J Clin Oncol 31, 2013 (suppl; abstr 5)

aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer.

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Abstract

Background: In estrogen-receptor-positive (ER+) early breast cancer, 5 years of tamoxifen reduces breast cancer death rates by about a third throughout years 0-14. It has been uncertain how 10 years of tamoxifen compares with this. **Methods:** During 1991-2005, 6,953 women with ER+ (n=2755), or ER untested (4198, estimated 80% ER+ if status known) invasive breast cancer from 176 UK centres were, after 5 years of tamoxifen, randomized to stop tamoxifen or continue to year 10. Annual follow-up recorded compliance, recurrence, mortality, and hospital admissions. **Results:** Allocation to continue tamoxifen reduced breast cancer recurrence (580/3468 vs 672/3485, p=0.003). This reduction was time dependent: rate ratio 0.99 during years 5-6 [95%CI 0.86-1.15], 0.84 [0.73-0.95] during years 7-9, and 0.75 [0.66-0.86] later. Longer treatment also reduced breast cancer mortality (392 vs 443 deaths after recurrence, p=0.05), rate ratio 1.03 [0.84-1.27] during years 5-9 and 0.77 [0.64-0.92] later; and overall mortality (849 vs 910 deaths, p=0.1), rate ratio 1.05 [0.90-1.22] during years 5-9 and 0.86 [0.75-0.97] later. Non-breast-cancer mortality was little affected (457 vs 467 deaths, rate ratio 0.94 [0.82-1.07]). There were 102 vs 45 endometrial cancers RR=2.20 (1.31-2.34, p<0.0001) with 37 (1.1%) vs 20 (0.6%) deaths (absolute hazard 0.5%, p=0.02). Combining the similar results of aTTom and its international counterpart ATLAS (Lancet 2013) enhances statistical significance of recurrence (p<0.0001), breast cancer mortality (p=0.002) and overall survival (p=0.005) benefits. **Conclusions:** aTTom confirms that, in ER+ disease, continuing tamoxifen to year 10 rather than just to year 5 produces further reductions in recurrence, from year 7 onward, and breast cancer mortality after year 10. Taken together with the reduction in breast cancer deaths seen in trials of 5 years of tamoxifen vs none, these results indicate that 10 years of adjuvant tamoxifen, compared to no tamoxifen, reduces breast cancer mortality by about one third in the first 10 years following diagnosis and by a half subsequently. Clinical trial information: **ISRCTN17222211**.

J Clin Oncol 31, 2013 (suppl; abstr 500)

Clinical and translational results of CALGB 40601: A neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer.

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Abstract

Background: Recent trials in HER2-positive (HER2+) breast cancer (BrCa) demonstrate increased pathological complete response (pCR) using dual HER2-targeting in the neoadjuvant setting and increased progression-free survival in metastatic disease. CALGB 40601 aimed to further quantify the pCR rates of weekly paclitaxel (T) and trastuzumab (H) alone or combined HER2-blockade of H with the small molecule lapatinib (L), and to identify biomarkers of sensitivity to these HER2-targeted agents. **Methods:** Eligible patients had newly diagnosed, noninflammatory stage II-III HER2+ BrCa and were randomized to receive T (80mg/m2/week IV) + H (4mg/kg then 2mg/kg/week IV) alone (TH) or with the addition of L (750 mg/d PO) (THL) for 16 weeks preoperatively. A third arm, T + L (1500 mg/d) (TL), was closed early when negative efficacy and toxicity data emerged from preliminary analysis of ALTTO. After surgery, 4 cycles of adjuvant dose-dense AC and 1 year H was recommended. Tumors were biopsied for research before therapy; post-Rx samples of residual disease were requested. The primary endpoint was in-breast pCR rate; the study had 85% power to detect an increase from 30% (TH) to 50% (THL). **Results:** 305 patients were randomized (118 THL, 120 TH, 67 TL); 68% were clinical stage II and 59% hormone receptor-positive. Grade 3+ toxicity was higher among L-containing arms, including neutropenia (12% TL, 7% THL, 2% TH), rash (15% TL, 14% THL, 2% TH), and diarrhea (20% TL, 20% THL, 2% TH). Breast pCR rates with 95% confidence limits were: 51% (42-60%) THL, 40% (32-49%) TH, 32% (22-44%) TL. pCR rate in the TH arm was higher than previous studies, and was not significantly different from THL (p=0.11). We will present molecular subtype, sequence and gene copy number abnormalities in primary tumors and residual disease. **Conclusions:** pCR rate was higher with combined THL compared with standard TH but did not reach statistical significance. These results are qualitatively similar to other neoadjuvant studies in HER2+ BrCa, and contribute to estimates of pCR rates after these agents. Tissue-based studies may illuminate which patients benefit from HER2-targeting using these agents. Clinical trial information: **NCT00770809**.

J Clin Oncol 31, 2013 (suppl; abstr 502)

ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T → FEC+T) in HER2+ operable breast cancer.

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Abstract

Background: Neoadjuvant chemotherapy (NAC) and concomitant trastuzumab (T) have produced high pathologic complete response (pCR) rates in HER2+ breast cancers. Z1041 addresses the timing of initiation of T with NAC. **Methods:** Women with operable HER2+ invasive breast cancer were randomized 1:1 to: FEC → P+T (Arm 1) or P+T → FEC+T (Arm 2) where treatment was administered as 5-FU 500 mg/m2, epirubicin 75 mg/m2 and cyclophosphamide 500 mg/m2 day 1 of a 21-day cycle x 4 (FEC); paclitaxel 80 mg/m2 weekly x 12 and trastuzumab 4 mg/kg once then 2 mg/kg weekly x 11. Eligibility also included: tumor > 2 cm or a positive lymph node and left ventricular ejection fraction > 55%. The primary aim was to compare the pCR rates in the breast (pBCR) between the regimens. Secondary endpoints were pCR rate in the breast and lymph nodes (pBNCR) and safety profile. All pts who began study treatment were included in the analyses. With 128 pts per regimen, a two-sided alpha=0.05 test of proportions would have a 90% chance of detecting a difference of 20% or more in the pBCR rates, when the pBCR rate with the poorer regimen is ≤ 25%. **Results:** From September 15, 2007 to December 15, 2011, 282 women (Arm 1: 140 pts) were enrolled. Two pts (Arm 1) withdrew without receiving treatment. The two arms were similar in age, stage, and hormone receptor (HR) status (HR neg: 40%). The severe (grade 3+) treatment-related toxicities included: neutropenia (Arm 1: 24.6%; Arm 2: 32.4%), fatigue (Arm 1: 4.3%; Arm 2: 8.5%), and neurosensory problems (Arm 1: 3.6%; Arm 2: 4.9%). The pBCR rate and pBNCR rates (Table) were not found to differ between the two regimens (Fisher's exact p values: 0.905 and 0.811, respectively). **Conclusions:** High pCR rates can be achieved with trastuzumab in combination with anthracyclines and taxanes. The pBCR or pBNCR was not different between regimens based on the timing of initiation of trastuzumab. Clinical trial information: **NCT00513292**.

	FEC → P+T	P+T → FEC+T
n	138	142
% pCR in breast	55.1	54.2
(95% CI)	46.4- 63.5	45.7-62.6
% pCR in breast and nodes	50.7	48.6
(95% CI)	42.1 – 59.3	40.1-57.1

J Clin Oncol 31, 2013 (suppl; abstr 511)

Array CGH and DNA sequencing to personalize targeted treatment of metastatic breast cancer (MBC) patients (pts): A prospective multicentric trial (SAFIR01).

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Abstract

Background: The aim of the present study was to profile the metastatic lesion of pts using high throughput technologies, and to treat them accordingly. **Methods:** SAFIR01 trial aimed to include 400 pts with MBC, selected for not presenting a progressive disease at the time of biopsy. A biopsy was done in a metastatic site. DNA was extracted if the tumor contained .50% cancer cells, and sent to one of the 5 genomic centers who performed array CGH (copy number changes) and sanger sequencing on PIK3CA (exon 10/21) and AKT1 (exon 3). A targeted therapy matched to the genomic alteration was expected to be proposed at the time of progressive disease. The primary endpoint was the % of pts who received a targeted therapy according to the genomic alteration. **Results:** A biopsy of metastatic site was done successfully in 408 out of the 423 included pts. Biopsy was complicated by a serious adverse event in 9 pts. A discrepancy between primary and metastatic lesion was observed in 8% and 19% of pts for Her2 and HR. Array CGH and sequencing were successfully obtained in 277 (68%) and 295 (72%) pts. The main reason for failure of genomic test was the low cellularity (n593). A targetable genomic alteration was identified in 204 pts. The most frequent genomic alterations were PIK3CA mutations, CCND1, FGF4 and FGFR1 amplifications. 76 pts presented a rare targetable genomic alteration (,5%), including AKT1 mutations, EGFR, FGFR2, PIK3CA, MDM2 amplifications. Early Feb 2013, 46 out of 277 pts with genomic analyses (17%) had received a targeted therapy matched to the genomic alteration, covering twelve different targets. Updated results on number of pts treated, together with efficacy data will be presented. Next generation sequencing on metastatic lesions is ongoing and results will be presented. **Conclusions:** This trial evaluated the concept of personalized medicine for MBC and provided a large scale genomic analysis of metastatic tissue. This study suggests that assessing the biology of metastatic tissue could allow driving pts to targeted therapy. A randomized trial (SAFIR02) testing this approach is expected to start during summer 2013. Clinical trial information: **NCT01414933**.

J Clin Oncol 31, 2013 (suppl; abstr LBA509)

Correlation of molecular alterations with efficacy of everolimus in hormone receptor–positive, HER2-negative advanced breast cancer: Results from BOLERO-2.

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Abstract

Background: Everolimus (EVE) plus exemestane (EXE) more than doubled progression-free survival (PFS) while maintaining quality of life vs EXE alone in postmenopausal women with hormone-receptor positive (HR+), HER2-negative (HER2-) advanced breast cancer (BOLERO-2 phase III; NCT00863655). PFS benefit was seen in all clinically defined subgroups. We evaluated genetic variations of a broad panel of cancer-related genes and explored their correlations with EVE benefit. **Methods:** Exon sequence and gene copy number variations were analyzed in 182 cancer-related genes by next-generation sequencing (NGS). Correlations with PFS were evaluated using both univariate and multivariate Cox models. **Results:** NGS data (>250x coverage) were successfully generated from archival tumor specimens from 227 patients (NGS population, 157 and 70 in EVE+EXE and EXE arms, respectively) whose baseline characteristics and clinical outcome were comparable with the trial population (PFS HR = 0.40 and 0.45, respectively). The treatment benefit of EVE+EXE over EXE is maintained in the subgroups defined by each of the nine genes with a mutation rate >10% (eg, PIK3CA, FGFR1, and CCND1), or when less frequently mutated genes (eg, PTEN, AKT1) were included in their respective pathways. Patients with no or only 1 genetic alteration in PI3K or FGFR pathways, or CCND1, had a greater treatment effect from EVE (HR = 0.27, 95% CI 0.18-0.41, adjusted by covariates, in 76% of the NGS population), indicating the value of these pathways for predicting sensitivity/resistance to EVE in this setting. **Conclusions:** This is the first global registration trial in which efficacy-predictive biomarkers were explored by correlating broad genetic variations with clinical efficacy. It demonstrated the feasibility of applying large-scale NGS and subsequent correlative analysis to such trials. The observations suggest that a large subgroup of patients (76%), defined by minimal genetic variations in the PI3K or FGFR pathways, or CCND1, derives the most benefit from EVE therapy (HR = 0.27 vs 0.40 for the full NGS population). These exploratory results and their implication in understanding the interplay of multiple pathways in tumor cells and testing new hypotheses for targeted combination therapies in HR+/HER2- BC will be further investigated. Clinical trial information: **NCT00863655**.

J Clin Oncol 31, 2013 (suppl; abstr 1000)

10-yr follow-up results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients.

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Abstract

Background: NSABP B-32, the largest surgical prospective randomized phase III trial was designed to compare overall survival (OS), disease-free survival (DFS), and morbidity between SNR alone vs SNR + AD in SN negative (-) pts. We present 10 yr outcome data for primary endpoints as well as updated data on the effect of occult metastases, found later in the SN by central, detailed pathologic analysis. **Methods:** 5,611 women with operable, clinically N0, invasive breast cancer were randomized to SNR + AD (Group [Grp] 1) or to SNR alone with AD only if SNs were positive (Grp2). 3,989 (71.1%) of 5,611 pts were SN-. 3,986 (99.9%) of these SN- pts had follow-up information: Grp 1: 1,975, Grp 2:2,011. Median time on study was 9.4 yrs. Cox proportional hazard models adjusting for study stratification variables were used to compare OS and DFS between the two groups. Two-sided p values were used. HR values > 1 indicate a more favorable outcome in Grp 1 **Results:** At 10 yrs, there continues to be no significant difference in OS between the two groups (HR: 1.11, p = 0.27). 10 yr Kaplan-Meier (K-M) estimates for OS are 87.8% for SNR alone and 88.9% for SNR + AD. There continues to be no significant difference in DFS between the two groups (HR: 1.01, p=0.92). 10-yr K-M estimates for DFS were 76.9% for both groups. Occult nodal disease was originally detected in 3,884 pts (15.8%) with SN- on initial H and E analysis. Comparisons between the groups with and without occult disease yielded an adjusted HR for OS: 1.25 (p = 0.08) with an absolute difference at 10 yrs of 2.8% and a HR for DFS: 1.24 (p = 0.018) with an absolute difference of 4.1%. The cumulative incidences of local-regional events were low (10-yr values: SNR 4.0%, SNR+AD, 4.3%) and not significant (HR: 0.95, p = 0.77). **Conclusions:** At 10 yrs there continues to be no significant differences in OS and DFS between SNR and SNR + AD in pts with negative SN. The relative increase in risk of DFS and OS for pts with occult SN metastases remains stable. Support: PHS grants: NSABP: U10CA-12027, U10CA-37377, U10CA-69651, U10CA-69974; VT Ca Cntr: P30 CA22435; DNK: 5RO1CA074137 NCI Dpt HHS. Clinical trial information: **NCT00003830**.

J Clin Oncol 31, 2013 (suppl; abstr 1004)

A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto).

Author(s): *Gunter Von Minckwitz, Andreas Schneeweiss, Christoph Salat, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens U. Blohmer, Hans Tesch, Fariba Khandan, Sebastian Jud, Christian Jackisch, Keyur Mehta, Sibylle Loibl, Michael Untch, German Breast Group; German Breast Group, Neu-Isenburg, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; Hematology Oncology Clinic, Munich, Germany; Breast Center Duesseldorf, Louis Hospital, Düsseldorf, Germany; Frauenklinik Gera, Gera, Germany; Praxisklinik Krebsheilkunde, Berlin, Germany; Brustzentrum Sankt-Gertrauden-Krankenhaus, Berlin, Germany; Onkologische Gemeinschaftspraxis am Bethanien-Krankenhaus, Frankfurt/Main, Germany; Frauenklinik, St. Markus Krankenhaus, Frankfurt, Germany; Frauenklinik, Universitätsklinikum, Erlangen, Germany; Klinikum Offenbach, Offenbach, Germany; Helios Klinikum Berlin-Buch, Berlin, Germany*

Abstract

Background: Use of carboplatin in neoadjuvant chemotherapy (NACT) has never been prospectively examined in breast cancer. Cohort studies suggest a high sensitivity to DNA-damaging agents (e.g., carboplatin in triple negative breast cancer [TNBC]), which have a high prevalence of BRCA mutations. Two trials examining carboplatin in HER2+ metastatic disease have shown conflicting results, but one was biased by different dosage of docetaxel in treatment arms. GeparSixto investigates the impact of carboplatin in addition to an identical, optimized cytotoxic-targeted regimen on pathological complete response (pCR) in these two breast cancer subtypes. **Methods:** In GeparSixto trial (NCT01426880) patients were treated for 18 weeks with paclitaxel 80mg/m² q1w and non-pegylated-liposomal doxorubicin (NPLD) 20mg/m² q1w. HER2+ patients received concurrently trastuzumab 6(8) mg/kg q3w and lapatinib 750mg daily. TNBC patients received concurrently Bevacizumab 15mg/kg i.v. q2w. All patients were randomized 1:1 to receive concurrently carboplatin AUC 1.5-2 q1w vs not, stratified by subtype. Primary objective is pCR rates (ypT0 ypN0), secondary objectives are pCR rate in predefined subgroups or by other definitions, clinical response rate, compliance and tolerability of carboplatin. Carboplatin dose was reduced from AUC 2.0 to 1.5 by an amendment after 330 patients due to carboplatin-related toxicity at pre-planned safety analyses. **Results:** 595 patients were recruited (8/2011 - 12/2012) in 51 German centers, 299 did not receive carboplatin. Median age was 47/48 years (no carb/carb), 36.8/36.5% were postmenopausal; 14.0/13.3% had T3, 5.0/3.7% T4, 41.8/37.6% N+, 93.0/92.9% ductal invasive, 64.5/65.3% G3 tumors; 46.2/46.3% had HER2+, 53.8/53.7% TNBC. 225 patients had a SAE (149 no carb/177 carb) and 3 died (postoperative pneumonia; reduced general condition; acute myocardial infarct), all in no carb arms. Final analysis on primary endpoint will be presented. **Conclusions:** This is first study, evaluating efficacy and safety of the addition of carboplatin to anthracycline-taxane containing NACT in patients with primary HER2+ and TNBC. Clinical trial information: **NCT 01426880**.

J Clin Oncol 31, 2013 (suppl; abstr 1007)

Comparison of doxorubicin and cyclophosphamide (AC) versus single-agent paclitaxel (T) as adjuvant therapy for breast cancer in women with 0-3 positive axillary nodes: CALGB 40101.

Author(s):*Lawrence N. Shulman, Donald A. Berry, Constance T. Cirrincione, Heather Becker, Edith A. Perez, Ruth O'Regan, Silvana Martino, Charles L. Shapiro, James Atkins, Charles Schneider,Gretchen Genevieve Kimmick, Harold J. Burstein, Larry Norton, Hyman Bernard Muss, Clifford Hudis, Eric P. Winer, Cancer and Leukemia Group B; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke Cancer Institute Biostatistics, Durham, NC; University of Chicago, Chicago, IL; Mayo Clinic, Jacksonville, FL; Georgia Cancer Center for Excellence at Grady Memorial Hospital, Atlanta, GA; The Angeles Clinic and Research Institute, Santa Monica, CA; The Ohio State University, Columbus, OH; Southeastern Medical Oncology Center, Goldsboro, NC; Christiana Care Health System, Newark, DE; Duke Cancer Institute, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Abstract

Background: Determining optimal adjuvant chemotherapy for early stage breast cancer depends on efficacy and toxicity. We sought to determine if T is equivalent to AC but with reduced toxicity. **Methods:** Pts with operable breast cancer with 0-3 positive nodes were enrolled on a 2x2 factorial design study which addressed (1) superiority of 6 vs. 4 cycles of therapy (previously reported, Shulman, *JCO* 2012) and (2) equivalence of single-agent T to standard AC, defined as upper bound of 95% confidence interval (CI) of hazard ratio (HR) of T vs. AC , 1.30 for the primary endpoint of relapse-free survival (RFS). A planned target of 567 RFS events required 4,646 pts with 4 yrs FU. At activation in 2002, T (80mg/m2) was q1wk for 12 or 18 wks and AC (60/600 mg/m2) was q3wk for 4 or 6 cycles. In 2003 (570 pts enrolled) schedules were revised to 4 or 6 cycles q2wk for both T (175 mg/m2) and AC. The 6-cycle arms were dropped in 2008 (3,171 pts enrolled) due to slow accrual. Relative effectiveness of T to AC is shown by hazard ratio (HR). Logrank p-values are measures of discordance but are not relevant for the equivalence question and are not adjusted for multiple comparisons. **Results:** After enrolling 3,871 pts, the study closed in 2010 due to slowing accrual. With a median follow-up of 6.1 yrs there are 437 RFS events. The HR of 1.26 (95% CI: 1.05-1.53; p 5 0.02) does not allow a conclusion of equivalence of T with AC. With 266 deaths the HR for overall survival (OS) is 1.27 (95% CI51.00-1.62; p 5 0.05), favoring AC. The estimated absolute advantage of AC at 5 yrs is 3% (91 vs. 88%) for RFS and 1% (95 vs. 94%) for OS. All 9 treatment-related deaths were in pts receiving AC and are included in the survival analysis. The incidence of Grade 31 toxicity for AC vs T was 33% vs. 4% for hematologic toxicity and 36% vs 22% for non-hematologic toxicity. **Conclusions:** This trial did not show equivalence of T to AC, a conclusion that is very unlikely to change with additional follow-up. T was less toxic than AC. Clinical trial information: **CDR0000069444/NCT00041119**.

J Clin Oncol 31, 2013 (suppl; abstr 1008)

S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer.

Author(s): *G. Thomas Budd, William E. Barlow, Halle C. F. Moore, Timothy J. Hobday, James A. Stewart, Claudine Isaacs, Muhammad Salim, Jonathan K. Cho, Kristine Rinn, Kathy S. Albain, Helen K. Chew, Gary Von Burton, Timothy David Moore, Gordan Srkalovic, Bradley Alexander McGregor, Lawrence E. Flaherty, Robert B. Livingston, Danika Lew, Julie Gralow, Gabriel N. Hortobagyi; Cleveland Clinic, Cleveland, OH; Cancer Research and Biostatistics, Seattle, WA; Mayo Clinic, Rochester, MN; Baystate Medical Center, Springfield, MA; Lombardi Comprehensive Cancer Center, Washington, DC; Allan Blair Cancer Center, Saskatoon, SK, Canada; Oncare Hawaii, Honolulu, HI; Swedish Cancer Institute, Seattle, WA; Loyola University Medical Center, Maywood, IL; University of California, Davis Cancer Center, Sacramento, CA; LSU Health Sciences Center, Shreveport, LA; Mid Ohio Oncology Hematology, Inc., Columbus, OH; Sparrow Regional Cancer Center, Lansing, MI; Willford Hall Medical Center, Lackland, TX; Wayne State University School of Medicine, Detroit, MI; Arizona Cancer Center, Tucson, AZ; Southwest Oncology Group Statistical Center, Seattle, WA; Seattle Cancer Care Alliance, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX*

Abstract

Background: S0221 is a SWOG-coordinated phase III adjuvant chemotherapy intergroup trial in node-positive and high-risk node-negative operable breast cancer which hypothesized that 1) the weekly AC+G regimen is superior to ddAC x 6 and 2) 12 weeks of weekly paclitaxel (wP) is superior to q 2 week paclitaxel x 6 (ddP). **Methods:** Between December 2003 and November 2010, 2,716 patients were randomized in a 2 x 2 factorial design to 1) AC+G vs ddAC and 2) P 80 mg/m^2/week x 12 vs P 175 mg/m^2 q 2 weeks x 6. If there was no significant interaction between the factors, the trial was powered to find a disease-free survival hazard ratio (HR) $\leq$ 0.82 for weekly vs q 2 week for each factor. At the first interim analysis, the AC randomization was halted for futility, and S0221 was closed to accrual 10 November 2010. S0221 reopened 15 December 2010, after which time all patients received 4 cycles of ddAC and randomization to P weekly x 12 and ddP x 6 continued. Accrual halted at a total of 3,294 in January 2012. **Results:** By September 7, 2012, 487 events and 340 deaths had occurred, prompting the third planned interim analysis. The Data Safety and Monitoring Committee recommended reporting the results since the futility boundary was crossed. A Cox model adjusting for the AC arms had a HR = 1.08 (95% CI 0.90-1.28; p=0.42), with the 99.5% CI excluding the original alternative hypothesis that the HR=0.82. There was no significant interaction of the two factors. Estimated 5-year progression-free survivals were 82% for weekly P and 81% for ddP. Toxicity data were available for 1,385 patients treated with ddP and 1,367 treated with weekly P. Grade 5 toxicity occurred in 4 patients on ddP and 2 on weekly P. Percent grade 3-4 toxicity per arm are shown in the Table. **Conclusions:** Either ddPx6 or weekly P x 12 are acceptable schedules of P administration. The differences in leukopenia likely reflect ascertainment bias against weekly P. If this is accepted, weekly P x 12 produces less overall toxicity than 6 cycles of ddP. Support: NCI grants CA32102, CA38926, CA21115, CA21076, CA77597, CA25224, CA77202, CCSRI15469, and Amgen, Inc. Clinical trial information: **NCT00070564**.

Grade 3-4 toxicity	ddP	Weekly P
Any	36%	35%
Allergy	14%	6%
Leukopenia	1%	6%

Grade 3-4 toxicity	ddP	Weekly P
Neutropenic fever	<1%	<1%
Dermatologic	3%	0.1%
Musculoskeletal pain	11%	3%
Neurologic	17%	10%

J Clin Oncol 31, 2013 (suppl; abstr LBA1001)

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: Final analysis of the EORTC AMAROS trial (10981/22023).

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Abstract

Background: Sentinel node biopsy (SNB) is standard in assessing axillary lymph node status for cN0 breast cancer patients. In case of a positive SNB, if treatment is advised, axillary lymph node dissection (ALND) is the current standard. Although ALND provides excellent regional control, it may give harmful side effects. Axillary radiotherapy (ART) instead of ALND was hypothesized to provide comparable regional control and less side effects. **Methods:** From 2001 to 2010, patients with cT1E2N0 primary breast cancer were enrolled in the EORTC phase III non-inferiority AMAROS trial. Patients were randomized between ALND and ART in case of a positive SNB. Primary endpoint was 5-year axillary recurrence rate. Secondary endpoints were overall survival (OS), disease-free survival (DFS), quality of life (QOL), shoulder movement and lymphedema at 1 and 5 years. **Results:** Of the 4,806 patients entered in the trial, 744 in the ALND-arm and 681 in the ART-arm had a positive SNB, 60% with a macrometastasis. The two treatment-arms were comparable regarding age, tumor size, grade, tumor type, and adjuvant systemic treatment. With a median follow up of 6.1 years, the 5-year axillary recurrence rate after a positive SNB was 0.54% (4/744) after ALND versus 1.03% (7/681) after ART. The planned non-inferiority test was underpowered because of the unexpectedly low number of events. The axillary recurrence rate after a negative SNB was 0.8% (25/3131). There were no significant differences between treatment arms regarding OS (5 yr estimates: 93.27% ALND, 92.52% ART, p=0.3386) and DFS (5 yr estimates: 86.90% ALND, 82.65% ART, p=0.1788). Lymphedema was found significantly more often after ALND (1yr: 40% ALND, 22% ART, p<0.0001 and 5yr: 28% ALND, 14% ART, p<0.0001). There was a nonsignificant trend toward more early shoulder movement impairment after ART. These findings were compatible with a trend in two QOL items in the arm symptom scale: swelling (ART better) and movement (ALND better). There were no other differences in QOL. **Conclusion:** ALND and ART after a positive SNB provide excellent and comparable regional control. ART reduces the risk of short-term and long-term lymphedema compared to ALND. Clinical trial information: **NCT00014612**.

J Clin Oncol 31, 2013 (suppl; abstr 2)

Effect of visual inspection with acetic acid (VIA) screening by primary health workers on cervical cancer mortality: A cluster randomized controlled trial in Mumbai, India.

Author(s): *Surendra Srinivas Shastri, Indraneel Mittra, Gauravi Mishra, Subhadra Gupta, Rajesh Dikshit, Rajendra A. Badwe; Tata Memorial Centre, Mumbai, India*

Abstract

Background: Cervical cancer is the most common cancer among women in developing countries and is the leading cause of cancer death in Indian women. Since cytology-based screening is not easily implementable in India, there is a need to evolve simpler alternatives. **Methods:** We initiated a cluster-randomized controlled trial in 1998 to investigate the efficacy of VIA screening by primary health workers (PHWs) in reducing cervical cancer mortality. Women aged 35-64 years with no prior history of cancer were included. The study was designed to include 20 clusters with an average of 7,500 eligible women per cluster. Four rounds of cancer education and VIA screening were conducted by PHWs at 24-month intervals in the screening group, while cancer education was offered once at recruitment to the control group. Recruitment was completed in March 31, 2002. Although the study was planned for 16 years, we analysed the results on the advice of the DSMC at 12 years. **Results:** We recruited 75,360 women from 10 clusters in the screening group and 76,178 women from 10 comparable clusters in the control group. The analysis is on an intention-to-treat basis. In the screening group, we achieved 89% participation for screening and 79% compliance for post-screening diagnostic confirmation. The quality of screening by PHWs was comparable to that of an expert gynecologist (κ=0.84). The incidence of invasive cervical cancer was 26.74 per 100,000 (95%CI: 23.41-30.74) in the screening group and 27.49 per 100,000 (95%CI: 23.66-32.09) in the control group. Compliance to treatment for invasive cancer was 86.34% in screening group and 72.29% in the control group. The screening group showed a 31% reduction in cervical cancer mortality (mortality rate ratio RR=0.69; 95%CI: 0.54-0.88; p=0.003) compared to the control group. A 7% reduction was also observed in all-cause mortality (mortality rate ratio RR=0.93; 95%CI: 0.79–1.10; p=0.41). **Conclusions:** VIA screening conducted by PHWs significantly reduced cervical cancer mortality. VIA screening is easily implementable and could prevent 22,000 cervical cancer deaths in India and 72,600 deaths in resource poor countries annually. Clinical trial information: **NCT00632047**.

J Clin Oncol 31, 2013 (suppl; abstr 1)

RTOG 0825: Phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM).

Author(s): *Mark R. Gilbert, James Dignam, Minhee Won, Deborah T. Blumenthal, Michael A. Vogelbaum, Kenneth D. Aldape, Howard Colman, Arnab Chakravarti, Robert Jeraj, Terri S. Armstrong, Jeffrey Scott Wefel, Paul D. Brown, Kurt A. Jaeckle, David Schiff, James Norman Atkins, David Brachman, Maria Werner-Wasik, Ritsuko Komaki, Erik P. Sulman, Minesh P. Mehta; University of Texas MD Anderson Cancer Center Department of Neuro-Oncology, Houston, TX; Radiation Therapy Oncology Group, Philadelphia, PA; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Cleveland Clinic Foundation, Cleveland, OH; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Arthur G. James Cancer Center, The Ohio State University, Columbus, OH; Department of Medical Physics, University of Wisconsin, Madison, WI; University of Texas Health Science Center School of Nursing, Houston, TX; Mayo Clinic, Jacksonville, FL; University of Virginia Medical Center, Charlottesville, VA; National Surgical Adjuvant Breast and Bowel Project and SCCC-CCOP, Goldboro, NC; Arizona Oncology Services Foundation, Phoenix, AZ; Thomas Jefferson University Hospital, Philadelphia, PA; University of Maryland, Baltimore, MD*

Abstract

Background: Chemoradiation (CRT) with temozolomide (TMZ/RT→TMZ) is the standard of care for newly diagnosed GBM. This trial determined if the addition of Bev to standard CRT improves survival (OS) or progression-free survival (PFS) in newly diagnosed GBM. **Methods:** This phase III trial was conducted by the RTOG, NCCTG, and ECOG. Neurologically stable pts > 18 yrs with KPS ≥ 60, and > 1cm3 tumor tissue block, were randomized to Arm 1: standard CRT + placebo or Arm 2: standard CRT plus Bev (10 mg/kg iv q 2wks). Experimental treatment began at wk 4 of radiation then thru 6-12 cycles of maintenance chemotherapy. Protocol specified co-primary endpoints were OS and PFS, with significance levels of .023 and .002, respectively. At progression, treatment was unblinded and pts allowed to crossover or continue Bev. Symptom, QOL and neurocognitive (NCF) testing was performed in the majority of pts. Secondary analyses evaluated impact of MGMT methylation (meth) and prognostic 9 gene signature status. **Results:** From 978 registered pts, 637 were randomized. Inadequate tissue (n=105) and blood on imaging (n=40) were key reasons for non-randomization. No difference was found between arms for OS (median 16.1 vs. 15.7 mo, p = 0.11). PFS was extended for Arm 2 (7.3 vs. 10.7 mo, p = 0.004). Pts with MGMT meth had superior OS (23.2 vs. 14.3 mo, p < 0.001) and PFS (14.1 vs. 8.2 mo, p < 0.001). Neither the 9 gene signature nor MGMT predicted selective benefit for Bev treatment, but best prognosis pts (MGMT meth, favorable 9-gene), had a worse survival trend with Bev (15.7 vs 25 mo p = 0.08). To date, 128 pts were unblinded on Arm 1 (salvage Bev in 86) and 87 pts on Arm 2 (continued Bev in 39). Increased grade ≥ 3 toxicity was seen with Bev, mostly neutropenia, hypertension, and DVT/PE. **Conclusions:** The addition of Bev for newly diagnosed GBM did not improve OS, did improve PFS but did not reach the significance criterion. MGMT and 9 gene profile did not identify selective benefit, but risk subset results suggested strongly against the upfront use of Bev in the best prognosis pts. Full interpretation of the PFS results incorporating symptom burden, QOL, and NCF is ongoing. Support: NCI U10 CA 21661, U10 CA37422, and Genentech. Clinical trial information: NCT00884741.

J Clin Oncol 31, 2013 (suppl; abstr 2001)

A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: The Dutch BELOB study.

Author(s):*Walter Taal, Hendrika M Oosterkamp, Annemiek M.E. Walenkamp, Laurens Victor Beerepoot, Monique Hanse, J. Buter, Aafke Honkoop, Dolf Boerman, Filip Yves Francine Leon De Vos, Rob L. Jansen, Franchette W.P.J. van den Berkmortel, Dieta Brandsma, Johan M Kros, Jacoline E Bromberg, Irene van Heuvel, Marion Smits, Bronno van der Holt, Rene Vernhout, Martin J. Van Den Bent, Landelijke Werkgroep voor NeuroOncologie; Erasmus MC, Rotterdam, Netherlands; Medisch Centrum Haaglanden, Den Haag, Netherlands; Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands; St Elisabeth Hospital, Tilburg, Netherlands; Catharina Ziekenhuis, Eindhoven, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Isala Kliniek, Zwolle, Netherlands; Rijnstate Ziekenhuis, Arnhem, Netherlands; Utrecht University Medical Center, Utrecht, Netherlands; Department of Medical Oncology, Maastricht University Medical Center, Maastricht, Netherlands; Atrium Medical Center, Heerlen, Netherlands; Department of Neurology, the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands; Department of Neuropathology, Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam, Netherlands*

Abstract

Background: Bevacizumab (BEV) is widely used in recurrent glioblastoma, alone or in combination with other agents. There is however no well-controlled trial to support the use for this indication. **Methods:** In a three-arm Dutch multicenter randomized phase II study (NTR 1929) patients were assigned to either BEV 10 mg/kg iv every 2 weeks, BEV 10 mg/kg iv every 2 weeks and 110 mg/m2 lomustine every 6 weeks, or lomustine 110 mg/m2every 6 weeks. Eligible were patients with histologically proven glioblastoma, with a first recurrence after chemo-irradiation with temozolomide, having concluded radiotherapy more than 3 months ago, with adequate bone marrow, renal and hepatic function, and WHO performance status (PS) 0-2. Primary endpoint was 9 months overall survival (OS); P0 was set at 35% and P1 at 55%. Progression was defined using RANO criteria. A safety review after the first 10 patients in the combination arm was preplanned. **Results:** Between December 2009 and November 2011, 153 patients were enrolled of whom 148 were considered eligible. Median age was 57 years (range, 24-77) and median WHO PS was 1. With respect to prognostic factors groups were well balanced. After review of the safety cohort the dosage lomustine in the combination arm was lowered to 90 mg/m2 because of hematological toxicity (predominantly thrombocytopenia without symptoms). At this lower lomustine dose level the combination treatment was in general well tolerated. Outcome: see Table. **Conclusions:** In this first well-controlled study on BEV in recurrent glioblastoma with a primary OS endpoint, combination treatment with bevacizumab and lomustine met the prespecified criterion for further investigation in clinical trials, whereas both drugs given as single agent failed to meet this criterion. Clinical trial information: **NTR1929**.

Treatment	n	% 9 mo OS [95% CI]	Median PFS (mo)	% 6 mo PFS [95% CI]
BEV	50	38% [25, 51]	3	18 [9, 30]
Lomustine	46	43% [29, 57]	2	11 [4, 22]
BEV/lomustine 90 mg/m^2	44	59% [43, 72]	4	41 [26, 55]
BEV/lomustine 110 mg/m^2	8	88% [39, 98]	11	50 [15, 77]

n: number of patients, PFS: progression free survival, CI: confidence interval, mo: months.

J Clin Oncol 31, 2013 (suppl; abstr 2003)

Comparative impact of treatment on patient reported outcomes (PROs) in patients with glioblastoma (GBM) enrolled in RTOG 0825.

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Abstract

Background: RTOG 0825 tested if adding bevicizumab (BEV) to standard chemoradiation improves survival (OS) or progression free survival (PFS) in newly diagnosed GBM. While OS was equivalent, PFS was longer with Bev (Arm 2) than with placebo (Arm 1). Patients completed quality of life and symptom PROs to evaluate clinical benefit. **Methods:** The M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) and the EORTC core Quality of life Questionnaire and brain tumor module (EORTC QLQ-C30/BN20), were completed by pts at baseline (B) and longitudinally (wk 6, 10, 22, 34, and 46) while on study. The difference between treatment arms were compared from B with evaluation in subsequent weeks in those pts without disease progression; and early change (EC) (baseline to wk 10) between those with and without progression as predictors for OS and PFS. **Results:** 542pts consented to participate on this trial, and 507 randomized pts participated, with completion of forms by 94% at baseline, 75% at wk 10, 61% at wk 22, and 58% at wk 34. There was a trend for all MDASI-BT symptom groupings to be worse in Arm 2, with significant findings in treatment symptoms at wk 22 and wk 34; both affective and generalized disease symptoms were also significantly worse. For EORTCQLQ30/BN20, differential effects varied at each time point, with no persistent differences. For the MDASI-BT, B neurologic symptom grouping and EC in cognitive symptoms were prognostic for both OS and PFS. For the EORTC QLQ30/BN20, global QOL and motor dysfunction at B as well as EC in communication and leg weakness were prognostic for OS; whereas physical function at B and EC in headaches, seizures, and weak legs were prognostic for PFS. **Conclusions:** The longitudinal collection of PROs in this phase III trial revealed important treatment-related differences as there was overall more deterioration in symptoms and QOL in Arm 2 as compared to Arm 1, with persistent significant differences in treatment associated symptoms. B and EC tumor associated symptoms on both PRO tools were prognostic for OS and PFS. Longitudinal modeling is ongoing to further assess for differential impact of treatment on symptoms and QOL. Support: U10 CA21661, U10 CA37422 and Genentech, Inc. Clinical trial information: **NCT00884741**.

J Clin Oncol 31, 2013 (suppl; abstr 2006)

Phase III randomized, double-blind, placebo-controlled trial of donepezil in irradiated brain tumor survivors.

Author(s):*Stephen R. Rapp, Doug Case, Ann Peiffer, Michelle Joy Naughton, Volker W. Stieber, Gerald K. Bayer,Paul A. Bilodeau, Dennis Frederic Moore, Steven Charles Falchuk, Burton M. Needles, James Piephoff, William j Edenfield, Jeffrey K. Giguere, Nicholette Erickson, Monica Elena Loghin, Edward G. Shaw; Wake Forest University, School of Medicine, Winston Salem, NC; Wake Forest University, School of Medicine,Winston-Salem, NC; Forsyth Regional Cancer Center, Winston-Salem, NC; Green Bay Oncology, Green Bay, WI; Medical College of Georgia, Augusta, GA; Cancer Center of Kansas, Wichita, KS; Medical Arts Pavil, Newark, DE; St John's Mercy Medical Center, St, Louis, MO; St. John's Mercy Hospital, St Louis, MO; Cancer Centers of the Carolinas, Greenville, SC; Cancer Centers of the Carolinas, Seneca, SC; Central Maine Medical Center, Lewiston, ME; The University of Texas MD Anderson Cancer Center, Houston, TX .*

Abstract

Background: This RCT assessed the effect of 24 weeks of 5-10 mg per day of donepezil, an acetyl cholinesterase inhibitor, on cognitive functioning (primary endpoint) and fatigue, mood and QOL in long-term brain tumor survivors following partial or whole-brain irradiation. Cognitive results are reported herein. **Methods:** From 2/08-12/11,198 adult primary and metastatic brain tumor survivors . 6 months post radiation treatment (.30 Gray) recruited at 24 sites affiliated with the Wake Forest Community Clinical Oncology Program Research Base, 3 CTSU sites and M.D. Anderson Cancer Center were randomly assigned to receive donepezil (n599) or placebo (n599). Cognitive function was assessed at baseline, 12 and 24 weeks with Hopkins Verbal Learning Test-Revised, Rey-Osterreith Complex Figure, Trail Making Test, Digit Span, Controlled Oral Word Association, and Grooved Pegboard. A Cognitive Composite (CC) score was the primary outcome. **Results:** The sample was 91% White, 54% female, and median age was 55 yrs. 66% had primary tumors, 27% brain metastases and 8% PCI. Median time since diagnosis: 38 mos. 95% had 0-1 ECOG performance status scores. 74% completed the study. CC score improved significantly by 24 weeks in both arms (p , .01); however, there was not a statistically significant difference between groups (p 5 .57). Donepezil group performed better than placebo on HVLT Recognition (p 5 .03) and Discrimination (p 5 .01) and GP-Dominant Hand (p 5 0.02). Significant interactions were found between treatment arm and baseline cognitive scores for: CC (p 5 .01), HVLT Immed. Recall (p 5 .03), HVLT %Savings (p , .01), Digit Span Forward (p 5 .01), ROCF Copy (p 5 .03), TMT-B (p 5 .05) and GP-Dominant (p , .01). In all cases, the benefit of donepezil, relative to placebo, was greater for those with worse baseline scores. **Conclusions:** Long-term brain tumor survivors treated with brain irradiation who have cognitive impairment can benefit from 5-10mg of donepezil for 24 weeks. Improvements in verbal memory, working memory, visuo- and psychomotor performance and executive functioning were observed in this group. (Study supported by NIH/NINR grant 5R01NR009675-04, NIH/NCI grant 2 U10 CA 81851-09-13 and Eisai, Inc.) Clinical trial information: **NCT00369785**.

J Clin Oncol 31, 2013 (suppl; abstr LBA2000)

Bevacizumab, irinotecan, and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, MGMT-nonmethylated glioblastoma patients: First results from the randomized multicenter GLARIUS trial.

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Abstract

Background: In patients with MGMT-nonmethylated glioblastoma (GBM), primary chemotherapy with temozolomide (TMZ) is at best moderately effective. There is an urgent need for more effective therapies in this large subgroup of GBM. Since results of phase II trials with the antiangiogenic agent bevacizumab (BEV) +/- irinotecan (IRI) are promising in recurrent GBM, the GLARIUS trial explored the efficacy of BEV/IRI as compared to standard TMZ in the first-line therapy of MGMT-non-methylated GBM. **Methods:** In the randomized, multicenter, open-label GLARIUS trial, adult patients with newly diagnosed, histologically confirmed and MGMT-non-methylated GBM received local radiotherapy (RT, 30 x 2 Gy) and were randomized (2:1) for experimental therapy with BEV (10 mg/kg q2w) during RT followed by maintenance BEV (10 mg/kg q2w) + IRI (125 mg/m² q2w (without enzyme-inducing antiepileptic drugs (EIAEDs)) or 340 mg/m² (with EIAEDs)) or standard therapy with daily TMZ (75 mg/m2) during RT followed by 6 courses of TMZ (150-200 mg/m2/day for 5 days q4w). The primary endpoint was progression-free survival rate after 6 months (PFS-6) as determined by central neuroradiological review. **Results:** The intent-to-treat population included 170 patients (67.1% male, median age 56 years (range 25-78 years), 48.8% complete resection rate, 78.8% of patients with KPS 90% or higher); 116 patients received BEV/IRI, 54 patients had TMZ. The frequencies of adverse events in both arms of the trial were within the expected range. The PFS-6 rate was significantly higher in the BEV/IRI arm (71.1%, 95% CI 58.1-80.8%) than in the TMZ arm (26.2%, 95% CI 13.1-41.4%, $p<0.0001$ logrank test). **Conclusions:** The significant and clinically meaningful increase in the primary endpoint PFS-6 upon BEV/IRI chemotherapy suggests that BEV/IRI is superior to standard TMZ therapy in newly diagnosed MGMT-nonmethylated GBM patients. Clinical trial information: **2009-010390-21**.

J Clin Oncol 31, 2013 (suppl; abstr 2500)

A first-in-human phase I study of the CDK4/6 inhibitor, LY2835219, for patients with advanced cancer.

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Abstract

Background: Cyclin dependent kinases 4 and 6 (CDK4/6) act with D-type cyclins to inactivate the retinoblastoma (Rb) tumor suppressor protein and enable cell cycle progression from G1 to S phase. LY2835219 is a selective inhibitor of CDK4/6 that shows antitumor activity in preclinical models of human cancer and also distributes efficiently to the brain. We performed a phase 1 study to evaluate safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LY2835219. **Methods:** 3+3 dose escalation was followed by expansions in 5 tumor types (brain metastases permitted): non-small cell lung cancer (NSCLC), glioblastoma, breast cancer, melanoma, and colorectal cancer. LY2835219 was taken orally every 12 or 24 hours (in escalation) and every 12 hours (in expansions) on days 1-28 of a 28-day cycle. **Results:** 55 patients (pts) received LY2835219. In escalation, 33 pts received LY2835219 on 1 of 2 schedules: 50, 100, 150, 225 mg every 24 hours (Q24H) or 75, 100, 150, 200, 275 mg every 12 hours (Q12H). On the Q24H schedule, the maximum tolerated dose (MTD) was not identified. On the Q12H schedule, the MTD was 200mg Q12H with dose limiting toxicity of G3 fatigue at 200 mg (1/6 evaluable pts) and 275 mg (2/3 evaluable pts). At 200mg Q12H, the mean C_{max} and $AUC_{0\text{-}24hr}$ at steady state were 285 ng/mL and 5502 ng-hr/ml, respectively. In skin, LY2835219 induced pharmacodynamic inhibition of both Rb phosphorylation and topoisomerase IIα expression. In the ongoing expansions, 22 pts have received LY2835219. Across the study, the most common related adverse events were diarrhea (52%, including 5% G3), nausea (30%, 4% G3), fatigue (21%, 7% G3), vomiting (18%, 2% G3), and neutropenia (16%, 7% G3). 15 pts have reached ≥4 cycles for stable disease or better with 3 pts achieving 8, 16, and 26 cycles. One pt with ovarian cancer had a durable CA-125 response with >50% decrease for 16 cycles. One pt with KRAS mutant NSCLC had a 27% decrease by RECIST. One pt with $CDKN2A^{-/-}$ NRAS mutant melanoma had a confirmed partial response. Early clinical activity has been observed in ovarian cancer, NSCLC, breast cancer, and melanoma. **Conclusions:** LY2835219 shows acceptable safety and early clinical activity as a single agent for patients with advanced cancer. Clinical trial information: **NCT01394016**.

J Clin Oncol 31, 2013 (suppl; abstr 2503)

Phase I study of safety and pharmacokinetics (PK) of GDC-0917, an antagonist of inhibitor of apoptosis (IAP) proteins in patients (Pts) with refractory solid tumors or lymphoma.

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Abstract

Background: GDCE0917 is a small molecule that triggers tumor cell apoptosis by selectively antagonizing IAP proteins. Preclinical studies demonstrated antitumor efficacy of GDC-0917 alone or in combination with chemotherapeutic agents. **Methods:** Oral GDC-0917 was given on Day (d) 1 followed by 2d off and a 2-week (w) on/ 1w off treatment (tx) schedule (21d cycle) starting d4. A modified continual reassessment method was used for dose escalation. Dose-limiting toxicity (DLT, assessed d1-24), PK, adverse events (AEs), pharmacodynamics (PD), and clinical activity were evaluated. **Results:** 42 pts of age 36-86 (median 60.5) were enrolled in 11 cohorts (5-600 mg) and received 1-15 cycles (median 2) of GDC-0917. One DLT, Grade (G) 3 fatigue, was observed at 450 mg. The maximum tolerated dose was not determined although plasma concentrations of preclinically defined IC90 were reached. The most frequent AEs were diarrhea, fatigue and nausea (26.2% each), vomiting (23.8%), and constipation (19%). The most frequent AEs reported as tx-related were mostly G1-2 and included fatigue and nausea (21.4% each), vomiting (14.3%), rash (11.9%) and pruritus (9.5%). AEs reported as tx-related that were ≥ G3 in > 1 pt were elevated AST and ALT (2 pts, at 450 and 600 mg). AEs reported as tx-related that resulted in tx discontinuation were G3 fatigue, G2 QTc prolongation, G2 drug hypersensitivity, G2 pneumonitis (1 pt each), and G3 pruritus/G2 rash (same pt). GDC-0917 peak concentrations were observed 2-3h post dosing. Exposure was dose-proportional with a mean plasma elimination $t_{1/2}$of 4-8h and no apparent accumulation at steady state. Rapid down-modulation of cIAP1 was observed in PBMCs at all dose levels. Evaluation of tumor biopsies demonstrated decreases in cIAP1 (2 pts total, at 40 and 200 mg) and increases in activated caspase-3 and cPARP (1 pt at 200 mg). Two pts (4.8%) had a complete response (both unconfirmed, ovarian Ca and MALT lymphoma [PET]); 4 pts (9.5%) had stable disease for ≥ 3 months. **Conclusions:** GDC-0917 had a favorable safety, PK and PD profile in pts with advanced malignancies. These encouraging results support further clinical evaluation of this agent. Clinical trial information: **NCT01226277**.

J Clin Oncol 31, 2013 (suppl; abstr 2513)

Final results of the phase I trial of niraparib (MK4827), a poly(ADP)ribose polymerase (PARP) inhibitor incorporating proof of concept biomarker studies and expansion cohorts involving BRCA1/2 mutation carriers, sporadic ovarian, and castration resistant prostate cancer (CRPC).

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Abstract

Background: Niraparib(N) is an oral, potent PARP1/2 inhibitor that induces synthetic lethality in BRCA1/2 deficient tumors. PARP is also implicated in transcription regulated by the androgen receptor (AR) and rearranged ETS genes; key targets in CRPC. **Methods:** Dose-escalation was enriched for *BRCA1/2*mutation carriers (BRCA-MCs). Two MTD expansion cohorts were undertaken in patients (pts) with sporadic high grade serous ovarian cancer (HGSOC) and CRPC. In CRPC pts, archival tissue and circulating tumor cells (CTC) were analyzed for PTEN deletion and ETS gene rearrangements. **Results:** 100 pts [ovary (49), CRPC (23), breast (12) others (16)], received N at 10 dose levels: 30mg to 400mg daily (od), continuously. Grade (G) 4 thrombocytopenia was dose limiting at 400mg od; MTD was established at 300mg od. Drug-related toxicities were G1-2 reversible anemia (48%), fatigue (42%), nausea (42%), thrombocytopenia (35%), anorexia (27%), neutropenia (24%), constipation (23%), and vomiting (20%). PKs were dose proportional with a mean elimination $t_{1/2}$of 40 hours. Peripheral blood mononuclear cells had >50% PARP inhibition from 80 mg od. gH2AX foci formation, a marker of DNA damage, was seen in CTCs. Antitumor activity occurred from 60mg od with RECIST and/or CA125 partial responses (PR) in 9/20 (45%) BRCA-MC ovarian cancer pts and 2/4 (50%) BRCA-MC breast cancer pts. Platinum-sensitive vs resistant BRCA-MC HGSOC response rate was 60% vs 33% with median time for responding pts of 429 and 340 days, respectively. In sporadic HGSOC, there were 2/3 PRs in platinum-sensitive pts, and 3/20 PRs plus 4/20 stable disease (SD) >16 weeks in platinum resistant pts. In CRPC, symptomatic benefit and SD >6 months (median 9 months) was seen in 9/21 (43%) pts treated at MTD. CTC declines of >30% (median 80%; range 36%-92%) were observed in 7/10 (70%) pts with evaluable CTC counts (≥5 cells/ 7.5mL blood). **Conclusions:** Niraparib was well tolerated and has promising antitumor activity in BRCA-MCs, sporadic HGSOC and CRPC. Clinical trial information: **NCT0074902**.

J Clin Oncol 31, 2013 (suppl; abstr 2516^)

A phase I study of the first-in-class mitochondrial metabolism inhibitor CPI-613 in patients with advanced hematologic malignancies.

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Abstract

Background: Altered metabolism is a hallmark of cancer, including hematologic malignancies. This altered metabolism is a possible therapeutic target. The lipoate derivative CPI-613 is a first in class agent that targets pyruvate dehydrogenase complex.This trial was designed to determine the maximally tolerated dose (MTD), safety, and efficacy of CPI-613 given as a single agent by IV infusion. **Methods:** CPI-613 was given over a 2 hour infusion on days 1 and 4 for 3 weeks every 28 days with a starting dose of 420 mg/m^2. The dose was escalated in 6 cohorts to a final dose of 3780 mg/m^2. Treatment could be continued if the patient experienced clinical benefit. **Results:** A total of 26 patients with advanced relapsed or refractory hematologic malignancies were enrolled. Patients were heavily pretreated with a median of 3 previous therapies (range 1-11). CPI-613 was well tolerated when infused over 2 hours, with no worsening of cytopenias at any dose level. After the dose was escalated to 2940 mg/m^2 the protocol was amended to a 1 hour infusion. When infused over 1 hour, 2 patients developed grade 3 renal failure. Infusion time was then returned to 2 hours and dose escalation resumed. At a dose of 3780 mg/m^2, one patient experienced prolonged grade 3 nausea and one patient grade 3 renal failure, defining this dose as above the MTD. Renal failure resolved in all but one patient who opted for hospice care. A total of 6 patients were treated at a dose of 2940 mg/m^2over 2 hours with no DLTs observed, establishing this as the MTD. Of the 21 patients evaluable for a response, eight achieved a response of stable disease or better for a response rate of 38%. Responses included a complete remission maintained over 27 cycles in one AML patient and clearance of marrow blasts in another, sustained partial response in both a Burkitt's and a cutaneous T cell lymphoma patient maintained over 17 and 8 cycles respectively, and stable disease in 2 multiple myeloma and 2 myelodysplasia patients. **Conclusions:** To our knowledge this is the first report of an agent with activity in aggressive hematological malignancies that is not myelosuppressive. The therapeutic index appears high suggesting CPI-613 should be further studied in phase II trials. Clinical trial information: **NCT01034475**.

J Clin Oncol 31, 2013 (suppl; abstr 2531)

Safety, pharmacokinetics, and preliminary activity of the α-specific PI3K inhibitor BYL719: Results from the first-in-human study.

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Abstract

Background: BYL719 is an oral small-molecule inhibitor of the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which is encoded by the *PIK3CA* gene, one of the most commonly mutated genes in human cancers. BYL719 inhibits proliferation of PI3Kα-driven cancer cell lines in vitro and causes regression of *PIK3CA*-mutant tumor models in vivo. **Methods:** This Ph I study was performed in patients (pts) with advanced solid tumors carrying a somatic mutation of *PIK3CA*. Dose escalation used an adaptive Bayesian logistic regression model with overdose control. Following determination of the maximum tolerated dose (MTD), an expansion cohort was opened at the MTD to evaluate safety, pharmacokinetics (PK), and clinical activity in pts with *PIK3CA*-mutant advanced solid tumors, including estrogen receptor-positive (ER+) metastatic breast cancer (mBC). **Results:** During dose escalation 36 pts received doses up to 450 mg/d, where 4/9 pts had dose-limiting toxicities (DLTs). The MTD for once-daily dosing was declared as 400 mg/d. As of Nov 20 2012, DLTs were hyperglycemia, nausea, vomiting, and diarrhea. The most common BYL719-related adverse events (all grades, all cohorts, >25%) were hyperglycemia (49%), nausea (45%), diarrhea (40%), decreased appetite (38%), vomiting (30%), and fatigue (27%). 39 pts are enrolled in the MTD dose-expansion cohort. Investigation of a twice-daily regimen is also ongoing. BYL719 has a favorable, approximately dose-proportional PK profile with a T_{max} of 2h and a $T_{½}$ of 11h at the MTD. Partial responses were seen in 7 pts (in ER+ breast [2], cervical, trichilemmal, endometrial, ovarian, and head &neck cancer [1 each]); 17 pts stayed on study for >24 weeks. For 67 pts (76%) treated at doses of ≥270 mg/d, the median progression-free survival (mPFS) was 3.6 months (mo; 95% CI: 3.5–5.5 mo). mPFS in 15 ER+ HER2– mBC pts treated at ≥270 mg/d was 5.5 mo (95% CI: 3–7 mo). **Conclusions:** BYL719 displays dose-proportional and predictable PK. The safety profile is favorable, with mostly manageable on-target toxicities. At doses of ≥270 mg/d, tumor regression and prolonged disease control were observed in heavily pretreated pts with various tumor types carrying a *PIK3CA* mutation. Clinical trial information: **NCT01219699**.

J Clin Oncol 31, 2013 (suppl; abstr LBA3502)

Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG).

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Abstract

Background: The optimal duration of chemotherapy and bevacizumab in mCRC is not well established. The CAIRO3 study investigated the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation in mCRC pts not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B). **Methods:** Previously untreated mCRC pts, PS 0-1, with stable disease or better after 6 cycles of CAPOX-B, not eligible for metastasectomy and eligible for future treatment with oxaliplatin, were randomized between observation (arm A) or maintenance treatment with capecitabine 625 mg/m2 bid dailycontinuouslyand bevacizumab 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were treated with CAPOX-B until second progression (PFS2, primary endpoint). For pts not able to receive CAPOX-B upon PFS1, PFS2 was considered equal to PFS1. Secondary endpoints were overall survival (OS) and time to second progression (TTP2), which was defined as the time to progression or death on any treatment following PFS1. All endpoints were calculated from the time of randomization. **Results:** A total of 558 pts were randomized. Median follow-up is 33 months. The median number of maintenance cycles in arm B was 9 (range 1-54). The median PFS1 in arm A vs B was 4.1 vs 7.4 months (HR 0.44, 95% CI 0.37-0.54, p,0.0001). Upon PFS1, 72% of pts received CAPOX-B in arm A and 44% in arm B. The median PFS2 was 10.4 vs 10.4 months (HR 0.86, 95% CI 0.7-1.04, p50.12). The median TTP2 in arm A vs B was 11.5 vs 15.4 months (HR 0.58, 95% CI 0.48-0.72, p,0.0001), and the median OS was 17.9 vs 21.7 months (HR 0.77, 95% CI 0.62-0.96, p50.02), respectively. **Conclusions:** Maintenance treatment with capecitabine plus bevacizumab after 6 cycles CAPOX-B did not significantly prolong PFS2, which may be due to the lower number of pts in arm B that received CAPOX-B following PFS1. Maintenance treatment significantly prolonged PFS1, TTP2 and OS. Our data support the use of bevacizumab plus capecitabine until progression or unacceptable toxicity. Updated results will be presented. Clinical trial information: **NCT00442637**.

J Clin Oncol 31, 2013 (suppl; abstr LBA3504)

A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study.

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Abstract

Background: Resection of liver metastases from colorectal cancer with or without neoadjuvant chemotherapy is the standard of care. The EPOC study (Nordlinger et al, Lancet 2008) randomised patients between surgery and surgery with chemotherapy and demonstrated an improvement in 3 year progression free survival (PFS) of 7·3% (from 28·1% to 35·4%). As a rational extension to the EPOC study data, the New EPOC study evaluates the benefit of cetuximab, an EGF receptor antibody, in addition to standard chemotherapy in patients with operable liver metastases. **Methods:** 272 patients were randomised between February 2007 and November 2012 into the New EPOC study. Eligible patients were required to be k-RAS wild type, have operable liver metastases and to be sufficiently fit for chemotherapy and surgery. Patients with the primary tumour in situ, and those who required short course rectal radiation were eligible. Patients were randomised to receive a fluoropyrimidine and oxaliplatin plus or minus cetuximab for 12 weeks before, then 12 weeks following surgery. Patients who had been treated with adjuvant oxaliplatin could receive irinotecan and 5 – fluorouracil. **Results:** Following a recommendation from the Independent Data Monitoring Committee on 19/11/2012, the New EPOC study was stopped when the study met a protocol pre-defined futility analysis. With 45.3% (96/212) of the expected events observed, progression free survival was significantly worse in the cetuximab arm (14.8 vs 24.2 months, HR (95%CI) 1.50037 (1.000707 to 2.249517) p, 0.048). The result of a pre-planned analysis excluding the 23 patients treated with irinotecan based chemotherapy was similar (15.2 vs 24.2 months, HR 1.565546 (1.014967-2.414793) P,0.043). **Conclusions:** Although the data are immature, the accumulation of more events is unlikely to change this result. In patients with resectable liver metastases and K-RAS wt tumours the addition of cetuximab to chemotherapy is not beneficial. Clinical trial information: **ISRCTN22944367**.

J Clin Oncol 31, 2013 (suppl; abstr 3505)

FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.

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Abstract

Background: Doublets plus bev are a standard option for the first-line treatment of mCRC. First-line FOLFOXIRI demonstrated superior RR, PFS and OS compared to FOLFIRI. A phase II study of FOLFOXIRI/bev showed promising activity and manageable toxicities. The objective of the TRIBE trial was to confirm the superiority of FOLFOXIRI vs FOLFIRI when bev is added to chemotherapy (CT). **Methods:** Eligibility criteria included: measurable and unresectable mCRC, age 18-75 years, no prior CT for advanced disease. Pts were randomized to either FOLFIRI/bev (arm A) or FOLFOXIRI/bev (arm B). Both treatments were administered for a maximum of 12 cycles followed by 5FU/bev until progression. Primary endpoint was PFS. **Results:** Between July 2008 and May 2011 508 pts were randomized. Pts characteristics were (arm A/arm B): median age 60/61, ECOG PS 1-2 11%/10%, synchronous metastases 81%/79%, multiple sites of disease 74%/70%, liver-only disease 18%/23%, prior adjuvant (adj) 12%/12%. At a median follow-up of 26.6 mos 424 pts progressed and 244 died. Median PFS and OS in the intention to treat (ITT) population were 10.9 and 30.9 mos. FOLFOXIRI/bev significantly increased PFS (median 9.7 vs 12.2 mos, HR 0.73 [0.60-0.88] p50.0012). Subgroup analyses based on stratification factors (PS, prior adj) and baseline characteristics (site of primary, liver only disease, resection of primary, Kohne score) did not evidence significant interactions between treatment and analyzed factors. A trend toward a more consistent effect of FOLFOXIRI/bev was reported in no prior adj (HR 0.68 [0.55-0.83]) compared to prior adj group (HR 1.18 [0.67-2.08], p for interaction50.071). Response rate (RECIST) was also significantly improved (53% vs 65% p50.006). FOLFOXIRI/bev did not increase the R0 secondary resection rate in the ITT population (12% vs 15%, p50.327), or in the liver-only subgroup (28% vs 32%, p50.823). **Conclusions:** FOLFOXIRI/bev compared to FOLFIRI/bev, significantly increases PFS and response rate. Subgroup analysis suggests a possible interaction between prior adj CT and PFS benefit. Secondary resection rate does not differ between treatment arms. Clinical trial information: **NCT00719797.**

J Clin Oncol 31, 2013 (suppl; abstr 3515)

Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer (mCRC) according to KRAS: Results of the GERCOR DREAM phase III trial.

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Abstract

Background: The primary analysis of DREAM demonstrated that a maintenance therapy (MT) with bevacizumab (Bev) + EGFR TKI erlotinib (E) significantly improved progression-free survival (PFS) after a 1st-line Bev-based induction therapy (IT) in patients (pts) with unresectable mCRC. **Methods:** Pts were randomized to MT after an IT with FOLFOX-bev or XELOX-bev or FOLFIRI-bev between Bev alone (Bev 7.5 mg/kg q3w; arm A) or Bev+E (Bev 7.5 mg/kg q3w, E 150 mg/d ; arm B) until PD or unacceptable toxicity. Primary endpoint was PFS on MT. Secondary endpoints included PFS from inclusion, overall survival (OS) and safety. The impact of KRAS tumor status on treatment efficacy was evaluated in an exploratory analysis. **Results:** 700 pts were registered and 452 pts were randomized (228 in arm A, 224 in arm B). KRAS status was available for 413/452 (91%) pts. The median duration of MT was 3.6 m. Results for MT are presented below (Table). In the registered population, median OS was 24.9m (22.5 – 27.3). **Conclusions:** Maintenance treatment with bev + erlotinib increases PFS over maintenance with bev alone in pts with mCRC but does not prolong OS. Further follow-up will determine the impact of 2nd or 3rd line anti-EGFR Mabs in this study. Contrasting with anti-EGFR Mabs, KRAS tumor status is not mandatory to select pts with mCRC for treatment with erlotinib. Clinical trial information: **NCT00265824**.

GERCOR DREAM study: KRAS analysis.

Endpoints, months (95% CI)	Arm A	Arm B	HR (95% CI)	P value
Maintenance population (MP) (n = 452)	n = 228	n = 224		
Median maintenance PFS	4.8 (4.1 - 5.7)	5.9 (4.5 - 6.4)	0.76 (0.61-0.94)	0.010
Median PFS	9.3 (8.7 – 10.1)	10.2 (9.5 – 11.5)	0.76 (0.61 - 0.94)	0.009
Median OS	27.9 (24.1 – 31.1)	28.5 (25.1 – 33.9)	0.89 (0.70-1.12)	0.312
MP - WT KRAS	n = 111	n = 129		
Median maintenance PFS	5.9 (4.0 – 6.5)	6.0 (4.5 – 7.8)	0.86 (0.64-0.1.16)	0.135
Median PFS	9.7 (8.7 – 11.0)	10.9 (9.8 – 12.6)	0.83 (0.61 - 1.11)	0.197
Median OS	31.5 (27.5 – 38.0)	31.8 (26.6 – 37.8)	0.92 (0.66 – 1.30)	0.644
MP - Mut KRAS (n = 173)	n = 95	n = 78		
Median maintenance PFS	4.4 (3.9 – 5.3)	4.7 (3.6 – 7.1)	0.77 (0.54 – 1.08)	0.124
Median PFS	9.9 (8.6 – 10.8)	9.8 (8.4 – 12.2)	0.80 (0.57 – 1.13)	0.212
Median OS	26.9 (22.4 – 33.2)	26.3 (21.0 – 34.4)	1.06 (0.72 - 1.55)	0.767

J Clin Oncol 31, 2013 (suppl; abstr LBA3506)

Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).

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Abstract

Background: In patients (pts) with KRAS, wild-type metastatic colorectal cancer (mCRC) a head to head comparison of anti-EGFR- and anti-VEGF-directed first-line therapy has not been reported with regard to the FOLFIRI backbone. The AIO KRK-0306 study was therefore designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in mCRC pts not pretreated for metastatic disease. **Methods:** Pts were randomized to FOLFIRI (Tournigand regimen) every two wks plus cetuximab (400 mg/m² day 1, followed by 250 mg/m² wkly = arm A) or bevacizumab (5 mg/kg every two wks = arm B). The intent-to-treat (ITT) population comprised all pts who had at least completed one application of therapy. While recruitment initially was independent of KRAS status, an amendment confined inclusion to KRAS wildtype (WT) tumors. Recruitment was completed in October 2012. The primary study endpoint was objective response rate (ORR, investigators read). **Results:** Among 735 pts of the ITT-population, KRAS-WT was identified in 592. Of these, 297 pts were randomized to arm A and 295 to arm B. Median age was 64 years, 66% of pts were male, and ECOG PS 0-1 was observed in 98% of pts. Median duration of treatment was 4.7 mo vs 5.3 mo, respectively. While in the ITT analysis, ORR was comparable in arms A vs B (62% vs 57%, odds ratio 1.249), a significant superiority was found for assessable pts in arm A. Median PFS of the ITT population was nearly identical (10.3 vs 10.4 mo, HR 1.04, p=0.69), however, overall survival (OS) showed a significantly better outcome in arm A vs arm B (28.8 vs 25.0 mo, HR 0.77, p=0.0164, 95% CI: 0.620-0.953). Sixty-day mortality was low in both arms (1.01% vs 2.71%). **Conclusions:** ORR was comparable between arms in the ITT analysis, but favored arm A in assessable pts. Significantly superior OS was observed in KRAS-WT patients receiving cetuximab plus FOLFIRI as first-line treatment. Clinical trial information: **NCT00433927**.

J Clin Oncol 31, 2013 (suppl; abstr 4005^)

Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates..

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Abstract

Background: *nab*-paclitaxel (*nab*-P; 130 nm albumin-bound paclitaxel) has demonstrated both single-agent activity and synergy with gemcitabine (G) in preclinical models of pancreatic cancer (PC). *nab*-P + G also demonstrated promising efficacy in a phase I/II study in metastatic PC (*J Clin Oncol.* 2011:4548-4554), warranting a phase III study of *nab*-P + G vs G for metastatic PC. **Methods:** 861 patients (pts) with metastatic PC and a Karnofsky performance status (KPS) ≥ 70 were randomized at 151 community and academic centers 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^{2}weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle ≥ 2). The primary endpoint was OS; secondary endpoints were PFS and ORR by independent review. **Results:** The median age was 63 years (range 27 - 88). KPS was 100 (16%), 90 (44%), 80 (32%), and 70 (7%). Pts had advanced disease with liver metastases (84%), ≥ 3 metastatic sites (46%), and CA19-9 ≥ 59 × ULN (46%). *nab*-P + G was superior to G for all efficacy endpoints: median OS was 8.5 vs. 6.7 mo (HR 0.72; 95% CI, 0.617 - 0.835; $P = 0.000015$); median PFS was 5.5 vs. 3.7 mo (HR 0.69; 95% CI, 0.581 - 0.821; $P = 0.000024$), and ORR was 23% vs. 7% ($P = 1.1 \times 10^{-10}$) by RECIST v1.0. Metabolic response by PET in 257 patients was 63% for *nab*-P + G vs 38% for G ($P = 0.000051$). CA19-9 response (≥ 90% decrease) was 31% for *nab*-P + G vs. 14% for G ($P < 0.0001$). Grade ≥ 3 AEs with *nab*-P + G vs. G included neutropenia (38% vs. 27%), fatigue (17 % vs. 7%), diarrhea (6% vs 1%), and febrile neutropenia (3% vs. 1%). Grade ≥ 3 peripheral neuropathy (PN) occurred in 17% vs. 1% of pts who received *nab*-P + G vs. G, respectively; for *nab*-P + G, PN improved to grade ≤ 1 in a median 29 days, and 44% of patients resumed *nab*-P treatment. The median duration of treatment was 3.9 mo for *nab*-P + G and 2.8 mo for G. **Conclusions:** MPACT was a large, international study performed at community and academic centers. *nab*-P + G was superior to G across all efficacy endpoints, had an acceptable toxicity profile, and is a new standard for the treatment of metastatic PC that could become the backbone for new regimens. Clinical trial information: **NCT00844649**.

J Clin Oncol 31, 2013 (suppl; abstr 4008)

JASPAC 01: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer.

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Abstract

Background: Adjuvant chemotherapy with gemcitabine (G) has been standard treatment for resected pancreatic cancer (PC). In the GEST study, S-1 (S) had shown non-inferiority to G in overall survival (OS) for unresectable PC. The aim of this phase III study is to investigate non-inferiority of S to G on OS as adjuvant chemotherapy for resected PC. **Methods:** Patients (pts) after macroscopically curative resection of PC with an ECOG PS of 0-1 and adequate organ functions were randomly assigned to G (1000 mg/m2, iv, d1, 8 and 15, q4w, for 6 courses) or S (80/100/120 mg/day based on BSA, po, d1-28, q6w, for 4 courses) with balancing by surgical margins (R), nodal status (N) and institution. Primary endpoint was OS. With 180 pts per arm, the study had 80% power to prove non-inferiority with a margin of hazard ratio (HR) 1.25 on the basis of expected HR 0.87, with 0.05 two-sided alpha. Secondary endpoints were relapse-free survival (RFS), safety, and quality of life (EQ-5D). One interim analysis was planned after 180 deaths. **Results:** From 4/2007 to 6/2010, 385 pts were enrolled from 33 hospitals in Japan. 378 pts (G/S: 191/187) were included in the full analysis set. Pts characteristics (G/S) were well balanced (PS0: 67%/70%, R0: 86%/88%, N0: 38%/36%). Based on the interim analysis with 205 OS events, IDMC recommended to publish the results. OS at 2-years were 53% for G and 70% for S. HR for S to G was 0.56 (95% CI, 0.42-0.74, $p<0.0001$ for non-inferiority, $p<0.0001$ for superiority). On subgroup analysis, HRs for R0/R1, N0/N1 pts were 0.57 (95% CI, 0.42-0.78)/0.53 (0.27-1.05), 0.48 (0.28-0.83)/0.58 (0.41-0.80), respectively. RFS at 2-years were 29% for G and 49% for S. HR of relapse for S to G was 0.56 (95% CI, 0.43-0.71, log-rank $p<0.0001$). Incidences of grade 3/4 toxicities in G/S were leukopenia 39%/9%, hemoglobin decrease 17%/13%, thrombocytopenia 9%/4%, elevated AST 5%/1%, fatigue 5%/5%, and anorexia 6%/8%. Relative dose intensity of G/S was 84%/97%. EQ-5D QOL score in S was significantly better than that in G ($p<0.0001$). **Conclusions:** S-1 adjuvant chemotherapy is shown non-inferior, and furthermore, even superior to GEM. S-1 is considered as the new standard treatment for resected PC pts. Clinical trial information: **UMIN000000655**.

J Clin Oncol 31, 2013 (suppl; abstr 4023)

Cougar-02: A randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma.

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Abstract

Background: Survival in patients who relapse after first-line chemotherapy (CT) for advanced esophago-gastric adenocarcinoma (EGC) is poor though recently randomised trials (RCT) have suggested a small benefit for second line chemotherapy with taxanes or irinotecan. There is very little data on health related quality of life (HRQL) or overall survival (OS), particularly in patients who progress shortly after first-line therapy. **Methods:** COUGAR-02 was a multicentre open-label, phase III RCT for patients with locally advanced or metastatic EGC of performance status (PS) 0-2 who had progressed within 6 months of previous platinum/fluoropyrimidine CT. Patients were randomised (1:1) to receive either docetaxel 75mg/m^{2}every 3 weeks for up to 6 cycles or active symptom control (ASC). The primary endpoint was OS. The secondary endpoint of HRQL, assessed using EORTC QLQ-C30 and QLQ-ST022, was analysed using standardised area under a curve and compared using Wilcoxon rank sum test. Sensitivity analysis adjusting for dropouts due to death were performed using quality adjusted survival. **Results:** 168 patients **(**84 patients in each arm) were recruited between April 2008 and April 2012. Median age was 65 years (range 28-84); 81% were males. PS at randomisation was 0 for 27%, 1 for 57% and 2 for 15%. 86% had metastatic disease. 43% progressed during previous CT, 28% progressed within 3 months of end of previous CT and 29% progressed between 3 and 6 months. Median number of cycles of docetaxel was 3. 23% completed 6 cycles. Docetaxel was well tolerated and resulted in a significantly improved OS over ASC alone (HR=0.67 (95% CI 0.49-0.92); p=0.01). Objective response rate was 7%. For QLQ-C30, patients on docetaxel arm reported significantly less pain (p=0.0008) and trend for less nausea and vomiting (p=0.02) and constipation (p=0.02) than those on ASC arm. Similar global HRQL seen (p=0.53).For QLQ-ST022, trend seen for less dysphagia (p=0.02) and pain symptoms (p=0.01) for patients on docetaxel arm than ASC **Conclusions:** Docetaxel provided a significant OS benefit over ASC with improvements in symptom scores and no loss in overall HRQL. Docetaxel can be considered a standard of care in this setting. Clinical trial information: **NCT00978549.**

J Clin Oncol 31, 2013 (suppl; abstr LBA4001)

Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial.

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Abstract

Background: HER2 amplification is common in upper GI tract (UGIT) adenocarcinomas and inhibition improves clinical outcomes. Lapatinib ditosylate (L), a dual anti EGFR and anti HER2 tyrosine kinase inhibitor with preclinical activity against these cancers, was investigated in a phase III, randomized, double blind trial evaluating efficacy and safety in combination with CapeOx as first-line treatment of advanced or metastatic HER2+ UGIT ACs. **Methods:** Subjects had measurable and/or non-measurable disease with overexpression or amplification of HER2 (IHC2+ and FISH amplified, or IHC 3+, or FISH, CISH, or SISH amplified). HER2 status was reviewed by the central lab. Subjects were randomized 1:1 to CapeOx q3w (oxaliplatin 130mg/m^2 day 1; capecitabine 850mg/m^2/BID days 1 – 14), and daily L (1250mg) (CapeOx+L) or placebo (CapeOx+P). The primary efficacy population (PEP) comprised all subjects whose tumors were centrally confirmed to be FISH amplified. The primary endpoint was overall survival (OS) of the PEP. Secondary endpoints included progression free survival (PFS), overall response rate (ORR) and safety. **Results:** 545 pts were randomized and 487 had HER2+ centrally confirmed. The primary endpoint was not reached with a hazard ratio (HR) for OS of CapeOx+L compared to CapeOx+P of 0.91 (95% CI 0.73, 1.12, p=0.35); median 12.2 vs. 10.5 months, respectively. HR for uncensored PFS was 0.86 (95% CI 0.71 - 1.04, p=0.10); median 6.0 vs. 5.4 months. The analysis of PFS censored by the time of subsequent anticancer therapy as per protocol showed a HR of 0.82 (95% CI 0.68, 1.00, p=0.04). ORR was 53% in the CapeOx+L arm and 40% in the CapeOx+P arm. Pre-specified subgroup analyses showed significant improvements in OS in Asian pts (HR= 0.68) and those under 60 years (HR=0.69). There was no association between IHC and OS. Toxicity profiles were similar except for increased overall diarrhea, and skin toxicity and grade 3+ diarrhea (12 vs 3%) with CapeOx+L. **Conclusions:** The addition of L to CapeOx did not reach its

primary endpoint, though certain subgroups showed improvement. Further clinical and molecular analyses will be presented. Clinical trial information: **NCT00680901**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4002)

SAMIT: A phase III randomized clinical trial of adjuvant paclitaxel followed by oral fluorinated pyrimidines for locally advanced gastric cancer.

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Abstract

Background: Adjuvant chemotherapy with tegafur/uracil (UFT) used to be a tentative Japanese standard treatment and has been replaced by S-1 according to the result of the ACTS-GC trial, although there has been no direct comparison. Paclitaxel (PTX) has been widely used as one of the key drugs for unresectable GC. A randomized phase III trial with a two-by-two factorial design was planned to assess the survival benefit of sequential use of PTX and oral fluorinated pyrimidines (FPs) in comparison with FPs alone, and to compare UFT and S-1. **Methods:** Patients with serosa-invading GC who underwent R0/1 resection with extended (D2) lymph node dissection were randomized to receive either UFT 267mg/m^2 daily (arm A), S-1 80mg/m^2 daily for 2 weeks every 3 weeks (B), weekly PTX 80 mg/m^2 followed by UFT (C), or PTX followed by S-1 (D) for 24 weeks. The primary endpoint was disease-free survival (DFS). 708 patients per groups were necessary to detect a hazard ratio of 0.8 with 90% power for superiority of the sequential arms, C+D, vs. A+B (two-sided 5.0% significance level). The number of patients was set to 370 per arm (total 1480) with an 88% power for noninferiority (1.33 as the margin) of UFT vs. S-1. **Results:** Between August 2004 and October 2007, 1,495 patients from 232 centers were randomized with the full analysis set of 1,433. Demographics were well balanced among arm A (n=359), B (n=364), C (n=355), and D (n=355); mean age was 64, 86% were PS 0, 68% of tumors were 8 cm or greater and 85% were clinically node positive. Grade 3-4 neutropenia or anorexia occurred in 11% or 6%, 13% or 7%, 13% or 2%, and 23% or 5% for arm A, B, C, and D, respectively. Other % grade 3-4 toxicities were less than 5%. Median follow-up was 1,875 days and 728 events occurred. Difference in DFS between C+D and A+B were not statistically significant (HR=0.92, 95%CI 0.80-1.07, p= 0.273). HR of A+C vs. B+D was 1.23 (95%CI 1.07-1.43) and hence the null hypothesis was not rejected. **Conclusions:** There was a trend for better DFS for sequential use of PTX followed by FPs. Comparison between the FPs demonstrated that UFT was inferior to S-1. Sequential PTX/S-1 is safe and effective for locally advanced GC in an adjuvant setting. Clinical trial information: **C000000082**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4003)

Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study.

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Abstract

Background: CRT in patients with LAPC controlled after induction CT could be superior to continuing CT (Huguet, JCO 2007). The role of erlotinib is unknown. We aimed to define the role of 1) CRT after disease control with gemcitabine, 2) erlotinib in LAPC. **Methods:** LAPC PS 0-2 patients were first randomized to gemcitabine alone or plus erlotinib 100 mg/d for 4 months (R1, stratification: center, PS). Patients with controlled disease were then randomized to 2 additional months of CT (Arm 1) or CRT (Arm 2) 54 Gy and capecitabine 1600 mg/m2/d (R2, stratification: center, initial arm). Patients receiving erlotinib at R1 had maintenance with this drug after protocol completion. Quality control for radiotherapy included dummy runs and assessment of treated patients. Primary objective: overall survival (OS) in R2 patients. Secondary objectives: role of erlotinib on OS (R1), tolerance, predictive markers, and circulating tumor cells. Taking into account a 30% progression rate between R1 and R2, and 5% lost to follow-up, 722 patients were required to observe 392 deaths to show a median OS increase from 9 to 12 m (HR=0.75) in the CRT arm (2 sided α=5% and β=20%) with planned interim analyses using alpha spending function and O'Brien Fleming boundaries (to reject H0 or H1). Kaplan-Meier, log rank and univariate Cox tests were used. **Results:** From 442 pts included for R1, 269 pts reached R2 (arm1:136; arm 2:133). Main baseline characteristics in arms 1/2: female 44%/56%, mean age 63/62, head tumor 65%/62%, PS 0 56%/48%. After a median follow-up of 36 m, 221 deaths had occurred allowing the planned interim analysis (information fraction 56.4%). OS in R2 pts was 16.5 m [15.5-18.5] and 15.3 m [13.9–17.3] in arms 1 and 2, respectively (HR=1.03 [0.79-1.34], p=0.83). IDMC has confirmed that the futility boundary for the hypothesis of CRT superiority was crossed and considered this as the final analysis of the study. **Conclusions:** Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT. Clinical trial information: **NCT00634725**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4004)

A phase III randomized trial of chemoimmunotherapy comprising gemcitabine and capecitabine with or without telomerase vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer.

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Abstract

Background: GV1001, a promiscuous class II epitope encompassing aa 611-626 of hTERT led to the development of CD4+ clones recognizing hTERT in patients with advanced pancreatic cancer (APC). Preclinically gemcitabine increases antigen cross-presentation, enhances T cell trafficking/activation, and reduces MDSCs and Tregs. **Methods:** Patients with APC were randomized 1:1:1 to: Arm 1 GemCap; 2 GemCap for 8/52 followed by GV1001 followed by further GemCap if no PD at week 8; 3 concurrent administration of GemCap and GV1001. 735 (69.2%) had metastatic disease and 948 (89.3%) had ECOG PS=0 or 1. Randomization was stratified by stage and PS. Primary endpoint was overall survival (OS); secondary endpoints included ORR, TTP, and AEs. Recruitment target was 1,110 patients (780 deaths) to permit detection of a hazard ratio of 0.748 between either GV1001 arm and Arm 1 using a 2-sided α=0.025 level of significance with at least 80% power. **Results:** 1,062 pts from 51 centers were randomized. Trial maturity was high (72.7% patients died): median follow-up was 6.11 months. The overall response rates were Arm 1=17.6%; Arm 2=8.9% (p=0.001); Arm 3: 15.5% (p=0.460 compared with Arm 1). **Conclusions:** OS with concurrent GemCap/GV1001 was not different to that with GemCap alone. OS with sequential GV1001 was not statistically different to GemCap alone as it did not meet the criterion for statistical significance (p<0.0175). The addition of a T helper epitope vaccine to GemCap did not improve outcome compared to GemCap alone. Clinical trial information: **43482138**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4504)

Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC).

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Abstract

Background: Sequential SUN (tyrosine kinase inhibitor, TKI) until progression of disease (PD) followed by EVE (mTOR inhibitor) is standard therapy for patients with mRCC. This open-label, multicenter, phase II trial compared 1st-line EVE to 1st-line SUN (NCT00903175). Sequential EVE¡SUN was also compared with standard SUN¡EVE. **Methods:** Patients with mRCC (clear or non-clear cell) naive to prior systemic therapy were randomized 1:1 to either 1st-line EVE 10 mg/day or SUN 50 mg/day (4 weeks on, 2 weeks off) until PD. Patients then crossed over and continued on the alternate drug until PD. Primary objective was to assess PFS noninferiority of 1st-line EVE to 1st-line SUN; defined as an observed hazard ratio (HR)1st EVE/SUN #1.1. Overall survival (OS), combined 1st-line and 2nd-line PFS, and safety were secondary end points. **Results:** From10/09 to 6/11, 471 patients enrolled (EVE¡SUN, n 5 238; SUN¡EVE, n 5 233). Median age was 62 years, 85.4% had clear-cell RCC, and MSKCC favorable/intermediate/poor risk was 30/56/14%. Median follow-up was 22.7 months. A total of 53.7% of patients who discontinued 1st-line EVE entered into 2nd-line SUN and 51.6% of patients who discontinued 1st-line SUN entered into 2nd-line EVE. Median PFS (95% CI) was 7.9 (5.6-8.2) months for 1st-line EVE and 10.7 (8.2-11.5) months for 1st-line SUN. HR1st EVE/1st SUN (95% CI) was 1.43 (1.15-1.77). Median OS (95% CI) was 22.4 (19.7-NA) months for EVE¡SUN and 32.0 (20.5-NA) months for SUN¡EVE; HREVE-SUN/SUN-EVE (95% CI) was 1.24 (0.94-1.64). A trend in favor of SUN¡EVE for OS was observed, but will need to be confirmed with final OS analysis. Additional efficacy results for secondary end points are forthcoming. Common treatmentemergent adverse events for 1st-line EVE vs SUN, respectively, were stomatitis (53% vs 57%), fatigue (45% vs 51%), and diarrhea (38% vs 57%). **Conclusions:** Noninferiority of PFS for 1st-line EVE compared with SUN was not achieved in this randomized phase II trial of mRCC patients. The treatment paradigm remains SUN¡EVE since the sequence achieved optimal clinical benefit. Clinical trial information: **NCT00903175**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4500)

A phase III trial of personalized chemotherapy based on serum tumor marker decline in poor-prognosis germ-cell tumors: Results of GETUG 13.

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Abstract

Background: Poor-prognosis GCT (IGCCCG, J Clin Oncol 1997) remains a challenge with no improvement in the 50% survival demonstrated in phase III trials for 25 years. Day 21 serum tumor marker decline rate identified a subgroup of patients (pts) with a better outcome (J Clin Oncol 2004, 22: 3868-76). The hypothesis we tested in this study is that treatment allocation based on early tumor marker decline will improve the progression-free survival (PFS). **Methods:** Pts with IGCCCG poor-prognosis GCT were treated with a first cycle of BEP. AFP and hCG were assessed at day 18–21: 1) Pts with a favorable decline continued BEP for a total of 4 courses (Fav-BEP); 2) Pts with an unfavorable decline were randomized to receive either BEP (Unfav-BEP) or a dose-dense regimen (Unfav-dose-dense), consisting of paclitaxel-BEP plus day-10 oxaliplatin x 2 cycles, followed by 2 cycles of cisplatin, ifosfamide, and continuous infusion bleomycin (depending on lung function) + G-CSF. The primary endpoint was PFS (hypothesis: 20% difference, type 1 error: 5%, power 80%, 196 randomized pts needed). **Results:** 263 pts were enrolled and 254 were evaluable at day 21 (6 early deaths, 3 withdrawals): 51 pts (20%) had favorable tumor marker decline and 203 had unfavorable decline (randomized: 105 Unfav-dose-dense arm, 98 Unfav-BEP). The prognostic value of early tumor marker decline (Fav-BEP vs Unfav-BEP) was confirmed: 70% vs 48% for 3-year PFS (p=0.01), and 84% vs 65% for overall survival (OS) (p=0.02). The 3-year PFS was 59% in the Unfav-dose-dense arm vs 48% in the Unfav-BEP arm (p=0.05; HR: 0.66 [0.44-1.00]). 3-year OS was 73% and 65%, respectively. More ≥ grade 2 neurotoxicity (21% vs 4%) and more hematotoxicity occurred in the dose-dense arm, with no excess febrile neutropenia (17% each arm) or toxic deaths (1 each arm). Salvage high-dose chemotherapy + stem-cell transplant were required in 6% in the Unfav-dose-dense arm and 16% in the Unfav-BEP arm (p=0.01). **Conclusions:** An algorithm of individualized treatment intensification determined by the rate of early tumor marker decline reduces the risk of progression or death in men with poor-prognosis GCT. Clinical trial information: **NCT00104676**.

J Clin Oncol 31, 2013 (suppl; abstr LBA4510)

Duration of androgen deprivation therapy in high-risk prostate cancer: A randomized trial.

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Abstract

Background: Radiotherapy (RT) and long-term androgen deprivation therapy (ADT) is a standard treatment for patients with high-risk prostate cancer. However, the optimal duration of ADT is not yet defined. The purpose of this randomized trial was to compare outcomes between 36 and 18 months of ADT in high-risk prostate cancer treated with RT (PCS IV trial). **Methods:** PCS IV randomized patients with node-negative high-risk prostate cancer (T3-4, PSA >20 ng/ml or Gleason score >7), to pelvic RT (whole pelvis 44 Gy/4 ½ weeks, prostate 70 Gy/7 weeks) and 36 (arm 1) vs 18 months (arm 2) of ADT (neo- adjuvant, concomitant, adjuvant). ADT consisted of bicalutamide 50 mg for one month and goserelin 10.8 mg every three months for 36 vs 18 months. Overall survival was the primary end point. From randomization, overall and cancer-specific survival rates were compared between arms with Kaplan-Meier log rank test and Cox regression. **Results:** From October 2000 to January 2008, 310 patients were randomized to arm 1 and 320 to arm 2. Patients' characteristics were well balanced between the two arms (median age 71 years, median PSA 16 ng/ml, median Gleason score 8). Most patients had T2-T3 disease. At a median follow-up of 78 months, 80/310 patients (25.8%) in arm 1 and 85/320 (26.6%) in arm 2 had died (p=0.829). 113 patients died of causes other than prostate cancer. Overall and cancer-specific survival hazard ratios were 1.15 (0.85-1.56), p=0.366 and 1.07 (0.62-1.84), p=0.819, respectively. 5-year overall and disease-specific survival rates were 91.1% (87.9-94.3) vs. 86.1% (82.3-90.0), p=0.06 and 96.6% (94.5-98.7) vs. 95.3% (92.8-97.7), p=0.427 and 10-year overall and disease-specific survival rates were 61.9% (54.1-69.7) vs. 58.6% (49.8-67.4), p=0.275 and 84.1% (77.6-90.6) vs. 83.7% (76.3-91.1), p=0.819 for arm 1 and arm 2, respectively. There were no significant differences in the rates of biochemical, regional, or distant failure between arms. **Conclusions:** With a median follow-up of 6.5 years, our study shows that long-term ADT can be safely reduced from 36 to 18 months without compromising outcomes. Analysis of treatment impact on quality of life is now under review. Source of Funding: AstraZeneca Pharmaceuticals Grant. Clinical trial information: **#NCT00223171**.

J Clin Oncol 31, 2013 (suppl; abstr 5005)

Prolaris: A novel genetic test for prostate cancer prognosis.

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Abstract

Background: The natural history of prostate cancer is highly variable and difficult to predict. Improved tools are needed to match treatment more appropriately to a patient's risk of progression. Therefore, we developed an expression signature composed of genes involved in cell cycle progression (Prolaris) and tested its utility in prostate cancer. **Methods:** We developed an expression signature composed of 31 cell cycle progression and 15 housekeeper genes. An expression score (Prolaris score) was derived as the mean of all cell cycle progression genes. The signature was tested at disease diagnosis in two conservatively managed cohorts from the UK (N=337 and 349), after radical prostatectomy in two cohorts from the U.S. (N=366 Scott & White Hospital, TX and 413 USCF, CA), and after external beam radiation therapy (N=141) in a cohort from Durham VA Medical Center. All studies were retrospective. **Results:** The cell cycle progression signature was a highly significant predictor of outcome in all five studies. In conservatively managed patients, the Prolaris score was the dominant variable for predicting death from prostate cancer in univariate analysis (p = 6.1 x 10-22 after diagnosis by TURP, and p = 8.6 x 10-10 after diagnosis by needle biopsy). In both studies, the Prolaris score remained highly significant in multivariate analysis making it a stronger predictor of disease-specific mortality than other prognostic variables. After prostatectomy, Prolaris predicted biochemical recurrence (BCR) in univariate analysis (S&W p = 5.6 x 10-9; UCSF p= 2.23 x 10-6) and provided additional prognostic information in multivariate analysis (S&W p = 3.3 x10-6; UCSF 9.5 x10-5). After radiation therapy, Prolaris predicted BCR (Phoenix) in univariate (p=0.0017) and multivariate analysis (p=0.034). In all five studies the HR per unit change in the Prolaris score was remarkably similar, ranging from 1.89 to 2.92, indicating that the effect size for the Prolaris score is robust to clinical setting and patient composition. **Conclusions:** The Prolaris test predicts prostate cancer outcome in multiple patient cohorts and diverse clinical settings. In all cases, it provides information beyond clinicopathologic variables to help differentiate aggressive from indolent disease.

J Clin Oncol 31, 2013 (suppl; abstr 5009)

Long-term safety and efficacy analysis of abiraterone acetate (AA) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC) without prior chemotherapy (COU-AA-302).

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Abstract

Background: AA, a CYP17 inhibitor, prolongs the lives of men with progressive pre- or post-chemotherapy treated mCRPC with a favorable safety profile (Rathkopf et al. ASCO-GU 2013. Abstr 5). This post hoc analysis examines the safety and tolerability of long-term treatment (≥ 24 mos) in study COU-AA-302. **Methods:** 1,088 pts were randomized 1:1 to AA 1000 mg + P 5 mg po BID vs placebo + P. Co-primary endpoints were radiographic progression-free survival (rPFS) and OS. Median times with 95% CI of the end points were estimated using the Kaplan-Meier (KM) method. Post hoc analysis of adverse events (AEs) was performed at pre-specified interim analysis (IA3) (55% OS events). **Results:** At a median follow-up = 27.1 mos (IA3): rPFS HR (95% CI) = 0.53 (0.45, 0.62), $p < 0.0001$ and OS was improved over P [0.79 (0.66, 0.96), $p = 0.0151$]; the latter did not reach the pre-specified efficacy boundary ($p = 0.0035$). All secondary endpoints favored the AA arm (Rathkopf et al. ASCO-GU 2013. Abstr 5). The incidence rate of selected AEs by duration of exposure is shown below (Table). There was no clinically relevant increase in the incidence rate of AEs with longer exposure using AA + P versus P alone; although pts on treatment for ≥ 24 mos may have had greater tolerability. The percentage of patients who came off study due to an AE was 8% (AA) versus 6% (P). **Conclusions:** The updated IA3 of COU-AA-302 in pts without prior chemotherapy confirms the delay in progression and prolongation of life with a favorable safety profile including pts treated for ≥ 24 mos with AA + P or P. Clinical trial information: **NCT00887198**.

	AA + P				P			
		Grade (%)				Grade (%)		
Exposure time, mos	N	All	1 / 2	3 / 4	N	All	1 / 2	3 / 4
Cardiac disorders								
< 3	542	6	5	1	540	5	4	1
12–15	302	5	3	1	184	8	7	1
≥ 24	154	7	6	1	76	9	9	0
Fatigue								
< 3	542	19	18	1	540	17	16	1
12–15	302	8	7	1	184	8	8	0
≥ 24	154	8	8	0	76	4	4	0
Hyperglycemia								
< 3	542	4	2	1	540	4	4	1
12–15	302	3	2	0	184	3	2	1
≥ 24	154	1	1	0	76	4	1	3
Hypertension								
< 3	542	8	7	1	540	8	6	2
12–15	302	5	4	1	184	3	2	2
≥ 24	154	2	1	1	76	1	1	0
Osteoporosis								
< 3	542	1	1	0	540	2	1	0
12–15	302	1	0	0	184	2	2	0
≥ 24	154	3	3	0	76	4	4	0
Weight gain								
< 3	542	2	1	0	540	2	2	0
12–15	302	1	1	0	184	0	0	0
≥ 24	154	2	2	0	76	1	1	0

J Clin Oncol 31, 2013 (suppl; abstr 3)

Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomized trial of the Gynecologic Oncology Group.

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Abstract

Background: Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab (B), a humanized anti-VEGF monoclonal antibody, has shown single-agent activity in pretreated recurrent disease. We aimed to evaluate B in chemotherapy (CTX)-naive recurrent/persistent/metastatic cervical cancer. **Methods:** Using a 2x2 factorial design, patients were randomly assigned to CTX with or without B 15 mg/kg. The CTX regimens included cisplatin 50 mg/m^2 plus paclitaxel 135-175 mg/m^2 and topotecan 0.75 mg/m^2 d1-3 plus paclitaxel 175 mg/m^{2}d1. Cycles were repeated every 21 days until disease progression, unacceptable toxicity, or complete response. Overall survival (OS) was the primary endpoint with a reduction in the hazard of death by 30% using anti-VEGF therapy considered important (90% power, 1-sided alpha=2.5%). Final analysis was planned when 346 deaths were observed. **Results:** 452 patients were accrued from 4/6/09 to 1/3/12. The scheduled interim analysis occurred after 174 patients had died and showed that the topotecan-paclitaxel backbone was not superior to the cisplatin-paclitaxel backbone. A second interim analysis was conducted after 271 deaths. A total of 225 patients received CTX alone and 227 patients received CTX plus B. The randomized treatment groups were similar with regard to age, histology, performance status, previous platinum as a radiosensitizer, and recurrence, persistence, or advanced disease. The B-to-no-B hazard ratio (HR) of death was 0.71 (97.6% CI 0.54-0.95; 1-sided p=0.0035). Median survival was 17 m (CTX plus B) and 13.3 m (CTX alone). The RR were 48% (CTX plus B) and 36% (CTX alone) (p=0.0078). Treatment with B was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%). **Conclusions:** For the first time a targeted agent significantly improved OS in gynecologic cancer. The second interim analysis crossed the boundary for efficacy, warranting early release of this information. The nearly 4-month increase in median OS with the addition of B to CTX in women with recurrent cervical cancer is considered to be clinically significant. Clinical trial information: **NCT00803062**.

J Clin Oncol 31, 2013 (suppl; abstr 5500)

Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer: Results from the MRC CHORUS trial.

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Abstract

Background: First line treatment of advanced ovarian cancer (OC) is accepted to be primary surgery (PS) followed by adjuvant platinum-based chemotherapy (P-CT). However, the EORTC55971 trial suggested neoadjuvant chemotherapy (NACT) is an alternative, showing increased optimal debulking rates and reduced surgical complications without detriment to survival. CHORUS (CRUK 07/009) is the 2nd phase III randomized controlled trial to investigate timing of initial surgery in OC. **Methods:** Patients (pts) with clinical FIGO stage III-IV OC (pelvic mass, extrapelvic metastases and CA125/CEA ratio .25) were randomized to standard treatment (PS followed by 6 cycles P-CT) or NACT (3 cycles P-CT either side of surgery). CHORUS was designed to demonstrate non-inferiority of NACT, excluding a 6% absolute detriment in 3yr survival from 50% expected with PS (1-sided alpha 10%). Primary outcome was overall survival (OS) and secondary outcomes were progression free survival (PFS), toxicity and quality of life. **Results:** 550 women (276 PS, 274 NACT) were randomized from 74 centres (72 UK, 2 NZ) between Mar 2004 and Aug 2010. Baseline characteristics were well balanced: median age 65yrs, median tumor size 80mm, 25% FIGO stage IV, 19% WHO PS 2. Median follow-up was 3yrs, 410 pts have died. Treatment data are summarized in the Table. 3yr survival in the control arm was 32%. Intention to treat analysis showed a median OS of 22.8 months for PS vs 24.5 months for NACT (hazard ratio (HR) 0.87 in favor of NACT, 80% CI 0.76 – 0.98) and median PFS of 10.2 vs 11.7 months (HR 0.91, 0.81 – 1.02). OS results represent a 5% absolute benefit in 3yr survival for NACT to 37% and the upper 80% CI allows us to exclude a survival benefit for PS. **Conclusions:** NACT was associated with increased optimal debulking, less early mortality and similar survival in this poor prognosis group. CHORUS results are consistent with EORTC55971 and strengthen evidence that NACT is a viable alternative to PS. Clinical trial information: **ISRCTN74802813**.

	PS (n=276)	NACT (n=274)
Treatment received	Surgery 90% P-CT 76%	P-CT 92% Surgery 78%
Surgery + 6 cycles P-CT	64%	68%
Postop AEs (grade 3+)		
Infection	6%	3%
Hemorrhage	3%	7%
VTE	2%	0%
Discharge within 14 days	74%	92%
Debulked to 0cm residual disease	15%	35%
12-month survival rate	70%	76%

J Clin Oncol 31, 2013 (suppl; abstr 5505)

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm).

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Abstract

Background: Previously, we reported that maintenance treatment with the oral PARP inhibitor olaparib (400 mg bid) led to a significant PFS improvement vs placebo in patients (pts) with platinum-sensitive relapsed SOC (Ledermann et al NEJM2012). A preplanned subgroup analysis from this randomized, double-blind Phase II trial (NCT00753545) suggested that olaparib may lead to a greater PFS, and an OS, benefit in pts with a known germline BRCAm (gBRCAm). Since gBRCA wild-type (gBRCAwt) pts may develop somatic tumor (t)BRCAm, efficacy analyses were performed for all pts with BRCAm. **Methods:** gBRCAm status was determined retrospectively for all consenting pts (n = 166) using blood samples taken before randomization. tBRCAm status was determined from archival tumor samples of 196 pts. We analyzed PFS/OS by gBRCAm and total BRCAm status. Preliminary data are reported. **Results:** gBRCA status was known for 218/265 pts (gBRCAm, 96; gBRCAwt, 122). Including tBRCAm, 136 pts had a BRCAm (BRCAwt, 116). gBRCAm pts had the greatest PFS benefit with olaparib maintenance vs placebo (median: 11.2 vs 4.1 months [m]; HR, 0.17; 95% CI 0.09-0.32; P<0.001) and a significant QoL improvement, as measured with Trial Outcome Index (OR, 4.08; 95% CI 1.11-19.85; p = 0.03). The PFS benefit was consistent when tBRCAm pts were included (median: 11.2 vs 4.3 m; HR, 0.19; 95% CI 0.11-0.32; p <0.0001). In an interim analysis of OS (58% maturity), a comparison of olaparib vs placebo in the overall population led to a HR of 0.88 (95% CI 0.64-1.21) with medians of 29.8 vs 27.8 m, respectively. Although HRs from the gBRCAm and gBRCAwt subgroups were similar (0.85 and 0.84, respectively), 13/37 gBRCAm placebo pts received a subsequent PARP inhibitor, confounding the OS data in this subgroup. The analysis of all BRCAm pts was less confounded and resulted in an OS HR of 0.74 (95% CI 0.46-1.19; median: 34.9 vs 31.9 m). 19 pts have received olaparib for >3 years. Olaparib tolerability was similar in BRCAm pts and the overall population. **Conclusions:** Olaparib maintenance treatment led to the greatest clinical benefit in pts with a BRCAm. These compelling data warrant confirmation in phase III trials. Clinical trial information: **NCT00753545**.

J Clin Oncol 31, 2013 (suppl; abstr LBA5501)

A randomized multicenter phase III study comparing weekly versus every 3 weeks carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicenter Italian Trials in Ovarian Cancer (MITO-7)—European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10) and Gynecologic Cancer Intergroup (GCIG) trial.

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Abstract

Background: Three-weekly (3w) CP is standard first-line chemotherapy for AOC pts. Weekly (w) P combined with 3w C prolonged PFS and OS in a JGOG phase III trial. MITO-7 is an academic randomized phase III study, comparing 3w vs. w CP. **Methods:** AOC chemonaive pts, stage IC-IV, age≤75, ECOG PS≤2, were randomized to 3wCP (C AUC6 + P 175mg/m², d1q21) for 6 cycles or to wCP (C AUC2 + P 60mg/m²) for 18 administrations. Coprimary endpoints were PFS and quality of life (QoL), measured by FACT-O and FACT/GOG-Ntx. With 80% power in detecting HR of 0.75, 2-sided α=0.05, 383 events were needed for PFS analysis. The arms were compared with a log-rank test and in a Cox model adjusted by stage, PS, residual disease, age and size of institution, following intention-to-treat. QoL was measured at baseline and weekly for 9 wks. Interaction between arm and QoL time was tested in a linear mixed model. Toxicity was coded by NCI-CTCAE v3.0. **Results:** 822 pts were enrolled by MITO, MANGO, and GINECO. Median age was 60; stage III (66%) and IV (18%) were prevalent. As of March 18, 2013, with median follow-up 20 months, 410 PFS events were recorded. Median PFS was 18.8 months with wCP and 16.5 months with 3wCP (HR 0.88, 95%CI 0.72-1.06, p=0.18). Lack of significant difference was confirmed (HR 0.87, 95%CI 0.71-1.05) in Cox model. For all scores, QoL course was significantly different between arms (p<0.0001). With 3wCP, QoL scores clearly worsened after each chemotherapy course (weeks 1, 4, 7), whilst with wCP, after a small and transient worsening at week 1, scores remained stable. Considering severe grades (≥3), wCP produced significantly less neutropenia, febrile neutropenia, thrombocytopenia, renal toxicity, and neuropathy. **Conclusions:** Compared to standard CP every 3 weeks, weekly CP did not demonstrate a significant benefit in PFS, but was associated with better QoL and toxicity. Clinical trial information: **NCT00660842**.

J Clin Oncol 31, 2013 (suppl; abstr LBA5503)

Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): Results of an international Intergroup trial (AGO-OVAR16).

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Abstract

Background: Pazopanib is an oral, multikinase inhibitor of VEGFR-1, -2, -3, PDGFR-α and -β, and c-Kit. Preclinical and clinical studies support VEGF(R) and PDGF(R) as targets for AEOC treatment. This study evaluated the efficacy, safety, and tolerability of pazopanib maintenance therapy in patients who have not progressed after first-line chemotherapy for AEOC. **Methods:** Patients with histologically confirmed AEOC, FIGO II-IV, and no evidence of progression after surgery and ≥ 5 cycles of platinum-taxane chemotherapy were randomized 1:1 to receive 800 mg pazopanib once daily or placebo for up to 24 months. Primary endpoint was progression-free survival (PFS) by RECIST. Secondary endpoints included overall survival, PFS by GCIG criteria, safety, and quality of life. **Results:** Most of the 940 randomized patients had stage III/IV disease (91%) at initial diagnosis, and no residual disease after surgery (58%). The median time from diagnosis to randomization was 7.1 months in the placebo arm and 7.0 months in the pazopanib arm. The median follow-up was 24 months. Patients in the pazopanib arm had a prolonged PFS vs placebo (HR = 0.766; 95% CI: 0.64-0.91; p = 0.0021; medians 17.9 vs 12.3 months, respectively). Sensitivity and subgroup analyses of PFS, and analysis of PFS by GCIG criteria, were consistent with the primary analysis. The first interim analysis for OS (only 189 OS events = 20.1% of population) showed no difference between arms. Pazopanib mean exposure was shorter vs placebo (8.9 vs 11.7 months). Pazopanib treatment was associated with a higher incidence of adverse events (AEs) and serious AEs (26% vs 11%) vs placebo. The most common AEs were hypertension, diarrhea, nausea, headache, fatigue, and neutropenia. Fatal SAEs were reported in three patients on pazopanib and one patient on placebo. **Conclusions:** Pazopanib maintenance therapy provided a statistically significant and clinically meaningful PFS benefit in patients with AEOC; OS data are not mature. The safety profile of pazopanib in this setting was consistent with its established profile. Clinical trial information: **NCT00866697**.

J Clin Oncol 31, 2013 (suppl; abstr 4)

Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial.

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Abstract

Background: Sorafenib, an orally active inhibitor of VEGFR1-3 and Raf kinases, has shown promising clinical activity in single-arm phase II studies in radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). The double-blind, randomized, multicenter phase III DECISION trial examined sorafenib efficacy and safety vs placebo in patients with progressive RAI-refractory DTC. Methods: Patients with locally advanced/metastatic RAI-refractory DTC who progressed in the preceding 14 months were randomized 1:1 to sorafenib 400 mg bid po or placebo. Placebo patients were allowed to receive sorafenib open-label upon progression. The primary endpoint was progression-free survival (PFS) assessed every 8 wks by independent radiologic review using modified RECIST 1.0 and analyzed by stratified log-rank statistics at $\alpha = 0.01$ (one-sided). Secondary endpoints included overall survival (OS), response rate (RR; complete + partial response [PR]), and safety. Results: A total of 417 patients were randomized (207 to sorafenib and 210 to placebo); median age 63 yr, 52% female. Tumor histology by independent assessment was 57% papillary, 25% follicular, and 10% poorly differentiated. 96% of patients had metastatic disease; the most common target lesions were lung (71%), lymph node (40%), and bone (14%). The primary endpoint was met: median PFS 10.8 months (sorafenib) vs 5.8 months (placebo); HR 0.58, 95% CI 0.45–0.75, p<0.0001. Median OS has not been reached in either arm; 70% of placebo patients started open-label sorafenib. RR (all PRs) in the sorafenib vs placebo arms was 12.2% and 0.5% (p<0.0001) and stable disease ≥ 6 months was 42% and 33%, respectively. The most common any-grade treatment-emergent adverse events in the sorafenib arm included hand–foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, weight loss and hypertension. One death in each arm was attributed to study drug. Conclusions: Sorafenib significantly improved PFS compared with placebo in patients with progressive RAI-refractory DTC. Tolerability was consistent with the known sorafenib safety profile. Clinical trial information: NCT00895674.

J Clin Oncol 31, 2013 (suppl; abstr 6009)

The Cancer Genome Atlas: Integrated analysis of genome alterations in squamous cell carcinoma of the head and neck.

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is a leading cause of cancer death in worldwide. **Methods:** The Cancer Genome Atlas (TCGA) is conducting DNA, RNA and miRNA sequencing along with DNA copy number profiling, quantification of mRNA expression, promoter methylation, and reverse-phase protein arrays on surgically resected samples from previously untreated patients with HNSCC. We report for the first time the integrated genomic alterations for 279 HNSCC patients. **Results:** The demographics of 279 patients enrolled in the study show a median age of 61 years (range: 19-90); 27% female, and history of tobacco smoking in 80%. Over 30 sites of significant somatic copy number alteration were identified as well as 15 significantly mutated genes at the false fiscovery rate of <0.01, including: CDKN2A, TP53, PIK3CA, FAT1, MLL2, TGFBR2, HLA-A, NOTCH1, HRAS, NFE2L2, and CASP8. Evidence of the human papilloma virus (HPV) was observed by sequencing in up to 25% of samples. Integrated genomics data supported expected patterns including the predominant role of HPV type 16 infection in nonsmoking patients with tumors of the oropharynx which are wild-type for the tumor suppressor genes p16, Rb, and p53. In addition, striking atypical cases and viral infections will be presented as well as novel anti-correlation of HPV infection with focal copy number alterations including EGFR amplification and chromosome 11q. By contrast co-occurrence of HPV with focal deletions of TRAF3 and mutations of the oncogene PIK3CA will be described. Integrated tumor subtypes defined by gene expression, methylation, and miRNA will be presented in conjunction with associated mutations exclusive to tumor subtypes. For example, alterations of the "antioxidant response elements" transcription activators NFE2L2 and KEAP1 will be documented in association with the "classical" expression subtype of HNSCC, as has been shown in lung squamous cell carcinoma. By contrast, co-occurrence of CASP8 and HRAS will be documented in the "Basal" subtype. **Conclusions:** While, HNSCC is a heterogeneous tumor, coordinated tumor alterations are observed, including potentially targetable genes and pathways. Results presented on behalf of TCGA.

J Clin Oncol 31, 2013 (suppl; abstr 6500)

Randomized trial of a web-based intervention to address barriers to clinical trials.

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Abstract:

Background: Cancer patients (pts) have knowledge and attitudinal barriers to participation in clinical trials (CT). We developed PRE-ACT (Preparatory Education About Clinical Trials), a tailored, interactive, web-based intervention to address these barriers and improve preparation for consideration of CT as a treatment option. **Methods:** We conducted a prospective, randomized, multicenter, phase III clinical trial of PRE-ACT vs. control (general text about CT excerpted from NCI materials). All assessments and interventions were conducted online. Cancer pts >18 years old were enrolled before initial oncologist consultation. Pts completed a baseline assessment including CT knowledge (19-item); CT attitudes (28-item); preparation for decision making (10-item); and validated measures of preferences for shared decision making and quality/length of life. PRE-ACT pts received a summary of their preferences and a list of their top CT barriers. Based on ranking of individual barriers, pts were presented with a video library of 30-90 second clips addressing their top barriers (10 maximum). After the educational intervention a follow up survey reassessed CT barriers and preparation. **Results:** 1255 pts were randomized; median age 59 (range 20-88); 58% female; 12% non-white / 2% Hispanic; 76.4% some college education. 1081 pts completed baseline and post-intervention assessments. The control and PRE-ACT groups both had improved knowledge, reduced attitudinal barriers, and improved preparation ($p<.0001$ for all comparisons). PRE-ACT was more effective than control in improving knowledge ($p=.0006$) and attitudes ($p<.0001$). Furthermore, pts in the PRE-ACT arm were more satisfied with the amount ($p=.002$) and format (<.0001) of information, and felt more prepared to consider CT ($p=.0003$). **Conclusions:** This large-scale randomized trial of a tailored, web-based, video intervention demonstrates that educational information delivered online before the oncologist visit can significantly reduce knowledge barriers and attitudinal barriers and improve preparation for consideration of clinical trials. Both text and PRE-ACT are effective, with greater improvements and satisfaction in the PRE-ACT group. Clinical trial information: **NCT00750009**.

J Clin Oncol 31, 2013 (suppl; abstr 6501)

Participation in cancer pharmacogenomic studies in 8,456 patients registered to Cancer and Leukemia Group B (Alliance) clinical trials.

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Abstract

Background: Clinically annotated specimens from cancer clinical trial participants offer an opportunity for discovery and validation of pharmacogenomic findings. This observational study assessed patient (pt) and institutional factors that may contribute to participation in pharmacogenomic components of prospective cancer clinical trials. No trial in the study used pharmacogenomic results to guide therapy, but germline DNA was collected from consenting pts for future study of potential heritable variations associated with clinical outcome. **Methods:** Pt demographic data (age, sex, diagnosis, self-reported race) and institutional characteristics (CALGB/CTSU site, diversity, accrual rate) were evaluated for 8546 pts enrolled in 7 CALGB phase III trials with a pharmacogenomic component. Participation was defined as pt consent specific to this component documented in the CALGB database. **Results:** Most pts (81%) enrolled on the clinical trials consented to participate in the pharmacogenomic component. In a multivariable analysis, site (CALGB vs CTSU), self-reported race (non-white vs white) and institutional diversity (% minority cancer pts on national trials) were significantly associated with participation. Pts from CALGB sites were more likely to participate than pts at CTSU sites (OR 2.09, CI 1.60-2.73, p<0.0001). Non-white pts were less likely to participate than white pts (OR 0.48, CI 0.41-0.56, p<0.0001). A significant interaction between site and race was observed (OR 0.41, CI 0.37-0.47, p<0.0001). As institutional diversity increased, likelihood of participation in the pharmacogenomic component decreased for both white (p=0.0001) and non-white pts (p=0.054). **Conclusions:** Pharmacogenomic studies are achievable in the context of multicenter cancer clinical trials, but optimization of pt and institution participation is needed. Institutional factorsappear to be more important than pt demographics. To promote equitable pt benefit, prospective studies should be conducted to understand barriers and incentives to participation in pharmacogenomic research at the patient, clinician and institutional levels.

J Clin Oncol 31, 2013 (suppl; abstr 6509)

Off-label and compendia use of chemotherapy in patients with metastatic cancer.

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Abstract

Background: In 2012, ASCO Identified opportunities to improve the quality and value of cancer care by reducing inappropriate and/or prolonged use of chemotherapy The NCCN compendium is recognized as an authoritative reference for insurance coverage for drug indications without FDA approval. We evaluated FDA-approved, compendia and unapproved use of chemotherapy. **Methods:** We useddata from the SEER-Medicare database to identify patients with metastatic cancer who received chemotherapy. For each tumor, drugs with >3 claims were identified. Each drug was classified as having an FDA-approved indication, an indication based on NCCN compendia guidelines or neither of these. The number of claims for each drug was calculated. Logistic regression was used to assess the factors that **Results:** Between 1998-2007, 37,351 subjects were identified as having received chemotherapy; of these, 24,876 (66.6%) received only FDA approved drugs, and 12,475 (33.4%) received at least one unapproved drug. Of those who received an unapproved drug, 8,669 (69%) received a drug with a compendia listing. Therefore, of the total population, 10% received a drug that was neither FDA nor compendia approved. The mean number of unapproved claims was 10.3 (SD=15.2) and the mean number of drugs was 1.3. Unapproved use was highest in subjects with prostate and lowest in patients with colon cancer. In a multivariate analysis, unapproved use decreased with increasing age and >2 comorbid conditions. Compared to prostate cancer, the odds of having an unapproved drug was lower for breast (OR=0.27), colon (OR=0.08), lung (OR=0.65), ovary (OR=0.38), uterus (OR=0.49) and myeloma (OR=0.60). No patients with colon or prostate cancer received compendia-approved drugs. Over 90% of unapproved use for breast, ovary and lung cancer were compendia-approved. Costs associated with unapproved/compendia use will be presented. **Conclusions:** A large fraction of patients who use chemotherapy receive FDA-unapproved drugs; however, the majority of those drugs are acknowledged by NCCN. A better understanding of the costs and benefits of compendia-approved drugs is warranted to reduce the costs of cancer care.

J Clin Oncol 31, 2013 (suppl; abstr 6510)

Impact of oncology drug shortages

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Abstract

Background: Drug shortages of common chemotherapeutics have been reported. What is the prevalence and consequence of these shortages? **Methods:** Between 9/2012 and 1/2013, a self-administered questionnaire was sent to a random sample of 455 board-certified U.S. oncologists selected from the American Society of Clinical Oncology directory to assess the prevalence of shortages and impact on therapeutic decision-making. 245 responses were received (response rate 55%), of whom 210 were practicing medical oncologists/hematologists. **Results:** Due to drug shortages in the prior 6 months, 92% (163) of oncologists reported that their patients' treatment was affected and 83% (174) were unable to prescribe standard chemotherapy. The five chemotherapy agents most commonly reported in shortage were: leucovorin (68%), liposomal doxorubicin (63%), 5-FU (19%), bleomycin (18%), and cytarabine (17%). Physicians adapted in many ways. 38% of the time, oncologists substituted more expensive branded drugs for those in shortage, such as levoleucovorin for leucovorin. Nearly 13% of the time, shortages prevented enrollment, delayed administration of a study drug, or suspended involvement of patients on clinical trials. Despite the prevalence of scarcities, 70% (146) of oncologists reported their cancer centers or practices lacked formal guidance for allocation decisions. **Conclusions:** Drug shortages in oncology are very common, compromise the delivery of standard care, impede research, and lead to higher costs by using branded drugs instead of generics. Oncologists also seem to lack formal guidance on how to address these shortages.

Adaptation to drug shortage	Number of oncologists reporting modification (n=173)
Switch regimens	79%
Substitute drug partway through therapy	77%
Delay treatment	43%
Choose among patients	37%
Omit doses	29%
Reduce doses	20%
Refer patients to another practice	17%

J Clin Oncol 31, 2013 (suppl; abstr 7001)

Impact of baseline mutations on response to ponatinib and end of treatment mutation analysis in patients with chronic myeloid leukemia.

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Abstract

Background: BCR-ABL kinase domain mutations frequently cause tyrosine kinase inhibitor (TKI) failure in chronic myeloid leukemia (CML). Ponatinib, a potent oral pan-BCR-ABL TKI, has shown preclinical activity against all single mutants tested, including T315I. The impact of baseline (BL) mutations on response to ponatinib (45 mg once daily) and end of treatment (EOT) mutations in pts discontinuing treatment were evaluated in the phase II PACE trial. **Methods:** Heavily pretreated chronic phase (CP) CML pts (93% received ≥2 prior TKIs, 60% ≥3) resistant or intolerant to dasatinib or nilotinib (N=203) or with T315I confirmed at BL (N=64) were enrolled. The primary endpt was major cytogenetic response (MCyR). Min follow up at analysis (9 Nov 2012) was 12 mos (median 15 [0.1-25]). Sanger sequencing was done at one central laboratory. **Results:** At BL, no mutations were detected in 51% of pts, 1 mutation in 39%, and ≥2 mutations in 10%; 26 unique mutations were observed. Responses were observed regardless of BL mutation status. MCyR rates were: 56% overall, 49% in pts with no mutations, 64% 1 mutation, 62% ≥2 mutations; 57% in pts with mutation(s) other than T315I, 74% T315I only, 57% T315I + other mutation(s). Responses were seen against each of the 15 mutations present in >1 pt at BL, including T315I, E255V, F359V, Y253H. 99 pts discontinued, 56 had EOT mutations assessed. 5 pts lost a mutation, 46 had no change, 5 gained mutations (Table). 11 pts lost MCyR (none with T315I); of the 6 discontinuing, 4 had EOT mutations assessed and no changes from BL were seen. **Conclusions:** Responses to ponatinib were observed regardless of BL mutation status. No single mutation conferring resistance to ponatinib in CP-CML has been observed to date. Data with a minimum follow up of 18 mos, including pts with advanced disease, will be presented. Clinical trial information: **NCT01207440.**

Relevant mutation history	BL mutation(s)	EOT mutation(s)[a]
E255V	None	E255V [10%][b]
T315I	None	T315I/F359V [100%/90%][c]
T315I	T315I	T315I/M351T [100%/40%][b]

Relevant mutation history	BL mutation(s)	EOT mutation(s)[a]
T315I	F359V	T315I [100%][d]
Y253H	V299L/F359V	Y253H/F359V [100%/100%][d]

aGained mutation = bold; % of transcripts with mutation = [%]. Reason for discontinuation: bOther. cAE. dProgressive disease.

J Clin Oncol 31, 2013 (suppl; abstr 7002)

A randomized study of lenalidomide (LEN) with or without EPO in RBC transfusion dependent (TD) IPSS low and int-1 (lower risk) myelodysplastic syndromes (MDS) without del 5q resistant to EPO.

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Abstract

Background: ESAs, the first line treatments of anemia in non del 5q lower risk MDS, yield only 40-50% responses. LEN gives RBC transfusion independence (TI) in about 25% of ESA resistant (or relapsing) TD lower risk MDS without del 5q (Raza, Blood, 2008), and a gene expression signature can predict response (Ebert, Plos Med 2008). We randomized in this patient population LEN alone and LEN1EPO. **Methods:** In this prospective multicenter open-label phase II study (NCT01718379), lower risk MDS patients without del 5q, with TD ($4 RBC units during the previous 8 weeks (w)) with ESA resistance or relapse after a response were randomized between LEN alone, 10mg/d x 21 d/4 w (L arm) or LEN (same schedule) 1 EPO beta, 60 000 U/w (LE arm). The primary endpoint was erythroid response (HI-E, IWG 2006 criteria) after 4 treatment cycles. Secondary objectives included identification of biomarkers of response. **Results:** Between July 2010 and June 2012, 132 patients (pts, 66 / arm), median age 73 (range 46-88), M/F: 88/44 were enrolled. Median TD was 6 RBC units/8w (range 2-18). IPSS was Low in 45% and Int-1 in 55% pts. Pretreatment characteristics did not differ between the 2 groups. All but 3 pts, who withdrew consent (2L11LE), were evaluable for response. In this ITT population, HI-E was obtained in 15 pts (23.4%) in L arm and 26 (40.0%) in LE arm (RR5 1.7, p5 0.043, chi2 test), and TI in 9 (14.1%) versus 16 (24.6%) pts (RR51.7, p5 0.13). In the 99 pts who completed 4 treatment cycles, 41 achieved HI-E, including 15/49 (30.6%) in L arm versus 26/50 (52.0%) in LE arm (p5 0.03), and TI in 9 (18.4%) versus 16 (32.0%) pts (RR5 1.7, p50.12). Side effects (cytopenias and 1 DVT/arm) were similar in the 2 arms. A 29-gene expression profile signature predicting HI-E to L or LE, different from that previously published, was identified and a polymorphism in the CRBN gene (Kosmider, submitted) was significantly associated with HI-E in the entire cohort (p50.034). **Conclusions:** LEN 1 EPO yielded a significantly better erythroid response than LEN alone in lower risk MDS patients with anemia resistant to ESA alone. A gene expression signature and a CRBN gene polymorphism correlated with the erythroid response. Clinical trial information: **NCT01718379**.

J Clin Oncol 31, 2013 (suppl; abstr 7004)

Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial.

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Abstract

Background: Chemoimmunotherapy (CIT) is standard of care in young and physically fit patients (pts) with CLL. Development of CIT for older and less fit CLL pts is ongoing, but data from phase III trials are sparse. CLL11 is the largest trial to evaluate three treatments in previously untreated CLL pts with comorbidities: Clb alone, GA101 + Clb (GClb), R + Clb (RClb). The final analysis of CLL11 stage 1 efficacy and safety results is presented here. **Methods:** Treatment-naïve CLL pts with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min were eligible. Pts received Clb alone (0.5 mg/kg po d1, d15 q28 days, 6 cycles), GClb (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1, 1000 mg d1 cycles 2-6), or RClb (375 mg/m2 iv d1 cycle 1, 500 mg/m2 d1 cycles 2-6). Primary endpoint was investigator-assessed progression-free survival (PFS). **Results:** Median age, CIRS score, and CrCl at baseline were 73 years, 8, and 61.1 mL/min for stage 1a (Clb vs GClb, 356 pts) and 73 years, 8, and 62.1 mL/min for stage 1b (Clb vs RClb, 351 pts, triggered by a different event rate). Key efficacy and safety results are shown in the Table.Grade 3-4 infusion-related reactions with GClb occurred at first infusion only. Management required splitting the first dose over 2 days. **Conclusions:** CIT with GClb or RClb significantly prolongs PFS vs Clb alone. The results demonstrate that GClb and RClb are very active in CLL and superior treament options in this population. GClb vs RClb will be compared in stage 2 analysis with more follow-up available. Clinical trial information: **NCT01010061**.

	Stage 1a		Stage 1b	
Total stage 1 N=589	**Clb N=118**	**GClb N=238**	**Clb N=118**	**RClb N=233**
Median observation time, months	13.6	14.5	14.2	15.3
Overall response rate, %	30.2	75.5	30.0	65.9
Complete responses, %	0	22.2	0	8.3
Median PFS, months	10.9	23.0*	10.8	15.7
HR, CI, p	0.14, 0.09-0.21, <.0001		0.32, 0.24-0.44, <.0001	
Grade 3-5 adverse events during treatment, %	41	67	41	46
Infusion-related reaction	-	21	-	4
Neutropenia	15	34	15	25
Infections	11	6	11	8

* Still immature, < 20% at risk at time of median.

J Clin Oncol 31, 2013 (suppl; abstr 7005)

A phase II study of the selective phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib (GS-1101) in combination with rituximab (R) in treatment-naive patients (pts) ≥65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

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Abstract

Background: PI3K-delta is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective oral inhibitor of PI3Kδ. When combined with R in 19 relapsed/refractory patients with CLL, the ORR was 78% (Coutre, ASH 2012). **Methods:** Treatment-naive pts ≥65 yrs with CLL or SLL were treated with R 375 mg/m2 weekly x 8 and idelalisib 150 mg bid continuously for 48 weeks (primary study). Pts completing 48 wks w/o progression could continue to receive idelalisib on an extension study. Responses and progression were based on investigator assessment using IWCLL criteria (Hallek, Blood 2008). **Results:** Data is presented here on the first 50 of 64 pts enrolled, 48 CLL/2 SLL, median age 71 yrs (range: 65-89), M/F 70/30 (%), Rai stage III/IV 10/32 (%), nodes ≥5 cm in 16%, WHO 0/1/2 in 34/64/2 (%); del(17p) in 6 pts and del(11q) in 13 pts. 32 pts completed 48 wks (18 discontinued, 11 due to AE, 4 due to death and 3 other); 30 pts entered the extension study and 26 remain on treatment. The median time on treatment was 16 months (range 0.8-27.5). The ORRwas 96% with 4% nonevaluable; median time to response was 1.9 mos (range 1.0-6.5). There have been no on-study relapses. The Kaplan-Meier estimated PFS is 91% at 24 mos. Of note, 6/6 pts with del(17p) responded (1 CR, 5 PR) and 3 remain on treatment for more than 21 months. 13/14 (93%) pts with thrombocytopenia and 12/12 (100%) pts with anemia at baseline responded. Of 20 pts with B symptoms at baseline, 13 (65%) were asymptomatic by 8 wks. Most frequent AEs (total%/ ≥G3%) were diarrhea (including reported as colitis) (46/16), pyrexia (42/4), chills (34/0), fatigue (34/2), rash (34/10), pneumonia (30/20) and nausea (28/0). Elevated ALT/AST was seen in 60%, Gr ≥3 in 22%. **Conclusions:** Idelalisib + R is highly active, resulting in durable disease control in treatment-naïve older pts with CLL. These results support the further development of idelalisib in frontline CLL. Clinical trial information: **NCT01203930**.

J Clin Oncol 31, 2013 (suppl; abstr 7500)

START: A phase III study of L-BLP25 cancer immunotherapy for unresectable stage III non-small cell lung cancer.

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Abstract

Background: L-BLP25 is a MUC1 antigen specific cancer immunotherapy. We report results from the phase III START study of L-BLP25 in patients (pts) not progressing after primary chemoradiotherapy (CRT) for stage III NSCLC. **Methods:** From Jan 2007 to Nov 2011, 1513 pts with unresectable stage III NSCLC that did not progress after CRT (platinum based chemo and ≥50 Gy) were randomized (2:1; double-blind) to L-BLP25 (806 µg lipopeptide) or placebo (PBO) SC weekly x 8 then Q6 weeks until disease progression or withdrawal. Cyclophosphamide 300 mg/m2 x 1 or saline was given 3 days prior to first L-BLP25/PBO dose. Primary endpoint was overall survival (OS). **Results:** The primary analysis population (n=1239) was defined prospectively to try to account for a clinical hold by excluding pts randomized 6 months (m) before the hold. Arms were balanced for baseline characteristics. Median age was 61 y; 38.2% had stage IIIA and 61.3% IIIB; 65% had concurrent and 35% sequential CRT. Median OS was 25.6 m with L-BLP25 vs. 22.3 m with PBO (adjusted HR 0.88, 95% CI 0.75-1.03, p=0.123). Secondary endpoints time-to-progression and time-to-symptom-progression support consistency of **Results:** HR 0.87 (95% CI 0.75-1.00, p=0.053) and 0.85 (95% CI 0.73-0.98, p=0.023). In predefined subgroup analyses, pts with concurrent CRT (n=806) had median OS of 30.8 m (L-BLP25) vs. 20.6 m (PBO; HR 0.78, 95% CI 0.64-0.95, p=0.016), while median OS with sequential CRT was 19.4 m (L-BLP25) vs. 24.6 m (PBO; HR 1.12, 95% CI 0.87-1.44, p=0.38; interaction p=0.032, Cox PH model). Sensitivity analyses revealed that there was no OS benefit in pts randomized 6 m before the hold (HR 1.09, CI 0.75-1.56, p=0.663). LEBLP25 was well tolerated with no safety concerns identified and no emergent evidence of immune related adverse events. **Conclusions:** L-BLP25 maintenance therapy in stage III NSCLC was well tolerated, but did not significantly prolong OS. Sensitivity analyses showed a smaller treatment effect due to the clinical hold, suggesting that longer uninterrupted treatment with L-BLP25 is required. Clinically meaningful prolongation of OS was observed in the predefined subgroup of pts with primary concurrent CRT. Clinical trial information: **NCT00409188**.

J Clin Oncol 31, 2013 (suppl; abstr 7501)

A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.

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Abstract

Background: The first objective of RTOG 0617 was to compare the overall survival(OS) of patients(pts) treated with standard-dose(SD)(60Gy) versus high-dose(HD)(74Gy) radiotherapy with concurrent chemotherapy(CT). **Methods:** This Phase III Intergroup trial randomized 464 pts with Stage III NSCLC to the SD(60Gy) vs. HD(74Gy) arms prior to closure of the HD arm. Concurrent CT included weekly paclitaxel(45 mg/m2) and carboplatin(AUC=2). Pts randomized to cetuximab received a 400 mg/m2 loading dose on Day 1 followed by weekly doses of 250 mg/m2. All pts were to receive consolidation CT. We are reporting the final results on radiation dose. **Results:** 464 pts were accrued prior to closure of the HD arm in 6/11, of which 419 were eligible for analysis. Median follow up was 17.2 months. There were 2 and 10 grade 5 treatment-related adverse events(AEs) on the SD and HD arms, respectively. Grade 3+AEs were 74.2% and 78.2% on SD and HD arms, respectively (p=0.34). The median survival times and 18-month OS rates for the SD and HD arms were 28.7 vs 19.5 months, and 66.9% vs 53.9% respectively (p=0.0007). The primary cause of death was lung cancer (72.2% vs 73.5%)(p=0.84). Local failure rates at 18 months were 25.1% vs 34.3% for SD and HD patients, respectively(p=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44%(p=0.04) and 42.4% vs 47.8%(p=0.16) for SD and HD arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy. **Conclusions:** In this setting of chemoradiation for locally-advanced Stage III NSCLC, 60 Gy is superior to 74 Gy in terms of OS and local-regional control. The effect of the anti-EGFR antibody (cetuximab) awaits further follow up. This project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC U24 CA 81647 from the National Cancer Institute (NCI) and Eli Lilly and Company. Clinical trial information: **NCT00533949.**

J Clin Oncol 31, 2013 (suppl; abstr 7503)

Neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIA/N2 non-small cell lung cancer (NSCLC): A randomized phase III trial by the Swiss Group for Clinical Cancer Research (SAKK trial 16/00).

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Abstract

Background: For stage III/N2 NSCLC neoadjuvant chemotherapy (NCT) followed by radical surgery is one standard treatment approach. In our previous trial, this strategy led to a median survival of 33 months (Betticher et al. JCO 2003). We now investigated whether the addition of preoperative radiotherapy (RT) would improve outcome. We report the results of a planned interim analysis on data of the first 219 patients (pts). The trial was closed to accrual in December 2012 due to futility after enrollment of 232 of 240 planned pts. **Methods:** Pts with pathologically proven, resectable stage IIIA/N2 NSCLC, performance status 0-1, adequate heart, kidney, liver and bone marrow function were randomized 1:1 to receive 3 cycles of NCT (cisplatin 100 mg/m2 and docetaxel 85 mg/m2 d1, q3weeks) followed by accelerated concomitant boost RT (44 Gy/22 fractions in 3 weeks) or NCT alone, with subsequent surgery for all pts. The primary endpoint was event-free survival (EFS). **Results:** 23 centers included 219 pts. Median age was 60 years. Pts characteristics were well balanced. Toxicity to CT was substantial, but 91% completed 3 cycles of NCT. RT-induced grade 3 esophagitis was seen in 5 pts, grade 3 skin toxicity in 2 pts. One pt in each treatment arm died during NCT, there was one postoperative death (arm NCT alone). The efficacy results are summarized below, all comparisons are statistically non-significant. **Conclusions:** This is the first completed phase III trial to investigate the value of the addition of neoadjuvant radiotherapy to CT and surgery. RT did not improve EFS or survival, nor did it reduce the local failure rate. Nevertheless, the overall survival rates of our neoadjuvant chemotherapy strategy confirm our previous report, and are among the best results reported to date in a multicenter setting. Clinical trial information: **NCT00030771**.

	CT - RT - Surgery	CT - Surgery
3 cycles of CT given	93% (91/98)	89% (85/96)
RT completed	85% (81/95)	Not applicable
Operated	82% (80/97)	81% (76/94)
Complete resection	90% (72/80)	80% (61/76)
Local failure	22% (21/97)	24% (23/94)
EFS, median (95% CI)	12.8 mo (8.1 , 22.6)	11.8 mo (7.1 , 16.1)
Survival, median (95%CI)	27.1 mo (18.8 , 42.8)	26.2 mo (21.0 , 52.1)

J Clin Oncol 31, 2013 (suppl; abstr 7506)

Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small cell lung cancer: A randomized, placebo controlled phase II study CALGB 30504 (ALLIANCE).

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Abstract

Background: Sunitinib (S) inhibits small cell lung cancer (SCLC) targets VEGFR1-3, PDGFR, and KIT. We tested whether giving S after chemotherapy (C) for extensive stage SCLC improves progression free survival (PFS). **Methods:** CALGB 30504 was a randomized, double-blind, placebo (P) controlled phase II study for untreated SCLC, performance status 0-2, adequate organ function, and no S risk factors: bleeding, hypertension, or brain metastases. Enrollment was prior to C: cisplatin 80 mg/m2 or carboplatin AUC5 day 1 plus etoposide 100 mg/m2days 1-3 every 21 days 4-6 cycles. Patients without progression after C were stratified cisplatin vs carboplatin, and 4-5 vs 6 cycles C, and randomized 1:1 to P or S 37.5 mg daily until progression assessed every 6 weeks. Prophylactic cranial irradiation was offered to responders (CR or PR) to start about 4-6 weeks after C. S was held during radiation. Crossover from P to S was allowed at progression. Primary endpoint was PFS (from time of randomization) for maintenance (M) P vs S using a 1-sided log rank test with a50.15; 80 randomized and treated patients provide »89% power to detect a hazard ratio (HR) of 1.67. **Results:** Between 5/09 and 12/11, 144 enrolled and 138 received C. Ninety five were randomized to P vs S; 10 did not receive M due to progression, refusal, and AE (5 each arm). Eighty five received M, 41 P and 44 S. Demographics were balanced. M toxicities grade . 3 and incidence . 5% included (%): grade 3 (S: fatigue 19, neutrophils 10, leukocytes 7, platelets 7) (P: fatigue 5); grade 4 (S: 1case GI hemorrhage, 1case lipase) P zero; grade 5 zero both arms. Efficacy (90% CI): PFS on maintenance after C was P 2.3 mo (CI: 1.7-2.6) and S 3.8 mo (2.7-4.4) (HR51.54, CI 1.03-2.32, p50.04). Overall survival (OS) was P 6.7 mo (5.5-9.5) and S 8.8 mo (8.0-9.8) (HR51.10, CI 0.71-1.70, p50.36). At progression on P, 17 received S and among 14 evaluable 10 (71%) had stable disease receiving 2-9 cycles S. **Conclusions:** The primary objective was met showing improved PFS for maintenance S. There was a non-significant trend toward improved OS despite crossover design. S was well tolerated. Further study of sunitinib after chemotherapy for SCLC is justified. Clinical trial information: **NCT00453154.**

J Clin Oncol 31, 2013 (suppl; abstr 8021)

Detection of EGFR-activating mutations from plasma DNA as a potent predictor of survival outcomes in FASTACT 2: A randomized phase III study on intercalated combination of erlotinib (E) and chemotherapy (C).

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Abstract

Background: Biomarker analysis of tumor from FASTACT 2 confirmed predictive power of EGFR mut on the benefit of intercalated combination of E and C as 1st line in advanced NSCLC (T. Mok, ESMO 2012). However, only limited tumor were available. Recent development allowed us to detect EGFR mut in cell-free DNA from plasma (pEGFRmut). In this study, we studied the concordance between pEGFRmut and EGFR mut in tumor (tEGFRmut), and the role of pEGFRmut as predictor of PFS and OS. **Methods:** Retrospective EGFR mut testing of FFPET and plasma from FASTACT 2 were performed with two allele-specific PCR assays, cobas EGFR_FFPET test and cobas EGFR_blood test (in development). Both tests are designed to detect EGFR activating mut (exon 19 deletions, L858R, G719X). One FFPET section was used for tissue test and 2-ml plasma was used for blood test. **Results:** Among 268 tumors from 451 enrolled pts, 90% (241/268) were analyzable. 40% (96/241) harbored at least one activating EGFR mut. All 427 plasmas from 451 enrolled pts were analyzable. 32% (136/427) were positive for EGFR activating mut. The concordance of two tests from 224 matched tissue and plasma samples was summarized below. Using tissue as comparator, the sensitivity of plasma test was 76% (68/89) and the specificity of plasma test was 96% (130/135) respectively. Positive and negative predictive values for EGFR activating mut were 93% (68/73) and 86% (130/151) respectively. Median PFS of patients with pEGFRmut treated with intercalated combination versus chemotherapy alone was 13.8 vs. 6.1 m (HR=0.21 p<0.0001), and for pEGFR wild-type, 6.7 vs. 6.0 m (HR=0.80, p=0.06). Median OS of patients with pEGFRmut treated with intercalated combination versus chemotherapy alone was 32.4 vs. 19.0 m (HR=0.51, p=0.0035), and for pEGFR wild-type, 16.1 vs 13.3 m (HR=0.89, p=0.39). **Conclusions:** cobas EGFR_*blood test* can be used to reliably detect EGFR mutations in plasma. pEGFRmut is a potent predictor of survival outcomes in FASTACT 2. Clinical trial information: **CTONG0902**.

N=224	EGFR mut*(P)	Wild-type† (P)
EGFR mut* (T)	68	21
Wild-type† (T)	5	130

J Clin Oncol 31, 2013 (suppl; abstr CRA8007)

A randomized study of ganetespib, a heat shock protein 90 inhibitor, in combination with docetaxel versus docetaxel alone for second-line therapy of lung adenocarcinoma (GALAXY-1).

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Abstract

Background: Heat shock protein 90 chaperone function is critical for the biological effects of several oncoproteins. Ganetespib (G) is a highly potent 2nd-generation Hsp90 inhibitor with a favorable safety profile and single-agent clinical activity. **Methods:** Based on synergistic preclinical interactions between docetaxel (D) and G, we conducted a randomized (1:1), international open-label study of D with or without G. Patients with advanced lung adenocarcinoma, one prior systemic therapy, and ECOG PS 0/1 were included. D was given at 75 mg/m2 on day 1 of a three-week cycle. In the experimental arm, D was given on day 1 and G at 150 mg/m2 on days 1 and 15. The co-primary endpoints were PFS in patients with elevated LDH (eLDH) levels, or tumors harboring KRAS mutations. Key secondary endpoints were OS and PFS in all adenocarcinoma patients. Target enrollment was 240 adenocarcinoma, 120 eLDH, and 80 mKRAS patients. Statistical tests are 1-sided. **Results:** Enrollment of 255 adenocarcinoma patients completed in November 2012; results are reported for this population. Patient characteristics were balanced (median age 60 years, males ~60%, PS 0 ~40% and never-smoker ~25%). For D+G vs. D the median number of cycles delivered was 5 vs. 4; the grade 3/4 adverse events were neutropenia 38% vs. 37%; fatigue 4% vs. 3%; anemia 7% vs. 6%; diarrhea 3% vs. 0; fever with neutropenia 8% vs. 2%. At the time of abstract submission OS HR was 0.69 (90% CI 0.48 to 0.99, p=0.093), the PFS HR was 0.70 (90% CI 0.53 to 0.94, p=0.012), and the ORR was 15% vs 11%, favoring D+G. For patients that were enrolled >6 months after diagnosis of advanced NSCLC (N=175; 69%), a prespecified stratification factor, the OS HR was 0.41 (90% CI 0.25 to 0.67, p=0.0009), the PFS HR was 0.47 (90% CI 0.32 to 0.69, p=0.0005), and the ORR was 16% vs 12%. Updated results for both populations above, as well as for the eLDH and mKRAS subsets, will be presented. **Conclusions:** D+G demonstrated improvement in OS, PFS, and ORR over D alone for second-line therapy of lung adenocarcinoma. A phase III study in second-line advanced adenocarcinoma patients (> 6 months from diagnosis) is ongoing (GALAXY-2). Clinical trial information: **NCT01348126**.

J Clin Oncol 31, 2013 (suppl; abstr 8008)

Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

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Abstract

Background: Human lung cancer expresses high levels of PD-L1, which may inhibit anti-cancer immune responses. MPDL3280A, a human monoclonal Ab containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. **Methods:** Pts with squamous or nonsquamous NSCLC received MPDL3280A IV q3w at doses between 1-20 mg/kg in a Ph I expansion study. Pts were treated for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. **Results:** As of Jan 10, 2013, 53 NSCLC pts were evaluable for safety and treated at doses of ≤1 (n=2), 10 (n=10), 15 (n=19) and 20 mg/kg (n=22). Pts had a median age of 61 y (range 24-83 y), 98% were PS 0-1, 89% had prior surgery and 55% had prior radiotherapy. 98% of pts received prior systemic therapy. Pts received treatment for a median duration of 106 days (range 1-324) of MPDL3280A. The incidence of all G3/4 AEs, regardless of attribution, was 34%, including pericardial effusion (6%), dehydration (4%), dyspnea (4%) and fatigue (4%). No G3-5 pneumonitis or diarrhea was reported. 37 NSCLC pts enrolled prior to Jul 1, 2012, were evaluable for efficacy. RECIST responses were observed at dose levels between 1 and 20 mg/kg, with all responses ongoing or improving. An ORR of 24% (9/37) was observed in pts with squamous and nonsquamous histologies, including several with rapid tumor shrinkage. Additional pts had delayed responses after apparent radiographic progression (not included in the ORR). The 24-week PFS was 48%. Analysis of biomarker data from archival tumor samples demonstrated a correlation between PD-L1 status and efficacy. Pts who were PD-L1 tumor status–positive showed an ORR of 100% (4/4) and a PD rate of 0% (0/4), while pts who were PD-L1 tumor status–negative showed an ORR of 15% (4/26) and a PD rate of 58% (15/26). Updated data will be presented. **Conclusions:** Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid and durable responses were observed. PD-L1 tumor status correlated with response to MPDL3280A. Clinical trial information: **NCT01375842**.

J Clin Oncol 31, 2013 (suppl; abstr 8010)

Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.

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Abstract:

Background: Lung cancers harboring anaplastic lymphoma kinase (ALK) gene rearrangements are sensitive to the tyrosine kinase inhibitor (TKI) crizotinib (CRZ), but invariably develop resistance. LDK378 is a novel, more potent ALK TKI than CRZ, with significant antitumor activity in preclinical models. **Methods:** In this multicenter phase I study, 131 patients (pts) with advanced malignancies harboring a genetic alteration in ALK, including 123 with ALK-rearranged (ALK+) NSCLC (as determined by FISH), were enrolled. LDK378 was administered orally at doses of 50–750 mg once daily. All pts were assessed for PK, response to therapy, and adverse events (AEs). In >20 pts with CRZ-resistant disease, tumor biopsy was performed before LDK378 treatment to identify CRZ resistance mutations. **Results:** As of November 8, 2012, 131 pts had been enrolled (38% male, median age 53 years), including 59 pts in the dose escalation phase, during which the MTD of 750 mg once daily was established, and 72 pts in an expanded cohort at the MTD. Among 88 evaluable NSCLC pts who received LDK378 at 400–750 mg daily, the overall response rate (ORR) was 70%, with 40 confirmed and 22 unconfirmed responses. In the subset of 64 CRZ-resistant pts, the ORR was 73%, with 31 confirmed and 16 unconfirmed responses. As of November 8, 2012 50% of pts with unconfirmed responses were ongoing. Responses were observed in pts with different CRZ resistance mutations as well as in pts without detectable mutation. Responses were also seen in pts with untreated CNS metastases. Among NSCLC pts with confirmed response, median duration of response (DOR) was 7.4 months (95% CI, 6.7 – NR), and 78% had a DOR of ≥6 months. In all 123 NSCLC pts, median PFS was 8.6 months (95% CI, 4.3 – 19.3). The most common AEs were nausea (72%), diarrhea (69%), vomiting (50%), and fatigue (31%). The most common Grade 3/4 AEs were ALT elevation (12%), diarrhea (7%), and AST elevation (6%). **Conclusions:** LDK378 induces durable responses in the majority of pts with advanced, ALK+ NSCLC, including CRZ-resistant pts with and without CRZ resistance mutations. These results suggest that more potent ALK inhibition by LDK378 represents a highly efficacious treatment strategy for ALK+ pts, particularly those who relapse on CRZ. Clinical trial information: **NCT01283516**.

J Clin Oncol 31, 2013 (suppl; abstr LBA8003)

Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab (PCB) followed by maintenance bevacizumab in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC).

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Abstract:

Background: PemC and PCB are regimens used for first-line treatment of advanced NS-NSCLC. The primary objective was to compare progression-free survival without Grade 4 toxicity (G4PFS) between two vs three drug regimen arms. **Methods:** Patients ≥18 years, Stage IV NS NSCLC, AJCC (v7.0), and ECOG PS 0/1 were enrolled. Patients were randomized (1:1); received 4 cycles of induction (PemC: Pem, 500 mg/m2 and C, AUC = 6; PCB: P, 200 mg/m2, C, AUC = 6, and B, 15 mg/kg) followed by Pem (PemC Arm) or B (PCB Arm) maintenance therapy in the absence of progressive disease or discontinuation. Secondary endpoints were PFS, overall survival (OS), overall response rate (ORR), and disease control rate (DCR). The study was powered for G4PFS; assuming hazard ratio (HR) of 0.75; there was 80% power to detect superiority of PemC over PCB with a 2-sided type I error of 0.10. Efficacy data were analyzed by intent-to-treat principle using the log-rank test for time-to-event variables, and an exact test for ORR and DCR. Safety data were evaluated using CTCAE v3 for patients who received ≥1 dose of study treatment. **Results:** Patients were randomized to PemC (N = 182) or PCB (N = 179). Baseline factors were balanced between arms: median age 66/66 years; % female 42/42; % PS=0, 47/47; % stage IV M1a 29/30; for PemC vs PCB, median G4PFS (months) was 3.91/2.86 (HR = 0.85, 90% CI 0.7, 1.04, p = 0.176); PFS and OS had HR = 1.06 (95% CI 0.84, 1.35), p = 0.610, and HR = 1.07 (95% CI 0.83, 1.36), p = 0.616, respectively. The ORR (%) 23.6/ 27.4 and DCR (%) 59.9/57.0 were for PemC vs PCB, respectively. Significantly more drug-related grade 3/4 anemia (18.7% vs 5.4%), and thrombocytopenia (24.0% vs 9.6%) were seen on PemC; significantly more grade 3/4 neutropenia (48.8% vs 24.6%) and grade 1/2 alopecia (28.3 % vs 8.2%) were seen on PCB. **Conclusions:** PemC was not superior to PCB in G4PFS; no difference in PFS or OS was observed for the two- vs three-drug regimens. There were no unexpected toxicities; the toxicity profiles demonstrated distinctions by arm, and both regimens demonstrated tolerability. Clinical trial information: **NCT00948675**.

J Clin Oncol 31, 2013 (suppl; abstr LBA8005)

Randomized proteomic stratified phase III study of second-line erlotinib (E) versus chemotherapy (CT) in patients with inoperable non-small cell lung cancer (PROSE).

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Abstract

Background: Second-line therapy for advanced NSCLC patients (pts) after progression on platinum-based regimens typically employs CT or E. Improved PFS in E-treated pts is associated with EGFR sensitizing mutations. However, a test for optimizing treatment in pts with wild-type or unknown EGFR mutation status or squamous histology is of clinical value. VeriStrat (VS) is a serum protein test that assigns "good" (VSG) or "poor" (VSP) classification and has demonstrated prognostic and predictive utility. PROSE is a multicenter prospective randomized biomarker validation trial, designed to evaluate the ability of VS to predict survival in second-line NSCLC pts treated with E or CT. It is the first completed prospective randomized biomarker validation trial following the MARVEL design (Freidlin et al. JNCI. 2010). **Methods:** 285 pts, stratified by ECOG-PS, smoking, and blinded pretreatment VS classification, were randomized 1:1 to receive E or CT at standard doses. Primary endpoint was overall survival (OS) and the primary hypothesis was significant interaction between VS status and treatment. Sample size was calculated based on an estimated 65%/35% VSG:VSP ratio and hazard ratio (HR) for interaction of 2.35, with a 2-sided α=0.05 and 90% power. **Results:** 285 pts were randomized and 263 (129 CT, 134 E) included in the per protocol primary analysis. 68% of pts in CT arm and 72% in E arm were classified as VSG. Analysis was performed at 226 events. The trial reached its primary objective of significant interaction between treatment and VeriStrat classification with an interaction p value of 0.037. Pts in the VSP group performed worse on E compared to CT (HR: 1.72, 95% CI: 1.08-2.74); there was no significant difference in OS between treatments in the VSG group (HR: 1.09, 95% CI:0.79-1.50). 194/198 pts with histologic diagnosis had tissue available for EGFR and KRAS mutations. **Conclusions:** The results suggest that VS status is predictive of differential OS benefit for E versus CT in second line setting, complementing the result from a retrospective analysis of NCIC BR.21 where the prognostic behavior of VS was established (Carbone et al. JTO. 2012). Clinical trial information: **NCT00989690**.

J Clin Oncol 31, 2013 (suppl; abstr LBA8011)

Nintedanib (BIBF 1120) plus docetaxel in NSCLC patients progressing after first-line chemotherapy: LUME Lung 1, a randomized, double-blind phase III trial.

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Abstract

Background: Nintedanib (N) inhibits VEGFRs, PDGFRs, and FGFRs. LUME Lung 1 is a placebo (P) controlled phase III trial of N + docetaxel (D) in patients (pts) with locally advanced/metastatic NSCLC progressing after first-line therapy. **Methods:** Stage IIIB/IV or recurrent NSCLC pts (stratified by histology, ECOG PS, prior bevacizumab, and brain metastases) were randomized to N 200 mg bid + D 75 mg/m2 q21d (n=655) or P + D (n=659). 1° endpoint was centrally reviewed PFS after 713 events (2 sided stratified log-rank, α=5%, β=10%). Key 2° endpoint of OS was analyzed hierarchically after 1,121 events (2 sided, adjusted α=4.98%, β=20%), first in adenocarcinoma (adeno) pts <9 mo since start of first-line therapy (T<9mo; identified as a prognostic/predictive biomarker [ASCO '13]), followed by all adeno pts and then all pts. Predefined sensitivity analyses added sum of longest diameters of target lesions (SLD) to stratification factors in the Cox model. **Results:** Pt characteristics were balanced between the arms. N + D significantly prolonged PFS vs P + D (HR 0.79; CI: 0.68, 0.92; p=0.0019; median 3.4 vs 2.7 mo) regardless of histology (squamous HR 0.77, p=0.02; adeno HR 0.77, p=0.02). OS was significantly prolonged in all adeno pts (HR 0.83; p=0.0359; median 12.6 vs 10.3 mo) with the greatest improvement seen in T<9mo adeno pts (HR 0.75; p=0.0073; median 10.9 vs 7.9 mo). A trend for improved OS was seen in all pts (HR 0.94; p=0.272; median 10.1 vs 9.1). When adjusted for SLD, a significant OS benefit was seen in all pts (HR 0.88; CI: 0.78, 0.99; p=0.0365). Disease control rates were significantly improved with N + D in all adeno pts (odds ratio [OR] 1.93; p<0.0001), T<9mo adeno pts (OR 2.90; p<0.0001) and all pts (OR 1.68; p<0.0001). The most common AEs were diarrhea (any: 42.3 vs 21.8%; Gr ≥3: 6.6 vs 2.6%) and ALT elevations (any: 28.5 vs 8.4%; Gr ≥3: 7.8 vs 0.9%). Incidence of CTCAE Gr ≥3 AEs was 71.3 vs 64.3%. Withdrawals due to AEs (22.7 vs 21.7%) were similar in both arms, as were Gr ≥3 hypertension, bleeding or thrombosis. **Conclusions:** N + D significantly improved PFS independent of histology, and prolonged OS for adeno pts. AEs were generally manageable with dose reductions and symptomatic treatment. Clinical trial information: **NCT00805194**.

J Clin Oncol 31, 2013 (suppl; abstr 8500)

Tolerability and activity of combinations of the PI3Kδ inhibitor idelalisib (GS-1101) with rituximab and/or bendamustine in patients with previously treated, indolent non-Hodgkin lymphoma (iNHL): Updated results from a phase I study.

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Abstract

Background: PI3K-delta signaling is critical for activation, proliferation and survival of B cells, and is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that has shown considerable monotherapy activity in recurrent iNHL (Kahl, ICML 2011), as well as combination therapy (Fowler, ASCO 2012). **Methods:** This phase I study evaluated the activity of continuous (48 weeks) idelalisib (Id), 100/150 mg BID, in combination with rituximab (R) (375 mg/m^2 weekly x 8 doses) (Id+R), with bendamustine (B) (90 mg/m^2 x 2, for 6 cycles) (Id+B), or in combination with R (375 mg/m^2 monthly x 6) and B (90 mg/m^2 x 2), for 6 cycles (Id+BR). Investigators assessed response according to standard criteria (Cheson 2007). Patients who continued to benefit were able to enroll on an extension study. **Results:** Study enrolled 78 pts with relapsed/refractory iNHL, with 34 (44%) pts continuing on treatment in the ongoing extension protocol. The 3 cohorts included Id+R (N=30), Id+B (N=34), and Id+BR (N=14). Pts were 67% male, median age [range] of 62 [37E84] years, 41% with refractory disease, 88% stage III/IV, and 36% of FL with high FLIPI scores. The median [range] number of prior therapies was 3 [1E10]. The median [range] duration of treatment was 10.6 [0.5-29.2] months. Overall response rate (ORR) was 63/78 (81%), with 22/78 (28%) CR. The ORR/CR for Id+R was 77%/20%, Id+B was 85%/29%, and Id+BR was 79%/43%. At 20 months, the PFS was 66%. For responders, 73% were progression-free at 20 months. Most common adverse events included (total%/≥G3%) pyrexia (56/4), fatigue (45/4), nausea (41/0), rash (40/8), cough (37/0), diarrhea (36/8), chills (18/0), URI (18/1), and pneumonia (17/15). Lab abnormalities included (total%/≥G3%) ALT/AST elevations (56/17). **Conclusions:** Idelalisib-based combination therapy is highly active and well tolerated in patients with relapsed/refractory iNHL. These data support further clinical development. Phase III trials evaluating the efficacy of idelalisib in combination with R, or BR in iNHL are ongoing (NCT01732913, NCT01732926). Clinical trial information: **NCT01732913, NCT01732929**.

J Clin Oncol 31, 2013 (suppl; abstr 8503)

Preventing hepatitis B reactivation in HBsAg-positive patients with untreated diffuse large B-cell lymphoma with R-CHOP chemotherapy: A prospective study to compare entecavir and lamivudine.

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Abstract

Background: Hepatitis B reactivation is a serious complication in lymphoma patients treated with rituximab-contained chemotherapy despite lamivudine prophylaxis. The optimal prophylactic antiviral protocol is undetermined. This prospective study was designed to compare the efficacy of prophylactic entecavir and lamivudine in preventing hepatitis B reactivation in HbsAg-positive patients with untreated diffuse large B cell lymphoma (DLBCL) under R-CHOP treatment. **Methods:** HBsAg carriers with untreated DLBCL, normal liver function and low serum HBV DNA levels (less than 10^3copys/ml)were randomized to receive entecavir or lamivudine during R-CHOP treatment and for 6 months after completion of chemotherapy. HBsAg, HBsAb, HBeAg, HBeAb and HBcAb were performed prior to initiation of treatment. Serum alanine aminotransferase (ALT), and HBV-DNA levels were prospectively monitored before every cycle of chemo and every month after completion of chemotherapy. **Results:** Between February 2008 and December 2012, a total of 229 patients older than 18y with newly diagnosed DLBCL were included. The present analysis is based on 121 HBsAg-positive patients, including 61 patients randomly assigned to entecavir and 60 patients to lamivudine .The primary efficacy end point was the incidence of HBV-related hepatitis. The secondary end point was chemotherapy disruption due to hepatitis. Compared with the lamivadine group, the entecavir group had significantly lower rates of hepatitis(8.2% vs 23.3%,P=0.022), hepatitis B reactivation (0 vs 13.3%,P=0.003),HBV reactiviation(6.6% vs 30.0%,P=0.001), delayed HBV-related hepatitis (0 vs 8.3%,P=0.027) and disruption of chemotherapy (1.6% vs 18.3%,P=0.002). 7 of 8 patients with hepatitis B reactivation had advanced stage(III–IV) disease. **Conclusions:** In HBsAg-positive DLBCL patients undergoing R-CHOP chemotherapy, entecavir is more effective than lamivudine in preventing hepatitis B reactivation. For patients with advanced stage disease, entecavir should be considered the primary preventive therapy. Clinical trial information: **CTR-TRC-11001687**.

J Clin Oncol 31, 2013 (suppl; abstr 8504)

Utility of post-therapy surveillance scans in DLBCL.

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma. The optimal follow-up strategy for patients (pts) in remission is not clear. The goal of this study is to determine the utility of surveillance scans in a large, prospective, multi-institutional cohort of DLBCL pts. **Methods:** Patients were enrolled in the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource (MER), a prospective cohort of newly diagnosed lymphoma pts. All pts were followed for events including relapse, re-treatment, and death with events verified by medical records. Patients eligible for this study had biopsy proven DLBCL and were treated with anthracycline based immunochemotherapy (IC). Initial and post-treatment management was per treating physician. Medical records were re-reviewed in pts with events for clinical details at relapse and relationship to planned follow-up visits and surveillance scans. **Results:** 644 pts with DLBCL treated with IC were enrolled in MER from 2002-2009. Median age was 63 years (range 18-92), 54% were men, and median f/u was 59 months (range 8-116). 537 pts entered post-treatment observation; 109 (20%) of the 537 pts relapsed and 41 died from other causes. 42% of relapses were in the first 12 months following diagnosis, 27% between 12-24 months, and 31% >24 months. In the 109 who relapsed, 62% of pts (62/100, 9 unknown) presented to their physician earlier than a planned follow-up visit due to symptoms. At the time of relapse, 68% were symptomatic, 42% of pts had abnormal physical exam, and 55% had elevated LDH; 87% of pts had ≥1 of these features. Of the 38 pts with relapse detected at a planned visit, 26 had clinical features of relapse and 12 pts had relapse detected solely by planned surveillance scan; 4 pts had relapse of low-grade or other subtype and 8 had DLBCL relapse (4 of whom had equivocal/positive PET at the end of IC). Thus, surveillance scanning detected DLBCL relapse prior to clinical manifestations in only 8/537 pts (1.5%) observed post DLBCL therapy. **Conclusions:** The vast majority of DLBCL relapses occur outside of planned follow-up visits and are accompanied by symptoms, physical exam, or laboratory abnormalities. Routine surveillance scans post-therapy add little to detection of DLBCL relapse.

J Clin Oncol 31, 2013 (suppl; abstr 8509)

Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients.

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Abstract

Background: The incorporation of new drugs into induction, consolidation, and maintenance therapy is changing the treatment paradigm of MM. **Methods:** At diagnosis, 402 pts (< 65 years) were randomly assigned to receive six MPR cycles (N=202) or tandem MEL200 (N=200). After MPR or MEL200, pts were further randomized, within each group, for no maintenance (N=204) or lenalidomide maintenance (N=198). A 2x2 factorial randomized trial was designed. The primary end point was PFS. An enrolment of 170 pts/arm was required to demonstrate a 15% improvement of PFS at 2 years (2-sides a = 0.05, 1- β 80%). **Results:** After a median follow-up of 45 mos from diagnosis, the median PFS was 25 mos with MPR and 39 mos with MEL200 (p=.0002). Median PFS were 37.5 mos for maintenance and 25.7 mos for no maintenance (p=.0008). The 4-year OS from diagnosis was 71% with MPR and 72% with MEL200 (p=0.71), 76% for maintenance and 68% for no maintenance (p=.08). After a median follow-up of 32 mos from start of maintenance, the median PFS was for 41 mos for maintenance and 18 mos for no maintenance (p<.0001). The 3-year OS from start of maintenance was 81% for maintenance and 72% for no maintenance (p=.04). **Conclusions:** MEL200 significantly prolonged PFS in comparison with MPR. Lenalidomide maintenance significantly reduced the risk of progression independently from the previous treatment. OS is similar between MPR and MEL200, with a trend for an improved OS in pts receiving lenalidomide as maintenance therapy. Clinical trial information: **NCT00551928**.

	First randomization			Second randomization		
	MPR	**MEL200**	**HR (95%CI; p value)**	**MAINT**	**No MAINT**	**HR (95%CI; p value)**
From diagnosis						
Median PFS (mos)	25	39	1.66 (1.27-2.18; .0002)	37.5	25.7	0.63 (0.48-0.83;.0008)
4-ys OS	71	72	1.08 (0.72-1.63;.71)	76	68	0.68 (0.45-1.04;.08)
	First randomization			Second randomization		
Start of maintenance	MPR	MEL200	HR (95%CI;p value)	MAINT	No MAINT	HR (95%CI; p value)
Median PFS (mos)	18	41	2.01 (1.45-2.79;<.0001)	41	18	0.50 (0.36-0.69;<.0001)
3-ys OS	77	76	0.98 (0.61-1.58;.94)	81	72	0.60 (0.37-0.97;.04)

J Clin Oncol 31, 2013 (suppl; abstr 8510)

MM-003: A phase III, multicenter, randomized, open-label study of pomalidomide (POM) plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).

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Abstract

Background: RRMM patients (pts) who have exhausted treatment (Tx) with bortezomib (BORT) and lenalidomide (LEN) or thalidomide have a poor prognosis with short overall survival (OS). HiDEX is a well-established standard Tx in RRMM. POM has demonstrated clinical efficacy in pts refractory to LEN and BORT. MM-003 compared POM + LoDEX vs. HiDEX in RRMM pts who failed LEN and BORT and who progressed on their last Tx. **Methods:** Pts must have been refractory to last prior Tx (progressive disease [PD] during Tx or within 60 days) and failed LEN and BORT after ≥ 2 consecutive cycles of each (alone or in combination). Pts were randomized 2:1 to receive 28-day cycles of POM 4 mg D1–21 + DEX 40 mg (20 mg for pts aged > 75 y) weekly or DEX 40 mg (20 mg for pts aged > 75 y) D1–4, 9–12, and 17–20. Tx continued until PD or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included OS, overall response rate (ORR; ≥ partial response), and safety. Analyses were based on intent to treat. **Results:** 455 pts were randomized to POM + LoDEX (n = 302) or HiDEX (n = 153). The median number of prior Tx was 5 (range 1-17). 72% were refractory to LEN and BORT. Median follow-up was 4 months. POM + LoDEX significantly extended median PFS (3.6 vs. 1.8 months, HR = 0.45, $P < .001$) and OS (not reached vs. 7.8 months, HR = 0.53, $P < .001$) vs. HiDEX. The OS benefit was observed despite 29% of HiDEX pts receiving POM after PD. The trial met the primary endpoint of PFS, crossed the upper boundary for OS superiority, and the Data Monitoring Committee recommended crossover from HiDEX to POM ± DEX. With updated data, the ORR was 21% for POM + LoDEX vs. 3% for HiDEX ($P < .001$) and 24% vs 3% for pts randomized ≥ 6 months post-enrollment ($P < .001$). The most frequent grade 3/4 adverse events (AEs) for POM + LoDEX vs. HiDEX were neutropenia (42% vs. 15%), anemia (27% vs. 29%), and infection (24% vs. 23%). Discontinuation due to AEs was infrequent (7% vs. 6%). Updated data will be presented. **Conclusions:** POM + LoDEX significantly extended PFS and OS vs. HiDEX in pts who failed LEN and BORT. POM + LoDEX should become a standard of care in RRMM pts who have exhausted Tx with LEN and BORT. Clinical trial information: **NCT01311687**.

J Clin Oncol 31, 2013 (suppl; abstr CRA9003)

Phase II study of selumetinib (sel) versus temozolomide (TMZ) in gnaq/Gna11 (Gq/11) mutant (mut) uveal melanoma (UM).

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Abstract

Background: Gq/11 mutations are early oncogenic events in UM resulting in MAPK pathway activation. We demonstrated decreased viability in UM cell lines harboring Gq/11 mut with sel, a small molecule inhibitor of MEK1/2 (Ambrosini, CCR 2012). **Methods:** We conducted a 16 center randomized phase II study of hyd-sulfate sel 75 mg BID vs TMZ 150 mg/m^2 daily for 5 days in 28-day cycles (or DTIC 1000 mg/m^2 q21 days) for patients (pts) with metastatic UM with a Q209 Gq/11 mut who have not received prior TMZ/DTIC. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall survival (OS) and response rate (RR). Select pts underwent tumor biopsies at baseline and after 14 (+/- 3 days) of sel. Our statistical plan required ≥80 pts randomized and ≥68 events to detect a PFS hazard ratio of 0.6 (p=0.1). Randomization was stratified by mut (Gq vs G11), M stage and number of prior therapies (tx). Tumor assessment occurred every 4 weeks (wks) for 8 wks and then every 8 wks using RECIST 1.1. Pts receiving TMZ who progressed could receive sel (TMZ→sel). **Results:** 80 pts were randomized. Sel (n=39): median age 66 (range 32-86), 54% male, 54% G11 mut, median ECOG PS 0 (range 0-1), 97% M1c, median prior tx 0 (range 0-2). TMZ (n=41): median age 60 (range 34-81), 63% male, 58% G11 mut, median ECOG PS 0 (range 0-1), 93% M1c, median prior tx 0 (range 0-2). 11/39 (28%) pts on sel experienced grade (gr) 3 toxicity (tox) manageable with dose modification (5 CPK elevation, 3 LFT elevation, 1 rash, 1 lymphopenia, 1 edema). 1/41 (2%) pt on TMZ experienced gr 3 tox (neutropenia). No gr 4/5 tox occurred. 28 pts on sel underwent paired tumor biopsies with inhibition of pERK and cyclinD1 observed by Western blot at day 14. At interim analysis (9/25/12), 55 pts were evaluable with 45 progression events and 16 deaths. Sel (n=27): median PFS 16 wks (95% CI 8-30.9), RR 11%, median OS 11.8 months (95% CI 4.8-not reached). TMZ (n=28): median PFS 4 wks (95% CI 3.7-15), RR 0%, median OS 4.7 months (95% CI 4.3-14.3). TMZ→sel (n=25): median PFS 8.1 wks (95% CI 7-15), RR 0%. **Conclusions:** Sel is the first drug to ever show improved clinical activity in UM relative to TMZ. Sustained target inhibition is observed with sel. Final results will be presented. Clinical trial information: **NCT01143402**.

J Clin Oncol 31, 2013 (suppl; abstr CRA9007)

Multicenter, randomized phase II trial of GM-CSF (GM) plus ipilimumab (Ipi) versus Ipi alone in metastatic melanoma: E1608.

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Abstract

Background: CTLA-4 blockade and GM secreting tumor vaccine combinations demonstrate therapeutic synergy in multiple preclinical models. GM has activity in prostate and ovarian carcinoma and is being evaluated in phase III adjuvant trials for melanoma and lymphoma. GM enhances dendritic cell activation and potentiates antitumor T and B cell responses. GM may induce regulatory immune responses. A key issue is whether systemic GM might synergize with CTLA-4 blockade. **Methods:** Eligibility: measureable disease, ≤1 prior therapy, no CNS mets, ECOG PS 0-1, > 4 wks prior therapy, adequate end organ function, no autoimmune disease, no prior CTLA-4 blockade/CD137 agonist. OS was primary endpoint. Pts randomized to Arm A Ipi 10 mg/kg q3 wks IV x 4 then q12 wks plus GM 250 μg SC days 1-14 of 21 day cycles vs. Arm B Ipi 10 mg/kg as in Arm A alone. Due to known inflammatory effects of treatments, pts were permitted to continue up to 100% increase in SPD and four new lesions in absence of declining performance status and discretion of treating physician. Drug supply, funding from Sanofi/Bristol-Myers Squibb. **Results:** 245 pts were enrolled. Arms were balanced for demographics. Median follow up 13.3 mos. RR Arm A 11.3 % (6.1, 18.6), Arm B 14.7% (8.6,22.8) (not significant;NS). PFS Arm A 3 mos (2.9,4.3), Arm B 3.2 mos (3,4) (NS). Median OS Arm A not reached, Arm B 12.6 mos (9.2,-). One year OS for Arm A was 67.9% (59%,76%), Arm B 51.2% (42.6%, 61.3%) (stratified log rank p1=0.016, p2=0.033). HR for mortality on Ipi + GM/Ipi=0.65. Per study design (overall one-sided type I error 0.10), OS interim analysis was conducted at 69% info time. O'Brien-Fleming boundary was crossed for OS. Toxicity assessed for all cases regardless of eligibility. Gr 3-5 AEs 45% Arm A, 57% Arm B (p2=0.078). Gr 5 AEs: Arm A colonic perforation (1), cardiac arrest (1); Arm B multiorgan failure (2), colonic perforation (2), hepatic failure (1), respiratory failure (2). **Conclusions:** Ipi plus GM significantly improves OS over Ipi alone. No significant differences in toxicity were observed. A trend toward improved tolerability is noted in the GM arm. Clinical trial information: **NCT01134614**.

J Clin Oncol 31, 2013 (suppl; abstr 9009)

Clinical efficacy and safety of lambrolizumab (MK-3475, Anti-PD-1 monoclonal antibody) in patients with advanced melanoma.

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Abstract

Background: Programmed death-1 (PD-1) is an inhibitory T-cell co-receptor that may lead to suppression of antitumor immunity. Lambrolizumab is a humanized monoclonal IgG4 antibody against PD-1. This study explored the safety and clinical activity of lambrolizumab in patients (pts) with advanced melanoma (MEL). **Methods:** In this ongoing phase 1b expansion study of MEL pts with or without previous ipilimumab (IPI) treatment, lambrolizumab was administered IV every 2 or 3 weeks until disease progression or unacceptable toxicity. Tumor response was assessed every 12 weeks by independent, central, blinded radiographic review per immune-related response criteria and RECIST 1.1. **Results:** As of December 1, 2012, 294 pts with MEL were enrolled, including 179 IPI-naive and 115 IPI-pretreated. Pts received lambrolizumab 10 mg/kg (n = 183) or 2 mg/kg (n = 111). Preliminary data from the first 85 consecutive pts dosed before April 25, 2012, who had independent radiologic review available as of December 3, 2012, indicate a confirmed overall response rate per RECIST 1.1 of greater than 35%, pooled across all doses and schedules and including both IPI-naive and IPI-pretreated patients. The median duration of response has not been reached as only 2 pts who had initial response discontinued due to disease progression, but the duration of confirmed responses range from 28+ to 240+ days (up to 8+ months). Among 133 pts who were dosed with lambrolizumab before July 31, 2012, and evaluable for adverse events (AEs) as of September 28, 2012, fatigue (22%), rash (18%), and pruritus (14%) were the most common drug-related AEs (mostly grade 1/2). The incidence of drug-related grade 3/4 AEs was 10% (24% regardless of attribution). Four drug-related cases of pneumonitis were reported, all of grade 1/2. Grade 3/4 drug-related hypothyroidism (n = 1) and hyperthyroidism (n = 1) were noted. **Conclusions:** Preliminary data suggest that lambrolizumab has significant antitumor activity and is well tolerated with manageable side effects in both IPI-naive and IPI-pretreated MEL pts. These data have led to an ongoing, international, randomized study of lambrolizumab versus chemotherapy in IPI-pretreated MEL. Clinical trial information: **NCT01295827**.

J Clin Oncol 31, 2013 (suppl; abstr 9010)

Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM).

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Abstract

Background: mM is an immunotherapy responsive disease where PD-L1 overexpression is prevalent. MPDL3280A, a human monoclonal antibody containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. Initial antitumor activity observed during dose escalation supported further expansion in mM with MPDL3280A as monotherapy and in combination with targeted therapy. **Methods:** Pts with mM of any histologic subtype received MPDL3280A administered IV q3w for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. In addition, a separate Ph 1b was initiated to evaluate the safety and efficacy of MPDL3280A with vemurafenib (vem) in pts with BRAF-V600 mutated mM. **Results:** As of Jan 10, 2013, 45 mM pts were treated at ≤1 (n=4), 10 (n=10), 25 (n=20) and 20 mg/kg (n=11) and evaluable for safety. Median pt age was 63 y (range 21-83 y), 100% were PS 0-1, 91% had prior surgery and 64% received prior systemic therapy. Pts received MPDL3280A treatment for a median duration of 127 days (range 1-282). The incidence of all G3/4 AEs, regardless of attribution, was 33%, including hyperglycemia (7%), elevated ALT (7%) and elevated AST (4%). No G3-5 pneumonitis was reported. No treatment-related deaths occurred on study. 35 mM pts who initiated treatment at doses of 1-20 mg/kg and enrolled prior to Jul 1, 2012, were evaluable for efficacy. An ORR of 26% (9/35) was observed, with all RECIST responses ongoing or improving. Further, some responding pts experienced tumor shrinkage within days of initial treatment. The 24-week PFS was 35%. Several additional pts had delayed antitumor activity after apparent radiographic progression and were counted as PD for the above analyses. Analysis of mandatory archival tumors showed a correlation between PD-L1 status and efficacy. Further, of three initial pts treated with MPDL3280A and vem, 2 experienced tumor shrinkage, including 1 CR. **Conclusions:** MPDL3280A was well tolerated as monotherapy, and durable ORs were observed. Therefore, further assessment of MPDL3280A as monotherapy and combination therapy is warranted. Clinical trial information: **NCT01375842**.

J Clin Oncol 31, 2013 (suppl; abstr 9011)

Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab.

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Abstract

Background: Nivolumab, an IgG4 fully human monoclonal antibody against checkpoint protein PD-1, is active in metastatic melanoma, renal cell and non-small cell lung cancer. It was administered with a multi-peptide vaccine to patients (pts) with unresectable melanoma who failed at least one regimen for metastatic disease and were ipilimumab naïve, or failed ipilimumab, to assess the toxicity and tolerability of the combination and perform correlative immune assays. **Methods:** Three cohorts of 10 HLA A0201 positive ipilimumab-naïve pts received nivolumab at 1, 3 or 10 mg/kg, then three additional cohorts of pts who had failed prior ipilimumab received nivolumab at 3 mg/kg: two cohorts of 10 pts each who were A0201 positive and had either grade 2 or less ipilimumab toxicity, or grade 3 dose limiting ipilimumab toxicity; finally 40 pts were treated with antibody who had grade 2 or less ipilimumab toxicity and were not HLA restricted. Pre-treatment archived tumor tissue as well as pre- and post-treatment peripheral blood cells were collected. **Results:** Median age for all pts was 59;76% were M1c. Response rates by RECIST were 28% in 34 pts naïve to, and 32% for 46 pts who failed prior ipilimumab. Nivolumab did not induce the same irAEs in pts with prior ipilimumab induced toxicity. No cohort had more than one dose limiting toxicity. 2 pts had grade 3 pneumonitis. Three of ten pts who failed nivolumb had stable disease or a partial response to subsequent ipilimumab. Biomarker studies showed that elevated NY-ESO 1 and MART-1 specific CD8 T cells pre-treatment were associated with non-response (p,0.005 and ,0.001), and that CTLA-4 positive CD4 T cells and T regulatory cells were elevated after treatment in non-responders (p,0.01). Immunohistochemical analysis of pre-treatment tumors indicated that PD-L1 staining was associated with response, but responses were also observed in pts whose tumors did not stain. **Conclusions:** Objective responses to nivolumab were observed after failing ipilimumab, and to ipilimumab after failing nivolumab. Elevation of CTLA-4 after nivolumab in non-responders suggest that sequential therapy with the combination should be tested. Tumor PD-L1 was associated with but not predictive of response. Clinical trial information: **NCT01176461**.

J Clin Oncol 31, 2013 (suppl; abstr 9012)

Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL).

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Abstract

Background: CTLA-4 and PD-1 are critical immune checkpoint receptors. In MEL pts, ipilimumab (anti-CTLA-4) prolonged survival in two phase III trials, and nivolumab (anti-PD-1) produced an objective response rate (ORR) of 31% (n5106) in a phase I trial. PD-1 is induced by CTLA-4 blockade, and combined blockade of CTLA-4/PD-1 showed enhanced antitumor activity in murine models. Thus, we initiated the first phase 1 study to evaluate nivolumab/ipilimumab combination therapy. **Methods:** MEL pts with #3 prior therapies received IV nivolumab and ipilimumab concurrently, q3 wk 3 4 doses, followed by nivolumab alone q3 wk 3 4 (Table). At wk 24, combined treatment was continued q12 wk 3 8 in pts with disease control and no DLT. In two sequenced-regimen cohorts, pts with prior standard ipilimumab therapy were treated with nivolumab (q2 wk 3 48). **Results:** As of Dec. 6, 2012, 69 pts were treated. We report efficacy data on 37 pts with concurrent therapy in completed cohorts 1-3 (Table); ORR was 38% (95% CI: 23-55). In cohort 2 (MTD), ORR was 47% and 41% of pts had $80% tumor reduction at 12 wk (Table) with some pts showing rapid responses, prompt symptom resolution, and durable CRs. Related adverse events (rAEs) for concurrent therapy were similar in nature with some higher in frequency than those typically seen for the monotherapies and were generally manageable using immunosuppressants. Cohort 3 exceeded the MTD (DLT: gr 3-4 1 lipase). At the MTD, gr 3-4 rAEs occurred in 59% of pts and included uveitis/choroiditis, colitis, and reversible lab abnormalities. **Conclusions:** Nivolumab and ipilimumab can be combined with a manageable safety profile. Clinical activity for concurrent therapy appears to exceed that of published monotherapy data, with rapid and deep tumor responses ($80% tumor reduction at 12 wk) in 30% (11/37) of pts. A phase III trial is planned to compare concurrent combination dosing with each monotherapy. Clinical trial information: **NCT01024231.**

Cohort	Ipilimumab (mg/kg) + nivolumab (mg/kg)	n[a]	CR[b] (n)	PR[b] (n)	ORR (%) [95% CI]	≥80% Tumor reduction at 12 wk (%)
1	3 + 0.3	14	1	2	21 [5-51]	4/14 (29)
2	3 + 1	17	3	5	47 [23-72]	7/17 (41)
3	3 + 3	6	0	3	50 [12-88]	0/6 (0)
2a	1 + 3	12			Ongoing	
6	Prior + 1	14			Ongoing	
7	Prior + 3	6			Ongoing	

Total treated; [b]mWHO criteria.

J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma.

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Abstract

Background: T-VEC is an oncolytic immunotherapy (OI) derived from herpes simplex virus type-1 designed to selectively replicate within tumors and to produce GM-CSF to enhance systemic antitumor immune responses. OPTiM is a randomized, phase III trial of T-VEC or GM-CSF in patients (pts) with unresected melanoma with regional or distant metastases. We report the primary results of the first phase III study of OI. **Methods:** Key criteria: age ≥18 yrs; ECOG ≤1; unresectable melanoma stage IIIB/C or IV; injectable cutaneous, SC, or nodal lesions; LDH ≤1.5X upper limit of normal; ≤3 visceral lesions (excluding lung), none >3 cm. Pts were randomized 2:1 to intralesional T-VEC (initially ≤ 4 mL x10^6 pfu/mL then after 3 wks, ≤ 4 mL x10^8 pfu/mL Q2W) or SC GM-CSF (125 μg/m^2qd x 14 days q28d). The primary endpoint was durable response rate (DRR): partial or complete response (CR) continuously for ≥6 mos starting within 12 mos. Responses were per modified WHO by blinded central review. A planned interim analysis of overall survival (OS; key secondary endpoint) was performed. **Results:** 436 pts are in the ITT set: 295 (68%) T-VEC, 141 (32%) GM-CSF. 57% were men; median age was 63 yrs. Stage distribution was: IIIB/C 30%, IVM1a 27%, IVM1b 21%, IVM1c 22%. Objective response rate with T-VEC was 26% (95% CI: 21%, 32%) with 11% CR, and with GM-CSF was 6% (95% CI: 2%, 10%) with 1% CR. DRR for T-VEC was 16% (95% CI: 12%, 21%) and 2% for GM-CSF (95% CI: 0%, 5%), p<0.0001. DRR by stage (T-VEC, GM-CSF) was IIIB/C (33%, 0%), M1a (16%, 2%), M1b (3%, 4%), and M1c (8%, 3%). Interim OS showed a trend in favor of T-VEC; HR 0.79 (95% CI: 0.61, 1.02). Most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. Serious AEs occurred in 26% of T-VEC and 13% of GM-CSF pts. No ≥ grade 3 AE occurred in ≥ 3% of pts in either arm. **Conclusions:** T-VEC demonstrated both a statistically significant improvement in DRR over GM-CSF in pts with unresectable stage IIIB-IV melanoma and a tolerable safety profile; an interim analysis showed a trend toward improved OS. T-VEC represents a novel potential tx option for melanoma with regional or distant metastases. Clinical trial information: **NCT00769704**.

J Clin Oncol 31, 2013 (suppl; abstr 9503)

A multicenter, randomized, double-blinded, placebo-controlled trial of modafinil for lung cancer-related fatigue: Dose response and patient satisfaction data.

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Abstract

Background: Fatigue is a very common, disabling symptom in cancer, and particularly severe in lung cancer. Modafinil is a novel central nervous system stimulant, which, along with methylphenidate, is cautiously recommended by the 2013 National Comprehensive Cancer Network Guidelines for fatigue. In this phase IV randomized placebo-controlled trial, we assessed the efficacy of modafinil for managing fatigue in lung cancer. **Methods:** Adults with locally advanced or metastatic non small cell lung cancer (stages III and IV), ECOG performance status (PS) 0-2 and suffering from fatigue (score 5/10 or greater) were randomised 1:1 to modafinil or matched placebo, 100mg daily for 14 days and 200mg daily for a further 14 days. The primary outcome measure was change in the Functional Assessment of Chronic Illness Therapy fatigue subscale (FACIT-fatigue) at 28 days. The trial was powered to detect a 5-point difference with 80% power and 5% significance allowing for 25% attrition. Dose-response, patient satisfaction and safety were also evaluated. **Results:** 208 patients were recruited from 24 UK centres. Baseline characteristics were well-balanced. 160 patients completed both baseline and 28 day questionnaires and were included in the modified-ITT analysis. FACIT-fatigue mean change from baseline was modafinil=5.28, placebo=5.11, difference=0.17, (95%CI -4.17, 3.82). Adjustment for baseline fatigue and PS had no impact on outcome. No dose response was seen; the majority of improvement on all scales was seen at 14 days and sustained to 28 days. 47% of the modafinil group and 23% of the placebo group stated the study treatment was not helpful (p=0.132). Adverse events were equal. **Conclusions:** Both modafinil and placebo led to a clinically significant 5-point improvement in FACIT-fatigue score, but there was no significant difference between the two groups. This well-powered study suggests that there is a large placebo effect and NCCN guidelines should be reviewed. Clinical trial information: **NCT00829322**.

FACIT-F score	Modafinil (mean, [SD] N)	Placebo (mean, [SD] N)
Baseline	24.64 [10.58] 104	24.98 [10.83] 103
Day 14	30.58 [12.17] 88	29.43 [11.57] 90
Day 28	31.28 [13.66] 75	30.66 [13.85] 85

J Clin Oncol 31, 2013 (suppl; abstr 9508)

Biomarker prediction of chemotherapy-related amenorrhea.

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Abstract

Background: Chemotherapy-related amenorrhea (CRA) is associated with infertility and may impact treatment decision-making. We investigated whether anti-mullerian hormone (AMH) levels before chemotherapy predict likelihood of CRA. **Methods:** 591 patients enrolled on the quality of life substudy of ECOG5103, which randomized breast cancer patients to doxorubicin-cyclophosphamide followed by paclitaxel: 1) alone; 2) with concurrent bevacizumab; or 3) with prolonged bevacizumab. 144 of the 195 women who reported a period <12 months before enrollment consented to serum collection prior to chemotherapy. AMH was measured in 143 with available serum. Participants self-reported menstrual frequency at 12 and 18 months after enrollment. 12-month CRA was defined as no menses for 6 months before the 12-month survey, and 18-month CRA as no menses for 6 months before the 18-month survey. Fisher's exact test was used to identify associations with CRA. **Results:** Of the 143, 16 were excluded due to bilateral oophorectomy or initiation of ovarian function suppression within 12 months, and 2 due to missing data at 12 months. In the remaining 125, median age at enrollment was 45 (range 25-55). 103 (82%) had CRA at 12 months, including 68% of patients </= 45 (43/63) and 97% of patients >45 (60/62). Median pre-chemotherapy AMH was 0.11 (range 0.01-8.63). 12-month CRA was more likely in women who received bevacizumab ($p<0.01$), were >45 ($p<0.01$), and had AMH </=0.11 ($p<0.01$) pre-treatment. Hormonal tx was not associated with 12-month CRA ($p=0.63$). 100 patients were eligible for 18-month CRA analysis: 81 (81%) had CRA, including 63% of patients </= 45 (33/52) and 100% (48/48) of patients >45. 18-month CRA was more likely in women >45 ($p<0.01$) and with AMH </=0.11 ($p<0.01$) pre-treatment. Bevacizumab ($p=0.15$) and hormonal tx ($p=0.07$) were not statistically significant predictors of 18-month CRA. **Conclusions:** Pre-chemotherapy AMH predicts risk of CRA at 12 and 18 months, and is a promising biomarker of ovarian reserve in young breast cancer survivors. Longer studies will be needed to ascertain whether lower pre-treatment AMH is associated with increased risk of later infertility. Clinical trial information: **NCT00433511**.

J Clin Oncol 31, 2013 (suppl; abstr 9511)

Predictive factors for chemotherapy feasibility in elderly patients with solid tumor: Results of GERCOR old prospective multicenter study.

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Abstract

Background: One quarter of patients with cancer are 75 year old and over. Previous studies suggested that geriatric parameters improved survival in elderly patients with solid advanced cancer and chemotherapy severe toxicity. A simplified scale would be helpful for oncologist to predict chemotherapy feasibility. The aim was to identify geriatric predictors of chemotherapy feasibility in chemo-naïve elderly patients. **Methods:** We conducted a prospective multicenter cohort study (NCT00664911). Inclusion criteria were: ≥ 75 years, solid tumor, able to receive at least 2/3 of the standard dose at the first course of treatment. Ten geriatric parameters were recorded at baseline by the oncologist: 1-three words test, 2-date and address for cognitive function, 3-Instrumental Activities of Daily Living (IADL), 4- monopodal stand-up test, 5-hospitalization during the previous year, 6-number of medicines taken for comorbidities, 7-creatinine clearance, 8-albumin serum level, 9-self-rated depressive mood question and 10-presence of a caregiver. The main outcome was chemotherapy feasibility defined by the ability to receive at least 3 months of the planned therapy. Multivariate logistic regression was used. **Results:** 576 patients were included in 49 centers from 2008 to 2012, 516 (89.6%) were eligible for analysis. Mean age was 81 years, 50.6% had colorectal cancer, 69.5% advanced stage and 83.6% had performance status 0-1. Chemotherapy feasibility was observed in 298 (57.8%) patients. Grade 3-4 toxicity was observed in 26.2% of patients. In multivariate analysis albuminemia < 30g/l (adjusted OR =2.34 CI95% [1.43-3.83]) and depressive mood (adjusted OR=1.55 CI95% [1.02-2.35]) were significantly associated with chemotherapy unfeasibility whereas others geriatrics parameters were not. **Conclusions:** Albuminemia and self rated depressive mood status were independently predictive for chemotherapy feasibility in elderly patients with solid tumor. Unexpectedly others geriatrics parameters were not independent predictors. Clinical trial information: **NCT00664911**.

J Clin Oncol 31, 2013 (suppl; abstr LBA9514)

Phase III study of NEPA, a fixed-dose combination of netupitant (NETU) and palonosetron (PALO), versus PALO for prevention of chemotherapy-induced nausea and vomiting (CINV) following moderately emetogenic chemotherapy (MEC).

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Abstract

Background: Management of CINV has been refined over the past several decades and CINV can now be managed with targeted prophylactic medications aimed at inhibiting several molecular pathways involved in emesis. NEPA, a fixed-dose combination of netupitant (NETU), a new NK_1 receptor antagonist (RA) and palonosetron (PALO), a pharmacologically distinct 5-HT_3RA, targets these dual antiemetic pathways and has been shown to uniquely work synergistically in vitro. **Methods:** This was a multinational, randomized, double-blind, parallel group study assessing the efficacy and safety of a single oral dose of NEPA (NETU 300mg + PALO 0.50 mg) versus a single oral 0.50 mg dose of PALO in 1,455 chemotherapy-naive patients (pts) receiving anthracycline-based chemotherapy (all pts received oral dexamethasone (DEX) 12 mg (NEPA) or 20 mg (PALO) on Day 1). The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the delayed (25-120h) phase. **Results:** Treatment groups had comparable demographic characteristics with the majority of the population being female (98%) and white (80%), with a mean age of 54 yrs; 97% pts had breast cancer. NEPA showed superior CR rates compared to PALO during the delayed, acute, and overall phases. NEPA was also superior to PALO during the delayed/overall phases for complete protection, no emesis, and no significant nausea. Most frequently reported study drug-related adverse events (AEs) for NEPA included headache (3.3%) and constipation (2.1%). The majority of adverse events for NEPA-treated pts were mild/moderate and there were very few (0.7%) severe drug-related AEs. The type and frequency of AEs were comparable between NEPA and PALO. There was no evidence of any cardiac safety concerns for NEPA or PALO. **Conclusions:** NEPA, a novel single-day fixed-dose combination targeting dual antiemetic pathways, is superior to PALO (both associated with DEX) in preventing CINV in pts receiving MEC. Clinical trial information: **NCT01339260**.

CR rates (% pts)	NEPA (N=724)	PALO (N=725)	P value
Delayed (25-120 h)	76.9%	69.5%	0.001
Acute (0-24 h)	88.4%	85.0%	0.047
Overall (0-120 h)	74.3%	66.6%	0.001