Abstract ID: LBA3 (151578)

Elective versus therapeutic neck dissection in the clinically node negative early oral cancer: A randomised control trial (RCT).

Authors: *Anil D'Cruz, Mitali Dandekar, Richa Vaish, Supreeta Arya, Gouri Pantvaidya, Pankaj Chaturvedi, Devendra Chaukar, P. S. Pai, Anuja Deshmukh, Shubhada Kane, Deepa Nair, Sudhir Vasudevan Nair, Asawari Patil, Rohini W Hawaldar, Manasi Dhopeshwarkar, Jaiprakash Agarwal; Tata Memorial Hospital, Mumbai, India; Tata Memorial Hospital, Navi Mumbai, India; Tata Memorial Centre, Mumbai, India*

Background: Management of the neck in early oral cancers has been a matter of debate with clinical equipoise between elective (END) or therapeutic neck dissection (TND). **Methods:** This is a prospective phase III RCT (NCT00193765) to test the superiority of END at the time of primary surgery over TND (neck dissection at the time of nodal relapse) in patients with lateralized T1 or T2 squamous carcinoma of oral cavity, amenable to peroral excision. Patients were stratified based on size, site, sex and preoperative neck ultrasound. The primary end point was overall survival (OS) and secondary end point was disease-free survival (DFS). The trial was planned to demonstrate a 10% superiority (1-sided $\alpha = 0.05$ and $\beta = 0.2$) in OS for END vs. TND, assuming 60% 5-year OS in TND arm, with a planned sample size of 710. **Results:** This trial was terminated after 596 patients were randomized between January 2004 and June 2014. An interim intent-to-treat analysis of initial 500 patients (255 in TND, 245 END) with a minimum follow-up of 9 months was performed as mandated by Data and Safety Monitoring Committee based on the number of observed deaths in each arm. Both arms were balanced for site and stage. There were 427 tongue, 68 buccal mucosa and 5 floor of mouth tumors; 221 were TI and 279 T2. At a median follow-up of 39 months there were 146 recurrences in TND and 81 in END arms respectively. The 3-year OS was significantly higher in END compared to TND arm (80.0% vs. 67.5%, HR = 0.63, 95%CI 0.44-0.89, $P = 0.01$) as was 3-year DFS (69.5% vs. 45.9%, HR = 0.44, 95%CI 0.34-0.58, $P < 0.001$). After adjusting for stratification factors in Cox regression, END continued to be significantly superior to TND for both OS and DFS. **Conclusions:** There were 8 excess deaths for every 15 excess recurrences in the TND arm. Elective neck dissection in patients with early oral SCC results in 37% reduction in mortality and should be considered the standard of care. Clinical trial information: NCT00193765.

Abstract ID: 6000 (149178)

Phase III randomized trial of standard fractionation radiotherapy (SFX) with concurrent cisplatin (CIS) versus accelerated fractionation radiotherapy (AFX) with panitumumab (PMab) in patients (pts) with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): NCIC Clinical Trials Group HN.6 trial.

Authors: *Lillian L. Siu, John N. Waldron, Bingshu E. Chen, Eric Winquist, Jim R. Wright, Abdenour Nabid, John H Hay, Jolie Ringash, Geoffrey Liu, Ana Johnson, George Shenouda, Martin Robert Chasen, Andrew Pearce, James B. Butler, Stephen Breen, Eric Xueyu Chen, T J Childs, Alexander Montenegro, Brian O'Sullivan, Wendy R. Parulekar; Princess Margaret Cancer Centre, Toronto, ON; NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, ON; London Health Sciences Centre, London, ON; Juravinski Cancer Ctr, Hamilton, ON; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC; British Columbia Cancer Agency, Vancouver, BC; Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON; Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON; Queen's University, Kingston, ON; McGill University Health Centre, Montreal, QC; Palliative Care, at The Ottawa Hospital Cancer Centre and the Medical Director of the Palliative Rehabilitation Program at the Élisabeth Bruyère Hospital, Ottawa, Ottawa, ON; North East Cancer Centre, Sudbury, ON; Cancer Care Manitoba, Winnipeg, MB; Princess Margaret Hospital, Toronto, ON*

Background: Concurrent administration of anti-EGFR monoclonal antibody with radiotherapy (RT) increases survival compared to RT alone in pts with LA-SCCHN. No prospective data are available comparing bioradiotherapy to standard chemoradiotherapy. **Methods:** Pts with TanyN+M0 or T3-4N0M0 LA-SCCHN were randomized 1:1 to receive SFX (70Gy/35 over 7 weeks) plus CIS at 100 mg/m^2 intravenous (IV) for 3 doses on weeks 1, 4 and 7 (Arm A) versus AFX (70Gy/35 over 6 weeks) plus the anti-EGFR monoclonal antibody PMab at 9 mg/kg IV for 3 doses on weeks -1, 3 and 6 (Arm B). Primary endpoint was progression-free survival (PFS). A total of 320 patients were accrued from 12/2008 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%) positive and 41 (19%) negative. A total of 93 PFS events occurred. By intention-to-treat, 2-year PFS was 73% (95% CI: 65-79%) in Arm A and 76% (95% CI: 68-82%) in Arm B, hazard ratio (HR) = 0.95; 95% CI: 0.6-1.5; 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: 82-92%) in ArmB, 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. **Conclusions:** With a median follow-up of 46.4 months, PFS of PMab+AFX was not superior to CIS+SFX in LA-SCCHN and non-inferiority was not proven.

Abstract ID: 6005 (146171)

Prognostic implication of persistent HPV16 DNA detection in oral rinses for HPV-positive oropharyngeal carcinoma.

Authors: *Eleni Marie Rettig, Alicia Wentz, Marshall R. Posner, Neil D. Gross, Robert I. Haddad, Maura L. Gillison, Harry Quon, Andrew Gregory Sikora, Will Stott, Jochen H. Lorch, Christine Gail Gourin, Brett Miles, Jeremy Richmon, Krzysztof Misiukiewicz, Christine H. Chung, Carole Fakhry, Gypsyamber D'Souza; Johns Hopkins School of Medicine, Department of Otolaryngology-Head and Neck Surgery, Baltimore, MD; Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD; Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Ohio State Univ, Columbus, OH; The Johns Hopkins University, Baltimore, MD; Baylor College of Medicine, Houston, TX; Oregon Health & Science University, Portland, OR; Dana Farber Cancer Inst/ Harvard Univ, Boston, MA; Johns Hopkins Univ, Baltimore, MD; Department of Otolaryngology, Mount Sinai Medical Center, New York, NY; Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

Background: Human papillomavirus-positive oropharyngeal carcinoma (HPV-OPC) has a favorable prognosis; however, 10-25% of HPV-OPC cases recur. Oral HPV DNA detection is associated with HPV-OPC, but its value as a prognostic biomarker is unclear. **Methods:** Patients with incident HPV-OPC treated with curative intent were enrolled from October 2009-May 2013 at four centers. Oral rinses were collected at baseline (diagnosis) and post-therapy at 9, 12, 18 and 24 months after diagnosis. Oral rinses were evaluated for 36 types of HPV DNA. Survival analyses were performed using Kaplan Meier method and Cox regression models. Disease free survival (DFS) and overall survival (OS) were estimated. **Results:** 151 patients were included and 124 (79%) had one or more post-treatment oral rinse (median three). Oral HPV16 DNA was common at baseline (N = 85, 56%). In contrast, oral HPV16 DNA was detected in only six patients in follow up (5%), including five who had HPV16 DNA at baseline (persistent oral HPV16 DNA) and one who did not. Two-year DFS and OS were 92.2% and 97.5%, respectively for all 151 cases. Persistent oral HPV16 DNA was associated with significantly worse DFS (adjusted HR 34.0, 95%CI 7.9-146) and OS (adjusted HR 16.9, 95%CI = 3.1-93). Among patients who recurred (n = 15, 10%), median time to recurrence was 15 months from diagnosis. All five patients with persistent oral HPV16 DNA recurred. Three of these cases included local recurrence. Median time from earliest post-treatment oral HPV16 DNA detection to recurrence was seven months (range 3-11). Among 108 patients with a post-treatment oral rinse collected 9-12 months after diagnosis, detection of persistent oral HPV16 DNA had 100% positive predictive value (3/3), 96% negative predictive value (4/108), 43% sensitivity (3/7) and 100% specificity (104/104) for predicting recurrence between 12-24 months. **Conclusions:** Oral HPV16 DNA detection in oral rinses is common at baseline but rare after treatment for HPV-OPC. Our data suggest that persistent oral HPV16 DNA in post-treatment rinses is strongly associated with poor prognosis, may have high positive and negative predictive value for recurrence, and is a potential tool for long-term tumor surveillance.

Abstract ID: LBA6008 (149051)

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.

Authors: *Tanguy Y. Seiwert, Robert I. Haddad, Shilpa Gupta, Ranee Mehra, Makoto Tahara, Raanan Berger, Se-Hoon Lee, Barbara Burtness, Dung T. Le, Karl Heath, Amy Blum, Marisa Dolled-Filhart, Kenneth Emancipator, Kumudu Pathiraja, Jonathan D. Cheng, Laura Q. Chow; The University of Chicago, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Fox Chase Cancer Center, Philadelphia, PA; National Cancer Center Hospital East, Kashiwa, Japan; Sheba Medical Center, Tel HaShomer, Israel; Seoul National University Hospital, Seoul, South Korea; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Sidney Kimmel Comprehensive Cancer Center at JHU, Baltimore, MD; Merck & Co., Inc., Kenilworth, NJ; Department of Medicine, Division of Oncology, University of Washington, Seattle, WA*

Background: Pembrolizumab (MK-3475) is a humanized monoclonal antibody that blocks interaction of PD-1 with its ligands, PD-L1 and PD-L2, thereby promoting activity of tumor-specific effector T cells. KEYNOTE 012 (NCT01848834) had previously demonstrated clinical activity of pembrolizumab 10 mg/kg every 2 weeks in patients (pts) with recurrent/metastatic SCCHN enriched for PD-L1–positive tumors with a response rate of 20%. We now report on the larger SCCHN expansion cohort of KEYNOTE 012, irrespective of biomarker status using a 3-weekly fixed dose. **Methods:** Pts with advanced SCCHN irrespective of PD-L1 expression or HPV status received a fixed dose of 200 mg pembrolizumab, intravenously, every 3 weeks. Pts were evaluated every 8 weeks with radiographic imaging. The primary end point was overall response rate (ORR) per investigator assessment (RECIST 1.1). Secondary objectives included progression-free survival (PFS) and overall survival (OS). Adverse events (AEs) were assessed according to CTCAE v4. PD-L1 was assessed retrospectively by immunohistochemistry. **Results:** 132 pts with recurrent/metastatic SCCHN were enrolled. Mean (SD) age was 58.9 (9.7) years; 83.3% were male; 56.8% had ≥ 2 lines of therapy for recurrent disease. 73/132 pts (55.3%) remain on treatment. Out of 132 treated pts, 99 pts were available for this preliminary efficacy analysis with a post-baseline scan or discontinued therapy prior to the scan due to clinical progression or AE. ORR (confirmed and unconfirmed) per RECIST 1.1 was 18.2% (95% CI, 11.1-27.2) with 18 partial responses and 31.3% with stable disease. Biomarker analysis is ongoing and results will be presented. Drug-related AEs of any grade occurred in 47% of all enrolled pts, and drug-related grade ≥ 3 AEs occurred in 7.6%. The most common drug-related AEs (≥ 5%) of any grade were fatigue (12.1%), decreased appetite (6.8%), pyrexia (6.1%), and rash (5.3%). **Conclusions:** Pembrolizumab given at a fixed dose of 200 mg every 3 weeks was well tolerated and demonstrated a clinically meaningful ORR of 18.2% in pts with recurrent/metastatic SCCHN. Clinical trial information: NCT01848834.

Abstract ID: 6009 (149962)

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).

Authors: *Hisham Mohamed Mehanna, Wai Lup Wong, Christopher C McConkey, Joy K Rahman, Max Robinson, Andrew G. J. Hartley, Christopher Nutting, Ned Powell, H Al-Booz, Martin Robinson, Elizabeth Junor, Claire Hulme, Alison Florence Smith, Peter Hall, Janet Dunn; InHANSE, School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom; Paul Strickland Scanner Centre, Mount Vernon Hospital, Middlesex, United Kingdom; Warwick University Clinical Trials Unit, Coventry, United Kingdom; Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle, United Kingdom; Queen Elizabeth Hospital, Birmingham, United Kingdom; Royal Marsden Hospital, London, United Kingdom; HPV Oncology Group, Institute of Cancer and Genetics, Cardiff University, Cardiff, United Kingdom; Bristol Haematology and Oncology Centre, Bristol, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; Edinburgh Cancer Centre, Western General Hospital, Edinburgh, United Kingdom; University of Leeds, Leeds, United Kingdom; St James University Hospital, Leeds, 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. In mainly retrospective single-institution studies, FDG-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 by 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.

Abstract ID: LBA 4(146056)

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.

Authors: *Paul D. Brown, Anthony L. Asher, Karla V. Ballman, Elana Farace, Jane H Cerhan, S. Keith Anderson, Xiomara W. Carrero, Frederick G. Barker II, Richard L. Deming, Stuart Burri, Cynthia Menard, Caroline Chung, Volker W. Stieber, Bruce E. Pollock, Evanthia Galanis, Jan C. Buckner, Kurt A. Jaeckle; The University of Texas MD Anderson Cancer Center, Houston, TX; Carolinas Healthcare System-Neuroscience Institute, Charlotte, NC; Mayo Clinic, Rochester, MN; Penn State Hershey Medical Center, Hershey, PA; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Massachusetts General Hospital, Boston, MA; Mercy Cancer Ctr, Des Moines, IA; Levine Cancer Institute-Radiation Oncology, Charlotte, NC; Princess Maraget Hospital, Toronto, ON; Princess Margaret Cancer Centre, University Health Network, Toronto, ON; Novant Health Forsyth Medical Center, Winston Salem, NC; Mayo Clinic Florida, Jacksonville, FL*

Background: WBRT significantly improves tumor control in the brain after SRS, yet the role of adjuvant WBRT remains undefined due to concerns regarding neurocognitive risks. **Methods:** Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk. **Results:** 213 patients were enrolled with 2 ineligible and 3 cancels prior to receiving treatment. Baseline characteristics were well-balanced between study arms. The median age was 60 and lung primary the most common (68%). CP at 3 months was more frequent after WBRT + SRS vs. SRS alone (88.0% vs. 61.9% respectively, $P = 0.002$). There was more deterioration in the WBRT + SRS arm in immediate recall (31% vs. 8%, $P = 0.007$), delayed recall (51% vs. 20%, $P = 0.002$), and verbal fluency (19% vs. 2%, $P = 0.02$). Intracranial tumor control at 6 and 12 months were 66.1% and 50.5% with SRS alone vs. 88.3% and 84.9% with SRS+WBRT ($P < 0.001$). Median OS was 10.7 for SRS alone vs. 7.5 months for SRS+WBRT respectively (HR = 1.02, $P = 0.93$). **Conclusions:** Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS. Clinical trial information: NCT00377156

Abstract ID: LBA109 (154634)

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).

Authors: *Luis Paz-Ares, Leora Horn, Hossein Borghaei, David R. Spigel, Martin Steins, Neal Ready, Laura Quan Man Chow, Everett E. Vokes, Enriqueta Felip, Esther Holgado, Fabrice Barlesi, Martin Kohlhaeufl, Oscar Arrieta, Marco Angelo Burgio, Jerome Fayette, Scott N. Gettinger, Christopher Harbison, Cécile Dorange, Friedrich Graf Finckenstein, Julie R. Brahmer; Hospital Universitario Doce de Octubre, Sevilla, Spain; Vanderbilt-Ingram Cancer Center, Nashville, TN; Fox Chase Cancer Center, Philadelphia, PA; Sarah Cannon Research Institute, Nashville, TN; Thoraxklinik-Heidelberg gGmbh, Heidelberg, Germany; Duke University Medical Center, Chapel Hill, NC; University of Washington, Seattle, WA; Department of Medicine, University of Chicago, Chicago, IL; Vall d'Hebron University Hospital, Barcelona, Spain; START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; Aix Marseille University - Assistance Publique Hopitaux De Marseille, Marseille, France; Hospital Schillerhoehe Gerlingen, Gerlingen, Germany; Instituto Nacional de Cancerología, Mexico City, Mexico; IRST-IRCCS, Meldola (FC), Italy; Centre Leon Berard, Lyon, France; Yale School of Medicine, New Haven, CT; Bristol-Myers Squibb, Princeton, NJ; Bristol‐Myers Squibb, Princeton, NJ; Bristol-Myers Squibb Co, Princeton, NJ; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Options for advanced non-SQ NSCLC patients (pts) who progress after platinum-based doublet chemotherapy (PT-DC) are limited, with minimal improvement in overall survival (OS). We report results from a randomized, global phase III study of NIVO, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, vs DOC in pts with advanced non-SQ NSCLC after failure of PT-DC and tyrosine kinase inhibitor, if eligible. **Methods:** Pts were randomized to NIVO 3 mg/kg Q2W (n=292) or DOC 75 mg/m^2 Q3W (n=290) until progression or discontinuation due to toxicity/other reasons. Primary objective was OS; secondary objectives were investigator-assessed objective response rate (ORR; per RECIST v1.1), progression-free survival (PFS), efficacy by PD-L1 expression, quality of life, and safety. **Results:** NIVO demonstrated superior OS (HR=0.73; 96% CI: 0.59, 0.89; *P*=0.00155) and improved ORR (19.2% vs 12.4%; *P*=0.0235). HR for PFS was 0.92 (95% CI: 0.77, 1.11; *P*=0.393). PD-L1 expression was associated with benefit from NIVO (Table). In PD-L1+ pts, NIVO showed improved efficacy across all endpoints at predefined 1%, 5%, and 10% cut- points. Grade 3–5 drug-related AEs occurred in 10.5% (30/287) of NIVO and 53.7% (144/268) of DOC pts. No deaths were related to NIVO vs 1 DOC-related death. After discontinuation, 42.1% of NIVO and 49.7% of DOC pts received subsequent systemic therapy. **Conclusions:** NIVO demonstrated superior OS vs DOC in pts with advanced non-SQ NSCLC after failure of PT-DC. The safety profile of NIVO 3 mg/kg Q2W was favorable vs DOC. NIVO demonstrated survival benefit across histologies in two randomized phase III trials. Clinical trial information: NCT01673867

Efficacy measure	NIVO(n=292)	DOC(n=290)
mOS,mo (95% CI)	12.2(9.7,15.0)	9.4(8.0,10.7)
1-yr OS,% (95% CI)	50.5(44.6,56.1)	39.0(33.3,44.6)
Median response duration, mo (95% CI)	17.1(8.4-not estimable)	5.6(4.4-7.0)
mPFS,mo (95% CI)	2.3(2.2,3.3)	4.2(3.4,4.9)
yr PFS,% (95% CI)	18.5(14.1,23.4)	8.1(5.1,12.0)
m=median		

PD-L1-quantifiable pls			
PD-L1 expression	NIVO,n (N=231)	DOC,n (N=224)	OS HR(95% CI)
<1%	108	101	0.9(0.66,1.24)
>=1%	123	123	0.59(0.43,0.81)
<5%	136	138	1.01(0.76,1.33)
>=5%	95	86	0.43(0.3,0.63)
<10%	145	145	1.00(0.76,1.31)
>=10%	86	79	0.4(0.27,0.59)

Abstract ID: 8001 (152181)

Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts)

Authors: *Lecia V. Sequist, Jonathan Wade Goldman, Heather A. Wakelee, D. Ross Camidge, Helena Alexandra Yu, Andrea Varga, Ben Solomon, Geoffrey R. Oxnard, Sai-Hong Ignatius Ou, Vassiliki Papadimitrakopoulou, Bo H. Chao, Stephen V. Liu, Karen L. Reckamp, Alexander I. Spira, Zofia Piotrowska, Darrin Despain, Chris Alan Karlovich, Sergey Yurasov, Jean-Charles Soria; Massachusetts General Hospital, Boston, MA; UCLA, Santa Monica, CA; Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA; University of Colorado Cancer Center, Aurora, CO; Memorial Sloan Kettering Cancer Center, New York, NY; Gustave Roussy Institute, Villejuif, France; Peter MacCallum Cancer Centre, East Melbourne, Australia; Dana-Farber Cancer Institute, Boston, MA; Chao Family Comp Cancer Ctr UC Irvine Medcl Ctr, Orange, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University, Columbus, OH; Georgetown Univ Hosp, Washington, DC; City of Hope, Department of Medical Oncology and Therapeutics Research, Duarte, CA; Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA; Massachusetts General Hospital Cancer Center, Boston, MA; Clovis Oncology, Inc., San Francisco, CA; Clovis Onc, San Francisco, CA; Clovis Oncology, San Francisco, CA; Gustave-Roussy Cancer Campus, Drug Development Department, Villejuif, France*

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 present data from the pt subset with T790M detected by plasma genotyping. **Methods:** For the overall phase 1/2 study, pts had EGFR-mutant NSCLC and treatment with ≥ 1 EGFR inhibitor, ECOG PS 0-1. Brain metastases were allowed. In phase 2, T790M pos by central tumor genotyping was required. Plasma EGFR status was assessed by BEAMing (Sysmex), a quantitative assay using emulsion PCR then flow cytometry. **Results:** 345 pts were enrolled at active doses, median age 62 yrs, 66% female, 69% ECOG 1, 87% from US sites, median prior therapies 3 (45% ≥ 2 prior TKIs). Response data are available for 219 with tissue genotyping and 113 with plasma genotyping. The RECIST objective response rate (ORR) was ~48% in T790M pos pts, regardless of genotyping 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 AEs in ≥ 15% patients were: hyperglycemia (40%), diarrhea (28%), nausea (23%), fatigue (21%), decreased appetite (17%). **Conclusions:** Rociletinib is associated with durable response and is well tolerated in pts with EGFR mutant 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.

Table: Outcome by genotype/ biopsy type		T790M +	T790M -
Tissue genotype	ORR (%)	ORR: 91/186 (49)	12/33 (36)
	DoR (days)	1-394+	1-283+
Plasma genotype	ORR	40/83 (48)	10/30 (33)
	DoR	1-394+	74-329

Abstract ID: 8005 (149588)

Whole brain radiotherapy for brain metastases from non-small lung cancer: Quality of life (QoL) and overall survival (OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061).

Authors: *Paula Mary Mulvenna, Matthew Guy Nankivell, Rachael Barton, Corinne Faivre-Finn, Paula Wilson, Barbara Moore, Elaine McColl, Iona Brisbane, David Ardron, Benjamin Sydes, Cheryl Pugh, Tanya Holt, Neil Bayman, Sally Morgan, Caroline Lee, Kathryn Waite, Richard Stephens, Mahesh M K Parmar, Ruth E Langley; Department of Clinical Oncology, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom; Medcl Rsrch Council, London, United Kingdom; Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom; Christie Hospital, Withington Manchester, United Kingdom; University Hospitals Bristol, Bristol, United Kingdom; NISCHR CRC, Cardiff, United Kingdom; Newcastle Clinical Trials Unit, Newcastle, United Kingdom; NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; Patient Representative, Barnsley, United Kingdom; MRC Clinical Trials Unit at UCL, London, United Kingdom; Clinical Trials Unit, Medical Research Council, London, United Kingdom; Mater Centre, Brisbane, Australia; The Christie NHS Foundation Trust, Manchester, United Kingdom; Nottingham University Hospitals, Nottingham, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; Queen Elizabeth Hospital Kings Lynn, Kings Lynn, United Kingdom; Retired, London, United Kingdom; Medical Research Council, Clinical Trials Unit at University College London, London, United Kingdom; Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom*

Background: Brain metastases affect up to 40% of patients with non-small cell lung cancer (NSCLC), and for inoperable cases whole brain radiotherapy (WBRT) and dexamethasone is standard treatment. However there are no randomised clinical trials to show whether WBRT improves either QoL or survival. **Methods:** A phase III randomised non-inferiority trial with a primary outcome measure of quality adjusted life years (QALYs). Patients with brain metastases from NSCLC (not suitable for resection or stereotactic radiotherapy) were randomly allocated to either optimal supportive care, including dexamethasone, plus WBRT 20 Gy/5f (OSC+WBRT) or OSC alone. QALYs were generated from OS and patients' weekly completion of the EQ-5D questionnaire. OSC alone was considered non-inferior to OSC+WBRT if not greater than 7 QALY days worse (80% power and a 1-sided 5% significance level required 534 patients.) Secondary outcome measures include sub-group analyses to identify/validate predictive classifications.**Results:** From 2007-2014 538 patients were recruited from 69 UK and 3 Australian centres. Baseline characteristics were balanced between arms and reflect everyday clinical practice: male 58%, median age 66 years (range 38 – 85), Karnofsky performance status < 70 38%, 54% had extracranial metastases, 30% had a solitary brain metastasis and 59% diagnosed with brain metastases within 28 days of randomisation. By January 2015 522/538 patients had died. There was no significant difference in OS from randomisation (hazard ratio 1.05 (95% CI 0.89 – 1.26) median survival OSC+WBRT v OSC (65 v 57 days)), overall QoL or steroid use between the 2 groups. The difference between the mean QALYs was -1.9 days (OSC+WBRT 43.3 v OSC 41.4 QALY days), two-sided 90% confidence interval for difference -9.1 to +6.6 QALY days. **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.

Abstract ID: 8006 (147124)

Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with BRAF V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC).

Authors: *David Planchard, Harry J.M. Groen, Tae Min Kim, James R. Rigas, Pierre Jean Souquet, Christina S. Baik, Fabrice Barlesi, Julien Mazières, Elisabeth A. Quoix, C. Martin Curtis Jr., Bijoyesh Mookerjee, Arundathy N. Bartlett-Pandite, Christine Tucker, Anthony D'Amelio Jr., Bruce E. Johnson; Gustave Roussy, Villejuif, France; University of Groningen and Department of Pulmonary Diseases, University Medical Center Groningen, Groningen, Netherlands; Seoul National University Hospital, Jongno-Gu, South Korea; Dartmouth-Hitchcock Medical Center, Lebanon, NH; Acute Respiratory Medicine and Thoracic Oncology Department, Lyon Sud Hospital and Lyon University Cancer Institute, Lyon University Hospital, Pierre Benite, France; University of Washington, Seattle Cancer Care Alliance, Seattle, WA; Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline, Collegeville, PA; Dana-Farber Cancer Institute, Boston, MA*

Background: In 78 BRAF V600E mut NSCLC pts, single agent D induced an overall response rate (ORR) of 32%. The combination of D and T (DT) has demonstrated significant improvements in efficacy compared with BRAFi monotherapy in BRAFV600 mut metastatic melanoma. Here, we report interim safety (33 pts) and efficacy (24 pts) data for NSCLC pts enrolled in this phase II DT study. **Methods:** This single-arm, 2-stage, phase II study was in advanced BRAFV600E mut NSCLC pts who failed at least 1 line of chemotherapy. D was dosed at 150 mg orally twice daily and T at 2 mg once daily. The primary endpoint was investigator-assessed ORR per RECIST 1.1 criteria. A minimum response rate (≥ 6 out of first 20 pts) was required to continue into the second stage. **Results:** Median age of 33 pts was 66 yrs (range 49–88 yrs). Most pts were female (64%), White (82%), former smokers (73%), and had adenocarcinoma (88%). Twenty-seven pts (82%) remain on therapy, and 6 have stopped (4 with disease progression, 2 due to adverse events [AEs]). Twenty-four pts were evaluable for efficacy (confirmed response). ORR was 63% (n = 15, partial responses; 95%CI 40.6%–81.2%), with responses being observed by the first scan (6 weeks) and disease control rate (DCR) for > 12 weeks was 88% (95% CI 67.6%–97.3%).Independent review response rates were consistent with investigator-assessed response. Most common (> 20%) AEs were pyrexia, diarrhea, nausea, vomiting, decreased appetite, asthenia, cough, peripheral edema, and rash, mostly grade 1 or 2. Grade 3 AEs occurred in 39% of pts; most frequent were hyponatremia (6%), neutropenia (6%), and dehydration (6%). One pt (3%) had a grade 4 AE (hyponatremia) and 1 pt (3%) had a fatal serious AE of pleural effusion. AEs leading to a dose reduction were reported in 9 pts (27%). Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 2 pts (6%). **Conclusions:** DT in BRAF V600E mut advanced NSCLC pts shows early antitumor activity with an ORR of 63% and a manageable safety profile. The study met the criteria for progression to the second stage.

Abstract ID: 8010 (150315)

Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR).

Authors: Alexander I. Spira, Keunchil Park, Julien Mazières, Johan F. Vansteenkiste, Achim Rittmeyer, Marcus Ballinger, Daniel Waterkamp, Marcin Kowanetz, Ahmad Mokatrin, Louis Fehrenbacher; Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA; Division of Hematology & Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Hôpital Larrey CHU Toulouse, Toulouse, France; University Hospital KU Leuven, Leuven, Belgium; Lungenfachklinik Immenhausen, Kassal, Germany; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd., Basel, Switzerland; NRG Oncology/NSABP, and Kaiser Permanente Northern California, Novato, CA

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, histology and prior lines of therapy and randomized to 1200 mg IV q3w MPDL3280A (M) or 75 mg/m2 IV q3w docetaxel (D). PD-L1 expression was centrally evaluated by IHC using the SP142 antibody assay. Pts were scored as TC0, 1, 2 or 3 and IC0, 1, 2 or 3. The primary endpoint was OS (data cutoff, January 30, 2015; median follow-up, 12 mo). **Results:** 287 pts were randomized. In this interim analysis, improved efficacy was observed with increasing PD-L1 expression (e.g., OS HR, 0.47; PFS HR, 0.56 and ORR, 38% vs 13% in TC3 or IC3 pts), while pts with the lowest PD-L1 levels (TC0 and IC0) did not appear to benefit from M (OS HR, 1.22; see table). ITT OS HR was 0.78. Safety was evaluable for 277 pts. Despite a longer median treatment duration for M (3.6 vs 2.1 mo for D), fewer pts receiving M (43%) vs D (56%) experienced Gr ≥ 3 AEs. There were no unexpected toxicities. **Conclusions:** This is the first randomized study in non-squamous and squamous NSCLC to demonstrate that inhibition of the PD-L1/PD-1 pathway may lead to improved survival. Furthermore, these data showed that PD-L1 biomarker selection, using a highly sensitive and specific IHC assay measuring PD-L1 on both TC and IC, can identify both pts most likely to derive improved OS, PFS and ORR and pts unlikely to benefit vs standard of care (NCT01903993). A second randomized study in this pt population is ongoing. Clinical trial information: NCT01903993

Efficacy.

	TC3 or IC3		TC2/3 or IC2/3		TC1/2/3 or IC1/2/3		TC0 and IC0		ITT	
	M	D	M	D	M	D	M	D	M	D
n =	24	23	50	55	93	102	51	41	144	143
OS										
Median, mo	NR	11.1	13	7.4	NR	9.1	9.7	9.7	11.4	9.5
HR[a] 95% CI	0.47 (0.20-1.11)		0.56 (0.33-0.95)		0.63 (0.42-0.95)		1.22 (0.69-2.14)		0.78 (0.59-1.03)	
PFS										
Median, mo	9.7	3.9	4.0	2.8	3.3	3.0	1.9	4.1	2.8	3.4
HR 95% CI	0.56 (0.28-1.11)		0.70 (0.45-1.08)		0.87 (0.63-1.20)		1.15 (0.72-1.82)		0.96 (0.76-1.20)	
ORR, % (confirmed)	38	13	22	15	18	18	8	10	15	15

NR, not reached. [a]Stratified HR for ITT and unstratified HR for subgroups.

Abstract ID: 7500 (150191)

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.

Authors: *Gerard Zalcman, Julien Mazières, Jacques Margery, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Oliver Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Henri Janicot, Radj Gervais, Chrystele Locher, Bernard Milleron, Quan Tran, Marie Paule Lebitasy, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, French Cooperative Thoracic Intergroup (IFCT); Caen Univ Hosp, Caen, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Gustave Roussy, Villejuif, France; Assistance Publique - Hopitaux De Marseille, Plan De Cuques, France; Service de Pneumologie - CH Toulon, Toulon, France; Thoracic Oncology Unit Teaching Hospital A Michallon, INSERM U823, Grenoble, France; Le Mans Regional Hospital, Le Mans, France; Rennes University Hospital, Rennes, France; CHI of Creteil, Creteil, France; Hôpital Tenon, AP-HP and Faculté de Médecine Pierre et Marie Curie, Université Paris VI, Paris, France; CHU, Clermont Ferrand, France; Centre François Baclesse, Caen, France; Centre Hospitalier de Meaux, Meaux, France; IFCT, Paris, France; Intergroupe Francophone De Cancerologie Thoracique, Paris, France; CHU, Caen, France; University Hospital of Lille Nord de France, Lille, 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 unresectable, histologically proved MPM, age < 76, no prior chemo, PS 0-2, no thrombosis, nor bleeding. Randomized patients (1:1) received pem 500 mg/m^2, CDDP 75 mg/m^2 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% a-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 85% 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 in the two arms (49.5% vs. 47.3%). Significantly more G3 proteinuria (0.0 vs. 3.1%), G3 hypertension (0.0 vs. 23%), 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 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.

Abstract ID: 7502 (148558)

Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028.

Authors: *Patrick Alexander Ott, Maria Elena Elez Fernandez, Sandrine Hiret, Dong-Wan Kim, Rebecca Anne Moss, Tammy Winser, Sammy Yuan, Jonathan D. Cheng, Bilal Piperdi, Janice M. Mehnert; Dana-Farber Cancer Institute, Boston, MA; Hospital Vall d'Hebron, Barcelona, Spain; ICO René Gauducheau, Nantes, France; Seoul National University Hospital, Seoul, South Korea; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Merck & Co., Inc., Kenilworth, NJ*

Background: Treatment options for pts with SCLC that progresses on platinum-based 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+SCLC. **Methods:** KEYNOTE-028 (ClinicalTrials.gov, NCT02054806) is an ongoing multicohort, phase Ib study of pembrolizumab in pts with PD-L1+ advanced solid tumors. Key eligibility criteria for the SCLC cohort include: confirmed, measurable disease; PD-L1 expression in ≥ 1% of cells in tumor nests or PD-L1+ bands in stroma as assessed by IHC at a central laboratory; failure of standard therapy; and absence of autoimmune disease or interstitial lung disease. Pembrolizumab 10 mg/kg is given every 2 wk for up to 2 y or until confirmed progression or unacceptable toxicity. Primary end points are safety, tolerability, and response assessed per RECIST v1.1 by investigator review every 8 wk for the first 6 mo and every 12 wk thereafter. **Results:** Of the 135 pts with SCLC screened, 37 (27%) had PD-L1+ tumors. Seventeen pts were enrolled from March 2014 through January 2015 (59% men; median age, 62 y; 59% ECOG PS 1). One pt was misenrolled and did not receive pembrolizumab. All 16 treated pts received prior platinum and etoposide. 9 pts (53%) experienced a drug-related AE (DRAE); only 1 pt had a grade ≥ 3 DRAE. There were no treatment-related deaths or discontinuations due to DRAEs. Four of 16 (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.

Abstract ID: 7503 (146138)

Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032.

Authors: *Scott Joseph Antonia, Johanna C. Bendell, Matthew Hiram Taylor, Emiliano Calvo, Dirk Jaeger, Filippo G. De Braud, Patrick Alexander Ott, M. Catherine Pietanza, Leora Horn, Dung T. Le, Michael Morse, Jose A. Lopez-Martin, Paolo Antonio Ascierto, Olaf Christensen, Joseph Grosso, Jason S. Simon, Chen-Sheng Lin, Joseph Paul Eder; Moffitt Cancer Center, Tampa, FL; Sarah Cannon Research Institute, Nashville, TN; Oregon Health and Science University, Portland, OR; START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Vanderbilt-Ingram Cancer Center, Nashville, TN; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Duke University Medical Center, Durham, NC; Hospital 12 de Octubre, Madrid, Spain; Istituto Nazionale Tumori IRCCS, Naples, Italy; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb Company, Princeton, NJ; Yale Cancer Center, Yale School of Medicine, New Haven, CT*

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 anti-tumor 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 SCLC pts are reported. **Methods:** Pts who were PLT 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 + 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 regimens. Drug-related adverse events (DrAEs) in ≥ 10% were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO; and fatigue (29%), diarrhea (17%), pruritus (14%), nausea, endocrine disorders and rash (11% each) with NIVO+IPI. Gr 3/4 DrAE 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) was seen in 6, 15% (duration of ongoing responses [DOR] 80-251+days); stable disease (SD) in 9, 22.5%; and progressive disease (PD) in 25, 62.5%. In 20 evaluable NIVO+IPI pts, 1 had complete response (CR), 5% (DOR 322+ days); 4 had a PR, 20% (DOR 41-83+ days); 6 had SD, 30%, and 9 had PD, 45%. In the NIVO+IPI arm, 12 pts had not reached first tumor assessment and 3 were not evaluable. Nine pts (23%) continue treatment with NIVO and 19 (54%) with NIVO+IPI. **Conclusions:** In this PD-L1 unselected SCLC population with progression post-PLT, NIVO alone or combined with IPI was tolerable. ORR was 15% (NIVO) and 25% (NIVO+IPI) for evaluable pts; durable responses were noted. Updated safety, clinical activity and biomarker analysis will be presented.

Abstract ID: 7506 (144034)

Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC).

Authors: *Suresh Senan, Anthony M. Brade, Luhua Wang, Johan F. Vansteenkiste, Shaker R. Dakhil, Bonne Biesma, Maite Martinez Aguillo, Joachim Aerts, Ramaswamy Govindan, Belén Rubio-Viqueira, Conrad R. Lewanski, David R. Gandara, Hak Choy, Tony Mok, Anwar Hossain, Neill Allan Iscoe, Joseph Treat, Andrew G. Koustenis, Nadia Chouaki, Everett E. Vokes; VU University Medical Center, Amsterdam, Netherlands; Princess Margaret Hospital, University of Toronto, Toronto, ON; Department of Radiation Oncology, Cancer Institute (Hospital) Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; University Hospital KU Leuven, Leuven, Belgium; Cancer Center of Kansas, Wichita, KS; Department of Pulmonology, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands; Medical Oncology Department, Hospital de Navarra, Irunarrea, Pamplona, Spain; Department of Pulmonology, Erasmus MC Rotterdam/Amphia Hospital Breda, Breda, Netherlands; Washington University School of Medicine, St. Louis, MO; Hospital Universitario Quirón Madrid, Madrid, Spain; Charing Cross Hospital, London, United Kingdom; University of California Davis Comprehensive Cancer Center, Sacramento, CA; The University of Texas Southwestern Medical Center, Dallas, TX; Chinese University of Hong Kong, Shatin, Hong Kong; Eli Lilly and Company, Indianapolis, IN; Eli Lilly Canada Inc., Toronto, ON; Eli Lilly and Company, Neuilly-Sur-Seine, France; Department of Medicine, University of Chicago, Chicago, IL*

Background: Efficacy and safety of concurrent Pem+Cis and TRT followed by consolidation Pem vs other CTX regimens were evaluated; interim safety results (concurrent phase) were presented previously (Vokes et al. 2013). **Methods:** Five hundred and ninety-eight patients (pts) with stage III unresectable nsNSCLC were randomized 1:1 to Pem+Cis (Pem 500 mg/m^2+Cis 75 mg/m^2, intravenously, plus vitamins) plus concurrent TRT (66.0 Gy) every 21 days (q21d) x 3 cycles followed by Pem consolidation q21d x 4 cycles vs the control arm Eto+Cis (Eto 50 mg/m^2+Cis 50 mg/m^2, intravenously) plus concurrent TRT (66.0 Gy) 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, 59.5/58.7; female, 41.2%/40.1%; stage IIIB, 53.5%/51.2%; positron emission tomography scans, 83.1%/81.1%; and Eastern Cooperative Oncology Group performance status 1, 50.5%/50.2%. Pem+Cis vs Eto+Cis median OS was 26.8 vs 25.0 mos (HR 0.98; 95% CI: 0.79, 1.20; P = 0.831) and median PFS was 11.4 vs 9.8 mos (HR 0.86; 95% CI: 0.71, 1.04; P = 0.130). Pem+Cis/Eto+Cis ORR was 35.9%/33.0% (P = 0.458) and disease control rate was 80.7%/70.7% (P = 0.004). Possibly related grade (G) 3/4 toxicities (Pem+Cis vs Eto+Cis) occurred in 64.0% vs 76.8% of pts (P = 0.001). The Pem+Cis arm had a lower incidence of possibly related G3/4 neutropenia/granulocytopenia vs the Eto+Cis arm: 24.4% vs 44.5% of pts (P < 0.001). Pem+Cis vs Eto+Cis rates of G3/4 pneumonitis/pulmonary infiltrates and esophagitis were 1.8% vs 2.6% and 15.5% vs 20.6%, respectively. **Conclusions:** The Pem+Cis arm did not improve OS vs the control arm, but did have a better safety profile than the Eto+Cis arm.

Abstract ID: 7507 (150635)

Randomized phase III trial of customized adjuvant chemotherapy (CT) according BRCA-1 expression levels in patients with node positive resected non-small cell lung cancer (NSCLS) SCAT: A Spanish Lung Cancer Group trial (Eudract:2007-000067-15; NCTgov: 00478699).

Authors: *Bartomeu Massuti, Manuel Cobo, Jose Manuel Rodriguez-Paniagua, Ana Isabel Ballesteros, Teresa Moran, Ricardo Arrabal, Jose Luis Gonzalez Larriba, Isidoro Barneto, Yat Wah Pun, Javier De Castro, Santiago Ponce Aix, Carlos Baamonde, Miguel Angel Munoz, Guillermo Lopez-Vivanco, Juan-Jose Rivas, Dolores Isla, Rafael Lopez, Jose Miguel Sanchez, Jose Sanchez-Paya, Rafael Rosell, Spanish Lung Cancer Group (GECP/SLCG); Alicante University Hospital, Alicante, Spain; Hosp Regional Universitario Carlos Haya Malaga, Malaga, Spain; Alicante University Hospital. Thoracic Surgery, Alicante, Spain; Hospital Universitario La Princesa, Madrid, Spain; Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Barcelona, Spain; Thoracic Surgery Hospital Universitario Carlos Haya, Malaga, Spain; Medical Oncology Department, Hospital Universitario Clínico San Carlos, Madrid, Spain; Hospital Reína Sofía, Córdoba, Spain; Thoracic Surgery Hospital La Princesa, Madrid, Spain; Hospital La Paz, Madrid, Spain; Hospital 12 de Octubre, Madrid, Spain; Thoracic Surgery Hospital Universitario Reina Sofia Cordoba, Cordoba, Spain; Fundacion Instituto Valenciano Oncologia, Valencia, Spain; Department of Medical Oncology, Hospital de Cruces, Barakaldo, Spain; Thoracic Surgery Hospital Universitario Miguel Servet, Zaragoza, Spain; Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain; Hospital Clinico Universitario de Santiago de Compostela, Santiago De Compostela, Spain; Hospital La Princesa, Madrid, Spain; Cancer Biology and Precision Medicine Program, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*

Background: Postop platinum-based CT improves outcomes in resected NSCLC with N+ (St II-IIIA). Analysis of expression of genes involved in DNA repair could be used to individualize optimal CT. BRCA1 may act as a differential regulator of response to cisplatin (Cis) and antimicrotubule agents. **Methods:** Phase III multicenter trial. After surgery, patients (p) with St II and III were random 1:3 to control arm (Cis-Docetaxel) or to experimental arm with treatm. according BRCA1 express. levels (low : Cis-Gemcitabine; intermediate : Cis-Doc; high: Doc alone). Stratification factors: N1 vs N2; age < or > 65 y; non-squamous vs squamous (Sq) ; lobectomy vs pneumonectomy). Planned PORT in N2. Primary end-point OS. Secondary: DFS, toxicity, compliance, recurrence pattern. Statistical hypothesis: 20% increase 5y surv. control group (45%). **Results:** From June 2007 to May 2013, 591 p were screened and 500 of them were random: 108 in control, 392 experimental (110 p Cis-Gem, 127 Cis-Doc and 110 Doc alone). No disbalance between arm for prognostic factors: Median age 64 y; 79% males, 21% females; 43% Sq, 49% Adeno; pneumonectomy 26%; N1 58%, N2 48%; smoking habit: 57% former, 32% current, 11% never. Median tumor size 4.4 cm (0.8-15.5). Median mRNA BRCA1 levels 15.78 (0.73-132). Mean BRCA1 levels 6.95 Adeno vs 20.29 Sq ($P < 0.001$). Median f-u 30 months (0-79 m). With a cut-off of March 15th median survival has not reached both arms and no significant diffs. have been seen for OS with HR 0.866 ($P = 0.45$) or DFS (HR 1). In exper. group HR for OS was 0.842 (NS) comparing low with high-BRCA1 levels. In p with high-BRCA1 levels control treatm. (Cis-Doc) was superior to exper. (Doc) with HR 1.24 (NS). For p receiving all planned treatm. HR is 0.63 with $P = 0.043$ compared with p not able to complete treatm. P with Sq histology showed a longer DFS (HR 0.73; $P = 0.05$) but without diff. in OR (HR 1). **Conclusions:** BRCA1 based adjuvant CT does not improve OS. In p with high-BRCA1 levels Doc alone is inferior to Cis-Doc. Full dose of planned treatm. confers a survival advantage, however, longer follow-up is still warranted.

Abstract ID: LBA500 (146144)

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.

Authors: Richard G. Margolese, Reena S. Cecchini, Thomas B. Julian, Patricia A. Ganz, Joseph P. Costantino, Laura Vallow, Kathy S. Albain, Pat W. Whitworth, Mary E. Cianfrocca, Adam Brufsky, Howard M. Gross, Gamini S. Soori, Judith O. Hopkins, Louis Fehrenbacher, Keren Sturtz, Timothy F. Wozniak, Thomas E. Seay, Eleftherios P. Mamounas, Norman Wolmark; NRG Oncology/NSABP, and The Jewish General Hospital, McGill University, Montréal, QC; NRG Oncology, and the University of Pittsburgh, Pittsburgh, PA; NRG Oncology/NSABP, and The Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA; NRG Oncology/NSABP, and the University of California, Los Angeles, Los Angeles, CA; NRG Oncology/NSABP, ALLIANCE/NCCRT, and Mayo Clinic, Jacksonville, FL, Jacksonville, FL; NRG Oncology/NSABP, SWOG, and Loyola University Chicago Stritch School of Medicine, Maywood, IL; NRG Oncology/NSABP, ALLIANCE/ACOSOG, and Nashville Breast Center, Nashville, TN; ECOG/ACRIN, SWOG, and Banner MD Anderson Cancer Center, Gilbert, AZ; NRG Oncology/NSABP, and Magee Women's Hospital, Pittsburgh, PA; NRG Oncology/NSABP, and Hem and Onc Div of Dayton Physicians LLC, Dayton, OH; NRG Oncology/NSABP, and Nebraska Cancer Specialists, Omaha, NE; NRG Oncology/NSABP, and SCOR NCORP and the Forsyth Regional Cancer Center, Winston Salem, NC; NRG Oncology/NSABP, and Kaiser Permanente Northern California, Novato, CA; Colorado Cancer Research Program, Denver, CO; NRG Oncology/NSABP, and CCOP, Christiana Care Health Systems, Newark, DE; NRG Oncology/NSABP, and the Atlanta Regional Community Clinical Oncology Program, Atlanta, GA; NRG Oncology/NSABP and UF Cancer Center at Orlando Health, Orlando, FL; NRG Oncology/NSABP, and the Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA

Background: The primary endpoint of NSABP B-35, a phase III trial comparing 1 mg/day anastrozole to 20 mg/day tamoxifen, each given for 5 years, was breast cancer-free interval (BCFI), defined as the time from randomization to any breast cancer (BC) event including local, regional, or distant recurrence or contralateral disease, invasive or DCIS. **Methods:** Postmenopausal women with ER-receptor or PgR-receptor positive (by IHC analysis) DCIS and no invasive BC who had undergone a lumpectomy with clear resection margins were randomly assigned to receive either 20 mg/day tam or 1 mg/day A (blinded) for 5 years. Stratification was by age (<60 v ≥60). **Results:** From 1/6/2003 to 6/15/2006, 3,104 pts were entered and randomized (1552 in groups tam and A each). As of 2/28/15, follow-up information was available on 3,083 pts for OS and on 3,077 pts for all other disease-free endpoints, with mean time of follow-up of 8.6 years. There were 198 BCFI events, 114 in the tam group and 84 in the A group (HR, 0.73; $P = 0.03$). 10-year point estimates for BCFI were 89.2% for tam and 93.5% for A. A significant time-by-treatment interaction ($P = 0.02$) indicated that the effect was not evident until later in the study. There was a significant interaction between treatment and age group ($P = 0.04$); benefit of A is only in women <60 years old. As to secondary endpoints, there were 495 DFS events, 260 in the tam group and 235 in the A group (HR, 0.89; $P = 0.21$). 10-year point estimates for DFS were 77.9% for tam and 82.7% for A. There were 186 deaths, 88 in the tam group and 98 in the A group (HR, 1.11; $P = 0.48$). 10-year point estimates for OS were 92.1% for tam, 92.5% for A. There were 8 deaths due to breast cancer in the tam group and 5 in the A group. There were 63 cases of invasive breast cancer in the tam group and 39 in the A group (HR, 0.61; $P = 0.02$). There was a non-significant trend for a reduction in breast second primary cancers with A (HR, 0.68; $P = 0.07$). **Conclusions:** Anastrozole provided a significant improvement compared to tamoxifen for BCFI, which was seen later in the study, primarily in women <60 years. Support: CA12027, 37377, 69651, 69974; 180868, 180822,

189867 196067, 114732; AstraZeneca Pharmaceuticals LP. Clinical trial information: NCT00053898

Abstract ID: LBA502 (154447)

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.

Authors: *Nicholas C. Turner, Jungsil Ro, Fabrice Andre, Sherene Loi, Sunil Verma, Hiroji Iwata, Nadia Harbeck, Sibylle Loibl, Cynthia Huang Bartlett, Ke Zhang, Carla Giorgetti, Sophia Randolph, Maria Koehler, Massimo Cristofanilli; Royal Marsden, London & Surrey, United Kingdom; Natl Cancer Ctr, Goyang-si, Korea South; Institut Gustave Roussy, Villejuif, France; Peter MacCallum Cancer Centre, East Melbourne, Australia; Sunnybrook Odette Cancer Centre, Toronto, ON; Aichi Cancer Center Hospital, Nagoya, Japan; University of Munich, Otterfing, Germany; German Breast Group, Neu-Isenburg, Germany; Pfizer Oncology, New York, NY; Pfizer Inc, San Diego, CA; Pfizer, Milan, Italy; Pfizer Oncology, La Jolla, CA; Pfizer Oncology, Narberth, PA; Thomas Jefferson University, Philadelphia, PA*

Background: The growth of hormone receptor (HR) positive breast cancer (BC) is dependent on the cyclin dependent kinases CDK4/6, that promote G1-S phase cell cycle progression. Resistance to endocrine treatment remains a major clinical problem for patients with hormone receptor positive breast cancer. The PALOMA3 study assessed the efficacy of palbociclib and fulvestrant in endocrine-resistant advanced breast cancer. **Methods:** In this double-blind phase 3 study women with HR positive/HER2 negative advanced metastatic BC whose cancer had relapsed or progressed on prior endocrine therapy, were randomized 2:1 to palbociclib (Palbo, 125 mg/d orally for 3 wk followed by 1 wk off) and fulvestrant (F, 500 mg per standard of care) or placebo (PLB) and F. Pre- and peri-menopausal women also received goserelin. One previous line of chemotherapy for metastatic disease was permitted. The primary endpoint was investigator assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), response assessment, patient-reported outcomes, and safety and tolerability. A pre-planned interim analysis was performed after 195 PFS events by an independent data monitoring committee. **Results:** 521 pts were randomized, 347 to receive Palbo+F and 174 to PLB+F. Baseline characteristics were well balanced. The median age was 57 and 56 years, 79% were post-menopausal, 60% had visceral disease, and 79% were sensitive to prior endocrine therapy. Prior therapy included chemotherapy for advanced disease in 33% of pts. At the time of the interim analysis the study met the primary endpoint, median PFS was 9.2 months for Palbo+F and 3.8 months for PLB+F (HR 0.422, 95% CI 0.318 to 0.560, $P<0.000001$). Consistent benefit from Palbo was seen in pre- and post-menopausal women. The most common adverse effects Palbo+F versus PLB+F were neutropenia (78.8% vs. 3.5%), leucopenia (45.5% vs. 4.1%), and fatigue (38.0% vs. 26.7%). Febrile neutropenia was reported in 0.6% pts on Palbo+F and 0.6% pts on PLB+F. The discontinuation rate due to adverse events was 2.0% on Palbo and 1.7% on PLB. **Conclusions:** Palbociclib combined with fulvestrant improved progression free survival in hormone receptor positive advanced breast cancer that had progressed on prior endocrine therapy, and can be considered as a treatment option for these patients. Clinical trial information: NCT01942135

Abstract ID: 504 (145508)

Adjuvant denosumab in breast cancer: Results from 3,425 postmenopausal patients of the ABCSG-18 trial.

Authors: *Michael Gnant, Georg Pfeiler, Peter Christian Dubsky, Michael Hubalek, Richard Greil, Raimund Jakesz, Viktor Wette, Marija Balic, Ferdinand Haslbauer, Elisabeth Melbinger-Zeinitzer, Vesna Bjelic Radisic, Jonas C. S. Bergh, Florian Fitzal, Daniel Egle, Brigitte Mlineritsch, Guenther G. Steger, Susan Talbot, Douglas J Warner, Christian Fesl, Christian F. Singer, ABCSG; Medical University of Vienna, Vienna, Austria; Med Univ of Vienna, Vienna, Austria; Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria; Paracelsus Medical University, Salzburg, Austria; Medical University Vienna, Wien, Austria; Breast Center/ Doctor´s Office Wette, St.Veit an Der Glan, Austria; Medical University Graz, Styria, Austria; Hospital Vöcklabruck/Department of Internal Medicine, Vöcklabruck, Austria; Hospital Wolfsberg/ Department of Surgery, Wolfsberg, Austria; Medical University Graz, Graz, Austria; Karolinska Institute and University Hospital, Stockholm, Sweden; Hospital of Sisters of Mercy Linz/ Breast Health Center, Linz, Austria; Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria; Paracelsus University of Salzburg, Salzburg, Austria; Amgen Ltd., Cambridge, United Kingdom; Amgen Inc., Thousand Oaks, CA; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; Medical University of Vienna, Vienna, Austria*

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, placebo-controlled, phase-III trial. Patients were randomized 1:1 to either 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 (1366 vs 1334), or serious adverse events (521 vs 511). Despite proactive 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.

Abstract ID: 507 (147990)

Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study.

Authors: *Paul Anthony Ellis, Carlos H. Barrios, Wolfgang Eiermann, Masakazu Toi, Young-Hyuck Im, Pier Franco Conte, Miguel Martin, Tadeusz Pienkowski, Xavier B. Pivot, Howard A. Burris III, Alexander Strasak, Monika Patre, Edith A. Perez; Guy's Hospital and Sarah Cannon Research Institute, London, United Kingdom; PUCRS School of Medicine, Porto Alegre, Brazil; Interdisciplinary Oncology Center, Munich, Germany; Graduate School of Medicine, Kyoto University, Kyoto, Japan; Samsung Medical Center, Seoul, South Korea; Department of Surgery, Oncology and Gastroenterology, University of Padova and Istituto Oncologico Veneto, Padova, Italy; Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain; Postgraduate Medical Education Center, Warsaw, Poland; University Hospital Jean Minjoz, Besançon, France; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; F. Hoffmann-La Roche Ltd, Basel, Switzerland; F. Hoffmann-La Roche Ltd., Basel, Switzerland; Mayo Clinic, Jacksonville, FL*

Background: In phase II and III studies, treatment with T-DM1 or with P + H + docetaxel has shown statistically significant increases in progression-free survival (PFS) and overall survival (OS) vs control regimens in patients with HER2-positive MBC. The combination of T-DM1 + P resulted in synergistic inhibition of tumor cell line proliferation in vitro. This and preliminary data from a phase II clinical trial provided the rationale for further study. **Methods:** In MARIANNE (NCT01120184), patients with centrally assessed HER2-positive (IHC3+ or ISH+) progressive/recurrent locally advanced BC or previously untreated MBC with a ≥ 6-month interval since treatment in the (neo)adjuvant setting with taxanes or vinca alkaloids were randomized 1:1:1 to HT (docetaxel or paclitaxel + H), T-DM1 (T-DM1 + placebo, hereafter T-DM1), or T-DM1 + P, at standard doses. The primary end point was PFS assessed by independent review. Comparisons between HT and T-DM1 or T-DM1 + P were considered separately. PFS was tested first for non-inferiority and for superiority only if non-inferiority was achieved. **Results:** At the clinical cutoff date, September 16, 2014, 365 patients had been randomized to HT, 367 to T-DM1, and 363 to T-DM1 + P. In each arm, approximately 31% of patients had prior (neo)adjuvant treatment with HER2-directed therapy. Approximately 37% overall had de novo disease. The study met the PFS non-inferiority end point, but not the superiority end point. OS was similar across treatment arms. **Conclusions:** These data demonstrate non-inferiority in PFS between T-DM1–containing arms and control. T-DM1–containing regimens were associated with a different toxicity profile than the control regimen. Clinical trial information: NCT01120184

Outcome	HT	T-DM1	T-DM1 + P
Median follow-up, mo	34.8	34.9	34.7
Median PFS, mo	13.7	14.1	15.2
HR [97.5% CI]	-	0.91 [0.73–1.13], P = 0.31 vs HT	0.87 [0.69–1.08], P = 0.14 vs HT 0.91 [0.73–1.13], P = 0.31 vs T-DM1
ORR, %	67.9	59.7	64.2
Median duration of response, mo	12.5	20.7	21.2
Grade 3−5 AEs, %	54.1	45.4	46.2

Most common grade 3−5 AEs, %			
Neutropenia	19.8	4.4	2.7
Febrile neutropenia	6.5	0	0
Anemia	2.8	4.7	6.0
AST increased	0.3	6.6	3.0
Thrombocytopenia	0	6.4	7.9

Outcome	HT	T-DM1	T-DM1 + P
Median follow-up, mo	34.8	34.9	34.7
Median PFS, mo	13.7	14.1	15.2
HR [97.5% CI]	-	0.91 [0.73–1.13], p = 0.31 vs HT	0.87 [0.69–1.08], p = 0.14 vs HT 0.91 [0.73–1.13], p = 0.31 vs T-DM1
ORR, %	67.9	59.7	64.2
Median duration of response, mo	12.5	20.7	21.2
Grade 3–5 AEs, %	54.1	45.4	46.2
Most common grade 3–5 AEs, %			
Neutropenia	19.8	4.4	2.7
Febrile neutropenia	6.5	0	0
Anemia	2.8	4.7	6.0
AST increased	0.3	6.6	3.0
Thrombocytopenia	0	6.4	7.9

Abstract ID: 508 (149972)

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 (ExteNET).

Authors: *Arlene Chan, Suzette Delaloge, Frankie Ann Holmes, Beverly Moy, Hiroji Iwata, Vernon J. Harvey, Nicholas J. Robert, Tajana Silovski, Erhan Gokmen, Gunter Von Minckwitz, Bent Ejlertsen, Stephen K. L. Chia, Janine Mansi, Carlos H. Barrios, Michael Gnant, Alvin Wong, Richard Bryce, Bin Yao, Miguel Martin; Breast Cancer Research Centre - WA & Curtin University, Perth, Australia; Institut Gustave Roussy, Villejuif, France; Texas Oncology, P.A., Houston, TX; Massachusetts General Hospital, Boston, MA; Aichi Cancer Center, Chikusa-Ku Nagoya, Japan; Auckland Hospital, Auckland, New Zealand; Virginia Cancer Specialists, The US Oncology Network, Fairfax, VA; University Hospital For Tumors, UHC "Sestre milosrdnice", Zagreb, Croatia; Ege University Faculty of Medicine, Division of Medical Oncology, Izmir, Turkey; Luisenkrankenhaus, GBG Forschungs GmbH, Düsseldorf, Neu-Isenburg, Germany; Rigshospitalet, Copenhagen, Denmark; BC Cancer Agency, Vancouver, BC; Guy's Hospital, London, United Kingdom; PUCRS School of Medicine, Porto Alegre, Brazil; Medical University of Vienna, Vienna, Austria; Puma Biotechnology Inc, Los Angeles, CA; Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain*

Background: Neratinib (N) is an irreversible pan-HER tyrosine kinase inhibitor with clinical efficacy in trastuzumab (T) pre-treated HER2-positive (HER2+) metastatic breast cancer. In HER2+ early breast cancer (EBC), a significant proportion of patients (pts) recur 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 locally confirmed HER2+ were eligible. Pts 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. Invasive DFS (IDFS) at 2y is the primary endpoint and other secondary endpoints include DFS + DCIS, distant DFS (DDFS), CNS incidence, and patient-reported outcomes. Overall survival (OS) is an event-driven secondary endpoint. 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 4.4m 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/PR+ 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 + T improves IDFS and DFS-DCIS at 2y in HER2+ EBC. Diarrhea, the most common AE, was manageable. Additional follow-up will allow assessment of 5-y IDFS and OS. ClinicalTrials.gov: NCT00878709.

	2-y rate, %			
Efficacy endpoint	**N (n=1,409)**	**P (n=1,412)**	**HR (95% CI)**	**P-value (1-sided) stratified log rank**
IDFS	93.9	91.6	0.67 (0.50–0.91)	0.0046
DFS-DCIS	93.9	91.0	0.63 (0.46–0.84)	0.0009
DDFS	95.1	93.7	0.75 (0.53–1.05)	0.0447

Abstract ID: 1001 (147950)

Phase III trial of etirinotecan pegol (EP) versus Treatment of Physician's Choice (TPC) in patients (pts) with advanced breast cancer (aBC) whose disease has progressed following anthracycline (A), taxane (T) and capecitabine (C): The BEACON study.

Authors: *Edith A. Perez, Ahmad Awada, Joyce O'Shaughnessy, Hope S. Rugo, Chris Twelves, Seock-Ah Im, Carol Zhao, Ute Hoch, Alison L. Hannah, Javier Cortes; Mayo Clinic, Jacksonville, FL; Jules Bordet Institute, Bruxelles, Belgium; Baylor Sammons Cancer Ctr US Onc, Dallas, TX; University of California, San Francisco, San Francisco, CA; LIMM, Leeds, United Kingdom; Seoul National University College of Medicine, Seoul, South Korea; Nektar Therapeutics, San Francisco, CA; Consultant, Sebastopol, CA; Vall D'Hebron University Hospital, Barcelona, Spain*

Background: EP is the first long-acting topoisomerase 1 inhibitor providing sustained levels of SN38. In Phase II, EP demonstrated a 29% ORR following a median of 2 prior regimens for aBC. BEACON study (NCT01492101) randomized (1:1) pts with aBC and progressive disease following A,T and C to EP (145 mg/m^2 q3w over 90 minutes) or TPC (any of 7 cytotoxics). **Methods:** Eligible pts had any ER/HER2 and ECOG 0-1; stable brain metastases were allowed. 852 pts enrolled over 20 months and reached target for events in Dec2014. The choice of TPC: eribulin 40%, vinorelbine 23%, gemcitabine 18%, taxane 15%, ixabepilone 4%. Primary efficacy endpoint was overall survival (OS) by 2-sided log-rank test stratified by region, prior eribulin and receptor status; the study had 90% power to detect a target Hazard Ratio (HR) of 0.77. Circulating tumor cells (CTCs) were isolated in ~80% of pts and analyzed for target-specific pharmacodynamic biomarkers. This is the first presentation of these data. **Results:** EP provided a 2.1 month improvement in median OS over TPC (12.4 vs 10.3 months; HR 0.87, P = 0.08). In a pre-specified subgroup of 67 pts with brain metastases, EP showed an improvement of 5.2 months in median OS (10.0 vs 4.8 months; HR 0.51, $P < 0.01$); the proportion of pts with brain metastases alive at 12-mo survival was higher with EP (44.4% vs 19.4%). Similarly, in pts with liver metastases (n = 456) median OS improved with EP (10.9 vs 8.3 months; HR 0.73, P = 0.002). Grade (G) ≥ 3 AEs were lower with EP (48%) than TPC (63%). Common G ≥ 3 AE with EP: diarrhea (9.6%), neutropenia (9.6%), anemia (4.7%) and fatigue (4.5%); TPC: neutropenia (30.5%), anemia (4.7%) and dyspnea (4.4%). Severe neuropathy: 3.7% of pts (TPC) vs 0.5% (EP). Alopecia was less with EP (10% vs 23%). Data on efficacy in CTC biomarker defined sub-groups (TOP1, TOP2) will be presented. **Conclusions:** EP provided a clinically meaningful benefit to pts with late-stage aBC, although this did not reach statistical significance.In pts with brain metastases, median OS doubled; improved survival was also seen in other pt subsets. Toxicity with EP was less than with TPC.

Abstract ID: 1003 (150040)

Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC).

Authors: *Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Joyce O'Shaughnessy, Javier Cortes, Ahmad Awada, Catherine Margaret Kelly, Maureen E. Trudeau, Peter Schmid, Luca Gianni, Laura García-Estevez, Rita Nanda, Foluso Olabisi Ademuyiwa, Stephen Chan, Joyce Leta Steinberg, Martha Elizabeth Blaney, Iulia Cristina Tudor, Hirdesh Uppal, Amy C. Peterson, Clifford A. Hudis; Memorial Sloan Kettering Cancer Center, New York, NY; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; Baylor Sammons Cancer Ctr US Onc, Dallas, TX; Vall D'Hebron University Hospital, Barcelona, Spain; Jules Bordet Institute, Bruxelles, Belgium; Mater Misericordiae University Hospital, Dublin, Ireland; Sunnybrook Health Sciences Centre, Toronto, ON; University of Sussex, London, United Kingdom; San Raffaele Hospital, Milano, Italy; Centro Integral Oncológico Clara Campal, Madrid, Spain; University of Chicago, Chicago, IL; Washington Univ School of Medicine, St. Louis, MO; Nottingham University Hospital City Campus, Nottingham, United Kingdom; Astellas Pharma US Inc, Northbrook, IL; Medivation, San Francisco, CA; Medivation, Inc., San Francisco, CA; Medivation Inc, San Francisco, CA*

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 PFS compared to bicalutamide in men with mCRPC (15.7 vs 5.8 mos; HR 0.44; p<0.0001). **Methods:** MDV3100-11 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 have non-measurable bone disease and unlimited prior regimens; CNS 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 IHC ≥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 of 26 Evaluable pts; H0 was rejected if CBR16 was ≥9 in 62 yielding 85% power 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 AR ≥10%. 118 pts were treated with ENZA; 43 pts were not Evaluable (29 AR <10%; 14 AR ≥10% but no response assessment). Key outcomes in the defined populations are below as shown in the Table. Over 50% received ENZA as 1st or 2nd line; mPFS in these pts was 32 wks in Dx+ and 9 wks in Dx-. Two CRs and 5 PRs have been observed. Related AEs in ≥10% of 118 pts were fatigue (34%), nausea (25%), decreased appetite (13%), diarrhea and hot flush (10%). Fatigue (5%) was the only AE ≥ Grade 3 in ≥5%. **Conclusions:** This is the largest study of an AR inhibitor in TNBC. IHC results suggest AR prevalence is higher than previously reported. 47% of pts had an androgen-related gene signature (Dx+) and clinical outcomes appeared 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.

	Evaluable (n=75)	Dx+ (n=56)	Dx- (n=62)
CBR16, % (95% CI)	35 (24-46)	39 (27-53)	11 (5-21)
CBR24, % (95% CI)	29 (20-41)	36 (24-49)	7 (2-16)
mPFS, wks (95% CI)	14 (8-19)	16 (10-32)	8 (7-13)

Abstract ID: 1008 (146776)

Relationship of omission of adjuvant radiotherapy to outcomes of locoregional control and disease-free survival in patients with or without pCR after neoadjuvant chemotherapy for breast cancer: A meta-analysis on 3481 patients from the Gepar-trials.

Authors: *David Krug, Bianca Lederer, Juergen Debus, Jens Uwe Blohmer, Serban Dan Costa, Holger Eidtmann, Claus Hanusch, Joern Hilfrich, Jens Bodo Huober, Christian Jackisch, Sherko Kümmel, Stefan Paepke, Andreas Schneeweiss, Michael Untch, Gunter Von Minckwitz, Sibylle Loibl; University Hospital Heidelberg, Heidelberg, Germany; German Breast Group, Neu-Isenburg, Germany; Charite Berlin, Berlin, Germany; University of Magdeburg, Magdeburg, Germany; University Kiel, Kiel, Germany; Rotkreuzklinikum, Munich, Germany; Frauenklinik Henriettenstiftung, Hannover, Germany; University of Ulm, Ulm, Germany; Sana Klinikum Offenbach GmbH, Offenbach, Germany; Kliniken Essen Mitte, Evang. Huyssens Stiftung/Knappschaft, Essen, Germany; Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; Heidelberg University, Heidelberg, Germany; Helios Klinikum Berlin-Buch, Berlin, Germany*

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 a pooled analysis of the randomized neoadjuvant trials GeparTrio, GeparQuattro and GeparQuinto including 3,481 patients with operable and non-operable 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. **Results:** Patients in the RT-group were older and received more mastectomies. Their tumors were more likely to be HER2-positive and there was a higher rate of pathologic complete response (pCR, ypT0 ypN0). 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, 90% vs. 81.5% without RT, logrank $P < 0.001$) and 5-year disease-free survival (DFS, 75.4% vs. 67.4%, 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-yr LRFS was 95.7%% with RT vs 86.6% without RT (HR 3.32, 95% CI 1.00-11.08; $P = 0.051$) and 5-yr 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-yr DFS was 72.6% vs 65.7%; HR 1.39, 95% CI 1.07-1.81; $P = 0.014$). Multivariate analyses with adjustment for baseline 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.

Abstract ID: 1002 (147276)

Low-dose oral cyclophosphamide-methotrexate maintenance (CMM) for receptor-negative early breast cancer (BC).

Authors: *Marco Colleoni, Kathryn P. Gray, Shari I. Gelber, Istvan Lang, Beat J. K. Thurlimann, Lorenzo Gianni, Ehtesham A. Abdi, Karen N. Price, Richard D. Gelber, Giuseppe Viale, Alan S. Coates, Aron Goldhirsch, International Breast Cancer Study Group; European Institute of Oncology, Milano, Italy; Dana-Farber Cancer Institute, Boston, MA; National Institute of Oncology, Budapest, Hungary; Kantonsspital, St Gallen, Switzerland; Onc Dept Infermi Hosp, Cesena, Italy; The Tweed Hospital, Tweed Heads, Australia; Dana-Farber Cancer Inst, Boston, MA; Division of Pathology, European Institute of Oncology, Milan, Italy; University of Sydney, Sydney, Australia*

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 (ITT 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 days 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 magnitude 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 SGPT was most frequently reported, followed by leukopenia. **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.

Group	Treatment	No. of Patients	DFS events	5-year DFS %	Univariate HR (95% CI)	Multivariable HR(95% CI)
All pts	CMM	542	124	78.1%	0.84 (0.66, 1.06)	0.82 (0.65,1.05)
	No CMM	539	147	74.7%		
TN	CMM	408	89	78.7%	0.80 (0.60, 1.06)	0.79 (0.60,1.04)
	No CMM	406	110	74.6%		
TN & N+	CMM	175	48	71.9%	0.71 (0.49, 1.03)	0.68 (0.47, 0.99)
	No CMM	175	64	64.2%		

Abstract ID: 1006 (142462)

The survival benefit offered by the surgical management of low-grade ductal carcinoma in situ of the breast.

Authors: *Yasuaki Sagara, William Thomas Barry, Melissa Anne Mallory, Stephanie M. Wong, Fatih Aydogan, Stephen DeSantis, Mehra Golshan; Department of Surgery, Brigham and Women's Hospital, Boston, MA; Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; Harvard School of Public Health, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: The current management of ductal carcinoma in situ (DCIS) of the breast includes lumpectomy with/without whole breast radiation or mastectomy, however the magnitude of benefit for surgery has not been well established. We sought to identify the survival benefit conferred by surgical resection over non-operative management in patients with low-grade DCIS. **Methods:** We performed a retrospective longitudinal cohort study using the Surveillance Epidemiology and End Results database. Between 1988 and 2011, 57,222 eligible cases of DCIS were identified. Patients (pts) were divided into a surgery and a non-surgery group; propensity score weighting was used to balance clinico-pathologic factors between groups. Breast cancer specific and overall survival (BCSS/OS) were assessed using a log-rank test and Cox proportional hazards model. **Results:** Of 57,222 cases of DCIS, 56,053 cases (98.0%) received definitive surgery (lumpectomy: 34,439 pts, mastectomy: 16,334 pts) and 1,169 cases (2.0%) were managed non-operatively. The proportion of the following clinico-pathologic factors was higher in the non-surgery group compared to the surgery group: age > 60, diagnosis after year 2000, black race, low-grade DCIS and absence of radiation therapy. There were 576 breast cancer-specific deaths over the 72-month median follow-up period. The weighted ten-year BCSS for the surgery group was 98.5%, compared to 93.5% ($P < 0.001$) for the non-surgery group. Survival benefit for the surgery group differed by nuclear grade ($P = 0.003$). The weighted ten-year BCSS of low-grade DCIS was similar between patients managed with and without surgery (98.8% and 98.6%, respectively; $P = 0.93$). **Conclusions:** The survival benefit offered by surgery for DCIS varies by nuclear grade. In contrast to high/intermediate grade DCIS, definitive local therapy of low-grade DCIS does not offer a significant survival advantage over non-operative management. [caption]Hazard ratio (HR) comparison between DCIS patients managed surgically versus non-operatively as adjusted by clinico-pathologic factors.

Grade	BCSS Weighted HR	95% CI	OS Weighted HR	95% CI
I	0.88	0.21 - 3.71	0.86	0.53 - 1.40
II	0.25	0.15 - 0.42	0.70	0.52 - 0.94
III	0.16	0.11 - 0.23	0.40	0.32 - 0.51

Abstract ID: 3500 (147521)

A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results.

Authors: *Yanhong Deng, Pan Chi, Ping Lan, Lei Wang, Long Cui, Daoda Chen, Jie Cao, Hongbo Wei, Xiang Peng, Zonghai Huang, Guangfu Cai, Ren Zhao, Zhongcheng Huang, Yiding Luo, Yuxin Zhang, Yue Cai, Jianping Wang; The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Xiehe Hospital, Fuzhou University, Fuzhou, China; Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Xinhua Hospital, Shanghai Jiao Tong University, Shanghai, China; Xiehe Hospital, Huazhong University of Science and Technology, Wuhan, China; The First People's Hospital, Guangzhou City, Guangzhou, China; The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; The First People's Hospital, Foshan City, Foshan, China; Zhujiang Hospital, Nanfang University of Medical Science, Guangzhou, China; General Hospital, Guangdong Province, Guangzhou, China; Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China; General Hospital, Hunan Province, Changsha, China; The First Affiliated Hospital, Xiamen University, Xiamen, China; General Military Hospital, Guangzhou District, Guangzhou, China; Gastrointestinal Hospital, Sun Yatsen University, Guangzhou, China*

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 randomly assigned to received 5-FU with radiation(RT) (control arm), or receive mFOLFOX6 with RT (FOLFOX-RT arm), or receive 4-6 cycles of mFOLFOX6 alone (FOLFOX arm), post-operative RT is allowed if needed. Primary endpoint is DFS. Here we report the preliminary results. **Results:** 495 patients were randomized (165 in each arm). 92% of patients accomplished at least 46 Gy of RT in FOLFOX-RT arm compared to 86.8% in control arm. 5% of FOLFOX arm patients received post-op RT. R0 resection rate was 90.1%, 88.2%, and 91.2%, respectively in control arm, FOLFOX-RT arm and FOLFOX arm. The pCR rate was 12.5%, 31.3% and 7.4% respectively (P = 0.001). Good down staging (ypTNM 0-1) 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.

	All patients			Subgroup(0-5cm)		
	Control	FOLFOX-RT	FOLFOX	Control	FOLFOX-RT	FOLFOX
Age Median(Range)	56.2(24-75)	52.0(27-73)	56.0(21-75)	56.2(24-75)	52.6(30-72)	56(28-73)
Clinical T4b(%)	8.6	8.6	3.0	11.1	8	4.8
Clinical staging III (%)	76.5	75	70.3	67.9	66.7	51.3
pCR(%)	12.5	31.3	7.4	14.3	43.2	8.8
ypTNM 0-I(%)	34.7	57.8	37.9	33.3	62.1	41.2
TRG 0-1(%)	33.2	65.6	38.5	33.3	52	26.1
R0 resection (%)	90.1	88.2	91.2	72.2	74	76.2
Sphincter preservation (%)	76.5	82.8	88.2	59.3	62	66.7
Grade 3/4 Leucopenia(%)	14.8	20.9	7.9	15.1	14.6	15.8
Grade 3/4 radiodermatitis(%)	13.6	20.0	-	17	20.8	-
Grade 3/4 radiation proctitis(%)	9.8	13.2	-	13.1	10.4	-
Anastomotic leakage(%)	24.3	18.8	6.3	20	18.4	3
Infection of incision (%)	25.7	29.9	9.5	30.8	39.5	9.1

Abstract ID: 3501(151361)

Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC).

Authors: *Theo Ruers, Cornelis J. A. Punt, Frits van Coevorden, Jean-Pierre Pierie, Inne Borel Rinkes, Jonathan A. Ledermann, Graeme John Poston, Wolf O. Bechstein, Marie-Ange Lentz, Murielle E. Mauer, Eric Van Cutsem, Manfred P. Lutz, Bernard Nordlinger; The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Leeuwarden Medical Center, Leeuwarden, Netherlands; University Medical Centre Utrecht, Utrecht, Netherlands; University College London Cancer Institute, London, United Kingdom; University Hospital Aintree, Liverpool, United Kingdom; Department of General and Visceral Surgery, University Hospital Frankfurt, Frankfurt Am Main, Germany; EORTC Headquarters, Brussels, Belgium; EORTC Headquarters , Brussels, Belgium; Digestive Oncology, University Hospital Gasthuisberg, Leuven, Belgium; Caritasklinikum St. Theresia, Saarbrücken, Germany; Centre Hospitalier Universitaire Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France*

Background: This study evaluates the benefit of combining systemic chemotherapy (CT) with local tumor destruction by RFA in patients with unresectable CRC LM up to 9 lesions and without extrahepatic disease. Overall survival (OS) at 30 months and progression free survival (PFS) results were reported (Ann Oncol. 23(10): 2619-26, 2012). We now report on OS results, after a long term median follow-up of 9.7 years. **Methods:** Between 2002 and 2007, 119 pts were randomized between CT alone (59) or RFA+CT (60). In both arms, CT consisted of 6 months FOLFOX (oxaliplatin 85mg/m^2 and LV5FU2) plus, since October 2005, bevacizumab. In the CT arm resection was allowed when unresectable disease was converted by CT to resectable disease. Primary objective was a 30-months OS rate > 38% for the combined treatment group. OS and PFS were secondary endpoints. **Results:** In the RFA+CT arm, 56 pts (93.3%) received RFA which was combined with resection in 27 pts (45%), 1 pt had all metastases resected (ineligible), 2 pts were not treated at all, in 1 pt no local treatment data were available. 51 patients (85%) in the RFA+CT arm received CT compared to all 59 in the CT arm. 6 pts in the CT arm eventually underwent hepatic resection. The primary endpoint was met, 30-months OS rate was 61.7% (95% CI: 48.2-73.9) for combined treatment. However, 30-month OS for systemic treatment only was 57.6% (95% CI: 44.1-70.4), higher than anticipated. At a median follow-up of 9.7 years, 92 deaths were reported, 53 in the CT arm and 39 in the RFA+CT arm.Causes of death in the CT arm were progressive disease (49 pts), and unknown for 4 pts, and in the RFA+CT arm, progressive disease (35 pts), other causes (2 pts) and unknown (2 pts). There was a significant difference in OS in favor of the RFA+CT arm (HR = 0.58, 95% CI: 0.38-0.88, $P = 0.01$). Observed median OS was 45.6 months (95% CI: 30.3 – 67.8) in the RFA+CT arm vs. 40.5 months (95% CI: 27.5 - 47.7) in the CT arm. **Conclusions:** This is the first study that prospectively investigated the efficacy of RFA +CT in pts with unresectable CRC LM. In this phase II trial, RFA+CT was associated with improved long-term OS compared to CT alone.

Abstract ID: 3502 (145884)

SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC).

Authors: *Peter Gibbs, Volker Heinemann, Navesh K. Sharma, Michael P. N. Findlay, Jens Ricke, Val Gebski, Mark Van Buskirk, Guy A. Van Hazel, SIRFLOX Study Group; Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians University of Munich, Munich, Germany; University of Maryland Medical Center, Baltimore, MD; Cancer Trials New Zealand, The University of Auckland, Auckland, New Zealand; University Clinic Magdeburg, Magdeburg, Germany; NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia; Data Reduction LLC, Chester, NJ; University of Western Australia, Perth, Australia*

Background: The SIRFLOX study was designed to assess the efficacy and safety of combining FOLFOX chemotherapy (± bev) with SIRT using yttrium-90 (Y-90) resin microspheres as first-line treatment of pts with liver metastases from mCRC. **Methods:** SIRFLOX was an international, multi-center, open-label, RCT in chemotherapy-naïve pts with non-resectable, liver only or liver dominant (liver plus lung and/or lymph node metastases) mCRC. Arm A: mFOLFOX6 ± bev was compared to arm B: mFOLFOX6 + SIRT (SIR-Spheres; Sirtex) administered once with cycle 1 ± bev until disease progression. The primary endpoint was progression free survival (PFS) using RECIST v1.0. Stratification variables included presence of extra hepatic disease (EHD; liver only v liver dominant), degree of liver involvement (≤ 25% v > 25%), and treatment with bev (at clinician discretion). **Results:** From Oct 2006 to Apr 2013, 530 pts were randomised (arm A, n = 263; arm B, n = 267), 212 (40%) had EHD. Median follow-up was 36.1 months. The median overall PFS was 10.2 v 10.7 months in arms A v B respectively (hazard ratio [HR]: 0.93; 95% CI 0.77–1.12; p=0.428) by Kaplan Meier analysis. The median PFS in the liver was 12.6 v 20.5 months in arm A v B (HR: 0.69; 95% CI 0.55–0.90; $p = 0.002$) by competing risk analysis. Overall response rate (PR + CR) was 68.0% v 76.4% in arm A v B, respectively ($P = 0.113$). Hepatic response rate was 68.8% v 78.7% in arm A v B ($P = 0.042$), including CR rate 1.9% v 6.0% ($P = 0.02$). The liver resection rate was 13.7% v 14.2% in arm A v B ($P = 0.857$). Adverse events ≥ grade 3 were noted in 73.3% v 85.4% of pts in arm A v B. Most common toxicities were hematologic; 32.9% v 51.2% and gastrointestinal; 21.2% v 32.9%, including gastric ulcer 0.0% v2.4%. **Conclusion:** In first-line treatment of pts with non-resectable CRC liver metastases, the addition of SIRT to standard chemotherapy failed to improve overall PFS. However, median liver PFS was significantly extended.The addition of SIRT was associated with acceptable toxicity. Overall survival analyses, combining data from SIRFLOX and two other ongoing studies in this disease setting, are awaited.

Abstract ID: 3503 (149805)

Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance).

Authors: *Kimmie Ng, Alan P. Venook, Kaori Sato, Chen Yuan, Bruce W. Hollis, Donna Niedzwiecki, Cynthia Ye, I-Wen Chang, Bert H. O'Neil, Federico Innocenti, Heinz-Josef Lenz, Charles David Blanke, Robert J. Mayer, Charles S. Fuchs, Jeffrey A. Meyerhardt; Dana-Farber Cancer Institute, Boston, MA; University of California, San Francisco, San Francisco, CA; Medical University of South Carolina, Charleston, SC; Duke University, Cary, NC; Duke University, Durham , NC; Southeastern Medical Oncology, Goldsboro, NC; Indiana University Health University Hospital, Indianapolis, IN; The University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; Oregon Health & Science University, Portland, OR; Dana Farber Cancer Institute, Boston, MA*

Background: Prospective epidemiologic data suggest that higher levels of 25-hydroxyvitamin D [25(OH)D] are associated with improved survival in patients with colorectal cancer, however the relationship between 25(OH)D and outcome in metastatic CRC (mCRC), specifically, is unknown. **Methods:** We prospectively assessed the association between plasma 25(OH)D and overall survival (OS) in previously untreated mCRC patients enrolled in CALGB/SWOG 80405, a randomized phase III trial of chemotherapy + bevacizumab, cetuximab, or both, prior to the KRAS wild type amendment. Progression-free survival (PFS) was a secondary endpoint. Plasma 25(OH)D levels were measured at baseline by radioimmunoassay, and dietary and lifestyle behaviors collected from self-administered questionnaires. Cox proportional hazards models were used to calculate hazard ratios (HR) adjusted for other prognostic variables. **Results:** Among 1,043 patients, median plasma 25(OH)D was 17.2 ng/mL (range 2.2-72.7). Male and black patients, those living in the northeast, patients with lower dietary and supplemental vitamin D intake, ECOG performance status 1 (vs. 0), tumoral RAS mutation, higher body-mass index, lower physical activity, and blood draw during the winter and spring had significantly lower levels of 25(OH)D. Patients in the highest quintile of 25(OH)D had significantly improved OS compared to those in the lowest after adjusting for pathologic and clinical prognostic factors (median 32.6 vs. 24.5 months; HR 0.65, 95% CI, 0.51-0.83; *P* trend = 0.001). Increasing concentrations of 25(OH)D were also significantly associated with improved PFS (median 12.2 vs. 10.1 months; HR 0.79, 95% CI, 0.63-0.99; *P* trend = 0.01). The results were consistent across subgroups of patient characteristics, including RAS status, and remained unchanged after excluding patients who died within 3 or 6 months of blood draw. **Conclusions:** Higher concentrations of plasma 25(OH)D are associated with significantly improved survival in mCRC patients treated with chemotherapy + biologics. Randomized trials of vitamin D supplementation are warranted and ongoing, and effect modification by SNPs in vitamin D pathway genes is currently being explored.

Abstract ID: 3504 (146901)

Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study.

Authors: *Simer Bains, Milada Mahic, Milada Cvancarova, Sheraz Yaqub, Liv Marit Dørum, Bjørn Atle Bjørnbeth, Bjørn Møller, Kristoffer Watten Brudvik, Kjetil Tasken; 1The Biotechnology Centre and Centre for Molecular Medicine Norway, Nordic EMBL Partnership, University of Oslo, Oslo, Norway, Oslo, Norway; Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, Norway; Department of Clinical Medicine, Oslo University Hospital, Oslo, Norway, Oslo, Norway; Department of Clinical Medicine and Department of Hepato-Pancreatico-Biliary Surgery, Oslo University Hospital, Oslo, Norway; Cancer Registry of Norway, Oslo, Norway; Department of Clinical Medicine and Department of Hepato-Pancreatico-Biliary Surgery, Oslo University Hospital, 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 examined. **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 99% 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.

Abstract ID: 4000 (147255)

Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study.

Authors: *David Cunningham, Niall C. Tebbutt, Irina Davidenko, André M. Murad, Salah-Eddin Al-Batran, David H. Ilson, Sergei Tjulandin, Evgeny Gotovkin, Boguslawa Karaszewska, Igor Bondarenko, Mohamedtaki Abdulaziz Tejani, Anghel Adrian Udrea, Mustapha Ali Tehfe, Nigel Baker, Kelly Smith Oliner, Yilong Zhang, Tien Hoang, Roger Sidhu, Daniel Virgil Thomas Catenacci; Royal Marsden Hospital, Sutton, Surrey, United Kingdom; Austin Health, Melbourne, Australia; Krasnodar City Oncology Center, Krasnodar, Russia; Hospital das Clínicas da Universidade Federal e Minas Gerais, Horizonte, Brazil; Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; Memorial Sloan Kettering Cancer Center, New York, NY; Russian Cancer Research Center, Moscow, Russia; Regional Budgetary Institution of Public Health Ivanovo Regional Oncology Dispensary, Ivanovo, Russia; Przychodnia Lekarska Komed Oddzial Jednego Dnia, Konin, Poland; Communal Institution Dnipropetrovsk City Multifield Clinical Hospital 4, Dnipropetrovsk, Ukraine; University of Rochester Medical Center, James P Wilmot Cancer Center, Rochester, NY; SC Medisprof SRL, Cluj-Napoca, Romania; Centre Hospitalier de L'Universite de Montreal Notre-Dame, Montreal, QC; Amgen Ltd., Cambridge, United Kingdom; Amgen Inc, Thousand Oaks, CA; Amgen Inc., Thousand Oaks, CA; University of Chicago, Chicago, IL*

Background: R is a fully human monoclonal antibody to hepatocyte growth factor. A phase 2 study showed improved overall survival (OS) and progression-free survival (PFS) with R + ECX vs P + ECX in MET-pos G/GEJ cancer (Lancet Oncol 2014;15:1007). This phase 3 trial evaluated the efficacy and safety of R + ECX in MET-pos G/GEJ cancer. **Methods:** Key eligibility criteria: ≥ 18 yr; previously untreated, pathologically confirmed unresectable advanced G/GEJ adenocarcinoma; ECOG score 0–1; tumor MET-pos by IHC; HER2-negative. Pts were randomized 1:1 to receive ECX (IV epirubicin 50 mg/m^2 D1, IV cisplatin 60 mg/m^2 D1, oral capecitabine 625 mg/m^2 BID D1−21) + R 15 mg/kg or P IV Q3W and stratified by disease extent (locally advanced vs metastatic) and ECOG score (0 vs 1). Primary endpoint: OS. A log-rank test stratified by randomization factors compared OS between arms. The study was powered to detect a HR of 0.69. Key secondary endpoints: PFS, 12-mo survival rate, objective response rate (ORR), safety and pharmacokinetics (PK). **Results:** 609 pts were randomized from Nov 2012 to Nov 2014. The study was stopped early based on an imbalance in deaths (R vs P: 128 vs 107 deaths, data cutoff: 27 Nov 2014). R was not superior to P for OS (one-sided test, p = 0.99). OS, PFS and ORR were statistically worse in the R arm. No subgroups seemed to benefit with R, including those with higher percentages of cells with ≥ 1+ MET expression. Most common AEs that were higher with R: peripheral edema, hypoalbuminemia, deep vein thrombosis and hypocalcemia. **Conclusions:** RILOMET-1 did not meet its primary endpoint; OS was statistically significantly worse with R. PK and MET biomarker analyses are pending.

	R (n = 304)	P (n = 305)	R vs P
Median OS,* mo	9.6 (7.9–11.4)	11.5 (9.7–13.1)	HR†= 1.37 (1.06–1.78) p = 0.016
Median PFS,* mo	5.7 (5.3–5.9)	5.7 (5.5–7.1)	HR†= 1.30 (1.05–1.62) p = 0.016
12-mo survival rate*	38.4% (30.2%–46.6%)	49.7% (41.5%–57.4%)	Diff = -11.4 (-22.9–0.2) p = 0.053
ORR*	30% (24.6%–36.0%)	39.2% (33.3%–45.4%)	Odds ratio = 0.67 (0.46–0.96) p = 0.027

*95% CI shown. †Stratified.

Abstract ID: 4001 (150958)

Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012.

Authors: *Yung-Jue Bang, Hyun-Choel Chung, Veena Shankaran, Ravit Geva, Daniel Virgil Thomas Catenacci, Shilpa Gupta, Joseph Paul Eder, Raanan Berger, Edward J. Gonzalez, Archana Ray, Marisa Dolled-Filhart, Kenneth Emancipator, Kumudu Pathiraja, Jared K. Lunceford, Jonathan D. Cheng, Minori Koshiji, Kei Muro; Seoul National University College of Medicine, Seoul, South Korea; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; University of Washington School of Medicine, Division of Medical Oncology, Seattle, WA; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; University of Chicago, Chicago, IL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Yale Cancer Center, New Haven, CT; Sheba Medical Center, Tel HaShomer, Israel; Merck & Co., Inc., Kenilworth, NJ; Aichi Cancer Center Hospital, Nagoya, Japan*

Background: Tumors use the PD-1 pathway to evade immune surveillance. Pembrolizumab, an anti–PD-1 monoclonal antibody, has shown antitumor activity in advanced cancers. We assessed the safety and efficacy of pembrolizumab in patients with advanced gastric cancer in KEYNOTE-012 (Clinicaltrials.gov identifier, NCT01848834). **Methods:** Archival tumor samples from patients from Asia-Pacific (AP) and rest of the world (ROW) with recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction were screened for PD-L1 expression using a prototype IHC assay with the 22C3 antibody. Only patients with distinctive stromal or ≥ 1% tumor nest cell PD-L1 staining were eligible. Patients received pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until complete response, progression, or unacceptable toxicity. Imaging was performed every 8 weeks. Primary efficacy end point is ORR assessed per RECIST v1.1 by independent central review. Secondary end points include duration of response, PFS, and OS. **Results:** Of the 162 patients screened, 65 (40%) were PD-L1+. Of these 65 patients, 39 enrolled (19 from AP, 20 from ROW; median age, 63 years [range, 33-78]). The number of prior therapies for advanced disease ranged from 0 to 5; 67% received ≥ 2 prior therapies. Median follow-up duration was 8.8 months (range, 6.2-12.6); 13 patients (33%) remain on therapy. Four patients experienced 5 total grade 3-5 drug-related adverse events: peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis (n = 1 each). There was 1 drug-related death (hypoxia). ORR was 22% (95% CI, 10-39) by central review and 33% (95% CI, 19-50) by investigator review. Median time to response was 8 weeks (range, 7-16), with a median response duration of 24 weeks (range, 8+ to 33+). PD-L1 expression level was associated with ORR (1-sided P = 0.10). The 6-month PFS rate was 24%. The 6-month OS rate was 69%. **Conclusions:** Pembrolizumab demonstrated manageable toxicity and promising antitumor activity in advanced gastric cancer. These results support the ongoing development of pembrolizumab for gastric cancer.

Abstract ID: 4005 (150169)

Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance).

Authors: *Matthew H. Kulke, Donna Niedzwiecki, Nathan R. Foster, Briant Fruth, Pamela L. Kunz, Hagen F. Kennecke, Edward M. Wolin, Alan P. Venook; Dana-Farber Cancer Institute, Boston, MA; Duke University, Cary, NC; North Central Cancer Treatment Group, Rochester, MN; Mayo Clinic Cancer Center, Rochester, MN; Stanford University School of Medicine, Stanford, CA; British Columbia Cancer Agency, Vancouver, BC; University of Kentucky, Lexington, KY; University of California, San Francisco, San Francisco, CA*

Background: Both VEGF pathway and mTOR inhibitors are active in pNET. Treatment with the mTOR inhibitor E improves progression free survival (PFS), but it is not known if the addition of a VEGF pathway inhibitor to an mTOR inhibitor enhances antitumor activity in pNET. This randomized phase II study evaluated E or E+B in pts with advanced pNET. **Methods:** Pts were randomized 1:1 to receive either E (10 mg po qd) or E (10 mg po qd) co-administered with B (10 mg/kg IV q 2 wks). Pts in both arms received concurrent standard dose octreotide. The primary endpoint was PFS. The potential superiority of E+B vs. E was assessed using a stratified log-rank test with 90% power (1-sided $\alpha = 0.15$) to detect a HR of 0.64. 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 1-44 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%; $P = 0.01$), hyponatremia (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%; $P < 0.0001$). 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 E but with more adverse events in this randomized phase II study. The RR was significantly higher in pts treated with E+B. The combination of E+B warrants further investigation in pts with advanced pNET.

Abstract ID: LBA5002 (144388)

A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521).

Authors: *Howard M. Sandler, Chen Hu, Seth A. Rosenthal, Oliver Sartor, Leonard G. Gomella, Mahul Amin, James Purdy, Jeff M. Michalski, Mark Garzotto, Nadeem Pervez, Alexander G. Balogh, George Rodrigues, Luis Souhami, M. Neil Reaume, Scott G. Williams, Raquibul Hannan, Eric M. Horwitz, Adam Raben, Rebecca Paulus, William U. Shipley; Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Sutter Cancer Center, Sacramento, CA; Tulane University School of Medicine, New Orleans, LA; The Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Cedars-Sinai Medical Center, Los Angeles, CA; UC Davis, Sacramento, CA; Washington University in St. Louis, St. Louis, MO; Portland VAMC, Portland, OR; Cross Cancer Institute, Edmonton, AB; Tom Baker Cancer Center, Calgary, AB; Department of Radiation Oncology, London Regional Cancer Program, London, ON; Department of Radiation Oncology, McGill University Health Centre, Montreal, QC; Ottawa Hospital Cancer Center, Ottawa, ON; Peter MacCallum Cancer Centre, East Melbourne, Australia; The University of Texas Southwestern Medical Center, Dallas, TX; Fox Chase Cancer Center, Philadelphia, PA; Helen F Graham Cancer Ctr, Newark, DE; Radiation Therapy Oncology Group, Statistical Center, Philadelphia, PA; Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: High-risk, localized prostate cancer (PCa) patients have a relatively poor prognosis. We hypothesized that the addition of adjuvant docetaxel and prednisone to long-term (24 month) AS and radiation therapy (RT) would improve overall survival (OS). **Methods:** RTOG 0521 opened December 2005 and closed August 2009 with targeted accrual of 600 cases. It was designed to detect improvement in 4-year OS from 86% to 93% with a 51% hazard reduction (HR = 0.49). Under a 0.05 1-sided type I error and 90% power, at least 78 deaths were required to analyze the OS endpoint. Patients had 1) Gleason (Gl) 7-8, any T-stage, and PSA > 20, or 2) Gl 8, ≥ T2, any PSA, or 3) Gl 9-10, any T-stage, any PSA. All had PSA ≤ 150. RT dose was 75.6 Gy. CT consisted of 6, 21-day cycles of docetaxel + prednisone starting 28 days after RT. **Results:** Of 612 enrolled, 50 were excluded for eligibility issues, leaving 562 evaluable. Median age = 66, median PSA = 15.1, 53% had Gl 9-10, 27% had cT3-4. Median follow-up = 5.5 yrs. 4-yr OS rates were 89% [95% CI: 84-92%] for the AS+RT arm and 93% [95% CI: 90-96%] for the AS+RT+CT arm (1-sided $P = 0.03$, HR = 0.68 [95% CI: 0.44, 1.03]). There were 52 centrally-reviewed deaths in the AS+RT arm and 36 in the AS+RT+CT arm, with fewer deaths both due to PCa/treatment (20 vs 16) and due to other causes/unknown (32 vs 20) in the AS+RT+CT arm. 5-yr disease-free survival rates were 66% for AS+RT and 73% for AS+RT+CT (2-sided $P = 0.05$, HR = 0.76 [95% CI: 0.57, 1.00]). There was 1, Gr 5 unlikely-related adverse event (AE) in the AS+RT arm and 2, Gr 5 possibly/probably-related AEs with AS+RT+CT. **Conclusions:** For high-risk, localized PCa, adjuvant CT improved the OS from 89% to 93% at 4 years. Toxicity was acceptable. This trial was designed with a short OS assessment period and additional follow-up is warranted to determine the long-term benefit of CT to the current standard of care of long-term AS+RT. This project was supported by grants U10CA21661, U10CA180868, U10CA180822, from the National Cancer Institute and Sanofi with additional support from AstraZeneca for Australian site participation. Clinical trial information: NCT00288080

Abstract ID: 5004 (145799)

Defining a molecular subclass of treatment resistant prostate cancer.

Authors: *Himisha Beltran, Davide Prandi, Juan Miguel Mosquera, Eugenia Giannopoulou, Loredana Puca, Clarisse Marotz, David M. Nanus, Scott T. Tagawa, Olivier Elemento, Eliezer Mendel Van Allen, Andrea Sboner, Levi A. Garraway, Mark A. Rubin, Francesca Demichelis; Weill Cornell Medical College, New York, NY; University of Trento, Trento, Italy; Department of Medicine, Institute for Precision Medicine, Weill Cornell Medical College and New York-Presbyterian Hospital, New York, NY; Weill Medical College of Cornell University, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Department of Medicine, Institute for Precision Medicine, Department of Pathology and Laboratory Medicine; Institute for Computational Biomedicine, Weill Cornell Medical College and New York-Presbyterian Hospital, New York, NY; University of Trento, New York, NY*

Background: A subset of advanced prostate cancers can progress from an androgen receptor (AR)-driven state to AR independence, often associated 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 of 124 metastatic tumors from 81 patients (35 with morphologic features of NEPC). Serial or synchronous samples were included to characterize heterogeneity and the transition from adenocarcinoma to NEPC. Computational analysis of clonality and allele-specific quantification were performed using CLONET. Quantitative mRNA assessments, including AR signaling genes and DNA methylation, were evaluated in the context of genomic changes. **Results:** The mutational landscape of NEPC and castration-resistant prostate cancer (CRPC) did not differ significantly by rate of non-synonymous mutations or copy number burden (average > 40% of genome was aberrant), and polyploidy 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 allele-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. A subgroup of CRPC demonstrates 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.

Abstract ID: 5006 (147682)

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.

Authors: *Christian Carrie, Ali Hasbini, Guy De Laroche, Muriel Habibian, Pierre Richaud, Stéphane Guérif, Igor Latorzeff, Stephane Supiot, Mathieu Bosset, Jean Leon Lagrange, Veronique Beckendorf, Francois Lesaunier, Bernard Dubray, Jean Philippe Wagner, TD N'Guyen, Jean-Philippe Suchaud, Gilles Crehange, Nicolas Barbier, Alain Ruffion, Sophie Dussart; Department of Radiation Oncology, Centre Léon Bérard, Lyon, France; Clinique Pasteur, Brest, France; Institut de Cancerologie de La Loire, St Priest En Jarez, France; UNICANCER, Paris, France; Institut Bergonie, 33076 Bordeaux, France; Poitiers CHU, Poitiers, France; Clinique Pasteur, Toulouse, France; Institut de Cancérologie de l'Ouest - René Gauducheau, Nantes, France; Hopital Jean Minjoz, Besancon, France; Hopital Henri Mondor, Paris, France; Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France; Centre Francois Baclesse, Caen, France; Centre Henri Becquerel, Rouen, France; Clinique de l'Orangerie, Strasbourg, France; Institut Jean Godinot, Reims, France; Centre Hospitalier de Roanne, Roanne, France; Georges François Leclerc Cancer Center, Dijon, France; Centre Catalan d'Oncologie, Perpignan, France; Department of Urology, Centre Hospitalier Lyon Sud, Pierre Benite, France; 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 vs RT+HT on progression-free survival (PFS) (biological or/and clinical relapse) for patients with BR after RP. Secondary objectives were overall survival (OS), toxicity and quality of life. **Methods:** Patients (pts) were randomized (1:1; stratification on risk factors at RP and type of planned RT) to RT alone (66Gy 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 PFS of 45% for RT arm, the trial required 369 pts per arm to detect an improvement of 12% on PFS in 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-y PFS of 62.1% (CI95%: 57-67) vs 79.6% (IC95%: 75-84) for RT and RT+HT, respectively (log-rank: $P < 0.0001$). The 5-y OS was 94.8% for RT vs 96.2% for RT+HT ($P = 0.18$). Cause of death was progressive disease in 2.1% pts on RT arm vs 0.8%. Acute toxicities occured 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 21.9%). No toxic death was observed. **Conclusions:** GETUG-AFU 16 is the first randomized trial comparing RT vs RT+ short HT as salvage treatment for BR after RP with undetectable post-op PSA. RT+HT significantly improve the 5-y PFS 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.

Abstract ID: 5007 (150983)

TROG 03.06 and VCOG PR 01-03: The "timing of androgen deprivation therapy in prostate cancer patients with a rising PSA (TOAD)" collaborative randomised phase III trial.

Authors: *Gillian M. Duchesne, Julie Bassett, Catherine D'Este, Mark Frydenberg, Leo Ledwich, Jeremy Laurence Millar, Roger L Milne, Rosemary Smith, Nigel Spry, Martin R. Stockler, Rodney Syme, Sandra Turner, Keen Hun Tai, Henry Woo, TROG & Cancer Council Victoria; Peter MacCallum Cancer Centre, East Melbourne, Australia; Cancer Epidemiology Centre, Cancer Council Victoria,, Melbourne, Australia; NCEPH, Australian National University, Canberra, Australia; Monash Health, Clayton, Australia; Consumer representative, Altona, Australia; Alfred Health, Melbourne Victoria, Australia; Cancer Council Victoria, Melbourne, Australia; Cancer Council Victoria Clinical Trials Office, Melbourne, Australia; Genesis Cancer Care, Perth, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia; Retired, Toorak, Australia; Westmead Hospital, Sydney, Australia; Westmead Private Hospital, Sydney, Australia*

Background: This randomized, prospective phase III trial investigated if immediate intervention with androgen deprivation therapy (ADT) (Arm B) improved overall survival compared to delayed ADT introduction (Arm A) in prostate cancer patients with PSA relapse after definitive therapy, or in asymptomatic men not suitable for curative therapy at diagnosis. **Methods:** Eligible patients were randomised 1:1, and stratified by planned intermittent or continuous (I or C) ADT; treatment centre; prior therapy (prostatectomy or radiation therapy); relapse-free interval $<$ or $\geq$ 2 years; and PSA doubling time of $<$ or $\geq$ 10 months. The primary endpoint was unadjusted overall survival by intention-to-treat. Secondary endpoints were cancer specific survival, time-to-clinical progression, time-to-castration resistance, cancer- and treatment-related complications, and quality of life. Sample size calculations for 80% power, α level of 5%, and a 2-sided statistical test required 750 patients to show a 10% improvement in survival. **Results:** From September 2004 to July 2012, 293 patients were randomised (A: 151, B:142) with a median follow-up of 5.0 years. There were 46 deaths, 30 for Arm A (delayed) and 16 for Arm B (immediate). Overall survival (OS) (log rank unadjusted) was significantly higher in Arm B than Arm A (P = 0.047), with 6-year survival rates of 86% and 79% respectively. The hazard ratio (HR) for death from all causes for Arm B relative to Arm A (Cox adjusted regression analysis) was 0.54, 95% confidence interval (CI) 0.27,1.06, P = 0.07. Death from prostate cancer was reduced in Arm B (HR 0.50 CI 0.17,1.51, P = 0.22), as was death from other causes (HR 0.57 CI 0.31,1.05, P = 0.07), both non-significantly. Overt local and distant disease progression were significantly reduced in Arm B (HR 0.51 CI 0.34,0.76, P = 0.001; HR 0.54 CI 0.32,0.90, P = 0.018). There was no difference in the time to castrate resistance. In Arm A 34% of patients started ADT within 2 years, while 49% started later than 4 years on trial or had not yet commenced therapy. **Conclusions:** Overall survival and time to clinical progression were significantly improved for immediate versus delayed ADT.

Abstract ID: 4503 (152881)

First-line randomized phase II study of gemcitabine/cisplatin plus apatorsen or placebo in patients with advanced bladder cancer: The International Borealis-1 trial.

Authors: *Joaquim Bellmunt, Bernhard J. Eigl, Elzbieta Senkus-Konefka, Yohann Loriot, Przemyslaw Twardowski, Daniel E. Castellano, Normand Blais, Srikala S. Sridhar, Cora N. Sternberg, Margitta Retz, Brent A. Blumenstein, Cindy Jacobs, Patricia S. Stewart, Daniel Peter Petrylak; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; BC Cancer Agency, Vancouver, BC; Medical University of Gdansk, Gdansk, Poland; Department of Cancer Medicine, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; City of Hope, Duarte, CA; Hospital Universitario 12 de Octubre, Madrid, Spain; Hopital Notre-Dame du CHUM, Montreal, QC; Princess Margaret Cancer Centre, University Health Network, Toronto, ON; San Camillo Forlanini Hospital, Rome, Italy; Department of Urology, Klinikum rechts der Isar, TU München, Munich, Germany; Trial Architecture Consulting, Washington, DC; OncoGenex Pharmaceuticals, Inc., Bothell, WA; OncoGenex Pharmaceuticals Inc., Bothell, WA; Yale Comprehensive Cancer Center, New Haven, CT*

Background: Heat shock protein 27 (Hsp27) is over-expressed in bladder cancer (BC) and postulated to increase tumor growth, metastasis, and chemotherapy resistance. Apatorsen (A; OGX-427), a novel antisense oligonucleotide, inhibits Hsp27 production and can potentially enhance the efficacy of chemotherapy. This trial was designed to evaluate efficacy and safety of A in combination with gemcitabine and cisplatin (GC) in patients (pts) with advanced BC. **Methods:** Chemotherapy naïve pts with advanced BC were randomized to GC+A 600 mg, GC+A 1000 mg, or GC + placebo. Pts were stratified by Karnofsky performance status (KPS) and visceral disease. The primary endpoint was overall survival (OS). Prognostic 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 disease. **Results:** A total of 179 pts were randomized/treated. Median OS was 15.2 months (m). When compared to GC + placebo, GC+A 600 demonstrated improved OS and PFS (OS HR = 0.856 and PFS HR = 0.830) versus GC+A 1000 (OS HR = 0.898; PFS HR = 0.927). Results from the post hoc model revealed that KPS, liver mets, alk phos, and hemoglobin were prognostic. A median prognostic score dichotomized pts into poor and good prognosis groups (50% each group). Pts with poor prognosis treated with GC+A 600 had a greater reduction in risk of death (HR = 0.717) than pts with good prognosis (HR = 1.44).The most significant prognostic factor was KPS ≤ 80% (35% pts in GC+A 600 vs GC) resulting in HR = 0.50 in favor of GC+A 600. Overall treatment 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 apatorsen 600mg combined with first line GC. Apatorsen may be impacting the intrinsic biology of patients with poor risk factors. Further evaluation is warranted in this pt population.

Abstract ID: 4505 (148692)

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.

Author(s): Thomas Powles, Robert Anthony Huddart, Tony Elliott, Robert Jones, Syed A. Hussain, Simon J. Crabb, Charlotte Ackerman, Satinder Jagdev, John D. Chester, Serena Hilman, Mark Beresford, A. Graham Macdonald, Santhanam Sundar, John A. Frew, Andrew Stockdale, Shah-Jalal Sarker, Daniel Berney, Simon Chowdhury; Barts Cancer Institute, Barts Health and the Royal Free NHS Trust, London, United Kingdom; Institute of Cancer Research, Sutton, United Kingdom; Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; University of Glasgow, Institute of Cancer Sciences, Glasgow, United Kingdom; University of Liverpool, Clatterbridge Cancer Centre, Liverpool, United Kingdom; University of Southampton, Southampton, United Kingdom; Barts Cancer Institute, London, United Kingdom; St James's Institute of Oncology, St. James's University Hospital, Leeds, United Kingdom; Cardiff University, Cardiff, United Kingdom; Bristol Haematology and Oncology Centre, Bristol, United Kingdom; Royal United Hospitals Bath, Bath, United Kingdom; Aberdeen Royal Infirmary, Aberdeen, United Kingdom; Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom; Arden Cancer Centre, University Hospital, Coventry, United Kingdom; St Bartholomew's Hospital, London, United Kingdom; Medical Oncology Department, Guy's and St. Thomas' NHS Foundation 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 TCC patients. **Method:** During first-line chemotherapy, patients 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 AEs 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 (HR 0.94, 0.99 and 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.

Abstract ID: 4506 (144564)

Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC).

Authors: *Robert Motzer, Thomas Hutson, Hilary Glen, Dror Michaelson, Ana M. Molina, Timothy Eisen, Jacek Jassem, Jakub Zolnierek, Pablo Maroto, Begona Mellado, Bohuslav Melichar, Jiri Tomasek, Han-Joo Kim, Karen Wood, Corina Dutcus, James M. G. Larkin; Memorial Sloan Kettering Cancer Center, New York, NY; Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas, TX; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Massachusetts General Hospital Cancer Center, Boston, MA; Weill Cornell Medical College-New York Presbyterian Hospital, New York, NY; Addenbrooke's Hospital, Cambridge, United Kingdom; Medical University, Gdansk, Poland; Centrum Onkologii, Instytut w Warszawie, Warsaw, Poland; Departamento de Oncología Médica, Barcelona, Spain; Translational Genomics and Targeted Therapeutics in Oncology.IDIBAPS. Medical Oncology Department. Hospital Clinic, Barcelona, Spain; Onkologicka Klinika, Lekarska Fakulta Univerzity Palackeho a Fakultni Nemocnice, Olomouc, Czech Republic; Masaryk Memorial Cancer Institute, Masaryk University, Brno, Czech Republic; Eisai Inc., Woodcliff Lake, NJ; Eisai Ltd., Hatfield, United Kingdom; Royal Marsden NHS Hospital, London, United Kingdom*

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 (CCP 2013;73:181). This phase II, open-label, multicenter study compared LEN, 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 (18+5 mg/d) in 28d cycles. The primary objective 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 data cutoff was June 13, 2014. **Results:** 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; hazard ratio [HR] 0.40; 95% confidence interval [CI] 0.24–0.68; $P < 0.001$). LEN alone also prolonged PFS vs EVE (HR 0.61; 95% CI 0.38–0.98; $P = 0.048$). LEN+EVE and LEN improved ORR vs EVE ($P < 0.001$ and $P = 0.007$, respectively). Median duration of response (months) was longest in LEN+EVE, 13.1; LEN, 7.5; EVE, 8.5. OS analysis showed a trend favoring LEN+EVE vs EVE (HR 0.55; 95% CI 0.30–1.01; $P = 0.062$); this reached significance (HR 0.51; 95% CI 0.30–0.88; $P = 0.024$) in an updated analysis on Dec 10, 2014. For LEN+EVE, most common any-grade treatment-emergent adverse events (TEAEs) were diarrhea (84%), decreased appetite (51%), and fatigue (47%). Most common grade ≥ 3 TEAEs were diarrhea (20%), hypertension (14%), and fatigue (10%). **Conclusions:** LEN+EVE improved PFS and ORR versus EVE alone in this phase II trial of pts with mRCC following prior VEGF-targeted therapy. Updated OS also showed improvement with LEN+EVE. A phase III randomized trial of the combination in mRCC is planned.

Primary analysis	LEN+EVE n = 51	LEN n = 52	EVE n = 50
Median survival, months (95% CI)			
PFS	14.6 (5.9–20.1)	7.4 (5.6–10.2)	5.5 (3.5–7.1)
OS	25.5 (20.8–25.5)	18.4 (13.3–NE)	17.5 (11.8–NE)
ORR, n (%)	22 (43)	14 (27)	3 (6)
Median duration of response, months (95% CI)	13.1 (3.8–NE)	7.5 (3.8–NE)	8.5 (7.5–9.4)
Median # of cycles, (range)	9.0 (1–25)	8.5 (1–25)	5.0 (1–22)

NE, not evaluable

Abstract ID: 4507 (147311)

Final clinical results of a randomized phase II international trial of everolimus vs. sunitinib in patients with metastatic non-clear cell renal cell carcinoma (ASPEN).

Authors: *Andrew J. Armstrong, Samuel Broderick, Tim Eisen, Walter Michael Stadler, Robert J. Jones, Jorge A. Garcia, Ulka N. Vaishampayan, Joel Picus, Robert E. Hawkins, John D. Hainsworth, Christian K. Kollmannsberger, Theodore F. Logan, Igor Puzanov, Lisa M. Pickering, Christopher W. Ryan, Andrew Protheroe, Christine M. Lusk, Sadie Oberg, Susan Halabi, Daniel J. George; Duke Cancer Institute, Duke University, Durham, NC; Duke Clinical Research Institute, Durham, NC; University of Cambridge, Cambridge, United Kingdom; University of Chicago, Chicago, IL; The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Cleveland Clinic, Cleveland, OH; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Division of Oncology, Washington University in St. Louis, St. Louis, MO; The Christie NHS Foundation Trust, Manchester, United Kingdom; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; BC Cancer Agency, Vancouver Cancer Centre, Vancouver, BC; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Vanderbilt University Medical Center, Nashville, TN; St Georges Healthcare Trust, London, United Kingdom; Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR; University of Oxford Medical Oncology Department, Oxford, United Kingdom; inVentiv Health Clinical, Pearland, TX; Inventiv Health Clinical, Durham, NC; Duke University Medical Center, Durham, NC; Duke Cancer Institute, 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; any MSKCC risk group, and 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 RECIST 1.1. With an expected 90 PFS events, there was 83% power to detect a 38% decrease in the hazard rate of progression/death assuming a two-sided type I error of 0.20 using a stratified log-rank statistic. **Results:** Between September 2010 and October 2013, we enrolled 108 subjects across 17 sites and 3 countries. Median age was 63, 75/25% male/female, 66% papillary, 15% chromophobe, 19% unclassified; 27/59/14% good/intermediate/poor risk; 57 vs. 51 were randomized to E vs S. Treatment arms were well balanced at baseline. With 87 PFS events, 53 deaths, and 2 pts remaining on study treatment, S improved overall PFS, meeting the primary endpoint. S improved PFS in good/intermediate risk and papillary/unclassified pts, but E improved PFS in poor risk and chromophobe pts (Table). No unexpected safety signals emerged. **Conclusions:** Sunitinib prolonged rPFS as compared with everolimus in patients with NC-RCC, but resulted in higher rates of severe toxicity. This is the largest trial to date in NC-RCC and the first to demonstrate an mTOR-sensitive subgroup of NC-RCC pts as compared with VEGF inhibition in the front-line setting, including chromophobe and poor risk RCC pts.

Endpoint	E (n=57)	S (N=51)	HR (80% CI) S as Reference	p-value
Median PFS (mo)	5.6	8.3	1.41	0.16
(80% CI)	5.5-6.0	5.8-11.1	(1.03-1.92)	
Papillary	5.5	8.1	1.52 (1.05-2.20)	
Chromophobe	11.4	5.5	0.71 (0.31-1.65)	
Unclassified	5.6	11.5	2.55 (1.01-6.45)	
Risk: Good	5.7	14.0	3.07 (1.51-6.28)	
Intermediate	4.9	6.5	1.38 (0.96-2.00)	
Poor	6.1	4.0	0.21 (0.06-0.69)	
Median OS (mo, 95% CI)	13.2	31.5	1.17 (0.65-2.14)	0.60
Objective Response Rate (%)	5	4	-	-
CR+ PR %	12	31		
SD %	67	61		
PD %	16	4		
Missing %				
>Grade 3 Treatment-Related AEs (%)	47%	65%	-	-

Abstract ID: 5001 (147721)

Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE (NCT00268476).

Authors: *Nicholas David James, Matthew Robert Sydes, Malcolm David Mason, Noel W. Clarke, David Paul Dearnaley, Melissa Ruth Spears, Robin Millman, Chris Parker, Alastair W S Ritchie, J. Martin Russell, John Staffurth, Robert J. Jones, Shaun P. Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison J. Birtle, Joe M. O'Sullivan, Richard Cathomas, Mahesh M K Parmar, STAMPEDE Investigators; University of Warwick, Coventry, United Kingdom; MRC Clinical Trials Unit at UCL, London, United Kingdom; Velindre Hospital, Cardiff, United Kingdom; The Christie and Salford Royal Hospitals, Manchester, United Kingdom; Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; TBA, UK, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Clatterbridge Hospital, Wirral, United Kingdom; South West Wales Cancer Institute, Swansea, United Kingdom; University of Oxford Medical Oncology Department, Oxford, United Kingdom; Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom; Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; Belfast City Hospital, Belfast, United Kingdom; Kantonsspital Chur, Chur, Switzerland*

Background: STAMPEDE is a randomised controlled trial using a novel multi-arm multi-stage design. It recruits men (pts) with high-risk locally advanced or metastatic prostate cancer (PCa) starting long-term hormone therapy (HT) for the first time. The trial initially assessed adding 1 or 2 of 3 treatment approaches to standard of care (SOC). We report primary survival results for 3 research comparisons that recruited through all their intermediate analyses: docetaxel (D), zoledronic acid (ZA) & the combination (D+ZA). **Methods:** SOC was hormone therapy for > = 3yrs; RT was encouraged for N0M0 pts up to Nov-2011, then mandated; RT was optional for N+M0 pts. Stratified randomisation allocated pts 2:1:1:1 to SOC (control), SOC+D, SOC+ZA or SOC+D+ZA. 4mg ZA was given for six 3-weekly cycles then 4-weekly until 2yrs. D was given as 75mg/m^2 for six 3-weekly cycles with prednisolone 10mg daily. The primary outcome measure was survival (time from randomisation to death from any cause). Pairwise comparisons to control on survival for each research arm had 90% power at 2.5% 1-sided alpha for a hazard ratio of 0.75 requiring ~400 control arm deaths, accounting for 3 intermediate lack-of-benefit analyses on failure-free survival. Analyses used the Cox model of the logrank test, adjusted for stratification factors. **Results:** From Oct-2005 to Mar-2013, 2,962 pts were randomised to the 4 arms. The groups were balanced with median age 65yrs; 61% metastatic, 14% N+/XM0, 22% N0M0; 93% diagnosed within 6m of randomisation; median PSA 65ng/ml. Median follow-up was 42m. Grade 3-5 toxicity was reported for 31% SOC, 50% SOC+D, 32% SOC+ZA and 52% SOC+D+ZA.There were 405 deaths on the control arm (84% from PCa). The hazard ratio was 0.76 (95% CI 0.63, 0.91; P = 0.003) for SOC+D vs SOC; 0.93 (95% CI 0.79, 1.11; P = 0.437) for SOC+ZA vs SOC; and 0.81 (95% CI 0.68, 0.97; P = 0.020) for SOC+D+ZA vs SOC. Median survival was increased by 10m from 67m on SOC to 77m on SOC+D. Results in M0 and M1 disease will be shown. **Conclusions:** Survival data from STAMPEDE show a clinically and statistically significant improvement in survival from adding docetaxel but not from adding zoledronic acid in men starting long-term hormone therapy for the first time.

Abstract ID: 5500 (144077)

A randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer, GOG-86P.

Authors: *Carol Aghajanian, Virginia L. Filiaci, Don S. Dizon, Jay Carlson, Matthew A. Powell, Angeles Alvarez Secord, Krishnansu Sujata Tewari, David Bender, David M. O'Malley, Ashley Stuckey, Jacob Rotmensch, Douglas A. Levine, Heather A. Lankes, Kathleen N. Moore; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; NRG Oncology and GOG Foundation Inc SDMC, Buffalo, NY; Massachusetts General Hospital, Boston, MA; Cancer Research for the Ozarks, Springfield, MO; Washington University School of Medicine in St. Louis, St. Louis, MO; Division of Gynecologic Oncology, Duke Cancer Institute, Duke University Medical Center, Durham, NC; UC Irvine Medical Center, Orange, CA; University of Iowa, Iowa City, IA; The Ohio State University College of Medicine, Columbus, OH; Women and Infants Hospital, Providence, RI; University Gyn Onc Assoc, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; Gyn Onc Grp, Buffalo, NY; University of Oklahoma Health Sciences Center, Oklahoma City, OK*

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) had received no prior chemotherapy. 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 70% received 6 cycles of C (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) of Tem 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 ($P < 0.001$), were 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 (0.63-1.02), 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 0.71 (0.55-0.91), 0.99 (0.78-1.26) and 0.97 (0.77-1.23)). **Conclusions:** PFS is not significantly increased in any Arm. OS is significantly increased in the PC + Bev arm.

	Arm 1 PC + Bev	Arm 2 PC + Tem	Arm 3 IC + Bev
Enrolled (N = 349)	116	115	118
Eligible and Treated (N = 329)	108	111	110
Median Age	62	63	65
PS			
0-1	106 (91%)	109 (95%)	113 (96%)
Stage			
III	12 (10%)	13 (11%)	10 (9%)
IV	58 (50%)	58 (51%)	62 (52%)
Recurrent	46 (40%)	44 (38%)	46 (39%)
Prior Pelvic RT			
No	99 (85%)	95 (83%)	98 (83%)
Yes	17 (15%)	20 (17%)	20 (17%)
Measurable Disease			
No	27 (23%)	30 (26%)	33 (28%)
Yes	89 (77%)	85 (74%)	85 (72%)
Histology			
Endometrioid G 1	17 (15%)	13 (11%)	15 (13%)
Endometrioid G 2	36 (31%)	24 (21%)	27 (23%)
Endometrioid G 3	30 (26%)	30 (26%)	22 (19%)
Serous	16 (14%)	26 (23%)	31 (26%)
Clear Cell	6 (5%)	4 (3%)	6 (5%)
Other	11 (9%)	18 (16%)	17 (14%)
RR (GOG209 51%)	60%	55%	53%

Abstract ID: 5508 (150121)

Results of ARIEL2: a Phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis.

Authors: *Iain A. McNeish, Amit M. Oza, Robert L. Coleman, Clare L. Scott, Gottfried E. Konecny, Anna Tinker, David M. O'Malley, James Brenton, Rebecca Sophie Kristeleit, Katherine Bell-McGuinn, Ana Oaknin, Alexandra Leary, Kevin Lin, Mitch Raponi, Heidi Giordano, Sandra Goble, Lindsey Rolfe, Roman Yelensky, Andrew R. Allen, Elizabeth M. Swisher; Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland; Princess Margaret Cancer Centre, University Health Network, Toronto, ON; The University of Texas MD Anderson Cancer Center, Houston, TX; Royal Melbourne Hospital, Parkville, Australia; UCLA, Santa Monica, CA; British Columbia Cancer Agency, Vancouver, BC; The Ohio State University College of Medicine, Columbus, OH; Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom; University College London Cancer Institute, London, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Vall d'Hebron University Hospital, Barcelona, Spain; Institut Gustave Roussy, Villejuif, France; Clovis Oncology, San Francisco, CA; Clovis Oncology, Boulder, CO; Clovis Oncology, Cambridge, United Kingdom; Foundation Medicine, Inc., Cambridge, MA; University of Washington School of Medicine, Seattle, WA*

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 BRCAwt HRD tumors likely to respond to a PARP inhibitor remains 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, BRCAwt/LOHhigh and BRCAwt/LOHlow. Known gBRCAmut pt 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 in ≥15% of pts were GI symptoms (nausea, dysgeusia, appetite, vomiting, constipation, diarrhea), fatigue, Hgb, and transient ALT/AST elevations with no other evidence of liver dysfunction. Efficacy data for 135 pts indicate RECIST + CA125 ORRs of 69%, 39%, and 11% in BRCAmut, BRCAwt/LOHhigh, and BRCAwt/LOHlow 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 15/161 (9%) BRCAwt tumors had a loss-of-function mutation or homozygous deletion in a HR gene; 4/15 (27%) alterations were in RAD51C. All 4 tumors were LOHhighand 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 identifies OC pts likely to respond to rucaparib.

Response by HRD status.

HRD Subgroup	# of Pts	RECIST, %	RECIST & CA-125, %
$BRCA^{mut}$	35	66	69
$BRCA^{wt}/LOH^{high}$	56	32	39
$BRCA^{wt}/LOH^{low}$	44	11	11

Abstract ID: 5509 (147268)

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: A phase Ib, open-label expansion trial.

Author(s): *Mary L. Disis, Manish R. Patel, Shubham Pant, Jeffrey R. Infante, A. Craig Lockhart, Karen Kelly, Joseph Thaddeus Beck, Michael S. Gordon, Glen J. Weiss, Samuel Ejadi, Matthew Hiram Taylor, Anja von Heydebreck, Kevin M. Chin, Jean-Marie Cuillerot, James L. Gulley; University of Washington School of Medicine, Seattle, WA; Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL; Peggy and Charles Stephenson Oklahoma Cancer Center, Oklahoma City, OK; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Washington University School of Medicine, St. Louis, MO; UC Davis Comprehensive Cancer Center, Sacramento, CA; Highlands Oncology Group, Rogers, AR; Pinnacle Oncology Hematology, Scottsdale, AZ; Western Regional Medical Center, Cancer Treatment Centers of America, Goodyear, AZ; Virginia G. Piper Cancer Center, Scottsdale, AZ; Oregon Health & Science University, Portland, OR; Merck KGaA, Darmstadt, Germany; EMD Serono, Billerica, MA; 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 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 confirmed and unconfirmed 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 PFS was 11.9 weeks (95% CI, 5.9, not reached), and the PFS rate at 24 weeks was 33.3% (95% CI, 11.5, 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 TEAEs occurred. The most commonly reported drug-related TEAEs (> 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.

Abstract ID: 5522 (143154)

CT perfusion as an early biomarker of treatment efficacy in advanced ovarian cancer: An ECOG-ACRIN and NRG GOG study.

Author(s): *Ting-Yim Lee, Chaan S. Ng, Zheng Zhang, Susanna Lee, Helga Marques, Kyle Burgers, Feng Su, Joseph Bauza, Robert S. Mannel, Joan L. Walker, Warner King Huh, Stephen C. Rubin, Paul DiSilvestro, Lainie P. Martin, John K. Chan, Michael A. Bookman, Robert L. Coleman; Lawson Health Research Institute, London, ON; The University of Texas MD Anderson Cancer Center, Houston, TX; Brown University, Providence, RI; Massachusetts General Hospital, Boston, MA; Robarts Research Institute, Western University, London, ON; Robarts Research Institute, Western University, London, England; ACRIN, Philadelphia, PA; University of Oklahoma, Oklahoma City, OK; Stephenson Cancer Center, OUHSC, Oklahoma City, OK; University of Alabama at Birmingham, Birmingham, AL; Fox Chase Cancer Ctr, Philadelphia, PA; Women and Infants Hospital/The Warren Alpert Medical School of Brown University, Providence, RI; California Pacific / Palo Alto Medical Foundation, Sutter Research Institute, San Francisco, CA; University of Arizona, Tucson, AZ*

Background: GOG-0262 is an advanced stage ovarian cancer phase III trial comparing standard paclitaxel (q3 week)/carboplatin to dose-dense paclitaxel (weekly)/carboplatin with and without bevacizumab per physician choice. ACRIN 6695's primary objective was to determine whether CT perfusion (CTP) parameters are prognostic of progression-free survival (PFS) at 6 months (PFS-6) in a cohort of GOG-262 patients. **Methods:** FIGO stage III or IV patients with suboptimal surgical cytoreduction or undergoing neoadjuvant therapy were recruited and underwent CTP studies before (T0) and at 3- (T1) and 4-weeks (T2) after chemotherapy initiation. Target lesion blood flow (BF) and blood volume were derived with CTP software (GE Healthcare). The association of BF changes from baseline to T2, dichotomized at zero (ΔBF±), and the response rate (best confirmed response by RECIST criteria) and PFS-6 rate were assessed with Fisher's exact tests. Cox regression model was used to assess the association between ΔBF± and time-to-progression (TTP) and overall survival (OS). **Results:** From August 2011 to July 2013, 120 patients were screened, yielding 76 evaluable (with both T0 and T2 CTP studies analyzable) patients from 19 centers. The median age and TTP of those 76 patients were 61 (range 25-87) years and 427 (95% CI: 372-505) days. Overall response and PFS-6 rates were 74% (56/76) and 96% (73/76), respectively. 11/76(14%) patients had increase in tumor BF from baseline to T2 (positive ΔBF±). Positive ΔBF± were significantly associated with lower response rate (45% vs. 78%, $P = 0.03$) and shorter TTP (median TTP 335 vs. 457 days, HR 2.9, 95% CI: 1.3-6.4, $P = 0.008$); and a trend towards lower PFS-6 rate (82% vs. 98%, $P = 0.053$). The significant association between ΔBF± and TTP remained after adjusting for age, baseline tumor volume, change in tumor volume or surgery status (adjuvant vs. neo-adjuvant) individually ($P < 0.02$). ΔBF± was not significantly associated with OS ($P = 0.28$). **Conclusions:** CTP parameters measured within 4 weeks of initiating therapy may provide early prognostic information for treatment response and TTP, and could be used to refine treatment interventions for advanced ovarian cancer in future clinical trials.

Abstract: 7002 (146941)

The international Prognostic Index for patients with CLL (CLL-IPI): An international meta-analysis.

Authors: *Nadine Kutsch, Jasmin Bahlo, John C. Byrd, Hartmut Dohner, Barbara Eichhorst, Monica Else, Christian Geisler, Michael R. Grever, Stephane Leprêtre, Manuela Bergman, Donna S. Neuberg, David Oscier, Richard Rosenquist, Tadeusz Robak, Tait D. Shanafelt, Stephan Stilgenbauer, Michael J. Hallek, International CLL-IPI working group; Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital Cologne, Cologne, Germany; Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University of Cologne, Cologne, Germany; Ohio State University Medical Center, Columbus, OH; Department for Internal Medicine III, University Hospital Ulm, Ulm, Germany; Division of Molecular Pathology, The Institute of Cancer Research London, London, United Kingdom; Rigshospitalet, Copenhagen, Denmark; Ohio State University, Columbus, OH; Henri Becquerel Hospital, Rouen, France; Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Klinikum Schwabing, Munich, Germany; Dana-Farber Cancer Institute, Boston, MA; Department of Haematology, Royal Bournemouth Hospital, Bournemouth, United Kingdom; Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden; Medical University of Lodz, Lodz, Poland; Mayo Clinic, Rochester, MN; University Hospital Ulm, Ulm, 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 (ms)]. 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 CLL pts from Mayo Clinic [median age 62 yr (range 25 - 89); 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 pt groups: low (score 0-1), intermediate (score 2-3), high (score 4-6) and 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 c = 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 into an easily applicable prognostic score for CLL pts. Moreover, it both discriminates between prognostic groups and is informative regarding current treatment recommendations.

Abstract: 7003 (146239)

Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML).

Author(s): *Mark J. Levis, Alexander E. Perl, Jessica K. Altman, Jorge E. Cortes, Ellen K. Ritchie, Richard A. Larson, Catherine Choy Smith, Eunice S. Wang, Stephen Anthony Strickland, Maria R. Baer, Mark Robert Litzow, David Claxton, Gary J. Schiller, Celalettin Ustun, Charles Liu, Stan Gill, Briana Sargent, Erkut Bahceci; Sidney Kimmel Comp Cancer Ctr at Johns Hopkins, Baltimore, MD; University of Pennsylvania, Philadelphia, PA; Northwestern University, Chicago, IL; The University of Texas MD Anderson Cancer Center, Houston, TX; Weill Cornell Medical College of Cornell University, New York, NY; University of Chicago, Chicago, IL; UC San Francisco, San Francisco, CA; Roswell Park Cancer Institute, Buffalo, NY; Vanderbilt Univ Med Ctr, Nashville, TN; University of Maryland Greenebaum Cancer Center, Baltimore, MD; Mayo Clinic, Rochester, MN; Penn State Milton S. Hershey Medical Center, Hershey, PA; David Geffen School of Medicine/UCLA, Los Angeles, CA; University of Minnesota, St. Paul, MN; Astellas Pharma Global Development, Northbrook, IL; Astellas, Northbrook, IL*

Background: FLT3 Internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations are seen in 30% of AML patients (pts) and are associated with poor survival. Secondary FLT3-TKD mutations are associated with treatment failure with tyrosine kinase inhibitors. ASP2215 is a potent inhibitor of FLT3 and Axl with activity against FLT3-ITD and FLT3-TKD. **Methods:** A phase I/II trial was conducted to investigate safety and efficacy in pts with R/R AML. The dose escalation followed a 3+3 design and evaluated doses from 20 to 450 mg once daily. A parallel multi-dose expansion cohort was initiated based on the efficacy seen in dose escalation. **Results:** 166 pts have enrolled between October 2013, and December 2014, 25 in the dose escalation and 141 in the dose expansion cohorts. At the 450 mg dose, 2 pts had a DLT (grade 3 diarrhea and ALT/AST elevation), and the maximum tolerated dose was determined to be 300 mg. Common possibly or probably drug related treatment emergent adverse events of any grade include fatigue (13%), constipation (10%), anemia (8%), nausea (8%), diarrhea (7%), thrombocytopenia (6%), decreased platelet count (6%), vomiting (6%), dizziness (6%), peripheral edema (5%), increased transaminases (5%) and hypomagnesemia (5%). 120 pts are evaluable for response. Overall response rate (ORR) was 57% in 82 pts with FLT3 mutations, and 63% in 68 pts in the 80 mg and higher dose levels. A plasma inhibitory activity assay confirmed effective, sustained in vivo FLT3 inhibition consistently in pts receiving doses of 80 mg and above. **Conclusions:** ASP2215, a potent inhibitor of FLT3/Axl, is well tolerated in patients with R/R AML and results in a high degree of clinical activity. Randomized phase III trials of ASP 2215 at 200 mg per day in newly diagnosed and R/R AML are planned.

Response	FLT3 mutated		FLT3 wild type
	20-300 mg n (%) (82 pts)	≥ 80 mg n (%) (65 pts)	n (%) (38 pts)
Complete Remission (CR)	4 (5%)	3 (5%)	0
CR, incomplete platelet recovery (CRp)	4 (5%)	4 (6%)	0
CR, incomplete hematologic recovery (CRi)	27 (33%)	25 (38%)	3 (8%)
Partial Remission (PR)	12 (15%)	10 (15%)	1 (3%)
Composite CR (CR+CRp+CRi)	35 (43%)	32 (49%)	3 (8%)
ORR (CRc+PR)	47 (57%)	42 (65%)	4 (11%)

Abstract: LBA7006 (150526)

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).

Authors: *Ruben A. Mesa, Miklos Egyed, Anita Szoke, Aleksandr Suvorov, Andrew Perkins, Jiri Mayer, Peter Ganly, Eric Jourdan, Harry C. Schouten, Patrizia Tosi, Charles Michael Farber, Pierre Zachee, Christof Scheid, James P. Dean, Paul Cernohous, Jyoti Nangalia, Jean-Jacques Kiladjian, Alessandro M. Vannucchi, Adam Mead, Claire N. Harrison; Mayo Clinic Cancer Center, Scottsdale, AZ; Kaposi Mor Teaching Hospital, Kaposvar, Hungary; Universisty of Szeged, Szeged, Hungary; First Republican Clinical Hospital of Udmurtia, Izhevsk, Russia; Chermside Medical Centre, Chermside, Australia; Hematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic; Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; Centre Hospitalier Universitaire de Nîmes, Nîmes, France; University Hosp Maastricht, Maastricht, Netherlands; Ospedale "Infermi", Rimini, Rimini, Italy; Morristown Memorial Hospital, Carol G. Simon Cancer Center, Morristown, NJ; ZNA Stuivenberg, Antwerp, Belgium; University of Cologne, Cologne, Germany; CTI BioPharma Corp., Seattle, WA; CTI BioPharma Corp, Seattle, WA; Cambridge Institute for Medical Research, Cambridge, United Kingdom; Hôpital Saint-Louis and Paris Diderot University, Paris, France; University of Florence, Florence, Italy; Oxford University Hospitals, Oxford, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

Background: PAC is a potent JAK2 inhibitor without significant JAK1 inhibition with minimal myelosuppression in early-phase studies in MF. **Methods:** The efficacy and safety of daily oral PAC was compared to BAT (2:1 randomization stratified for risk and platelet count). The 10 endpoint was the proportion of ITT patients (pts) achieving ≥ 35% spleen volume reduction (SVR) at week (wk) 24 by centrally reviewed MRI or CT. Secondary endpoints included the proportion achieving ≥ 50% reduction in total symptom score (TSS) at wk 24 using the MPN Symptom Assessment Form. **Results:** Patients:327 were enrolled (PAC:220, BAT:107), 62% with 10 MF. Median time from diagnosis was 1.12 years (PAC 0.99, BAT 1.60): 32% and 15% had a platelet counts < 100,000/μL or <50,000/ μL; 75% were JAK2V617F positive. Efficacy: The median duration of treatment was 16.2 months PAC and 5.9 months BAT. Sixty-two percent of BAT patients received active disease directed therapy. The SVR rates at week 24 were 19.1% for PAC vs. 4.7% for BAT (P = 0.0003) in ITT and 25% vs. 5.9% (P = 0.0001) in the evaluable population. 79% of BAT patients crossed over to PAC; 21% had achieved a >35% reduction in spleen volume at data cutoff. TSS composite V1 + V2 response rates were 24.5%for PAC vs. 6.5% for BAT (P < 0.0001) by ITT, and were 40.9% vs. 9.9% in evaluable pts (P < 0.0001). Efficacy with baseline cytopenias: In pts with <100,000 and <50,000 platelets/μ/L, the SVR rates were 16.7% for PAC vs. 0% for BAT (P = 0.009), and 22.9% vs. 0% (P = 0.045) by ITT and 23.5% vs. 0% (P = 0.007) and 33.3% vs. 0% (P = 0.037) in evaluable pts. In RBC transfusion dependent pts, 25.7% of PAC pts became RBC independent vs. 0% of BAT pts (P = 0.043). Safety: The most common adverse events (AE) for PAC were diarrhea, nausea, and vomiting; (grade 3 were <5%, <1%, <1% respectively). Hematologic AEs were similar between PAC and BAT. **Conclusions:** This study demonstrated PAC was well tolerated and induced significant and sustained SVR and symptom control even in patients with severe thrombocytopenia. PAC therapy resulted in RBC transfusion independence in a significant proportion of pts. Clinical trial information: NCT01773187

Abstract: 7010 (152001)

Efficacy and safety of CD19-targeted 19-28z CAR modified T cells in adult patients with relapsed or refractory B-ALL.

Authors: *Jae Hong Park, Isabelle Riviere, Xiuyan Wang, Yvette Bernal, Terence Purdon, Elizabeth Halton, Kevin Joseph Curran, Craig Steven Sauter, Michel Sadelain, Renier J. Brentjens; Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Adult patients (pts) 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:** Adult pts 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 1–3x106 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% (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 ≥ 6 months of follow-up. 6-month overall survival (OS) rate of all patients was 58% (95% CI: 36-74). Among the pts who achieved CR, OS rate at 6 months for pts who had allo-SCT vs. no allo-SCT following CAR T cells was 70% (95% CI: 33-89) vs. 61% (95% CI: 29-82; P = 0.30). Severe cytokine release syndrome (sCRS) requiring vasopressors or mechanical ventilation for hypoxia was observed in 7 patients, effectively managed with IL-6R inhibitor and/or corticosteroids. **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.

Abstract: LBA8502 (147837)

GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma.

Authors: *Laurie Helen Sehn, Neil Sun Chua, Jiri Mayer, Gregory Scott Dueck, Marek Trněný, Kamal Bouabdallah, Nathan Hale Fowler, Vincent Delwail, Oliver W. Press, Gilles A. Salles, John G. Gribben, Anne Lennard, Pieternella J. Lugtenburg, Natalie Franklin, Elisabeth Wassner Fritsch, Guenter Fingerle-Rowson, Bruce D. Cheson; BC Cancer Agency, Vancouver, BC; Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB; Hematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic; Department of Medical Oncology, BC Cancer Agency, Kelowna, BC; First Faculty of Medicine, Charles University General Hospital, Prague, Czech Republic; Department of Haematology, CHU Haut-Lévèque, Pessac, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Oncology-Hematology and Cell Therapy, University Hospital, Poitiers, France; Fred Hutchinson Cancer Research Center, Seattle, WA; Hospices Civils de Lyon, Université Claude Bernard, Pierre Bénite, France; Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom; Department of Hematology, Erasmus MC Cancer Insitute, Rotterdam, Netherlands; Biostatistics, F. Hoffmann-La Roche, Welwyn Garden City, United Kingdom; Pharma Development Oncology, F. Hoffmann-La Roche, Basel, Switzerland; Georgetown University Hospital, Washington, DC*

Background: Treatments are limited and outcomes poor in rituximab-refractory (Rit-Ref) iNHL. Bendamustine (B) has a 9 mo median PFS and 10 mo response duration in ph II trials. Obinutuzumab (GA101/Gazyva [G]) is a glycoengineered type II aCD20 mAb with activity and acceptable safety in Rit-Ref NHL. **Methods:** GADOLIN (NCT01059630) is a ph III open label study in pts with CD20+ Rit-Ref iNHL. In the B arm, pts received B 120 mg/m^2 (d1+2, c1–6) alone; GB arm pts received B 90 mg/m^2 (d1+2, c1–6) with G 1000 mg (d1, 8, 15 c1, d1 c2–6) for up to six 28d cycles. Non-PD GB pts then received G monotherapy every 2 mo for up to 2 yrs. Primary endpoint was PFS assessed by an independent radiology facility (IRF), with 80% power to detect 43% improvement in median PFS. **Results:** In the protocol specified interim analysis, 396 pts were randomized to receive B (n = 202 [198 treated]) or GB (n = 194). The IDMC recommended to unblind the study as the primary endpoint had been reached (4 Feb 2015). Baseline characteristics were balanced between arms. Median age was 63 yrs and pts had a median of 2 prior therapies. Median observation time was 20 mo (B) and 22 mo (GB). IRF-assessed median PFS was 14.9 mo (B) and not reached (NR) for GB (HR 0.55, 95% CI 0.4–0.74; p = 0.00011). Median investigator-assessed PFS was 14 mo for B and 29 mo for GB (HR 0.52, 95% CI 0.39–0.70; $p <$ 0.0001). There were no significant differences in IRF-assessed ORR (63.0% B vs 69.1% GB) or CR (12.2% B vs 11.2% GB) at end of induction, in IRF-assessed best overall response up to 12 mo from start of treatment (76.6% B vs 78.6% GB), or in preliminary OS (median OS NR in either arm). In the treatment period, there were fewer Grade ≥ 3 adverse events with B than GB (62.1% B vs 68% GB), notably neutropenia (26.3% B vs 33.0% GB) and infusion-related reactions (3.5% B vs 8.8% GB), but more Grade ≥ 3 thrombocytopenia (16.2% B vs 10.8% GB), anemia (10.1% B vs 7.7% GB) and pneumonia (5.6% B vs 2.6% GB). **Conclusions:** G combined with B (90 mg/m2) followed by G maintenance significantly improved PFS vs B alone (120 mg/m2) in Rit-Ref iNHL. The clinically meaningful PFS improvement with GB is the first randomized evidence of benefit for a novel aCD20 mAb in Rit-Ref iNHL. Clinical trial information: NCT01059630

Abstract: 8508 (144025)

ELOQUENT-2: A phase III, randomized, open-label study of lenalidomide (Len)/dexamethasone (dex) with/without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

Authors: *Sagar Lonial, Meletios A. Dimopoulos, Antonio Palumbo, Darrell White, Sebastian Grosicki, Ivan Spicka, Adam Walter-Croneck, Philippe Moreau, María-Victoria Mateos, Hila Magen-Nativ, Andrew Belch, Donna Ellen Reece, Meral Beksac, Masafumi Taniwaki, Christoph Röllig, Anil K. Singhal, Jessica Katz, Eric W. Bleickardt, Valerie Poulart, Paul G. Richardson, ELOQUENT-2 Investigators; Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; National and Kapodistrian University of Athens, Athens, Greece; A. O. U. San Giovanni Battista di Torino - Ospedale Molinette, Torino, Italy; QEII Health Sciences Center, Dalhousie University, Halifax, NS; Department of Cancer Prevention, Faculty of Public Health, Silesian Medical University, Katowice, Poland; Prague General Hospital, Prague, Czech Republic; Medical University of Lublin, Lublin, Poland; University Hospital, Nantes, France; University Hospital of Salamanca-IBSAL, Salamanca, Spain; Tel Aviv University, Ramat Aviv, Israel; Cross Cancer Institute and University of Alberta, Edmonton, AB; Princess Margaret Hospital, Toronto, ON; Ankara University, Ankara, Turkey; Kyoto Prefectural University of Medicine, Kyoto, Japan; Universitatsklinikum der TU, Dresden, Germany; AbbVie Biotherapeutics Inc. (ABR), Redwood City, CA; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Braine-l'Alleud, Belgium; Dana-Farber Cancer Institute, Boston, MA*

Background: Elo, a monoclonal antibody (mAb) targeting Signaling Lymphocytic Activation Molecule F7 (SLAMF7), kills myeloma cells with minimal effect on normal tissue. Elo showed encouraging activity with Len/dex (Ld) in a phase Ib/II study in pts with RRMM. This phase III study (NCT01239797) compared efficacy and safety of Elo/Len/dex (ELd) vs Ld. **Methods:** Pts with RRMM, 1–3 prior therapies (not Len-refractory), were randomized 1:1 to ELd or Ld in 28-day cycles to disease progression/unacceptable toxicity: Elo (10 mg/kg intravenously) weekly cycles 1+2 then biweekly; Len (25 mg) D1–21; dex weekly (40 mg or [Elo wks] 28 mg oral + 8 mg intravenous). Response/progression was assessed by independent review committee by EBMT criteria. Primary endpoints were progression-free survival (PFS) and overall response rate (ORR). Results of an interim analysis are reported. **Results:** Six hundred and forty-six pts were randomized (321 ELd, 325 Ld; median age 66; del(17p) 32%; t[4;14] 9%; refractory to last therapy 35%). Median (range) prior therapies: 2 (1–4), including bortezomib 70%, thalidomide 48%, Len 6%. At data cut-off (4 November 2014), 35% (ELd) and 21% (Ld) of pts remained on therapy; discontinuation was mainly for disease progression (42% ELd, 47% Ld). Median follow-up was 24 months; median (95% CI) PFS: ELd 19.4 (16.6, 22.2) months, Ld 14.9 (12.1, 17.2) months (HR [95% CI] 0.70 [0.57, 0.85]; $P = 0.0004$). 1-year PFS was 68% ELd, 57% Ld; 2-year PFS: 41% ELd, 27% Ld. PFS benefit with ELd was consistent across key subgroups. ORR (95% CI) was 79% (74, 83) ELd, 66% (60, 71) Ld ($P = 0.0002$). G3–4 adverse events ≥ 15% (ELd vs Ld) were neutropenia (25%, 33%); anemia (15%, 16%). Exposure-adjusted infection rate was the same in both arms (incidence rate/100 person-years of exposure, 197). Infusion reactions (IRs) occurred in 10% of pts with ELd (mostly G1–2). There were 210 deaths (94 ELd, 116 Ld). **Conclusions:** A clinically relevant 30% reduction in risk of progression or death was seen with ELd vs Ld. More pts remain on ELd vs Ld and follow-up for long-term outcomes, including survival, is ongoing. IRs were manageable. Elo, a mAb with a novel immunotherapeutic mechanism of action, showed improved PFS, with minimal added toxicity in combination with Ld vs Ld alone, in pts with multiple myeloma.

Abstract: LBA8512 (150339)

Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius).

Authors: *Sagar Lonial, Brendan M. Weiss, Saad Zafar Usmani, Seema Singhal, Ajai Chari, Nizar J. Bahlis, Andrew Belch, Amrita Y. Krishnan, Robert A. Vescio, María-Victoria Mateos, Amitabha Mazumder, Robert Z. Orlowski, Heather J Sutherland, Joan Blade, Emma Catherine Scott, Huaibao Feng, Imran Khan, Clarissa M. Uhlar, Tahamtan Ahmadi, Peter Michael Voorhees; Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; Division of Hematology & Oncology, Department of Medicine, Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Levine Cancer Institute/Carolinas Healthcare System, Charlotte, NC; Robert H. Lurie Comprehensive Cancer Center, Division of Hem./Onc., Northwestern University Feinberg School of Medicine, Chicago, IL; Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; Tom Baker Cancer Center - University of Calgary, Calgary, AB; Cross Cancer Institute, Department of Medical Oncology, Edmonton, AB; Department Hematology and Hematopoietic Stem Cell Transplant, City of Hope, Duarte, CA; Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA; University Hospital of Salamanca/IBSAL, Salamanca, Spain; NYU Perlmutter Cancer Center, New York, NY; Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; Leukemia/Bone Marrow Transplant Program, University of British Columbia, Vancouver, BC; IDIBAPS, Hospital Clinic de Barcelona, Barcelona, Spain; Knight Cancer Institute, Oregon Health and Science University, Portland, OR; Janssen Research & Development, Spring House, PA; Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: DARA, a human anti-CD38 IgG1κ mAb, has single agent activity and is well-tolerated in rel/ref MM (Lokhorst HM et al. ASCO 2014). This ongoing phase 2 study (NCT01985126) evaluated DARA monotherapy in the FDA breakthrough therapy designation population: MM patients with ≥ 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or double refractory to a PI and IMiD. Preliminary results are reported. **Methods:** MMY2002 is a 2-part, open-label, international, multicenter study. In part 1 stage 1, 34 patients were randomized to DARA 8 mg/kg (n = 18) q4w or 16 mg/kg (n = 16) qw x 8 wk, q2w x 16 wk, then q4w in a Simon-2-stage design to determine the most effective dose. Subsequently, 90 additional patients were enrolled in the 16 mg/kg DARA group. The primary endpoint was overall response rate (ORR) by independent review (IRC). **Results:** Data for the 16 mg/kg DARA group are presented (n = 106). Baseline characteristics: median time since diagnosis, 4.8 y; median prior treatment lines, 5; 75% ISS ⩾ 2. Refractory to: last line of therapy, 96%; last PI and IMiD, 95%; pomalidomide, 63%: carfilzomib, 48%; alkylating agents, 78%. Adverse events (AE; ⩾ 20%) were fatigue (39.6%), anemia (33.0%), nausea (29.2%), thrombocytopenia (25.5%), back pain (22.6%), neutropenia (22.6%), cough (20.8%). Infusion-related reactions (IRR, 42.5%) were mainly grade 1/2 during first infusion (grade 3 4.7%; no grade 4). No patients discontinued study due to IRRs; 5 (4.7%) discontinued treatment due to AEs. None of these AEs were assessed by the investigator to be DARA-related. ORR (IRC assessed) was 29.2%, with 3 sCR, 10 VGPR, and 18 PR with a 7.4 month median duration of response. ORR was consistent across clinically relevant subgroups. Median time to progression was 3.7 months. Median overall survival has not been reached and the estimated 1-year OS rate is 65%. After a median follow up of 9.4 months 14/31 (45.2%) of responders remain on therapy. **Conclusions:** In a heavily pre-treated MM population (95% refractory to last PI and IMiD), DARA at 16 mg/kg showed meaningful durable single agent activity, with deep responses and a favorable safety profile. Clinical trial information: NCT01985126

Abstract: 8516 (152821)

Phase IIa trial of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas.

Authors: *Stephen J. Schuster, Jakub Svoboda, Sunita Nasta, David L. Porter, Anthony Mato, Gaurav D. Shah, Daniel Jeffrey Landsburg, Elise A Chong, Simon F. Lacey, Jan J. Melenhorst, Anne Chew, Jens Hasskarl, Nirav Niranjan Shah, Mariusz A. Wasik, Katherine Marcucci, Zhaohui Zheng, Bruce Levine, Carl H. June; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Health Syst, Philadelphia, PA; Novartis Pharmaceuticals, Florham Park, NJ; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Novartis, Basel, Switzerland; University of Pennsylvania, Translational Research Program, Philadelphia, PA*

Background: Autologous T cells expressing a chimeric antigen receptor with an external anti-CD19 single chain antibody domain and CD3ζ and 4-1BB signaling domains (CTL019 cells) mediate anti-tumor effects in patients (pts) with relapsed/refractory (r/r) CD19+ leukemias. We are conducting a phase IIa clinical trial of CTL019 cells in r/r CD19+ non-Hodgkin lymphomas. **Methods:** Eligible pts have CD19+ follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), or mantle cell lymphoma (MCL) with anticipated survival less than 2 years. After collection of peripheral blood leukocytes, pts receive lymphodepleting chemotherapy based on histology and past therapies. One to 4 days after chemotherapy, pts receive 5 x 108CTL019 cells intravenously. Blood and marrow samples are collected for correlative studies. Response assessment is 3 months (mo) after infusion. Enrollment began February 2014; data reported are through January 2015. **Results:** Twenty-nine pts (19 DLBCL; 8 FL; 2 MCL) have enrolled. Median age is 56 (range: 25-77), male:female ratio 17:12, median prior therapies 4 (range: 1-8), and pts with prior ASCT 9 (31%). At enrollment, stages were: IV, 16 pts (55%); III, 5 pts (17%); II, 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 inadequate T cell expansion; 1 pt received < protocol-specified cell 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 grade 2; 2 grade 3); neurologic toxicity in 3 pts: transient delirium (1 grade 2, 1 grade 3) and 1 possibly related, grade 5 encephalopathy. For 18 pts evaluable for response at 3 mo (12 DLBCL; 6 FL), overall response rate is 67% (DLBCL 50%; FL 100%). At median follow up 6 mo, progression-free survival for evaluable pts is 59% (DLBCL 37%; FL 100%). **Conclusions:** CTL019 cells induce durable responses in pts with r/r DLBCL and FL with acceptable toxicity.

Abstract ID: LBA1 (144621)

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).

Authors: *Jedd D. Wolchok, Vanna Chiarion-Sileni, Rene Gonzalez, Piotr Rutkowski, Jean Jacques Grob, Charles Lance Cowey, Christopher D. Lao, Dirk Schadendorf, Pier Francesco Ferrucci, Michael Smylie, Reinhard Dummer, Andrew Graham Hill, John B. A. G. Haanen, Michele Maio, Grant A. McArthur, Arvin Yang, Linda Rollin, Christine E. Horak, James M. G. Larkin, F. Stephen Hodi; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Oncology Institute of Veneto IRCCS, Padua, Italy; University of Colorado Cancer Center, Denver, CO; Maria Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland; Hospital de la Timone, Marseille, France; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; University of Michigan, Ann Arbor, MI; Department of Dermatology, University of Essen, Essen, Germany; European Institute of Oncology, Milan, Italy; Cross Cancer Institute, Edmonton, AB; Universitäts Spital, Zurich, Switzerland; Tasman Oncology Research, Queensland, Australia; Netherlands Cancer Institute, Amsterdam, Netherlands; University Hospital of Siena, Siena, Italy; Peter MacCallum Cancer Centre, East Melbourne, Australia; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Wallingford, CT; Royal Marsden Hospital, London, United Kingdom; Dana-Farber Cancer Institute, Boston, MA*

Background: The results of a phase I study in MEL suggested complementary clinical activity with NIVO (a PD-1 checkpoint inhibitor) plus IPI (a CTLA-4 checkpoint inhibitor). Here, we report the results of a randomized, double-blind, phase III trial designed to evaluate NIVO combined with IPI or NIVO alone vs IPI alone in MEL. **Methods:** Treatment-naïve pts (N = 945) were randomized 1:1:1 to NIVO 1 mg/kg Q2W + IPI 3 mg/kg Q3W for 4 doses followed by NIVO 3 mg/kg Q2W, NIVO 3 mg/kg Q2W + placebo, or IPI 3 mg/kg Q3W for 4 doses + placebo, until progression or unacceptable toxicity. Pts were stratified by PD-L1 status, BRAF mutation status, and M-stage. Co-primary endpoints are progression-free survival (PFS) (reported here) and overall survival (pts continue to be followed). Secondary endpoints include objective response rate (ORR) by RECIST v1.1 and safety. **Results:** At a minimum follow-up of 9 months, NIVO + IPI and NIVO alone significantly improved PFS and ORR vs IPI (Table). Grade 3-4 drug-related adverse events (AEs) occurred in 55.0%, 16.3%, and 27.3% of pts in the NIVO + IPI, NIVO, and IPI arms, respectively (most commonly diarrhea [9.3%, 2.2%, 6.1%], increased lipase [8.6%, 3.5%, 3.9%], increased alanine aminotransferase [8.3%, 1.3%, 1.6%], and colitis [7.7%, 0.6%, 8.7%]). Drug-related AEs led to discontinuation in 36.4%, 7.7%, and 14.8% of pts in the NIVO + IPI, NIVO, and IPI arms, with 0, 1, and 1 drug-related deaths, respectively. Efficacy outcomes by PD-L1 status will also be presented. **Conclusions:** NIVO + IPI and NIVO alone had superior clinical activity vs IPI alone. The results with NIVO + IPI and NIVO alone further suggest complementary activity of the two agents. There were no new safety signals or drug-related deaths observed with the combination. Clinical trial information: NCT01844505

	NIVO+IPI(N=314)	NIVO(N=316)	IPI(N=315)
Median PFS, months(95% CI)	11.5(8.9-16.7)	6.9(4.3-9.5)	2.9(2.8-3.4)
HR(95% CI) vs IPI	0.42(0.31-0.57)*	0.57(0.43-0.76)*	--
HR(95% CI) vs NIVO	0.74(0.60-0.92)**	--	--
ORR(95% CI)	57.6%(52.0-63.2)*	43.7%(38.1-49.3)*	19.0%(14.9-23.8)
CR rate	11.5%	8.9%	2.2%

*p<0.00001 vs IPI.**Study not statistically powered for this comparison

Abstract ID: 102 (149861)

Overall survival in COMBI-d, a randomized, double-blinded, phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/Kmutation-positive cutaneous melanoma.

Authors: *Georgina V. Long, Daniil Stroyakovskiy, Helen Gogas, Evgeny Levchenko, Filippo G. De Braud, James M. G. Larkin, Claus Garbe, Thomas Jouary, Axel Hauschild, Jean Jacques Grob, Vanna Chiarion-Sileni, Celeste Lebbe, Mario Mandalà, Michael Millward, Douglas James DeMarini, Jhangir G Irani, Fan Jin, R. Suzanne Swann, Bijoyesh Mookerjee, Keith Flaherty; Melanoma Institute Australia and The University of Sydney, North Sydney, Australia; Moscow City Oncology Hospital #62, Chemotherapy Department, Moscow, Russia; 1st Department of Medicine, Medical School, University of Athens, Athens, Greece; Petrov Research Institute of Oncology, Saint Petersburg, Russia; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; The Royal Marsden NHS Foundation Trust, London, United Kingdom; University of Tübingen, Tübingen, Germany; Hôpital François Mitterrand, Pau, France; University of Kiel, Kiel, Germany; Aix-Marseille University, Hopital de la Timone, Marseille, France; Veneto Oncology Institute, Padova, Italy; Dermatology Department, Hôpital Saint-Louis, Assistance-Publique-Hôpitaux de Paris, Paris, France; Papa Giovanni XXIII Hospital, Bergamo, Italy; Sir Charles Gairdner Hospital, Perth, Australia; GlaxoSmithKline, Collegeville, PA; Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: This phase III study (NCT01584648) of dabrafenib (D) + trametinib (T) compared with D + placebo (P) demonstrated superior progression-free survival (PFS) for D+T compared with D+P (HR = 0.75 ; 95% CI: 0.57–0.99; $P = 0.035$) in pts with BRAF V600E/K mutant, metastatic melanoma at the primary analysis (N Engl J Med 2014;371:1877). The interim overall survival (OS) favored D+T (40 deaths on D+T vs 55 on D+P), but did not cross the pre-planned stopping boundary for efficacy. Median time on study at the primary analysis was 9 months (0–16 months). Rates of adverse events (AEs) were similar for both arms. More pts had AEs leading to dose modifications with D+T vs D+P, and fewer hyperproliferative skin AEs were reported with D+T. The study was continued after the primary analysis to evaluate OS without crossover from D+P to D+T. **Methods:** Pts were randomized 1:1 to receive D (150mg twice daily) + T (2mg once daily) or D+P as first-line therapy. Eligible pts were age 18 or older, ECOG performance status ≤ 1, and had histologically confirmed unresectable stage IIIC or IV, BRAF V600E/K mutant cutaneous melanoma. The primary endpoint was investigator-assessed PFS; secondary endpoints were OS, overall response rate (ORR), duration of response (DoR), and safety. The final statistical OS comparison was to be initiated when 220 events were reported. **Results:** From May 2012 to January 2013, 423 pts were randomized (211 to D+T, 212 to D+P). The 220th death was reported on Jan 12, 2015; analysis is expected to be completed in Mar 2015. Estimated median time on study at data cut off is 20 months (0-31 months). **Conclusions:** The statistical analysis will evaluate the superiority of D+T vs D+P for OS. A 2-year OS landmark analysis, updated PFS, ORR, DoR, and safety will be presented.

Abstract ID: 9000 (149209)

Oral nicotinamide to reduce actinic cancer: A phase 3 double-blind randomized controlled trial.

Authors: *Andrew James Martin, Andrew Chen, Bonita Choy, Pablo Fernandez Penas, Gary Halliday, Robyn Dalziell, Catriona McKenzie, Richard A Scolyer, Haryana M. Dhillon, Janette L. Vardy, Gaya St George, Nira Chinniah, Diona Damian; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Department of Dermatology, Royal Prince Alfred Hospital / Dermatology, University of Sydney, Sydney, Australia; Department of Dermatology, Westmead Hospital / Sydney Medical School, The University of Sydney, Sydney, Australia; Dermatology, University of Sydney, Sydney, Australia; Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, Australia; Melanoma Institute Australia/Sydney Medical School University of Sydney/Tissue Pathology and Diagnostic Oncology Royal Prince Alfred Hospital, Sydney, Australia; CeMPED, School of Psychology, University of Sydney / Concord Clinical School, Sydney Medical School, University of Sydney, Sydney, Australia; Concord Cancer Centre, University of Sydney, Sydney, Australia; Dermatology, Westmead Clinical School, University of Sydney, Sydney, Australia; Dermatology University of Sydney at Royal Prince Alfred Hospital/Melanoma Institute Australia, Sydney, Australia*

Background: Nicotinamide (vitamin B3) enhances DNA repair and prevents cutaneous immune suppression after ultraviolet (UV) radiation exposure. It reduces photocarcinogenesis in mice, and human non-melanoma skin cancers (NMSC) in Phase 2 clinical trials. We report the outcomes of the Phase 3 Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) Study. **Methods:** ONTRAC was a double-blind RCT conducted in two tertiary treatment centers in Sydney, Australia from 2012-2014. 386 immune competent participants with ≥ 2 histologically-confirmed NMSC in the past 5 years were randomized (1:1) to oral nicotinamide 500mg bd (NIC) or matched placebo (PBO) for 12 months. The primary endpoint was the number of new NMSCs to 12 months. Secondary endpoints included number of squamous cell carcinomas (SCCs), basal cell carcinomas (BCCs), and actinic keratoses (AKs) to 12 months. Skin reviews by dermatologists were performed 3 monthly. The sample size provided 90% power to detect a 33% difference in NMSC rates. Analysis was by intention-to-treat. **Results:** The mean age of study population was 66 years, the mean number of NMSC in the past 5 years was 8, and 63% were men. Treatment discontinuation rates were 9% for PBO versus 10% for NIC. 99% of patients underwent at least one post-baseline skin assessment. The average NMSC rate was significantly lower for NIC (1.77) than PBO (2.42). The estimated relative rate reduction (RRR) was 0.23 (95% CI: 0.04 to 0.38, $P = 0.02$) adjusting for center and NMSC history, and 0.27 (95% CI: 0.05 to 0.44; $P = 0.02$) with no adjustment. Treatment effects of comparable magnitude were found for both BCCs (RRR = 0.20, 95% CI: -0.06 to 0.39, $P = 0.1$) and SCCs (RRR = 0.30, 95% CI: 0 to 0.51, $P = 0.05$). AK counts were reduced for NIC compared to PBO by 11% at 3 months ($P = 0.01$), 14% at 6 months ($P < 0.001$), 20% at 9 months ($P < 0.0001$) and 13% at 12 months ($P < 0.005$). There were no clinically relevant differences in adverse event rates between the two arms. **Conclusions:** Nicotinamide reduces NMSC formation in high risk patients and is well tolerated. Furthermore, it is widely accessible as an inexpensive over-the-counter vitamin supplement and presents a new chemopreventive opportunity against NMSCs that is readily translatable into clinical practice.

Abstract ID: 9001 (143627)

Long term follow up of survival in a randomised trial of wide or narrow excision margins in high risk primary melanoma.

Authors: *Andrew J Hayes, Lauren Maynard, Roger A'Hern, Gillian Coombes, Julia Newton-Bishop, Michael Timmons, Martin Cook, Jeffery Theaker, Judith Bliss, Joseph Meirion Thomas; The Royal Marsden NHS Trust, London, United Kingdom; The Institute of Cancer Research, Clinical Trials Unit, Surrey, United Kingdom; Leeds Institute of Cancer and Pathology, Leeds, United Kingdom; Bradford Royal Infirmary, West Yorkshire, United Kingdom; Royal Surrey County Hospital, Guildford, United Kingdom; University Hospitals Southampton, Southampton, United Kingdom*

Background: Our randomized trial of 1 versus 3 cm clinical excision margins for high risk melanoma showed that narrow margins were associated with an increase in loco-regional relapse, but with no significant difference in melanoma-specific survival (MSS). We now report long-term melanoma-specific and overall survival from that trial. **Methods:** Patients with primary cutaneous melanoma two mm or more in Breslow thickness were randomized to a 1 or 3 cm excision. **Results:** Four hundred and fifty-three patients were randomized to a 1 cm margin and 447 patients to a 3 cm margin. Median age was 58.7 (IQR 47.2-69.2), median tumour thickness and percentage ulceration were similar in both groups (1 cm group: 3.0 mm and 31.8%, 3 cm group: 3.1 mm and 34.5%) . At a median follow-up of 8.8 years (IQR 6.3-11.3), 494 patients have died, with 359 of these deaths from melanoma. There were 194 melanoma deaths in the 1 cm group and 165 in the 3 cm group. Relative rate of melanoma death was estimated to be 24% higher in the 1 cm group than the 3 cm group on univariable analysis (hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.00 to 1.52; P = 0.05). This effect was similar in multivariable analysis, adjusting for known prognostic factors (table). While there was an increase in the number of overall deaths in the 1 cm group compared to the 3 cm group (253 versus 241), this difference was not statistically significant in univariable analysis (HR 1.14: 95% CI 0.96 to 1.36, P = 0.14). **Conclusions:** With longer follow up, the previously reported increase in loco-regional relapse associated with narrow excision margins has translated into a significant increase in melanoma specific mortality.

			Overall Survival	Melanoma-Specific Survival
		N (%)	HR (95% CI) p value	HR (95% CI) p value
Margin	3cm	387 (50.2)	1.00	1.00
	1cm	384 (49.8)	1.19 (0.99-1.45) 0.07	1.27 (1.02-1.59) 0.036
Sex	Female	419 (54.3)	1.00	1.00
	Male	352 (45.7)	1.38 (1.11-1.71) 0.003	1.38 (1.07-1.17) 0.013
Thickness		771 (100)	1.18 (1.10-1.27) < 0.001	1.23 (1.13-1.3) < 0.001
Ulceration	Absent	475 (61.6)	1.00	
	Present	296 (38.4)	1.68 (1.38-2.04) < 0.001	1.75 (1.39-2.20) < 0.001
Site	Distal limb	244 (31.6)	1.00	1.00
	Proximal limb	173 (22.4)	1.23 (0.93-1.63) 0.03	1.44 (1.03-2.03) 0.003
	Trunk	354 (45.9)	1.41 (1.09-1.81)	1.69 (1.24-2.29)

Abstract ID: LBA9002 (146329)

Survival of SLNB-positive melanoma patients with and without complete lymph node dissection: A multicenter, randomized DECOG trial.

Authors: *Ulrike Leiter, Rudolf Stadler, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Klaus-Werner Schulte, Percy Lehmann, Thomas Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Claus Garbe; Department of Dermatooncology, University of Tuebingen, Tuebingen, Germany; Dept of Dermatology Medical Ctr Minden, Minden, Germany; University of Cologne, Cologne, Germany; University of Erlangen, Erlangen, Germany; Dept. of Dermatology, Ruhr University of Bochum, Bochum, Germany; Department of Dermatology, University of Munich (LMU), Munich, Germany; University Department of Dermatology, Münster, Germany; SRH Wald-Klinikum Gera, Gera, Germany; Dept. of Dermatology, Heinrich Heine university of Duesseldorf, Duesseldorf, Germany; Dept. of Dermatology Wuppertal, University of Witten/Herdecke, Wuppertal, Germany; Department of Dermatology, University Hospital, Regensburg, Germany; Medical Center Quedlinburg, Quedlinburg, Germany; Department of Dermatology, Erfurt, Germany; Dept. of Dermatology, Hospital of Karlsruhe, Karlsruhe, Germany; Dept. of Dermatology, Universtiy of Leipzig, Leipzig, Germany; Dept. of Dermatology, University of Tuebingen, Tuebingen, Germany; University of Tübingen, Tübingen, Germany*

Background: Complete lymph node dissection (CLND) following positive sentinel node biopsy (SLNB) was evaluated in a randomized phase III trial. **Methods:** 1,258 patients with cutaneous melanoma of the trunk and extremities and with positive SLNB were evaluated. Of these, 483 (39%) agreed to randomization into the clinical trial. 241 patients underwent observation only, 242 received CLND. Both groups had a subsequent 3-years follow-up. Recurrence-free (RFS), distant metastases free (DMFS) and melanoma specific (MSS) survival were analyzed as endpoints. **Results:** Patient enrolment was performed from January 2006 to December 2014. In the intent to treat analysis, both groups did not differ significantly in distribution of age, gender, localization, ulceration, tumor thickness (median 2,4 mm in both groups), number of positive nodes, or tumor burden in the SN. The mean follow-up time was 34 months (SD ± 22.1). No significant treatment-related difference was seen in the 5-years RFS ($P = 0.72$), DMFS ($P = 0\ .76$) and MSS ($P = 0.86$) in the overall study population. **Conclusions:** In this early analysis of trial results, no survival benefit was achieved by CLND in melanoma patients with positive SLNB. A subsequent analysis three years after inclusion of the last patient is planned.

Abstract: LBA2 (148284)

Reduction in late mortality among 5-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

Author(s): *Gregory T. Armstrong, Yutaka Yasui, Yan Chen, Wendy M. Leisenring, Todd M. Gibson, Ann Mertens, Marilyn Stovall, Melissa M. Hudson, Kevin C. Oeffinger, Smita Bhatia, Kevin R. Krull, Paul C. Nathan, Joseph Philip Neglia, Daniel M. Green, Leslie L. Robison; St. Jude Children's Research Hospital, Memphis, TN; University of Alberta, Edmonton, AB; Fred Hutchinson Cancer Research Center, Seattle, WA; Emory University, Atlanta, GA; Department of Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; University of Alabama at Birmingham, Birmingham, AL; The Hospital for Sick Children, Toronto, ON; University of Minnesota, Minneapolis, MN*

Background: Over the past four decades, treatment of many childhood cancers has been modified with the aim of achieving high survival rates while reducing the risk of life-threatening late-effects, and promoting risk-based follow-up care of survivors. **Methods:** Late mortality was evaluated in 34,033 5-year survivors (diagnosed < 21 years of age from 1970-1999, median follow-up 21 years, range 5-38) using cumulative incidence and Poisson regression models adjusted for demographic and disease factors to calculate relative risk (RR) and 95% confidence intervals (CI). Mortality due to non-recurrence/non-external (NR/NE) causes, which includes deaths that reflect late-effects of cancer therapy, was evaluated. **Results:** 1,622 (41%) of the 3,958 deaths were attributable to NR/NE causes, including 751 subsequent neoplasm (SN), 243 cardiac, and 136 pulmonary deaths. Changes in therapy by decade included reduced rates of: cranial radiotherapy (RT) for acute lymphoblastic leukemia (ALL, 86%, 54%, 22%), RT for Wilms tumor (WT, 77%, 54%, 49%) and RT for Hodgkin lymphoma (HL, 96%, 88%, 77%). Reductions in 15 year cumulative NR/NE mortality were observed across treatment eras for ALL ($P < .001$), HL ($P = .005$), and WT ($P = .005$). Cardiac deaths decreased in ALL ($P = .002$), HL ($P = .06$), and WT ($P = .04$), and SN deaths decreased in WT ($P < .001$). Year of diagnosis (adjusted for age, sex, diagnosis, follow-up time) was significantly associated with a reduced risk of all-cause mortality (RR = 0.85, CI 0.83-0.87), NR/NE death (RR = 0.87, CI 0.84-0.91), death from SN (RR = 0.84, CI 0.80-0.89), cardiac death (RR = 0.78, CI 0.69-0.87) and pulmonary death (RR = 0.79, CI 0.68-0.91). **Conclusions:** The CCSS cohort provides evidence that the strategy of modifying therapy to reduce the occurrence of late-effects, and promotion of early detection, is successfully translating into a significant reduction in observed late mortality.

Cumulative incidence(%) of death at 15 years from diagnosis.

Treatment era	All-Cause	NR/NE Causes	SN	Cardiac	Pulmonary
1970-74	12.4	3.5	1.8	0.5	0.4
1975-79	9.7	2.8	1.5	0.4	0.2
1980-84	8.8	2.7	1.4	0.3	0.3
1985-89	6.9	2.2	1.3	0.2	0.2
1990-94	6.0	2.1	1.0	0.1	0.1
P-value	<0.001	<0.001	<0.001	0.001	0.02

Abstract: 9500 (149475)

Phase III trials of anamorelin in patients with advanced non-small cell lung cancer (NSCLC) and cachexia (ROMANA 1 and 2).

Authors: *Jennifer S. Temel, David Christopher Currow, Kenneth Fearon, Ying Yan, John Friend, Amy Pickar Abernethy; Massachusetts General Hospital, Boston, MA; Flinders University, Adelaide, SA, Australia; Western General Hospital, Edinburgh, United Kingdom; Helsinn Therapeutics (US), Inc., Bridgewater, NJ; Duke University, Durham, NC*

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 (≥ 5% weight loss within prior 6 months or BMI < 20 kg/m^2) 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 symptom 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, $P < 0.001$), 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 hyperglycemia and diabetes as the most frequent drug-related adverse events (≤ 5%). Median 1-year survival was not different between study arms. **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.

Abstract: 9501 (147845)

CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. longer interval dosing of zoledronic acid in metastatic cancer.

Authors: *Andrew Louis Himelstein, Rui Qin, Paul J. Novotny, Drew K. Seisler, James L. Khatcheressian, John D. Roberts, Stephen S. Grubbs, Tracey O'Connor, Douglas Weckstein, Charles L. Loprinzi, Charles L. Shapiro; Helen F. Graham Cancer Center & Research Institute, Newark, DE; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Virginia Cancer Institute, Richmond, VA; Yale University, New Haven, CT; Roswell Park Cancer Institute, Buffalo, NY; New Hampshire Onc-Hem PA, Hooksett, NH; Mayo Clinic, Rochester, MN; Mount Sinai School of Medicine, New York, NY*

Background: Zoledronic acid (ZA) given monthly for 24 months (mo) reduces bone pain and skeletal-related events (SRE) in patients (pts) with bone metastases. We tested whether ZA every 3 mo would be non-inferior to monthly for 24 mo, with less toxicity, in a randomized trial in 1822 pts: breast (n= 833), prostate (n= 674), myeloma (n = 270), and other (n = 45). **Methods:** SRE were defined as radiation therapy (RT) to bone, fractures, spinal cord compression or surgery to bone within 24 mo. ZA doses were adjusted for creatinine clearance. The primary endpoint was the proportion of pts in each group who had ≥ 1 SRE; secondary endpoints included skeletal morbidity rates, performance status, pain using the Brief Pain Inventory, and incidences of jaw osteonecrosis and renal dysfunction. The trial design was non-inferiority (NI) with stratification and pre-planned analyses by disease. The NI margin was 7% absolute difference. With 1,230 pts (planned sample size 1758 with 30% allowance for inevaluable pts), the power was > 82% when the NI margin was < 0 using a 1-sided test at a 5% significance level. **Results:** Between May 1, 2009 and April 13, 2012, 1822 pts were randomized. Baseline characteristics of the 2 groups were comparable. Dose delays were more common with ZA monthly. The 2-year cumulative incidences of SRE and selected toxicities are presented in the Table. The proportions of SRE were 29.5% vs 28.6% (95% CI for margin: -3.3% to 5.1%, Cochran-Maentel-Hanzel p= 0.79) for monthly and every 3 mo, respectively. **Conclusions:** ZA administered every 3 mo is non-inferior to ZA administered monthly for 24 mo in breast cancer, prostate cancer and multiple myeloma. Bone turnover markers in a subset of pts and a cost analysis will be presented.

	Q Month (N = 911)	Q 3 Months (N = 911)	HR (P-value)
Total ZA dose (median)	56 mg	24 mg	— (< 0.01)
Dose delays	62%	37%	— (< 0.01)
Any SRE	260	253	1.05 (0.60)
Any SRE – breast pts (N = 820)	113	119	0.90 (0.43)
Any SRE – prostate pts (N = 660)	107	101	1.15 (0.31)
Any SRE – myeloma pts (N = 265)	35	30	1.30 (0.29)
Bone RT	185	163	1.16 (0.18)
Bone fractures	62	79	0.78 (0.13)
Spinal cord compression	23	30	0.75 (0.30)
Bone surgery	22	42	0.51 (0.01)
Jaw osteonecrosis	18	9	— (0.08)
Grade 2-4 creatinine increase	11	5	— (0.46)

Abstract: 9503 (152832)

Chemotherapy-related cognitive impairment (CRCI), and neurotransmitter signaling, longevity, and inflammation pathways in 366 breast cancer (BC) patients and 366 age-matched cancer-free controls: A prospective, nationwide, longitudinal URCC NCORP study.

Authors: *Michelle Christine Janelsins, Song Yao, Karen Michelle Mustian, Luke Joseph Peppone, Charles E. Heckler, Benjamin Esparaz, Jeffrey K. Giguere, Robert Irwin, Barbara Neilan, Tim Ahles, Christine B. Ambrosone, Gary R. Morrow; Department of Surgery, University of Rochester Medical Center, Rochester, NY; Roswell Park Cancer Institute, Buffalo, NY; University of Rochester Medical Center, Rochester, NY; Heartland NCORP, Decatur, IL; NCORP of the Carolinas, Greenville, SC; Northwest NCORP, Tacoma, WA; Delaware/Christiana NCORP, Christiana, DE; Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CRCI is a burdensome clinical problem for many BC patients. Large studies are needed to definitively assess CRCI and elucidate its' biological underpinnings. We conducted the largest longitudinal, observational study to date assessing CRCI in BC patients and controls, and assessed whether neurotransmitter signaling, longevity, and inflammation pathways are involved in CRCI. **Methods:** We recruited non-metastatic BC patients (n= 366) without previous chemotherapy (CT) and age-matched controls (n= 366). Cognitive function was assessed within 1 wk pre-CT and within 4 wks post-CT using the FACT-Cog to assess self-reported function and neuropsychological assessment (computerized CANTAB Verbal Memory (VM), paper-based Controlled Oral Word Association (COWA), phone-based word recall (RAVLT) and backward counting) to assess executive function. Controls were assessed at the same time intervals as patients. SNPs involved in neurotransmitter signaling (COMT) and longevity (FOXO3), and pre- and post-CT cytokines (IL-1β, MCP-1, sTNFR1) were measured in patients. **Results:** BC patients (89% white, mean age = 53) reported more CRCI on the FACT-Cog (total score and all 4 domains) from pre- to post-CT and performed worse on all 4 executive function tests over time via t-tests (all $P < 0.05$). Using ANCOVA, adjusting for age, education, WRAT-4 reading, anxiety (STAI), and pre-CT cognitive score, BC patients performed worse on all measures post-CT compared to controls: FACT-Cog Effect Size (ES) = 0.74, VM ES = 0.27, COWA ES = 0.33, RAVLT ES = 0.27, Backward Count ES = 0.19; all $P < 0.05$. FOXO3 and COMT SNPs predicted level of CRCI on the FACT-Cog (both $P = 0.07$). Decreases in executive function were associated with increases in IL-1β, MCP-1 (both $P < 0.05$) and sTNFR1 ($P = 0.08$). **Conclusions:** This is the largest longitudinal study showing significant CRCI among BC patients receiving CT compared to cancer-free controls. CRCI in BC patients is influenced by neurotransmitter signaling and longevity genes and leads to increased inflammation. NCI UG1CA18996, K07CA168886.

Abstract: 9521 (145384)

Long-term safety of fertility preservation by ovarian stimulation and concurrent aromatase inhibitor treatment in women with breast cancer.

Authors: *Kutluk Oktay, Volkan Turan, Jayeon Kim; Institute for Fertility Preservation and New York Medical College, New York, NY; New York Medical College, Valhalla, NY; Cha University, Seoul, South Korea*

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 24-45 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 ($P = 0.18$), nor undergoing FP before breast surgery ($P = 0.56$) 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%; livebirth/embryo transfer rate: 45.0%). The livebirth 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 the preservation of fertility 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.

Abstract ID: 106 (147273)

Successful implementation of a novel trial model: The Signature program.

Authors: *Julio Antonio Peguero, James A. Knost, Todd Michael Bauer, Matthew Hiram Taylor, Fadi S. Braiteh, Joseph Paul Eder, Howard Safran, Bert H. O'Neil, Ajjai Shivaram Alva, Lincoln Nadauld, Prashant Joshi, Flora Miranda, Rajinder Sidhu, Joy Ero, Eric Daniel Slosberg, Claudia Lebedinsky, Barinder Kang, Sudha Parasuraman, Sarina Anne Piha-Paul; Oncology Consultants PA, Houston, TX; Illinois Cancer Care, Peoria, IL; Sarah Cannon Research Institute / Tennessee Oncology, PLLC., Nashville, TN; Oregon Health and Science University, Portland, OR; Comprehensive Cancer Centers of Nevada, University of Nevada School of Medicine, Las Vegas, NV; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Brown University Oncology Research Group, Providence, RI; Indiana University Health University Hospital, Indianapolis, IN; Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Intermountain Healthcare, St George, UT; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharmaceuticals, East Hanover, NJ; Novartis Oncology, East Hanover, NJ; Novartis Inst for BioMedcl Rsrch, Lexington, MA; Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Here we describe 8 ongoing single agent clinical protocols under Novartis' "Signature" program involving buparlisib (BKM120, PI3Ki), dovitinib (TKI258, multikinase inhibitor), binimetinib (MEK162, MEKi), encorafenib (LGX818, RAFi), ribociclib (LEE011, CDK4/6i), BGJ398 (FGFRi), ceritinib (LDK378, ALKi) and sonidegib (LDE225; SMOi). 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' for pts 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 preidentified with a local test performed in a CLIA laboratory for an actionable genetic alteration. Indications where existing data showed no 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), and binimetinib (lung). 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 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.

Abstract ID: 2500 (146991)

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.

Authors: *Udai Banerji, Emma Jane Dean, Jose Alejandro Perez-Fidalgo, Gerald Batist, Philippe L. Bedard, Benoit You, Shannon Neville Westin, Peter Kabos, Barry Davies, Paul Elvin, Peter Lawrence, James W T Yates, Helen Ambrose, Paul Rugman, Andrew Foxley, Shaista Salim, Ed Casson, Justin P O Lindemann, Jan H. M. Schellens; The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom; The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; INCLIVA Biomedical Research Institute, Hospital Clínico Universitario of Valencia, Valencia, Spain; Jewish General Hospital, Montreal, QC; The Princess Margaret Cancer Centre, Division of Medical Oncology & Hematology, Toronto, ON; Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, Université Lyon 1, Lyon, France; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Colorado Cancer Center, Aurora, CO; AstraZeneca, Macclesfield, United Kingdom; AstraZeneca, Cambridge, United Kingdom; The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: AZD5363 is a novel potent pan-AKT inhibitor (IC50of AKT1, AKT2 and AKT3 of 3, 7 and 7nM respectively) with preclinical activity across a range of models. **Methods:** The trial had an adaptive design that allowed changes in schedule based on toxicity, PK, and PD findings. AZD5363 was administered orally (PO) twice a day (BID). Three schedules were explored: continuous dosing (7/7), four days a week, (4/7) and two days a week (2/7). PD biomarkers including pAKT, pGSK3β, and pPRAS40 were measured by IHC in pre- and post-treatment tumor biopsies. Once a RP2D was established, two expansion cohorts of PIK3CA-mutant ER+ve 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 Css,max of 1426ng/mL and AUCssof 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 R2PD for single agent AZD5363, with the option of using 640mg BID (2/7) as a pharmacologically active dose for future combination studies. Target lesion shrinkage was observed in 7/15 and 4/14 in the B and G cohorts respectively to date, 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.

Abstract ID: 2508 (151354)

Phase II multicenter proof of concept study of AZD4547 in FGFR amplified tumours.

Authors: *Elizabeth Catherine Smyth, Nicholas C. Turner, Clare Peckitt, Alex Pearson, Gina Brown, Sue Chua, Angela Gillbanks, Stephen R. D. Johnston, NOELIA TARAZONA, Ros Cutts, Elaine Kilgour, Claire Rooney, Neil R. Smith, Katherine Anne Sumpter, Mazhar A. Ajaz, Anne L. Thomas, David Watkins, Ian Chau, Sanjay Popat, David Cunningham; Royal Marsden, London & Surrey, United Kingdom; Institute of Cancer Research, London, United Kingdom; AstraZeneca Oncology Innovative Medicines, Macclesfield, United Kingdom; Northern Center for Cancer Treatment, Newcastle-upon-Tyne, United Kingdom; Royal Surrey County Hospital, Guildford, United Kingdom; Leicester Royal Infirmary, Leicester, United Kingdom*

Background: FGFR1/2 amplification acts as an oncogenic driver in multiple cancers. We investigated the efficacy of AZD4547, a potent orally available selective inhibitor of FGFR 1,2 & 3 receptor tyrosine kinases, in FGFR1/2 amplified cancers. **Methods:** This is a phase II Simon 2 stage design for patients (pts) with FGFR1 (HER2 negative breast/NSCLC) or FGFR2 (gastroesophageal) amplified tumors treated with AZD4547 80mg twice daily on an intermittent (2 weeks (wks) on, 1 wk off) or continuous schedule. Eligible pts had progressed following ≥ 1 line of prior therapy. FGFR1/2 amplification was determined centrally using FISH. Primary endpoint is centrally reviewed confirmed response rate (RR), with the study concluding efficacy if ≥ 3/17 patients in a cohort had a confirmed response. PET-CT was performed at baseline, D14 and 8 wks, biopsy at baseline and D14 and optionally on progression. Biomarker assessment included phospho-immunohistochemistry, FGFR copy number variation in tumor and plasma, and whole exome sequencing. **Results:** We screened 285 pts with advanced cancer, identifying FGFR1 amplification in 18% (20/111) HER2 negative breast cancer (BC), 9.5% (4/42) NSCLC, and FGFR2 amplification in 7.6% (10/132) gastroesophageal (GC). Confirmed RR was 33% (3/9) in FGFR2 amplified GC, and 12.5% (1/8) FGFR1 amplified BC. All 3 GC responders had a PET response on D14 PET. GC responses were durable; time on treatment was 45, 29 and 27 wks with the last pt ongoing. Common toxicities (all grades and schedules) included fatigue (71%), mucositis (41%), nausea (35%), and nail changes (24%). Asymptomatic retinal pigmented epithelial detachment occurred in 1 pt. Phosphate was elevated in most pts. Exploratory analysis revealed all GC pts with PR had FGFR2 FISH ratio > 8. Elevated FGFR2 copy number was detected in free plasma DNA of all GC pts with PR, and no non-responding pt. Analysis of progression biopsies in a responding GC pt identified acquired KRAS amplification in progressing disease. **Conclusions:** AZD4547 demonstrated high activity in FGFR2 amplified GC and lower activity in FGFR1 amplified BC. Assessment of FGFR2 copy number in cell free plasma DNA may provide a screening tool to identify FGFR2 amplified GC. Clinical trial information: NCT01795768.

Abstract ID: 3004 (147130)

A phase I study of PF-05082566 (anti-4-1BB) + rituximab in patients with CD20+ NHL.

Authors: *Ajay K. Gopal, Nancy L. Bartlett, Ronald Levy, Roch Houot, Stephen Douglas Smith, Neil Howard Segal, Aron D. Thall, Ganesh Mugundu, Bo Huang, Craig Davis, Holbrook Edwin Kohrt; University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; Washington University, Siteman Cancer Center, St Louis, MO; Division of Oncology, Stanford University School of Medicine, Stanford, CA; Centre Hospitalier Universitaire Pontchaillou, Rennes, France; University of Washington/SCCA, Seattle, WA; Memorial Sloan Kettering Cancer Center, New York, NY; Pfizer, San Diego, CA; Pfizer Oncology, Groton, CT; Center for Clinical Sciences Research Stanford, Stanford, CA*

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 binding to endogenous 4-1BBL. **Methods:** This Phase I study evaluated PF-566 in doses ranging from 0.03-10 mg/kg in combination with 375 mg/m^2 rituximab (R) in patients (pts) with relapsed or refractory CD20+ 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 1o endpoint was first 2-cycle DLT with PK/PD, safety, and anti-tumor activity as 2o endpoints. **Results:** 35 pts with CD20 + NHL were treated with PF-566 combined with R: Follicular (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 cells, and activated NK cells were observed. For pts up to 2.4 mg/kg (higher doses under evaluation for efficacy), the ORR was 21% (6/28), and in R-refractory pts the ORR was 29% (4/14), with 2 CR (0.03 and 0.12 mg/kg, both FL) with a duration of response > 2 years and 2 PR (FL and MCL). Enrollment into an expansion cohort is ongoing. The PFS for all of the R-refractory responders was > 6 mo and for all R-refractory pts the 6 mo PFS rate was 66% by Kaplan-Meier. **Conclusions:** PF-05082566 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.

Abstract ID: 3011 (147820)

Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort.

Authors: *Neil Howard Segal, Sai-Hong Ignatius Ou, Ani Sarkis Balmanoukian, Matthew G. Fury, Erminia Massarelli, Julie R. Brahmer, Jared Weiss, Patrick Schoffski, Scott Joseph Antonia, Christophe Massard, Dan Paul Zandberg, Samir Khleif, Xia Li, Marlon Rebelatto, Keith Steele, Paul B. Robbins, John A. Blake-Haskins, Marcus O. Butler; Memorial Sloan Kettering Cancer Center, New York, NY; UC Irvine School of Medicine, Irvine, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; University Hospitals Leuven, Leuven, Belgium; Moffitt Cancer Center, Tampa, FL; Institut Gustave Roussy, Villejuif, France; University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; Georgia Regents University Cancer Center, Augusta, GA; MedImmune, Gaithersburg, MD; Princess Margaret Cancer Centre, Toronto, ON*

Background: Outcomes are poor for patients (pts) with recurrent/metastatic (R/M) SCCHN, and new treatments are needed. An ongoing phase I/II, multicenter, open-label study (NCT01693562) is evaluating the safety and efficacy of MEDI4736 (M), a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity, in multiple solid tumor types including SCCHN. PD-L1 is expressed in SCCHN tumors and may be associated with response to anti-PD-L1 treatment. **Methods:** Pts with R/M SCCHN, an ECOG of 0 or 1, without prior anti-PD-1/PD-L1 exposure are eligible. M is administered IV every 2 weeks at 10 mg/kg for 12 months. Retreatment is permitted upon progression after 12 months. PD-L1 expression is assessed by IHC using the Ventana SP263 clone. Prior documented HPV status is collected at study entry. Response is based on investigator assessment per RECIST v1.1. Data included represent a larger population with more mature follow up than previously reported (Fury M, et al. Poster presented at ESMO 2014, 988PD). **Results:** As of 31 Oct 2014, 62 pts (mean age 58 years [range 24–96]; 86% male; 64% current/prior smokers; ECOG 0/1: 38%/62%; HPV pos/neg/unk: 40%/39%/21%), with a median of 3 prior systemic treatments (1–10), received a median of 6 doses (1–26). Drug-related AEs were observed in 60% of pts; the most frequent were fatigue (11%), diarrhea, (8%), and nausea (7%). Grade ≥ 3 related AEs were reported in 7% of pts: rash (2 pts), and increased GGT, fatigue, and tumor inflammation (1 pt each). No drug-related AEs led to discontinuation or death. No colitis or grade ≥ 3 pneumonitis was observed. Overall, 51 pts were evaluable for response with ≥ 24 weeks of follow up; ORR was 12% (25% in PD-L1+ pts), and DCR at 24 weeks was 16% (25% in PD-L1+ pts). Responses are ongoing in 5/6 responding pts, with response durations ranging from 4+ to 43+ weeks. Median duration of response has not been reached. **Conclusions:** With more mature follow up, the safety profile of M in SCCHN is manageable and consistent with previous reports. Responses are durable; ORR and DCR are higher in PD-L1+ pts. A registration program is underway in pts with SCCHN for M alone and in combination with tremelimumab.

Abstract ID: 3012 (150479)

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).

Authors: *Igor Puzanov, Reinhard Dummer, Jacob Schachter, Anna C. Pavlick, Rene Gonzalez, Paolo Antonio Ascierto, Kim Allyson Margolin, Omid Hamid, Sanjiv S. Agarwala, Matteo S. Carlino, Jochen Utikal, Michal Lotem, Antoni Ribas, Peter Mohr, Charlotte M. Roach, Marisa Dolled-Filhart, Xiaoyun Nicole Li, Scot Ebbinghaus, Soonmo Peter Kang, Adil Daud; Vanderbilt University Medical Center, Nashville, TN; University Hospital Zurich, Zurich, Switzerland; Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Ramat-Gan, Israel; NYU Clinical Cancer Center, New York, NY; University of Colorado Cancer Center, Aurora, CO; Istituto Nazionale Tumori Fondazione, Napoli, Italy; Stanford University Division of Oncology, Stanford, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; St. Luke's Cancer Center, Bethlehem, PA; Westmead and Blacktown Hospitals; Melanoma Institute Australia, Sydney, Australia; Skin Cancer Unit, German Cancer Research Center (DKFZ), and Department of Dermatology, Venerology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany; Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; UCLA, Los Angeles, CA; Elbe-Klinikum Buxtehude, Buxtehude, Germany; Dako, North America, Carpinteria, CA; Merck & Co., Inc., Kenilworth, NJ; UC San Francisco, San Francisco, CA*

Background: Pembro is an anti–PD-1 antibody approved for treating advanced MEL that progressed following IPI and, if BRAFV600 mutant, a BRAF inhibitor. In KEYNOTE-002 (NCT01704287), pembro doses of 2 mg/kg and 10 mg/kg every 3 wk (Q3W) significantly improved PFS compared with investigator-choice chemotherapy in IPI-R MEL ($P < .0001$), with no difference between pembro 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 in PD-L1+ and PD-L1– MEL pts enrolled in KEYNOTE-002. **Methods:** 540 pts with advanced IPI-R MEL were randomized 1:1:1 to pembro 2 or 10 mg/kg every 3 wk (Q3W) or chemotherapy. PD-L1 expression was assessed centrally by IHC using the 22C3 antibody. 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 planned after 370 deaths occur). ORR and the relationship between PD-L1 expression and efficacy were secondary end points. Data for the pembro arms were pooled. **Results:** 421/540 pts enrolled (78%) had tumors evaluable for PD-L1 expression; 291 (69%) were PD-L1+, 130 (31%) were PD-L1–. Pembro prolonged PFS and increased ORR compared with control in PD-L1+ and PD-L1– pts (Table). Among pembro-treated pts, ORR was higher in PD-L1+ pts, but the CIs were overlapping, and there was no difference in duration of response (DOR) based on PD-L1 expression. There was no prognostic effect in the control arm. **Conclusions:** Pembro improved efficacy over chemotherapy in both PD-L1+ and PD-L1– IPI-R advanced MEL. These data indicate that in IPI-R MEL pts, pembro therapy should not be limited to pts with PD-L1+ tumors.

	Total		PD-L1+		PD-L1-	
	Pembro n = 361	Control n = 179	Pembro n = 193	Control n = 98	Pembro n = 93	Control n = 37
PFS, HR[a] (95% CI)	0.53 (0.43–0.65)		0.52 (0.39–0.68)		0.60 (0.38–0.94)	
6-mo PFS, %	36	16	40	13	26	22
ORR, % (95% CI)	23 (19–28)	4 (2–9)	26 (20–33)	4 (1–10)	15 (8–24)	8 (2–22)
DOR, wk, median (range)	NR (5+ – 50+)	37 (7+ – 41)	NR (5+ – 50+)	41 (18 + – 41)	NR (6+ – 48+)	37 (7+ – 37)

[a]Pembro vs control.