.05).

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
TPS10080  Poster Session (Board #149b), Sun, 8:00 AM-11:30 AM

Long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 (IL2) activity and efficacy in high-risk relapsed/refractory neuroblastoma patients. First Author: Holger N. Lode, University Med Ctr of the Ernst-Moritz-Amund Universitat Greifswald, Greifswald, Germany

Background: Long-term infusion of anti-GD antibody ch14.18/CHO may improve outcome in patients (pts) with high risk relapsed/refractory neuroblastoma (NB). Methods: 97 pts received 6x10^9 IU/m^2 sc IL2 (d1-5; 8-12), 11 of 100 mg/m^2 ch14.18/CHO (d8-17) and 160 mg/m^2 oral APN311-303 (d8-12), LTI of 100 mg/m2 ch14.18/CHO (d8-17) and 160 mg/m2 oral APN311-303. Response assessments followed INRG criteria. Fc receptor polymorphisms FCGR2A (H131R, -3A (V158F) and -3B (NA1/ NA2) were determined. Results: A decreasing degree of morphine usage and low pain scores were observed. Clinical overall responses were 30% (APN311-303) and 31% (APN311-270). The survival update of the APN311-303 cohort revealed a 1- & 4-y OS of 94.2±3.2% & 69.0±9.0% (median FU 2.9y [0.7-5.2y]) and a 1- & 4-y PFS of 54.4±6.9% & 32.3±6.9% (median FU 2.8y [0.7-4.9y]). Median TTP was 57d (95% CI: 232.7d). The comparator is the reported historical gold standard with 1- & 4-y PFS of 19-2% & 8-3% and OS of 56-3% & 14-4% and a median TTP of 63 d (95% CI: 56.8d). NB pts with high affinity FCGR alleles and an increase in ADCC (cut off 15%) are associated with longer PFS and OS rates (p < 0.03; p < 0.005), which supports NK-cell mediated ADCC as the mechanism of action. Parameters of immune modulation (CDC, and WBT) and pharmacokinetics (PK) of ch14.18/CHO were comparable between APN311-202 and -303 cohorts. PK of ch14.18/CHO was analyzed in cycle 1: Cmax = 12.2±0.4 µg/ml, t1/2 = 8.4±1.1 d, AUC = 145.3±5.5 µg·ml-1·d-1, Vd = 9.3±0.51·l/m². A pro-inflammatory cytokine response (IL-2, IL-6, IL-8, IFNγ) translated into the expansion of effector NK- (3x) and T cells (1.5x). WBT in HACA negative patients, levels of ch14.18/CHO and functional parameters (CDC, WBT) were similar before subsequent treatment cycles indicate persistent anti-NB activity for the entire treatment period.

Conclusion: LTI of ch14.18/CHO is active and effective in high-risk relapsed/refractory NB. Clinical trial information: NCT01701479.

TPS10082  Poster Session (Board #150b), Sun, 8:00 AM-11:30 AM

A randomised phase IIb trial of BEvACizumab added to Temozolomide ± Irinotecan for children with refractory/refractory Neuroblastoma - BEACON-Neuroblastoma, a European Innovative Therapies for Children with Cancer (ITCC) - International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. First Author: Lucas Moreno, CNIO, Spanish National Cancer Research Centre, Madrid, Spain

Background: Current therapy for relapsed/refractory high-risk neuroblastoma is not evidence based and long-term disease control is poor. Advances in frontline therapy have been achieved through randomised clinical trials. BEACON-Neuroblastoma is designed to define the role of chemotherapy regimens to be combined with targeted agents and determine if inhibiting angiogenesis with bevacizumab (B) adds to the activity of chemotherapy. It is the first randomized European study for refractory/ relapsed neuroblastoma Methods: BEACON-Neuroblastoma is a factorial phase 2, multicentre, international, randomized clinical trial (EudraCT 2012-000072-42, sponsored by the University of Birmingham). Patients 1-21 years with relapsed/refractory high-risk neuroblastoma are randomised to 1 of 4 arms: T (temozolomide), IT (irinotecan-temozolomide), BT (B-T) or BIT (B-IT). The trial tests whether B added to chemotherapy (T or IT) demonstrates activity and whether the addition of I to T increases activity. Primary endpoint is best response at any time during trial treatment. During 2015, whether the addition of topotecan to T increases activity will be addressed by changing to 3 x 2 design with 6 arms and requiring 160 patients. The trial incorporates functional imaging (FI) to elucidate the role of these agents in the clinical role of biomarkers in the study measuring neuroblastoma mRNAs and molecular characterisation. This work is supported by Cancer Research UK [grant number CRUK/11/ 056] and Imagine for Margo. 21 sites in 7 countries are open (11 further sites are to open). From Jul-2013 to Jan-2015, 30 patients have been included. BEACON-Neuroblastoma is the recommended approach for relapsed/refractory neuroblastoma in SIOPEN/ITCC. The trial will answer 2 randomised questions in a small population and has developed a European network of centres performing biomarker and FI studies. It will be correlated in the future Clinical trial information: NCT02308527.

TPS10081  Poster Session (Board #150a), Sun, 8:00 AM-11:30 AM

A phase II study of pazopanib in children, adolescents, and young adults with refractory solid tumors. First Author: Alice Lee, Columbia University, New York, NY

Background: Pazopanib (VOTRIENT; GlaxoSmithKline) is an angiogenesis inhibitor targeting VEGFR-1, -2, -3; PDGFRα and β; and c-Kit, and is indicated for the treatment of adults with advanced RCC and advanced soft tissue sarcoma. Data from adults with sarcoma support the study of soft tissue and bone sarcomas, as well as embryonal tumors, in pediatric subjects. The current Phase II study undertaken by the Children’s Oncology Group (COG-ADVL1322; VEG116731) was preceded by a Phase I trial of pazopanib tablets and powder for oral suspension (Pios) in children (N = 51). The maximum tolerated dose (MTD) for tablets was 450 mg/m²/dose and 160 mg/m²/dose for the Pios, with two dose-limiting toxicities (DLTs) seen at 225 mg/m² of the Pios. Hematologic and non-hematologic toxicities were generally mild. One subject each with hepatoblastoma or desmoplastic small round cell tumor had a partial response; 8 had stable disease (> 6 cycles); 7 of these had sarcoma (Glade Bender; J. Clin, Oncol. 2013; 31:3034). Given these findings, this Phase II trial will further evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics in children. Methods: This is a multi-center study of pazopanib in US and Canadian subjects age 1 to 18 years with solid tumors relapsed or refractory to prior therapy. Tumor types include rhabdomyosarcoma, non-rhabdomyosarcoma- soft tissue sarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, and hepatoblastoma. Subjects will be stratified by tumor type, and the response rate to pazopanib will be assessed for each of the six strata using a two-stage design. Pazopanib will be administered orally once daily as a tablet at 450 mg/m² or as Pios at 225 mg/m². The phase I Pios MTD of 160 mg/m² may result in suboptimal exposure. Given that the toxicity at 225mg/m² was isolated and reversible, the first 6 patients receiving Pios will be dosed at 225 mg/m² and assessed for first-cycle DLTs and PK. The study will also evaluate pazopanib pharmacokinetics and toxicity in this pediatric population and will assess the relationship between efficacy and levels of cytokines and angiogenic factors, and VEGF and KDR polymorphisms. Four of 77 subjects have been enrolled. (NCT01956669) Study funded by GSK. Clinical trial information: NCT01956669.

TPS10083  Poster Session (Board #151a), Sun, 8:00 AM-11:30 AM

Early detection of transformation of plexiform neurofibromas to malignant peripheral nerve sheath tumors in neurofibromatosis type 1. First Author: Sucharita Bhaukim, Children’s Natl Med Ctr, Washington, DC

Background: Neurofibromatosis 1 (NF1), an autosomal dominant genetic disorder, is characterized by development of benign plexiform neurofibromas (PN) and malignant peripheral nerve sheath tumors (MPNST) that often develops from malignant transformation in a preexisting PN. Complete surgical resection is only curative treatment, making early detection of malignant transformation an important goal. A preliminary study by Motorola et al (Pediatr Blood Cancer 2013, 60(1): 59-64) using 18F-fluorodeoxy-glucose positron emission tomography (FDG-PET) to identify concerning lesions, described high FDG uptake in both malignant and benign NF1. [%3-F-3-fluoro-3-deoxy-L-thymidine (FLT) PET] MET measures cell cycling and proliferation. We hypothesize that FLT-PET may be more sensitive and specific in the identification of malignancy. This pilot study in NF1 patients with lesions concerning for MPNST will evaluate 1) feasibility of FLT-PET 2) ability of FLT-PET to distinguish benign from malignant and 3) perform comprehensive genomic analyses from tumor and blood samples. Methods: Trial design: Fifteen patients with NF1 and lesions concerning for malignan transformation are eligible. Patients undergo clinical evaluation of NF1 manifestations, whole body MRI with volumetric analysis of tumor burden, FDG and FLT-PET, guided biopsies of the concerning lesion and of adjacent presumably benign PN for detailed pathology analysis. Germline blood samples, tissue samples from concerning lesion and surrounding parenchyma of benign PN will be collected. The major objective of the PET studies will be blinded to the pathologic diagnostic. Exploratory statistical methods will be used to evaluate the differences in uptake between the two groups (FDG and FLT), followed by logistic regression to identify uptake values most associated with benign versus malignant classification. Clinical, imaging, histopathologic, and genomic features will be correlated in an exploratory fashion, to describe features associated with malignant transformation. This single institution trial (NCT02211768) is open for enrollment at the NCI, and has enrolled the first patient. Clinical trial information: NCT02211768.
A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor α (PDGFRA) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Options for patients (pts) with unresectable metastatic STS are limited. While Dox is standard of care, Dox combinations have yet to improve overall survival (OS) over Dox alone. Olaratumab (IMC-3G3), a fully human monoclonal antibody, selectively binds PDGFRα (a signaling protein overexpressed in STS), blocks ligand binding and antagonizes PDGF activity in preclinical sarcoma models. Methods: We conducted a phase Ib, open-label, randomized phase II study of Dox or olaratumab, in untreated STS (NCT01185964). Pts received Dox (75 mg/m² Day 1) with (Arm A) or without (Arm B) olaratumab (15 mg/kg Days 1 and 8, every 21 days) and chemotherapy until disease progression or unacceptable toxicity. In Arm B, pts could cross over to olaratumab at progression. The primary endpoint was progression-free survival (PFS; target hazard ratio [HR] = 0.67, 80% power, α = 0.2) with OS as a secondary endpoint. Results: Of 133 pts randomized, 129 (97%) were treated (64, Arm A; 65, Arm B). Demographics were balanced. Final PFS analysis (103 events) revealed medians of 6.6 months (Arm A) and 4.1 months (Arm B) (stratified HR; 95% confidence interval [CI]: 0.672 [0.442-1.021]; p = 0.0615). Interim OS analysis (83 deaths) revealed medians of 25.0 months (Arm A) and 14.7 months (Arm B) (HR = 0.44; p = 0.0005). Objective response rates were 18.8% (Arm A) and 12.3% (Arm B) (p = 0.407). The following Grade ≥ 3 adverse events (AEs) occurred in ≥ 5% of the population: Arm A > Arm B, neutropenia (51.5% vs 33.8%); anemia (12.5% vs 7.7%); fatigue (9.4% vs 3.1%); thrombocytopenia (9.4% vs 7.7%); Arm A < Arm B, febrile neutropenia (12.5% vs 13.8%); infections (6.3% vs 10.8%). Conclusions: This study of olaratumab in combination with Dox met its primary PFS endpoint and achieved an improvement of 10.3 months in median OS that was highly statistically significant (HR = 0.44; p = 0.0005). Olaratumab is the first agent added to Dox to improve OS in advanced/metastatic STS in a randomized trial. Clinical trial information: NCT01185964.
Activity of regorafenib (RE) in leiomyosarcomas (LMS) and other types of soft-tissue sarcomas (STS): Results of a double-blind, randomized placebo (PL) controlled phase II trial. First Author: Olivier Mir, Institut Gustave Roussy, Villejuif, France

Background: RE is a multitargeted kinase inhibitor that has demonstrated activity in gastrointestinal stromal tumors. We investigated its activity and safety in anthracycline pretreated metastatic soft tissue sarcomas (STS). Methods: REGOSARC (NCT01900743) consisted of four independent cohorts of patients (pts) with LMS, OTS, synovial, and adipocytic sarcomas who were randomized (1:1) to receive either RE (160 mgq, 21/28 or PL, with optional cross-over. Key eligibility criteria were age ≥18, measurable Progressing STS not amenable to curative-intent surgery, ≤3 previous lines of treatment for metastatic STS. The primary endpoint was progression-free survival (PFS) with blinded central radiological review. Statistical assumptions for LMS cohort (48 pts) were 16.6 months (mo) with PL, PFS = 4.6 mo with RE, 1-sided α = 0.1 and β = 0.05. Results: From July 2013 to July 2014, 57 LMS and 53 OTS pts were enrolled (55 with PL, 55 with RE). The two most common OTS types were Undifferentiated Pleomorphic Sarcomas (n = 21, 40%) and Solitary Fibrous Tumors (n = 7, 13%). Eighty-four (77%) tumors were grade 3. In both cohorts, the most common primary sites were retroperitoneum and uterus (n = 23, 21%, each). There were 48 men (44%). The median age was 60 (20-81) years. The median number of prior lines was 2 (1-3); 106% (97), 59%, 34% (35%) and 4 (4%) pts were previously treated with doxorubicin, ifosfamide, trabectedin and pazopanib, respectively. Both arms in each cohort were well balanced. The most common Gr 3 AE were hypertension (10 vs 2 pts; RE vs PL), skin toxicity (9 vs 1), asthenia (9 vs 3) and diabetes (6 vs 2). There was no Gr5 AE and 1 Gr4 AE (anemia in RE arm). The median PFS of LMS pts was 4.0 mo with RE versus 1.9 mo with PL (HR = 0.49, 95% CI 0.27-0.89; P = 0.02). The median PFS of OTS (n = 6) was 4.1 mo with RE and PL respectively (HR = 0.38, 95% CI 0.20-0.74; p = 0.002). The 6-mo OS rate of LMS pts was higher in the RE arm (87.0% vs 75.9%; HR = 0.25; 95% CI 0.08-0.81; p = 0.13), this difference was not significant in the OTS cohort (79% vs 62.0%; HR = 0.64, 95% CI 0.26-1.56; p = 0.39). RE did not display an acceptable toxicity profile that warrant further clinical evaluation in LMS and OTS pts. Clinical trial information: NCT01205743.

A phase Ib/Ii study of MEK162 (binimetinib [BNI]) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST). First Author: Ping Chi, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ETV1, a lineage-specific survival factor for GIST and its precursor intestinal cells of Cajal, represents a promising therapeutic target in GIST. In preclinical models, MEK inhibition with BNI, synergizes with imatinib in destabilizing ETV1 protein and suppressing GIST tumorigenesis and progression. Combined MEK and KIT inhibition therefore represents a novel therapeutic approach for patients with GIST. Methods: The phase Ib portion of the imatinib (400 mg daily) plus BNI was performed in patients (pts) with imatinib-resistant advanced GIST. A standard 3+3 dose escalation was utilized to determine the recommended phase II dose (RP2D) of this combination. Additional pts were enrolled on an expansion cohort at the RP2D. Responses were assessed by RECIST 1.1 and Choi criteria every 8 weeks. Custom targeted next-generation sequencing with the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) was performed on archived tumor samples for all pts. Results: Eighteen pts enrolled to the phase I portion, with 9 pts each in the dose escalation and the expansion cohorts. Median age 60 (range 30-74), 44% women, median prior therapy 3 (range 1-6, 14/18 pts had ≥3 prior therapies). Imatinib 400 mg daily with BNI 45mg BID was established as the RP2D. Dose limiting toxicity (DLT) was asymptomatic grade 4 Creatinine Phosphokinase (CPK) elevation (1/6 pts at RP2D). The most common non-DLT grade 3/4 toxicities were rash (5/18) and neutropenia (3/18). Other Common Grade 2 toxicities include peripheral edema (5/18), rash (3/18). No unexpected toxicities observed. Of the 15 pts with evaluable CT scans, 5 pts (33%) had Choi PR; and 9 pts had RECIST SD at 8 weeks. Seven pts remain on trial at data cutoff (range 4-53 months). Median progression-free survival is not reached. Correlation of outcome with IMPACT is forthcoming. Conclusions: BNI and imatinib combination is well-tolerated and has clinical activity in imatinib-refractory GIST. Phase II study is on-going in untreated GIST pts and a larger clinical trial in the imatinib-resistant GIST population is warranted. Clinical trial information: NCT01991379.
The somatic mutational landscape in soft tissue sarcoma: Early results from TCGA data. **First Author:** Andrew Scott Brohl, Icahn School of Medicine at Mount Sinai, New York, NY

**Background:** The widespread use of next-generation sequencing has uncovered the genomic landscape in many tumor types. Given the disease rarity and histologic diversity, much less is known about the somatic mutational landscape in many tumor types. **Methods:** Publicly available whole exome sequencing data from the Cancer Genome Atlas (TCGA) sarcoma project was downloaded and processed using well-established bioinformatics pipelines. Recurrent mutations were analyzed for statistical significance and potential oncologic relevance. Pan-sarcoma and histology-specific mutational frequencies were calculated. **Results:** Matched tumor-normal whole exome sequencing was available for 242 patients at the time of analysis. The disease histologies include 92 leiomyosarcoma, 51 dedifferentiated liposarcoma, 44 undifferentiated pleomorphic sarcoma, 24 myxofibrosarcoma, 9 malignant peripheral nerve sheath tumor, 8 synovial sarcoma, 1 desmoid tumor, and 13 lacking clinical annotation at the time of analysis. There were a median 475 high-confidence somatic variants detected ([range 127-7153]). Statistically significant recurrent mutations include recurrent inactivating mutations in 3 well-established tumor suppressors, TP53, ATRX, and RB1, found in 27.3%, 8.7% and 6.2% of the total cohort respectively. Differential mutational frequency of these genes was noted between histological subtypes. Additional statistically significant recurrent mutations in genes of less clear oncologic significance are noted, as are additional recurrent mutations in other known cancer genes, but found in frequencies not meeting statistical significance. **Conclusions:** To our knowledge this is the first attempt to analyze the somatic mutational landscape in soft tissue sarcoma from TCGA whole exome sequencing data. We report statistically significant recurrent mutation in three tumor suppressor genes with clear oncogenic implication. Additional recurrent mutations of interest due to either mutational frequency or mutational impact in other cancer types are noted. A comprehensive analysis of genomic data is underway by the TCGA sarcoma analysis group.

Clinical application of prognostic gene expression signature in fusion gene-negative rhabdomyosarcoma: A report from the Children’s Oncology Group. **First Author:** Pooja Hingorani, Phoenix Childrens Hosp, Phoenix, AZ

**Background:** Pediatric rhabdomyosarcoma has two common histological subtypes: embryonal (ERMS) and alveolar (ARMS). **Methods:** PAX/FOXO1 fusion gene status is a more reliable prognostic marker than alveolar histology while fusion gene-negative (FN) ARMS patients are clinically similar to ERMS patients. A five-gene expression signature (MG5) previously identified two diverse risk groups within the fusion-negative RMS (FN-RMS) patients but this has not been independently validated. The goal of the current study was to test whether expression of the MG5 metastase, measured using a technical platform that can be applied to routine pathology material, would correlate with outcome in an unrelated cohort of patients with FN-RMS. **Methods:** A series of cases were taken from the Children’s Oncology Group (COG) D9803 study of children with intermediate-risk RMS and gene expression profiling of the MG5 genes was performed using the nCounter assay. The MG5 score was correlated with clinical and pathological characteristics as well as overall and event-free survival. **Results:** MG5 standardized score showed no significant association with any of the available clinical-pathological variables. The MG5 signature score showed a significant correlation with overall (N = 57; HR 7.3 95%CI(1.9-27.0), p = 0.003) and failure-free survival (N = 57; HR 6.1 95%CI(1.9-19.7), p = 0.002). **Conclusions:** This represents the first validated molecular prognostic signature for patients with FN-RMS who otherwise have intermediate-risk disease. The capacity to measure the expression of a small number of genes in routine pathology material and apply a simple mathematical formula to calculate the MG5 metastase score promises a clear path toward better risk stratification in a future, prospective clinical trial.

The who and what of imaging in sarcoma and correlation with survival. **First Author:** Vadim S Koshkin, University of Michigan, Ann Arbor, MI

**Background:** Response and progression are surrogates for survival that inform clinical decisions. Comparison of anatomic and functional imaging modalities in a large prospective clinical trial can suggest the optimal method of selecting patients to benefit from new targeted therapy. **Methods:** In the context of the National Cancer Institute’s National Sarcoma Network, a prospective, prospective, chemotherapeutic, stroma-refractory Ewing’s Sarcoma were treated with R1507, a human monoclonal antibody directed at IGf-1 receptor, as part of SARCO11 study (U.C. CA, Errico, 2012). Each patient had anatomic imaging with CT/ MRI at baseline and 6-week intervals and FDG-PET at baseline and on day 9. Anatomic imaging results were reported by each of the 31 sarcoma centers using WHO criteria. An expert central radiology group performed an independent review and volumetric analysis on 76 pts. Using log-rank analysis we defined the optimal volume cut points for progression and response at 6 wk imaging which correlated with OS, and compared this model to previously established criteria including WHO (both central and local), RECIST and PERCIST. **Results:** Volume increase of 175% for prior lesions at 6 wks was the optimal cutoff for decreased OS (p = 0.001) and thus progression. Optimal cutoff for response was a 45% volume decrease. OS of patients with PD at 6 wks was significantly reduced compared to non-progressors based on Volume (R² = 0.17) as well as other criteria: RECIST (R² = 0.17), WHO_Central (R² = 0.16), WHO_Local (R² = 0.14). Patients with PD by PERCIST on day 9 had reduced OS vs. non-progressors (p = 0.001). Progression type impacted survival, as pts with progressive lesions, whether progressing prior to or after, had decreased OS compared to pts with either variable alone. **Conclusions:** In a large clinical trial we identified pts with decreased OS based on multiple anatomic imaging criteria at week 6 and functional imaging criteria at day 9. A new model using volumetric analysis with cutoffs different from those extrapolated from RECIST or WHO was introduced, and its utility should be assessed in a prospective clinical trial. Clinical trial information: NCT00642941.
10512 Poster Discussion Session; Displayed in Poster Session (Board #116), Sun, 8:00 AM-11:30 AM, Discuss in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Event-free survival and overall survival in 2,253 patients with osteosarcoma registered to EUAROMS-1. First Author: Sigbjørn Smeland, Oslo University Hospital, The Norwegian Radium Hospital, Scandinavian Sarcoma Group, Oslo, Norway

Background: EUAROMS-1 (NCT00134030) is an international study in osteosarcoma including two Phase III randomized controlled trials that investigated postoperative treatment optimization on the basis of histological response to preoperative chemotherapy (CT). Our study aim was to report outcomes from diagnosis for all registered patients in this large, intergroup study. Methods: Patients (pts) were eligible for registration if: < 30 days from diagnostic biopsy; age ≥ 40yrs; with localized or primary metastatic, high-grade extremity or axial osteosarcoma; resectable disease; fit for treatment and NOS. Treatment: adjuvant CT (doxorubicin, cisplatin (MAP), surgery and then post-op MAP-based CT according to response and optional randomization. The primary outcome measure was event-free survival (EFS), defined as time from diagnostic biopsy until the earliest of: death, local recurrence, new metastatic disease, progression of metastatic disease or secondary malignancy, or date of last contact; a secondary outcome measure was overall survival (OS). Standard statistical methods were used. Results: 2260 pts from 17 countries & > 300 centres were registered from 2005 to 2011; this analysis excludes 7 ineligible pts. The site was 13% proximal femur or humerus, 82% other limb site, 5% axial skeleton; 16% had definitive preoperative chemotherapy. Median age was 14yrs (quartiles 11, 17). 1334 (59%) were randomized; 919 (41%) were not, mostly for non-consent. Median follow-up was 5.2 yrs. 1000 EFS events and 634 deaths were reported. From biopsy, 5-yr EFS was 54% (95% CI 52%, 57%), and 5-yr OS was 76% (95% CI 73%, 79%). In 1881 pts with localized disease: 5-yr EFS was 59% (95% CI 57%, 62%) and 5-yr OS was 75% (95% CI 73%, 77%); in 357 pts with metastases 5-yr EFS was 29% (95% CI 24%, 34%) and 5-yr OS was 46% (95% CI 41%, 52%); metastases were unreported for 15 pts. Prognostic models will be presented. Conclusions: EFS and OS rates in this multi-center study were comparable to centres’ reported series. We used broader eligibility criteria than most osteosarcoma studies, by including patients with axial or metastatic disease. However, this extends recruitment and relevance of our findings. Clinical trial information: 67613327.

10513 Poster Discussion Session; Displayed in Poster Session (Board #117), Sun, 8:00 AM-11:30 AM, Discuss in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Forty years of randomized trials in advanced/metastatic soft tissue sarcoma (STS): Endpoint selection, surrogacy and quality of reporting. First Author: Alona Zer, Princess Margaret Cancer Center, Toronto, ON, Canada

Background: Randomized controlled trials (RCTs) in STS have utilized varying endpoints. Surrogacy of intermediate endpoints such as progression-free survival (PFS), response rate (RR), 3 month progression free survival (3mPFS) and 6 month progression free survival (6mPFS) with overall survival (OS) has not been established. The quality of reporting of efficacy and toxicity also remains uncertain. Methods: A systematic review of MEDLINE and EBASE indexed RCTs of systemic therapy in STS. Surrogacy between intermediate endpoints and OS was explored using meta-regression comprising a linear regression weighted by study sample size for the hazard ratio (HR) for OS with the HR for PFS or the odds ratio (OR) for RR, 3mPFS and 6mPFS. Quality of reporting of efficacy and toxicity were defined as described previously (Verdú-Badillo et al, Ann Oncol 2013). Results: Of 3329 articles initially identified; 52 RCTs published between 1974 and 2014 and comprising 9762 patients met the inclusion criteria. There was a moderate correlation between PFS and OS and between RR and OS (Table 1). The correlation between 3mPFS and 6mPFS with OS was however, weak. Only 44% of studies defined the primary endpoint clearly, but this deficiency improved over time (p for trend < 0.01). There has been a significant reduction in the use of RR as the primary endpoint over time, favouring time-based events (p for trend = 0.02). In 14% of RCTs, despite the primary endpoint not being met, the concluding statement suggested benefit from the experimental therapy. Toxicity was comprehensively reported in just 52% of RCTs while 17% reported toxicity poorly. Quality of toxicity reporting has not changed significantly over time (p = 0.25). Conclusions: In advanced STS RCTs PFS is a better surrogate for OS than RR. The correlation between 3mPFS/6mPFR and OS is weak and its use should be reconsidered. Although the quality of RCT reporting has improved over time, toxicity reporting and interpretation of toxicities has remained unchanged.

Surrogate endpoint Correlation coefficient with OS

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<th>HR for PFS</th>
<th>OR for RR</th>
<th>OR for 3mPFS</th>
<th>OR for 6mPFR</th>
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10514 Poster Discussion Session; Displayed in Poster Session (Board #118), Sun, 8:00 AM-11:30 AM, Discuss in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

A phase Ib dose-escalation study of TRC105 (anti-endoglin antibody) in combination with pazopanib in patients with advanced soft tissue sarcoma (STS). First Author: Steven Attia, Mayo Clinic, Jacksonville, FL

Background: The VEGFR inhibitor pazopanib is approved for the treatment of metastatic STS. Resistance to pazopanib is a challenge in the treatment of STS, and endoglin (CD105) activation may be an important resistance mechanism. Endoglin is an angiogenic receptor expressed on proliferating tumor vessels, which are angiographically visible. Therefore, it is targeted for conventional osteosarcoma. Median age was 14yrs (quartiles 11, 17). 1334 (59%) were randomized; 919 (41%) were not, mostly for non-consent. Median follow-up was 5.2 yrs. 1000 EFS events and 634 deaths were reported. From biopsy, 5-yr EFS was 54% (95% CI 52%, 57%), and 5-yr OS was 76% (95% CI 73%, 79%). In 1881 pts with localized disease: 5-yr EFS was 59% (95% CI 57%, 62%) and 5-yr OS was 75% (95% CI 73%, 77%); in 357 pts with metastases 5-yr EFS was 29% (95% CI 24%, 34%) and 5-yr OS was 46% (95% CI 41%, 52%); metastases were unreported for 15 pts. Prognostic models will be presented. Conclusions: EFS and OS rates in this multi-center study were comparable to centres’ reported series. We used broader eligibility criteria than most osteosarcoma studies, by including patients with axial or metastatic disease. However, this extends recruitment and relevance of our findings. Clinical trial information: 67613327.

10515 Poster Discussion Session; Displayed in Poster Session (Board #119), Sun, 8:00 AM-11:30 AM, Discuss in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

A phase II study of tivozanib in patients with metastatic and non-resectable soft tissue sarcoma. First Author: Mark Aguilnik, Northwestern University, Feinberg School of Medicine, Chicago, IL

Background: Despite a multi-modality approach, many patients (pts) with early stage soft tissue sarcomas (STS) will develop recurrent or metastatic disease. Treatment options for these pts are limited, thus necessitating new antitumor agents. VEGFR1, VEGFR2 and VEGFR3 are high affinity receptor tyrosine kinases localized in the endothelium of tumor vasculature and are involved in tumor angiogenesis. VEGFR tyrosine kinase inhibitors (TKI) block phosphorylation of the VEGFR and inhibit activation of angiogenesis and, indirectly, tumor growth. Tivozanib is a potent and selective VEGFR 1, 2 & 3 TKI with a long half-life, and thus a potential novel agent in the treatment of metastatic STS. Methods: A multicenter phase II study of tivozanib in pts with metastatic and non-resectable STS was conducted through the Midwest Sarcoma Trials Partnership. Adequate performance status, organ function, measurable disease (RECIST 1.1) and 1-4 prior therapies were required. Tivozanib 1.5 mg PO daily was given in 28 day cycles (21 days on, 7 days off) for up to 12.3+ months. Efficacy endpoints will be correlated with endoglin expression by immunohistochemistry. Conclusions: Tivozanib was well tolerated at its recommended phase 2 dose of 10 mg/kg weekly, in combination with daily oral pazopanib, in pts with advanced STS, and the combination exhibited evidence of activity. A multicenter phase 2 trial of Tivozanib + pazopanib is ongoing. Clinical trial information: NCT01975519.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase II clinical trial of belinostat (PXD101) in combination with doxorubicin in patients with soft tissue sarcomas (STS). First Author: Joanna Vitfell-Rasmussen, Department of Oncology, Herlev hospital, Herlev, Denmark

Background: Belinostat is a novel histone deacetylase (HDAC) inhibitor. This study evaluated the MTD and DLTs of the combination of belinostat and doxorubicin in solid tumours (phase I) and efficacy as measured by response rate (RR) in advanced STS (phase II). Methods: Belinostat was administered as a 30-minute IV infusion on Day 1 and on Day 5 in combination with doxorubicin. It was dose escalated using a belinostat starting dose of 600 mg/m² combined with 50 mg/m² doxorubicin (cohort 1), in subsequent cohorts doxorubicin was administered at 75 mg/m² with 600 mg/m² belinostat (cohort 2), 800 mg/m² (cohort 3) and 1000 mg/m² (cohort 4). A phase II trial was then performed in STS patients (pts) using the doses in cohort 4. A stopping rule determined that the phase II trial was stopped if no more than 2 responses (CR/PR) were seen among the 20 pts within the first 2 treatment cycles. The following pharmacoki-netic parameters were determined: elimination half-life (t1/2), maximum concentration (Cmax), time to maximum concentration (tmax), area under the curve (AUC0-t), AUC∞ and elimination rate constant (k2) and volume of distribution (Vc and Vss).

Results: A total of 41 pts were included (25 in phase I, 20 in phase II (including 4 pts with STS from cohort 4). Common drug-related toxicities included: fatigue (95%), nausea (76%) and alopecia (63%). One DLT was observed, Rash - Hand and Foot Syndrome, CTC grade 3, in cohort 3 on Day 22. The MTD was declared the highest tested dose level: belinostat 1000 mg/m² combined with 75 mg/m² doxorubicin. Dose normalised AUC0-∞ and Cmax appeared relatively consistent across the different cohorts on both Days 4 and 5 indicating that belinostat exhibited linear pharmacokinetics across the dose range and that doxorubicin had no effect on belinostat exposure. Two responses were observed in phase I at cycle 4 (2 PR, RR of 8% (95% CI, 1 - 26%)) and in the phase II trial there were 4 PR (4/1 CR, 92%) at 13% (95% CI, 2 - 38%) and 9 SD, hence the trial was stopped after 20 pts were enrolled. Conclusions: The combination of belinostat and doxorubicin was well tolerated and showed activity in 12/20 pts in the metastatic GIST population, which warrants further investigation. Clinical trial information: NCT00878800.

Plasma sequencing to detect a multitude of secondary KIT resistance mutations in metastatic gastrointestinal stromal tumors (GIST). First Author: Sebastian Bauer, Universitaetsklinikum Essen-Innere Medizin-Essen, Essen, Germany

Background: Resistance to kinase inhibitors is associated with a marked genomic heterogeneity of secondary mutations of KIT in metastatic GIST which is poorly represented in single tumor biopsies. We sought to evaluate plasma sequencing (plasma seq) as a novel approach to detect or monitor the spectrum of resistance mutations in GIST. Methods: We prospectively collected 30 plasma samples from 22 patients with metastatic GIST (incl. corresponding tumor from same time point: n = 13; median pretreatment: n = 2). Circulating free DNA (cf DNA) and tumor DNA were sequenced on an Illumina MiSeq platform using a custom designed targeted sequencing panel. Mutations with a percentage < 0.5% of total reads were excluded. Results: We detected 87 non-synonymous KIT mutations in plasma samples with various percentages of total reads (0.5-20% of cf-DNA). Primary mutations were found in 41% (all matching the tumor analysis), resistance mutations were seen in 26% of the plasma samples. Future validations should include comprehensive sequencing of corresponding tumor tissue. Handling of plasma samples should be standardized in order to maximize the yield of mutant DNA. The clinical value of plasma seq should be tested in randomized trials.

Detection of KIT mutations in circulating tumor DNA (ctDNA) and their association with ponatinib anti-tumor activity in patients (pts) with advanced gastrointestinal stromal tumors (GIST). First Author: Michael C. Heinrich, Knight Cancer Institute and Portland VA Medical Center, Oregon Health & Science University, Portland, OR

Background: Ponatinib is a multi-targeted tyrosine kinase inhibitor with potent preclinical activity against a broad range of clinically relevant KIT mutants, including primary-activating (especially exon 11) and secondary-resistance (including exons 12/13) mutants. Ponatinib is being evaluated in a phase 2 trial (NCT101874665), in which TKI-resistant metastatic GIST pts are enrolled in 2 cohorts based on the presence (A) or absence (B) of KIT exon 11 mutations in tumor specimens. We used ctDNA to explore the association between KIT mutation status and anti-tumor activity of ponatinib. Methods: Plasma samples were collected at baseline (BL) and every 8 wks, and a subset analyzed for 7 primary (exons 9, 11, 13) and 20 secondary (exons 13, 14, 17, 18) mutations using BEAMing. The primary end point was anti-tumor activity (PR, CR, SD or PD in the cohort of A or B). Results: 61 pts with evaluable ctDNA were enrolled. 33 were evaluable (20 had KIT exon 11 mutations). 27 were evaluable in cohort A (exons 9, 11, 13) and 34 in B (exons 13, 14, 17, 18). 23/27 (86%) and 25/34 (74%) of the evaluable pts showed no detectable ctDNA for at least 1 mutation. Conclusions: ctDNA from plasma is a potential non-invasive disease monitoring tool in GIST patients treated with ponatinib. Clinical trial information: NCT01874665.

An NGS assay strategy with FFPE and cfDNA to determine primary and secondary mutations across the initial diagnosis and subsequent recurrence/progression of patients with localized, recurrent and metastatic GIST. First Author: Nagavalli Somasundaram, National Cancer Centre, Singapore, Singapore

Background: Primary and secondary mutations in GIST affect prognosis and treatment response and impacts treatment decision making. A single driver mutation (primary) in GIST patients is detectable in plasma DNA and tissue DNA. Common driver mutations include primary-activating (especially exon 11) and secondary-resistance (commonly BRAF, KRAS and NRAS). However, in patients without GIST, sensitive and specific detection of driver mutations in plasma DNA is challenging. Method: A panel of GIST driver mutations was developed using a Next-Generation Sequencing (NGS) assay and applied to FFPE samples, plasma, and serial blood specimens from patients with recurrent or metastatic GIST. Results: The panel (47 mutations) was used to determine driver mutations in 80% (42/52) of patients in whom the panel was applied. Truck driver mutations were found in 34% (18/52) of patients. Conclusions: The NGS assay strategy demonstrates a high sensitivity and specificity for detecting driver mutations in FFPE samples and plasma samples. Further exploration is needed to determine its role in the management of GIST patients.
A phase II trial of sorafenib (SO) in advanced chordoma patients (pt). First Author: Eric Amela, Centre Oscar Lambret, Lille, France

Background: To report in a hypothesis-generating phase II study the activity and safety of SO in advanced chordomas. Methods: pts received 400 mg/d until progression, intolerance or up to 9 months (mo) and intolerance. The primary endpoint was progression-free survival according to RECIST 1.1. Secondary end-points were RR, OS and toxicity. Results: From 07/2011 to 01/2014, 27 pts were enrolled (median age 64, range 30-86), including 17 men and 10 women. The primary tumor locations were sacrum (21, 77.7%), rachis (4, 14.8%) and clivus (3, 11.1%). Metastasis was present in 14 pts (58.3%). Twenty-six pts (96.3%) had prior treatment, including surgery (18, 66.7%), radiotherapy (18, 66.7%) and prior systemic therapies (MTT; 12, 44.4%; median number of lines 1, range 1-3). The duration of SO treatment was 4.9 months (range, 0.5-10.1). The median relative dose-intensity was 1 (range, 0.43-1). Because of toxicity, treatment was temporarily discontinued for 11 pts (40.7%) and dose-reduction was necessary in 10 cases (37.0%) A 6 mo, we have observed 1 delayed RECIST-based partial response confirmed at 9 mo. The median follow-up was 8.7 mo (1.2-31.0 mo). The 12 month-PFS rate was 67.4% (95CI 34.7-74.7%) in the whole population, and 63.6% (32.7-83.3) and 47.1% (15.2-74.1) in pts naive to and those previously treated by MTT, respectively. The 12 month-OS rate was 86.5% (55.8-96.5). Three (11.1%) and 14 (51.8%) pts experienced grade Gr 4 and Gr 3 toxicities. The Gr 4 toxicities were thyrotoxicosis (1 case), skin toxicity (1 case) and arterial hypertension (1 case). The most common Gr 3 toxicities were arterial hypertension (5), skin toxicity (5) and diarrhea (5, 18.5%). One keratoacanthoma occurred during follow-up. Conclusions: This trial showed a promising activity of SO in advanced chordoma. Further clinical explorations (e.g. randomization trial with discontinuation design) are warranted. Clinical trial information: 2009-017002-59.

Perioperative chemotherapy with cisplatin (CP) and doxorubicin (DOX) with and without high-dose methotrexate (HDM) in adult osteosarcoma (AOT): Is methotrexate warranted? First Author: Lucila Soares Da Silva Rocha, Instituto Do Cancer Do Estado De Sao Paolo, Sao Paulo, SP, Brazil

Background: Ewing's sarcoma is the second most common primary bone malignancy in children and adolescents. While front-line intensive multimodal treatment significantly improves survival in first line treatment, the prognosis for metastatic patients with either disease relapse within two years of initial therapy or initially resistant to chemotherapy is very poor with few long-term survivors and 1-year survival generally less than 20%. Methods: We implemented a Phase I trial of 12 metastatic Ewing's sarcoma patients who were either multiply recurrent (n = 11) or had failed frontline treatment within 2 years (n = 1). Patients received Vigil (previously called FANG) vaccine dosed between 1x10^4, 4x10^4, 1x10^5 or 2.5x10^5 cells/ intraderal injection/month for ≤ 4 months. Vigil is comprised of irradiated autologous tumor transfected with a dual DNA plasmid expressive of GMCSF and bi-shRNA furin components. Knockdown of furin down regulates both downstream TGFβ1 and TGFβ2 expression. Safety and clinical responses were monitored. Patient immune responsiveness to unmodified tumor cells was assessed by sequential IFNγ-ELISPOT assay using whole blood mononuclear samples starting at baseline (pretreatment) and sequentially after treatment. Results: None of the 12 patients (47 vaccinations) developed Grade 2/3/4 drug related toxicity. Median product release GMCSF expression was 1858 pg/10^6 cells; median knockdown of TGFβ1 and TGFβ2 was 100% and 99%, respectively. Eight patients have been sequentially assessed for circulating mononuclear cell IFNγELISPOT assay at baseline, 1, 3 and 6 months. Two patients presented positive ELISPOT frequencies occurring at baseline (1 case) and 6 months (1 case). One patient achieved a partial tumor response (38% tumor reduction, RECIST 1.1). The estimated Kaplan- Meier median survival of these 12 patients at Year 1 was 75%. Conclusions: In this phase I study in patients with Ewing's sarcoma, Vigil immunotherapy was well tolerated, elicited a tumor-specific systemic immune response in all patients, and was associated with favorable 1-year survival. Further clinical testing is warranted. Clinical trial information: NCT01061840.

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Prognostic relevance of miRNA let-7e in localized intestinal GIST: A Spanish Group for Research on Sarcoma (GEIS) Study. First Author: Javier Martín Broto, Hospital Universitario Virgen del Rocío, Sevilla, Spain

Background: Risk estimation of recurrence in localized GIST relies on factors as mitosis, size, site or capsule rupture. Recently, genotypy has shown to add prognostic value at least in intermediate risk group. Nevertheless, there is a remarkable lack of molecular prognostic variables in localized GIST. We had previously performed miRNA arrays in a subset of localized intestinal GIST comparing relapsed vs no-relapsed patients. We identified let-7e (FC = -1183.9; p < 0.0001) and miR-550 (FC = +204.2; p < 0.0001) as the most significantly downregulated and upregulated miRNAs respectively. Here we analyze the prognostic role of these miRNA in a validation set (VS) of intestinal GIST Methods: Selection criteria used for VS were intestinal GIST, RO surgery, no tumor rupture, no adjuvant imatinib and size larger than 2 cm. RNA extraction was performed using the RecoverAll Total RNA Extraction kit (Ambion). The expression of miRNAs was determined by means qRT-PCR using specific Taq-Man probes, let-7e and miR-550 expression levels were categorized as above or below median values. Kaplan-Meier and log-rank test were the statistics used and relapse free survival (RFS) was the clinical endpoint Results: A subset of 112 patients was selected as VS, 23 of which were excluded (metastatic, tumor rupture, etc). Thus, 89 patients were selected, 58 of whom recurred after median follow of 117 months. Median of size and mitoses were 10 cm and 10 x 50hf. In univariate analyses, let-7e showed statistical significant difference in median RFS: 19.4 vs 42.6 (p = 0.004) (24.6-39.7) months for below and above median values respectively (p = 0.011). For miR-550 no significant differences were seen vs 29 months (p = 0.99). Mitosis ≤ 5/5 > 5 with 162 vs 26 months (p = 0.002) and size ≤ 10 cm > 10 with 37 vs 29 months (p = 0.05) showed also prognostic relevance. In multivariate analysis, mitosis HR 2.7 (1.4-5.3; p = 0.004) and let-7e HR 2.1 (1.2-3.8, p = 0.009) were independent prognostic factors for RFS Conclusions: miRNA let-7e has demonstrated to be a relevant prognostic factor for RFS in intestinal GIST patients and deserves to be explored for targeting purposes. A further analysis is planned in a larger series of GIST including also gastric cases.

High dose ifosfamide in metastatic high-grade osteosarcoma, after failure of standard multimodal chemotherapy. First Author: Emanuela Palmerini, Istituto Ortopedico Rizzoli, Bologna, Italy

Background: Extra Skeletal Osteosarcoma (ESO) account 1% among soft tissue sarcomas. There is no agreement on the best strategy of treatment. Methods: An ESOS collaborative study was performed and data of patients treated for an ESO the last 5 years were collected. ESOS criteria were: 174 cases evaluable. Median age was 53 years(13-84). There were 95 males, 52 females. 114 had localized disease and 32 were metastatic, 11 unknown. Median tumor size was 10 cm, median interval from symptoms onset to diagnosis was 4 months. Primary tumor site was lower limb in 73 patients, upper limb in 33 patients.12 were in viscera. 109/114 with localized disease had surgical resection of primary tumor, 80 had R0 resection, 23 R1, 6 unknown. Among 114 patients, 12 were in viscera. 109/114 with localized disease had surgical resection of primary tumor, 80 had R0 resection, 23 R1, 6 unknown. Among 114 patients, 12 were in viscera. 109/114 with localized disease had surgical resection of primary tumor, 80 had R0 resection, 23 R1, 6 unknown. Among 114 patients, 12 were in viscera. 109/114 with localized disease had surgical resection of primary tumor, 80 had R0 resection, 23 R1, 6 unknown. Among 114 patients with localized disease, local relapse occurred in 29/114 (25%), distant metastases in 41/114 (36%). In patients with localized disease the probability of 5yr OS according to tumor and treatment variables is reported in the table below. The MetaeICESS 2007 protocol constitutes a feasible option for patients with advanced pediatric ES and RMS. A larger cohort is mandatory to verify OS or RFS improvement over current protocols.

Stem cell rescue from irradiation of multiple tumor sites combined with high-dose chemotherapy, followed by reduced intensity conditioning and autologous stem cell transplantation in patients with advanced pediatric sarcomas: Preliminary results of the MetaEICESS 2007 protocol. First Author: Stefan Burdach, Technische Universität München, Munich, Germany

Background: Advanced pediatric sarcomas are associated with poor prognosis. These truly rare diseases include Ewing’s sarcomas (ES), metastatic to more than one bone or early relapse as well as stage IV rhabdomyosarcomas (RMS). We assessed toxicity, relapse free survival (RFS) and overall survival (OS) of advanced ES and RMS patients treated a single institution with the MetaEICESS 2007 protocol. Methods: From 2007 to 2015, 9 patients, 7 with ES (≥ three bones/organs or marrow involved at diagnosis, n = 4, or relapse in 3-24 months after diagnosis, n = 2) and 2 with stage IV RMS patients were enrolled. The protocol comprised induction-chemotherapy, whole-body MICE/PET directed radiotherapy to the primary tumor and to all metastases, surgery, tandem high-dose chemotherapy with autologous rescue and allogeneic stem cell transplantation (allo-SCT). Data was censored on February 1st 2015. Radiotherapy was delivered to the primary tumor (n = 8, total dose 50-60 Gy), to the lungs (n = 4, 15-18 Gy), and to lymph node and osseous metastases (n = 3 and n = 7, 45-50 Gy). Target volumes ranged from 453 – 9.407 cm3 (median of 2.762 cm3). One patient received proton, all others photon irradiation. Results: 5 patients are surviving in CR at a median of 27 months (range 0-62) after allo-SCT. Median RFS after allo-SCT was 17 months (range 0-62), 8 patients had reached complete remission (CR) before allo-SCT, three of whom relapsed thereafter, predominantly outside the radiotherapy treatment fields. 4 patients received donor lymphocyte infusions (DLI), of whom two patients showed clinical responses. One patient had to be retransplanted after initial graft rejection, 3 patients suffered ADV reactivation, 3 patients developed acute- and 1 patient chronic GVHD. Conclusions: The MetaEICESS 2007 protocol constitutes a feasible option for patients with advanced pediatric ES and RMS. A larger cohort is mandatory to verify OS or RFS improvement over current protocols.
Sustained response of complex giant cell tumors with denosumab: Single center 8-year experience. 
First Author: Neal Shiv Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: GCTB are aggressive osteolytic tumors, which are characterized by local bone destruction and soft tissue invasion. There have been limited non-surgical treatments, including radiation therapy. However, an unacceptable rate of post radiation sarcomas has been well established. Such tumors have osteoclast like giant cells/stromal cells that express surface RANK ligand. Denosumab is an FDA approved drug used in the treatment of unosteclastable GCTB or GCTB with severe morbidity related surgery. It is a monoclonal antibody that targets the RANK ligand characteristic to GCTB. We report our 8-year experience in the treatment of complex GCTB using denosumab.

Methods: Review of 43 skeletally mature patients (N = 43) who were treated with subcutaneous (SC) denosumab for the treatment of GCTB. The scheme consisted of G 800 mg/m2 i.v. d1 and 8 cycles in OS. Additionally, our group had conducted a phase I trial with data showed activity of rapamycin in xenograft murine models of OS and in complex GCTB using denosumab.

Conclusions: This study represents the longest reported single center use of denosumab in the treatment of GCTB. Overall, it shows the safety and efficacy in the use of denosumab in the treatment of GCTB.
Background: Advanced GIST is treated with the tyrosine kinase inhibitors imatinib, sunitinib and regorafenib, but the majority of patients develop heterogeneous resistance to these agents. In an attempt to overcome such resistance, we tested the efficacy of dovitinib which acts against VEGF, FGFR, FLT3, PDGFRβ and KIT, using patient-derived (PD) xenograft models. Methods: NMR nu/nu mice (n = 47) were transplanted bilaterally with the human GIST xenografts UZLX-GIST2 (KIT p.A502_Y503dup), -GIST9 (KIT p.P575del+, p.W557LX5+-p.D280G) and were treated in 4 cohorts: control (untreated), imatinib (50 mg/kg/bid p.o.), imatinib (100 mg/kg/bid p.o.) and dovitinib (30 mg/kg/p.o.). Efficacy was assessed by tumor volume measurement (3x/week), histopathology, immunohistochemistry (Ki67, phospho-Histone H3 (pH3), cleaved PARP) and Western blotting analysis of KIT signaling. Histologic response (HR) was graded according to Antonescu et al. Clin Cancer Res 2005; 11:4182-90. Microvascular density (MVD) was assessed by counting CD31 positive vessels. Mann Whitney U test was used for statistical analysis. Results: After three weeks of treatment, dovitinib caused tumor volume reduction (to 37% of baseline) in UZLX-GIST2 and disease stabilization in -GIST9. It induced grade 2-3 HR in > 50% of tumors in both models. Compared to control, dovitinib reduced mitotic activity by 22.6-fold (p < 0.0001) in UZLX-GIST2, whereas no significant difference was observed in the other model. Results were confirmed by pH3 and Ki67 stainings. Apoptotic activity was decreased in dovitinib treated UZLX-GIST2 tumors compared to control. MVD was reduced in both UZLX-GIST2 (1.6 fold; p < 0.05) and -GIST9 (1.3 fold; p < 0.01) tumors. Downregulation of KIT, AKT and 4EBP-1 phosphorylation was observed in UZLX-GIST2. Conclusions: Dovitinib showed anti-tumor efficacy in GIST xenograft models, with more pronounced effects in -KIT exon 11 (82%). Five pts related.
Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in gastrointestinal tract. Approximately 85-90% of GISTs are harboring oncogenic mutations in KIT or PDGFRA, and the tyrosine kinase inhibitor (TKI) drastically improved the prognosis of GIST patients. On the other hand, a subset of GISTs acquire secondary resistance to TKI and show primary resistance to TKIs. Recent studies report that the disorder of the protein phosphatase 2, regulatory subunit A, alpha (PPP2R1A) is responsible for the constitutive phosphorylation of its substrates including TKs, and the constitutive phosphorylation of TKs plays an important role in the tumorgenesis and the progression of ovarian and uterine carcinomas. The aim of this study was to elucidate the frequency of PPP2R1A mutations and their impact on the clinicopathological factors in GISTs. Methods: Ninety-six cases of GISTs (formalin-fixed paraffin-embedded material) with prognostic information were collected. These cases were examined for PPP2R1A mutations (exon 5 and 6) by PCR followed by direct sequences, and the impacts of PPP2R1A mutations on the clinicopathological features were examined. In addition, PPP2R1A mutated GISTs were also examined for the mutation status of KIT, PDGFRA and KRAS. Results: Seventeen cases (17.7%) of GISTs harbored mutations in PPP2R1A, and types of mutations were various. Among 17 cases, 15 cases (88.2%) harbored either KIT or PDGFRA mutations, and one case had point mutations in both KIT and PDGFRA. Among two cases of KIT/PDGFRA mutation-negative GISTs, one case showed KRAS mutation. GIST cases with PPP2R1A mutations had a tendency for shorter disease free survival (DFS) and overall survival (OS) rate, respectively (p < 0.05; DFS: p < 0.05; OS). Conclusions: These results suggest that PPP2R1A mutations play an important role in the tumor progression of GISTS. The effect of PPP2R1A alterations on the phosphorylation status of TKs including KIT and PDGFRA are under evaluation.

Background: Imatinib (IM) revolutionized the outcome of patients with advanced GISTs; however, disease progression eventually occurs due to IM resistance or intolerance. Sunitinib (SU) is an oral multi-targeted tyrosine kinase inhibitor approved for advanced second line treatment of advanced GIST after IM failure. Clinical trials have shown that clinical activity of SU after IM failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases. However, since mutational status is not mandatory in the workup of GIST patients, it is difficult to predict response to second line SU. The aim of this study was to explore whether results of SU therapy after IM failure, might be related to the duration of IM treatment. Methods: All patients with advanced GIST that are insured by Clalit Health Services, Israel's largest health-care organization were identified. Only patients, who progressed on second-line SU, after receiving IM as first-line therapy, were included. Last date of patient recruitment was Dec 31, 2014. A linear regression model was used to identify the relation between first-line IM duration of response (the independent variable) and duration of response of second line SU. Results: We identified 31 consecutive patients with advanced GIST treated with IM and SU, consequently. There were 18 male and 13 female patients, with median age at the start of SU therapy 63.5 years (range: 34-85). Only 7% of patients (n = 3) received adjuvant IM therapy after resection of their primary tumor and metastases. Duration of response of second-line SU was 25.8 months (2.3-67.4) for IM and 5.2 months (0.8-32.7) for SU. The linear model predicted duration of second-line SU therapy (Y) in relation to duration of IM first-line therapy (X) best with: Y = 2.36 + 0.282X, (R² = 20.6%, p < 0.01). Conclusions: In our study, results of SU therapy in advanced GIST patients were found to positively relate with the duration of first line IM treatment. This relation may serve as a handy estimate for SU duration in the clinic. However, further studies in wider cohorts of patients are needed to confirm this observation.

Background: Adjuvant IM treatment improves survival in pts with primary GIST with significant risk of recurrence. However, optimal treatment duration has not been determined. The ongoing PERSIST-5 trial is evaluating 5 years of adjuvant IM treatment. Methods: Beginning in 2009, this single-arm trial has included pts at significant risk of recurrence, defined as either primary tumor > 2 cm at any site and ≥ 5 mitoses/50 high-power fields or nongastric primary GIST ≥ 5 cm. After complete resection of primary KIT + GIST, pts received IM 400 mg/day for 5 yr or until progression, relapse, or intolerance. The primary endpoint was recurrence-free survival (RFS). We report data from a planned 3-year interim analysis. Results: Of 91 eligible pts (median age 60 yr; range, 30-90y), median tumor size was 6.5 cm (range, 2.3-30.0 cm), 55% had gastric GIST, and 99% underwent R0 resection. In 85 evaluable pts, the most common GIST genotypes were KIT exon 11 (68%) and PDGFRA exon 18 (9%). Median time from resection to first IM dose was 9.6 wk (range, 3.1-12.3 wk). As of the data cutoff (May 9, 2014), median treatment duration was 34.2 mo (range, 0.5-55.8 mo). Overall, 4 pts (4%) recurred. There was 1 death; this pt had an IM-resistant PDGFRA D842V mutation. No pts without this resistant mutation who stayed on IM recurred. All 3 surviving pts who recurred discontinued (D/C) IM prior to recurrence (range, 7.3-23.1 mo between D/C and recurrence). The most common reasons for D/C (n = 33) were adverse events (AEs; n = 13) or consent withdrawal (n = 13). Grade 3/4 AEs leading to D/C were elevated liver enzymes, alopecia, and renal cell carcinoma (n = 1 each). The most common AEs were nausea (67%), diarrhea (53%), and fatigue (44%). Dose reduction, occurring in 31 pts (34%) was most frequently due to D/C (n = 18). Finally, IDO/kynurenine pathway enzymes and their impact on the clinicopathological features were examined. In addition, PPP2R1A mutated GISTs were also examined for the mutation status of KIT, PDGFRA and KRAS. Results: Seventeen cases (17.7%) of GISTs harbored mutations in PPP2R1A, and types of mutations were various. Among 17 cases, 15 cases (88.2%) harbored either KIT or PDGFRA mutations, and one case had point mutations in both KIT and PDGFRA. Among two cases of KIT/PDGFRA mutation-negative GISTs, one case showed KRAS mutation. GIST cases with PPP2R1A mutations had a tendency for shorter disease free survival (DFS) and overall survival (OS) rate, respectively (p < 0.05; DFS: p < 0.05; OS). Conclusions: These results suggest that PPP2R1A mutations play an important role in the tumor progression of GISTS. The effect of PPP2R1A alterations on the phosphorylation status of TKs including KIT and PDGFRA are under evaluation.

Background: GISTs are predominantly defined by KIT/PDGFRα mutations which are targetable with a range of kinase inhibitors, however the majority become TKI-resistant (TKI-R). Double (KIT/PDGFRα) wildtype (D-WT) GISTs represent a rare subset of GIST patients in need of treatment options. We investigated a commercial database of theranostic biomarkers for the identification of novel therapy options for GIST. Methods: 217 GIST cases were evaluated for D-WT and TKI-R. A multiplatform approach of biomarker testing was used and included a combination of sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH). Results: D-WT (n = 15) and TKI-R (n = 23) (including 7 with resistance mutations in the absence of a primary, activating KIT mutation and 4 PDGFRA D842V) were studied for additional targetable alterations: IHC and ISH tests revealed no overexpression or amplification in CMET, EGFR, or HER2. PTEN was intact (positive expression) in the majority of GISTS (92.9% (13/14) D-WT; 100% (19/19) TKI-R). Mutational screening revealed variants in 6/47 genes (excluding cKIT and PDGFRA), most of which are potentially targetable with therapies currently available, or in clinical trials: PIK3CA, ABL, cMET, JAK3, RB1, and VHL. ABL and JAK3 mutations were exclusively found in the TKI-R subgroup. PD-1 positive tumor infiltrating lymphocytes were found in 33% (1/3 D-WT) and 60% (3/5 TKI-R), while PD-L1 tumor expression was found in 67% (2/3 D-WT) and 73% (3/5 TKI-R). Although chemotherapy has historically elicited poor responses in GIST (non-selected patient trials), we observed a high frequency of low expression of predictive markers for gemcitabine (RRM1) and paclitaxel (TUBB3) (77%, 90%; 57%, 73% for D-WT and TKI-R, respectively) which were recently shown to be cytotoxic in TKI-R GIST cell lines (Boichuk, 2014). Conclusions: A multiplatform approach of theranostic biomarkers identified non-cKIT/PDGFRα therapy options for rare and resistant GIST. Opportunities for investigating new targetable agents and potentially re-visiting cytotoxics with biomarker guidance in these subpopulations are warranted.
Patients with rhabdomyosarcoma, even with metastasis, should be seriously underestimated. A retrospective study was conducted to identify the prognostic value of aggressive local treatment in paediatric metastatic rhabdomyosarcoma. Methods: Patients with metastatic rhabdomyosarcoma age 1 to 21 treated in France from 1998 to 2011 according to European protocols MMX-4, 89, 4-91, 98 and recent national guidelines were selected. Survival comparison were performed between patients with “aggressive local treatment” (surgery and radiotherapy) and exclusive surgery or radiotherapy, after exclusion of patients with early progression. Endpoints were event-free and overall survival (OS). Results: A total of 101 children, median age 9 years, with majority of primaries in unfavourable sites (73 patients, pts), T2 tumours (66 pts), alveolar subtypes (65 pts) and large tumours (> 5cm, 83 pts) received various chemotherapy regimens. On univariate and multivariate analysis, OS was better after “aggressive local treatment” (49 pts; 44.3 ± 8%), than after exclusive surgery (10 pts; 18.8% ± 15.5%) or exclusive radiotherapy (29 pts; 16.1 ± 7.2%, P < 0.006). Moreover, OS was better in the case of surgery with complete resection (41.1 ± 10.2%) or microscopic residue (56.4 ± 14.9%) than macroscopic residue (20.0 ± 12.6%; P < 0.03). Conclusions: In this large retrospective analysis, OS appeared to be better for patients receiving “aggressive local treatment” even after adjustment for the initial patient and tumour characteristics. Isolated debulking surgery is associated with a very poor outcome and should be avoided. Aggressive local treatment in patients with rhabdomyosarcoma, even with metastasis, should be seriously considered.

Activity of crizotinib (C) in patients (pts) with clear cell sarcoma (CCSA) in EORTC phase II trial 90101 “CREATE”. First Author: Patrick Schoffski, University Hospitals Leuven, Leuven, Belgium

Background: This phase II trial assesses the safety and activity of the ALK/MET inhibitor C in 6 different ALK- or MET-driven tumor types including CCSA, an orphan, treatment-refractory malignancy. The chimeric EWS-ATF1 and EWSR1-CREBI fusion genes are hallmarks of CCSA and activate MET through the melanocoyte master transcription factor. Methods: Pts with local diagnosis of advanced/metastatic CCSA consented for shipment of a non-returnable tumor tissue block and were screened for trial participation after central confirmation of the diagnosis and Vysis EWSR1 break apart FISH (Abbot Molecular). Eligible pts received C 250 mg twice daily p.o. A Simon’s optimal two stage design was implemented independently in each disease-specific study cohort. If at least 2 of the first 12 MET+ pts were eligible and evaluable CCSA pts achieved a confirmed RECIST 1.1 PR or CR, a maximum of 35 pts were to be enrolled and treated to assess the activity of C, with no interruption of recruitment planned between the two stages. The abstract presents CCSA enrollment characteristics and activity according to the Simon’s design stopping rule. Updated activity/safety results of the fully recruited cohort will be available at ASCO. Results: Between 01/2013 and 12/2014, 16 investigational sites in 8 European countries recruited 43 pts, of whom 32 had a centrally confirmed diagnosis of MET+ CCSA (tissue blocks available from 97.7% of pts). Central histological and molecular work-up took a mean lab turnaround time of 4 days (range, 2-14) after receipt of unstained slides. Among the first 12 MET+ eligible and evaluable MET+ cases, no RECIST responses were observed; best response was SD in 7 and PD in 5 pts. The mean duration of treatment was 6-7 cycles (range, 2-14; cycle length 3 weeks). Conclusions: EORTC is able to perform molecularly driven screening phase II trials in orphan malignancies with mandatory collection of tumor tissue and real time confirmation of diagnosis and genetic profiling. C did not meet pre-specified response rates in MET+ CCSA, but achieved long-lasting disease control in a clinically relevant subset of pts, which prompted ongoing correlative studies using available tissue, genetic and clinical data. Clinical trial information: NCT01524926.

Background: Doxorubicin (DOX) as a single agent has been a standard treatment option for high-risk STS of extremity and trunk wall. The potential for avoiding RT has been explored in limited groups of patients (pts), e.g., small STS. We retrospectively explored the role of RT in high-risk STS treated at a treatment center over a more recent time span. Methods: Consecutive pts affected by primary, localized, extremity and trunk wall STS surgically treated between 2000 and 2012 were reviewed. All tumors were > 5 cm, deep, and G2-G3 according to FNCLCC grade. Ewing/pPNET and pediatric STS were excluded. Two groups were identified: Group A, pts who received adjuvant/neoadjuvant RT; Group B, pts who did not. Local recurrence-free survival (LRSF) was analyzed. Results: Study population included 404 pts. Median follow up was 53 months for alive pts (IQR, 30-85). Median size was 10 cm. In Group A, 319 pts received RT (106 preoperative, 211 postoperative, 2 pre- and post). In Group B, 85 pts did not receive RT for individualized reasons. No significant differences were found between groups according to tumor size, age, sex, histotypes. Margins in Group A were R0/R1 in 252 (78.9%), and 67 (21%) cases, respectively; in Group B, 63 (74.1%) and 22 (25.9%), respectively (P value = .380). Group A and Group B were different for: G3 tumors (80.6% and 68.2%, respectively; P value = .0184); trunk tumors (77.3% and 63.3%, respectively; P value = .0013); postoperative neoadjuvant therapy (57.7% and 38.8%, respectively; P value = .002). Five-years LRSF was 83.9% in Group A, and 81.1% in Group B (P value = .1302). No differences in LRSF were found neither between R0 pts treated in Group A and B (P = .1417), nor between R1 pts treated in Group A and B (P = .6971). Conclusions: Local outcome of high-risk STS in pts individually treated without radiation therapy was not significantly different compared to those treated by surgery plus RT. Further studies are needed to investigate which subgroups of high-risk STS may benefit from surgery alone, possibly distinguishing between extremity and trunk sites, as well as between G2 and G3 tumors.
Association of hematological toxicity (tox) and outcome to doxorubicin (DOX) in advanced soft tissue sarcoma (STS). A retrospective analysis of the EORTC-Soft Tissue and Bone Sarcoma Group database. First Author: Stefan Sleijfer, Erasmus MC, Rotterdam, Netherlands

Background: DOX pharmacokinetics vary substantially between patients leading to large differences in systemic drug levels. Given potential dose-effect relations, patients with the greatest tox may also have the best outcome. We assessed whether severity of hematological tox during treatment is associated with outcome in advanced STS patients treated with first-line DOX (monotherapy; 75 mg/m2 q 3 weeks). Methods: Worst tox (anemia, leukopenia, neutropenia and thrombocytopenia) scored during treatment according to CTCAE v4.0 was included in this analysis. Differences in overall survival (OS), progression free survival (PFS) and response rate (RR) between patients with or without high haematological tox (grade 0-2 vs 3-4) were assessed using conventional statistical tests in landmarked subsets, to avoid bias from patients stopping treatment early. Potential confounders were collected including relative dose intensity (RDI), patients’ and tumor characteristics. Results: In 557 patients eligible for this analysis, 32% were between 50-60 years, 51% female, 72% had a grade II/I tumor. Leimyosarcoma (28%) and liposarcoma (15%) were the most common subtypes. 47.2% of the patients received at least 6 cycles of treatment; 45% stopped treatment early due to progression, 3% because of tox. RDI was constant over the cycles. During treatment, grades 3/4 anemia, leukopenia, neutropenia and thrombocytopenia were observed in 6.1%, 35.9%, 51.9%, and 1.6%, respectively. After cycle 1, grade 3 tox occurrence was constant over the diverse cycles, grade 4 tended to decrease after cycle 1 (21.0% at cycle 2, 12% at cycle 3). OS and PFS did not differ between patients experiencing high versus low tox at the end of cycles 1, 2 and 3. Also for RR, no association was seen with severity of haematological tox. Conclusions: In this large series, there was no association between outcome and haematological tox during DOX. This information may be useful to reassure advanced STS patients that failure to experience haematological tox during treatment does not equate to undertreatment.

Long term cardiac safety of aldoxorubicin. First Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: Aldoxorubicin (6-maleimidocaproyl acid hydrazide) is a novel prodrug of doxorubicin that binds to the thiol group of cysteine-34 amino acid in circulating albumin. The circulating albumin-drug conjugate preferentially accumulates within tumors, bypassing uptake by most normal tissues, including the heart, liver, kidneys and GI tract. Doxorubicin is released in the acidic tumor environment, either intra- or extra-cellularly, thus avoiding the cumulative toxicity that can occur with doxorubicin treatment. Conclusions: In this large series, there was no association between outcome and haematological tox during DOX. This information may be useful to reassure advanced STS patients that failure to experience haematological tox during treatment does not equate to undertreatment.

Surrogate properties of survival endpoints in metastatic soft-tissue sarcoma: A meta-analysis. First Author: Marion Savina, INSERM U897 (Cancer Axis), ISPED, Bordeaux, France

Background: Alternative endpoints to overall survival (OS) such as progression-free survival (PFS), time-to-progression (TTP) or time-to-treatment failure (TTF) are increasingly used to assess treatment efficacy in randomized controlled trials (RCT) to reduce inclusions and trials’ duration. Their properties in terms of surrogate markers need to be assessed to ensure that they can adequately replace OS. Methods: We conducted a literature review to identify, rate by cancer type and study characteristics, and rate surrogate endpoints for OS. In the absence of data on the convergence of OS and survival endpoints, we leveraged data on survival endpoints from randomized controlled trials (RCTs) of advanced STS. We relied on a meta-analytical framework to estimate individual-level association (association between the candidate surrogate endpoint and OS) and trial-level associations (association between the treatment effects on the candidate surrogate and on OS). Statistical methods included weighted linear regression (WLR) and the two-stage method introduced by Burzykowski et al., which relies on the joint modeling of 2 survival endpoints with a copula function and a regression model. Results: Individual data of 2020 patients from 10 European RCTs were analyzed. We censored OS at 2 years and PFS, TTP and TTF at 1 year. Regardless of the method, the highest individual-level association was observed for PFS (R² = 0.62 IC95% [0.27; 0.76]; Kendall’s tau = 0.43 IC95% [0.40; 0.46]). Even if WLR suggested that PFS had the highest trial-level association, it was not significant for all RCTs. For both methods, R² = 0.01 were observed (P-value of the regression model: R² = 0.01 IC95% [0.46; 0.48]). Conclusions: Out of the 3 endpoints, PFS had the best surrogate properties. Associations with OS were however moderate and cannot validate PFS as a surrogate for OS. This could be partly explained by a lack of precision due to our small sample size in terms of patients and trials. STS are rare tumors (< 2% of all cancers) which explains the low number of available trials with usually smaller sample sizes compared to other cancers. We are however collecting additional trials to improve these estimations and complementary analyses are ongoing to validate our regression models on external data.
Background: Preoperative and postoperative radiotherapy (RT) for extremity soft tissue sarcoma (STS) have similar recurrence and overall survival outcomes. However, side effect profiles, costs and long-term functional outcomes are different. The aim of the study was to determine the optimal sequencing of RT in these patients through decision analysis. Methods: A cost-effectiveness analysis was conducted using a Markov model, with quality adjusted life years (QALYs) as the primary outcome. Utility values, rates of acute and chronic complications, transition probabilities and cost data were extracted from the published literature. Overall and progression free outcomes were internally validated. One-way and two-way sensitivity analyses were performed to determine the thresholds at which each strategy would be preferred. Probabilistic sensitivity analysis was performed for complication rates and costs to assess the robustness of this model. The time horizon was 5 years with a cycle length of 3 months. QALYs and costs were discounted at a rate of 3%. Results: Preoperative RT is a more cost effective strategy ($9,760/QALY) when compared to postoperative RT ($11,752/QALY). Preoperative RT is the preferred strategy for all acute wound complication rates tested on one-way sensitivity analysis. Postoperative RT is the preferred strategy when chronic complications with this modality is less than 17%, or when the rate seen in preoperative RT is greater than 61%. On probabilistic sensitivity analysis, preoperative RT is the preferred strategy in 75% of cases at a willingness to pay threshold of $50,000. Conclusions: Our model suggests that preoperative RT is more cost-effective than postoperative RT in the management of resectable extremity STS, primarily due to the lower incidence of chronic wound complications.

Targeted next generation sequencing in well-differentiated/dedifferentiated liposarcoma (WD/DD LPS): Multiple gene amplifications but few mutations. First Author: Neela Somaiah, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: WD/DD LPS is a common soft tissue sarcoma with approximately 1500 new cases per year. Surgery is the mainstay of treatment but recurrences are frequent and limited systemic options make treatment challenging. ‘Tumor genotyping’ is becoming more common in clinical practice as it offers the hope of personalized targeted therapy. We wanted to evaluate the results and the clinical utility of available tumor genotyping panels in WD/DD LPS. Methods: TMDAC patients (pt) who had their tumor analyzed by either Foundation One (FM) (244 gene panel for solid tumors, tumor only) or the institutional T200 panel (202 gene panel, tumor and normal) were included. There were 124 overlapping genes in these panels. FFPE sections were sequenced on the T200 panel using the Illumina HiSeq2000 platform. On average, the cutoff for calling variants on the T200 is 1%-5% for high coverage data (> 500x) and 10-15% for lower coverage (< 200x). Results: Total of 20 pt samples were identified, 7 on T200 (1 WD + 6 DD) and 13 on FM (5 WD + 8 DD). Significant copy number alterations (CNA) were identified in all samples. Only recurrent, potentially clinically actionable CNA (out of the 166 identified) are tabulated below. The 7 pt samples on T200, 27 mutations were detected. 8 genes (CTNNB1, MECOM, ZNF536, EMT4, CSMD3, PBRM1, PPP1R3A) were identified as deleterious (on Condel, PolyPhen and SIFT) and a truncating mutation was found in NF2. Of these only the EMT4 and NF2 are known driver mutations and potentially actionable. These mutations have not been reported previously in DD LPS. On the FM panel, ZNF536, CSMD3 and PPP1R3A were not evaluated (NE) and no mutations were reported. Conclusions: In this series, 20/20 (100%) of the WD/DD LPS had MDM2 and CDK4 amplified. Additional recurrent novel deleterious genetic changes were identified, but further studies are needed to determine their therapeutic and pathogenic significance.

Epidemiology, treatment (tx) patterns and outcomes in Asian soft tissue sarcoma (STS) patients: Results from the Soft Tissue Sarcoma in the Asia Pacific Region (STAR) study. First Author: Richard Hong Hui Quek, National Cancer Centre, Division of Medical Oncology, Singapore, Singapore

Background: There is a paucity of STS epidemiology and tx pattern information in the Asia Pacific region, with published data only from small or single country studies. STAR, a large multicountry observational study, was initiated to describe epidemiology, tx patterns and clinical outcomes in STS patients (pts) diagnosed in 2006–2010 at tertiary referral centers in Hong Kong, Indonesia, the Philippines, Singapore and Thailand. Methods: Data were collected by retrospective chart review. Kaposi’s sarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, bone sarcoma and extraskeletal osteosarcoma were excluded. Demographics, tumor characteristics and tx patterns were analyzed descriptively. Overall survival (OS) and progression free survival (PFS) were estimated by the Kaplan Meier method. Results: STAR included 635 adult pts, 25% of whom presented with metastatic STS. Main histological subtypes: leiomyosarcoma (19%), liposarcoma (19%), undifferentiated pleomorphic sarcoma (UPS; 18%), synovial sarcoma (9%) and angiosarcoma (7%). Of 230 pts who had chemotherapy (CTx), 32% had neoadjuvant or adjuvant CTx only and 68% had palliative CTx. In the palliative setting, most pts had 1 (57%) or 2 (27%) lines of systemic tx. Combination CTx was more common than monotherapy (54% vs 47% of regimens). The most common first line (1L) regimens were doxorubicin (29%) and dacarbazine (19%). The most common 2L regimens were gemcitabine/docetaxel (29%), gemcitabine (9%) and trabectedin (9%). Median PFS (95% CI) for 1L, 2L and 3L palliative CTx were 3.8 (2.2–5.5) months, 4.0 (2.1–5.8) months and 1.9 (1.3–2.6) months, respectively. Median OS of pts who presented with metastatic STS was 11.7 (9.9–14.5) months. Conclusions: In the first large observational study to capture STS epidemiology, tx patterns and outcomes across Asia. UPS prevalence was similar to published data, suggesting acceptable pathologic quality, while angiosarcoma prevalence appeared slightly higher than in Western studies. During this period, most CTx regimens were combinations and palliative CTx beyond 2L was uncommon. Funding: GlaxoSmithKline.

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10552 Poster Session (Board #198), Sun, 8:00 AM-11:30 AM
Multimodal treatment of pulmonary artery sarcoma: A single center experience. First Author: Simona Secondino, Medical Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Background: Pulmonary artery sarcoma (PAS) is a rare disease arising from the endothelial cells of the pulmonary artery wall, generally presenting with pulmonary hypertension (PH). The therapeutic approach, mainly based on surgery, either pneumonectomy or pulmonary endarterectomy (PEA), depends on the extent of the disease and the patient’s clinical condition. The prognosis is extremely poor as survival rarely exceeds 1 year from diagnosis. Methods: From October 2010 to December 2014, 8 patients (pts) referred to our Institution for symptoms of acute or chronic pulmonary thromboembolic disease were diagnosed to have PAS. Five pts had PI, one with severe hemodynamic instability requiring emergency surgical treatment. Median age was 64 years (range 32-77), 5 pts were female. In 6 pts the disease was bilateral, and 3 had lung metastases. Results: All pts underwent PEA, none having life threatening complications from surgery. Pathology showed 4 high grade and 4 intermediate grade sarcomas. Following PEA and a short course of cardiopulmonary rehabilitation, 7 pts were able to receive conventional chemotherapy (CT) with doxorubicin and ifosfamide, starting a median of 42 days (range 22-69) from surgery. Two pts also received radiotherapy after completion of the CT program. Four pts have died for disease progression at 6, 6, 8, and 26 months from surgery while 4 are alive, three being disease free at 8, 15, and 40 months. Conclusions: In pts with PAS a multimodal approach including PEA, CT and radiotherapy is feasible. Other than improving quality of life, it appears to considerably extend life expectancy.

10553 Poster Session (Board #197), Sun, 8:00 AM-11:30 AM
Metastatic dermatofibrosarcoma protubersan (DFSP) and fibrosarcomatous DFSP (FS-DFSP): Sensitivity to imatinib (IM) and gene expression profile. First Author: Silvia Stacchiotti, Istituto Nazionale dei Tumori, Milan, Italy
Background: We report on IM activity in patients (pts) with metastatic DFSP/FS-DFSP and on the gene expression profile (GEP) analysis of pure DFSP versus FS-DFSP, aimed at identifying prognostic markers Methods: All pts treated with IM at our institution from 2007 to 2014 for metastatic DFSP/FS-DFSP were selected. To estimate the PFS, pts progressing after IM discontinuation who responded after restarting IM were considered PD at the time of definitive PD on IM. Path and cytogenetics of the primary lesion and metastases were compared. We performed RNA Sequencing of 5 DFSP and 5 FS-DFSP (3 metastatic) on HiScanSQ platform. In 2 pts the analysis was done on samples taken before and after IM. GEP analysis was done with Python function htsq-count, differential expression with Bioconductor package edgeR, hierarchical clustering and Principal Component Analysis (PCA) with Multiple Array Viewer. SNV, Ins/del, fusion transcript analyses are ongoing Results: 10 pts were identified, all evaluable for response. All showed a FS component in the metastatic tumor, 7/10 in the primary lesion. COLLA1-PDGFb was detected in all cases. Best RECIST response was: 8 PR, 1 SD, 1 PD. 5 pts received complete surgery after IM (4 while under response, 1 after PD) with evidence of path response in 4 (with aspects depending on surgical timing, affecting tumor cells and pericytes). All pts relapsed. IM was restored in 4 pts with a new response. Median FFS was 11 mos (range 2-14+). By PCA all DFSP displayed a unique GEP, clearly different from FS-DFSP. At the supervised analysis, FS-DFSP were marked by over-expression of potential biomarkers such as MCAM and TGM2 (involved in metastatic process and chemoresistance). Many genes were upregulated in pure DFSP, reflecting the enrichment in neural markers and cell adhesion molecules Conclusions: All metastatic cases were FS-DFSP. Most pts responded to IM but PFS was shorter than reported in series including all DFSP. All pts who were operated after IM relapsed, suggesting that IM cannot eradicate metastatic DFSP/FS-DFSP and the role of surgery is limited. Restart IM after surgery, as done in GIST, is to be evaluated. DFSP and FS-DFSP presented a clearly different GEP.

10554 Poster Session (Board #198), Sun, 8:00 AM-11:30 AM
Natural history and outcome in a large series of primary dermatofibrosarcoma protubersan (DFSP) treated at a reference institution. First Author: Andrea Pierluigi Fontana, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Background: DFSP is a rare sarcoma, characterized by an indolent course, although local recurrences (LR) and occasional distant metastases (DM) are described. We sought to investigate its natural history and prognostic factors in a large series of patients (pts). Methods: All consecutive pts affected by primary DFSP, located at any sites, treated at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, from January 1993 to December 2012, were retrospectively reviewed. Overall Survival (OS), surgical margins status, LR and DM were analyzed. Results: 270 pts were identified, 246 (91.1%) affected by classic (C)-DFSP and 24 (8.9%) by fibrosarcomatous (FS)-DFSP. All pts are alive at a median follow-up (FU) of 6 yrs (range 1-15), save for two of them, dead for other diseases. All pts underwent macroscopic complete surgery. Microscopic margins were negative in 247 cases (91.5%), positive (PM) in 23 (8.5%). Overall, LR occurred in 4 pts (1.5%), 2/21 C-DFSP with PM, 2/2 FS-DFSP with PM, respectively. 3 of the LR were located to the scalp, 1 in the groin. A wider resection was repeated on 3 pts, who are disease-free (DF) after 2, 4 and 8 yrs, respectively. One pt refused surgery, her disease is under control with imatinib (IM) after 3 yrs. DM occurred in 3 pts (1.1% of the whole series; 12.5% of FS-DFSP), all affected by FS-DFSP (2 lung and 1 pancreatic metastases). 2 pts were treated with a lung wedge resection. One pt was resected for 78 mos, the other resected again after 14 mos and was further treated with a combination of IM and a second surgery. He is still on IM and DF after 6 mos. The last metastatic pts is on IM and progression-free after 4 mos. Conclusions: Negative margin resection is always curative for C-DFSP, as the observed metastatic risk is nil. PM may be accepted, when cosmesis is an issue, because LR risk remains low and salvaged by a subsequent wider resection. FS-DFSP has a more aggressive course, LR being highly predictable by PM and DM occurring in as many as 12.5% of pts. This should be used to inform treatment decision for the two DFSP variants.

<table>
<thead>
<tr>
<th>pts</th>
<th>PM</th>
<th>LR</th>
<th>LR/PM</th>
<th>DM</th>
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<tbody>
<tr>
<td>C-DFSP</td>
<td>246</td>
<td>21</td>
<td>(8.5%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>FS-DFSP</td>
<td>24</td>
<td>2</td>
<td>(8.3%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>270</td>
<td>23</td>
<td>(8.5%)</td>
<td>4 (1.5%)</td>
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10555 Poster Session (Board #199), Sun, 8:00 AM-11:30 AM
The lipogenic phenotype reprograms the epigenome in sarcomas. First Author: Warren Allen Chow, City of Hope, Duarte, CA
Background: The "lipogenic phenotype of cancer" enhances the metastatic potential of cancers by promoting the de novo synthesis of fatty acids (FAs) to maintain their enhanced metabolism. Further, epigenetic reprogramming also promotes the malignant sarcoma phenotype. We hypothesized that development of the "lipogenic phenotype" reprograms the sarcoma epigenome to enhance their malignant potential. Methods: Soft-tissue (STS) and bone sarcoma cell lines (SK-UT-1 leiomyosarcoma, HT1080 fibrosarcoma, and Saos-2 osteosarcoma) were transduced with a fatty acid synthase (FASN)-expressing retrovirus. FASN catalyzes the synthesis of long-chain FAs from acetyl-CoA. Acetyl-CoA is generated from pyruvate, the excess end-product of aerobic glycolysis, better recognized as the "Warburg effect." FASN-expressing clones were subjected to proliferation, migration, and immunoblot assays. Transcriptome-wide sequencing and DNA methylation arrays were also performed. Finally, FASN expression was detected in STS clinical specimens by immunohistochemistry (IHC). Results: FASN overexpression increased sarcoma proliferation (35-47%), enhanced migration (scratch-wound assay), and increased methylation and acetylation of selected histone 3 lysines (H3K9me3 and H3K27ac). Whole transcriptome sequencing demonstrated multiple up- and downregulated genes, which generally correlated with the methylation status of their respective promoters. Finally, FASN expression was detected 1-3+ by IHC in 14/18 STS tumors by a blinded pathologist. Conclusions: FASN overexpression induces histone modifications that repress and induce genes that may enhance the malignant phenotype in sarcoma cell lines. Further, FASN is variably expressed in a majority of STS. Therapeutic targeting of FASN and epigenetic reprogramming may be a novel therapeutic approach to recurrent sarcomas.
Primary high-grade myxofibrosarcoma/pleomorphic malignant fibrous histiocytoma: Percent myxoid component to improve outcome prediction. First Author: Ann Yeelin Lee, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Myxofibrosarcoma and pleomorphic malignant fibrous histiocytoma (PMFH) are aggressive genetically complex sarcomas. We investigated the association of percent myxoid component (MC) with disease-specific (DS) and disease-free survival (DFS) in a large high-grade myxofibrosarcoma and PMFH and determined the optimal %MC cutoffs for defining subgroups.

Methods: A retrospective database identified 200 patients with primary, high-grade, extremity-only myxofibrosarcoma or PMFH treated during 1992-2013. Histology was reviewed and %MC determined for each case. Optimal %MC cutoffs were determined from minimum p-value analysis of the entire cohort. DSS and DRFS were analyzed using the Kaplan-Meier method, log-rank test and Cox regression.

Results: Median follow-up for survivors was 58.6 years. Median tumor size was 9.5 cm (range 2.5-30 cm). The optimal %MC cutoffs for both DSS and DRFS were 5% and 70%. Sarcomas with <5% MC were classified as myxofibrosarcoma (n = 128) and >5% MC (n = 72) as PMFH. The 5-year DRFS was 64% for >70% MC myxofibrosarcoma, 49% for 5-70% MC myxofibrosarcoma, and 23% for PMFH, %MC, tumor size, and age were independently associated with DSS, while %MC and size were associated with DRFS (Table). Conclusions: Percent MC is an important predictor of DSS and DRFS in primary high-grade myxofibrosarcoma and PMFH. Histology-based classification of %MC improves stratification of patient outcome and will aid in selection of patients for systemic therapy and clinical trials.

Multivariate analysis of clinical and pathological variables associated with DSS and DRFS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>DSS: Multivariate HR (95% CI)</th>
<th>DSS: p-value</th>
<th>DRFS: Multivariate HR (95% CI)</th>
<th>DRFS: p-value</th>
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<tr>
<td>MC 5-70% (vs &gt;70%)</td>
<td>1.6 (0.9-3.0)</td>
<td>0.11</td>
<td>1.9 (1.1-3.3)</td>
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<td>MC &gt;70% (vs &gt;70%)</td>
<td>2.1 (1.7-4.8)</td>
<td>&lt;0.0001</td>
<td>2.3 (1.5-3.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Size (&gt; 8 cm vs &lt; 8 cm)</td>
<td>2.5 (1.5-4.0)</td>
<td>&lt;0.0001</td>
<td>2.3 (1.5-3.6)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Age (&gt; 65 years vs ≤ 65 years)</td>
<td>1.6 (1.0-2.5)</td>
<td>0.03</td>
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</table>

Validation of the Royal Marsden Hospital (RMH) prognostic score in 100 patients with advanced sarcoma enrolled in early phase clinical trials at a major cancer center. First Author: Michael Wagner, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Standard therapy refractory, metastatic and advanced sarcoma patients (pts) have few therapeutic options, and may benefit from enrollment in early stage clinical trials. The Royal Marsden Hospital (RMH) score predicts survival in pts prior to enrollment in Phase I clinical trials. We sought to validate the RMH score as a predictive marker in this cohort. DRFS and DFS were analyzed using the Kaplan-Meier method, log-rank test and Cox regression.

Conclusions: The RMH score is a significant predictor of overall survival in high-grade RPS patients. As such, adjuvant RT should be considered for high-grade RPS. We hypothesized that any benefit in OS for RPS would most likely exist in those with high-grade tumors. Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients with pathology-confirmed retroperitoneal soft tissue sarcoma from 1973 to 2010. Clinical characteristics and outcomes were described according to SEER score (abdomen, LDH, and number of metastatic sites), and the presence or absence of chromosomal translocations. Results: Among the 100 sarcoma pts (soft tissue (STS) (n = 79); bone (n = 21) analyzed, the median age at trial enrollment was 48 (range 14-80). 46 pts (46%) were male. 26 pts (26%) had identifiable chromosomal translocations (17 with EWSR1 rearrangements). Clinical trial enrollment included 51 pts on VEGF/VEGFR/mTOR inhibitor based Phase I clinical trials. We sought to validate the RMH score as a predictive marker in this population and to assess the pretreatment characteristics that would predict benefit in Phase I clinical trials with targeted agents. Methods: Data from medical records of pts referred for enrollment in predominantly VEGF/VEGFR/mTOR inhibitor based Phase I clinical trials at M.D. Anderson Cancer Center were systematically reviewed. Pts were stratified according to DSS score (abdomen, bone, and number of metastatic sites), and the presence or absence of chromosomal translocations. Results: Among the 100 sarcoma pts (soft tissue (STS) (n = 79); bone (n = 21)) analyzed, the median age at trial enrollment was 48 (range 14-80). 46 pts (46%) were male. 26 pts (26%) had identifiable chromosomal translocations (17 with EWSR1 rearrangements). Clinical trial enrollment included 51 pts on VEGF agent alone, 16 pts on mTOR inhibitor alone, 13 pts on VEGF+ mTOR, 11 pts on VEGF+ chemotherapy, 6 pts on VEGF+ mTOR+ chemotherapy and 23 pts on other targeted agents. Median OS of pts with an RMH score of 0, 1, 2 or greater was 18.9 mos, 7.5 mos, and 4.0 mos, respectively (HR 2.1 (1.5, 2.9) p = 0.0001). Median PFS in pts with a translocation was 3.8 mos, and without was 3.5 mos [HR 0.97 (0.60, 1.57), p = 0.89]. Median OS in pts with translocation was 9.5 mos and without was 10.1 mos [HR 1.19 (0.74-1.94), p = 0.48]. Median PFS in STS pts was 4.2 mos (2.8-6.3), and bone sarcoma pts was 2.8 mos (2.0-7.6). Median OS in STS pts was 10.2 mos (95% CI: 8.4-15), and in bone sarcoma pts 7.8 mos (95% CI: 6.5-29). Clinical benefit rate (CR + PR + SD > 6 mos) across all Phase I trials was 35% (4 PR + 31 SD > 6 mos). Conclusions: RMH score is a significant predictor of overall survival in primary high-grade sarcoma pts treated on Phase I therapies. The presence of a chromosomal translocation had no effect on outcomes on sarcoma pts enrolled in Phase I trials.
A phase II study of temsirolimus and liposomal doxorubicin for patients with recurrent and refractory bone and soft tissue sarcomas. First Author: Christian Frederick Meyer, Johns Hopkins Hosp, Baltimore, MD

Background: Sarcomas are a heterogeneous group of connective tissue malignancies with limited palliative treatment options in the unresectable, metastatic setting. Standard chemotherapy treatment offers progression free survival (PFS) benefit measured in months while a significant impact from targeted therapy has not yet been realized. We conducted a phase I/II study of liposomal doxorubicin with temsirolimus in soft tissue and bone sarcomas based on preclinical data showing synergy against sarcoma stem cells. We previously reported the phase I dose finding data. Here, we report the results of patients treated at the recommended phase II dose.

Methods: 18 patients were treated at liposomal doxorubicin 30 mg/m² monthly with temsirolimus 20 mg/m² weekly. A variety of subtypes were enrolled including: rhabdomyosarcoma, 3 leiomyosarcomas, and 2 mesenchymal chondrosarcomas. 11 of the 18 patients had prior doxorubicin exposure and a median of 2 prior lines of chemotherapy. Results: PFS was 315 days (range 27-799) and event free survival (EFS) was 119 days. Response rate, defined as stable disease (SD) or better for 60 days (2 cycles) was 53% (8 of 15) at the recommended phase II dosing (RP2D) and 56% (10 of 18) including the subjects treated with the higher dose of temsirolimus. Those who responded to therapy (defined as SD or better at first evaluation) tended to have prolonged responses, with median PFS of 358 days (range = 75 – 799) and median EFS of 249 days. Pharmacodynamic analysis of target inhibition in 12 evaluable patients revealed concordance between inhibition of pS6K and response in 8 patients and inhibition of pAKT and response in 9 patients. The treatment was well-tolerated with only 4 patients experiencing a significant change in their ECOG performance status. Conclusions: Overall, the synergy of this combination bears further investigation of both metabolic and traditional chemotherapeutic agents in sarcomas. Clinical trial information: NCT00949325.

Sunitinib malate in advanced alveolar soft part sarcoma (ASPS): A final update after the closure of the named use program. First Author: Nadia Hindi, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Background: We already reported on the activity of sunitinib (SM) in 9 patients (pts) of ASPS. This series is an update. In addition, based on recent evidence demonstrating a role for lactate metabolism in ASPS pathogenesis, we explored the role of MCT1 and MCT4 lactate transporters in this group of 358 days (range 27-799) and event free survival (EFS) was 119 days. Response rate, defined as stable disease (SD) or better for 60 days (2 cycles) was 53% (8 of 15) at the recommended phase II dosing (RP2D) and 56% (10 of 18) including the subjects treated with the higher dose of temsirolimus. Those who responded to therapy (defined as SD or better at first evaluation) tended to have prolonged responses, with median PFS of 358 days (range = 75 – 799) and median EFS of 249 days. Pharmacodynamic analysis of target inhibition in 12 evaluable patients revealed concordance between inhibition of pS6K and response in 8 patients and inhibition of pAKT and response in 9 patients. The treatment was well-tolerated with only 4 patients experiencing a significant change in their ECOG performance status. Conclusions: Overall, the synergy of this combination bears further investigation of both metabolic and traditional chemotherapeutic agents in sarcomas. Clinical trial information: NCT00949325.

Imatinib mesylate (IM) activity in patients (pts) with locally advanced tenosynovial giant cell tumor/pigmented villonodular synovitits (TGCT). First Author: Philippe Alexandre Cassier, Centre Léon Bérard, Department of Medicine, Lyon, France

Background: TGCT is a rare disease affecting the synovium and tendon sheaths of young adults. This usually benign neoplasm is driven by overexpression of CSF1, in some cases as a result of fusion of the CSF1 gene to the COL6A3 promoter in the (11;2) translocation. The bulk of the tumor is made of CSF1 receptor (CSF1R) expressing cells. We previously reported on the activity of IM in this disease, here we present updated results.

Methods: This is a multi-institutional retrospective study to assess the activity of IM in locally advanced/metastatic TGCT. Results: Forty-nine pts from 10 centers from Europe, Australia and the US were included. There were 31 females, median age was 38 (range 1.3-76) at diagnosis and 47 (range 21-80) at the time IM was started. The knee (n = 27; 55%), ankle (n = 9; 18%) and hip (n = 5; 10%) were the most common sites of disease. Most pts had locally advanced disease and/or local relapse (n = 47) and 2 pts had metastatic disease (lung and bone). The median number operations before IM was 2 (range 0-9), and only 4 patients never had surgery prior to IM. All but one pts were treated with IM 400 mg/day. Median follow-up was 18 (range 3-78) months and all pts were evaluable for response: 2 pt (4%) had a CR, 8 (16%) had a PR (ORR 20%) and 69 (37%) had SD. The two pts with metastatic disease had no response to imatinib. Ten patients were operated after a median of 6 (range 1-10) months of IM. Forty pts had symptom improvement. Median symptom-free survival was not reached. In 11 patients who had symptom improvement and stopped IM before PD, symptom control persisted beyond IM interruption (mean 27 months, median not reached). The most common side effects were grade 1 or 2 fatigue and edema seen in 19 (38%) pts, followed by nausea and skin toxicity reported in 8 (16%) and 5 (10%) pts respectively. Five patients had grade 3-4 events and overall, 7 patients (14%) discontinued treatment because of poor tolerance.

Conclusions: These data confirm the value of IM in patients with advanced symptomatic TGCT, in some patients symptom control may persist beyond IM interruption.

Phase II trial of PF-03084014 in adults with desmoid tumors/aggressive fibromatosis. First Author: Shivaani Kummar, Phase I Clinical Research Program Stanford University School of Medicine, Stanford, CA

Background: Desmoids are rare, invasive, slow growing soft tissue tumors that are sporadic or associated with familial genetic syndromes, such as familial adenomatous polyposis. Desmoids are characterized by stabilization and abnor- mals in localization. Mutations in the WNT16 gene are found in 85-90% of desmoids. Gamma-secretase cleaves intracellular Notch resulting in Notch signaling. PF-03084014 (PF) is an oral reversible γ-secretase inhibitor (GSI) that is well tolerated. Based on encouraging data from a phase I trial, we conducted a phase II study of PF in patients (pts) with symptomatic desmoid tumors progressing following at least one line of therapy. Objectives: determine the response rate (RR), assess symptom improvement and identify potential genotyping for germline/somatic mutations in APC and CTNNB1 genes.

Methods: PF was administered orally at 150mg BID; for 21 day cycles. Archival samples were sequenced for germline and somatic mutations in APC and CTNNB1 genes. Dynamic contrast-enhanced MRI (DCE-MRI) was used to assess symptoms. Results: Accrual completed. 13/17 pts (76.4%) remain on study; 4 pts stopped treatment by choice/co-morbid conditions. No pt has progressed to date. Median follow-up time is 10 months (range 2-14), 6 pts remain on study ≥ 1 year. Grade 3 toxicities include hypophosphatemia (3 pts, 17.6%) and diarrhea (1 pt, 5.8%). Dose reduction to 100mg BID daily occurred in 2 pts, 16 pts (94%) have stable disease with 1 (5.8%) uncontrolled. In 15/17 pts (88.2%), a somatic or germ line mutation was identified. DCE-MRI and symptom scale analysis ongoing. Conclusions: PF is active at the selected dose, with a manageable side effect profile. Copy number analysis, transcriptome sequencing and DNA methylation analysis of archival samples as well as paired biopsies obtained on study is ongoing. Clinical trial information: NCT01981351.
A phase I trial of the human double minute 2 (HDMD2) inhibitor MK-8242 in patients (pts) with advanced solid tumors. First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: HDMD2 binds and inhibits wild-type (WT) p53 thereby promoting oncogenicity. MK-8242 is a potent, orally bioavailable, small-molecule inhibitor of the HDMD2:p53 protein-protein interaction under development as a novel cancer therapy. Methods: A multi-center, 2-part (dose escalation/Part I and confirmation/Part II; using modified TIPi design) Phase I study of MK-8242, administered p.o. BID on days 1-7 in 21 day cycles, was performed to determine the safety, tolerability, and recommended Phase 2 dose (RP2D) in pts with advanced solid tumors with WT p53. RP2D was based on tolerability, plasma pharmacokinetics (PK), and pharmacodynamics (PD) in tumor/blood, including expression of the p53 target PHLDA3. Other objectives were characterizing PK/PD relationship, correlation of biomarkers with response, and assessment of tumor response (RECIST v1.1). Results: 47 pts received MK-8242 across 8 dose levels ranging from 60 mg to 500 mg. Initially, 6 pts developed DLTs (G2 nausea at 120 mg; G3 fatigue at 250 mg; G2 nausea and G4 thrombocytopenia at 350 mg; G3 vomiting and G3 diarrhea at 500 mg). DLT criteria were revised to permit management of G1 toxicity, and 4 additional DLTs were observed (G4 neutropenia and G4 thrombocytopenia at 400 mg; G4 thrombocytopenia [2 pts] at 500 mg). Other drug-related G3-4 events included anemia, leukopenia, pancytopenia, nausea, hyperbilirubinemia, hypophosphatemia, and anorexia. The RP2D was established at 400 mg as tolerability (i.e., 2 pts at 500 mg). Other drug-related G3-4 events included anemia, leukopenia, pancytopenia, nausea, hyperbilirubinemia, hypophosphatemia, and anorexia. The RP2D was established at 400 mg as tolerability (i.e., 2 DLTs in 14 evaluable pts), PK, and PD targets were achieved at this dose level. Plasma PK analysis of 400 mg on Day 7 found AUC0-12hr of 16.7 μM*hr/L, Cmax 3.1 μM, T1/2 2.6 hr, and T1/2 6.5 hr. Blood concentration of PHLDA3 correlated with drug exposure (R2 = 0.69, p < .0010). In 41 pts who had post-baseline scans, 31 showed SD, 2 achieved PR (both with anti-PD-L1 antibody; (Clone: J45, R&D System), and 28/54 interrupted treatment in absence of progression, while 28/54 patients received T until progression. Time to secondary resistance was defined as time from the first cycle of T to progression, whenever it occurs (including under T reintroduction). Results: In the 28 pts in whom Trabectedin was interrupted (11 for surgery of the residual disease, 1 for radiotherapy, 3 for toxicity and 13 for shared decision with clinician), this was done after a median of 14 cycles (range = 6-21) and the median PFS was 24 months. 17 of them resumed treatment at the time of progression (F = 8, M = 9, median age = 51, range = 32-76). After rechallenge, no PD was seen at first assessment, and time to secondary resistance was 48 months. In the 26 pts who went on with T until progression, PFS (i.e., time to secondary resistance) was 11 months. Conclusions: Rechallenge with T may be successful in selected patients with myxoid liposarcoma primarily responding to the drug and stopping it after a while. In this series, the choice to continue or stop the drug after response was of course at the discretion of the clinician, and selection biases are likely. Prospective studies on optimization of treatment strategy with T in MRCLPS are worthwhile.

Clinical pattern and implication of PD-L1 expression in soft-tissue sarcoma. First Author: Chan Kim, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

Background: PD-1/PD-L1 axis plays a paramount role in tumor immune escape by negative regulation of T-cell functions. Recently, immune checkpoint inhibitors targeting this axis displayed promising anti-tumor activity with durable response, and the predictive role of PD-L1 expression is being investigated in various solid tumors. In the present study, we aimed to characterize the PD-L1 expression pattern and its clinical implications in soft-tissue sarcomas (STS). Methods: We analyzed PD-L1 expression in 82 STS patients with 5 subtypes including rhabdomyosarcoma (n = 32), synovial sarcoma (n = 19), Ewing sarcoma (n = 18), epitheloid chondrosarcoma (n = 7), and mesenchymal chondrosarcoma (n = 6). PD-L1 expression was evaluated using anti-PD-L1 antibody (clone: 130021, R&D System), and PD-L1 positivity was defined as more than 10% of PD-L1 staining in tumor cells. PD-L1 expression was compared with other clinicopathological variables. Results: Median age at diagnosis of patient cohort was 26 (range: 1-78) and male-to-female ratio was 1.6. Initial disease presentation was locoregional disease in 80% of patients and metastatic disease in the remaining 20%. PD-L1 expression was identified in 43% of STS patients. Histologic subtype of STS was significantly associated with PD-L1 expression (p = 0.004). Proportion of PD-L1 expressing tumors was highest in epithelioid sarcoma (100%, 7/7), followed by synovial sarcoma (53%, 10/19), rhabdomyosarcoma (38%, 12/32), and Ewing sarcoma (33%, 5/18), while it was not expressed in mesenchymal chondrosarcoma (0%, 0/6). Baseline clinical characteristics other than histologic subtype was not correlated with PD-L1 expression. Patients with PD-L1 expression had worse overall survival compared with those without PD-L1 expression (5-year survival rate: 85% vs 48%, respectively, p = 0.0015). Moreover, this negative prognostic role of PD-L1 expression in STS was also confirmed by multivariate analysis with Cox regression model (HR: 2.67, p = 0.017). Conclusions: PD-L1 is not only expressed in STS but also stand as an independent negative prognostic factor for overall survival of STS patients. Thus, PD-L1 needs to be pursued as a potential therapeutic target in patients with STS.
A new simple low-cost multiplexed targeted sequencing assay to detect recurrent fusion genes in sarcomas. First Author: Emile Angot, Department of Pathology, University of Rouen, Rouen, France

Background: Sarcomas represent a heterogeneous group of tumors comprising more than 50 histological different types. Ten to fifteen percent of sarcomas are characterized by specific translocations which are routinely used as molecular markers for diagnosis, providing crucial information for prognosis and therapeutic decision. Today, translocations are detected by FISH or RT-PCR. However, these methods can only detect a limited number of translocations simultaneously. Since the development of high throughput sequencing, the number of specific translocations continues to grow and it seems that we have reached the limits of this molecular “one-shot” approach. Methods: We have developed a simple low-cost (less than 6 dollars per patient) assay based on multiplex ligation-dependent RT-PCR for simultaneous screening of more than 50 rearrangements present in sarcomas. To validate this assay, we selected 42 formalin fixed and paraffin embedded (FFPE) sarcomas with known molecular alteration. In the case of non-contributive results, we repeated the analyses with snap-frozen tissue. Results: We detected fusion transcript for 9 synovial sarcomas (9/9), 9 alveolar rhabdomyosarcomas (9/9), 4 Ewing sarcomas (4/6), 2 Ewing-like sarcomas with BCOR-CCNB3 fusion transcript (2/2), 6 myxoid liposarcomas (6/7), 2 desmoplastic small round cell tumors (2/2), 1 dermatofibrosarcoma protuberans (1/2), 1 clear cell sarcoma (1/1), 2 angiomatoid fibrous histiocytomas (2/2), 1 infantile fibrosarcoma (1/1) and 1 solitary fibrous tumor (1/1). For 7 tumors, sequence quality was only reached using cryopreserved tissue. We did not detect transcript for 2 primary bone Ewing sarcomas and 1 dermatofibrosarcoma protuberans. Unfortunately, for these latter tumors we did not have cryopreserved tissue. One myxoid liposarcoma was not detected using FFPE and cryopreserved tissue. Conclusions: We have developed a simple low-cost assay that can reveal a very large number of gene fusions in sarcomas with good sensitivity and excellent specificity. These promising results provide an opening for this new rapid simple low-cost multiplexed targeted sequencing assay as an alternative method to FISH and RT-PCR for routine diagnosis.

Pattern of relapse in limb/girdle low-grade liposarcoma/atypical lipomatous tumor (ALT) during guidelines-suggested follow up (FU). First Author: Raimondo Piana, Department of Orthopaedic Oncology and Reconstructive Surgery, Azienda Ospedaliera Universitaria Città della Salute e della Scienza, CTO Hospital, Torino, Italy

Background: In soft tissue sarcomas (STS) after complete (marginal/wide/ radical margins) surgery, surveillance should be tailored to individual patient’s (pts) risk that depends on histotype, grading and site of origin. Unfortunately there is a substantial lack of evidence to personalize FU and most guidelines (GL) suggest both clinical (history and physical examination) and imaging procedures (X-rays, CT, US, MRI) taking into account two broad categories (low- and high-grade STS) but ignoring histotype heterogeneity. We reviewed our prospectively collected STS database to assess ALT pattern and risk of relapse in order to improve our future FU policy. Methods: In 2001 our regional-based health system adopted a STS GL (www.reteoncologica.it) suggesting the following FU: pts examination every 4-6 months in the first 3 years, every 6 months until the 5th year, then yearly. Pts underwent local and chest imaging (either CT or X-rays). Average cost and exposure to X-rays were computed for the entire FU. We searched for pts affected by ALT with complete clinical follow-up (centrally reviewed histology, surgical record, and at least 3-year FU). ALT-specific overall survival (OS), relapse-free survival (RFS) and local-RFS (LRFs) were estimated according to Kaplan-Meier method. Results: Between 2001 and 2011 we took care of 163 patients affected by LGL. Complete records were available in 152 patients (87%): 19 pts (12.5%) died during FU, 107 (70%) were available for analysis. Median follow-up time was 127 (78%) pts (median age 58, IQR 50-67; median size 14 cm, IQR 8-19). Median FU was 117 months (95% CI 95-140). Ten-year OS, RFS and LRFs were 100%, 74% and 74%, respectively. Among the 13 (10%) relapsed pts, we observed 13 local relapses and no distant metastases. All relapses were surgically amenable. Two pts died during their FU and now because of systemic progression. The chest X-rays estimated 10-year FU cost is 450 euros per pts with an average total exposure of 0.9 mSv. Conclusions: Until a hardly foreseeable randomized trial on FU will be performed, our study, though retrospective, does not support the systematic use of chest imaging in ALT FU that adds apparently needless costs and low, but not negligible, ionizing radiation risks.
Local control following resection of primary retroperitoneal sarcoma with and without preoperative radiotherapy. First Author: Carol Jane Swallow, Department of Surgery, Toronto General Hospital, Toronto, ON, Canada

Background: Retroperitoneal sarcoma (RPS) represents a therapeutic challenge due to its typically advanced stage at presentation, with local failure a harbinger of death from sarcoma following resection of primary RPS. Preoperative external beam radiotherapy (Pre-op RT) offers the potential for sterilization of margins and better local control. We present mature outcomes according to histologic subtype and treatment of patients with primary RPS managed at our center. Methods: All patients presenting with primary RPS between 01/96 and 06/11 identified from a prospective database were eligible. Distant metastases or unresectability at presentation, receipt of pre-op chemotherapy or post-op radiotherapy were exclusion criteria. All biopsy and resection specimens were re-analysed by an expert pathologist and mdm2 status used to facilitate histologic subtyping. Cumulative-incident rate curves were constructed for local and distant recurrence (LR, DR). Results: All 120 included patients underwent total gross resection. In this cohort, overall survival was 75% and 64% at 5 and 10 years, median 206 mos, and disease specific survival was 85% and 76% at 5 and 10 years, median 290 mos. Pre-op RT was given to 101 patients while 19 had surgery alone. Surgical approach, histologic subtype (80% liposarcoma, LPS) and follow-up (median 59 mos) did not differ between treatment groups; median size was larger (28 vs. 19 cm) and histologic grade lower in the surgery alone group. For the 120 patients, DR occurred in 12; at a median 26 mos (range 2-131) postoperatively and varied significantly by histology (4/65 DD-LPS; 0/31 WD-LPS; 7/17 LMS; 1/7 other; p < 0.01), but not treatment group. LR occurred in 24 at a median 22.5 mos (range 2-103) and varied significantly by histology (22/65 DD-LPS; 2/31 WD-LPS; 0/24 other; p = 0.01). For the entire cohort, LR rate was 20% and 28% at 5 and 10 yrs. LR at 5 yrs varied significantly by treatment group (16% for pre-op RT, 51% for surgery alone, p < 0.01). Conclusions: Pre-op RT was associated with improved local control compared with a contemporaneous control. Participation in the EORTC randomized trial of pre-opRT vs. surgery alone is essential to determine the true benefit of pre-op RT in primary RPS.

Preoperative external beam radiotherapy (Pre-op RT) offers the potential for sterilization of margins and better local control. We present mature outcomes according to histologic subtype and treatment of patients with primary RPS managed at our center. Methods: All patients presenting with primary RPS between 01/96 and 06/11 identified from a prospective database were eligible. Distant metastases or unresectability at presentation, receipt of pre-op chemotherapy or post-op radiotherapy were exclusion criteria. All biopsy and resection specimens were re-analysed by an expert pathologist and mdm2 status used to facilitate histologic subtyping. Cumulative-incident rate curves were constructed for local and distant recurrence (LR, DR). Results: All 120 included patients underwent total gross resection. In this cohort, overall survival was 75% and 64% at 5 and 10 years, median 206 mos, and disease specific survival was 85% and 76% at 5 and 10 years, median 290 mos. Pre-op RT was given to 101 patients while 19 had surgery alone. Surgical approach, histologic subtype (80% liposarcoma, LPS) and follow-up (median 59 mos) did not differ between treatment groups; median size was larger (28 vs. 19 cm) and histologic grade lower in the surgery alone group. For the 120 patients, DR occurred in 12; at a median 26 mos (range 2-131) postoperatively and varied significantly by histology (4/65 DD-LPS; 0/31 WD-LPS; 7/17 LMS; 1/7 other; p < 0.01), but not treatment group. LR occurred in 24 at a median 22.5 mos (range 2-103) and varied significantly by histology (22/65 DD-LPS; 2/31 WD-LPS; 0/24 other; p = 0.01). For the entire cohort, LR rate was 20% and 28% at 5 and 10 yrs. LR at 5 yrs varied significantly by treatment group (16% for pre-op RT, 51% for surgery alone, p < 0.01). Conclusions: Pre-op RT was associated with improved local control compared with a contemporaneous control. Participation in the EORTC randomized trial of pre-opRT vs. surgery alone is essential to determine the true benefit of pre-op RT in primary RPS.

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A randomized phase II trial comparing pazopanib with doxorubicin as first line treatment in elderly patients with metastatic or advanced soft tissue sarcoma of the Working Group Medical Oncology (AIO) and German Interdisciplinary Sarcoma Group (GISG). First Author: Viktor Gruenwald, Medical School of Hannover, Hannover, Germany

Background: 1/3 of STS patients are 60 years and older. Single agent doxorubicin is the mainstay of therapy in metastatic disease, which is frequently associated with hematologic toxicity (grade 4 neutropenia in 34%; febrile neutropenia in 9%). We assume that comorbidities in the elderly population may limit tolerability of doxorubicin and novel agents may improve health-related quality of life (HR-QoL), while maintaining efficacy. Methods: This is a randomized, open-label, multicenter phase II study that compares pazopanib 800 mg OD to doxorubicin 75 mg/m² as first line treatment in elderly patients with metastatic or advanced STS (NCT01861951). A total of 120 patients will be recruited and randomized 2:1 to receive either pazopanib or doxorubicin, stratified by performance status (0-1 vs. 2) and histological subtype. HR-QoL (QLQ-C30) and comprehensive geriatric assessment (elderly minimal dataset of EORTC ETF) is determined throughout the course of the study, in order to assess the impact of treatment on the patient’s quality of life and daily living. Key inclusion criteria: age ≥ 60 years; progressive intermediate or high grade STS; ECOG PS 0-2; measurable disease (RECIST 1.1); availability of archived STS tissue; adequate organ function; no prior therapy for metastatic disease. Primary endpoint: Progression free survival (PFS) based on local tumor assessment according to RECIST 1.1. Key secondary endpoints include: incidence of grade 4 neutropenia and febrile neutropenia. For the latter endpoints, sensitivity analyses will be conducted to adjust for primary prophylaxis of granulocytopenia or febrile neutropenia. For the latter endpoints, sensitivity analyses will be conducted to adjust for primary prophylaxis of granulocytopenia or febrile neutropenia. Other secondary endpoints include: HR-QoL, geriatric assessment, safety and tolerability, overall survival, objective response rate, PFS rate at 12 and 26 weeks, time to onset of response, and predictive biomarkers. The first patient was randomized on October 12, 2012. Currently, a total of 85 patients have been randomized. Clinical trial information: NCT01861951.

A study of the safety and efficacy of the combination of gemcitabine and docetaxel with ontuxizumab (MORAB-004) in metastatic soft tissue sarcoma. First Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: Ontuxizumab is a humanized immunoglobulin G-1-kappa monoclonal antibody (mAb) that is the first clinical stage agent to target endostatin. Endostatin (TEM-1/CD248) is a cell surface glycoprotein expressed on cells involved in the development of tumor vasculature, but has generally limited expression in normal tissue. In some tumors, such as sarcomas, endostatin is expressed directly by the tumor cells and therefore soft tissue sarcomas (STS) may be a suitable treatment target. Methods: This Phase 2 multicenter study in subjects with metastatic STS (0-2 prior regimens) is being conducted in two sequential parts. Part 1 was an open label, dose-escalation, safety lead in: 4, 6 and 8 mg/kg ontuxizumab (administered on days 1 and 8 of a 21 day cycle) combined with gemcitabine and docetaxel (G/D) (900 mg/m² on days 1/8 and 75 mg/m² on day 8, respectively). Based on the observed safety profile in Part 1, 8 mg/kg was utilized in Part 2 efficacy design. In Part 2 subjects are randomized in a double-blind 2:1 ratio to G/D plus ontuxizumab (8 mg/kg) or G/D plus placebo. Using an adaptive population finder design, randomization is stratified by four histological cohorts (liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma, and other STS). An independent unblinded statistical committee (ISC) monitors the trial adaptations for futility, success, or maximal cohort sizes (60). Primary objective is progression-free survival (PFS) by RECIST1.1. Secondary objectives include overall survival (OS), overall response rate (ORR), and predictive/ response biomarkers. Enrollment ended in August 2014 with 209 subjects randomized. Primary result analysis is anticipated in December, 2015. Clinical trial information: NCT01574716.

Immune checkpoint inhibition with antibodies (abs) to cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) have made a significant therapeutic impact in metastatic melanoma. Abs targeting the PD-1/PD-L1 axis also exhibited clinical activity in solid tumors that are not considered "immuno-genic", e.g., lung and bladder cancer. The significance of the PD-1/PD-L1 impact in metastatic melanoma. Abs targeting the PD-1/PD-L1 axis also exhibited clinical activity in solid tumors that are not considered "immuno-genic", e.g., lung and bladder cancer. The significance of the PD-1/PD-L1 axis is currently being elucidated in sarcoma. Over 150 sarcomas of various histologic subtypes have been analyzed for PD-L1 tumor expression and the presence of PD-1+ tumor infiltrating lymphocytes (TIL): up to 65% of sarcomas expressed PD-L1 which, along with PD-1 TIL positivity, correlated with poorer overall survival and aggressive tumor features. We seek to determine the efficacy of PD-1 blockade with the anti-PD-1 ab pembrolizumab in pts with advanced soft tissue (STS) and bone sarcomas. Methods: This is an open label, multicenter, single stage, phase II study of P in pts with advanced sarcomas. First Author: Melissa Amber Burgess, University of Pittsburgh Physicians, Pittsburgh, PA

Background: Immune checkpoint inhibition with antibodies (abs) to cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) have made a significant therapeutic impact in metastatic melanoma. Abs targeting the PD-1/PD-L1 axis also exhibited clinical activity in solid tumors that are not considered "immuno-genic", e.g., lung and bladder cancer. The significance of the PD-1/PD-L1 axis is currently being elucidated in sarcoma. Over 150 sarcomas of various histologic subtypes have been analyzed for PD-L1 tumor expression and the presence of PD-1+ tumor infiltrating lymphocytes (TIL): up to 65% of sarcomas expressed PD-L1 which, along with PD-1 TIL positivity, correlated with poorer overall survival and aggressive tumor features. We seek to determine the efficacy of PD-1 blockade with the anti-PD-1 ab pembrolizumab in pts with advanced soft tissue (STS) and bone sarcomas. Methods: This is an open label, multicenter, single stage, phase II study of P in pts with advanced sarcomas. First Author: Melissa Amber Burgess, University of Pittsburgh Physicians, Pittsburgh, PA

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Identifying somatic oncogenic mutations in leukocytes that infiltrate primary breast cancers. *First Author: Elizabeth Anne Comen, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** In the past decade, sequencing studies have delineated somatic mutations in human cancers. Given that cancer cells interact with their microenvironment and the presence of somatic mutations in a subset of elderly individuals with clonal hematopoiesis, we hypothesized that white blood cells within tumors might be characterized by clonally selected mutations in known cancer genes. Here we provide direct evidence of the presence of clonal somatic mutations affecting known cancer genes in tumor-infiltrating leukocytes from breast cancer (BC) patients.

**Methods:** We evaluated tumor infiltrating leukocytes in 17 primary BC samples: 13 patients had triple negative BC, 2 had ER+, HER2+ BC, and 2 had ER+, HER2- BC. Fluorescent activated cell sorting was employed to separate CD45-positive hematopoietic cells from CD45-negative epithelial cells from each tumor. Whole exome sequencing of tumor infiltrating leukocytes revealed candidate somatic mutations in known cancer genes, including BCOR, NOTCH2, TET2, NF1, EZH2 and JAK1. To validate our findings, we expanded our sample size to 20 patients and performed targeted capture massively parallel sequencing of matched tumor-infiltrating leukocytes and germline DNA. Laser-capture microdissected cancer cells were subjected to high-depth sequencing to rule out the presence in cancer cells of the somatic mutations found in leukocytes. Results: In 10 of the 20 patients, we identified and validated somatic mutations, including mutations affecting genes associated with leukemia in tumor infiltrating leukocytes but not in laser-capture microdissected BC cells from the same patients. Targeted sequencing indicated that these mutations are enriched in tumor-infiltrating leukocytes as compared to circulating leukocytes.

**Conclusions:** We identified clonal somatic mutations in known cancer genes in tumor infiltrating leukocytes. These data suggest a novel relationship between cancer cells and mutant infiltrating leukocytes. Studies are underway to investigate functional interactions between BC cells and hematopoietic cells harboring somatic mutations.

**Discordance between HER2-phenotype on circulating tumor cells and primary tumor in women with advanced breast cancer.** *First Author: Amelie Schrannm, Universitaetsfrauenklinik Ulm, Ulm, Germany*

**Background:** In the DETECT study program, women with HER2-negative metastatic breast cancer (MBC) are screened for circulating tumor cells (CTCs) to evaluate eligibility for different DETECT treatment intervention trials based on presence and HER2 phenotype of CTCs. Here we present data on the association of CTC prevalence and positive HER2-status on CTCs with patient and tumor characteristics.

**Methods:** As of January 2015, number of CTCs using the FDA-cleared CellSearch System (Janssen Diagnostics, LLC) and their HER2 status have been evaluated in 1052 women with HER2-negative MBC screened for the DETECT Study program. Patients were defined as CTC positive if at least 1 CTC was detected in 7.5 ml of peripheral blood, and the cutoff for HER2 positivity was the presence of at least 1 CTC with a strong (+ +) immunohistochemical HER2 staining intensity.

**Results:** Overall, CTCs were detected in 661 (62.8%) of the 1052 screened patients (median 7 CTCs, range 1 – 35078). CTC prevalence was associated with a higher proportion of pN2/pN3 tumors (28.0 vs. 20.2%; p = 0.021) and a higher proportion of lobular carcinomas (22.4% vs. 9.5%; p < 0.001) compared to CTC-negative patients. Among the 661 patients with CTCs, at least one HER2-positive CTC was found in 130 patients (19.7%), indicating a discordance between primary tumor and CTCs with regard to HER2-status. Patients with HER2-positive CTCs had less often G3 tumors (27.7% vs. 39.0%; p = 0.024), and more often lobular carcinomas (22.6% vs. 13.3%; p = 0.013) compared to patients without HER2-positive CTCs. In addition, patients with triple-negative tumors were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone-receptor positive tumors (6.6 vs. 22.8%; p < 0.001).

**Conclusions:** Our data confirm discordance in HER2-status between primary tumor and CTCs with regard to HER2-status. Patients with HER2-positive CTCs had less often G3 tumors and more often lobular carcinomas compared to patients without HER2-positive CTCs. In addition, patients with triple-negative tumors were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone-receptor positive tumors. Awareness of the HER2-phenotype of CTCs may have important implications for further personalized therapy options.
Detection rate of actionable mutations in diverse cancers using a biopsy-free (blood) circulating tumor DNA assay. First Author: Razelle Kurzrock, UCSF/Diego Mesones Cancer Center, La Jolla, CA

Background: Analysis of cell-free DNA using next generation sequencing (NGS) is a potentially powerful tool for the detection/monitoring of circulating tumor DNA (ctDNA). We report the findings of a biopsy-free NGS ctDNA assay in a series of 103 patients with advanced cancer. Methods: Between June 1, 2014 and January 16, 2015, plasma samples from 103 patients with a variety of cancers were analyzed for ctDNA. Single nucleotide variants (SNVs) in 54 genes and copy number variants (CNVs) in 3 genes (EGFR, ERBB2 and MET) are reported quantitatively as the fractional mutant allele concentrations in cell-free DNA and the absolute copy numbers of the genes measured, respectively (Guardant360, Guardant Health, Inc.). This ctDNA assay has high sensitivity (detects 85%+ of the single nucleotide variants (SNVs) detected in tissue in advanced cancer patients) and analytic specificity (> 99.9999%). Results: Of the 103 patients, there were 40 with breast and 40 with lung cancer; and 23 various other malignancies. Of the total, 78 (75.7%) had at least one detectable mutation (mean = 2.1/patient). In 222 healthy volunteers used to validate that assay, only 1 had an alteration. Within the breast cancer cohort, 22% had 1 alteration; 50%, 2 or more (range 0-12; mean = 2.2/patient). TP53 alterations were the most common, found in 32.5%. Interestingly, 25% of patients had an EGFR alteration (amplification or SNV), higher than previously reported. Mutations in PIK3CA were detected in 10 cases. In the 40 lung cancer patients, 82.5% had at least 1 alteration (mean = 2.2/patient). TP53 alterations were present in 50%; EGFR alterations, in 30%; and MET amplification/variation, in 22.5%. Sixty-two of 103 patients (60% of all patients; 80% of patients with an alteration) had alterations that were conceivably actionable by an FDA approved drug and/or an agent in clinical trials. Conclusions: In this single institution series, 75.7% of the patients had an alteration on a 54 gene panel ctDNA assay. Importantly, of patients with at least 1 alteration, 80% had alterations actionable by existing drugs. ctDNA testing in blood identifies a high number of potentially actionable abnormalities in a broad range of cancer types.

Safety and activity of DCR-MYC, a first-in-class Dicer-substrate small interfering RNA (DsRNA) targeting MYC, in a phase I study in patients with advanced solid tumors. First Author: Anthony W. Tolcher, START, San Antonio, TX

Background: MYC, an oncprotein deregulated in over half of all human malignancies, has thus far been considered “undruggable” with conventional approaches. RNA interference (RNAi), a therapeutic approach that can be used to silence the MYC oncogene, has been shown to inhibit cancer growth in animal models. Synthetic DsRNA with specificity for MYC have demonstrated highly potent activity in vitro (picoMolar IC₅₀), and anti-MYC DsRNA formulated in EnCore lipid nanoparticles (DCR-MYC) have demonstrated activity in vivo across various tumor models. DCR-MYC is the first MYC-targeting siRNA to enter clinical trials. Methods: This phase I, dose-escalation study (1+1 design) evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity of DCR-MYC in patients (pts) with advanced solid tumors, multiple myeloma or lymphoma. DCR-MYC is administered as a 2-hr IV infusion on Day 1 and 8 of a 21 day cycle. Given the role of MYC in tumor metabolism, FDG-PET is obtained after cycle 1 to assess early metabolic response, while RECIST response is assessed after every 2 cycles. Results: Nineteen pts have been treated across 5 dose levels (0.1, 0.125, 0.156, 0.2, 0.3 mg/kg): 8M/11F, median age 58 yrs, ECOG PS 0.5, 1.14). Tumor types include NET (4), MBC (4), CRC (3), Ovarian (2), Appendiceal (2), other (4). The most common treatment-related AEs (all grades/grade 3) include fatigue (70%), nausea (50%), pyrexia (40%), rash (31%), anorexia (31%), neutropenia (21%), fatigue (12%), diarrhea (9%), vomiting (9%), AST (8%), and anemia (8%). Two patients experienced DLT (transient grade 3 AST and fatigue). This pt experienced a complete metabolic response (based on FDG-PET) after cycle 1 which has been sustained for > 8 months without further treatment. Metabolic responses after cycle 1, as well as evidence of tumor shrinkage have been observed in multiple patients. Preliminary PK analysis from the first two dose levels shows dose proportional changes in AUC and Cmax. Conclusions: DCR-MYC, a novel MYC inhibitor, is well tolerated and shows promising initial clinical and metabolic responses across various dose levels. These data support early validation of MYC as a therapeutic target. Updated results from the ongoing study will be presented. Clinical trial information: NCT02110563.

Protein expression by genetic mutations identified in gene panels (hotspots) and efficacy of targeted treatments. First Author: Stephen Charles Brown, Ve33 Genomics, Sanford, CA

Background: Treatment decision support by next generation sequencing of gene panels is currently limited to the analysis of somatic (tumor) data from DNA sequencing without taking into consideration expression of mutated genes. We present here a supercomputer-driven, cloud-based integrated analysis of genomic (DNA) and transcriptomic (RNA) sequencing data to 1) directly identify driver variants between somatic and germline (normal) DNA and 2) to determine expression of identified mutations in a cohort of 3,784 patients, thereby establishing therapeutic relevance of the mutated genes overcoming the limitations of panels. Methods: This large scale 3,784 patient genomic (DNA and RNA sequencing) data set from 19 anatomical tumor types was processed to detect DNA variants (germline vs somatic) and RNA expression, and to establish not only the existence but also the expression level of hotspot mutations in the following oncogenes: PIK3CA, KRAS, NRAS, AKT1, BRAF, IDH1, CTNNB1, and IDH2. Results: Of the 3,784 patients in this analysis, 720 were found to have mutations in the oncogenes listed above. Remarkably, only 38 (5.3%) of these patients had better than 90% expression by RNAseq, and 36 patients (5.0%) with identified hotspot mutations had no or low (< 10%) expression. For example, mutations at position E545 in the PI3K protein encoded by the PIK3CA gene, which has been targeted by both pan-PI3K and mutant-targeted drugs in clinical trials, showed low or no expression in 12% (5/41) of breast cancer patients and not a single patient showed relatively maximal (> 90%) expression. Similarly of the 204 thyroid cancer patients with a BRAF V600 hotspot mutation, 7.5% (15/204) had low or no expression and none had relatively maximal expression. Conclusions: These findings illustrate that genetic mutations in gene panels (hotspots) do not always result in protein expression. Given that many gene mutations were not expressed, we conclude that an informed molecularly-driven clinical treatment decision requires insight into downstream protein expression and not just DNA alterations alone.

Comprehensive genomic profiling (CGP) of advanced cancers to identify MET exon 14 alterations that confer sensitivity to MET inhibitors. First Author: Garrett Michael Frampton, Foundation Medicine, Cambridge, MA

Background: Amplifications and activating mutations in the c-MET proto-oncogene are known oncogenic drivers that have proven responsive to targeted therapy. Alterations affecting the splice sites of MET exon 14 have been identified, which cause exon skipping, MET activation, and predict sensitivity to MET inhibitors in vitro. We undertook comprehensive genomic profiling (CGP) of a large series of advanced cancers to identify MET exon 14 alterations. Methods: DNA was typically extracted from 40 microns of FFPE sections from 34,735 cases examined between April 2012 and January 2015. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of > 500x. All classes of genomic alterations (GA) were evaluated. Results: CGP of 34,735 patients identified 200 cases harboring METex14 alterations. The alterations in diverse sequence composition, with > 100 distinct sequence variants represented. The 200 patients had a median age of 68.2 years (range 15-83), with 86 males and 114 females. The cases were comprised of lung carcinoma (173), carcinomas of unknown primary (14), brain glioma (6), and one each of adrenal cortical carcinoma, hepatocellular carcinoma, melanoma, Merkel cell carcinoma renal cell carcinoma, rhabdomyosarcoma, sarcoma NOS, and synovial sarcoma. The majority were stage IV. Identification of this alteration via CGP in routine clinical care has led to treatment with MET inhibitors such as crizotinib, and to durable partial responses or better exceeding 3 months in histiocytic sarcoma (1), sarcomatoid lung carcinoma (1), and nsclc (1+1). Multiple patients (5+) have initiated treatment on either crizotinib or MET inhibitors in clinical development, and additional outcome data will be reported. Conclusions: MET exon 14 alterations define a hereto unrecognized population of advanced cancers. Early reports of patients demonstrate cases harboring such alterations are responsive to multiple small molecule MET inhibitors. This finding expands the population of advanced cancer patients who can derive benefit from MET-targeted therapies.

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11008 Oral Abstract Session, Mon, 3:00 PM-6:00 PM Altering the tumor microenvironment: A phase II study of copper depletion using tetraiodomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence. First Author: Nicole Naccys, New York Presbyterian Hosp-Weill Cornell, New York, NY Background: Bone marrow derived endothelial progenitor cells (EPCs) and copper-dependent pathways are critical components to remodeling the tumor microenvironment and creating the pre-metastatic niche. Copper depletion (CD) inhibits tumor metastases in preclinical models. We hypothesized that TM-associated CD would reduce EPCs and other copper dependent processes in the pre-metastatic niche in BC pts at high risk for relapse. We investigated the relationship between CD and its effect on EPCs and other components of the tumor microenvironment including lysyl oxidase (LOX). Methods: In this single arm, phase II study, BC pts at high risk for recurrence, defined as node+ triple negative (TN), stage 3 and 4 with a median time from diagnosis of 5 years were enrolled on a trial of CD with TM. We utilized TM to maintain ceruloplasmin (Cp) between 5-17 mg/dl until end of treatment or relapse. The primary endpoint was change in EPCs measured by flow cytometry before and during treatment with TM. Secondary endpoints included tolerability, safety, and its effect on other markers including LOX. Results: We enrolled 75 pts. The study treatment duration was 24 cycles (28 days each). Over 2021 cycles have been administered. The median age is 51 (range 29-66). 45 pts have Stage 2/3 BC and 30 are Stage 4 NED. 48% of pts have TNBC, and 40% of pts are Stage 4 NED. Median Cp level decreased from 28 at baseline to 16 (p < 0.0001) after one cycle. Copper depletion was associated with a decrease in Cp. A was well tolerated and the only grade 3/4 toxicities were reversible neutropenia (2.5%) and anemia (0.04%). CD was associated with a significant decrease in EPCs (p < 0.0001) and LOX (p < 0.001) in the 2 year analysis; the 5 year analysis is ongoing. The PFS for all 75 pts from the start of TM treatment was 81% including a PFS of 94% for all stage 2/3 pts with TNBC at median f/u of 5.6 yrs. The hazard ratio for relapse is zero at two years. Conclusions: TM is safe, well tolerated and appears to affect multiple components of the tumor microenvironment creating an inhospitable environment for tumor progression. This seems to be most striking in TNBC. Further phase III trials are warranted. Clinical trial information: NCT00195091.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Imaging peritoneal metastasis of gastric cancer with PET/CT and the radiotracer 18F-fluorothymidine (18F-FLT): Proof-of-concept study. First Author: Yoshitaka Honma, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan.

Background: Peritoneal metastasis (PM) is the most frequent form of metastasis in gastric cancer (GC), especially in diffuse type adenocarcinoma (DTAC). Microscopic PM can be identified accurately only in laparoscopic staging. The utility of metabolic imaging for GC is limited because DTAC are not 18F-fluorodeoxyglucose (FDG) avid, and the sensitivity of detecting PM by FDG/PET is known to be low in GC. 18F-fluorothymidine (18F-FLT) was developed for imaging cellular proliferation, and its physiological accumulation to the intestinal tract is known to be less than FDG. In previous reports, 18F-FLT-PET had higher sensitivity than FDG and could visualize the primary lesion or lymph node metastasis of GC with sufficient contrast, even in DTAC. In this proof-of-concept study, we explored the capability of 18F-FLT PET/CT for detecting macroscopic PM of GC. Methods: The key eligibility criteria were: (i) histologically proven gastric adenocarcinoma; (ii) PM detected by CT imaging; (iii) PS: 0-2; and (iv) sufficient organ function. 18F-FLT PET/CT was performed at the National Cancer Center Hospital, and the PET/CTs were interpreted by two independent radiologists who were not informed of the patient background. Detection sensitivity (DS) was defined as proportion of patients for whom 18F-FLT PET/CT noted at least one of the lesions detected in CT. Results: DS of 18F-FLT PET/CT was 73.7% for all patients and 80.0% for those not receiving prior chemotherapy. One patient was diagnosed as gastric lymphoma by pathological review, who was excluded from the analysis. Fifteen of 19 patients (78.9%) had DTAC. PM was detected by 18F-FLT PET/CT in 14 of 19 patients (SUVMAX: 1.697-13.21, DS = 73.7%). Classifying the patterns of PM into omental-cake-type and nodule-type, 7 of 14 patients (50%) were oPM, all of which were detected by 18F-FLT PET/CT (SUVMAX: 1.771-13.21, DS = 100%). Meanwhile, in a total of 42 nodules detected by CT in the 12 patients with nPM, 20 nodules were detected by 18F-FLT PET/CT (SUVMAX for positive cases: 1.697-6.524, DS = 47.6%). Conclusion: This proof-of-concept study clear the criteria of DS by 18F-FLT PET/CT for proceeding to the future study investigating clinical utility of 18F-FLT PET/CT for PM of GC. Clinical trial information: UMIN000009329.
A head-to-head comparison of Mammaprint and Oncotype Dx: A McGill University Health Center Experience. First Author: Ralph Maroun, Department of Oncology, McGill University Health Center, Montreal, QC, Canada

Background: The objective of our study was to investigate the concordance of patient results from a single university centre tested with the 21-gene recurrence score assay, Oncotype DX (ODX) when compared to the 70-gene signature Mammaprint (MP), the 80 gene signature of BluePrint (BP) and TargetPrint (TP).

Methods: Eighty-six consecutive patient-slides node negative hormone positive breast cancer tissue tested with the ODX were enrolled. Based on the ODX recurrence scores (RS) patients were placed either on Chemotherapy and hormonal therapy or hormonal therapy alone. MP was performed on all of the slides previously tested with ODX, and results were reported as either Low or high recurrence risk and were compared with those of the ODX. Results: Of the 50 ODX low RS cases, 33 were low risk by MP (66 % agreement) and of the 9 ODX high RS, 7 were high risk by MP (78% agreement). Of ODX intermediate risk cases (27), 14 of were MP Low risk (52 %), (48 %) 13 were MP high risk. Of BP low risk luminal tumors, 33/49 (67%) were ODX low, 14/49 (29%) ODX intermediate, and 2/49 (4%) ODX high Risk (Table). BP class was correlated with ER, PR and HER2 results. Overall agreement between clinical ER, PR, HER2 (IH3 + FISH) results with TP results were 98% (81/83), 83% (69/83), 99% (82/83), and percent positive agreement for HER2 was 91% (of unequivocally HER2 positive cases identified correctly by TP). Conclusions: Results from our institution show that they are real differences in risk assignments between BP and MP that may affect treatment decisions. There was close correlation between pathologic variables and MP and BP. These results underscore the need for a proper validation of the ODX and MP genetic signatures with outcomes in order to avoid misclassification of both low and high risk patients.

ODX vs. MP.

<table>
<thead>
<tr>
<th>Oncotype</th>
<th>Mammaprint</th>
<th>BluePrint</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
<th>Total</th>
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<tr>
<td>High risk MP</td>
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<tr>
<td>Luminally</td>
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<td>0</td>
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11109

Poster Discussion Session; Displayed in Poster Session (Board #231), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Prospective study comparing outcomes in patients with advanced malignancies on molecular alteration-matched versus non-matched therapy. First Author: Jennifer J. Wheler, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX

Background: With the paradigm shift to precision medicine, we hypothesized that matched patients to therapy based on molecular profile could significantly improve outcomes. Methods: Archival tissues from patients treated in MDACC's Phase I clinic were sent to Foundation Medicine, where next-generation sequencing (NGS)-based comprehensive genomic profiling (236 genes) was performed. Patients with actionable molecular alterations were preferentially treated on pathway-matched therapies. A direct match was defined when the drug targeted an alteration or its immediate downstream effector, an indirect match, when the drug targeted a protein > 1 effector removed from the alteration. Based on matching and the number of alterations in patients’ tumors, an exploratory scoring system was evaluated; each direct match was given a 1, each indirect match 0.5, and no match a value of zero, normalized by the number of alterations per patient. Progression-free survival (PFS) and overall survival (OS) were analyzed (Kaplan-Meier method; log-rank test). Results: Of the 50 ODX low RS cases, 33 were low risk by MP (66 % agreement) and of the 9 ODX high RS, 7 were high risk by MP (78% agreement). Of ODX intermediate risk cases (27), 14 of were MP Low risk (52 %), (48 %) 13 were MP high risk. Of BP low risk luminal tumors, 33/49 (67%) were ODX low, 14/49 (29%) ODX intermediate, and 2/49 (4%) ODX high Risk (Table). BP class was correlated with ER, PR and HER2 results. Overall agreement between clinical ER, PR, HER2 (IH3 + FISH) results with TP results were 98% (81/83), 83% (69/83), 99% (82/83), and percent positive agreement for HER2 was 91% (of unequivocally HER2 positive cases identified correctly by TP). Conclusions: Results from our institution show that they are real differences in risk assignments between BP and MP that may affect treatment decisions. There was close correlation between pathologic variables and MP and BP. These results underscore the need for a proper validation of the ODX and MP genetic signatures with outcomes in order to avoid misclassification of both low and high risk patients.

Outcome by therapy and scoring system.

<table>
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<th>Treatment</th>
<th>Patients (n = 175)</th>
<th>Median PFS (months)</th>
<th>p-value</th>
<th>Median OS (months)</th>
<th>p-value</th>
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</thead>
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<td>10.8</td>
<td>0.018</td>
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<tr>
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Circulating tumor cell (CTC) EMT and stem cell biomarker expression predict overall survival (OS) in mCRC by a combined immunomagnetic qRT-PCR approach. First Author: Yany Ning, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Background: CTCs harboring epithelial, mesenchymal and stem cells direct the metastatic process. CTC enumeration and biomarker expression have been associated with clinical outcomes in mCRC patients (pts). We developed and validated a combined immunomagnetic qRT-PCR protocol for colorectal CTC characterization based on epithelial, EMT, and stem cell biomarkers with sufficient sensitivity, specificity, and efficiency. The goal of this study was to test whether molecular characterization of CTCs will more effectively predict OS. Methods: CTCs were obtained from 94 pts with mCRC Median age: 64 (46-86) years, 34 (36%) were women, 92 were stage IV, and OS: 11.4 (9.0, 21.1) mos. All pts were refractory to standard treatments and were enrolled in clinical trials at USC from 2009 to 2014. Prior to treatment initiation, peripheral blood was collected for CTC isolation. Immuno-magnetic qRT-PCR was used for CTC detection based on the presence of CK20 and survivin gene expression. We then selected, based on functional roles and reliability of detection in CTCs, and quantified markers of EMT (PI3Ka, Akt-2) and stem cell (ALDH1) pathway activation in CTC-positive mCRC pts with AdmaGen primer mixture. Cut-off values were determined by Receiver-operating characteristic (ROC) curves. Results: 74 of 94 (79%) pts with CTCs based on a combined qRT-PCR EMT and stem cell biomarker expression (CTC-positive group) had a significantly worse OS (10 mos v. not yet reached;) compared with the CTC-negative group (21%) in both univariate (HR:3.383 [1.04, 11.01], P = 0.001) and multivariate analyses (HR: 4.557 [1.097, 18.926], P = 0.037). All CTC-positive pts, with matched (6%) and 85% identified and ALDH1 (26.3 mos) and independent, independently predicted OS based on cut-off values of each marker. Higher gene expression associated with significantly worse OS compared to those with lower gene expression: PI3Ka: 6.4 v. 10.4 mos; Akt-2: 8.6 v. 23.6 mos; ALDH1: 7.8 v. 10.3 mos (P < 0.001 for all comparisons). Conclusions: OX2 positivity is the first to demonstrate that gene expression signature of this CTC EMT and stem cell gene signature in mCRC pts. This technology may allow real time molecular monitoring of drug efficacy.

11180

Poster Discussion Session; Displayed in Poster Session (Board #232), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Comprehensive genomic profiling of sarcomas from 267 adolescents and young adults to reveal a spectrum of targetable genomic alterations. First Author: Deborah Morosini, Foundation Medicine, Inc., Cambridge, MA

Background: Sarcomas comprise nearly 10% of all cancers (CA) in adolescents and young adults (AYA, age 15-39). Despite high unmet clinical need for better treatments, comprehensive genomic profiling (CGP) of AYA sarcomas has not been reported. To identify the genomic alterations (GA) and potential therapeutic targets, we performed CGP on 267 AYA sarcomas. Methods: DNA and RNA were extracted from 267 AYA sarcomas. CGP was performed on hybridization-captured libraries to a mean coverage depth of > 500X for 405, 315, or 265 (DNA) and 333 (RNA) CA-related genes, plus select intronic regions frequently rearranged in CA. Results were analyzed for base substitutions, insertions/deletions, copy number alterations, and fusions/rearrangements. We compared pediatric (peds) (n = 51), AYA (n = 267) and > 39yo (n = 853) patients and complex karyotype driven (CKD) versus fusion driven (FD) subtypes. Results: In AYA sarcoma, the most common GAs were in TPS5 (25%), CKD2N4 (16%), and EWSR1 (12%). An average of 37% had a GA. Clinically relevant GAs (associated with approved drugs or mechanism based trials) were present in 60% of cases. Cell cycle alterations (CCND1,2,3, CCNE1, CDK4/6, CDKN2A/B, RB1) were enriched in > 39 yo (53%) vs AYA sarcomas (33%, p < 0.001, Fisher’s exact test), Comparison of CKD and FD AYA sarcomas revealed differing frequency by age grouping. CKD sarcomas were less frequent in the AYA group (15%) compared to either the peds (20%) or > 39 yo (22%). FD sarcomas seem more frequent in AYA tumors (5%) vs > 39 yo (0.5%), but less frequent than in the peds (35%). FD tumors were enriched for GA in EWSR1 and SS18 corresponding to the frequency of Ewing and synovial sarcoma, respectively, seen in AYA CA. Novel fusions were also found, such as a LNMW1-NTR1 fusion in a YA with metastatic sarcoma, enabling enrollment in a clinical trial of NTRK-specific therapy. Conclusions: A combined DNA and RNA CGP assay can characterize tumor specific GA in AYA sarcomas and guide novel treatment decisions. Further use of this assay in these patients has the potential to increase AYA enrollment in clinical trials of targeted therapies and lead to improved outcomes for these aggressive forms of CA.
Comparison of tumor-infiltrating lymphocytes between primary and metastatic tumors in breast cancer patients. First Author: Rin Oguya, Tokai University, School of Medicine, Japan. Viewed: In-situ hybridization.

Background: The assessment of tumor-infiltrating lymphocytes (TILs) in primary breast cancer allows to predict prognosis and chemotherapy benefit, particularly in triple-negative (TN) and HER2-positive breast cancer. In the latter, it predicts also benefit from HER2-targeted agents. A little is known about the change of TILs during the metastatic progression. We compared TILs in paired samples from primary and metastatic TN and HER2-positive tumors. Methods: We retrospectively identified 25 patients with triple-negative or HER2-positive early breast cancer diagnosed between 1990 and 2010 at a single institution and subsequently experienced a distant recurrence confirmed by tumor biopsy/resection. Hematoxylin- and eosin-stained slides for these paired match cases were evaluated for stromal-TILs in paired samples from primary and metastatic TN and HER2-positive tumors. Results: We evaluated 25 breast cancer patients (n = 11 TN; n = 14 HER2+). Primary tumors had 28% (LPBC), 52% (intermediate-TIL) and 20% (low-TIL). Corresponding first metastatic recurrences had 64% (intermediate-TIL) and 56% (low-TIL). Overall, TILs in primary tumors were significantly higher (average 34.6%) than at metastatic recurrences (average 15.7%) (paired t-test, p = 0.004). This difference was similar in HER2+ (p = 0.036) and TN (p = 0.06). In 13/25 (66%) cases the percentage of TILs decreased and in 3/25 increased (difference >10%). We performed an exploratory analysis of post-progression overall-survival according to TIL at distant site of recurrence. The group with low-TIL had a significantly lower overall-survival than intermediate-TIL (HR = 3.77, CI 95% 0.99-14.9; logrank test p = 0.038).

Conclusions: Tumor at first metastatic recurrence in TN and HER2+ breast cancer had lower infiltrating-lymphocytes compared to primary tumors, supporting a role for immune escape in tumor progression. Low-TIL at recurrences seemed to be associated with worst overall survival suggesting a more aggressive phenotype. These findings warrant independent confirmation.

Complications following immediate breast reconstruction and influence on breast cancer recurrence rates. First Author: Suzanne M Beecher, University Hospital Galway, Galway, Ireland.

Background: The rate of immediate breast reconstruction has risen over the past number of years. Post-operative infections are more frequent in patients who undergo reconstruction. The inflammatory response to a postoperative infection can increase the risk of tumour recurrence in other forms of cancer through the release of pro-inflammatory mediators. The aim of this study was to assess the relationship between complications and breast cancer recurrence in patients who undergo immediate breast reconstructive surgery. Methods: A review of a prospectively maintained database of all patients who had immediate breast reconstruction between 2004 & 2009 was conducted. All patients had a minimum 5-year follow up. Univariate & multivariate Cox Regression analysis was performed using SPSS v21. Results: 229 patients who underwent immediate breast reconstruction were identified. The overall 5-year disease-free survival was 86%. 53 (23%) patients had wound complications. 43 (19%) had a wound infection. There was a significantly greater risk of developing systemic recurrence in patients who experienced a post-operative wound complication compared to those without (HR: 4.94; 95% CI: 2.72 - 8.95; P < 0.00001). The five-year disease free survival rate for patients who had a wound complication was 64% compared to 91% in patients without a complication (p < 0.0001). Conclusions: This study demonstrates that wound complications after immediate breast reconstructive surgery may have survival implications for breast cancer patients. Further research is warranted to confirm this relationship. In addition, strategies are required to minimize the risk of post-operative wound complications in breast cancer patients undergoing reconstruction.
Circulating tumor DNA (ctDNA) as a prognostic marker for recurrence in resected pancreatic cancer.

**First Author:** Judy Sing-Zan Wang, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

**Background:** Despite aggressive therapeutic interventions with pancreati-coduodenectomy and adjuvant chemotherapoy, recurrence rates remain high for patients with resectable pancreatic cancer. Additionally, current post-operative surveillance methods including tumor marker CA19-9, clinical symptoms, and CT scans lack sensitivity and specificity for early recurrence. Hence, a practical, blood-based biomarker that could identify cancer at an earlier time point, and prompt a change in management, would be clinically important. **Methods:** Using a highly sensitive digital DNA quantification approach, we measured KRAS mutation-associated circulating tumor DNA (ctDNA) in the archived sera of 46 resected pancreatic adenocarcinoma patients taken 8-10 weeks post-operatively, after confirming the mutational presence in the primary tumor. Approximately 10 years of patient data were available from chart review and clinical databases to assess disease recurrence. A mutant allele fraction > 0.02% was considered positive. **Results:** In a subgroup analysis, patients whose tumor had a p.G12V KRAS mutation and who did not have detectable levels of ctDNA had significantly longer time to disease recurrence than did patients with detectable ctDNA (p = 0.02; CI 1.037 to 12.77). Amongst patients whose tumor harbored a p.G12R KRAS mutation, those with undetectable ctDNA also had significantly longer time to disease recurrence as compared to those with detectable ctDNA (p = 0.01; CI 1.241 to 36.99). In combination, 14 of the total 46 patients who had undetectable ctDNA following their resection trended, though statistically insignificant, towards longer time to disease recurrence (median time 545 to 471 days; HR = 0.58; p = 0.3) including 3 ctDNA-negative patients who still remain disease free. **Conclusions:** This retrospective analysis demonstrates that ctDNA can be detected in peripheral blood, and may be a valuable clinical biomarker for specific tumor mutations. Additional larger, prospective studies are needed to validate the clinical utility as a prognostic biomarker for recurrence in resected pancreatic cancer.

Subclassification of prostate cancer circulating tumor cells (CTCs) by nuclear size reveals very small nuclear CTCs in patients with visceral metastases.

**First Author:** Yi-Tsing Lu, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

**Background:** In prostate cancer (PCa), morphologic classification remains a standard clinical practice in pathology. It has been shown that nuclear size and shape in tumor sections correlate with distant metastasis and death, but this relationship has not been explored in emerging tissue sources such as circulating tumor cells (CTCs). Using NanoVelcro chip, our group sub-classified CTCs in PCa patients by shape features focusing on nuclear size and related this to clinical information, particularly the lethal progression to visceral metastasis (VM). **Methods:** A total of 148 blood samples were obtained from 57 PCa patients across the spectrum of metastatic states: no metastases, non-Visceral (osseous and/or nodal) metastases, and visceral (hepatic and/or pulmonary) metastases. CTCs captured and enumerated on NanoVelcro Chips were subjected to pathologic review including nuclear size. The distribution of nuclear size was analyzed using a Gaussian Mixture Model. Correlations were made between CTC subsets and metastatic status. **Results:** Statistical modeling of nuclear size distribution revealed 3 distinct subgroups: large-nuclear (> 15 μm), small-nuclear (snCTCs, 8.54 - 15 μm), and very-small-nuclear CTCs (vsnCTCs, < 8.54 μm). The proportions of the 3 CTC nuclear subsets varied significantly among different metastatic states (p < 0.001). snCTC + vsnCTC identified patients with metastatic disease from those without (0.35 ± 0.66 versus 2.02 ± 3.36 cells/mL of blood, p < 0.001), vsnCTC counts also correlated with liver involvement with VM when compared to those without (0.36 ± 0.69 vs. 1.95 ± 3.77 cells/mL blood, p < 0.001). Serial enumerations suggested the emergence of vsnCTCs prior to radiographic detection of newly developed VM. **Conclusions:** There are morphologic subsets of CTCs that can be identified by fundamental pathologic procedures, such as nuclear size, that may provide a clinically significant biomarker for disease progression.

Molecular profiling of circulating tumor cells in non-metastatic breast cancer.

**First Author:** Victoria Forte, Norris Comprehensive Cancer Center, Los Angeles, CA

**Background:** Circulating tumor cells are prognostic in all stages of breast cancer (BC), yet few studies have examined their molecular biology in non-metastatic BC. We have previously reported a method for isolation and gene expression profiling of pure CTCs that permits gene expression profiling without background subtraction of leukocytes. We hypothesized that transcriptional profiling of CTCs prior to therapy may predict for pathologic complete response (pCR) to neoadjuvant chemotherapy (NC) in Stage II-III breast cancer. **Methods:** We are currently enrolling patients to a prospective, observational clinical study in which CTCs are enumerated and captured from 20 mL peripheral blood (PB) via immunomagnetic enrichment based on EpCam followed by fluorescence-activated cell sorting (FACS). CTCs and tumors are profiled with RNA Seq via the Illumina HiSeq (primary predictor); NanoString PAM50 and real-time polymerase chain reaction will be used as validation studies. **Results:** To date, we have isolated CTCs from 29/33 patients (88%). No CTCs were found in 23 healthy controls. The median number of CTCs isolated was 7 (range 0-65). We will analyze our primary endpoint when n = 20 and n = 40 NC treated patients. Currently 12/33 patients had NC and 21 had no NC; 10/12 patients had CTCs isolated and 5/10 patients had a pCR. RNA Seq of the first 17 patients CTCs shows clear differentiation between CTCs and PB with 253 differentially expressed genes with a fold-change of at least 2 (false-discovery rate adjusted p < 0.001). A gene set enrichment analysis of the 17 CTC samples demonstrated up-regulation of cancer related pathways (p < 0.001). RNA Seq and validation studies of additional CTC and tumor samples is currently in progress. **Conclusions:** RNA Seq of rare CTCs is feasible in Stage II-III breast cancer and shows evidence of oncogenes and tumor suppressor genes.
Applying a mitotic index to circulating tumor cells and its prognostic significance: A cytological approach to patient stratification. 

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**Background:** It has been well documented that enumeration of Circulating Tumor Cells (CTCs) isolated from the peripheral blood of breast cancer patients can be used as a prognostic indicator of survival. Typically, CTC identification relies on immunohistochemical stains used in an absent/present method (i.e. CK+/CD45-). However, the methodology for identification of CTCs is highly subjective, and histological cytology remains the standard identifier of cancer cells. We expand upon our work regarding the cytological criteria of CTCs, Adams et al., Cytometry 2015. CTCs were further subtyped by 1) number of pathologically definable CTCs (PDCTCs) and 2) presence of mitotic events, identified by standard visual cues (e.g., prophase, anaphase, etc.). Kaplan-Meier plots and Hazard ratios were determined at 24 months. 

**Results:** PDCTCs were found in 87% (26 of 30) of patient samples tested. Of the 14 patients who had >5 CTCs/7.5mL, 36% (5 of 14) survived 24 months. Of the 16 patients who had <5 CTCs/7.5mL, 81% (13 of 16) survived 24 months. By contrast, 12% of the 30 patients who had ≥1 CTC with a mitotic event, 17% (2 of 12) survived 24 months. Of the 18 patients who had no mitotic CTCs, 89% (16 of 18) survived 24 months. 

**Conclusions:** Stratification of breast cancer patients based on number of CTCs is a prognostic indicator of patient survival. Our data suggests that prognostic value is increased by subtyping CTCs based on their mitotic index as assessed by overall survival over a 24 month period.

**Background:** Almost 50% of melanomas harbor mutations in BRAF, mainly V600E. The mutations are usually identified in the primary tumor. However, the primary tumor is often no longer available and metastases not always reflect the characteristics of the primary tumor. In melanoma it is not clear whether these cells belong to melanoma clone due to the presence of the BRAF gene mutation in these cells. For this reason, the analysis of multiple isolated CTCs from individual patients for BRAF gene mutations was performed. 

**Methods:** Blood from patients with malignant melanoma was analyzed for cells positive for the EpCAM and Melan-A using the maintrac approach, avoiding cell selection and using an image analysis system for detection. Subsequently, between 8-20 EpCAM and Melan-A positive cells from each patient were isolated individually using a semi-automated capillary approach and deposited one by one into micro cups. The DNA of individual cells was amplified by whole genome amplification and assayed using the cobas BRAF V600 mutation test. Furthermore, we performed mutation analysis of cells after magnetic bead enrichment which is known to contain a mixture of CTCs and leukocytes. 

**Results:** DNA could be amplified from all individually isolated cells. In addition, we analyzed the presence of V600 BRAF mutation in plasma after magnetic bead enrichment. A BRAF V600E mutation was detected in 20 - 75 % of evaluable cells in patients with BRAF mutation in primary tumor. In advanced stage or metastatic patients under Vemurafenib therapy, we were not able to find mutated CTCs. 

**Conclusions:** Individually isolated CTCs from the peripheral blood from patients with melanoma allow not only to detect mutations but also to determine the frequency of mutated cells. This proves that at least part of the CTCs is originated from the primary tumor. Furthermore, detection of BRAF mutation in CTCs may be crucial for a successful molecular-targeted therapy.

**Background:** Circulating tumor cells are a real-time reflection of the ad hoc relevant subpopulation in patients with progressive disease. The study comprises the clinical application of a liquid biopsy to assess the PIK3CA genotype at a single cell level. 

**Methods:** Using CellSearch and DEPAarray we purified single and groups of CTCs and WBCs from peripheral blood in 29 patients with metastatic hormone receptor-positive breast cancer. 

**Background:** Folate Receptor-Positive Circulating tumor cell detected by LT-PCR based method as a diagnostic biomarker for non-small cell lung cancer. 

First Author: Xiaoxia Chen, Tongji University Medical School Cancer Institute, Shanghai, China

**Background:** To investigate the diagnostic performance of folate receptor (FR) positive circulating tumor cells (CTCs) in distinguishing non-small cell lung cancer (NSCLC) from lung benign disease by using a novel ligand-targeted polymerase chain reaction (LT-PCR) detection technique. 

**Methods:** CTCs were enriched from 3ml peripheral blood by immune-magnetic depletion of leukocytes and then labeled with a conjugate of a tumor-specific ligand folic acid and a synthesized oligonucleotide. After washing off free conjugates, the stripped bound conjugates were analyzed by quantitative PCR. 

**Results:** 756 participants (473 patients with NSCLC, 227 patients with lung benign disease, and 56 healthy donors) were randomly assigned to a training set and a test set. The CTC levels in patients with NSCLC were significant higher than those with lung benign disease (P < 0.001) and healthy donors (P < 0.001). Compared with CEA, NSE, and Cyfra21-1, CTCs displayed the highest area under curve (AUC) (training set: 0.815; validation set: 0.813) in the diagnosis of NSCLC, with a markedly sensitivity (training set: 72.46%; validation set: 76.37%) and specificity (training set: 88.65%; validation set: 82.39%). The model combining CTCs with CEA, NSE, and Cyfra21-1 was more effective for the diagnosis of NSCLC than tumor makers alone (sensitivity and specificity in the training set: 84.21%, 83.91%; validation set: 88.78%, 87.36%). In addition, the CTC levels were higher in patients with stage III/IV NSCLC compared with those with stage I/Ii disease. 

**Conclusions:** LT-PCR technique was feasible and reliable for detecting FR-positive CTCs in NSCLC patients and CTC levels could be used as a useful biomarker for the diagnosis of NSCLC.
Background: Basing on preliminary observations of OPUS and PRIME studies, our group retrospectively suggested that KRAS mutational status could affect response to oxaliplatin. We further confirmed this evidence in vitro demonstrating that KRAS mutated cell lines were more sensitive to oxaliplatin due to their inability to induce ERCC1 after drug exposure. Using CTCs as a surrogate, dynamic tissue, in this study we sought to confirm in vivo the relationship between KRAS mutational status, ERCC1 induction and clinical outcome in oxaliplatin-treated colorectal cancer patients.

Methods: We collected blood samples from colorectal cancer patients treated with oxaliplatin-based regimen at 0 and 48 hours during the first cycle of chemotherapy. The presence of CTC was detected by AdnaGene system followed by multiplex RT-PCR including ERCC1 transcript. In CTC-positive ERCC1-positive patients, ERCC1 mRNA expression was measured using a quantitative real time RT-PCR method, before and after drug exposure. We evaluated the relationship between ERCC1 induction and KRAS mutational status and we tried to correlate this association with clinical outcome.

Results: On a total of 38 patients enrolled, 19 were KRAS wild type and 19 KRAS mutated. CTCs were detected in 12 (31.5%) patients. ERCC1 was expressed in 8/12 CTCs-positive patients, 5 KRAS wild type and 3 mutated. After Oxaliplatin exposure, among ERCC1-positive patients, only 3 showed a significant induction of ERCC1 expression; interestingly all of them were KRAS wild-type and experienced a rapid progression of disease. The median PFS of patients with ERCC1 induction was shorter than that observed in patients with stable or reduced ERCC1 (2.5 months vs 7.2 months). Notably, out of 21 patients, 12 with stable or reduced ERCC1 after Oxaliplatin therapy. ERCC1-induce CTCs was able to induce ERCC1 and median PFS was 11.6 months.

Conclusions: Although based on a small sample size, this study could support the relationship between KRAS mutational status, ERCC1 inducibility, and clinical outcome, corroborating our hypothesis that KRAS mutational status could be a surrogate marker of efficacy of oxaliplatin therapy. Further studies are warranted to study this association.
Background: Adjuvant chemotherapy is a standard therapy for gastric cancer patients, however, treatment response is quite heterogeneous. Molecular biomarkers will be highly valuable to guide the therapy. The antioxidant enzymes superoxide dismutase 2 (SOD2) and glutathione S-transferase pi 1 (GSTP1) are involved in oxidative stress and drug detoxification, which modulate the efficacy of anticancer drugs. Here, we investigated the clinical associations of two single nucleotide polymorphisms of SOD2 and GSTP1 in stage II-III postoperative gastric cancer patients. Methods: SOD2 rs4880 and GSTP1 rs16951 were genotyped in 207 patients received postoperative platinum and fluorouracil based chemotherapy and 304 patients who did not. The genotyping were examined in DNA samples extracted from paraffin-embedded tumor tissue. Association of the 2 SNPs with each clinicopathologic feature was analyzed using the Pearson chi square test. Gastric cancer-specific overall survival was analyzed using Kaplan-Meier curves and log-rank tests. Multivariate Cox regression analyses of these SNPs also were performed. Results: SOD2 rs4880 CT/CC genotype was significantly associated with decreased median overall survival time of 23 months when compared to the TT genotype (mean overall survival time of 65.2 months, P=0.002) only for patients received adjuvant chemotherapy. Stratification analysis showed SOD2 rs4880 CT/CC affected most significantly the clinical outcome for patients with tumor arising at gastric body (HR; 5.707, P=0.002), well to moderately differentiated adenocarcinoma (HR, 4.900, P<0.001), tumor of intestinal type (HR, 4.398, P<0.001), or tumor size less or equal to 5 cm (HR, 2.490, P=0.004); while GSTP1 rs16951 G/G was significantly decreased survival time among patients with tumor arising at fundus or cardia (HR, 3.001, P=0.004), or mucinous or signet-ring cell carcinoma (HR, 4.750, P=0.042). Conclusions: The present study suggested the two polymorphisms would affect the adjuvant chemotherapy outcome in specific subtype of gastric cancer. SOD2 rs4880 could be used as a biomarker to predict the prognosis and response to therapy.

Background: Toll-like receptors (TLRs) play crucial roles in carcinogenesis. We tested the hypothesis that genetic variations of TLR6 will modulate the efficacy of anticancer drugs. Here, We investigated the clinical associations of two single nucleotide polymorphisms of TLR6 and TLR9 in 543 mCRC patients enrolled in the FIRE3 trial and treated in first-line with FOLFIRI/bevacizumab. Conclusions: The TLR6 polymorphism associated with overall survival in metastatic colorectal cancer (mCRC) patients treated with FOLFIRI/bevacizumab enrolled in the FIRE3 trial. The polymorphism is associated with outcome in patients with wild type KRAS mCRC treated with bevacizumab based chemotherapy.

Background: The BREAC trial was a multicenter, retrospective study to investigate the novel biomarkers of anti-EGFR antibody therapy. RAS and BRAF mutations were detected by targeted sequencing using FFPE materials of mCRC pts who received anti-EGFR antibody after a failure to standard therapies. Progression-free survival (PFS), overall survival (OS), and response rate (RR) were evaluated according to expanded RAS/BRAF mutational status. Results: Of 184 pts enrolled in the study, RAS/BRAF testing was succeeded in 150 pts. Patients characteristics were as follows; male/female 87/63, median age 63.5 years (range, 28-85), PS 0/1/2 81/65/4. Median PFS, OS, and RR were 4.0 months, 12.4 months, and 21%, respectively. Expanded RAS and BRAF mutations were detected in 40 pts (26.7%, KRAS/NRAS 29/11) and in 16 pts (10.7%, BRAFV600E 9/7). Conclusions: Expanded RAS mutations might predict a lack of response for mCRC pts who received anti-EGFR antibody. Further investigation is warranted to confirm the clinical impact of expanded BRAF mutations.
Effect of mutant TP53 genotypes on the outcome of breast cancer (BC) patients in different clinical tumor subtypes. First Author: George Fountzilas, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece.

Background: Comprehending the clinical utility of the massively produced BC genomic data remains a challenge. Here, we examined the impact of BC genotypes on patient outcome with respect to clinical (immunohistochemical) tumor subtypes and treatment. Methods: Paraffin DNA from 1664 tumors (556 Luminal A, 439 Luminal B, 291 Luminal-HER2, 157 HER2-enriched and 221 triple-negative (TNBC)) yielded informative results upon targeted parallel sequencing for 58 genes. Patients had operable BC and had been treated in 4 prospective trials with adjuvant anthracycline-based chemotherapy in the pre- and post-trastuzumab (T) era. Analysis was performed in training and validation sets and in the entire cohort. Results: Eligible mutations (mut, n = 3086) were observed in 56 genes and were distributed in various combinations (1 to > 20 mutatn genes) in 1043 tumors (63%), PIK3CA mut were found in 466 (44%); TP53 in 420 (40%); GATA3 in 128 (12%); and, CDH1 in 121 (11.5%) tumors. PIK3CA mut were more common in Luminal A/B tumors (49%), while TP53 in HER2-positive (57%) and TNBC (73%) (all p < 0.001). Both PIK3CA and TP53 mut were observed in 7% of all tumors. TP53 mut conferred increased risk for relapse in patients with Luminal A/B (HR = 2.00; 95% CI 1.42-2.82; Wald p < 0.001) and TNBC (HR = 1.82; 95% CI 1.04-3.20; Wald p = 0.037). In the same context, PIK3CA mut were associated with favorable prognosis in the absence of TP53 mut; this effect disappeared in tumors with mut in both genes. In HER2-positive patients in the pre-T era, TP53 mut alone or in combination with PIK3CA mut did not interfere with outcome. By contrast, these mutant genotypes tended to confer decreased risk for relapse in patients treated with T (HR = 0.51; 95% CI 0.23-1.14; Wald p = 0.101). All described effects were equally significant in the training and validation sets. Conclusions: TP53 mutant genotypes are unfavorable prognosticators in Luminal A/B and TNBC patients, but may predict benefit in HER2-positive patients with operable BC treated with T. PIK3CA mut do not seem to interfere with patient outcome in the latter context. If validated in independent large studies, these findings may have important clinical implications.

Piwi-RNAs (piRNAs) are small non-coding RNAs (24-32 nt) that are key to understanding cancer biology. First Author: Nuria Vinolas, Hospital Clinic, Barcelona, Spain.

Background: Piwi-RNAs are part of a highly conserved class of small non-coding RNAs that are associated with epigenetic changes. Their role in cancer is not yet fully understood. Methods: Expression of piRNA-651 was evaluated by real-time PCR and by chromogenic in situ hybridization in paraffin-fixed cancer tissue samples. Results: piRNA-651 expression was analyzed from formalin-fixed paraffin-embedded samples of 590 patients with stage I-III surgically resected NSCLC between March 1996 and June 2007 in a single institution. TP53 and/or adjuvant treatment. The incidence of breast cancer and its molecular subtype are age-related. Patient age may be associated with breast cancer biology through subtype-determining genetic factors (e.g. BRCA1 germline mutation) or aging of the tissue of origin (e.g. telomere shortening or epigenetic modifications in breast epithelium). EZH2 catalyzes trimethylation of histone H3 at lysine 27 (H3K27me3), an epigenetic change playing a role in gene silencing and epigenetic co-incidences of associated biomarkers, which will be described. Of note, endometrial, breast, cervical, anal squamous cell, and bladder cancers had the highest PIK3CA mutation rate (37%, n = 1600; 31%, n = 2282; 29%, n = 284; 28%, n = 67, 22%, n = 303, respectively). Patterns in AKT1 and PTEN mutation rates differed by cancer, as did PTEN loss - hepatocellular, 57%, prostate, 52%, and endometrial 50% loss. Co-mutation of PIK3CA and AKT1 and PTEN mutations were collated across cancers. Conclusions: Patterns of biomarker co-alterations across cancers may provide new insights relevant to targeted therapy and may be crucial to optimizing combination treatments.
Identification of novel prognostic markers of glioblastoma using computational strategies on four genomic datasets. First Author: Haruka Itakura, Stanford Univ Medical Center, Stanford, CA

**Background:** We sought to discover novel biomarkers using computational strategies on four genomic/epigenomic datasets to improve prognostication in glioblastoma (GBM).

**Methods:** We obtained survival, clinical, gene expression, copy number variation (CNV), microRNA, and methylation data from The Cancer Genome Atlas on GBM subjects. Our study design was to fit Cox proportional hazards regression models using penalized maximum likelihood on the four datasets to predict overall survival, our analysis endpoint. We trained and tested our Cox models using 10-fold cross-validation on combined datasets created by three different integration strategies: concatenation, partial integration with double penalized maximum likelihood, and combination of weighted predictions from each dataset. We compared three, final Cox regression models using: 1) molecular features selected by the highest-performing integration strategy, 2) established risk factors (age, performance status (KPS), IDH1, MGMT, CIMP, and) 3) combined molecular and established features. **Results:** 243 subjects, who possessed survival and all four genomic datasets, were included for analysis. Selecting the top 25% varying genes, gene expression data contained 4453, CNV 5770, microRNA 534, and methylation data 4643 features. The integration strategy based on weighted predictions produced the highest performing prediction model (p = 0.0006). The final molecular feature only-model yielded a multivariable combination of 17 prognostic features (p = 3.89x10^-15). The established features model produced three prognostic features (p = 5.0x10^-8); age, gender, and KPS. In the combined molecular-established risk model, 11 molecular features (one gene expression, three CNV, four microRNA, and three methylation features) and three clinical features (age, CIMP status, and KPS) were prognostic (p = 1.7x10^-8). **Conclusions:** Using four genomic datasets and novel computational strategies, we identified 11 molecular features that could improve GBM prognostication beyond the current set of established risk factors. These features warrant closer investigation as novel markers for disease prognostication and targets for therapy.

Low frequency KRAS G12/13 mutations in urine cell-free (cf) DNA from patients with BRAF V600E-mutant advanced cancers. First Author: Filip Janku, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Tumor heterogeneity and clonal selection contribute to resistance to molecular targeted therapies. Dynamic tracking of urine cfDNA mutations can offer a non-invasive tool for monitoring therapeutic efficacy.

**Methods:** cfDNA was isolated from single or sequential urine samples from patients with advanced cancers and archival tumor tissue with BRAF V600E from a CLIA-certified laboratory. Assays for quantitative detection of BRAF V600E and KRAS G12/13 mutations in urine cfDNA were developed using digital droplet (dd) PCR and next generation sequencing. Analytical sensitivity of BRAF V600E and KRAS G12/13 assays is 0.03% and 0.006% mutant alleles in wild-type DNA background.

**Results:** Urine cfDNA was examined in 34 patients (melanoma, n = 11; colorectal cancer, n = 8; papillary thyroid carcinoma, n = 5; non-small cell lung cancer, n = 5; other, n = 5) with BRAF V600E in tumor tissue. 32 of 34 patients (94%) had the same mutation in urine cfDNA (mutant, n = 22; low-mutant, n = 10). Longitudinal analysis in 25 (74%) patients (treated with: BRAFi, n = 22; MEKi, n = 1; others) showed that changes in BRAF V600E cfDNA amounts correlated with percent changes in target lesions on imaging (p = 0.68, p < 0.001). Patients with decreased BRAF V600E cfDNA (n = 16) compared to others (n = 8) had a trend to a longer median time-to-treatment failure (8.8 months, 95% CI 1.8-9.5 vs. 2.2 months, 95% CI 0.4-11.6; p = 0.07) on BRAFi or MEKi therapy. Moreover, 6 (42%) patients had a low frequency KRAS G12/13 mutation (median 3.4 copies/10⁶ genome equivalents) in urine cfDNA that was previously undetected in tumor by CLIA, except in one case. 9 of 9 patients with urine examined at the time of progression had detectable cfDNA KRAS G12/13. Re-analysis of the retrieved archival tumor tissues from 8 patients found a previously undetected low frequency (1.3%) KRAS mutation in one sample by ddPCR.

**Conclusions:** Our results suggest that 65% of patients with advanced cancers and BRAF mutation in tumor tissue have low frequency KRAS G12/13 mutations in urine cfDNA undetected in tumor samples by standard CLIA technologies. Low frequency KRAS mutations can plausibly drive resistance to BRAF targeting agents, and therefore may be detected in urine cfDNA.
Prosigna (PAM50) to predict response to neoadjuvant chemotherapy (NAC) in HR+/HER2- early breast cancer (EBC) patients. First Author: Begona Jiménez Rodríguez, Fundación Pública Rehabilitación, Madrid, Spain

Background: Prosigna has been clinically validated in 2 large randomized studies to predict the risk of distant and late recurrence in HR+/HER2- patients treated with endocrine therapy, NAC efficacy is evaluated through pathological surrogates such as residual cancer burden (RCB) and pathological complete response (pCR), and this response has been correlated to improved survival. HR+/HER2- tumors typically have low rates of a genetic response, however, genomic tests may be able to differentiate between patients who would or would not respond to NAC. We evaluate the correlation between ProsignaROR score and response to NAC. 

Methods: Retrospective analysis was performed on FTFE HR+/HER2- breast tumors from EBC patients who were treated with a contemporary NAC regimen (antracyclines+taxanes) in a multi-center Spanish cohort. The Prosigna assay was performed on the NanoString nCounter Dx Analysis System at Hu Virgen de la Victoria. 

Comparisons were stratified by nodal stage: node negative (N0, n = 248), node positive (N+, n = 253). 

Results: 592s Tumor Biology 

Conclusions: Prosigna ROR reliably predicted response to NAC in this HR+/HER2- population. High-risk tumors were significantly more likely to respond to NAC than lower-risk tumors. The intrinsic subtypes were also predictive of chemosensitivity with Luminal A tumors being resistant to NAC, supporting the current St. Gallen consensus guideline where intrinsic subtype determines chemotherapy use.

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PD-L1/PD-1. Interestingly, they overexpress PD-L1 and may benefit therapies inhibiting a distinct entity with probably different involved oncogenic pathways. Inter-specific survival of 33 months (p < 0.0001), and in most of cases, characterized by an inactivation of the tumor suppressor gene VHL (Von Hippel-Lindau). This inactivation causes an overexpression of the target genes of HIF-dependent transcription factor. VHL/HIF/VEGF pathway thus has a major role in oncogenesis and is currently targeted by anti-VEGF therapy. The emergence of resistance leads to the development of immunotherapy. The interaction of programmed death-1 ligand (PD-L1) with its receptor (PD-1) on T cells inactivates antitumor immune responses. PD-L1 expression appears to be associated with poor outcome in ccRCC. The correlation between complete VHL status and the expression of PD-L1 has not yet been investigated. Methods: In this study, we correlated the expression of PD-L1 in 98 ccRCCs with pathological criteria, expression of PDL1 and clinical outcome. For these patients, we had 64 months median follow-up. From frozen tumor sections, VHL gene deletion, mutation and promoter hypermethylation were screened. PD-L1 expression was analyzed by immunohistochemistry on the highest Fuhrman nuclear grade and considered positive when any membranous tumor cell staining was detected. Results: 33.6% of ccRCCs had 0 or 1 alteration (no inactivated VHL) versus 66.3% with 2 inactivating events (inactivated VHL). Non inactivated VHL ccRCCs were associated with a higher Fuhrman grade 4 (p = 0.02), metastases (p = 0.04), sarcomatoid component (p = 0.01) and dense lymphocytic infiltrate (p = 0.013). Furthermore, in this group, wild type VHL tumors (no alteration of the VHL gene, 11.2%), were particularly associated with PD-L1 expression (p < 0.0001), and had a worse outcome with a median specific survival of 33 months (p = 0.016). Conclusions: This long-term study shows that wild type ccRCCs treated with bevacizumab released a cytokine mix that reduced monocyte migration in a bevacizumab dependent manner, showing a functional response with the combination of MMR deficiency and bevacizumab. CCL18 is a potential marker for the administration of bevacizumab in a clinical setting that is specific to bevacizumab treatment in combination with MMR deficient tumor cells via immune cell modulation.  

Detection of rare somatic mutational profiles in metastatic colorectal cancer (mCRC) during routine RAS sequencing using next generation sequencing (NGS). First Author: Jean-Louis Merlin, Institut de Cancérologie de Lorraine, Service de Biopathologie, CNRS UMR 7039 CRAN Université de Lorraine, Nancy, France  

Background: In most patients with mCRC who are being considered for anti-EGFR antibody therapy, RAS mutation testing i.e. KRAS and NRAS exon 2, 3, and 4 is routinely assessed using PCR-based assays only detecting major hotspot mutations of exon (ex) 2 (codon 12 and 13), 3 (codon 59 and 61) and 4 (codon 117 and 146). We performed deep sequencing of the entire exons using NGS as an alternative to detect additional rare mutational profiles with significant frequency of mutated allele (FMA). Methods: 188 formalin-fixed paraffin-embedded tumor samples from primary or metastatic lesions of patients (M/F sex ratio 1.27, mean age 69 years, range 32-90) with mCRC (150 colon, 38 rectum) were analyzed. DNA was extracted from macrodissected slides (mean tumor cell content 43.3%, range 5-80). Results: RAS mutation testing was routinely assessed using NGS in 177 mCRC samples. NGS could not be performed in 11 cases (6.2%) due to the insufficient quantity or quality of DNA. NGS sensitivity was 1% at X1000 depth. RAS mutations were found in 98 ccRCC samples (62%) and relatively distributed as 69.9% KRAS ex2, 3.9% KRAS ex3, 14.6% KRAS ex4, 4.8% NRAS ex2, 1.0% NRAS ex3, 1.0% NRAS ex4 and 4.8% multiple mutations. Uncommon mutational profiles were detected in 10 cases (9.7%): 2 KRAS ex2 c.37G>T p.G12C single mutation treated with FMA. 7 silent mutations (n = 3) with lower but significant FMA (> 1%), and 6 multiple mutation profiles among which 2 double hotspot mutation (KRAS ex2 c.34G>T p.G12D and NRAS ex3 c.181C>T p.G61K, KRAS ex2 c.34G>T p.G12D and NRAS ex2 c.38G>T p.Q13R). 1 secondary mutation associated with a KRAS ex2 c.35G>T p.A119D hotspot mutation, and 3 multiple mutations only with rare but potentially deleterious mutations located around the loops responsible for nucleotide (GTP) binding. In only 1 FMA, the FMA of the secondary mutation was < 1%. As a whole, 7 cases (6.8%) had RAS mutations out of hotspot, the conclusion that proved 13% of patients with mCRC to have a potential patient response to anti-EGFR antibody.  

First Author: Peter Conti, University of Southern California, Los Angeles, CA  

Background: To develop a practicable method of synthesizing [18F]-labeled 2’-deoxy-2’-fluoro-5-methyl-1-β-D-arabinofuranosyluracil ([18F]FMAU) for clinical investigation and study, we developed a new route to [18F]FMAU in patients with non-small lung cancer to obtain data on safety, circulating metabolite, tumor imaging feasibility, and radiation dosimetry. Methods: Various reaction factors, such as time, temperature, and solvent effect, were explored to optimize [18F]FMAU synthesis. A total of nine breast cancer patients were scanned. [18F]FMAU, 10 mCi i.v. injection in saline was administered to the patient through venous line. Multi-bed position PET scans over tumor-bearing region(s) were obtained, along with attenuation correction images, through-out the time period between 1 and 120 minutes post injection. Throughout the procedure, study staff monitored and recorded patient vital signs. Results: A simplified synthesis of [18F]FMAU with shorter synthesis time and higher radiochemical yield was achieved as compared to previously reported methods. The total synthesis time was about 90 min from the end of bombardment.Radiochemical purity was > 99% and specific activity was > 400 mCi/μmol. The PET imaging showed excellent primary breast tumor as well as metastatic disease uptake of [18F]FMAU. No adverse reactions were observed for all studied patients. No major circulating metabolites were identified in human blood at 1 h post injection of [18F]FMAU. The preliminary dosimetry of [18F]FMAU was estimated as 5.0 rem in liver (primary organ), 4.2 rem in kidneys (secondary organ), 0.76 rem in blood, 0.02 rem in bone, 0.54 rem in spleen, and 0.45 rem in gonads per single administration. Conclusions: A simplified one-pot synthesis of [18F]FMAU has been developed, which is well suitable for clinical investigations. Our pilot trial achieved its goals of obtaining data on safety, circulating metabolite, tumor imaging feasibility, and radiation dosimetry of [18F]FMAU in humans. The data provided a solid foundation for proceeding to larger clinical trials to confirm the utility of [18F]FMAU as an in vivo cell proliferation marker for non-invasively and serially estimating DNA synthesis in patients with cancer.
uptake between 1h and 2h was observed and no lesion was detected only at tively. Bone MRI had 94% sensitivity. Brain lesions were only detected by Overall sensitivity of CT and FDG-PET/CT was 74.6% and 84.7%, respec-

in brain. Overall sensitivity of immuno-PET was 93.8%, with 100% (9.5 to 1359.0). To date, 515 lesions were confirmed as pathologic by the

for off-label use of therapy approved in another condition, information

tions, gene fusions, and gene expression findings were reviewed at an

underwent comprehensive next generation sequencing (Illumina) of a

targets for therapy.

(120 nmol of unlabeled TF2 binding CEA) and 68Ga-IMP288 pretargeted by

body immuno-PET/CT at 1h and 2h after injection of 150 MBq of

is found to have germline mutations conferring increased cancer risk.

58% (26%) died within 5 months of enrollment. Conclusions: These
data demonstrate that comprehensive tumor genome analysis can identify

somatic aberrations within a tumor, which may identify alterations of biological relevance were identified in 176 cases (96%). 100 pts (95%)
had potentially actionable results. 79 samples (92%) received 1st-line palliative chemotherapy, there was no difference in PFS in

v concurrent chemo-XRT, there was no PFS difference for the

KRAS/TP53

significantly more Caucasians (96%

KRAS/TP53

Background:

Conclusion:

First Author: Pascale Tormasini, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada

Background:

Molecular interrogation of TEP-based liquid biopsies may leverage cancer diagnostics. TEPs provide a circulating biosource for pan-cancer, multiclass, and molecular cancer classification. Of interest, this tool might also allow for blood-based highly sensitive early-stage cancer screening.

Allowance of tumor-educated platelets for multiclass liquid biopsy-based diagnosis of cancer. First Author: Myron Best, Department of Neurosurgery, VU University Medical Center, Amsterdam, Netherlands

Background: Cancer diagnosis is frequently hampered by limited access to adequate tissue of the primary tumor or metastatic lesions. To overcome such limitations, the use of blood-based liquid biopsies has been suggested. Blood represents a biosource of tumor-educated platelets (TEPs) that sequester biomolecules during tumor growth, thereby altering the platelet mRNA profile. Methods: Blood platelet samples of 188 cancer patients covering six tumor types (40 non-small cell lung cancer, 39 glioblastoma, 37 colorectal cancer, 35 pancreatic cancer, 24 breast cancer, and 13 hepatobiliary cancer) and of 52 healthy donors were isolated from whole blood by differential centrifugation. RNA was isolated, subjected to SMARTer mRNA amplification and submitted for whole transcriptome mRNA sequencing in a Illumina platform. Here, we report the results of cancer, and individual cancer classes were distinguished by a self-

learning support vector machine (SVM) algorithm, using transcripts with moderate to high expression. Results: The 240 blood platelet samples were successfully sequenced and demonstrated a good intersample correlation of the detected mRNAs. Based on mRNA profiles, all tumor samples were clearly distinguished from healthy donors: the pan-cancer SVM-supported classification test reached a sensitivity of 97% and a specificity of 90% to distinguish cancer patients from healthy donors. Also, all patients without overt metastases were correctly predicted as cancer patients. Moreover, a multiclass cancer diagnostics TEP-test, to distinguish multiple tumor subclasses and healthy donors provided an overall accuracy of 73%, far exceeding random classification. In addition, we distinguished HER2-positive, and mutant KRAS and EGFR tumors from their wild-type counter-

parts. Also, patients with metastatic tumors in lung, brain, and liver were accurately diagnosed at the time of diagnosis. Early in the course of the study, many pts died shortly after enrollment. This experience led us to employ this strategy earlier in the therapeutic algorithm.

Improvement in imaging of metastatic breast cancer (BC) with a novel pretargeted immuno-PET targeting CEA: First clinical results. First Author: Caroline Rouesseau, ICO Cancer Center, Nuclear Medicine Department, Saint Herblain, France

Background: New phenotypic imaging with noninvasive antibody imaging methods targeting membranous antigens have been tested in BC trials. A new generation of immuno-PET comprising anti-CEA x anti-HSG humanized trivalent TF2 bispecific Mab and 68Ga-IMP288 HSG peptide is being assessed. This study aimed to compare the sensitivity of anti-CEA immuno-PET/CT comparing this immune-PET to morphological imaging and FDG-PET/CT in metastatic BC patients. Methods: Thirteen patients with metastatic BC enrolled in an optimization immuno-PET study had whole-body immuno-PET/CT at 1h and 2h after injection of 150 MBq of 68Ga-IMP288 pretargeted by 120 nmol of unlabeled TF2 binding CEA and thy-

EG peptide injected 24h to 30h before. Thoracic-abdominal-pelvic CT and FDG-PET/CT were also performed. The gold standard was determined by follow-up and a lesion detected by at least 2 imaging modalities was considered as positive. Results: Median serum CEA was 46.15 μg/L (9.5 to 1359.0). To date, 615 lesions were confirmed as pathologic by the gold standard: 18 in LN, 4 in lung, 94 in liver, 399 in bone, 1 in skin, and 4 in brain. Overall sensitivity of immuno-PET was 93.8%, with 100% sensitivity for bone, liver, skin, and brain, 94% for LN, and 37.5% for lung. Overall sensitivity of CT and FDG-PET/CT was 74.6% and 84.7%, respect-

ively. Bone MRI had 94% sensitivity. Brain lesions were only detected by immuno-PET/CT and confirmed by MRI. Median tumor SUVpeak was on immuno-PET at 1h and 2h was 9.58 (3.52 to 24.55) and 11.04 (3.09-34.27), respectively. In half of patients (7/13) an increased tumor uptake between 1h and 2h was observed and no lesion was detected only at 2h. Conclusions: These results demonstrate the high accuracy of anti-CEA pretargeted immuno-PET/CT for staging pts with metastatic BC, especially for bone, liver and brain evaluation. Immuno-PET allowed detection of bone lesions in areas not explored by MRI. Clinical trial information: NCT01730612.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Detection of low abundant somatic mutations in circulating exosomal RNA and cfDNA with next-generation sequencing. First Author: Vincent J. O’Neill, Exosome Diagnostics, Cambridge, MA

Background: Circulating nucleic acids (NA) in the bloodstream of cancer patients are of interest because of their potential to provide tumor mutation status without requiring a tissue sample. Blood plasma contains at least two sources of circulating cell-free NA: circulating free DNA (cfDNA), from apoptotic/necrotic cells, and RNA enclosed in exosomes (exoRNA), which are secreted by living cells through active metabolic processes. However, tumor derived mutated sequences are often of very low abundance against a background of wildtype. Therefore, efficient extraction of all available circulating NA as well as a highly sensitive mutation detection method, are paramount to development of clinically relevant liquid biopsies. Methods: We used a single-step isolation protocol for both exoRNA and cfDNA from plasma (EXO52) in combination with a quantitative NGS method detecting a panel of actionable mutations (EXO1000). The assay uses a PCR-based selection of 9 mutation hotspots from 6 genes, a custom library preparation protocol and bioinformatics pipeline. We analyzed mutations present in nucleic acids from plasma of patients with various types of cancer including NSCLC, mCRC and melanoma. Results: EXO52 columns simultaneously isolate both cfDNA and exoRNA from plasma samples up to 4 mL with close to 100% efficiency, allowing somatic mutations to be readily detected in both exoRNA and cfDNA. The combination of both was found to provide a superior mutation signal and yield compared to cfDNA alone. The EXO1000 actionable mutation panel and associated bioinformatics pipeline were demonstrated to be quantitative, reproducible and highly sensitive. The assay faithfully detected low copy numbers of mutations using clinical plasma samples from 102 patients with different types of cancer. Conclusions: We demonstrate the superiority of isolating both cfDNA and exoRNA from plasma for the purpose of detecting circulating somatic mutations in cancer patients. The EXO52 isolation method combined with the EXO1000 actionable mutation panel overcomes current technical limitations by maximizing mutation signal from all sources of circulating NA, thereby enhancing assay sensitivity.

Towards rapid and cost-effective point-of-care detection of TMPRSS2:ERG fusion transcripts in urine via a novel methodology. First Author: Eugene J.H. Wee, The University of Queensland, Australian Institute for Bioengineering and Nanotechnology, Brisbane, Australia

Background: The TMPRSS2:ERG gene fusion is a highly-specific prostate cancer biomarker which is present in about 50% of all prostate cancer cases. The present use of serum PSA for prostate cancer screening is controversial due to its lack of specificity as a screening biomarker. In contrast, the presence of TMPRSS2:ERG fusions could offer better screening potential. However, current detection methodologies of TMPRSS2:ERG, such as RT-PCR or FISH, are time consuming, expensive and require specialized equipment. Therefore, a new rapid and cost-effective point-of-care detection methodology is needed to enhance and enable the clinical utility of TMPRSS2:ERG and other cancer-related fusion transcripts. Methods: We developed a methodology by combining robust isothermal amplification with a novel readout based on amplified DNA-mediated bridging flocculation. This instrument-free visual evaluation of successful amplification complements the binary biomarker characteristic of TMPRSS2:ERG to give a simple positive/negative outcome. Results: The method is sensitive to as few as 10^3 copies (single cell level) of TMPRSS2:ERG fusion transcripts. We were also able to detect fusion transcripts in both whole urine and urinary sediments. Finally, to demonstrate clinical utility, the method was applied to 10 metastatic, castration-resistant prostate cancer urine specimens and results were validated with standard PCR-based methods. Conclusions: A simple, rapid (< 90 min) and inexpensive (< $5 USD) assay was developed to detect TMPRSS2:ERG fusion transcripts in urine. The approach may have broader applications in detecting other gene fusion events in prostate cancer or other cancers to enable quick and convenient clinical decisions.

Assessing HER2 testing quality in breast cancer (BC): Variables that influence HER2-positivity from a large, multicenter, observational study in Germany. First Author: Josef Ruschow, Institut für Pathologie Nordhessen, Kassel, Germany

Background: Despite > 10 years of routine HER2 testing in BC, quality is still an issue. It is often assumed that inter- and intra-laboratory variations in testing quality can be assessed by HER2-positivity rates. However, the extent to which patient- or tumor-related factors influence HER2-positivity rates has not been systematically studied. Methods: This observational, prospective study in Germany monitored routine HER2 testing to identify patient- or tumor-related factors that influence HER2-positivity rates, and to identify centers with HER2-positivity rates that could not be explained by these factors. Data collected from eligible BC specimens included test result, patient- and tumor-related factors, sample source, and method of retrieval. Factors influencing HER2-positivity rates were identified by multiple logistic regression (MLR) analysis. Center effects were assessed in an extended MLR model by their statistical significance after adjusting for the combined effect of covariates and multiple testing. Results: From Jan 2013 to Aug 2014, data were collected from 16,528 BC specimens and 57 centers. Final analyses included 15,332 invasive BC specimens. Center grade showed the highest correlation with HER2-positivity, followed by hormone receptor status, carcinoma subtype, age, and nodal status (all P< .0001). No significant correlation was found for specimen source. Overall HER2-positivity rate across centers was 14.4%. Adjusting for patient- or tumor-related covariates and multiple testing, a statistically significant center effect on HER2-positivity rate was identified for three centers and a significant trend toward center effect for a further three. Conclusions: This study is the first of its kind, reporting on the multifactorial parameters that can impact on routine HER2-positivity rates. Results highlight that assessing HER2 testing quality by comparing positivity rates only, as recommended, may be insufficient, and that patient characteristics should be considered to assess HER2 testing quality effectively. As therapy options for HER2-positive BC continue to evolve, identifying the right patients is key.

Preliminary direct evidence of a dose-response relationship for [Y-90]-microsphere selective internal radionuclide therapy (SIRT) in hepatic malignancy. First Author: Dale L Bailey, University of Sydney, Lidcombe, Australia

Background: [Y-90]-SIRT has an established role in managing patients with primary and secondary hepatic neoplasia. Recently, imaging of the regional distribution of the implanted [Y-90]-microspheres with positron emission tomography (PET), usually imaged on a hybrid device incorporating X-ray CT (PET/CT), has been implemented. Aims: #1 - To determine SIRT dose (in Gy) to liver lesions identified on FDG PET/CT; #2 - To use early follow-up FDG PET/CT to examine metabolic response; and, #3 - To relate metabolic response to SIRT dose. Methods: Prospective data collection of baseline and early follow-up FDG PET/CT as well as Y-90 images within 24 hrs of SIRT (SIR-Spheres microspheres, Sirtex Medical, Sydney, AUS) between January 2013 and June 2014. Within a PET-defined volume of interest (VOI) we measured Total Lesion Glycolysis (TLG = lesion volume on FDG PET × average SUVmax) for up to 5 target lesions. Fractional change (%) in TLG between baseline and follow-up was determined and compared to the average dose within the FDG-defined target lesion VOIs applied to the Y-90 PET images converted to dose maps. A positive change in TLG reflects a decrease in uptake (i.e., positive response). Results: Fifteen patients containing 32 measurable lesions (CRC = 18, HCC = 6, other = 8) were examined. Mean time from treatment to follow-up FDG PET/CT was 62 ± 15 days. The data were fitted with a log function and showed a good correlation between dose and response (R^2 = 0.79). A significant metabolic response, defined as change in TLG of ≥ 50%, was seen in all lesions receiving a mean dose of ≥ 30 Gy. No relationship was observed between site of origin of the malignancy/pathology and response. Conclusions: Dose to tumour and normal tissue can be determined using Y-90 PET/CT imaging. The dose delivered correlates with the metabolic response. The dose maps can be used to immediately (with 24 hrs) determine if a therapeutic dose of Y-90 SIRT has been delivered on a lesion-by-lesion basis and, if sub-therapeutic, further action can be instigated.
11065 Poster Session (Board #278), Sun, 8:00 AM-11:30 AM

Background: Tumors express PD-L1 to contribute to escape from immunosurveillance. We developed a PD-L1 IHC assay to investigate whether it could predict response to pembrolizumab in NSCLC patients (pts) and be used as a companion diagnostic.

Methods: The assay uses the 28-anti-PD-L1 mouse monoclonal antibody on the Dako platform. One pathologist scored each tumor sample by 4 methods: percentage of cells staining at any intensity (PS1), percentage of cells staining at moderate intensity (PS2), percentage of cells staining at strong intensity (PS3), and H-score (HS = PS1 + PS2 + PS3). Only cells with at least partial membrane staining were counted. Receiver operating characteristic (ROC) analysis was used to compare scoring methods and determine a cutoff using data from 146 NSCLC pts treated with pembrolizumab in KEYNOTE-001 who had tumor evaluable for PD-L1 expression by IHC and data for response (immune-related response criteria, investigator review). Samples from the first 31 pts were also tested with a prototype assay by a different pathologist who scored the presence or absence of a regional, primarily inflammatory cell or “interface” pattern in addition to the above. IHC and OS were assessed in the 146 pts with measurable disease (RECIST 1.1, central review). PFS and OS were assessed in the 146 pts with tumor evaluable for PD-L1 expression by IHC and data for response (immune-related response criteria, investigator review).

Results: The various scoring methods are summarized in the table. Incorporating the interface pattern did not improve scoring. Using PS1, 19 (43%) of 44 pts with ≥50% tumor cell staining responded, versus only 8 (8%) of 102 pts with <50% tumor cell staining (odds ratio = 8.93). Median PFS and OS were 4.0 mo and not yet reached, respectively, for pts with ≥50% staining and 2.1 and 6.1 mo, respectively, for pts with <50% cell staining. Conclusions: The PD-L1 IHC assay is potentially useful to enrich trial populations and as a companion diagnostic in NSCLC. While all 4 scoring methods assessed performed similarly, the percentage of cells staining at any intensity with a cutoff of 50% is the simplest and easiest method to implement in practice. Clinical trial information: NCT01295930.

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<tr>
<th>Area Under Curve</th>
<th>Positive Rate, %</th>
<th>True Positive Rate, %</th>
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| PS1              | 0.743           | 0.494
| PS2              | 0.758           | 0.462
| PS3              | 0.756           | 0.502
| HS               | 0.502           | 0.758

596s Tumor Biology

11067 Poster Session (Board #281), Sun, 8:00 AM-11:30 AM
Non-invasive determination of HER2-expression in metastatic breast cancer by using 68Ga-ABY025 PET/CT. First Author: Henrik Lindman, Department of Oncology, Uppsala University, Uppsala, Sweden

Background: To present imaging results of using [68Ga]ABY025 PET/CT for imaging HER2 expression in metastatic breast cancer.

Methods: Sixteen metastases in 12 patients were biopsied and evaluated by immunohistochemistry and in-situ hybridization. Uptake (SUV, mean ± SD) in two metastases was 10.9 ± 5.1 in HER2-pos (n = 7) vs 3.4 ± 2.1 in HER2-neg (n = 9) (p = 0.001). SUV at 4h was 15.0 ± 3.4 in HER2-pos (n = 6) vs 2.9 ± 1.9 in HER2-neg (n = 6) (p < 0.001, no overlap). The test-retest intra-class correlation was R = 0.996. [68Ga]ABY025 PET led to change in HER2-targeting treatment in 3 of the 16 patients due to receptor up- or down-regulation. Moreover, the PET data indicates occurrence of intra-patient heterogeneity of HER2-expression in several cases.


11068 Poster Session (Board #282), Sun, 8:00 AM-11:30 AM
A prospective evaluation of cell free DNA (cfDNA) genotyping and circulating tumor cells (CTC) in EGFR mutant NSCLC patients (pts) treated with erlotinib. First Author: Masahiko Yanagita, Dana Farber Cancer Institute, Boston, MA

Background: Genotype directed therapy is now standard of care for advanced NSCLC pts. However, adequate tumor tissue for comprehensive genotyping remains a challenge. Recent research suggests that CTC capture or cfDNA analysis allows for non-invasive diagnosis and monitoring of treatment. This prospective trial was designed to quantify the predictive value of CTC and cfDNA analyses of EGFR-mutant NSCLC pts treated with first-line erlotinib. Methods: TKI naïve EGFR mutant NSCLC pts were enrolled in a phase II trial of erlotinib treatment. Paired blood for cfDNA and CTC analysis was collected at baseline prior to therapy and every 2 months during follow ups. Plasma genotyping was performed by ddPCR for EGFR19del, L858R, T790M while CTCs were isolated by CellSearch and analyzed by IF and MET-FISH. Repeat biopsies at progression were performed when feasible.

Results: Between 2/10 and 1/15, 60 EGFRmutant pts (L858R:17, 19del:38, other:5) were enrolled. As of 1/15, 44 patients have discontinued therapy (39 for RECIST progression; 5 for adverse events). Blood was available for cfDNA analysis on 53 and 33 pts at baseline and progression respectively, and EGFR mutations were detected in 25/53 pts (47.1%, median: 5 copies/mL plasma, range: 2-16499) and 10/33 pts (30.3%, median, 71 copies/mL, range: 5-25300). Blood was available for CTC analysis on 47 and 33 pts and CTCs were detected in 17/47 pts (36.1%, median 12 CTCs/mL blood, range: 1-328) at progression. METamplification was identified in CTCs of 2 pts. For 18 pts with detectable cfDNA at baseline and > 3 follow up blood draws, treatment reduced cfDNA levels to non-detectable for > 4 months in 83.3 % (15/18). In contrast, for 17 pts with detectable CTCs at baseline, CTCs continued to intermittently detectable on treatment in 58.9% (10/17) of pts. Conclusions: cfDNA and CTCs are complementary non-invasive assays for EGFRmut NSCLC although the low yield of CTCs may preclude genotyping. Serial cfDNA monitoring may be a better predictor of treatment efficacy than CTCs. Funding: R01-CA153257, P50-CA090578, Conquer Cancer Foundation, Genentech
Background: Contrast-enhanced spectral mammography (CESM) is a new study to detect contrast enhancing malignancy that may not be visible on conventional mammogram. Limited studies have shown that adding CESM to diagnostic workup in adjunct with mammogram and breast ultrasound does increase sensitivity for breast cancer detection. More studies are needed to compare the sensitivity of CESM to BMRI to further define the role of CESM in breast cancer diagnosis. This study involved 66 malignant breasts in 58 women retrospectively chosen from of 1020 patients in our institution during the period of October 2012 to October 2014. Both CESM and BMRI were done for each patient within 30 days. The positive findings were confirmed by pathology reports. The number of malignant lesions was quantified. The size of lesions was classified into three categories based on standard of breast cancer stages. The enhancement intensity on both studies has been quantified based on a scale of 0-3. The scores of each case were calculated for average size of index lesion and statistical analysis. Sensitivity and positive predictive value (PPV) were calculated for each study. Morphology consistence was evaluated by the percentage of the consistent findings between CESM and BMRI. The mean study time for each test was recorded and analyzed for statistical significance. Results: Both CESM and BMRI are shown to have sensitivity of 98% for breast cancer detection. No statistical significance was identified on the mean size of index cancer (p = 0.39). The enhancement intensity of breast parenchyma is significantly lower on CESM than on BMRI (p < 0.01). The mean score of enhancement intensity of index lesions on CESM was significantly less than that for BMRI (p < 0.01). The smallest cancer can be detected by both CESM and BMRI is less than 0.5 cm. Morphology consistence was 93% (98.3%). CESM has a higher PPV than BMRI (98.0% versus 92.6%). The average test time for CESM is significantly shorter than BMRI (10 minutes versus 25 minutes). Conclusions: CESM and BMRI are consistent on morphology and equal sensitivity for detection of breast cancer lesions. CESM has less enhancement intensity than BMRI and higher PPV (reflecting a higher specificity) than BMRI.

Background: Glioblastoma is the most aggressive type of primary brain tumor with a median survival of 15 months and limited therapy options. Trials of genomically targeted matched therapies for brain tumors requiring recent tissue samples for next generation sequencing (NGS) has limited progress. Recently, a cell-free circulating tumor DNA (cfDNA) NGS panel of 54 genes has become available. We sought to evaluate whether this biopsy-free approach would allow us to interrogate genomic alterations in glioblastoma and other primary brain tumor patients. Methods: Fifty-nine consecutive patients with primary brain tumors were tested prospectively with the Guardant360 cfDNA panel at a CLIA-certified, CAP-accredited clinical laboratory. Single nucleotide variants (SNVs) in 54 genes and copy number variations (CNVs) in 3 genes (EGFR, ERBB2 and MET) were analyzed, quantitatively as the fractional mutant allele concentrations in cell-free DNA and the absolute copy numbers of the genes measured, respectively. The test is sensitive to a single DNA fragment of mutated cfDNA in a 10 ml blood sample and analytic specificity is 99.999%. Results: Average patient age was 53 (range 24-87) and 61% were male. Histopathological subtypes tested were glioblastoma (34), astrocytoma (9), meningioma (6), oligodendroglioma (5), glioma NOS (4) and ependymoma (1). 22 (37.3%) of patients had at least one genomic alteration detected and 4 (6.8%) had two genomic alterations detected. SNVs detected included TP53 (7), NOTCH (4), JAK2 (2), and KIT, ERBB2, ALK, APC, ATM, EGFR, AR and HNF1A (1 each). A single copy number amplification in MET was reported. Cell-free DNA was sufficient to complete the sequencing assay in 100% of cases. Conclusions: Contrary to other ctDNA studies where it was postulated that ctDNA would not cross the blood-brain barrier and restrict the systemic circulation, we found that over one-third of primary brain tumor patients, including glioblastoma patients, had detectable ctDNA with the Guardant360 assay.

Background: Molecular alterations in colorectal cancer (CRC) have been associated with progression and survival, and new targeted therapies have been developed for specific alterations, including KRAS and NRAS mutations. However, it is unclear which patients benefit from these therapies. Patients and Methods: We studied blood samples of 95 CRC patients at our center, who had multi-line therapy resistant advanced CRC. DNA was extracted from plasma and sequenced using an NGS panel of MSK-IMPACT, which was analyzed using a modified Sanger sequencing technique. Results: Of the 95 patients, 12 patients had detectable circulating tumor DNA. Of these, 4 patients had actionable somatic alterations including point and indel mutations, copy number alterations, and selected structural rearrangements. Of these, 3 patients had KRAS mutations in codons 12 and 13, and 1 patient had a PIK3CA mutation. None of the patients had detectable NRAS mutations. Conclusions: Circulating tumor DNA provides targetable somatic alterations in a subset of advanced CRC patients, and could potentially improve survival and response to therapy.

Background: The emergence of targeted therapies for advanced colorectal cancer (CRC) has been promising. However, only a subset of patients benefit from these therapies, and identify the biomarkers that predict response and resistance is crucial. Patients and Methods: We studied 298 CRC patients with multi-line therapy resistant advanced CRC. DNA was extracted from plasma and sequenced using an NGS panel of MSK-IMPACT. Results: Of the 298 patients, 12 had detectable circulating tumor DNA. Of these, 8 patients had actionable somatic alterations including point and indel mutations, copy number alterations, and selected structural rearrangements. Of these, 3 patients had KRAS mutations in codons 12 and 13, and 1 patient had a PIK3CA mutation. None of the patients had detectable NRAS mutations. Conclusions: Circulating tumor DNA provides targetable somatic alterations in a subset of advanced CRC patients, and could potentially improve survival and response to therapy.

Background: The use of circulating tumor DNA (ctDNA) to detect somatic alterations in colorectal cancer (CRC) has emerged as a promising non-invasive approach for molecular characterization of CRC. ctDNA is detectable in a large proportion of CRC patients and can identify somatic alterations even in patients with KRAS mutations, which are undetectable by traditional tissue analysis. However, the clinical utility of ctDNA in CRC is not yet fully elucidated. Patients and Methods: We studied 150 CRC patients with multi-line therapy resistant advanced CRC. DNA was extracted from plasma and sequenced using an NGS panel of MSK-IMPACT. Results: Of the 150 patients, 12 had detectable circulating tumor DNA. Of these, 8 patients had actionable somatic alterations including point and indel mutations, copy number alterations, and selected structural rearrangements. Of these, 3 patients had KRAS mutations in codons 12 and 13, and 1 patient had a PIK3CA mutation. None of the patients had detectable NRAS mutations. Conclusions: Circulating tumor DNA provides targetable somatic alterations in a subset of advanced CRC patients, and could potentially improve survival and response to therapy.
Background: Matrix metalloproteinase (MMP) mediated degradation of the extracellular matrix (ECM) play an important role in the development of cancer. One of the most abundant ECM proteins is type I collagen, which is commonly dysregulated and degraded in early stages of tumorigenesis. However, MMP mediated tissue destruction has not been quantified in larger, prospective cancer outcome studies. The aim of this study was to investigate if a biomarker reflecting MMP-mediated degradation of type I collagen (C1M) could be used for early detection of cancer, in a large prospective study. Methods: From 1999-2001, 5,856 women aged 60-85 participated in the Prospective Epidemiologic Risk Factor (PERF I) study, which addresses age-related diseases. Demographics and serum samples were collected at time of enrollment. Cancer diagnoses were collected from the Danish Cancer Registry ultimo 2014. Serum C1M levels were measured by ELISA and compared to time of diagnosis and to non-cancer diagnosed and non-diseased women (healthy). Women diagnosed with cancer prior to PERF I enrollment were excluded from analysis. Data was analyzed using one way ANOVA on log transformed data and by Pearson’s correlation coefficient. Results: A total of 1,154 women were diagnosed with cancer following PERF I enrollment. C1M, at baseline, was significantly elevated in women diagnosed less than 6 months after blood draw compared to healthy women (p=0.016) and to women diagnosed more than 45 months after blood draw (p=0.016) after blood draw (see table). Furthermore, C1M correlated with time to diagnosis up to 3 years after blood draw (r = -0.143, p = 0.0146, n = 289). Conclusions: The levels of MMP-degraded type I collagen (C1M) were significantly elevated in serum from women diagnosed up to 6 months after enrollment in PERF I and correlated with time to diagnosis up to 3 years after blood draw. Further investigations into C1M as an early detection tool for cancer could be highly relevant.

11075 Poster Session (Board #289), Sun, 8:00 AM-11:30 AM
A phase I, first-in-human dose study of the dual PI3K/mTOR inhibitor LY3023414 (LY) in patients (pts) with advanced cancer. First Author: Kwon, N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK
Background: The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is dysregulated in many malignant diseases. LY3023414 (LY) is an oral ATP competitive inhibitor of the class I PI3K isoforms, mTOR and DNA-PK. Based on preclinical results, we investigated LY in patients with advanced solid tumors. Methods: In this 3+3 dose escalating phase I study, patients with solid tumors refractory to standard therapies received LY once daily (QD) or twice daily (BID). The primary objective was to determine a recommended phase II dose (RPTD). Additional objectives were to assess LY dosing safety, pharmacokinetic/ pharmacodynamic (PK/PD) profiles, drug–drug interaction with midazolam, and to document anecdotal antitumor activity. Results: As of September 2014, 47 pts have received LY either QD (at 20, 40, 80, 150, 225, 345, 450 mg) or BID (at 150, 200, 250 mg). Dose-limiting toxicities (DLTs) have been observed for LY QD only at 450 mg and consisted of grade [G] 4 thrombocytopenia, G4 hypotension, G3 hyperkalemia in 3/3 patients treated. For BID dosing, DLTs were observed in 3/3 patients at 250 mg (G4 hypophosphatemia, G3 fatigue, G3 mucositis) and in 1/5 patients at 200 mg (G2 nausea). Common treatment-related adverse events (all grades) included nausea (38%), fatigue (31%), vomiting (27%), and diarrhea (17%). PK analyses showed a dose-proportional increase in LY exposures (AUC) at tolerated dose levels with a half-life of 1.9 hours and a body clearance of 85 L/hr. Midazolam PK data indicated that LY is a weak inhibitor of CYP3A4. Biomarker assessment demonstrated dose-related target inhibition in peripheral mononuclear cells at LY doses ≥ 150 mg. Durable partial response according to RECIST was observed in an endome trial cancer patient harboring PIK3R1 and PTEN mutations and 22 additional patients (47%) had stable disease as their best response. Conclusions: LY appears to be safe when administered as single agent up to 325 mg QD or 200 mg BID. The RPTD of single-agent LY is 200 mg BID based on safety, tolerability, and PK/PD data. LY is currently studied in two randomized, specific expansion cohorts for mesothelioma, breast cancer, indolent Non-Hodgkin Lymphoma and squamous NSCLC. Clinical trial information: NCT01655225.

11076 Poster Session (Board #290), Sun, 8:00 AM-11:30 AM
Lung cancer patients with HER2 mutations treated with chemotherapy and HER2 targeted drugs: Results form the EUHER2 cohort study. First Author: Julien Maizieres, Hôpital Larrey CHU Toulouse, Toulouse, France
Background: HER2 mutations are identified in about 2% of non-small cell lung cancer (NSCLC) and behave as an oncogenic driver. Little is known about the efficacy of chemotherapy and of HER2 targeted drugs in this population. We aimed to study therapeutic outcomes of patients harboring HER2 mutations (HER2+1) in order to establish the efficacy of various drug regimens and to orient future clinical trials. Methods: We conducted a retrospective cohort study in EU-European centers with NSCLC patients for HER2. Eligible patients had advanced stage NSCLC, known HER2 exon 20 insertions by local testing, and treatment with chemotherapy and/or targeted drugs. Clinicians had to obtain informed consent and IRB approval according to local regulations, and response were assessed according to RECIST version 1.1. Data were anonymized and analyzed centrally. Results: We identified 101 eligible patients from 38 centers. Our population was characterized by a median age of 61 yrs (30-87), a high proportion of women (63 vs. 38 men, 62.4%), and of never smokers (61, 60.4%). All tumors were adenocarcinomas. Concomitant EGFR mutation, ALK translocation and ROS translocation were observed in 5, 1 and 1 patients respectively. The median number of treatment lines was 3 (1-11). Overall survival of the whole population (n = 101) was 24 months (m.). Response rate (RR) and median progression free survival (PFS) for patients treated with conventional chemotherapy (excluding targeted therapy) were 43.5% and 6 months (95% CL: 4.3 to 6.9), respectively. RR and PFS for patients treated with conventional chemotherapy plus targeted therapy were 52.5% and 23 months (95% CL: 20.4 to 25.5), respectively. Conclusions: HER2+1 patients treated with conventional chemotherapy had better survival compared to HER2+1 patients treated with conventional chemotherapy plus targeted therapy. Further studies are needed to confirm these findings.
11078 Poster Session (Board #292), Sun, 8:00 AM-11:30 AM
Identifying driver mutations in squamous cell lung cancer (SCC): The Lung Cancer Genomics Ireland (LCGI) study. First Author: Sheeren Rafiee, St. James’s Hospital, Dublin, Ireland.

Background: Targeting oncogenic drivers has transformed the care of lung adenocarcinoma. However, there is no approved targeted therapy for lung SCC. LGCI aims to identify potential targets in lung SCC. Methods: The LGCI study is being carried out in patients with surgically resected lung SCC. We used the platform of Sequenom’s MassArray to perform genotyping for 548 somatic hotspot mutations in 49 genes including genes in the MAFPK and PI3K pathways. We have evaluated EGFGR amplification by fluorescence in situ hybridization (FISH) and MET protein expression by immunohistochemistry (IHC). Results: Lung SCCs from 201 patients have been tested by Sequenom MassArray to date. Lung SCCs from 150 patients have been evaluated for MET protein expression and 89 for EGFGR amplification. 134 (66.7%) patients were male. The median age of the cohort was 68. 76% of patients were current (32.8%) or former (44.2%) smokers at the time of diagnosis. 104 (57.1%) were stage II (33.8%) stage I (24.5%). Stage IV (14.5%) was stage III. (9.5%) were stage II (14.5%). Stage IV (14.5%) stage III (9.5%) were stage II (14.5%). Stage IV (14.5%) stage III (9.5%) were stage II (14.5%), stage I (14.5%) or unknown (21.4%). Conclusions: 40.3% of lung SCC patients have an aberrant, potentially targetable driver oncogene in their tumor. The presence of two or more aberrant oncogenes is a poor prognostic factor. These findings can be used to guide clinical trials in lung SCC.

Frequency of driver mutations in LGCI compared to The Cancer Genome Atlas (TCGA) study.

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<tr>
<th>Mutation</th>
<th>LGCI (n = 201)</th>
<th>TCGA (n = 178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFGR amp (n = 89)</td>
<td>12.4%</td>
<td>16.8%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>13.8%</td>
<td>10.1%</td>
</tr>
<tr>
<td>KRAS</td>
<td>6.0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>PTEN</td>
<td>4.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>FLT3</td>
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</tr>
<tr>
<td>TP53</td>
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<td>1.3%</td>
</tr>
<tr>
<td>NAB8</td>
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<tr>
<td>GNA11</td>
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<td>STK11</td>
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</tr>
<tr>
<td>CTNNB1</td>
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<td>1.3%</td>
</tr>
<tr>
<td>FBXW7</td>
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<td>3.4%</td>
</tr>
<tr>
<td>MET</td>
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<td>1.7%</td>
</tr>
<tr>
<td>TGFBR2</td>
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</tr>
<tr>
<td>EGFR</td>
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<td>2.8%</td>
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<td>AKT1</td>
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</tr>
<tr>
<td>CDKN1A</td>
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<td>GNAS</td>
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<td>MAP2K1</td>
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</tr>
<tr>
<td>DDR2</td>
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11080 Poster Session (Board #294), Sun, 8:00 AM-11:30 AM
TBCRC-010: Phase II study of dasatinib in combination with zoledronic acid (ZA) for the treatment of breast cancer bone metastasis (MBC-bone). First Author: Zahi Ibrahim Mitri, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Osteoclast activation and subsequent bone resorption release growth factors that promote tumor growth. These events are blocked by the Src/PDGf receptor. Dasatinib, the tyrosine kinase Src phosphorylates and activates the ER in ligand-independent manner. Dasatinib, in combination, may facilitate the antitumor effect of endocrine therapy. Methods: A phase II study was completed by the TBCRC at three institutions: MD Anderson Cancer Center, Houston, TX, Duke University, and University of Michigan. Pts with HER-2-negative, MBC-bone received standard dose ZA IV on day 1 and Dasatinib 100 mg QD, days 1-28 of each 28 day cycle. Prior therapy with bone-modifying agents was allowed. Response was assessed by RECIST (non-bone disease) and MDACC density (MVD) determined by CD34. Results: Dasatinib was well tolerated, and may have benefit in a subset of pts. Clinical trial information: NCT00566618.

Characteristics of patients treated at RP2D.

<table>
<thead>
<tr>
<th>Patients</th>
<th>24</th>
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<tbody>
<tr>
<td>Median Age, (Range)</td>
<td>45, (26-74)</td>
</tr>
<tr>
<td>Hormone receptor positive</td>
<td>21</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
</tr>
<tr>
<td>NTX at baseline Low</td>
<td>16</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
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</tr>
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<td>AE</td>
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</table>
HRAS is mutated in head and neck cancer (3.9%), bladder cancer (5.1%), vulvar squamous cell carcinoma (9.3%), cutaneous squamous cell carcinoma and lung cancer (3.8%). However, mutant HRAS as a drug target has not been investigated so far. Methods: Cell Proliferation and Viability Assays: Cell proliferation was measured with the Cell-Titer-Glo Reagent (Promega) according to manufacturer’s instructions. Cells were plated in clear-bottomed 96-well plates at a density of 500 - 2500 cells per well. The next day, drugs were added at indicated concentrations and cell proliferation was measured 4 days later. Apoptosis assays: Cell lines were treated with indicated concentrations of inhibitors and apoptosis was measured after 48h and 72h. Apoptosis was assessed by Annexin-V–APC (Enzo Lifescience) and propidium iodide (PI) (Sigma-Aldrich) by FACS. Results: Here, we show that mutant HRAS activates the RAS and mTOR pathway in various cancer cell lines including lung, bladder and esophagus cancer. HRAS mutation sensitized toward growth inhibition by the MEK inhibitors AZD6244, MEK162 and PD0325901. Further, we found that MEK inhibitors induce apoptosis in mutant HRAS cell lines but not in cell lines lacking RSAS mutations. In addition, knockdown of HRAS by siRNA blocked cell growth in mutant HRAS cell lines. Inhibition of the PI3K pathway alone or in combination with MEK inhibitors did not alter signaling nor had an impact on viability. However, combined inhibition of MEK and mTOR reduced cell growth in a synergistic manner. Conclusions: Our results show that HRAS mutations in cancer activate the RAS and mTOR pathways that might serve as a therapeutic option for mutated lung cancer patients.

Germline variants in cancer risk genes detected by NGS-based comprehensive tumor genomic profiling (CGP). First Author: Michael J. Hall, Fox Chase Cancer Ctr, Philadelphia, PA

Background: NGS-based CGP is increasingly used in oncology to assess patient eligibility for targeted therapies. Previous work has demonstrated that variant germline/somatic status may be accurately predicted for research use from data generated by CGP (AACR 2014 #1893). The prevalence of germline variants in hereditary cancer risks genes and their potential clinical implications have not been previously reported in patients referred for CGP. Methods: Germline variants were predicted in data from 15060 tumor samples analyzed by Foundation Medicine. Variant analyses focused on 20 penetrant hereditary cancer risk genes identified by the ACMG as high priority for disclosure to patients if discovered during genomic testing. Pathogenicity of each variant and association with tumor histology (known vs unexpected) was assessed through expert review of clinical evidence from public variant annotation databases (dbSNP/ClinVar, BIC, HGMD), and other resources (PubMed, Internet). Results: Of tumors tested, 30.8% (4633/15060) had > 1 germline variant in a cancer risk gene, with 521 unique variants identified overall. A likely pathogenic variant (PV) was found in 3.1% tumors (n = 466/15060), and an additional 3.9% (587/15060) had a suspicious variant but conflicting pathogenicity data. PV prevalence appeared higher than in the general population (CGP PV prevalence; estimated population prevalence): MUTYH (1.3%; 0.02%), RET (0.7%; 0.02%), BRCA1 (0.6%; 0.001%), BRCA2 (0.5%; 0.001%) CDH1 (0.5%; 0.001%), MLH1 (0.5%; 0.001%), PMS2 (0.2%; 0.001%), and TP53 (0.02%; 0.0002%). Early-onset cancer was most strongly associated with PV in BRCA1 (p < 0.001). Bladder cancer (4.1%, 10/243 tumors tested), squamous cell lung cancer (4.4%, 13/293) and kidney cancer (3.4%, 5/148) had the most unexpected PV. Data were insufficient to determine clinical pathogenicity for the majority of the missense variants identified. Conclusions: Germline PV in cancer risk genes are found in 3-7% of patients tested by CGP. There is a pressing need for further research to determine the association of these variants to disease risk. Additional clinical resources are needed to guide oncoloists in the interpretation and management of potential PV uncovered by CGP.

Stereotactic ablative radiotherapy (SABR) as re-irradiation for an isolated infield lymph node recurrence. First Author: Neal Bhatt, University of Louisville, Louisville, KY

Background: Oligometastatic disease presents a unique opportunity for local therapy to provide cure. The aims of this study were to evaluate the safety and efficacy of stereotactic ablative radiotherapy (SABR) as a local treatment for isolated lymph node recurrence in a previously irradiated field. Methods: Between January of 2010 and September of 2014, 33 patients were reviewed from a prospectively collected database. Eighteen of 33 patients had biopsy proven recurrence and all patients were shown to have isolated metastases by positron emission tomography (PET) – CT. All patients had previously received full dose radiation treatment with radical intent, with a median total dose of 56 Gy (range, 46-74) delivered with standard fractionation. The median duration from initial radiotherapy to lymph node recurrence was 11.2 months. The overall survival (OS), local control (LC) rate, and disease progression-free survival (DPFS) rate were calculated according to the Kaplan-Meier method. Comparison between prognosis groups and toxicities was performed using log-rank analysis. Results: All patients completed the prescribed treatment. The median tumor dose and fractions administered was 40 Gy (range, 24-50) in 5 fractions. The median follow-up was 10 months (range, 1-33). Three grade 3 toxicities were observed including radiation pneumonitis, displaced fracture, and pelvic pain. No Grade 4 toxicities were recorded. Results at last follow up demonstrated a local control of 90.9%, Regional control (adjacent nodal station) of 66.7%, and distant failure of 27.3%. The median time to any failure was 4.5 months with a 1 year OS of 45.5%, and DPFS 62.3%. Conclusions: SABR salvage to macroscopic nodal recurrences provides local control and long-term disease-free survival in carefully selected patients with a low incidence of toxicities. Further investigation is warranted to identify those patients who benefit most from this treatment modality.
Background: Metabotropic glutamate receptor 1 (GRM1) activates MAPK and PI3K/AKT signaling and is implicated in multiple cancers including breast, prostate and melanoma. GRM1 overexpression stimulates tumor angiogenesis via enhanced microvesicle secretion to facilitate endothelial cell growth. Riluzole (R) is a clinically available inhibitor of GRM1 signaling. Sorafenib (S), a kinase inhibitor that inhibits MAPK and PI3K/AKT signaling through CRAF and B-RAF inhibition with antiangiogenic effects, was identified in preclinical screens to have synergistic antitumor activity when combined with R. This phase I trial identified the maximum tolerated dose (MTD) of R combined with S in patients (pts) with advanced cancer.

Methods: Pts with refractory solid tumors were enrolled utilizing a standard 3+3 dose-escalation design. R was given in 28 day cycles at the highest dose used in clinical practice (100 mg BID) in combination with S, beginning at 200 mg daily and escalating in 200 mg increments per cohort. Restaging evaluations were performed every 2 cycles using RECIST criteria. Results: 29 pts enrolled, median age 59 (22-85), 13F, 16M, PS 0 (48%), 1 (3%) or 2 (17%). The most common toxicities were nausea (31%), fatigue (62%) and diarrhea (41%), anorexia (31%), rash (27% PPE, 31% other), and hypophosphatemia (34%). Grade 3-4 toxicities included hypophosphatemia (10%), elevated lipase (10%), LFT abnormalities (10%), rash/PPE (14%), and fatigue (13%). The most frequent dose limiting toxicity (DLT) was rash, observed in 3 pts at the MTD, dose level (DL) 4 (R 200 mg bid/S 400 mg bid). Best responses were SD in 9 pts (31%), lasting >3 months in 1 pt each with sarcoma, lung, colon, ovarian, and melanoma; and 1 GIST (9+ cycles with modest tumor reduction). Conclusions: R combined with S is safe with DLT of rash. While rash is a known side effect of sorafenib, its incidence and severity appeared increased in this study. An expansion cohort in pts with melanoma and sarcoma at DL3 (R 200 mg bid/S 400 mg qd) is ongoing. Planned correlative assessments include circulating microvesicle quantification and immunohistochemical and western blotting to assess changes in activated signaling targets in pre and post treatment samples. Clinical trial information: NCT01303341.

Characterization of LASEP3 as a serological and prognostic biomarker and a therapeutic target for lung cancer. First Author: Atsushi Takano, Center for antibody and vaccine, The University of Tokyo, Tokyo, Japan

Background: Characterization of cancer-specific oncoproteins could lead to the development of novel diagnostic/prognostic biomarkers or therapeutic targets. Methods: To develop new cancer biomarkers and therapies targeting oncoproteins, we used the strategies as follows: i) Identification of up-regulated genes in non-small cell lung cancers (NSCLCs) by means of cDNA microarray, ii) Validation of clinicopathological significance of their protein expression by tissue microarray, iv) Examination of the growth/ invasive effect on cancer cells by siRNA assay, and v) Measurement of their serum protein levels by ELISA. Results: We identified a secreted protein, LASEP3 (lung cancer-associated serum protein 3) as a candidate. Immunohistochemical staining of LASEP3 showed that strong LASEP3 positivity was observed in 198 (54.8%) of 361 earlier stage NSCLCs that had undergone curative surgery. High level of LASEP3 expression was associated with poor prognosis for NSCLC patients. (P = 0.0183 by log-rank test). Serum LASEP3 levels were higher in NSCLC patients than in healthy volunteers. The proportion of serum LASEP3-positive cases was 160 (61.8%) of 259 NSCLCs (49.4% for stage I-II, 67.4% for stage III-IIV), while 6 (5.5%) of 109 healthy volunteers were falsely diagnosed. Moreover serum LASEP3 levels were significantly higher in breast and colon cancer patients than in healthy volunteers. Furthermore, reduction of LASEP3 by siRNAs suppressed lung cancer cell proliferation and invasion. Flow cytometric analysis of these tumor cells transfected with siRNAs for LASEP3 revealed a significant increase of the cells at the sub G1 phase and induced the apoptosis of the cancer cells. Furthermore, subsequent microarray analysis of these cancer cells transfected with siRNAs identified several candidate downstream genes of LASEP3 that relate to cell growth/invasion signals. Conclusions: LASEP3 is a possible diagnostic and prognostic biomarker and a therapeutic target for lung and various types of solid cancer.

Identification and functional characterization of a long non-coding RNA driving hormone-independent prostate cancer progression. First Author: Francisco Crea, BC Cancer Research Centre, Vancouver, BC, Canada

Background: Despite recent therapeutic advancements, castration-resistant prostate cancer (CRPC) remains an incurable disease. Most CRPCs display an aberrantly activated androgen receptor (AR) pathway, but the mechanisms underlying this phenomenon are not entirely elucidated. Long non-coding RNAs (IncRNAs) are non-translated transcripts, encoded by more than 50,000 loci of the human genome. Some IncRNAs are emerging as crucial mediators of nanostatic progression. We hypothesize that IncRNAs are functionally relevant in CRPC, and therefore they can be exploited as novel therapeutic targets. Methods: We developed isogenic pairs of patient-derived, prostate cancer xenografts (PCXs), showing opposite sensitivity to castration. We then profiled the transcriptome of sensitive vs. resistant PCXs and set out functional characterization of the most differentially expressed IncRNA. Results: Transcriptomic analysis revealed more than 100 IncRNAs specifically up-regulated (> 2 fold) in the castration-resistant models. These uncharacterized genes have been named HORAS: Hormone Resistance Associated Sequences. The most highly up-regulated IncRNA was HORAS1, a gene mapping on chromosome 21. Using qPCR, we have confirmed dramatic HORAS1 up-regulation in three isogenic castration-resistant/sensitive PCX pairs (5- to 113-fold change). HORAS1 was highly expressed in AR-positive PCa cell lines and was prevalently localized in the cytoplasm. We then tested the function of HORAS1 in two PCa cell lines grown in media containing castrate testosterone levels. HORAS1 silencing induced a dramatic growth arrest and activation of caspase 3/7, 8 and 9 (two distinct small-interfering RNAs vs. negative control; p < 0.01). ANOVA and Tukey post-test for all the above mentioned experiments). HORAS1 silencing also induced down-regulation of AR target genes. RNA Seq, analysis on 208 primary prostate cancer samples revealed that higher HORAS1 expression predicts shorter disease-free survival (p < 0.01, log-rank test). Conclusions: HORAS1 is a previously uncharacterized regulator of the AR pathway. This IncRNA is required for hormone-independent prostate cancer proliferation.

A prospective validation of plasma ddPCR for rapid EGFR and KRAS genotyping of advanced NSCLC patients (pts). First Author: Adrian G. Sacher, Dana-Farber Cancer Inst, Cambridge, MA

Background: Plasma genotyping of cell-free DNA (cfDNA) has the potential to allow for noninvasive genotyping while avoiding the inherent shortcomings of tissue genotyping and repeat biopsies. We have developed a quantitative droplet digital PCR (ddPCR)-based plasma genotyping assay capable of detecting common EGFR and KRAS mutations (Oxnard et al., CCR 2014). This is the first prospective study designed to validate the test characteristics of plasma ddPCR in advanced NSCLC. Methods: Pts with newly diagnosed or progressive advanced NSCLC were eligible. All pts were required to have a biopsy available or planned for tissue genotyping which has a rapid TAT and high specificity suggesting it could be used to avoid biopsies for genotyping in some pts with advanced NSCLC. The false positive rate for T790M is likely related to tumor heterogeneity in resistant disease. This assay is currently being transitioned into the pathology laboratory for clinical use. Funding: US Department of Defense, Conquer Cancer Foundation of ASCO, Stading-Younger Cancer Research Foundation
Ocular toxicity with MEK inhibitors in phase I trials: A single centre experience across six clinical trials. First Author: Vanlili Michalaarea, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: MEK is a crucial signalling protein downstream of multiple receptor and non-receptor protein kinases that drive cancer. A range of allosteric MEK inhibitors have been developed and one has been licensed for use in malignant melanoma. We have assessed ocular toxicity in detail across a range of MEK inhibitors. Methods: Patients enrolled in phase I trials of MEK inhibitors between February 2009 and November 2014 were considered eligible for this study. Patients underwent testing of visual acuity by Snellen’s chart, ocular pressure assessment and ocular tomography (OCT) at baseline and at various points in each trial. Results: 94 (MF: 42:52) patients were assessed in 6 trials. The most common tumour types included colorectal, lung, ovarian cancer and melanoma. Significant retinal changes on OCT were detected in 30/94 (31%) patients. 15 (50%) of these patients were symptomatic due to peripheral epithelial detachment (PED), central serous detachment (CSR) and a combination (PED+CSR) in 9/15, 3/15 and 3/15 cases. In 15 asymptomatic patients, significant retinal changes on OCT included PED in 13/15 and PED+CSR in 2/15. National Cancer Institute Common Toxicity Criteria (NCI-CTC) Grade 0, 1, 2 and 3 numbered 60, 30, 4 and 2 events respectively. In patients where OCT was performed, there was a statistically significant difference in average thickness and central thickness of the macula (p = 0.0009 and p < 0.0001, respectively), but not in total macular volume (p = 0.67), between patients who reported any Grade 0-3 ocular toxicities on ANOVA. There were no episodes of toxicity related drug discontinuations or irreversible ocular toxicity. Conclusions: Reversible retinal changes occur across a diverse number of MEK inhibitors indicating this to be a class effect. Approximately half of patients were symptomatic; however, with careful monitoring by OCT, appropriate dose delays and dose reductions, it is possible to continue treatment in most instances.

A functional kinase screen to identify pathways of anthracycline resistance in patient-derived breast cancer cells. First Author: Hannah Richards, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Despite 5 decades of generalized anthracycline use in breast cancer, rates of progression following exposure remain very high. In order to identify biologic mechanisms contributing to resistance, we performed high-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. Methods: Cells were isolated directly from metastatic tumors and peritoneal effusions from patients with anthracycline-resistant breast cancer (n = 26, recruitment ongoing), expanded in culture, confirmed to be of epithelial origin by expression of keratin and stem cell markers (CD44+, CD24-), and could be grown as organoids. Low passage cells were transfected in triplicate with siRNAs targeting 713 kinases alone (IC0) or in combination with doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. Despite 5 decades of generalized anthracycline use in breast cancer, rates of progression following exposure remain very high. In order to identify biologic mechanisms contributing to resistance, we performed high-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. The presence of doxorubicin (IC30, inhibitory concentration 30%) and in the presence of doxorubicin (IC30, inhibitory concentration 30%), or pleural effusions from patients with anthracycline-resistant breast cancer. High-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines.

Conclusions: Reversible retinal changes occur across a diverse number of MEK inhibitors indicating this to be a class effect. Approximately half of patients were symptomatic; however, with careful monitoring by OCT, appropriate dose delays and dose reductions, it is possible to continue treatment in most instances.

Investigation of non-V600 BRAF mutations commonly found in NSCLC for their sensitivity to dabrafenib or trametinib. First Author: Amir Noeapartar, Medical Oncology, OLVG Hospital, Amsterdam, The Netherlands

Background: The most common BRAF mutations in non-small cell lung cancer (NSCLC) are non-V600 in contrast to melanoma. BRAF pathway inhibitors have not been systematically investigated in non-V600 mutations in vitro and in the clinic. We tested the effect of two clinically available BRAF pathway inhibitors (Trametinib and Dabrafenib) on a subset of clinically identified BRAF mutations in a cohort of lung cancers enriched for adenocarcinoma in patients with no or limited smoking history. Methods: NSCLC tumor samples (FFPE) were tested for the presence of EGFR, KRAS, NRAS, HRAS and BRAF mutations by DGGE or NGS-based methods. We generated 15 BRAF expression plasmids, harboring the mutations found in the given cohort and others described in the literature. BRAF mutants were subjected to an in vitro kinase assay. BRAF constructs were also expressed in HEK293T cells (with and without wt-CRAF) to study their impact on ERK signaling and determine the effect of inhibitors. Results: Among 229 NSCLC patients, 12 patients (5.2%) were found to harbor a BRAF mutation in their tumor; V600 (25%), G469A (16.7%), G469W (8.3%), D594N (25%), D594E (8.3%), G596C (9.3%) and G466V (8.3%). Mutations were characterized as activating or kinase-impaired (in-vitro kinase assay). Kinase-impaired BRAF mutants could still activate the ERK pathway in a CRAF-dependent manner, more than wt-BRAF/wt-CRAF co-transfectant. A MEK inhibitor (Trametinib) and a selective BRAF-inhibitor (Dabrafenib) were tested at clinically relevant doses on HEK293T transfectants (either expressing BRAF mutant alone or together with CRAF). ERK signaling induced by activating mutations was reduced in response to both inhibitors separately. Trametinib inhibited the CRAF-dependent ERK signaling induced by impaired-kinase BRAF mutations. Dabrafenib activated the ERK pathway in cells expressing only CRAF as well as cells co-expressing a kinase-impaired BRAF mutation and CRAF. Conclusions: This study predicts sensitivity of activating non-V600 BRAF mutations in lung cancer to Trametinib or Dabrafenib. Targeting kinase impaired BRAF mutations which signal through CRAF using Dabrafenib will require the addition of Trametinib.
antiangiogenic tyrosine kinase inhibitor (TKIs) administration may impact on the clinical outcomes. 

Background: Programmed death-ligand 1 (PD-L1) expression in cancer cells or tumor microenvironment is under investigation as a candidate biomarker in the new drug development of immuno-oncology field. Preparation of tumor tissues for PD-L1 expression has some challenges. The soluble form of PD-L1 (sPD-L1) is suggested as retaining immunosuppressive activity. In this study, we measure the levels of sPD-L1 in serum and evaluate its role in prediction of overall survival (OS) in biliary tract cancer (BTC) patients.

Methods: Seventy seven BTC patients’ serum was collected before initiation of standard palliative chemotherapy. sPD-L1 was measured using an enzyme-linked immunosorbent assay. Clinical data including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII, neutrophil X platelet/lymphocyte) were collected. Cut-off of each variable for OS prediction was determined by ROC curve. Results: The primary site of BTCs were; 30 HCC, 28 GB ca, 8 EHBTC, 11 Aoe ca. OS of all patients was 10.7 months (95% CI; 8.53-14.93) and 1-year overall survival rate was 46.8%. Median sPD-L1 level was 1.20 ng/ml (range 0.02-7.3, mean 1.48, SD 1.19). Median values of NLR, PLR, SII were 2.34, 8.81 and 514.8 respectively. High level of sPD-L1 (> 1.10 ng/ml) conferred poor prognosis (OS 7.7 m vs 17.7 m, p=0.001). High levels of NLR (> 2.10), PLR (> 9.5), SII (> 650) were also significant factors for poor OS (P=0.029, P=0.015, P=0.002). However, in multivariate analysis, only sPD-L1 predicts worse survival (HR 2.16, p=0.008). Patients with high sPD-L1 showed decreased albumin level, high NLR, PLR, SII. Among 77 patients, 19 outliers with longer survival (OS >20m) had lower levels of sPD-L1 (P=0.007). Conclusions: The soluble form of PD-L1 (sPD-L1) can be measured in the serum of BTC patients, and it has significant impact on the prognosis of BTC patients treated with standard chemotherapy.

Effect of the timing of sunitinib administration on the predictive value of biomarkers in renal cell cancer (mRCC)

First Author: John Michael Louis Ebies, Roswell Park Cancer Institute, Buffalo, NY

Background: Angiogenic cytokines influence tumor growth in mRCC patients (pts) and are modulated by diurnal fluctuations. The timing of antiangiogenic tyrosine kinase inhibitor (TKIs) administration may impact efficacy, toxicity and biomarker expression. Methods: 34 mRCC pts, randomized to receive sunitinib at 8 AM or 8 PM on a 28 days (d) on/14 d off schedule, had blood sampling before and during Rx on the first cycle for potential biomarkers including: sunitinib and metabolite blood levels, 18 circulating angiogenic factors (CAFs) and 4 circulating angiogenic cell types including circulating endothelial cells (CECs). Results: Spearman analysis of the 24 biomarkers obtained on 14 showed significantly better correlations with OS and PFS in PM-treated pts. Three CAFs in PM-treated pts significantly correlated with both OS and PFS. These included Leptin (r=0.7182, p=0.0128 and r=0.8364, p=0.0022, respectively), IL-8 (r=-0.6353, p=0.0485 and r=-0.5735, p=0.031, respectively) and PDGF-ββ (r=-0.8455, p=0.001 and r=-0.6818, p=0.0251, respectively). Circulating Leptin levels correlated with sunitinib-metabolite levels in both AM and PM-treated patients (r=0.7832, p=0.0038 and r=0.6848, p=0.0347, respectively). Conclusions: This is the first study to suggest that a consistent sunitinib dosing time may improve the predictive value of some biomarkers for OS and PFS in mRCC pts. A panel of predictive circulating cytokines (Leptin, IL-8, and PDGF-ββ) was identified for pts receiving Rx at night. Furthermore, Leptin may have value as a biomarker of sunitinib-metabolite levels independent of dosing timing. The potential impact of Rx-time on the predictive value of some biomarkers has been hampered the discovery of consistently useful predictive biomarkers for sunitinib efficacy in mRCC patients to date. Clinical trial information: OCT125.

Correlation of cancer-associated macrophage-like cells with systemic therapy and pathological stage in numerous malignancies

First Author: Daniel L Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ

Background: Recently we published preliminary data on the presence of Cancer Associated Macrophage-Like cells (CAMLs) in a variety of malignancies and their clinical use in tracking cancer progression (Adams et al., PNAS 2014). This report is a follow-up in identifying and tracking CAMLs, with an emphasis on correlating clinical and pathological stage from baseline samples. Methods: This multi-institutional prospective pilot study consisted of 105 patient (pt) samples: Stage I-II (30/14); breast (n=34), prostate (n=30), pancreatic (n=25), pancreatic (n=7). Evaluators were blinded to the source and stage of the pts. Additionally, 30 non-blinded healthy controls with no known malignant disease were analyzed. 7.5 ML of whole blood was collected, filtered by the CellSieve filtration assay, and stained with DAPI, CK 8/18/19, EpCAM and CD45. CAMLs were enumerated and identified as large multinucleated circulating myeloid cells (e.g. CD14+). We report CAML number at clinical stage in relation to healthy controls and compare with patient’s pathological stage. Results: CAMLs were identified in 98/105 samples (93%), ranging from 0-105 CAMLs per peripheral blood sample at baseline, while 0 were found in 30 healthy controls; Sensitivity = 93.3% (C195% 87-97%) and Specificity = 100% (C195% 88-100%). Pts with breast, prostate and pancreatic cancer underwent surgical procedures and pathologically staged (n=98). The number of CAMLs at baseline had a weak association with clinical stage; stage I (8.7 per sample), Stage II (6.3), Stage III (16), Stage IV (26.1). R2=0.82. However, the number of CAMLs at baseline highly correlated with final pathological staging; stage I (4.3), Stage II (6.3), Stage III (14), Stage IV (24.6). R2=0.94. Conclusions: Our data suggests that 1) CAMLs are circulating immune cells specific to malignant disease and 2) the number of CAMLs is weakly associated with clinical stage but highly correlatively with pathological stage in a variety of malignancies. These findings indicate that CAMLs may be a valuable supplement to current screening and staging procedures.

Background: CDK4/6 inhibitors in combination with hormone therapies have shown activity in estrogen receptor positive (ER+ve) breast cancers. We investigated whether CDK4/6 inhibitors have activity in subsets of Triple Negative Breast Cancer (TNBC), and assessed combination therapeutic approaches. Methods: We screened 18 TNBC cell lines for sensitivity to the CDK4/6 inhibitor palbociclib in long-term clonogenic assays, with assessment of combination effect with Combination Index and Bliss Independence (BI). Cell lines were ascribed to Lehmuth subtypes. BRDU proliferation assays, mRNA expression and western blots were conducted to investigate the mechanisms of sensitivity to CDK4/6 inhibition in specific subsets. In addition we interrogated datasets from the TCGA breast cancer cohort to compare gene expression, copy number alterations or cell cycle genes across the different TNBC subtypes. Results: TNBC cell lines of the luminal-androgen (LAR) and mesenchymal-stem like (MSL) subsets were sensitive to palbociclib in both clonogenic and BRDU proliferation assays (p < 0.0001 LAR vs basal-like subtypes). Sensitivity was associated with expression of androgen receptor (p = 0.0013), and the absence/or low levels of cyclin E1 (p = 0.01). Resistant mesenchymal (M) and basal TNBC cell lines had elevated levels of cyclin E1 mRNA and protein. Analysis of TCGA data revealed that high-level amplification of cyclin E1 is more common in basal tumours compared to the luminal subgroups (p = 0.0069). Sensitivity of TNBC LAR/MSL cell lines to palbociclib was limited by low-level cell cycle entry despite CDK4/6 inhibition. Combination studies highlighted PI3K inhibition was synergistic with CDK4/6 inhibition in PIK3CA mutated TNBC cell lines (BI score: < 1.0), with a greater effect in LAR/MSL subgroups compared to M basal subgroups (p = 0.015). The combination induced sustained proliferative arrest compared to palbociclib alone in LAR sub group (p = 0.0007).

Conclusions: We demonstrate that LAR cell lines represent a TNBC subgroup that may benefit from CDK4/6 inhibition. Interestingly, TNBC with PIK3CA mutations could also benefit by targeting both cell cycle and PI3K-mTOR signaling.

Association of paclitaxel-induced sensory peripheral neuropathy with the ABCB1 gene variant and age. First Author: Chikako Shimizu, Rati Cancer Ctr Hosp. Tokyo, Japan.

Background: The development of paclitaxel-induced peripheral neuropathy (PIPN) is influenced by the age and genetic composition of patients. Paclitaxel is known to act as a substrate in SLC01B3-mediated influx, ABCB1-mediated efflux from cancer cells, and CYP2C8-mediated metabolism. We conducted a prospective study to investigate whether age and these single nucleotide polymorphisms (SNPs) are correlated with PIPN. Methods: Breast cancer patients who received adjuvant weekly paclitaxel were genotyped for five SNPs in three genes, including rs4149117 in SLC01B3; rs2032582, rs1045642, and rs1128503 in ABCB1; and rs10509681 in CYP2C8, using PCR genotyping probe method. Clinical data, including the paclitaxel dose and onset and severity of neuropathy, were correlated with the genetic data. Results: We enrolled 127 Japanese patients with a median age of 50 years (range, 25–75 years). The mean total paclitaxel dose administered was 933 mg/m² (range, 560–960 mg/m²), and 85% received the full dose intensity treatment (960 mg/m² over 12 weeks). The majority of patients (98.4%) developed all grade neuropathy, and 51.9% of patients exhibited grade 2 or higher severity. Severe neuropathy, defined as those requiring a dose delay, dose reduction, or early termination of chemotherapy, occurred in 15.0% of patients. Of the five SNPs evaluated, the ABCB1 (rs1128503) TT genotype was associated with a grade 2 or higher neuropathy compared with the CC/CT genotype (p = 0.05). Of note, patients with the TT genotype aged > 60 years had a higher incidence of grade 2 or higher severity (p = 0.008) than those with the CC/CT genotype. Patients without PIPN were all wild type for the five SNPs. Patients aged > 60 years had a higher incidence of grade 2 or higher severity (p = 0.006) than younger patients, regardless of the SNPs. Conclusions: ABCB1 rs1128503 SNP and advanced age are correlated with PIPN. This findings may help clinicians determine which patients should avoid paclitaxel. Clinical trial information: UMIN000005294.

Squamousness: Next-generation sequencing to reveal shared molecular features across squamous tumor types. First Author: Maria Clemence Schwaederle, UC San Diego Moores Cancer Center, La Jolla, CA.

Background: In order to gain a better understanding of the underlying biology of squamous cell carcinoma (SCC), we tested the hypothesis that SCC originating from different organs may possess common molecular alterations. Methods: SCC samples (N = 361) were examined using clinical-grade targeted next-generation sequencing (NGS) (182 or 236 cancer-related genes). Results: The most frequent SCC tumor types were head and neck, lung, cutaneous, gastrointestinal and genitourinary. The most common gene alterations were TP53 (64.5% of patients), PIK3CA (28.5%), CDKN2A (24.4%), SOX2 (17.7%), and CCND1 (15.8%). By comparing NGS results of our SCC cohort to a non-SCC cohort (N = 277), we found that CDKN2A, SOX2, NOTCH1, TP53, PIK3CA, CCND1, and FBXW7 were significantly more frequently altered, unlike KRAS, which was less frequently altered in SCC specimens (all P < 0.05; multivariable analysis). Therefore, we identified “squamousness” gene signatures (TP53, PIK3CA, CCND1, CDKN2A, SOX2, NOTCH1, and FBXW7 aberrations, and absence of KRAS alterations) that were significantly more frequent in SCC versus non-SCC histologies. A multivariable co-alteration analysis established two SCC subgroups: (i) patients in whom TP53 and cyclin pathway (CDKN2A and CCND1) alterations strongly correlated but in whom PIK3CA aberrations were less frequent; and (ii) patients with PIK3CA alterations in whom TP53 mutations were less frequent (all P = 0.001; multivariable analysis).

Conclusions: We identified a set of eight genes altered with significantly different frequencies when SCC and non-SCC were compared, suggesting the existence of patterns for “squamousness.” Targeting the PI3K-AKT-mTOR and/or cyclin pathway components in SCC may be warranted.
Impact of BMI on survival and toxicity in early breast cancer: An exploratory analysis of prospective randomized phase III study N-SAS BC02 and 03. 
First Author: Yoichi Naito, National Cancer Center Hospital East, Chiba, Japan

Background: Obesity is reported to be associated with worse prognosis in early breast cancer. As obesity is rare and low BMI is relatively common in Japanese population compared to Caucasians, the impact of BMI on survival and toxicity in Japanese cohort should be assessed. Here we report an exploratory analysis of the data included in randomized phase III trials for early breast cancer in Japan. Methods: Patients included in phase III trial N-SAS BC02 or BC03 were analyzed. N-SAS BC02 investigated four arms of adjuvant chemotherapy consisted of taxane alone or in combination with anthracycline-containing regimen (median follow up of 6.1 years). NSAS BC03 compared anastorozole with tamoxifen as adjuvant endocrine therapy (median follow up of 6.4 years). The correlations of BMI and overall survival or toxicity were retrospectively analyzed. Results: A total of 1726 patients were included in our study. Median age was 56 years, 71.2% of tumors were ER positive, and 9.7% were HER2 overexpressed, 76% had lymph node metastasis. Mean value of BMI was 23.3 and only 4.6% of patients had BMI over 30. 33.1% of patients had BMI under 22 and 4.8% had BMI under 18.5. In the Cox proportional hazards model adjusted randomized arms, lower BMI was significantly associated with worse prognosis (BMI > 27 vs <27, HR 0.55, p = 0.025). The same trend was observed in adjusted analysis for prognostic factors (HR 0.61, p = 0.064). Subgroup analysis of hormone receptor positive cohort showed that higher BMI was correlated with worse prognosis in premenopausal patients; on the other hand, in postmenopausal patients higher BMI was correlated with better prognosis. There was no significant correlation between BMI and toxicity. Conclusions: We confirmed that obesity is rare in Japanese patients with early breast cancer. In this non-obese population, lower BMI was correlated with worse prognosis without significant impact on toxicity. Subgroup analysis suggested interaction between menopausal status and BMI on survival. Detrimental effect of higher BMI on survival is limited to premenopausal hormone receptor positive patients.

Pharmacodynamic (PD) assessment using FLT-PET/CT imaging in patients treated with an interrupted high-dose axitinib schedule. 
First Author: Ludmila Cavalcante, University of Wisconsin, Madison, WI

Background: Axitinib (AX) is a potent inhibitor of receptor tyrosine kinases (RTK) of VEGFR-1, 2, 3. We previously showed that exposure to AX resulted in a decrease in tumor proliferation and vascular parameters, and during acute AX withdrawal, a rebound flare (proliferative and vascular) was present during cycle 1 (C1). Here we evaluate the impact of AX dose on the rebound pharmacodynamics, as well as assess whether this flare persists in later cycles of therapy with AX using an intermittent therapy schedule. Methods: Pts with prostate cancer or other advanced solid malignancies were enrolled. In the safety cohort, AX was administered at 7 mg BID on a 2 week on, 1 week off schedule. In the PD cohort, static/dynamic FLT/PET/CT scans were obtained at baseline, week 2 (on AX), and wk 3 (off AX) in C1, and repeated again in C3 (pre-day 1, wk 2, wk 3). Plasma VEGF and AX PK levels were obtained at each imaging timepoint. Results: 24 pts were enrolled (safety cohort n = 8, PD cohort n = 16). Pts in the safety cohort received AX starting at 7 mg BID. Three pts developed significant hypertension and thrombovascular events; hence it was not felt that this starting dose was appropriate. For the PD cohort, AX dose was administered at 5 mg BID. 14 pts had scans on C1, and 5 pts completed scans during C3. Similar changes in proliferation/vasculature parameters were seen in C1 as previously reported. Decreases in proliferation/vasculature parameters were also seen in C3 (on AX) with rebound flare present at wk 3. Conclusions: Although AX dose of 7 mg BID (up to 15 mg BID) was feasible in renal cell cancer, use of intermittent AX at a starting dose of 7 mg BID was not feasible in our non-RCC pt population. We confirm previous findings that AX exposure results in a decrease in proliferation/vasculature parameters and that acute AX withdrawal results in a tumor/vasculature rebound. We show with ongoing intermittent AX therapy, a similar PD change was observed in pts during C3. This result supports a sequential strategy of using intermittent AX in combination with S-phase specific chemotherapy in order to exploit the tumor/vasculature rebound in order to improve the therapeutic index of the cytotoxic chemotherapy. Clinical trial information: NCT01540526.
Background: Several distinct cancers are caused by human papillomavirus (HPV)- including squamous cell carcinomas of the cervix (SCC), anal canal (ASCc), and oropharynx (OSCc).

Methods: 201 ASCc, 351 CSe, and 258 OSCc tumor samples underwent molecular profiling with a multiparameter approach (Caris Life Sciences). TP53 wild type status was used as a surrogate for HPV. Testing included sequencing (NGS), copy number (CNV), and protein expression (IHC) CNV and CNV were assessed through IHC. The 2x2 Fisher’s exact test (p≤0.05), JMP10.0 (SAS Institute Inc., Cary, NC) was utilized for statistical analysis. Results: Of the 593 patients evaluated, 197 ASCc, 317 OSCC and 317 SCC were included in the study. Multiparameter profiling revealed marked similarities among the HPV-induced cancers. None of the frequencies observed displayed statistically significant differences. Selected results are provided below.

Conclusions: Unlike the genomic instability observed in many solid tumors, HPV-induced carcinogenesis yields a more homogenous phenotype. These data support previous work identifying the PIK3CA-AKT-mTOR pathway as a potential target. Given the phenomenon of HPV E6 & E7-induced oncogene addiction, following viral integration, the need to explore mTOR pathway as a potential target. Given the phenomenon of HPV E6 & E7-induced oncogene addiction following viral integration, the need to explore mTOR pathway as a potential target.
Background: While many targeted agents are approved for specific cancers, molecular profiling has increasingly led to the identification of genetic abnormalities in tumor types for which targeted agents are not currently approved. MyPathway explores the activity and safety of therapies that target HER2, EGFR, BRAF, and Hedgehog pathways in cancers for which these treatments are not FDA-approved. **Methods:** MyPathway (trial registration NCT02091141) is a multicenter, non-randomized, phase IIa study of patients with advanced solid tumors that have progressed following standard therapy or for which there is no approved treatment. Eligible patients have a tumor with a potentially actionable genetic alteration, as determined by a Clinical Laboratory Improvement Amendments-certified laboratory. Patients with >1 mutation are treated based on the mutation considered most critical by the investigator; they may later enroll based on a different mutation, if initial therapy fails. For each pathway, treatments are dosed based on the approved regimen. Patients are evaluated for response after 2 cycles of therapy, those with an objective response or stable disease may continue therapy until tumor progression or unacceptable toxicity. Safety is monitored in real time and reviewed every 3–6 mos. The primary outcome is response rate. Secondary outcomes are disease control rate, progression-free survival, and 1-year survival. Outcomes will be studied by tumor type and pathway (tumor-pathway cohorts). Sample sizes for tumor-pathway cohorts are based on Simon’s 2-stage design procedure. Use of the master protocol will allow possible future exploration of additional pathways as new agents become available. Evidence of activity in this trial may be studied in larger dedicated trials. Clinical trial information: NCT02091141.

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<tr>
<th>Pathway</th>
<th>Molecular alteration</th>
<th>Treatment(s)</th>
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<tr>
<td>HER2</td>
<td>Overexpression of HER2 or activating mutation</td>
<td>Trastuzumab and pertuzumab, Erlotinib</td>
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<tr>
<td>EGFR</td>
<td>EGFR-activating mutation</td>
<td>Erlotinib</td>
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<tr>
<td>BRAF</td>
<td>BRAF-activating mutation (V600E and others)</td>
<td>Vemurafenib</td>
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<tr>
<td>Hedgehog</td>
<td>SMO-activating/mutation, PTC7-1</td>
<td>Vismodegib</td>
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**Conclusion:** The SHIVA trial randomized patients to treatment based on tumor subtype and pathway. Clinical trial information: NCT01872975.

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