Abstract ID: LBA2 (163254)

A phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (CCTG CE.6, EORTC26062-22061, TROG 08.02, NCT00482677).

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Background: The EORTC (26981-22981)/NCIC CTG (CE.3) RCT in newly diagnosed glioblastoma (GB) showed increased overall survival (OS) with concomitant and adjuvant temozolomide (TMZ) added to radiotherapy (RT). Pts were 18-71 (median 56) years; however a trend of decreasing benefit from the addition of TMZ with increasing age was noted. Recent RCTs in elderly GB detected non-inferiority of 40 Gy/15 v 60 Gy/30 RT and superior survival was noted for MGMT-methylatedpts treated with TMZ alone. However, whether the addition of TMZ to RT improves survival inelderly pts remained unanswered. **Methods:** We conducted a global randomized phase III clinical trial for patients ≥ 65 yrs with histologically confirmed newly diagnosed GB, ECOG 0-2, randomized 1:1 to receive 40Gy/15 RT v 40Gy/15 RT with 3 weeks of concomitant TMZ plus monthly adjuvant TMZ until progression or 12 cycles. Stratification was by centre, age (65-70, 71-75, or 76+), ECOG 0, 1 vs 2, and biopsy vs resection.

Abstract ID: 6007 (164086)

Gemcitabine plus cisplatin (GP) versus 5-FU plus cisplatin (FP) as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC): A randomized, open-label, multicenter, phase III trial.

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Background: There are no well-established first-line chemotherapy regimens for recurrent or metastatic (R/M) NPC. Several small phase II trials suggest that GP has promising efficacy and acceptable toxicities. This phase III trial compared the efficacy and safety of GP versus FP as first-line therapy for patients with R/M NPC. This trial has been selected as “Trials in Progress” and presented in the poseter session in 2015 ASCO meeting (Abstract No. TPS6098). **Methods:** Eligible patients were randomized in 1:1 ratio to receive either GP (gemcitabine 1 g/m2 on days 1, 8, cisplatin 80 mg/m2 on day 1, q3w) or FP regimens (5-FU 4 g/m2 CIV over 96 hours, cisplatin 80 mg/m2 on day 1, q3w) for up to 6 cycles. The primary endpoint was progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), safety and quality of life. **Results:** From February 2012 to October 2015, 362 patients from 22 institutions were randomly assigned to GP (n = 181) or FP (n = 181) group. Baseline characteristics were similar between both arms. The median PFS was 6.83 months in the GP group and 5.70 months in the FP group (HR = 0.57; 95% CI [0.46-0.71]; p < 0.0001). At 1 year, the PFS rate was 21% (95% CI, 18 to 24) with GP versus 6% (95% CI, 4 to 8) with FP. This effect was consistent for the best ORR (GP 68.3% versus FP 47.1%; p = 0.0001). The most common grade ≥ 3 related adverse events (AEs) were leukopenia (21.1%) and thrombocytopenia (11.1%) with GP and mucositis (12.9%) with FP. Treatment discontinuation due to related AEs was similar between both arms (GP 3.9% versus FP 5.5%; p = 0.458). **Conclusions:** First-line GP significantly improved PFS compared to FP in R/M NPC. Consistent benefit was seen with ORR. AEs were manageable with similar low discontinuation rates in both arms. Updated and OS data will be presented at ASCO meeting. Clinical trial information: NCT01528618.

Abstract ID: 6000 (170084)

Induction docetaxel platinum 5-FU (TPF) followed by cetuximab-radiotherapy (cetux-RT) versus concurrent chemo-radiotherapy (CT/RT) in patients with N2b/c-N3 non operated stage III-IV squamous cell cancer of the head and neck (SCCHN): Results of the GORTEC 2007-02 phase III randomized trial.

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Background: Both CT/RT, and cetux-RT have been established as standard treatments in non-operated locally advanced SCCHN. Taxotere-Platinum-5FU (TPF) is a reference induction regimen in this type of cancer and it is not known whether the addition of induction TPF followed by cetux-RT could improve the outcome of patients with locally advanced SCCHN, as compared to standard CT/RT. **Methods:** GORTEC 2007-02 trial was restricted to patients (pts) with palpable cervical nodes (N2b/c-N3) and was run in parallel with GORTEC 2007-01 randomized trial testing the addition of concurrent chemotherapy (CT) to cetux-RT in pts with N0-N2a disease. Selection criteria were pts fit for receiving CT with non-metastatic, non-operated stage III-IV SCC of oral cavity, oro/hypopharynx and larynx, regardless of HPV status. Pts were randomized to receive concurrent CT/RT (arm A) or induction TPF plus cetux-RT (arm B). RT was 70 Gy (2 Gy per day, 5 days per week). Concurrent CT was: 3 cycles of carboplatin 70mg/m²/d + 5FU 600mg/m²/d D1-4 (Calais JNCI 1999). Primary end point was progression free survival (PFS). To detect a hazard ratio of 0.66, inclusion of 370 pts was required to achieve 80% power at 2-sided significance level of 0.05. **Results:** Between 2009 and 2013, 370 pts were randomized. The median follow-up was 31.2 months. There is no difference in PFS, median 11.5 m (arm A) vs 12.5 m (arm B); HR = 0.95, [95%CI 0.72-1.27; p = 0.74]. At the analysis time, 103 deaths were observed in arm A and 107 in arm B. There is no difference in median OS, 24.6 m vs 22.8 m; HR = 1.10; [95%CI 0.84-1.45; p = 0.48]. At 24 months, loco-regional control was 46.6% vs 43.3; HR = 0.97; [95%CI 0.73-1.30; p = 0.85] and distant free metastasis 86.4% vs 92.9% HR = 0.50; [95%CI 0.22-1.11; p = 0.081]. Grade 3-4 neutropenia occurred in 25.8% of pts in arm B vs none in arm A. **Conclusions:** GORTEC 2007-02 failed to demonstrate any superiority of induction TPF followed by cetux-RT vs CT/RT in this category of very poor prognosis locally advanced SCCHN. CT/RT remains the standard of care in this population.

Abstract ID: 6009 (164984)

Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): CheckMate141.

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Background: Patients (pts) with R/M SCCHN have poor prognosis, and median OS for pts with platinum-refractory disease is ≤6 mo. We investigated if nivo, a fully human IgG4 anti-PD-1 mAb improves OS in pts with platinum-refractory R/M SCCHN compared to IC. **Methods:** Pts aged ≥18 yr with R/M SCCHN and ECOG PS 0–1 were randomized 2:1 to nivo 3 mg/kg q2w (until PD or toxicity) or single-agent IC (MTX, docetaxel, or cetuximab). The primary endpoint was OS; top line data were presented at AACR. Secondary endpoints included ORR and PFS (RECIST 1.1). Here we report additional endpoints: quality of life (QoL) assessments, correlative biomarkers, and safety. OS, PFS, and ORR were compared between treatment arms, by PD-L1 expression (≥1%, 5%, and 10%) and HPV (p16 IHC) status. Cellular and serum biomarkers are being evaluated. Pts aged ≥18 yr with R/M SCCHN and ECOG PS 0–1 were randomized 2:1 to nivo 3 mg/kg q2w (until PD or toxicity) or single-agent IC (MTX, docetaxel, or cetuximab). The primary endpoint was OS; top line data were presented at AACR. Secondary endpoints included ORR and PFS (RECIST 1.1). Here we report additional endpoints: quality of life (QoL) assessments, correlative biomarkers, and safety. OS, PFS, and ORR were compared between treatment arms, by PD-L1 expression (≥1%, 5%, and 10%) and HPV (p16 IHC) status. Cellular and serum biomarkers are being evaluated. **Results:** 361 pts were randomized, 240 to nivo and 121 to IC. A 30% reduction in risk of death was observed for nivo-treated pts with a median OS of 7.5 mo (95% CI: 5.5–9.1) for nivo and 5.1 mo (95% CI: 4.0–6.0) for IC. Among pts with PD-L1 ≥1% expression, median OS for nivo vs IC was 8.7 vs 4.6 mo in pts ≥1%, 8.8 vs 4.6 mo for ≥5%, and 8.7 vs 5.2 mo for ≥10%. Overall hazard ratio (HR) for OS of 0.70 (97.73% CI: 0.51–0.96) was consistently better for PD-L1 expression ≥1%: 0.56 (95% CI: 0.37–0.84), for ≥5%: 0.50 (95% CI: 0.30–0.83), and for ≥10%: 0.56 (95% CI: 0.31–0.99). Median PFS for nivo vs IC was 2.1 vs 2.0 mo (HR 0.64; 95% CI: 0.44–0.93) for PD-L1 ≥1%, 3.2 vs 2.0 mo (HR 0.53; 0.33–0.84) for ≥5%, and 2.1 vs 2.1 mo (HR 0.53; 0.31–0.88) for ≥10%. ORR for nivo with PD-L1 ≥1%, ≥5%, and ≥10% was 18.2%, 25.9%, and 32.6%, respectively, compared to 3.3%, 2.3%, and 2.9% for IC. Any grade treatment-related AEs (TRAEs) occurred in 59.3% and 77.5% of pts on nivo or IC, respectively. Grade 3/4 TRAEs occurred in 13.6% and 35.1% of pts. QoL and correlative biomarker data will be presented. **Conclusions:** Nivo demonstrated significant OS benefit compared to IC. OS and ORR improvement was greater with PD-L1 expression ≥1%. Nivo had a lower incidence of TRAEs compared to IC. Nivo is the first immune checkpoint inhibitor to demonstrate improved OS in a randomized controlled trial in R/M SCCHN.

Abstract ID: 6011 (166094)

Preliminary results from KEYNOTE-055: Pembrolizumab after platinum and cetuximab failure in head and neck squamous cell carcinoma (HNSCC).

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Background: Current treatment options for patients (pts) with recurrent/metastatic (R/M) HNSCC who progress on platinum and cetuximab have very limited efficacy. Pembrolizumab, an anti–PD-1 antibody that blocks the interaction between PD-1 and PD-L1 and PD-L2, showed promising antitumor activity in R/M HNSCC in the KEYNOTE-012 trial. We present preliminary results from the phase 2, nonrandomized KEYNOTE-055 (NCT02255097) study evaluating pembrolizumab after progression on platinum and cetuximab in R/M HNSCC. **Methods:** Pts receive pembrolizumab 200 mg every 3 weeks. Key eligibility criteria include R/M HNSCC resistant to platinum and cetuximab therapies, measurable disease, and ECOG PS 0-1. Primary outcomes include overall response rate (ORR, RECIST v1.1 by central imaging vendor) performed every 6-9 wk and safety. Adverse events (AEs) were graded using CTCAE, v4.0. **Results:** In total, 172 pts were enrolled for safety, efficacy, and biomarker analyses. Preliminary analyses for this abstract focus on the first 50 pts enrolled. Median age was 59 y; 80% were male; 84% had ≥ 2 prior lines of therapy for metastatic disease. Median follow-up time was 6.8 mo (range, 0-12.1). Thirty-five (70%) pts experienced a treatment-related AE (TRAE), with 6 (12.0%) pts experiencing a grade 3-5 TRAE. Two (4%) pts discontinued and 1 (2%) pt died because of a TRAE. AEs of special immunologic interest occurred in 11 (22%) pts; hypothyroidism (n = 7; all grade 2) and pneumonitis (n = 2, grade 2; n = 1, grade 5) were the most common. Nine pts had a confirmed PR for an ORR of 18.0% (95% CI 8.6-31.4). Five pts had ongoing responses at the data cutoff. The stable disease rate was 18.0% (n = 9; 95% CI 8.6-31.4). **Conclusions:** These preliminary results confirm findings from KEYNOTE-012, which demonstrate that pembrolizumab has clinically significant antitumor activity and is well tolerated among pts with heavily pretreated R/M HNSCC. Further analyses in the total study population, including HPV status and response by anatomic site, will be presented.

Abstract ID: 9012 (163941)

A phase II open-label single-arm study of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC): Luret study.

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Background: *RET* fusions were identified as new driver oncogenes of NSCLC in 2012 and observed in 1-2% of all NSCLC. Vandetanib is a multi-targeted tyrosine kinase inhibitor having RET kinase activity. **Methods:** This was a multicenter, single-arm phase II study to evaluate the efficacy and safety of vandetanib in pts with advanced *RET*-rearranged NSCLC who failed at least one prior chemotherapy. Vandetanib was administered orally at 300 mg once daily in 28-day cycles. *RET* fusion positive-pts were screened by a nationwide genomic screening network with 196 institutions in Japan participating (LC-SCRUM-Japan). The primary endpoint was objective response rate by independent review committee (ORR). This study required 17 pts, with ORR of 30% considered non-promising and 60% promising (one-sided alpha = 0.05; beta = 0.2). **Results:** 1536 pts with advanced NSCLC without *EGFR* mutation were screened in the LC-SCRUM-Japan from February 2013 to March 2015 and 34 pts (2%) with *RET*-rearranged NSCLC were identified. A total of 19 pts (10 *KIF5B-RET*, 6 *CCDC6-RET*, and 3 unknown-*RET*) were enrolled in this study and 17 pts were eligible for efficacy analysis. The median age was 59 (range 41-80 years) and 74% were female. All pts had adenocarcinoma and 68% were never a smoker. 63% of pts had received 2 or more prior chemotherapy (range 1-12). Among 17 eligible pts, ORR was 53% (90% CI, 31 to 74) of which 9 partial responses met the primary endpoint, and disease control rate was 88%. The median progression-free survival (PFS) was 4.7 months (95% CI, 2.8 to 8.3). According to *RET* fusion subtypes, ORR and median PFS were 83% (5/6) and 8.3 months in pts with *CCDC6-RET* versus 20% (2/10) and 2.9 months in those with *KIF5B-RET*. The median overall survival was 11.1 months (95% CI, 9.4 to not reached). The safety profile of vandetanib was similar to that reported previously. The most common G3/4 toxicities were hypertension (58%), rash (16%), diarrhea (11%), and QTc prolongation (11%). **Conclusions:** Vandetanib showed marked antitumor activity in pts with advanced *RET*-rearranged NSCLC. In particular, it was indicated that *CCDC6-RET* subtype showed much higher sensitivity to vandetanib.

Abstract ID: 9004 (169928)

Local consolidative therapy (LCT) to improve progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC) who receive induction systemic therapy (IST): Results of a multi-institutional phase II randomized study.

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Background: We performed a randomized study to assess the effect of aggressive LCT in patients with oligometastatic NSCLC who did not progress after IST. **Methods:** This study was performed at MD Anderson, U. Colorado, and London HSC, Canada. Eligibility: 1) histologically confirmed NSCLC, 2) Stage IV disease, 3) ≤ 3 metastases, and 4) no RECIST progression after IST. Appropriate IST was defined as either ≥ 4 cycles of platinum doublet therapy or ≥ 3 months of erlotinib/crizotinib for patients with EGFR mutations/ALK fusions, respectively. Patients were randomized to either LCT ([chemo]radiation or surgical resection of all sites) +/- systemic therapy (ST) vs. ST alone. The ST regimen was physician choice from predefined standard-of-care regimens. The primary endpoint was PFS, with the hypothesis that immediate LCT would improve PFS time from 4 months to 7months (HR = 0.57) using ITT analysis. The planned study size was 94 randomized patients. Randomization was balanced dynamically by number of metastases, IST response, CNS metastases, nodal status, and EGFR/ALK status.

Abstract ID: 108 (167889)

Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC).

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Background: *MET* alterations leading to exon 14 skipping occur in ~4% of lung carcinomas, resulting in MET activation and sensitivity to MET inhibitors in vitro. Crizotinib, initially developed as a MET inhibitor, is currently approved for the treatment of *ALK*-positive NSCLC. We present crizotinib antitumor activity and safety data in pts with advanced *MET* exon 14-altered NSCLC. **Methods:** Pts with *MET* exon 14-altered NSCLC were enrolled into an expansion cohort of the ongoing phase I PROFILE 1001 study (NCT00585195) and received crizotinib at a starting dose of 250 mg BID. Responses were assessed using RECIST v1.0. **Results:** As of the data cut-off of Oct 30, 2015, 18 pts with *MET* exon 14-altered NSCLC had enrolled and 17 received treatment (15 response-evaluable, 2 not yet evaluable). Two pts discontinued treatment (1 due to an AE, 1 preferred another treatment formulation). Median age was 68 y (range 59−87). Tumor histology was as follows: 71% adenocarcinoma, 18% sarcomatoid adenocarcinoma, 6% adenosquamous carcinoma, and 6% squamous cell carcinoma. 65% were former and 35% never-smokers. Duration of treatment ranged from 0.5 to 9.1+ mo, with 88% of pts (15/17) still ongoing. Evidence of antitumor activity per RECIST was documented in 10/15 pts: 5 with confirmed PRs (all seen at the first scheduled tumor assessment at 8 wk ± 1 wk) and 5 with unconfirmed PRs (3 pts remained evaluable). Median PFS could not be calculated, with no deaths or PD by the data cut-off. Treatment-related AEs (TRAEs) were reported in 82% of pts; the most common were edema (35%) nausea (35%), vision disorder (29%), bradycardia (24%), and vomiting (24%). Most TRAEs were grade 1/2 in severity. One grade 3 TRAE (edema) and no grade 4/5 TRAEs were reported. Accrual of pts with *MET* exon 14-altered NSCLC continues. Updated data with a cut-off of Feb 2016 will be presented. **Conclusions:** Crizotinib has antitumor activity in pts with *MET* exon 14-altered NSCLC. The drug has a generally tolerable AE profile, consistent with that previously reported for pts with *ALK*-positive or *ROS1*-rearranged NSCLC. Further study of crizotinib in this pt population is warranted.

Abstract ID: 9008 (167434)

Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from the J-ALEX study.

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Background: ALC showed promising efficacy and tolerability in the phase I/II study (AF-001JP). Here, we conducted the randomized open-label phase III trial (J-ALEX study, JapicCTI-132316) to prove superior progression-free survival (PFS) of ALC to CRZ in *ALK*+ NSCLC patients (pts) without prior ALK inhibitor treatment. **Methods:** *ALK*+ NSCLC pts were randomized 1:1 either to receive ALC (300 mg b.i.d.) or CRZ (250 mg b.i.d.) and stratified by ECOG PS (0/1 vs 2), treatment line (1^{st} vs 2^{nd}), and clinical stage (IIIB/IV vs recurrence). Treatment on both arms was continued until disease progression or unacceptable toxicity. Primary endpoint was PFS according to the blinded independent review board. Secondary endpoints included overall survival, objective response rate, and safety. Under an assumption of expected hazard ratio (HR) of 0.643, 164 events were required to have 80% power with 2-sided alpha of 0.05. Three interim analyses (IA) for early stopping due to efficacy were planned after 33%, 50%, and 75% of required PFS events occurred. **Results:** 207 pts were enrolled at 41 centers in Japan between November 2013 and August 2015. 98%, 73%, and 64% of the pts were PS0-1, stage IV, and 1st line, respectively. A second IA was performed on 6^{th} February 2016. Independent data monitoring committee recommended the release of study data because the superiority in PFS had been demonstrated. The PFS HR of ALC arm to CRZ arm was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank $p<0.0001$). Median PFS was not reached (95% CI: 20.3-Not Estimated) in ALC arm while it was 10.2 months (95%CI: 8.2-12.0) in CRZ arm. In the ALC arm, only constipation (36%) was an adverse event with >30% frequency, while in the CRZ arm nausea (74%), diarrhea (73%), vomiting (59%), visual disturbance (55%), dysgeusia (52%), constipation (46%), ALT elevation (32%), and AST elevation (31%) were seen in >30% pts. Grade 3-4 AEs occurred with greater frequency in the CRZ arm (ALC arm: 27% vs CRZ arm: 51%). There were no treatment-related deaths in either arm. **Conclusions:** At J-ALEX IA, ALC demonstrated significantly prolonged PFS compared with CRZ and was well tolerated with a favorable AE profile.

Abstract ID: 8500 (168506)

Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer.

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Background: We assessed rates of and time to treatment failure (TF) [either grade ≥ 3 radiation pneumonitis (RP) or local recurrence (LR) within 12 months] in a Bayesian randomized trial of intensity-modulated radiotherapy (IMRT) vs. 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced non-small cell lung cancer (NSCLC). **Methods:** Assumptions for chosen sample size (n = 150) were that TF rate is log-normally distributed; IMRT will produce TF rates of 30% at 6 months (mos) and 40% at 12 mos; and 3DPT would reduce the TF rate by 10%. Pairs of IMRT and 3DPT plans were created for each patient. Patients were eligible for randomization only if both plans satisfied normal tissue constraints at the same radiation dose. Patients not eligible for randomization (NR) were treated with the modality producing the better plan. Patients denied coverage for protocol treatment were treated with the modality that was covered. **Results:** Of 255 enrolled patients, 149 were randomly allocated to IMRT (n = 92) or 3DPT (n = 57), and 106 received NRIMRT (n = 70) or NR3DPT (n = 36). Among randomized patients, patient characteristics were well balanced, but in 3DPT group, target volumes were larger (P= 0.071), and more patients received higher doses to tumors and had larger lung volumes receiving ≥ 30-80 Gy (V30-80) than that in IMRT group. TF rates at 12 mo were 20.7% in all, 15.6% in IMRT, and 24.6% in 3DPT groups; corresponding median times to TF were 10.5 mos in all, in IMRT, and 3DPT groups. RP rates were 8.7% in all, 7.2% in IMRT, and 11.0% in 3DPT groups. The median times to RP were 4.3, 4.5, and 4.0 mos in all, in IMRT, and in 3DPT. The incidence of LR were 23.5%, 22.8%, and 24.6% in all, in IMRT, and in 3DPT. The median times to LR were 13.0, 12.7, and 13.4 mos in all, in IMRT, and in 3DPT. Among nonrandomized patients, the IMRT group was younger (P= 0.013) and had higher-stage disease (P= 0.071); lung V20-40 was significantly lower in NR-3DPT patients, but was not different at other dose levels. The TF rates and time to TF were no different for NR-IMRT vs. NR-3DPT. **Conclusions:** No differences were found between IMRT vs. 3DPT in TF in this randomized trial.

Abstract ID: 8507 (166472)

E1505: Adjuvant chemotherapy +/- bevacizumab for early stage NSCLC—Outcomes basedon chemotherapy subsets.

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Background: Adjuvant chemotherapy (chemo) for resected early stage NSCLC provides modest survival benefit. E1505 offers the first opportunity to study 4 modern cisplatin-based regimens in the adjuvant setting in the context of a single trial. As previously reported from this trial, the addition of bevacizumab (B) to adjuvant chemo failed to improve the primary endpoint of overall survival (OS HR=0.99; 95% CI: 0.82-1.19, p=0.91) or disease free survival (DFS HR=0.99; 95%CI: 0.85-1.15, p=0.89). Here we explore outcomes by chemo regimen utilized. **Methods:** Patients (pts) with resected early stage NSCLC, stratified by stage, histology, sex, and chemo option, were randomized 1:1 to chemo alone or chemo with B (15 mg/kg every 3 weeks for up to 1 year). Chemo consisted of a planned 4 cycles of every 3-week cisplatin (75 mg/m^2 d1) with investigator's choice of vinorelbine (V) (30 mg/m^2 d1,8), docetaxel (D) (75 mg/m^2 d1), gemcitabine (G) (1200 mg/m^2 d1,8), or pemetrexed (P) (500 mg/m^{2}d1). P was added in 2009 for non-squamous (NSq) pts only. **Results:** From 7/2007 to 9/2013, 1501 pts were enrolled: V 25%, D 23%, G 19% and P 33%. Arms were well balanced for known prognostic factors; 28% had Sq histology. Median f/up per chemo group is: V 54.3 months (mos); D 60.3 mos; G 57.0 mos; P 40.6 mos. When pts were pooled across +/- B arms and divided into NSq and Sq cohorts (to account for P restriction to NSq pts) there was no significant difference in OS or DFS by chemo regimen with the following logrank p-values: OS NSq, p=0.19; DFS NSq, p=0.67; OS Sq, p=0.96; DFS Sq, p=0.85. Toxicities were consistent with known profiles of the drugs. V was associated with more neutropenia and G with more thrombocytopenia. Sq pts had no differences in total Gr 3-5 toxicity by chemo groups, but NSq pts who received P had significantly less total Gr 3-5 toxicity (p<0.001) than NSq pts receiving other regimens. **Conclusions:** No differences in OS or DFS were observed between 4 different adjuvant cisplatin-based chemotherapy regimens for surgically resected early stage NSCLC patients.

Abstract ID: LBA8505 (162941)

Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC).

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Background: SCLC remains among the most deadly of malignancies. Rovalpituzumab tesirine is a first-in-class ADC comprised of a humanized monoclonal antibody against DLL3, a dipeptide linker, and a pyrrolobenzodiazepine (PBD) dimer toxin. DLL3 is highly expressed in neuroendocrine tumors, including approximately 80% of SCLC. The emerging results of the SCLC patients (pts) in a first-in-human study (NCT01901653) are reported here. **Methods:** Pts with progressive SCLC after at least 1 previous systemic therapy were eligible. Efficacy was assessed by the investigator via RECIST v1.1, and toxicity graded per CTCAE v4.03. When available, archived tumor tissue was assessed retrospectively for DLL3 expression by immunohistochemistry.

Abstract ID: 8504 (165387)

CONVERT: An international randomised trial of concurrent chemo-radiotherapy (cCTRT) comparing twice-daily (BD) and once-daily (OD) radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status (PS).

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Background: cCTRT is the standard of care for good PS LS-SCLC but there is no international consensus on a standard regimen. BD RT has not been adopted widely due to concerns regarding logistics and toxicity. Our aim was to compare overall survival and toxicity of BD with OD RT using modern conformal RT techniques given concurrently with chemotherapy. **Methods:** Patients were randomised 1:1 to receive 45Gy in 30 BD fractions over 3 weeks or 66Gy in 33 OD fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy (4 to 6 cycles of Cisplatin 25mg/m^2 days 1-3 or 75mg/m^2 day 1 with Etoposide 100mg/m^2 days 1-3), followed by PCI if indicated. RT was planned using 3D conformal or IMRT. Patients were stratified by centre, 4/6 cycles CT and PS 0,1/2. The primary endpoint was 2-year survival and all analyses were by intention to treat. **Results:** 547 patients (274 BD and 273 OD) were recruited between April 2008 and November 2013 from 88 centres. Patients' characteristics were well balanced in both arms. 88% and 86% of patients in BD and OD arms received PCI. At a median follow up of 45 months for those alive; two-year survival was 56% (95% CI 50-61) vs 51% (95% CI 45-57) and median overall survival was 30 months (95% CI 24-34) versus 25 months (95% CI 21-31) (HR 1.17, 95% CI 0.95-1.45; p = 0.15) for BD and OD treatment, respectively. Toxicities were comparable except for significantly more grade 3/4 neutropenia (74% BD vs 65% OD, p = 0.03). There was no statistical difference, between BD and OD respectively, in rates of febrile neutropenia (23.4%, 18%), grade 2 oesophagitis (63%, 55%), grade 3/4 oesophagitis (19%, 19%), and grade 3/4 radiation pneumonitis was rare (2.5%, 2.2%). 3 patients died from RT toxicity within 3 months of completing RT (1 BD vs 2 OD). **Conclusions**: OD RT did not result in a superior survival or worse toxicity than BD RT, supporting the use of either regimen for standard of care treatment of LS-SCLC with good PS. The survival for both regimens was higher than previously reported and using modern RT techniques radiation toxicities were lower than expected.

Abstract ID: LBA1 (164642)

A randomized trial (MA.17R) of extending adjuvant letrozole for 5 years after completing an initial 5 years of aromatase inhibitor therapy alone or preceded by tamoxifen in postmenopausal women with early-stage breast cancer.

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Background: Five years of aromatase inhibitor (AI) therapy either as up-front treatment or after 2-5 years of tamoxifen has become the standard of care for postmenopausal women with hormone receptor positive early breast cancer. Extending treatment with an AI to 10 years may further reduce the risk of breast cancer recurrence. **Methods:** We conducted a double-blind, placebo-controlled trial (Canadian Cancer Trials Group MA.17R) to test the efficacy of extending AI treatment for an additional five years using letrozole. The primary endpoint was disease-free survival.

Abstract ID: 512 (165547)

Efficacy of palbociclib plus fulvestrant (P+F) in patients (pts) with metastatic breast cancer (MBC) and ESR1 mutations (mus) in circulating tumor DNA (ctDNA).

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Background: PALOMA-3 is a randomized, double-blind, phase III study comparing P+F with fulvestrant plus placebo (F+Pla) in pre- and postmenopausal women with HR+/HER2– MBC that progressed on prior endocrine therapy. Recent studies have implicated ESR1 mu as a mechanism for acquired endocrine resistance in MBC. ctDNA assessed in plasma is a potential surrogate for a tumor's genetic profile. Here, we assess the relationship between ctDNA ESR1 mu status and palbociclib sensitivity, and the reproducibility of ESR1 ctDNA analysis. **Methods:** 396 baseline plasma samples from 521 pts enrolled in PALOMA-3 were collected and consented for use in this study. DNA was extracted from 2 mL aliquots using the QIAamp Circulating Nucleic Acid Kit and 12 ESR1 ligand-binding domain mus were analyzed in exons 5, 7, and 8 by Sysmex Inostics. To assess reproducibility of ESR1 mu analysis, separate samples were analysed by droplet digital PCR. **Results:** ESR1 mus were detected in 106 (26.8%) of the 395 plasma samples tested, most frequently D538G (14.1%), E380Q (8.1%), Y537S (7.3%), and Y537N (4.5%). Mus were poly-clonal in 10.1% of pts. All 106 pts with ESR1 mus were previously treated with an aromatase inhibitor; no ESR1 mus were identified in pts previously treated with tamoxifen only. Overall, median progression-free survival (PFS) was 5.7 months (mos) (95% confidence interval [CI]: 3.7–9.4) for pts with ESR1 mus versus 9.2 mos (95% CI: 7.5–10.9) for pts without ESR1 mus (hazard ratio [HR] = 1.33 [95% CI: 0.99–1.80]; 2-sided P= 0.0572). Median PFS was significantly longer in the P+F group compared with the F+Pla group both in pts without a detectable ESR1 mu (9.5 vs 3.8 mos; HR = 0.44 [95% CI: 0.31–0.62], 1-sided P< 0.0001) and in pts with an ESR1 mu (9.4 vs 4.1 mos; HR = 0.52 [95% CI: 0.32–0.87], 1-sided P= 0.0052). In samples independently tested by droplet digital PCR (353/395), the concordance between the two assays was 94.1% (Kappa = 0.84). **Conclusions:** ESR1 mus, detected in plasma ctDNA, were identified in a high percentage of pts with HR+ MBC confirming an important role in endocrine-resistance. P+F treatment provided significant benefit for MBC pts with and without ESR1 mus.

Abstract ID: 507 (165131)

PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2– advanced breast cancer (ABC).

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Background: Hormonal therapy (HT) is the mainstay for patients (pts) with ER+ BC. P, a cyclin-dependent kinase 4/6 inhibitor, blocks growth of ER+/HER2– BC preclinical models. In PALOMA-1, an open-label Ph 2 trial, addition of P to L improved median PFS vs L alone (20.2 months [mo] vs 10.2 mo) in pts with first-line ER+/HER2– ABC with acceptable safety, leading to accelerated FDA approval. PALOMA-2 is a randomized double-blind Ph 3 trial designed to confirm these results. **Methods:** 666 postmenopausal pts with no prior systemic therapy for ABC were randomized 2:1 to receive P (oral 125 mg/d; 3 wks on/1 wk off) + L (2.5 mg/d continuously) or PLB + L every 28 days until disease progression, consent withdrawal or death. Pts were stratified by disease site, disease-free interval from end of (neo)adjuvant therapy, and prior HT (yes/no). Primary endpoint: investigator-assessed PFS; key secondary endpoints: overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR=CR + PR + SD $\geqslant$24 wks), patient-reported outcomes and safety. Tumor assessments were every 12 wks. 347 events were needed with 90% power to detect a hazard ratio (HR) $\leqslant$0.69 in favor of P+L (1-sided α =0.025). **Results:** By 26 Feb 2016, 331 PFS events occurred. Baseline characteristics were well balanced. Median PFS was 24.8 mo (P+L) vs 14.5 mo (PLB+L) (HR=0.58 [0.46–0.72], P<0.000001). ORR was improved with P+L (42.1% vs 34.7%, P=0.031; 55.3% vs 44.4% in pts with measurable disease [P=0.013]). CBR was 84.9% vs 70.3% (P<.0001). Common adverse events (AEs; all grades) with P+L vs PLB+L were neutropenia (79.5% vs 6.3%), fatigue (37.4% vs 27.5%), nausea (35.1% vs 26.1%), arthralgia (33.3% vs 33.8%) and alopecia (32.9% vs 15.8%). Most common severity seen was G3 for neutropenia (56.1%) and G1 for the other AEs. Febrile neutropenia was seen only with P+L (2.5%). Permanent discontinuation due to AEs was 9.7% (P+L) vs 5.9% (PLB+L). OS data are immature; final OS analysis is pending. **Conclusion:** PALOMA-2 expands and confirms the significant clinical benefit and safety of P+L in ER+/HER2– ABC pts who had not received prior systemic therapy for their advanced disease.

Abstract ID: 500 (166834)

Pathologic complete response (pCR) rates after neoadjuvant trastuzumab emtansine (T-DM1[K]) + pertuzumab (P) vs docetaxel + carboplatin + trastuzumab + P (TCHP) treatment in patientswith HER2-positive (HER2+) early breast cancer (EBC) (KRISTINE).

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Background: K and P bind different HER2 domains and have marked antitumor activity in HER2+ breast cancer. KRISTINE (NCT02131064) is an open-label phase 3 study comparing neoadjuvant K + P (KP) vs TCHP in patients with HER2+ EBC. This provides the first phase 3 data for a complete neoadjuvant regimen omitting standard chemotherapy. **Methods:** The primary endpoint was pCR rate (ypT0/is, ypN0). Treatment-naive women with stage II-IIIC centrally assessed HER2+ EBC were randomized to 6 cycles of KP or TCHP and were then evaluated for pCR. The Cochran Mantel-Haenszel $\chi 2$-test stratified by hormone receptor status and clinical stage was used to compare pCR rates. The study had 90% power to detect a 15 percentage point increase in pCR from 60% (TCHP) to 75% (KP). Secondary endpoints included breast conserving surgery (BCS) rate, safety, and patient-reported outcomes. **Results:** Baseline demographic and disease characteristics were comparable between the TCHP (n = 221) and KP (n = 223) arms. pCR rates were 55.7% (95% CI 48.8–62.3%) and 44.4% (95% CI 37.8–51.2%) in the TCHP and KP arms, respectively (p= 0.0155). More women in the TCHP vs KP arm underwent BCS (52.6% vs 41.7%, p= 0.0228). In patients with ER+ EBC, pCR was 44.8% in the TCHP arm and 37.9% in the KP arm; it was 72.4% with TCHP and 53.8% with KP in women with ER-EBC. The incidence of grade $\geqslant$ 3 AEs and SAEs was lower with KP in the safety population (Table). Time to a $\geqslant$ 10-pt decrease from baseline in health related quality of life (HRQoL, 4.6 vs 3.0 months) and physical function (4.9 vs 2.8 months) was longer in the KP arm. **Conclusion:** While treatment with KP led to pCR in 44.4% of women, TCHP yielded a significantly higher pCR rate. However, KP had a notably better safety profile, and HRQoL and physical functioning were maintained longer.

Abstract ID: LBA503 (162159)

Heritage: A phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-1401O versus Herceptin

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Background: Trastuzumab has revolutionized treatment of HER2+ breast cancer. Globally accessible alternatives are a critical need. We evaluated Myl-1401O, a proposed trastuzumab biosimilar, as treatment for HER2+ metastatic breast cancer (MBC), based on physicochemic alanalyses, nonclinical, pharmacokinetic and pharmacodynamic studies*. **Methods:** Heritage is adouble-blind, randomized clinical trial designed to evaluate comparative efficacy and safety of Myl-1401O vs Herceptin. Eligible patients (pts) had centrally confirmed, measurable HER2+ MBC without prior chemotherapy or trastuzumab for metastatic disease. Pts were randomized to receive either Myl-1401O or Herceptin with docetaxel or paclitaxel for a minimum of 8 cycles. Trastuzumabwas continued until progression. The primary endpoint was overall response (ORR) at Week 24 byblinded central evaluation using RECIST 1.1. Secondary endpoints include progression free survival (PFS), overall survival, and safety. A sample size of 456 pts was calculated to demonstrate equivalence in ORR at Week 24 for MYL-1401O vs Herceptin, defined as a 90% confidence interval(CI) for the ratio of best ORR within the equivalence margin (0.81, 1.24).

Abstract ID: 1000 (166500)

Interim joint analysis of the ABC (anthracyclines in early breast cancer) phase III trials(USOR 06-090, NSABP B-46I/USOR 07132, NSABP B-49 [NRG Oncology]) comparing docetaxel +cyclophosphamide (TC) v anthracycline/taxane-based chemotherapy regimens (TaxAC) in womenwith high-risk, HER2-negative breast cancer.

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Background: The ABC adjuvant trials (5/2007-11/2013) were developed by USOR and NSABP to determine if a regimen of TC for 6 cycles is non-inferior to combination regimens of doxorubicin/cyclophosphamide with docetaxel or paclitaxel (TaxAC) in women with resected high-risk, HER2-negative breast cancer. 1870 patients (pts) from B-49 were combined with 1077 from the Tax AC and TC groups of B-46-I/USOR 07132, and 1295 from USOR 06-090, for a total of 4242. A detailed history of this collaborative effort will be discussed. **Methods:** The primary endpoint was invasive disease-free survival (iDFS), defined as time to local, regional or distant recurrence, invasive contralateral breast cancer, second primary cancer, or death. Pts were stratified for: parent trial, pos nodes (0, 1-3, 4-9, 10+), and hormonal status (neg, pos). A hazard ratio (HR) from a stratified Cox model of 1.18 or more was pre-defined as inferior. HRs above 1 favor TaxAC. Our pre-specified interim monitoring plan was to report early for futility if HR was >1.18 when 334 iDFS events were observed (50% of planned 668 events for definitive analysis). **Results:** 2078 pts randomized to TC and 2052 to TaxAC (total 4130) began assigned therapy and comprise the analysis set. Median follow-up: 3.2 yrs. Pt and tumor characteristics are balanced by treatment: 69% hormone pos, 41% node neg, 51% high grade. With 334 iDFS events, observed HR for TC v TaxAC is 1.202 (95% CI 0.97-1.49), which exceeds 1.18, thus we are reporting early for futility. With 397 iDFS events, 3 yr iDFS is 91.7% for TC v 92.4% for TaxAC. For TNBC: 86.6% v 89.6%, HR, 1.42, (1.04-1.94). For hormone pos: 94.1% v 93.7%, HR, 1.08 (0.84-1.40). Tests for treatment interaction by hormone receptor, nodal status, and protocol were negative. **Conclusions:** Statistical non-inferiority of the non-anthracycline regime could not be demonstrated. Longer follow-

up should clarify the clinical utility of these initial findings. **SUPPORT:** U10CA-180868, -21115, -189867, -180822, -180820; 180821; 180791; Genentech

Abstract ID: 1007 (170337)

Ten-year survival results of ACOSOG Z0011: A randomized trial of axillary node dissection inwomen with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node (Alliance).

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Background: The early results of ACOSOG Z0011 showed that selected sentinel node (SN)-positive patients (pts) treated with sentinel node biopsy (SNB), whole breast irradiation, and adjuvant systemic therapy experienced overall survival (OS) and disease-free survival (DFS) not inferior to those treated with axillary lymph node dissection (ALND). There were concerns that thefollow-up was inadequate to assure non-inferiority. The 10-year survival results of Z0011 are reported here. **Methods:** Clinically node-negative pts with 1 or 2 SNs with H&E-detected metastases were randomized to ALND or no further axillary specific treatment. All pts were toreceive whole breast irradiation and systemic therapy. OS and DFS were evaluated. **Results:** 446 pts were randomized to SNB alone and 445 to SNB + ALND. Pts in both arms were similar with respect to age, tumor size, Bloom-Richardson score, estrogen receptor status, adjuvant systemic therapy, tumor type, and stage. Pts randomized to SNB alone had a median of two lymph nodes removed whereas patients randomized to ALND had a median of 17 nodes removed. 17.6% of ALND pts had 3 or more involved nodes compared to 5.0% of SNB pts ($p < 0.001$). At a median follow-up of 9.25 years, there were no statistically significant differences in local ($p = 0.11$) or regional recurrence ($p = 0.45$) There were only 2 nodal recurrences in the ALND arm and 5 in the SNB alone arm. The 10-year locoregional recurrence-free survival was 93.2% for the ALND arm and 94.1% for the SNB alone arm ($p = 0.36$). The 10-year OS for pts undergoing SNB + ALND was 83.6% compared to 86.3% for SNB ($p = 0.40$), and DFS was 78.3% compared to 80.3%, respectively ($p = 0.30$). Eleven percent of pts did not receive radiation, and there were differences in radiation delivery noted upon review of 228 detailed radiation therapy records: supraclavicular field (18.9%) or high tangents (50%). Variations in radiation delivery were equally distributed among the three arms. **Conclusions:** Long-term results of ACOSOG Z0011 support the initial conclusion that SNB can achieve survival results not inferior to ALND. **Support**: U10CA180821, U10CA180882. **ClinicalTrials.gov Id**: NCT00003855

Abstract ID: 1005 (170268)

A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish Study (Protocol MF07-01).

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Background: The MF07-01 trial is a multicenter phase III randomized trial of treatment naivestage IV BC patients comparing loco-regional surgery (LRS) followed by appropriate systemictherapy (ST) vs ST alone. Aims: To compare 3-year survival and loco-regional progression (LRP). **Methods:** At initial diagnosis patients were randomized 1:1 to LRS group or ST group. After consideration of retrospective studies, we hypothesized at 36 months a survival difference between the two groups to be 18%. Assuming a 10% drop out rate and with a one sided log-rank test with a 95% CI and a 90% power 271 patients needed to be randomized. **Results**: 274 patients were accrued; 138 in the LRS group and 136 in the ST group. The groups were comparable regarding age, BMI, HER2 neu, tumor type and size, histologic grade, and bone and visceral metastasis (all $p > 0.05$). There were 76 (55%) deaths in the LRS group and 101 (74%) in the ST group during the median 40 (20-51) months follow-up. At 36 months the survival rate was similar the LRS group and the ST group (60% and 51%, respectively; $p = 0.5$). Overall survival (OS) was 34% higher in the LRS group compared to the ST group (HR: 0.66, 95%CI 0.49-0.88: $p = 0.005$). In unplanned subgroup analyses, OS was statistically higher in LRS group than ST group; ER/PR (+) (HR: 0.64, 0.46-0.91, $p = 0.01$), HER2 neu (-) (HR: 0.64, 95%CI 0.45-0.91; $p = 0.01$), patients < 55 years (HR: 95%CI 0.57, 0.38-0.86; $p = 0.006$), and solitary bone only metastasis (HR: 0.47, 95%CI 0.23-0.98; $p = 0.04$). The median survival was 14 months higher in the LRS group comparing with the ST group in bone only metastasis (56 vs 42 months, respectively; HR 0.67, 95%CI 0.43-1.07; $p = 0.09$). LRP was 1% ($n = 2$) in the LRS group and it was 11% ($n = 15$) in the ST group ($p = 0.001$). **Conclusion:** In this trial we did not observe improvement in 36 month survival with surgery. However, longer follow up revealed statistically significant improvement in median survival with surgery (46 vs.37 months) at median 40 months follow up. Additionally, patients with a more indolent form of metastatic BC such as ER (+), HER2 neu (-), solitary bone metastasis, and patients < 55 years old have a significant survival benefit with initial surgery.

Abstract ID: LBA509 (166552)

Therapy of relapsed/refractory metastatic triple-negative breast cancer (mTNBC) with an anti-Trop-2-SN-38 antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132): Phase II results.

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Background: Pts with mTNBC have an aggressive course with limited effective therapyoptions. Sacituzumab govitecan (IMMU-132) is a novel ADC comprising SN-38, the activemetabolite of the topoisomerase inhibitor, irinotecan, conjugated to an anti-Trop-2 humanized mAb. The mAb and ADC show immunotherapy effects in vitro (ADCC). Trop-2's expression isincreased in most epithelial cancers (>80%), including TNBC. **Methods:** A Phase I/II clinical trial(ClinicalTrials.gov, NCT01631552) enrolled relapsed/refractive (R/R) pts with mTNBC dosed with intravenous IMMU-132 on days 1 and 8 of 21-day treatment cycles. Treatment continued based ontolerance or until progression. Results, including complete responses (CR), partial response (PR), stable disease (SD), and clinical benefit ratio (CBR6), from the phase II are given.

Abstract ID: 3504 (161936)

Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance).

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Background: 80405 found no OS or PFS difference when Bevacizumab (BV) or Cetuximab (Cet) was added to 1st-line FOLFOX or FOLFIRI in mCRC pts. As location of the 1° may affect mCRC outcome, we assessed the impact of 1° side (R v L) on OS and PFS in 80405 pts. **Methods:** 1° location was determined by chart review: 1137 pts w/KRAS *wt* (codons 12 and 13) in main cohort; 252 pts w/ KRAS *mut* tumors treated w/ BV or Cet pre-amendment. R-sided = cecum to hepatic flexure; L-sided = splenic flexure to rectum. Transverse (T) = hepatic to splenic flexure. PFS per investigator. Kaplan Meier and Cox regression methods used. **Results:** KRAS *wt* pts: Median age = 59; synchronous = 78%. 1° site: R – 280 (25%); L – 689 (61%); T- 62 (5%); unsure – 106 (9%). OS & PFS (Table) difference by side statistically significant if adjusted for age, gender, BV / Cet, chemotherapy, prior therapy. There was a significant 1° side by biologic interaction (P int = 0.003, PFS and OS) but not by chemo, gender or RAS. OS, L-sided: Cet v BV, superiority (Log rank p = 0.04); R-sided: BV v Cet, superiority (p = 0.03). Results similar for PFS and if T colon allocated to R side. KRAS *mut* pts: 1°s: R - 35%; L- 50%. No statistically significant difference in any subset although OS favors L > R (only OS data shown). **Conclusions**: mCRC arising in the R v L colon are clinically different. In KRAS *wt* mCRC, pts w/ L-sided 1° tumor have superior OS and PFS v pts w/ R-sided 1°. Though not pre-planned analyses, OS and PFS were prolonged w/ Cet in L and w/BV in R but were poorer w/ Cet in R. Forthcoming molecular analysis of 1°s - e.g. BRAF, MSI, methylation - may provide a biological explanation. For now, stratification in mCRC studies by R v L 1° sidedness is indicated. These data support BV in 1st line treatment for mCRC pts w/R-sided 1° tumor regardless of KRAS status. Support: U10CA180821, U10CA180882.

Abstract ID: 3507 (169602)

CREST: Randomised phase III study of stenting as a bridge to surgery in obstructingcolorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST).

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Background: Uncertainty remains about the efficacy and safety of endoluminal stenting as an alternative to emergency surgery in patients with potentially curable obstructing left sided colorectal cancer. Emergency presentations still account for 20% of all colorectal cancer cases; obstruction is present in 80% of these. **Methods:** Patients presenting in the emergency setting with left-sided colonic obstruction needing urgent decompression and radiological features of a carcinoma were randomized to either: endoluminal stenting as a bridge to surgery or surgical decompression. Patients were stratified according to curative intent based on pre-operative staging investigations. A combined endoscopic/fluoroscopic technique was standardized in stent workshops with elective surgery performed 1-4 weeks later. **Results:** 246 patients from 39 units were randomized between 2009 and 2014 with 98% complying with allocated treatment. 92% were treated with curative intent. 30-day post-operative mortality (5.3% vs 4.4%) and length of hospital stay [15.5 days (IQR 10-26) vs 16 days (10-27)] were similar with stenting and surgery. Stenting achieved relief of obstruction in 82% of patients and reduced stoma formation; 69% emergency surgery v 45% with stenting as a bridge to surgery ($p < 0.001$). There were no significant differences in QoL at 3 and 12 months or critical care utilization. 1 year mortality for potentially curative patients did not differ by treatment group. **Conclusions:** CReST is the largest trial of endoluminal stenting in obstructing colorectal cancer. In patients fit enough to undergo surgery, stenting as a bridge to surgery reduced stoma formation without a detrimental effect on one-year survival. Post-operative mortality, length of hospital stay, critical care usage and Quality of Life were not different between the two treatment groups.

Abstract ID: 3511 (169716)

The potential of circulating tumor DNA (ctDNA) to reshape the design of clinical trialstesting adjuvant therapy in patients with early stage cancers.

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Background: The conventional approach to testing the benefit of adjuvant therapies in patients (pts) with relatively favorable prognoses is to follow a large number of pts for long periods of time, hoping that mature outcome data will document an improved outcome compared to control pts. We reasoned that the design of such trials could be improved if pts with minimal residual disease could be identified a priori through the presence of ctDNA, and the effects of adjuvant therapy then assessed through serial ctDNA assays. **Methods:** We carried out a prospective trial in 231 pts with Stage II colon cancer. Serial plasma samples were collected every 3 months starting 4-10 weeks after surgery. Somatic mutations in pts' tumors were identified via sequencing of 15 genes commonly mutated in colon cancer. We then designed personalized assays to quantify ctDNA in plasma samples. Adjuvant chemotherapy was administered at clinician discretion, blinded to ctDNA analysis. **Results:** Somatic mutations were identified in 230 (99.6%) of tumors. Matching ctDNA was detected in the immediate post-operative period in 14 of 178 (8%) pts not treated with chemotherapy, 11 of whom had recurred (79%) at a median follow-up of 27 months. In contrast, recurrence occurred in only 16 (10%) of the 164 pts with negative ctDNA not treated with chemotherapy (HR 15.66, log-rank P<0.0001). ctDNA was detected in the immediate post-operative period in 6 of 52 pts who went on to receive chemotherapy. The ctDNA status turned from positive to negative during adjuvant treatment phase in all 6 pts (100%) but became positive again following completion of chemotherapy in 2 pts, both of whom have recurred. In patients with serial samples available, the median lead-time between ctDNA detection and radiologic-recurrence was 167 days. **Conclusions:** Detection of ctDNA in pts with resected stage II colon cancer provides direct evidence of residual disease. As well as defining pts at very high risk of later radiologic-recurrence, serial ctDNA analysis may provide an early readout of adjuvant treatment effect. Including ctDNA analyses would increase the efficiency of clinical trials testing the benefit of adjuvant treatment.

Abstract ID: 3512 (168547)

FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 –accord 21 (METHEP-2), a unicancer GI trial.

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Background: Liver metastases (LM) from colorectal cancer (CRC) are initially resectable in only 10-15% of patients (pts). The conversion to resectability following induction chemotherapy is an important strategy to increase survival. Our study was designed to determine the most appropriate chemotherapy (associated with a targeted therapy) for CRC pts with LM considered as initially unresectable. **Methods:** This French phase II, multicenter, prospective trial, randomized pts between bi-chemotherapy (BiCT) versus tri-chemotherapy (TriCT). The population was initially stratified by targeted therapy depending on KRAS status and then by RAS status (from 02 Dec 2013 due to the change in cetuximab's [Cet] marketing authorization): Cet for wt(K)RAS pts and bevacizumab (Bev) for mtRAS pts. The hypothesis was to increase the rate of LM resection (R0-R1) from 50% with BiCT to 70% with TriCT (bilateral α-test 5%; power 90%). **Results:** 256 patients were randomized in 33 sites from February 2011 till April 2015: 126 BiCT (FOLFIRI [56 pts]; FOLFOX4 [70 pts]) and 130 TriCT (FOLFIRINOX). The resection rate (R0 or R1; CI95%) of the LM was 45.2% [36; 54] for pts treated with BiCT vs 56.9% [48; 66] for TriCT (p = 0.062).The LM resection rate (R0 or R1; CI95%) was 44.7% [35; 55] for pts treated with Bev (mtRAS) vs 55.6% [47; 64] for Cet (wtRAS) (p = 0.087). At the time of data analysis, the median follow-up (CI95%) was 22.5 months [19.6;29.5] for the BiCT pts and 23.5 months [19.8; 28.8] for the TriCT pts and at analysis 78 patients had died. The median overall survival (OS) is significantly different (p = 0.048): in the TriCT Arm the median OS was not reached and is 36 months [23.5;40.6] in the BiCT Arm. The severe toxicity rate was 37.6% for BiCT vs 41.7% for TriCT (p = 0.503). 38 BiCT pts and 34 TriCT pts had surgical complications, with two deaths in each arm. **Conclusions:** First line FOLFIRINOX chemotherapy, in association with a targeted therapy, showed a higher rate of LM R0/R1 resections than standard BiCT (FOLFIRI or FOLFOX4) combined with the same targeted therapy, with a statistically significant difference in terms of OS.

Abstract ID: 3503 (169985)

NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA).

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Background: The incidence of SCCA continues to rise annually in the US. 20% of patients (pts) will develop metastatic (met) disease which lacks a consensus approach to treatment. SCCA is largely driven by immune evasion of HPV-specific CD8 and CD4 T cells which promote oncogenesis for SCCA. Nivolumab (Nivo), a monoclonal antibody targeting PD-1 on T cells, promotes immune-mediated anti-tumor activity of T cells against HPV-positive cells in vitro. This is the first phase II trial of Nivo for pts with refractory met SCCA. **Methods:** Previously treated but immunotherapy naïve met SCCA pts were eligible. PD-L1 expression was not required. HIV+ (CD4 count > 300/uL) and hepatitis B/C pts were eligible. A Simon two-stage phase II trial (Ho: $p < .05$, Ha: $p \geq .20$) was conducted. All pts were evaluated by RECIST Criteria 1.1. Pts received Nivo (3 mg/kg) IV every 2 weeks. Optional pre-treatment and on-treatment tissue biopsies and plasma samples were collected for immune biomarkers and HPV/p16 status. All correlatives were evaluated at MDACC by the Immunotherapy Platform team and the Core Facility. **Results:** 39 pts were screened across the ETCTN network (May 2015 - October 2015); 37 pts were eligible. Median age was 56 years (interquartile range [IQR], 51.1-63.6); M:F was 12:25. Median number of prior therapies: 2 (range 1-8). All pts were evaluable for toxicity; 33 pts were evaluable for response. Median number of cycles: 6 (IQR, 3-10). Seven (21%) pts had a partial response and 19 (58%) pts had stable disease; disease control rate of 79%. Ten pts (one HIV+) remain on study [7 pts for > 6 months (M)]. Median progression-free survival was 4.1M. Common adverse events (AE): fatigue, nausea, and rash. Six pts had grade 3 AE's: fatigue (N = 2) and one pt each of pneumonitis, rash, anemia, and hyperglycemia. **Conclusions:** Currently, there is no consensus approach for met SCCA. NCI9673 is the first prospective phase II trial of nivolumab in refractory metastatic SCCA. Single agent nivolumab demonstrated potentially meaningful activity and was well tolerated. Further evaluation of immune checkpoint therapy in met SCCA is justified. Updated clinical results will be presented. Exploratory correlative work is ongoing.

Abstract ID: LBA4001 (164788)

FAST: An international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18.2 antibody, as first-linetherapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GEJ) adenocarcinoma.

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Background: Claudin18.2 (CLDN18.2) is a tight junction protein expressed by several cancers including gastric and GEJ adenocarcinoma. IMAB362 is a chimeric monoclonal antibody that mediates specific killing of CLDN18.2-positive cancer cells by activation of immune effector mechanisms. IMAB362 has demonstrated single-agent activity and was safe and tolerable inpatients (pts) with pretreated gastric cancer. **Methods:** Pts with advanced/recurrent gastric and GEJ cancer were centrally evaluated for CLDN18.2 expression by IHC (validated CLAUDETECT18.2 Kit). Eligible pts had a CLDN18.2 expression of ≥ 2+ in ≥ 40% tumor cells, an ECOG PS of 0–1 and were not eligible for trastuzumab. Pts were randomized 1:1 to first-line EOX (epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 d1, and capecitabine 625 mg/m^2 bid, d1–21; qd22) with or without IMAB362 (loading dose 800 mg/m^2, then 600 mg/m^2 d1, qd21). The study was extended by an exploratory Arm3 (N = 85) to investigate a high dose IMAB362 (1000 mg/m^2) plus EOX, (not subject here). The primary study endpoint was PFS (Arm 1 v 2, 70% power, HR 0.72, 1-sided p = 0.1).

Abstract ID: 4003 (171166)

Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC)- CALGB 80802 (Alliance).

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Background: An exploratory analysis of a randomized phase II study in HCC comparing doxorubicin (D) alone to doxorubicin plus sorafenib (D+S) showed a significant improvement in overall survival favoring D+S (JAMA, 2011). The results appeared promising compared to the historic outcomes seen in the pivotal sorafenib (S) trials. CALGB 80802 was designed to determine if D+S improved survival compared to S alone. **Methods:** Patients with histologically proven advanced HCC, no prior systemic therapy and Child-Pugh A were randomized to receive D 60 mg/m2 every 21 days plus S 400 mg PO twice daily (D+S) or S alone. For bilirubin ≥ 1.3x normal, D and S doses were halved. D was maxed out at 360 mg/m2. The study was stratified by extent of disease (locally advanced; metastatic), the primary endpoint was overall survival (OS); and secondary endpoint progression-free survival (PFS). The final analysis was to occur when 364 events were observed among 480 total patients, with 90% power to detect a 37% increase in median OS (10.7 to 14.7 months; 1-sided $\alpha = 0.05$). **Results:** The Alliance DSMB halted the study after accrual of 346 patients (173 on each of D+S and S) when a futility boundary was crossed at a planned interim analysis. With 107 events in each arm, median OS was 9.3 months (95%CI 7.1-12.9) for D+S, and 10.5 months (95% CI 7.4-14.3) for S with a hazard ratio (HR) 1.06 (95% CI 0.8- 1.4) for D+S vs. S. Median PFS was 3.6 (95% CI 2.8-4.6) and 3.2 months (95% CI 2.3-4.1), respectively (HR = 0.90, 95% CI 0.72-1.2). There were 38 deaths on treatment: 18 on D+S and 20 on S. Among these 8 [sepsis (1), dysphagia (1), pneumonia (1), cardiac (2), hepatic failure (2), and not otherwise specified (1)] on D+S, and 3 [fatigue (1), hepatic failure (1), and a secondary malignancy (1)] on S, were at least possibly related to treatment. A maximum grade 3 or 4 only hematologic adverse events (AE) occurred in 37.8% of patients on D+S and 8.1% of patients on S. Non-hematologic AEs were comparable, in 63.6% and 61.5% of patients, respectively. **Conclusions:** The addition of D to S resulted in higher toxicity and did not improve OS or PFS. The S median OS of about 10 months is consistent with previous reports.
NCI Grant U10CA180821

Abstract ID: 4005 (170054)

NETTER-1 phase III: Efficacy and safety results in patients with midgut neuroendocrine tumors treated with ^{177}Lu-DOTATATE.

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Background: There are limited therapeutic options for patients with advanced midgut NETs progressing on first-line somatostatin analog therapy. The purpose of this phase III trial was to evaluate the efficacy and safety of 177Lu-DOTA0-Tyr3-Octreotate (Lutathera) in patients with advanced, progressive sstr positive midgut NETs. **Methods:** 230 patients with grade 1-2 metastatic midgut NETs were randomized to Lutathera, 7.4 GBq every 8 weeks (x 4 administrations) vs Octreotide LAR 60 mg every 4 weeks. Primary endpoint was PFS (RECIST 1.1) with tumor assessment every 12 weeks. Secondary objectives included ORR, OS, toxicity and QoL. **Results:** In the intent-to-treat population (ITT), the median PFS was not reached for Lutathera and was 8.4 months with control ($p < 0.0001$, HR 0.21). There were 23 centrally confirmed disease progressions or deaths in the Lutathera arm and 67 in the Octreotide LAR 60 mg arm. The objective radiographic response rate (ORR) was 18% with Lutathera and 3% with control ($p = 0.0008$). Besides the scintigraphic 111In-pentetreotide tumor uptake score (Krenning scale > = 2), tumor burden and Ki67 grade had no significant effect on clinical efficacy outcomes (PFS, OS, TTP) in the Cox regression models. Interim OS analysis (13 deaths in Lutathera group and 22 in control group; $p = 0.019$) strongly suggests an improvement in OS. Only 5% (6 patients) experienced dose modifying toxicity with Lutathera. Grade 3 or 4 adverse events of neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in Lutathera arm vs. none in controls. **Conclusions:** The NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS and ORR, and suggests a potential survival benefit in patients with advanced midgut NETs treated with Lutathera in both ITT and PP analyses. Lutathera safety profile was found to be very favorable.

Abstract ID: 4000 (165706)

A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First resultsfrom the CRITICS study.

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Background: The mainstay of potentially curative treatment of gastric cancer is radical surgical resection. Because most patients in the Western world present with advanced stages long-term survival remains poor at about 25%, with local recurrences as part of treatment failure in up to 80% of cases. Postoperative chemoradiotherapy (CRT) and perioperative chemotherapy (CT) have demonstrated a survival benefit over surgery alone. The current randomized phase III CRITICS-study (NCT00407186) investigated whether chemoradiotherapy after neo-adjuvant chemotherapy and adequate (D2) surgery leads to improved overall survival (OS) in comparison with postoperative chemotherapy. Furthermore, toxicity of both treatment regimens was explored. **Methods:** Patients with stage Ib-IVa resectable gastric cancer were randomized after diagnosis. Neo-adjuvant CT was prescribed in both arms and consisted of 3 courses of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). After gastric cancer resection, patients received another 3 courses of ECC/EOC or CRT (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine). Primary endpoint is OS; secondary endpoints are: disease free survival, toxicity profile and quality of life. **Results:** Between January 2007 and April 2015, 788 patients from The Netherlands, Sweden and Denmark were randomized (393 CT; 395 CRT). Baseline characteristics were well balanced with 70% males and a median age of 61 years. 84% completed 3 cycles before surgery. In the CT arm 46% and in the CRT arm 55% completed treatment according to protocol. After a median follow-up of 50 months, 405 patients have died. The 5-year survival is 41.3% for CT and 40.9% for CRT (p=0.99). Toxicity was mainly hematological (grade III or higher: 44% vs 34%; p=0.01) and gastrointestinal (grade III or higher: 37% vs 42%; p=0.14) for CT and CRT, respectively. **Conclusion:** No significant difference in overall survival was found between postoperative chemotherapy and chemoradiotherapy.

Abstract ID: LBA4006 (162546)

ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial ofadjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma.

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Background: The ESPAC-3 trial compared adjuvant GEM with 5-fluorouracil/folinic acid forresected pancreatic cancer. GEM is the standard of care based on similar survival and less toxicity. ESPAC-4 aimed to determine whether combination chemotherapy with GEM/CAP improved survival compared to GEM monotherapy. **Methods:** Patients with pancreatic ductal adenocarcinoma were randomized within 12 weeks of surgery (stratified for R0/R1 resection margin status and country) to have either six 4 week cycles of IV GEM alone or GEM with oral CAP. The primary endpoint was overall survival; secondary endpoints were toxicity, relapse free survival, 2 and 5 year survival and quality of life. 722 patients (480 expected events), 361 in eacharm, were needed to detect a 10% difference in 2 year survival rates with 90% power (log-rank testwith 5% two-sided alpha).

Abstract ID: 5006 (166318)

Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA).

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Background: The Phase III TROPIC study (NCT00417079) reported significant improvement in overall survival (OS) for cabazitaxel 25 mg/m^{2}IV Q3W plus prednisone 10 mg PO QD (P) vs. mitoxantrone plus P in mCRPC pts previously treated with a docetaxel (D)-containing regimen. The FIRSTANA study examined if cabazitaxel 20 mg/m ^{2}(C20) or 25 mg/m ^{2}(C25) IV Q3W plus P is superior to docetaxel 75 mg/m ^{2}(D75) IV Q3W plus P in terms of OS in CN mCRPC pts. **Methods:** In this multinational, open label phase III study, mCRPC pts, ECOG PS 0-2, who had progressed after castration were randomized 1:1:1 to C20, C25 or D75 IV Q3W plus P. The primary endpoint was OS. Key secondary endpoints were safety, progression free survival (PFS), tumor PFS, tumor response (RECIST 1.1), PSA response, PSA PFS, pain response, pain PFS, time to skeletal-related events (SRE) and health-related quality of life (HRQOL). **Results:** Between May 2011 and April 2013, 1168 pts were randomized (C20=391, C25=389, D75=388). Baseline demographics and disease characteristics were similar across cohorts. The median number of treatment cycles was 9 for all dose groups. In the ITT analysis, median OS was 24.5 months for C20, 25.2 months for C25 and 24.3 months for D75. HR for C20 vs. D75 was 1.009 (0.85 to 1.197, p=0.9967) and for C25 vs. D75 was 0.97 (0.819 to 1.16, p=0.7574), indicating that C20 and C25 were not superior to D75 in terms of OS. PFS was 4.4 months for C20, 5.1 months for C25 and 5.3 months for D75 (NS). Tumor responses were superior in C25 (41.6%) compared to D75 (30.9%), p=0.0370. Other secondary endpoints did not significantly differ across dose groups. Adverse events (AEs) grade 3-4 were 41.2% in C20, 60.1% in C25 and 46.0% in D75; pts discontinuing treatment due to an AE were 25.2% in C20, 31.7% in C25 and 33.9% in D75. Febrile neutropenia, diarrhea and hematuria were more frequent in C25; peripheral neuropathy, peripheral edema, alopecia and nail disorders were more frequent in D75. **Conclusions:** C20 and C25 did not demonstrate superiority for OS compared to D75 in CN mCRPC pts. Among secondary endpoints only tumor responses were significantly superior for C25. AEs were less frequent in C20 for most categories.

Abstract ID: 5008 (169889)

Phase III non-inferiority study of cabazitaxel (C) 20 mg/m^2 (C20) versus 25 mg/m^2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D).

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Background: The Phase III TROPIC study (NCT00417079) reported a significant improvement in overall survival (OS) for C plus prednisone (P) (25 mg/m^2 once every 3 weeks plus 10 mg orally once daily) versus mitoxantrone plus P (Hazard Ratio [HR] 0.70; P < 0.0001) in pts with mCRPC previously treated with D. This PROSELICA study (NCT01308580) was designed to determine the relative efficacy and safety profile of C20 plus P compared with C25 plus P. **Methods:** In this randomized, open-label, multinational phase III study, pts with mCRPC and ECOG performance status 0–2, who progressed after treatment with D, were stratified (ECOG, RECIST, region) and randomized 1:1 to C20 or C25. To show that C20 could preserve ≥ 50% of the efficacy benefit showed by C25 in TROPIC, the HR of C20 vs C25 for the primary endpoint OS could not exceed 1.214 under 1-sided 98.89% confidence level adjusted after interim analyses. Secondary endpoints included progression free survival (PFS), safety, PSA, pain and tumor responses and quality of life. **Results:** From April 2011 to December 2013, 1200 pts were randomized (C20 n = 598; C25 n = 602). Patient characteristics were similar for C20 and C25. Median number of C cycles was 6 for C20 and 7 for C25. The median survival of C20 and C25 did not differ significantly and the HR boundaries (99% confidence level) were within the non-inferiority margins assumptions, therefore meeting the study's non-inferiority endpoint. PSA and RECIST response rates were higher in C25 (see Table). Grade 3–4 adverse events: 39.7% C20; 54.5% C25. Grade 4 laboratory neutropenia: 21.3% C20; 48.6% C25. Neutropenic sepsis/infection: 2.2% C20; 6.1% C25. **Conclusions:** In pts with mCRPC progressing after treatment with D, C20 demonstrates non-inferiority for OS compared with C25 and an improved overall safety profile.

Abstract ID: 5001 (166934)

A randomized phase III trial between adjuvant docetaxel and surveillance after radical prostatectomy for high risk prostate cancer: Results of SPCG12.

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Background: Docetaxel has proved to prolong survival in advanced castrate resistant prostate cancer (PCa) and we therefore started this trial to evaluate if six courses of docetaxel improves biochemical disease free survival (BDFS) after radical prostatectomy for high risk PCa. **Methods:** A total of 459 patients were randomised in 2005-2010 in this multinational openlabeled phase III study, to receive either 6 cycles of adjuvant docetaxel 75mg/m2 q 3 weeks (Arm A) or Surveillance (Arm B). Primary end-point was a rising PSA >0.5ng/ml. High risk prostate cancer was defined as pT2 with a positive margin if Gleasonscore (GS) 4+3 or higher, pT3b >GS 3+4, any lymph node positive disease with >GS 3+4, patients were followed for 5 years with PSA every 3 months. The study was powered to show a 15% difference at 5 years follow up. **Results:** All six cycles were completed by 79.1% of the patients. Salvage radiotherapy before the primary end-point was reached was given to 8% in Arm A and 10% in Arm B. Mean age was 62.2 years, mean baseline PSA 0.156, 83.7% had pT3 disease and 37.5% had GS 8-10 at randomisation. Of the 308 patients that had a lymph node dissection, 55 (17.5%) had metastasis. Median follow up was 56.8 months. The endpoint was reached in 43.2% of patients; 47.9% in Arm A and 38.9% in Arm B. In a Kaplan-Meier analysis there was no significant difference between the BDFS curves (p=0.078), but the curve of Arm A crossed the curve of Arm B at 15 months and it was parallel at a 10% lower level beyond 24 months. There were 6 deaths from prostate cancer in Arm A and only 3 in Arm B. Febrile neutropenia occurred in 18.7% of the patients in Arm A. No deaths were related to treatment. In a Cox multivariate analysis excluding lymph node status, GS (p<0.001), pT-stage (p=0.002) and positive surgical margin (p=0.009) were significant predictors of progression while randomisation arm (p=0.09) did not reach significance. **Conclusions:** Adjuvant docetaxel without hormonal therapy did not improve BDFS after radical prostatectomy for high risk prostate cancer. Instead, docetaxel as monotherapy seems to generate a more rapid biochemical progression in a subgroup of patients. Further analysis of this subgroup is warranted.

Abstract ID: 5003 (165234)

A randomized trial of a shorter radiation fractionation schedule for the treatment of localized prostate cancer.

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Background: Men with localized prostate cancer (PC) are often treated with high dose radiotherapy (RT) over 8-9 weeks. The α-β ratio which describes the dose-response of tumors and normal tissues to fractionated RT is low for PC. Hence, hypofractionation RT may be more efficacious in PC. **Objective:** To determine whether an 8-week course of escalated dose conformal RT can be compressed safely, and with similar efficacy into a 4-week course in intermediate risk PC. **Methods:** Men with intermediate risk PC (T1-2 Gleason 6 and PSA 10-20 ng/ml or T2b-c Gleason 6 and PSA < 20 ng/ml or T1-2 Gleason 7 and PSA < 20 ng/ml) were randomized to conventional (CON) RT, 78Gy in 39 fractions over 8 weeks or hypofractionated (HYP) RT, 60Gy in 20 fractions over 4 weeks, without hormone therapy. RT was planned to respect predefined dose constraints to a risk-adapted volume that included prostate +/- base of seminal vesicles. Daily image guidance was mandated and RT plans underwent real-time central review. The primary outcome is biochemical-clinical failure (BCF) defined by any of: PSA failure (nadir+2), hormonal intervention, clinical local or distant failure, or death. The trial was designed to show that the 5-year BCF of the HYP RT regimen is no higher than CON RT by up to 7.5% (hazard ratio [HR] up to 1.32) with 85% power and one-sided α = 5%. Acute and late GU/GI toxicity were assessed using RTOG criteria. **Results:** Between 2006 and 2011, 1,206 men from 27 sites in Canada, Australia and France were allocated to HYP RT (608) or CON RT (598). Mean age was 71 (48-88) years. Baseline characteristics were similar between arms. Median follow-up is 6.0 years. To date, 164 patients receiving HYP RT experienced a BCF event compared to 173 in the CON RT group. The BCF event rate at 5 years in both arms was 21%. The observed HR is 0.96 with 90% CI, 0.80 to 1.15. Overall 75 patients have died in each group. GU/GI toxicity grade > 3 was comparable in the acute period; however, late toxicity favored the HYPO RT arm: 3.5% vs. 5.4%, diff = -1.9%, 95% CI, - 4.3 to 0.43%. **Conclusion:** The HYP RT regimen was not inferior to conventional RT with no increase in acute or late toxicity. Thus, it is a consideration for men with intermediate risk PC. (ClinicalTrials.gov Identifier: NCT00304759).

Abstract ID: 5004 (171187)

Quality of life (QOL) analysis from CHAARTED: Chemohormonal androgen ablation randomized trial in prostate cancer (E3805).

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Background: Androgen deprivation therapy plus docetaxel (ADT+D) for metastatic hormone sensitive prostate cancer (mHSPC) improves overall survival over ADT. However, docetaxel's adverse event profile that can diminish QOL **Methods:** Patients were randomized to ADT+D (6 cycles) or ADT. QOL instruments including Functional Assessment of Cancer Therapy-Prostate (FACT-P), FACT-Taxane, FACIT-Fatigue, and Brief Pain Inventory (BPI) were collected at baseline, 3, 6, 9 & 12 months (mo) post randomization. Wilcoxon signed rank tests examined change over time. Mixed effect models compared QOL between arms at each time point. **Results:** 790 patients were randomized to ADT+D (N = 397) or ADT alone (N = 393) and completed QOL assessments (90% baseline; 84% 3 mo; 74% 9 mo; 69% 12 mo). ADT+D patients reported significant decline in FACT-P at 3 mo ($p < .001$), but did not differ significantly from baseline to 12 mo ($p = .38$). ADT+D was associated with significantly worse FACT-P scores at 3 mo ($p = 0.02$), yet significantly better scores at 12 mo ($p = .04$). ADT+D patients reported significantly worse FACIT-F scores at 3 mo ($p < .001$). ADT+D and ADT patients both reported significantly worse follow-up FACT-Taxane scores at all time points ($P < .001$) and significantly worse BPI scores at 9 and 12 mo ($p < .05$). BPI scores did not differ significantly between arms over time. **Conclusions:** Although ADT+D is associated with decreased QOL at 3 mo, 12 mo QOL was better for ADT+D than ADT patients. While both ADT+D and ADT patients report some increased symptoms over time, this study suggests that ADT+D not only provides a survival benefit, but also preserves a better QOL for mHSPC longer than ADT alone. [caption] Mixed effects model FACT-P total score[1]. [/caption]

Abstract ID: 4506 (167275)

Overall survival (OS) in METEOR, a randomized phase 3 trial of cabozantinib (Cabo) versus everolimus (Eve) in patients (pts) with advanced renal cell carcinoma (RCC).

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Background: Cabo is an inhibitor of tyrosine kinases including MET, VEGF receptors, and AXL, which are oncogenic drivers in RCC. In the METEOR trial (NCT01865747), Cabo showed a statistically significant improvement in progression-free survival (PFS, the primary endpoint) compared with Eve in pts with previously treated RCC (median of 7.4 vs 3.8 mo; HR=0.58, 95% CI 0.45–0.75; *P* <0.001) and improved the objective response rate (Choueiri NEJM 2015). The safety profile of Cabo was acceptable and similar to other VEGFR TKIs in this population. Interim analysis of the secondary endpoint of OS with a minimum follow-up of 6 mo revealed a favorable trend for Cabo vs Eve (HR=0.67, 95% CI 0.51–0.89; P=0.005). Here we present the final OS results, arising from a second interim analysis. **Methods:** Pts with measurable clear cell RCC, KPS ≥70, and ≥1 prior VEGFR TKI were randomized 1:1 to Cabo (60 mg qd) or Eve (10 mg qd) stratified by MSKCC risk group and number of prior VEGFR TKIs (1 or ≥2). The study was designed to detect a HR for OS of 0.75 (80% power, 2-sided α=0.04). **Results:** From Aug 2013–Nov 2014, 658 pts were randomized. As of 31 Dec 2015, with a minimum follow-up of 13 mo, 320 deaths were recorded (140 for Cabo and 180 for Eve). 74 (22%) pts remained on therapy in the Cabo arm vs 25 (8%) pts in the Eve arm. The secondary endpoint of improved OS for Cabo-treated pts was met. The median OS was 21.4 mo for Cabo vs 16.5 mo for Eve, with a 33% reduction in the rate of death (HR 0.67, 95% CI 0.53 to 0.83, P=0.0003). Landmark estimates of survival at 18 mo were 58% in the Cabo arm vs 47% of the Eve arm. OS benefit with Cabo was consistently observed across all prespecified subgroups including MSKCC risk group, number and type of prior VEGFR TKIs, prior anti-PD-1/PD-L1 treatment, location and extent of tumor metastases, and tumor MET expression level. SAEs were consistent with the safety profile previously reported. **Conclusions:** Cabo is the only agent to demonstrate a significant benefit in OS, PFS, and ORR in a Phase 3 trial in previously treated pts with advanced RCC. Cabo is an important new treatment option for these patients.

Abstract ID: LBA4500 (170759)

Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1.

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Background: Cisplatin-based chemo is a standard 1L treatment (tx) for mUC and the only tx thatprolongs OS; however, age or comorbidities render many pts ineligible, and 30-50% receive no tx.Atezo (MPDL3280A) is active and well tolerated in platinum-treated mUC, justifying testing atezoas 1L tx in cisplatin-ineligible pts. **Methods:** Pts were chemo naive in the metastatic setting and cisplatin ineligible (renal [GFR > 30 but < 60 mL/min]/hearing impairment, ≥ G2 peripheralneuropathy [PN] or ≥ ECOG PS2). Atezo 1200 mg was given IV q3w until PD (RECIST v1.1). Centrally assessed PD-L1 on tumor infiltrating immune cells (IC; SP142 IHC assay) was scored IC2/3, 1 or 0. The primary efficacy endpoint was confirmed ORR assessed per RECIST v1.1 (central independent review facility) using a data cutoff of Sep 14, 2015.

Abstract ID: 4503 (168539)

Limited versus extended pelvic lymphadenectomy in patients with bladder cancer undergoing radical cystectomy: Survival results from a prospective, randomized trial (LEA AUO AB 25/02).

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Background: The extent of pelvic lymph node dissection (PLND) in bladder cancer patients (pts.) undergoing radical cystectomy may affect survival according to retrospective studies. The German Urologic Oncology Group (AUO) reports mature data of the first prospective, randomized clinical trial to evaluate the impact of a limited versus an extended PLND. **Methods:** Pts. with high-grade T1 or invasive urothelial bladder cancer (cT2-T4a) from 16 German centers were randomized 1:1 to receive a limited versus an extended PLND at the time of radical cystectomy. Limited PLND included 6 fields (bilateral obturator, internal and external iliac nodes) and extended PLND defined 14 fields (in addition bilateral deep obturator fossa, presacral, paracaval, interaortocaval and paraaortal nodes up to the inferior mesenteric artery). Pts. with neoadjuvant chemo- or radiotherapy were excluded, adjuvant chemotherapy was allowed. The primary endpoint was recurrence-free survival (RFS). Cancer-specific survival (CSS) was a secondary endpoint. The planned total sample size was 400 to detect an improvement in 5-year RFS from 50% to 65% (90% power, 2-sided test, $p < 0.05$) in the extended arm. **Results:** In total, 375 of 437 pts. were randomized from 02/2006 to 08/2010 and eligible for intention-to-treat analysis (191 limited and 184 extended PLND). The tumor was locally confined (≤ pT2 pN0) in 49.6% of patients and 24.0% were node positive (pN+). The median number of dissected nodes was 19 in the limited and 32 in the extended arm. The 5-year RFS rate was 62.0% in the limited compared to 69.3% in the extended arm which was statistically not significant (Hazard ratio (HR) = 0.80, 95% Confidence Interval (CI) (0.54-1.19); log-rank p = 0.28). The 5-year CSS rate was improved from 66.2% in the limited to 77.5% in the extended arm which was statistically not significant (HR = 0.70, 95%CI 0.45-1.10; log-rank p = 0.13). **Conclusions:** We observed a trend but no significant difference toward improved RFS and CSS with an extended PLND. The rate of recurrence was lower than expected in the limited arm, which might be due to the high number of resected nodes in this arm. NCT01215071.

Abstract ID: 5501 (166142)

Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis.

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Background: In a phase II study (NCT00753545, Study 19), maintenance monotherapy with the EU/US-approved PARP inhibitor olaparib significantly improved PFS, and times to first and second subsequent therapy or death (TFST and TSST), vs placebo in PSR SOC pts. Pts with a *BRCA1/2* mutation (*BRCA*m) derived the greatest benefit from olaparib. Analyses after a data cut-off (DCO) on Nov 26, 2012 did not show a significant OS improvement with olaparib in the full analysis set (FAS) (58% maturity; HR 0.88, 95% CI 0.64–1.21, *P* =0.44) or *BRCA*m subgroup (52% maturity; HR 0.73, 95% CI 0.45–1.17, *P*= 0.19) (Ledermann *et al*, *Lancet Oncol* 2014). We report updated OS, evaluated after 77% of pts had died (DCO: Sep 30, 2015). **Methods:** Pts received olaparib (400 mg bid, capsules) or placebo after response to platinum-based therapy. *BRCA*m status was known for 254/265 pts (96%) from germline or tumor tests. **Results:** Maintenance olaparib gave pts an OS advantage vs placebo; analyses suggest that the results seen in the FAS may have been driven by the *BRCA*m group. Investigations into the contribution of pts who were non-*BRCA*m but homologous recombination repair deficient are ongoing. In the FAS, 5-yr survival was 29.2% and 20.4% in the olaparib and placebo arms, respectively (36.9% and 24.3% in *BRCA*m pts). At the 2015 DCO, 15 pts remained on olaparib (*BRCA*m, n = 8) and 1 on placebo (*BRCA*m, n = 1). 18/136 FAS pts (13.2%) received olaparib for > 5 yrs (by subgroup: 11/74 *BRCA*m pts [14.9%]; 7/62 non-*BRCA*m pts [11.3%]). There was no change to the safety profile and no new cases of MDS/AML were reported since the 2012 DCO. **Conclusions:** There is an OS advantage for pts in Study 19 receiving maintenance olaparib after response to platinum therapy. Long-term treatment with maintenance olaparib was observed. This analysis supports prior Study 19 data in pts with *BRCA*m PSR SOC showing a significant PFS benefit and delay to TFST and TSST with olaparib.

Abstract ID: 5507 (170021)

Performance characteristics and stage distribution of invasive epithelial ovarian/tubal/peritoneal cancers in UKCTOCS.

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Background: We report on the overall performance of the screening strategies and stage distribution of invasive epithelial ovarian/tubal/peritoneal (iEO/T/PP) cancers **Methods:** Postmenopausal women aged 50-74 were randomised (1:1:2 ratio) to annual multimodal (MMS) using the Risk of Ovarian Cancer Algorithm (ROCA) or ultrasound (USS) screening, or no screening (control, C). Women with abnormal screens had repeat tests and those with persistent abnormality underwent clinical evaluation and, where appropriate, surgery. **Results:** Of 202,638 women randomised, 50,624 MMS, 50,623 USS and 101,299 C were eligible for analysis. At median follow-up 11.1 years, 299 MMS, 259 USS and 574 C women developed iEO/T/PP cancers. In the C group, 26% (149/574; 95% CI 22.4, 29.7) were stage I/II/IIIA (low volume disease, LVD). In the subgroup of screen detected cancers, in both MMS (44.2%; 80/181; 95% CI 36.8, 51.8; p<0 0001) and USS (42.9%; 45/105; 95% CI 33.2, 52.9; p=0.00042) group, there was significantly more LVD compared to C. However, across all iEO/T/PP cancers, while proportions of women with LVD remained significantly higher in the MMS (40.1%; 120/299; 95% CI 34.5, 45.9; p<0 0001) versus C comparison, there was no evidence of a difference between the USS (23.9%; 62/259; 95% CI 18.9, 29.6; p= 0.57) and C. **Conclusions:** While LVD was significantly more frequent in women with screen detected iEO/T/PP cancers in both screen arms compared to C, when all iEO/T/PP cancers were analysed, the difference only persisted in the MMS arm. The latter is a reflection of the high sensitivity of multimodal screening. The findings are in keeping with the emerging mortality reduction observed in the MMS arm in UKCTOCS. [caption]Performance characteristics for iEO/T/PP cancers diagnosed <1 year of screen. [/caption]

Abstract ID: LBA5503 (168863)

OV21/PETROC: A randomized Gynecologic Cancer Intergroup (GCIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC).

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Background: The aim of this 2 stage randomized trial was to evaluate whether womenundergoing neoadjuvant IV chemotherapy followed by delayed debulking surgery benefit from the addition of IP/IV treatment after surgery **Methods:** Stage 1 was a randomized 3-arm design including 2 IP platinum regimens: 153 women who received 3-4 courses of IV platinum-based chemo for stage IIB-III (IV pleural effusion only) EOC followed by optimal debulking surgery (< 1cm) were randomized to: ARM1 D1 IV paclitaxel (pacli) 135mg/m^2 + IV Carboplatin AUC 5/6 withd8 pacli IV 60 mg/m^2 Q 21d X3; ARM 2 D1 IV pacli 135mg/m^2 + IP cisplatin (Cis) 75 mg/m^2 and d8 IP pacli 60 mg/m^2 Q21d X3; or ARM 3 d1 IV pacli 135mg/m^2+ IP Carboplatin AUC 5/6 and d8 IPpacli 60 mg/m^2 Q21dX3. A planned DSMC review confirmed dropping ARM2 (IP cis) and continuing study as an expanded phase II comparing 200 patients randomized to ARMs 1 and 3, which has 80% power to detect a 19% difference in progression rate at 9 mo (PD9, primary endpoint), 2-sidedα = 0.05. Progression free survival (PFS) and overall survival (OS) are secondary efficacy endpoints.

Abstract ID: 5508 (167372)

Baseline quality of life (QOL) as a predictor of stopping chemotherapy early, and of overall survival, in platinum-resistant/refractory ovarian cancer (PRROC): The GCIG symptom benefitstudy (SBS).

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Background: 110 (19%) of the 570 women with PRROC enrolled in SBS stopped chemotherapy within 8 weeks. We sought to identify baseline characteristics, including QOL and clinical factors, that were associated with overall survival and stopping chemotherapy early. **Methods:** QOL domains were measured with the EORTC QLQ-C30 and QLQ-OV28. QLQ-C30 subscales were dichotomised using cut-points recommended by Diouf et al (The Oncologist 2015). Cox's Proportional Hazards regression was used to assess univariable and multivariable associations with overall survival. Clinical factors for the multivariable model were selected using backward elimination; candidate variables included those with $P<0.05$ in univariable analyses. The association between baseline QOL domains and stopping chemotherapy early was determined by categorising the QOL domains and using a chi-squared test. **Results:** Univariable analyses of baseline QOL data (N=545) showed that physical function (PF), role function (RF), global health status (GHS) and abdominal/GI symptoms (AGIS) were significantly associated with OS (all $p<0.001$). Multivariable analyses included haemoglobin, ascites, neutrophil to lymphocyte ratio, platelet count, log serum CA125, and abdominal/GI symptoms. All 4 QOL domains remained significant in multivariable models ($p=0.001$, $p=0.005$, $p=0.014$, $p=0.027$ respectively). Low GHS, RF, PF and high AGIS were all significantly associated with stopping chemotherapy within 8 weeks (all $p<0.007$). **Conclusions:** GHS, PF, RF and AGIS were independent predictors for OS and are significantly associated with stopping chemotherapy early. Assessment of QOL could help identify patients with PRROC unlikely to benefit from palliative chemotherapy.

Abstract ID: 7009 (168695)

Results of a phase 1b study of venetoclax plus decitabine or azacitidine in untreated acute myeloid leukemia patients ≥ 65 years ineligible for standard induction therapy.

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Background: Venetoclax (VEN) is a potent, orally bioavailable BCL-2 inhibitor with single-agent activity in relapsed/refractory acute myeloid leukemia (AML) patients (pts), displaying synergistic activity with hypomethylating agents in preclinical studies. This trial evaluates VEN plus decitabine (DEC) or azacitidine (AZA) in treatment (Tx)-naive AML pts ≥ 65 y (NCT02203773). **Methods:** Tx-naive pts (ECOG PS ≤ 2, ≥ 65 y, intermediate- or poor-risk karyotype) not eligible for standard induction therapy received DEC (Arm A: 20 mg/m2 iv) daily on days (D) 1−5 or AZA (Arm B: 75 mg/m2; subcutaneous or iv) daily on D 1−7 of each 28-D cycle in combination with once-daily continuous oral VEN. VEN dose escalation follows a 3+3 design; 1200 mg is the final dose level. Objectives include safety, preliminary efficacy, and biomarker evaluations. **Results:** As of 11/28/15, 39 pts (49% male; median age 74 y [65–85 y]) have been enrolled in Arm A (n = 20) and Arm B (n = 19). Median time on study is 111 D (6−375 D); 16 pts (41%) remain on therapy. Biomarker analysis and response evaluations have been completed in 34 pts with 400-mg and 800-mg VEN doses. As of 9/19/15, overall response rate (ORR; complete response [CR]/CR with incomplete marrow recovery [CRi]/partial remission [PR]) within this population was 76% (CR: 13/CRi: 11/PR: 2; 26/34 pts). Poor-risk cytogenetics and IDH1/2 mutations were reported in 24% (8/34) and 32% (11/34) of pts; ORR was 88% (7/8) and 82% (9/11), respectively. Median time to CR/CRi was 29.5 D (24−112 D). Most common TEAEs were nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). No dose-limiting toxicity was reported. Febrile neutropenia (41%) and neutropenia (33%) were the most common Grade 3/4 TEAEs. Most frequent serious AE was febrile neutropenia (28%). Four relapses occurred, all on Arm A. Six deaths occurred (3 disease progression, 1 sepsis, 1 respiratory failure, 1 bacteremia). MTD has not been reached. **Conclusions:** Tx with VEN plus DEC or AZA shows a tolerable safety profile, with high response rates observed in Tx-naive AML pts ≥ 65 y, including those with adverse biologic disease features.

Abstract ID: 7008 (170782)

Crenolanib besylate, a type I pan-FLT3 inhibitor, to demonstrate clinical activity in multiply relapsed FLT3-ITD and D835 AML.

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Background: We investigated the clinical activity, PK, safety and resistance mechanisms to single-agent crenolanib patients (pts) with refractory/relapsed acute myeloid leukemia (R/R AML) with FLT3 ITD. **Methods:** From Aug 2012 to May 2015, 69 pts (65 evaluable) with R/R FLT3+ AML (29 ITD, 11 D835, 29 ITD+D835) were treated with crenolanib 100 mg TID (42) or 200 mg/m2/d in 3 divided doses (27). **Results:** Crenolanib therapy resulted in a 39% CRi and 11% PR amongst the 18 pts (6 D835, 9 ITD, 3 ITD+D835) with R/R FLT3 AML who had not received prior FLT3 inhibitors (Cohort A). OS was 234d (238d in pts with ≤ 2 prior therapies and 133d in ≥ 3 prior therapies). Activity was seen in FLT3 ITD (OS 238d), TKD (OS 185d), and TKD+ITD (128d). Pts < 60 had a higher survival (OS 234d) than those ≥ 60 (OS 185d). 36 pts received crenolanib after progressing on prior TKIs (Cohort B), sorafenib (28), quizartinib (11), midostaurin (3), pexidartinib (4), gilteritinib (2) and FLX-925 (1). 10 pts had received ≥ 2 prior TKIs. FLT3-TKD mutations were acquired in 25 pts following TKI exposure: 19/36 had dual mutations with FLT3-ITD and FLT3-D835 (15 ITD, 2 D835). Overall RR was 31% (6 CRi, 5 PRs). OS was 94d in this cohort (158d in ITD, 63d in the dual ITD+D835 mutants). Cohort C consisted of 11 pts who developed FLT3+ AML after prior MDS (8 pts), and 1 pt each after prior myelofibrosis, polycythemia vera and systemic mastocytosis. These pts had only transient benefit from crenolanib, with OS of 55d. Crenolanib had predictable PKs (tmax 2 hrs, T1/27.5 hrs), with no accumulation seen with repeated dosing. Median Day 15 trough level was 352 nM documenting therapeutic drug levels. Common AEs included nausea/vomiting, transaminitis and fluid retention (majority Grade 1/2). Only 2 pts discontinued crenolanib due to related AEs. No pt acquired a secondary FLT3 mutation at the time of relapse following crenolanib. **Conclusions:** Encouraging single-agent activity, safety and PK is observed with crenolanib in multiply relapsed FLT3+ AML (including 40 pts with FLT3 D835 mutations). Crenolanib is now being assessed in combination with standard chemotherapy in newly diagnosed and R/R AML. NCT01522469 NCT01657682

Abstract ID: 7000 (165504)

Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML.

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Background: Older patients with secondary AML have poor outcomes following first-line cytarabine and anthracycline-based treatment. CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio with enhanced efficacy among poor risk AML patients. We report final results from a randomized open-label study of first-line CPX-351 in patients with high-risk sAML (NCT01696084). **Methods:** Patients 60-75 years of age with untreated AML with a history of prior cytotoxic treatment, antecedent MDS or CMML (+/- prior hypomethylator treatment), or AML with WHO-defined MDS-related cytogenetic abnormalities were eligible. 300 patients were to be randomized 1:1 to CPX-351 (100 units/m2, days 1, 3, 5) or 7+3 (cytarabine 100 mg/m2/day x 7 days, daunorubicin 60 mg/m2 days 1, 2, 3) induction therapy. Endpoints included: overall (OS, 1o) and event free survival (EFS) assessed by stratified log rank analysis, independent blinded assessment of CR+CRi, and 60-day mortality. Patient enrollment was from Dec 2012 to Nov 2014 at 39 US and Canadian sites. Study assumptions included: exponential survival, control median OS=192d, accrual of 135 pt/yr, and analysis after 236 deaths, resulting in 93.7% power to detect a HR=0.635, p=0.05 (2-sided). **Results:** A total of 309 patients were randomized (153 to CPX-351 + 156 to 7+3) and were well balanced for sex, race, age, performance status, AML-subtype, MDS-related cytogenetics and prior HMA therapy. After minimum follow-up of 13.7 months final analysis began. CPX-351 treatment resulted in superior overall survival (HR=0.69; P=0.005; median OS 9.56 vs. 5.95 months), EFS (HR=0.74; P=0.021), and CR+CRi response (47.7% vs. 33.3%; P=0.016). 60-day mortality favored CPX-351 (13.7% vs. 21.2%). Grade 3-5 AEs were equal (92% vs. 91%) and were similar in frequency and severity in both arms. Similar numbers of patients were transplanted in both arms. **Conclusion:** CPX-351 treatment significantly improved overall survival, event free survival, and response without an increase in 60-day mortality or AE frequency or severity. CPX-351 should become the standard of care for older patients with secondary AML.

Abstract ID: 7001 (166320)

Treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronicphase (CML-CP) treated with frontline nilotinib: Results from the ENESTFreedom study.

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Background: In prior clinical trials, ≈40-60% of pts with CML-CP and sustained deep molecular response (MR) maintained TFR after stopping long-term imatinib (median duration: ≈ 5-7 y). The single-arm phase 2 ENESTfreedom study (NCT01784068) is the first to specifically investigate TFR following frontline nilotinib. **Methods:** Pts with CML-CP with typical b2a2 or b3a2 *BCR-ABL1* transcripts, ≥ 2 y of frontline nilotinib, and $MR^{4.5}$ (*BCR-ABL1*^{IS} ≤ 0.0032%) at prescreening were eligible. Upon enrollment, pts continued nilotinib for 1 y, with RQ-PCR assessments every 12 wk (consolidation [CONS] phase) at a central standardized laboratory. Pts with no assessment worse than MR^4 (*BCR-ABL1*^{IS} ≤ 0.01%), ≤ 2 assessments between MR^4 and $MR^{4.5}$, and $MR^{4.5}$ in the last assessment of the CONS phase were eligible to stop treatment (TFR phase). Loss of major MR (MMR [*BCR-ABL1*^{IS}≤ 0.1%]) triggered re-initiation of nilotinib (ReRx phase). The data cutoff for this analysis was 30 Nov 2015, when all pts who entered the TFR phase had completed 48 wk of TFR, entered the ReRx phase, or discontinued from the study. **Results:** A total of 215 pts entered the CONS phase. Of these, 190 stopped nilotinib and entered the TFR phase (median age at baseline: 55 y; median time from first $MR^{4.5}$ to study entry: 18 mo; median nilotinib duration prior to TFR: 43 mo [range: 33-89 mo]). At wk 48 of the TFR phase, 51.6% (95% CI: 44.2-58.9%) of these 190 pts were in MMR and had not re-initiated treatment (primary endpoint). Of 86 pts who entered the ReRx phase due to loss of MMR by the data cutoff, 85 regained MMR (1 pt discontinued from the study [pt decision] without MMR 7.1 wk after entering the ReRx phase) and 76 regained $MR^{4.5}$ (median time to MMR and $MR^{4.5}$ among all pts who entered the ReRx phase: 7.9 wk and 13.1 wk, respectively). No new safety signals were observed on treatment. During the TFR phase, 24.7% of pts experienced musculoskeletal pain (grade 3/4 in 1.1%). **Conclusions:** These data demonstrate the feasibility of TFR following frontline nilotinib. Nilotinib is the first tyrosine kinase inhibitor to emonstrate successful TFR in a large proportion of eligible pts after relatively short exposure (median: ≈ 3.6 y)

Abstract ID: 7504 (164161)

Randomized phase III study on the effect of early intensification of rituximab in combination with 2-weekly CHOP chemotherapy followed by rituximab or no maintenance in patients with diffuse large B-cell lymphoma: Results from a HOVON-Nordic Lymphoma Group study.

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Background: Rituximab (R)-CHOP is standard treatment for patients with diffuse large B-cell lymphoma (DLBCL). The optimal R dose and schedule is not known. We compared R-CHOP-14 with the same regimen combined with 4 extra R administrations during the first 4 cycles. Patients in complete remission after induction treatment were randomized between observation and R maintenance. Here we report the efficacy results of the first randomization. **Methods:** Patients with DLBCL, stage II-IV, were randomized between R-CHOP-14 and an experimental arm with R-CHOP-14 combined with extra R 375 mg/m^2 IV on day 8 of the first 4 cycles. Response was evaluated using PET-CT scans (Lugano criteria 2014). A Deauville score of ≤ 3 was considered as a complete response. The primary endpoint was metabolic complete remission rate after induction treatment. (www.trialregister.nlNTR1014). **Results:** 575 patients were randomized (standard arm 286 patients, experimental arm 289 patients). Median age was 65 years (range, 18-80), 50% of patients were 66 years or older and 52% were male. The majority of patients (57%) had a high-intermediate or high aa-IPI score. Baseline patient and disease characteristics were well balanced between treatment arms. No significant difference in CR rate was observed between the two treatment arms, standard arm 84% CR and experimental arm 82% CR (odds ratio = 0.83, 95% CI 0.54-1.28, p=0.40). The observed CR rates in patients ≤ or > 65 years were identical. With a median follow-up of 49 months (maximum 90 months), 3- and 5-year progression free survival (PFS) were 74% and 68% in the standard arm and 71% and 61% in the experimental arm (hazard ratio = 1.23, 95% CI 0.92-1.63, p=0.16). No significant improvement in PFS was noted in subgroups by age (≤ or > 65 years) or gender. Toxicity data will be available at ASCO. **Conclusions:** In patients with DLBCL treated with R-CHOP-14 rituximab intensification early during treatment did not improve the CR rate or the 3-year PFS. No clinical subgroup benefited from rituximab intensification.

Abstract ID: 7508 (165119)

A phase 2 trial of ABVD followed by brentuximab vedotin consolidation in limited stage non-bulky Hodgkin lymphoma.

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Background: The current standard for limited stage Hodgkin lymphoma (HL) is chemotherapy with or without radiation therapy. Given the unclear overall survival advantage and the long-term side effects associated with consolidative radiation, the use of this modality remains controversial in the treatment of HL. Brentuximab vedotin (BV) has emerged as one of the most active therapeutic agents in HL. We hypothesize that BV may be safe and effective in eradicating residual disease after induction chemotherapy and may replace radiation for consolidation in patients with limited stage HL. **Methods:** In this phase 2 multicenter study, patients with previously untreated limited stage non-bulky HL received ABVD followed by BV **(NCT01578967)**. The primary objective was to estimate the proportion of patients who achieve PET-negative disease (Deauville score ≤ 2) after ABVD followed by BV consolidation. Patients received 2 to 6 cycles of ABVD based on their baseline risk factors and the interim PET scan result. Approximately 6 weeks after the induction therapy, 1.8 mg/kg of BV was given every 3 weeks for 6 cycles. **Results:** Forty one patients were enrolled from April 2012 through December 2015. Out of 40 evaluable patients, the median age was 29 years (range 19 – 67), and 46% presented with unfavorable disease. Over 90% of patients received ≤ 4 cycles of ABVD, and one patient received radiation due to disease progression. Grade ≥ 3 toxicities associated with BV included neutropenia in 3 patients and peripheral neuropathy and rash in 1 patient each. There was one death due to sepsis and hepatic failure, a very rare but known complication of BV, and all reported $\geq$ grade 4 toxicities were associated with this event. After 2 cycles of ABVD, 72% of patients achieved PET-negative disease, and 90% of patients were PET-negative after the completion of BV. The estimated one-year progression free and overall survival rates are 91% and 96%, respectively, with a median follow up of 12 months. **Conclusions:** BV demonstrates promising safety and clinical activity following ABVD. BV consolidation may obviate the need for radiation therapy and achieve similar survival outcomes in the majority of patients with limited stage non-bulky HL.

Abstract ID: 7501 (167138)

A prospective, multicenter, randomized study of anti-CCR4 monoclonal antibody mogamulizumab (moga) vs investigator's choice (IC) in the treatment of patients (pts) with relapsed/refractory (R/R) adult T-cell leukemia-lymphoma (ATL).

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Background: ATL is a malignancy of T-cells infected with HTLV-1. Prognosis is poor and subtype related. There is no consensus treatment for R/R patients with aggressive ATL in whom median OS is < 3 months. Moga, a monoclonal antibody directed against CCR4 (expressed in >90% of ATL patients), is approved in Japan for the treatment of CCR4+ ATL, PTCL, and CTCL. **Methods:** To evaluate moga outside of Japan, pts from sites in the USA, EU, and Latin America with aggressive R/R ATL (acute, lymphomatous, and chronic subtypes) were randomized 2:1 to treatment with moga, 1.0 mg/kg, given weekly for the first 4-week cycle and then biweekly, or to 1 of 3 investigator choice (IC) regimens (Gem/Ox, DHAP or pralatrexate). Due to the rarity of the disorder and lack of effective therapy, no power calculation was performed. Pts in the IC arm were permitted to cross-over to moga upon progression. The primary endpoint was objective response rate (ORR) based on modified Tsukasaki criteria. ORR was assessed by the treating investigator (IA) and in blinded fashion by independent review (IR). **Results:** 71 pts were randomized (47 to moga, 24 to IC). Tissue /blood from 65/71 pts (91.5%) expressed CCR4. In the moga treated group, ORR was 23.4% (11/47) by IR and 34.0% (16/47) by IA; in the IC group, ORR was 2/24 (8.3%) by IR and 0/24 by IA. Confirmed ORR (maintained response after 1 month) for moga was 10.6% by IR and 14.9% by IA; there were no confirmed responses in the IC group. 18 IC pts crossed over to moga and 3 responded. Median duration of response for moga was 5.0 months by IR (range: 3.8 – 9.6 mos) and 1 pt had CR lasting >9 months. Survival data are not yet mature. The most frequently observed treatment-emergent, drug-related adverse events in the moga arm were infusion reactions (46.8%), rash/drug eruption (25.5%) and infections (14.9%). **Conclusions:** This was the largest randomized clinical trial of R/R ATL thus far conducted. In patients with aggressive R/R ATL commonly used cytotoxic regimens provided limited therapeutic benefit whereas treatment with moga resulted in an ORR that supports its therapeutic potential in this setting.

Abstract ID: 7506 (163467)

PILLAR-2: A randomized, double-blind, placebo-controlled, phase III study of adjuvant everolimus (EVE) in patients (pts) with poor-risk diffuse large B-cell lymphoma (DLBCL).

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Background: The goal of PILLAR-2 (NCT00790036) was to reduce DLBCL relapse by providing 1 year of adjuvant EVE to poor-risk (International Prognostic Index [IPI] ≥3) pts who had achieved a CR with R-chemo. **Methods:** PILLAR-2 was a multicenter double-blind, placebo (PBO)-controlled, phase 3 study. Pts with histologically confirmed stage III/IV poor-risk (IPI ≥3) DLBLC who had a PET/CT-confirmed CR to first-line R-chemo were randomized 1:1 to EVE 10 mg/day or PBO for 1 year or until disease relapse, unacceptable toxicity, or death. The primary endpoint was disease-free survival (DFS) by local assessment using revised IWRC; secondary endpoints were overall survival (OS), lymphoma-specific survival (LSS), and safety. **Results:** Median study follow-up was 50.4 months (range, 24.0–76.9 months). Of the 742 pts randomized, 177 (48%) pts in the EVE and 249 (67%) in the PBO arms completed the study treatment as per protocol. Overall, 47% pts were ≥65 years, 50% were male and 42% had an IPI of 4+5. Adjuvant EVE did not improve DFS vs. PBO (Log-rank p = 0.276) (**Table**). The 2-yr DFS rates (95% CI) were 78% (73-82%) in EVE vs 77% (72-81%) in PBO. However, trends favoring EVE were observed for OS and LSS, and for exploratory analyses of DFS and OS in males and those with IPI 4+5. Common grade 3/4 AEs with > 3% difference for EVE vs PBO included neutropenia, stomatitis, CD4 lymphocytes decreased, lymphopenia and anemia. **Conclusions:** In poor-risk DLBCL patients with a CR after R-chemo, adjuvant EVE for 1 year did not improve DFS. A trend favoring EVE for OS and LSS, overall and for DFS in selected patient subgroups suggests that everolimus may provide anti-lymphoma activity in high-risk DLBCL, and warrant further investigation.

Abstract ID: 7503 (169547)

Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of aprospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial)

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Background: Rituximab maintenance is part of a standard treatment approach for follicular lymphoma. In mantle cell lymphoma (MCL), however, it is not yet common practice. In this study we compared the effect of rituximab maintenance vs observation after first-line treatment with B-R in patients with previously untreated MCL.
Methods: Patients were required to have stage II (with bulky disease > 7 cm), III, or IV disease for registration in this study. Primary endpoint was progression free survival (PFS). Secondary endpoints included response rates, overall survival (OS), time to progression, event free survival, toxicity. Patients were treated with up to 6 cycles of B-R plus 2 additional rituximab cycles. 120 Patients who have responded to B-R were then randomized to either rituximab maintenance (375 mg/m2every 2 months for a total of 2 years) or observation only. **Results:** A total of 120 patients were evaluable for the analysis, 59 (49%) were randomized to maintenance with rituximab and 61 (51%) to observation, respectively. Patient characteristics were comparable for both groups. Median patient age was 70 years, median time of observation was 54.2 months at the time of this analysis (January 2016). No significant difference in PFS between both arms could be observed (p = 0.130, 47 events, HR 0.64, 95% CI 0.36 – 1.14). The median for R maintenance was not yet reached, whereas for the observation arm the median was 54.7 months (95% CI 40.1. – n. y. r.). The results for overall survival showed no difference (p = 0.271, 27 events, HR 1.53, 95% CI 0.73 – 3.32) with a median of 69.6 months for R maintenance versus a median not yet reached in the observation arm. **Conclusions:** After a median observation time of 4.5 years, the results are yet inconclusive. Up to date we were not able to demonstrate statistical evidence supporting the benefit of R maintenance after B-R in the treatment of patients with MCL. Longer follow-up is needed before final results can be presented.

Abstract ID: LBA4 (172609)

Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study.

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Background: Daratumumab (D), a human anti-CD38 IgG κ mAb, induces deep and durable responses with a favorable safety profile in RRMM pts. We report a pre-specified interim analysis of the first randomized controlled study of D (CASTOR; NCT02136134). **Methods:** Pts with ≥1 prior line of therapy were randomized (1:1) to 8 cycles (q3w) of bortezomib (V)/dexamethasone (d) (V: 1.3 mg/m2sc on Days 1, 4, 8, 11; d: 20 mg po on Days 1, 2, 4, 5, 8, 9, 11, 12) ± D (16 mg/kg iv qw in Cycles 1-3, Day 1 of Cycles 4-8, then q4w until progression). Primary endpoint was PFS.

Abstract ID: 8000 (167867)

Upfront autologous stem cell transplantation (ASCT) versus novel agent-based therapy for multiple myeloma (MM): A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial).

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Background: The role of upfront ASCT for newly diagnosed (ND) MM (NDMM) patients (pts) has been questioned in the novel agent era. **Methods:** A phase 3 study was designed to compare [random (R) 1] 4 cycles of bortezomib-melphalan-prednisone (VMP) vs high-dose melphalan (HDM) and single or double ASCT (this latter limited to centers applying a tandem ASCT policy) as intensification therapy following induction with bortezomib-cyclophosphamide-dexamethasone and subsequent collection of peripheral blood stem cells. Consolidation therapy with bortezomib-lenalidomide-dexamethasone vs no consolidation (R2) was planned after VMP and HDM, followed by lenalidomide maintenance until progression or toxicity in both treatment arms. Primary study end point was progression-free survival (PFS) from R1. A first prespecified interim analysis was performed in January 2016 when at least 33% of the required events had been observed. Results are herein reported. **Results:** From February 2011 through April 2014, 1503 pts aged ≤65 years with symptomatic NDMM were registered. Of these, 1308 pts were eligible for R1 and 1266 who were randomized (1:1 ratio; stratification by ISS stage) to VMP (512 pts) or HDM (1±2 ASCT) (754 pts) were analyzed. Median follow up from R1 was 24 months. PFS was significantly prolonged in pts randomized to HDM (HR=0.76; 95% CI=0.61-0.94; P=0.010), a benefit retained across predefined pt subgroups, including those with revised ISS stage III (HR=0.52; CI=0.32-0.84; P=0.008) and high-risk cytogenetics [t(4;14) ± del(17p) ± del(1p) ± 1q gain] (HR=0.72; CI=0.54-0.97; P=0.028). Superior rate of ≥ very good partial response was observed with HDM (84%) vs VMP (74%) (odds ratio=1.90; CI=1.42-2.54; P<0.0001). In a Cox regression analysis, randomization to HDM (HR=0.61, CI=0.45-0.82; P=0.001) was confirmed to be an independent predictor of prolonged PFS. Overall survival was not yet mature and no difference between the treatment groups was evident. **Conclusions:** Upfront ASCT still remains the preferred treatment for younger NDMM pts. Further follow-up of the study is needed.

Abstract ID: 8001 (168948)

Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS).

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Background: Several studies demonstrate that LEN MNTC post ASCT reduces the risk of disease progression or death in patients (pts) with MM by ≈ 50% (Attal *NEJM* 2012; McCarthy *NEJM* 2012; Palumbo *NEJM* 2014). However, these studies were not powered for OS. To assess the effect of LEN MNTC post ASCT on OS, an MA was conducted. **Methods:** A prospectively planned MA assessed the OS of LEN vs placebo/no MNTC (control; CTL) after ASCT. A search identified 17 randomized controlled trials (RCTs) using LEN post ASCT. 3 RCTs (IFM 2005-02, CALGB 100104 [Alliance], GIMEMA RV-209) met prespecified inclusion criteria (had pt-level data, a CTL arm, and achieved database lock for primary efficacy analysis of NDMM pts receiving LEN post ASCT). A March 2015 cutoff of the 3 RCTs enabled sufficient OS events to test treatment effect (HR = 0.78). **Results:** In the 3 RCTs, 1209 pts were randomized from 2005 to 2009 to receive LEN (n = 605) 10 mg/day on days 1-21/28 (GIMEMA) or 1-28/28 (IFM and CALGB) or CTL (n = 604). With a median follow-up of 6.6 yrs, 491 pts (41%) had died. Baseline characteristics were generally balanced in the pooled data. After induction and single (82%) or tandem (18%) ASCT, 55% of pts achieved a complete response (CR) or very good partial response (VGPR). Median OS for LEN vs CTL was not reached vs 86 mos (HR = 0.74; 95% CI, 0.62-0.89; log-rank *P* = .001), and 5-, 6-, and 7-yr OS were longer in LEN vs CTL group (71% vs 66%, 65% vs 58%, and 62% vs 50%, respectively). Fisher's combination test confirmed the significant OS benefit of the MA (*P* = .001). Pts who achieved ≤ PR post ASCT benefited from LEN (HR = 0.86; 95% CI, 0.65-1.15) as well as pts with CR/VGPR (HR = 0.70; 95% CI, 0.54-0.90). OS benefit was generally consistent across subgroups. Heterogeneity test showed significant difference across trials (*P* = .047). The potential impact of baseline/disease characteristics, as well as 2nd - line therapy (IFM and CALGB), on OS will be explored and presented. Second primary malignancy data will be presented. **Conclusions:** This large MA demonstrates that LEN MNTC significantly prolonged OS vs CTL post ASCT, including in pts who achieved CR, demonstrating benefit in pts in all response categories.

Abstract ID: 8009 (164111)

A phase Ib dose escalation trial of isatuximab (SAR650984, anti-CD38 mAb) plus lenalidomide and dexamethasone (Len/Dex) in relapsed/refractory multiple myeloma (RRMM): Interim results from two new dose cohorts.

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Background: Isatuximab (ISA), a humanized anti-CD38 monoclonal antibody, has demonstrated activity in patients (pts) with RRMM in combination with Len/Dex in an ongoing Phase 1b study (NCT01749969). Overall response rate (ORR) was 63% at ISA 10 mg/kg Q2W (n = 24). Here, we report data from 2 new cohorts evaluating a higher ISA dose and a different administration schedule. **Methods:** Pts with RRMM (≥ 2 prior MM therapies) were sequentially enrolled to ISA 10 or 20 mg/kg (weekly × 4 doses, then every 2 wks; initial infusion rate 175 and 250 mg/h at 10 and 20 mg/kg, respectively) plus Len 25 mg (days [D] 1–21) and Dex 40 mg (D1, 8, 15, and 22), in 28-day cycles. Primary objective: to determine the maximum tolerated dose (MTD). **Results:** An additional 26 pts were treated in the 2 cohorts: median age 65 (42–76) yrs; median yrs from diagnosis 4.5 (1.8–16.6). Median 4.5 (1–8) & 6 (3–10) prior lines of therapy at 10 & 20 mg/kg, respectively; Len-refractory (67% & 86%), pomalidomide+carfilzomib-refractory (25% & 64%), immunomodulatory drug+proteasome inhibitor-refractory (50% & 86%). At data cut-off (Dec 2015), median duration of dosing was 21.5 wks (10 mg/kg) and 9.9 wks (20 mg/kg); 13 pts remain on treatment. 4 pts discontinued therapy due to adverse events (AEs) (grade [Gr] 3 infusion-associated reactions [IARs] [n = 3], dose-limiting toxicity of Gr 3 pneumonia [n = 1]), all at 20 mg/kg in Cycle 1; these pts were excluded from the efficacy analysis. Most frequent AEs were fatigue (46%), pyrexia (35%) and diarrhea (31%). IARs occurred in 65% of pts, mostly Gr ≤ 2, and > 90% during 1st infusion. MTD has not been reached. In evaluable pts, ORR (IMWG criteria; confirmed responses) was 50% in both cohorts (10 mg/kg [n = 12]: VGPR 25%; PR 25%. 20 mg/kg [n = 10]: VGPR 20%; PR 30%). Clinical benefit rate (≥ MR) was 83% and 50% in the 10 and 20 mg/kg cohorts, respectively. Median time to 1st response was 4 (4–16) wks. **Conclusions:** The combination of ISA ≥ 10 mg/kg and Len/Dex was generally tolerated and clinically active in heavily pretreated RRMM. Responses were observed after approximately 4 wks. PK, biomarker, and longer term follow-up data will be presented.

Abstract ID: 8003 (170498)

Genetic plasma cell signatures in high-risk smoldering myeloma versus multiple myeloma patients

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Background: Smoldering myeloma (SMM) is an ill-defined clinical myeloma precursor state. Recently, treatment studies targeting high-risk SMM patients have been conducted, showing promising clinical outcomes. Limited information is available on the biology of SMM. Using samples from a prospective clinical trial based on carfilzomib, lenalidomide and dexamethasone (CRd) (Korde et al. JAMA Oncology 2015), we showed near complete response (CR) or better in 28 of 45 (62%) patients with newly diagnosed multiple myeloma (NDMM); in high-risk SMM patients we reported stringent CR in 12 of 12 (100%) and 11 of 12 were MRD negative. Here, we sequenced the patients on our clinical trial and provide novel insights on tumor cell biology. **Methods:** We performed whole exome sequencing (median 125x, range 105-184x) and RNA sequencing of plasma cells obtained from baseline bone marrow samples in 39 patients with NDMM and 12 patients with high-risk SMM. **Results:** Whole exome sequencing on the 39 patients with NDMM identified a total of 2273 non-synonymous variants (median 53, range 26-139). Amongst the 12 SMM patients, 692 non-synonymous variants were identified (median 44, range 26-124). Previously reported recurrently mutated genes in multiple myeloma patients (BRAF, DIS3, FAM46C, IDH1, INTS12, IRF4, KRAS, NRAS, PRDM1, TP53, TRAF3, CYLD, RB1, ACTG1, LTB, HIST1H1E and MAX) were observed in 16 of 39 (41%) NDMM patients. In the high-risk SMM cohort, we did not detect any non-synonymous mutations amongst these genes. **Conclusions:** Amongst patients with NDMM and high-risk SMM enrolled in a prospective clinical trial of treatment with CRd, we confirmed previously reported recurrent mutations in NDMM. While the number of non-synonymous variants was similar in the two groups, none of the high-risk SMM patients had mutations in these genes. Our novel results suggest that at least a proportion of high-risk SMM patients have different molecular profiles compared to NDMM patients, which could have implications for risk determination and initiation of therapy. Additional analysis including clonal heterogeneity and subclonal architecture will be presented at the meeting.

Abstract ID: 9503 (167363)

Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001.

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Background: The anti–PD-1 antibody pembro (pembro; MK-3475) prevents PD-1 from binding to its ligands, PD-L1 and PD-L2, and is approved for treating advanced melanoma at a dose of 2 mg/kg every 3 wk (Q3W). Pembro demonstrated superior PFS over chemotherapy for ipilimumab (ipi)-refractory melanoma (KEYNOTE-002) and superior OS and PFS over ipi for advanced melanoma (KEYNOTE-006). We present 3-year OS data for all patients (pts) with melanoma enrolled in the phase 1b KEYNOTE-001 study (NCT01295827). **Methods:** Pts were enrolled in ipi-naive and ipi-treated cohorts and received pembro 2 or 10 mg/kg Q3W or 10 mg/kg Q2W until intolerable toxicity, progression, or investigator decision. Clinically stable pts with radiographic progression could remain on pembro until progression was confirmed. Response was assessed by RECIST v1.1 every 12 wk. After pembro discontinuation, pts were contacted to assess survival every 3 mo. OS was estimated using the Kaplan-Meier method. **Results:** Of the 655 pts enrolled, 24% had *BRAF*^{V600} mutation, 78% had stage M1c disease, 38% had elevated LDH, 75% had ≥1 prior therapy, and 52% had prior ipi. As of the Sep 18, 2015, data cutoff date, median follow-up duration was 32 mo (range 24-46) and 358 (55%) pts had died. The 36-mo OS rate was 40% and median OS was 23.8 mo (95% CI, 20.2-29.0), with similar results for each dose (Table). 36-mo OS rates were 41% in both ipi-treated and ipi-naive pts and 45% in treatment-naive pts (Table). Examination of the OS curve suggests a long-term OS benefit for a fraction of pts treated with pembro. Additional data, including PFS, ORR, duration of response, and safety, will be available for presentation. **Conclusions:** Pembro provides long-term survival benefit in pts with ipi-naive and ipi-treated advanced melanoma, with 40% of pts alive at 3 years. These data support the use of pembrolizumab in pts with advanced melanoma regardless of prior treatment.

Abstract ID: 9505 (165588)

Updated results from a phase III trial of nivolumab (NIVO) combined with ipilimumab (IPI)in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067).

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Background: In CheckMate 067, NIVO (anti-PD-1) plus IPI (anti-CTLA-4) significantly improved progression-free survival (PFS) and objective response rate (ORR) vs IPI alone in pts with MEL (N Engl J Med 2015;373:23). We report updated efficacy and safety results from this study. **Methods:** Treatment-naïve pts (N=945) were randomized 1:1:1 to NIVO 1 mg/kg Q3W + IPI 3 mg/kg Q3W for 4 doses (followed by NIVO 3 mg/kg Q2W), NIVO 3 mg/kg Q2W + placebo, or IPI 3 mg/kg Q3W for 4 doses + placebo, until progression or unacceptable toxicity. Pts were stratified by PD-L1 status, *BRAF*mutation status, and M-stage. Co-primary endpoints were PFS and overall survival (data remain immature). Secondary endpoints included efficacy by PD-L1 status and safety. **Results:** At ≥18 months of follow-up, median PFS continued to be significantly longer for NIVO+IPI and NIVO vs IPI (P<0.001), and was numerically longer for NIVO+IPI vs NIVO alone (Table). Median duration of response in 181/314 (57.6%) NIVO+IPI responders has not been reached, and was 22.3 and 14.4 months in 138/316 (43.7%) NIVO and 60/315 (19.0%) IPI responders, respectively. Median PFS was also numerically longer with NIVO+IPI vs NIVO or IPI regardless of PD-L1 tumor expression (Table). For NIVO+IPI, NIVO, and IPI groups, median PFS was 15.5, 5.6, and 4.0 months in pts with a *BRAF* mutation and was 11.3, 7.1, and 2.8 months in pts with wild-type *BRAF*, respectively. The frequency and types of drug-related grade 3/4 AEs were consistent with earlier reports (NIVO+IPI, 56.5%; NIVO, 19.8%; IPI, 27.0%). **Conclusions:** NIVO+IPI and NIVO alone continue to demonstrate superior clinical activity vs IPI monotherapy. NIVO+IPI appears to have greater efficacy than either agent alone, regardless of PD-L1 expression or *BRAF* mutation status.

Abstract ID: 9506 (167092)

Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE-029 expansion cohort.

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Background: Pembro (MK-3475), an anti–PD-1 antibody that prevents PD-1 from binding to its ligands, PD-L1 and PD-L2, is approved in several countries for treating advanced melanoma. In KEYNOTE-006, pembro showed superior OS over the anti–CTLA-4 inhibitor ipi. In a phase 3 trial, combination therapy with reduced-dose nivolumab (anti–PD-1) and standard-dose ipi showed higher ORR and longer PFS than either checkpoint inhibitor alone but was associated with increased toxicity. Preliminary data from the phase 1 KEYNOTE-029 study (NCT02089685) suggested that standard-dose pembro + reduced-dose ipi was safe and provided robust antitumor activity. Here, we present data from a larger population of patients (pts) treated with pembro + ipi in the KEYNOTE-029 expansion cohort. **Methods:** Eligible pts had advanced melanoma, ECOG PS 0-1, no active brain metastases, and no prior immune checkpoint inhibitor therapy. Pts received pembro 2 mg/kg Q3W + ipi 1 mg/kg Q3W for 4 doses, then pembro 2 mg/kg Q3W until intolerable toxicity, progression, or 2 y. Response was assessed by RECIST v1.1 at wk 12, every 6 wk until wk 30, then every 12 wk thereafter. **Results:** Of 153 pts enrolled in the expansion, 107 had ≥18 wk of follow-up (median 6.4 mo, range 4.3-9.4) by the Oct 26, 2015, data cutoff and were eligible for analysis. 18% of pts had elevated LDH, 55% had stage M1c disease, 36% were *BRAF*V600mutant, 13% received ≥1 prior therapy, and 12% received a prior BRAF ± MEK inhibitor; 84% had PD-L1–positive tumors (ie, ≥1% staining in tumor and adjacent immune cells). 79 pts (74%) received all 4 ipi doses; 73 pts (68%) remained on pembro. 41 pts (38%) had ≥1 grade 3-4 drug-related AE (DRAE); 68% of these DRAEs resolved by data cutoff. DRAEs led to discontinuation of pembro and ipi in 9 pts (8%), ipi alone in 11 (10%), and pembro alone in 4 (4%); there were no treatment-related deaths. Immune-mediated AEs of any grade and grade 3-4 severity occurred in 57 (53%) and 21 (20%) pts. ORR by investigator review was 57%, with 5 (5%) CR and 56 (52%) PR; by central review, ORR was 51%, with 9% CR and 42% PR. **Conclusions:** Pembro 2 mg/kg in combination with 4 doses of ipi 1 mg/kg has a manageable toxicity profile and provides robust antitumor activity in pts with advanced melanoma.

Abstract ID: 9504 (165198)

Pembrolizumab versus ipilimumab for advanced melanoma: Final overall survival analysis of KEYNOTE-006.

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Background: In the phase III KEYNOTE-006 study (NCT01866319), pembro (anti–PD-1) provided superior OS and PFS and a lower incidence of grade 3-5 treatment-related AEs compared with ipi (anti–CTLA-4) in patients (pts) with advanced melanoma and ≤ 1 prior therapy. Here, we present the final OS analysis. **Methods:** 834 pts were randomized 1:1:1 to 24 mo of pembro 10 mg/kg Q3W or Q2W or to 4 doses of ipi 3 mg/kg Q3W. Clinically stable pts with radiologic progression could receive treatment until confirmed progression. Response was assessed per RECIST v1.1 by central review at wk 12, every 6 wk until wk 48, then every 12 wk thereafter. Survival follow-up was every 12 wk. Final OS analysis occurred after all pts were followed for ≥ 21 mo. Differences in OS were assessed in the intention-to-treat population using the stratified log-rank test with the Hochberg procedure. **Results:** As of Dec 3, 2015, median follow-up duration was 22.9 mo and 383 pts had died. Pembro continued to provide superior OS, PFS, and ORR over ipi, with no difference between pembro schedules (Table). Median OS was not reached for pembro vs 16.0 mo with ipi; estimated 24-mo OS rates were 55% and 43%, respectively. The PFS KM curves appeared to flatten after ~20 mo for all arms, with estimated 24-mo rates of ~30% for pembro and 14% for ipi. KM estimates suggest ~70% of responding pts have a response lasting ≥ 72 wk. There was 1 treatment-related death (sepsis in the pembro Q2W arm). The safety profile was consistent with that previously reported. **Conclusions:** With an additional 9 mo of follow-up, median OS was not reached for pembro, and the superiority of pembro over ipi for advanced melanoma was confirmed. Coupled with the durability of response and manageable safety profile, these data support pembro as a standard of care for advanced melanoma.

Abstract ID: 9502 (168199)

Genomic analysis and 3-y efficacy and safety update of COMBI-d: A phase 3 study of dabrafenib (D) + trametinib (T) vs D monotherapy in patients (pts) with unresectable or metastatic *BRAF* V600E/K-mutant cutaneous melanoma.

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Background: Previous analysis of COMBI-d (NCT01584648) showed that D+T compared with D monotherapy improved ORR (69% [95% CI, 62%-75%] vs 53% [95% CI, 46%-60%]; *P* = 0.0014), reduced risk of progression (HR, 0.67 [95% CI, 0.53-0.84]; *P* = 0.0004) and death (HR, 0.71 [95% CI, 0.55-0.92]; *P* = 0.0107), and increased 2-y OS rate (51% vs 42%) in *BRAF*V600–mutant melanoma. **Methods:** In this phase 3, randomized, double-blind study, pts with histologically confirmed unresectable stage IIIC or IV, *BRAF* V600E/K–mutant melanoma were randomized 1:1 to receive frontline D 150 mg twice daily (BID) + T 2 mg once daily or D 150 mg BID only. The primary endpoint was PFS; secondary endpoints were OS, ORR, duration of response, and safety. Whole-exome sequencing was used to assess somatic mutations and copy number changes in pretreatment tumor (mean target coverage [MTC], 170×) and matched normal blood samples (MTC, 100×) collected from > 140 pts to further characterize *BRAF* V600–mutant melanoma and explore whether individual gene changes or genetic profiles were associated with treatment benefit. **Results:** A total of 423 pts were randomized to D+T (n = 211) or D (n = 212). As expected, initial genetic analysis of 130 pts showed that *BRAF* was the most frequently mutated gene (V600E, 83%; V600K, 15%). Additional mutations were observed in genes related to tumor suppression (*TP53*, *PTEN*, *CDKND2A*) and resistance to MAPK pathway inhibition (*MEK1*, *MEK2*, *NRAS*, *NF1, RAC1*), and amplifications were observed in *BRAF* and *MITF*. Overall mutation rate was higher in V600K vs V600E pts (median mutations per sample, 1701 vs 419; *P*< 0.0001). Updated genomic analysis, including OS and mutation rate association, and efficacy and safety results, including 3-y OS, will be presented. **Conclusions:** Preliminary genetic analyses showed additional mutations related to tumor suppression and MAPK inhibitor resistance were present in pts with *BRAF*-mutant melanoma, with a higher overall mutation rate in V600K-mutant tumors. Updated genetic analysis and 3-y efficacy and safety analysis will be presented.

Abstract ID: 10001 (162825)

Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants in SWOG clinical trials.

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Background: Neuropathy is a debilitating toxicity associated with various chemotherapy agents. We evaluated the association between common comorbid conditions and the development of peripheral neuropathy in patients treated with taxane-based chemotherapy. **Methods:** We examined the SWOG database to identify phase II/III trials that included taxane therapy from 1999-2011. We linked the SWOG clinical records to Medicare claims data according to social security number, sex, and date of birth. The following disease conditions potentially associated with peripheral neuropathy were evaluated: diabetes, hypothyroid, hypercholesterolemia, hypertension, varicella zoster, peripheral vascular disease, and autoimmune diseases. Multivariate logistic regression was used to model the odds of experiencing Grade 2-4 neuropathy. **Results:** A total of n = 1401 patients from 23 studies were included in the analysis. Of these 251/1401 patients (18%) had Grade 2-4 neuropathy. Patients receiving paclitaxel were more likely to experience neuropathy (25% vs. 12%; OR = 2.20, 95% CI: 1.52-3.18, p < .0001) compared to docetaxel. The inclusion of a platinum agent in addition to a taxane was also associated with greater neuropathy (OR = 1.68, 95% CI: 1.18-2.40, p = .004). For each increase in age of one year, the odds of neuropathy increased 4% (p = .006). Patients with complications from diabetes had twice the odds of neuropathy (OR = 2.13, 95% CI: 1.31-3.46, p = .002) compared to patients with no diabetes. In contrast, patients with autoimmune disease were half as likely to experience neuropathy (OR = 0.49, 95%CI: 0.24-1.02, p = .06). There were higher rates of Grade 2-4 neuropathy (22% vs. 0%, p = .0005) among diabetics on taxane therapy compared diabetics who did not receive a taxane or a platinum agent. **Conclusions:** In summary, we found that in addition to drug-related factors, age and history of diabetes are independent predictors of the development of CIPN. Interestingly, we also observed that a history of autoimmune disease was associated with reduced odds of neuropathy. Patients with diabetic complications may choose to avoid paclitaxel, or taxane/platinum combination therapies, if other efficacious options exist.

Abstract ID: 10006 (163730)

Benefits of physician orders for scope of treatment (POST) forms on end-of-life care incancer patients: Insights from the West Virginia registry.

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Background: The West Virginia POST form, a POLST Paradigm form (www.polst.org), converts patient preferences into medical orders and implements advance care planning for patients with advanced illness for whom their physicians would not be surprised if they died in the next year. Few studies have evaluated the benefits of POST forms to cancer patients. The objective of this study was to compare the outcomes from the use of POST forms versus advance directives (ADs) on end-of-life care quality metrics in cancer patients. **Methods:** A retrospective study of West Virginians who submitted POST forms or ADs to the West Virginia e-Directory Registry and died from cancer between 1/1/2011 and 6/30/2014. **Results:** Of patients in the West Virginia e-Directive Registry during the study period, 1129 patients were identified who died from cancer: 538 (47.7%) with ADs and 591 (52.3%) with POST forms. Of patients with POST forms, 323 (54.7%) were referred to hospice compared to 146 (27.1%) with ADs ($p<.001$). In-hospital death occurred in 163 (30.3%) of patients with ADs compared to only 66 (11.2%) of patients with POST forms; the unadjusted odds ratio for an out-of-hospital death for patients with POST forms compared to AD was 3.46 ($p<.001$). Of the 591 POST forms, 31 oncologists completed 82 (13.9%), 20 palliative care physicians completed 205 (34.7%), and 195 primary care physicians completed 304 (51.4%). Median time from POST form completion to death was only .95 months. **Conclusions:** Utilization of POST forms compared to advance directives in cancer patients is associated with a greater achievement of two quality metrics for end-of-life care: referral to hospice and out-of-hospital death. Oncologist use of the surprise question and earlier POST form discussions may contribute to higher quality end-of-life care for patients with advanced cancer.

Abstract ID: 10000 (170470)

A URCC NCORP nationwide randomized controlled trial investigating the effect of exercise on chemotherapy-induced peripheral neuropathy in 314 cancer patients.

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Background: Over 50% of cancer patients receiving chemotherapy regimens including platinums, vinca alkaloids, and taxanes experience chemotherapy-induced peripheral neuropathy (CIPN), which presents as numbness, tingling, pain, and movement problems. CIPN is a dose-limiting toxicity that reduces quality of life and can increase mortality. There are no FDA-approved drugs to treat CIPN and behavioral interventions like exercise have received little research attention. We conducted a secondary analysis of our nationwide phase III randomized controlled trial to examine the effect of exercise on CIPN and possible moderators to identify for whom exercise best treats CIPN. **Methods:** Cancer patients (N = 314, 56 ±11 yrs, 92% female, 78% breast cancer) receiving platinum, vinca alkaloid, or taxane regimens were randomized to standard chemotherapy or chemotherapy plus Exercise for Cancer Patients (EXCAP). EXCAP is a standardized, individualized, moderate-intensity, home-based, six-week progressive walking and resistance exercise program. We assessed CIPN pre- and post-intervention using patient-reported numbness and tingling (0-10 scale; 10 = as bad as you can imagine). Moderators tested included sex, age, BMI, and cancer stage. **Results:** Exercise reduced CIPN compared to control (p = 0.04, effect size [ES] = 0.26, ANCOVA). Older patients benefitted more from exercise than younger patients, compared to control (p = 0.06, ES= 1.05 for ages 28-47 vs. ages 64-79). We found no evidence of moderation by other variables. **Conclusions:** Exercise reduces CIPN for patients receiving platinum, vinca alkaloid, and taxane chemotherapy regimens, especially for older patients. Clinicians should consider prescribing exercise for patients receiving platinums, vinca alkaloids, and taxanes and especially for their geriatric patients. Funded by NCI grants R25 CA102618, UG1 CA189961, and 2U10 CA037420-20.

Abstract ID: 10003 (166829)

Randomized trial of early integrated palliative and oncology care.

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Background: Early palliative care (PC) improves outcomes in patients with newly diagnosed metastatic non-small cell lung cancer (NSCLC) and in patients identified by clinicians as having poor prognosis, advanced cancer. We evaluated the impact of early, integrated palliative and oncology care in patients with newly diagnosed lung and gastrointestinal (GI) cancer. **Methods:** We randomly assigned patients with newly diagnosed incurable lung (NSCLC, small cell, mesothelioma) or GI (pancreas, hepatobiliary, gastric, esophageal) cancer to PC integrated with oncology care (at least monthly visits with PC) or usual oncology care. We used the Functional Assessment of Cancer Therapy-General (FACT-G) to assess quality of life (QOL) and the Patient Health Questionniare-9 (PHQ-9) and Hospital Anxiety and Depression Scale (HADS) for mood at baseline, weeks 12 and 24. We assessed patients' perception of their likelihood of cure and their communication about their end of life (EOL) preferences. WBe used linear regression controlling for baseline values and clinical characteristics to evaluate the impact of group assignment on QOL and mood and chi-square to evaluate report of treatment intent and communication about EOL. **Results:** Between 5/2/11 and 7/20/15, we randomized 350 patients (175 per group), including 191 lung and 159 GI cancer patients. Patients assigned to early PC had higher QOL (β=4.98, 95%CI: 1.58 to 8.38, p=0.004) and less depression on the PHQ-9 (β=-1.22, 95% CI: -2.40 to -0.02, p=0.047) at 24 weeks, but not at 12 weeks. There were no between-group differences in HADS at either time point. At 24 weeks, similar proportions of patients reported that their cancer was unlikely to be cured (36/105 [33.6%] in PC and 43/115 [37.4%] in usual care) but more patients assigned to early PC reported they discussed their EOL preferences (31/116 [30.2%] versus 71/117 [14.5%], p=0.005). Patterns of change in QOL over time differed between lung and GI patients. **Conclusions:** Early PC improved QOL, decreased depression, and increased the frequency of EOL discussions in patients with newly diagnosed lung and GI cancer. The benefits of the integrated care model extend to other populations with newly diagnosed disease and include improved communication about EOL care.

Abstract ID: 10019 (161961)

Placebo-controlled phase III study comparing dexamethasone on day 1 to on day 1-3 with NK_1 receptor antagonist and palonosetoron in high emetogenic chemotherapy.

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Background: Standard antiemetic therapy for chemotherapy-induced nausea and vomiting in high emetogenic chemotherapy (HEC) is a combination of NK1 receptor antagonist, 5-HT_3 receptor antagonist and dexamethasone (DEX) on day 1-3. This study compared the efficacy of DEX on day 1 to on day 1-3 due to reduce side effects of DEX. **Methods:** Patients with a malignant solid tumor to receive HEC (containing > 50 mg/m^2 of cisplatin or anthracycline+cyclophosphamide) were randomly assigned to Arm A (DEX on day 1-3) or Arm B (DEX on day 1) with NK_1 receptor antagonist and palonosetron. Primary endpoint was complete response (CR) rate defined as no emetic episodes and no rescue medications in the overall (0-120h) phase. Secondary endpoints included CR rates in the acute (0-24h) and delayed (24-120h) phases, severity of nausea, adverse events (AEs) related to DEX and chemotherapy with CTCAE ver 4.0 on day 1-5, and quality of life with EROTC QLQ-C30 on day 5. The planned sample size of 400 provided power of 80% to detect the non-inferiority of Arm B to Arm A with the non-inferiority margin of difference by 15% in CR rate (one-sided α=0.025). **Results:** 401pts were enrolled and 396 pts were evaluable. Baseline characteristics were well-balanced. CR rates in the overall phase were 46.9% in Arm A and 44.0% in Arm B (risk difference: -2.9%, 95%CI: -12.6%-6.8%, *P*=0.007 for non-inferiority). CR rates in Arm A and in Arm B were 63.3% and 64.5% (risk difference: 1.2%, 95% CI: -8.1%-10.6%, *P*<0.001) in the acute phase; 56.6% and 51.5% (risk difference: -5.1%, 95% CI: -14.8%-4.6%, *P*=0.023) in the delayed phase, respectively. The severity of nausea was not significantly different between 2 arms on each day. AEs related to DEX depends on the duration of DEX administration: hot flushes on day 4 (*P*=0.013) and 5 (*P*=0.038) and tremor on day 5 (*P*=0.041) were observed more frequently in Arm A, while anorexia on day 2 (*P*=0.039) and 3 (*P*=0.006), depression on day

2 (*P*=0.045) and fatigue on day 2 (*P*=0.001) and 3 (*P*=0.004) were more in Arm B. Other grade >3 AEs and Global health status in QOL were similar between 2 arms. **Conclusions:** Administration of DEX can be limited to on day 1 in anti-emetic therapy for HEC.

Abstract ID: 2500 (164336)

Phase Ib study of BGJ398 in combination with BYL719 in patients (pts) with select advanced solid tumors.

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Background: Phosphatidylinositol-3-kinase (PI3K) and fibroblast growth factor receptor (FGFR) pathway dysregulation can co-occur in tumors. In this study (NCT01928459), safety, tolerability,and preliminary activity of the pan-FGFR (BGJ398) + α-specific PI3K (BYL719) inhibitors were evaluated and maximum tolerated dose (MTD) was established in pts w/ advanced solid tumors w/PI3K catalytic subunit (PIK3CA) mutations ± FGFR alterations. **Methods:** Pts w/ solid tumorsreceived once-daily (QD) BGJ on D1-D21 of each 28-D cycle (C) and BYL continuously duringescalation (PIK3CA-mutant ± FGFR-altered) and expansion (arm 1, PIK3CA-mutant [n = 15]; arm 2, PIK3CA-mutant + FGFR-altered [n = 10]; arm 3, PIK3CA-mutant + FGFR-altered breast cancer [n =10]). **Results:** Of 62 pts enrolled, 44% had ≥ 4 prior therapies. The MTD, 125 BGJ + 300 BYL, was determined based on 32 evaluable pts' data during escalation. C1 dose-limiting toxicities (DLTs) occurred in 4 pts (table). During expansion, 24 pts in arms 1 (n = 12), 2 (n = 6), and 3 (n = 6) received the MTD. At data cutoff (Nov 6, 2015), 4 pts were ongoing; median treatment duration was 64 D (range, 7-456 D). Common adverse events (AEs) included diarrhea (60%), fatigue (53%), nausea (48%), and on-target AEs (hyperphosphatemia [37%], hyperglycemia [36%]); most were G1/2. At the MTD, 61% of pts had ≥ 1 BGJ dose reduction; 61% of pts had ≥ 1 BYL dose reduction. Eight pts had partial responses (PRs), w/ 4 confirmed in urothelial, head and neck, melanoma, and anal cancer. One pt w/ *FGFR3-TACC3* fusion urothelial carcinoma w/ PR had a complete shrinkage in target lesions lasting 4 mo. **Conclusions:** The MTD for BGJ + BYL was determined as QD 125 BGJ on D1-D21 of each C + 300 BYL continuously. Given the high number of reductions w/ chronic treatment, lower starting doses may be warranted in future studies. Responses were observed in tumors w/ specific genetic alterations; however, it is not known if BGJ + BYL in combination offers improved efficacy over single agents. [caption]Dose-escalation DLTs.[/caption]

Abstract ID: 2503 (171083)

Phase I study of sapacitabine and seliciclib in patients with advanced solid tumors.

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Background: Sapacitabine is an oral nucleoside analogue; the active metabolite CNDAC generatesss DNA breaks that are converted to dsDNA breaks (DSB) during subsequent replication, resulting incell death. CNDAC-induced DSB repair is dependent on homologous recombination (HR). Seliciclibis an oral CDK2, 7 and 9 inhibitor, and sensitizes cells to CNDAC by decreasing DSB repairvia compromise of HR protein activation. This phase I study evaluates sequential and concomitantsapacitabine and seliciclib treatment. **Methods:** Dose escalation was conducted in patients withincurable solid tumors with sapacitabine b.i.d. x 7 consecutive days (d 1-7) followed by seliciclibb.i.d. x 3 consecutive days (d 8-10) or sapacitabine q.d. concomitantly with seliciclib q.d. x 5 daysper week x 2 weeks (d 1-5, 8-12). MTD was the highest dose level at which less than one-third of atleast 6 patients experienced cycle 1 DLT. Skin biopsies were obtained to assess DNA damage following sapacitabine and seliciclib treatment. **Results:** 67 patients were treated including 45 BRCA mutation carriers (BRCA +ves). MTDs are sapacitabine 50 mg b.i.d./seliciclib 1200 mg b.i.d. and sapacitabine 250 mg q.d./seliciclib 200 mg q.d. respectively. DLTs were reversible elevations in transaminase and bilirubin, neutropenia/febrile neutropenia and pneumonia. The most frequent grade 3/4 adverse events included elevations in ALT (10%), AST (13%), bilirubin (6%) and alkaline phosphatase (7%), neutropenia (21%), febrile neutropenia (6%), hyperglycemia (6%), hypokalemia (6%), and abdominal pain (7%). Skin biopsies showed a 2.3-fold increase in gH2AX staining post-sapacitabine (n = 16; p = 0.007) and a further 0.58-fold increase post-seliciclib (n = 12; p = 0.069). Six confirmed PRs occurred in BRCA +ves with pancreatic, ovarian and breast cancer. Response durations range from 49 to > 224 weeks in 4 ovarian and breast patients. SD was observed in 10 additional BRCA +ves with durations ranging from 26 to 81 weeks in 5 ovarian and breast cancer patients. **Conclusions:** Sequential and concomitant sapacitabine and seliciclib is safe with preliminary antitumor activity (35% PR + SD) in BRCA +ves, the status of which may be a potential biomarker for response across multiple tumor types.

Abstract ID: 100 (163413)

Checkmate 032: Nivolumab (N) alone or in combination with ipilimumab (I) for thetreatment of recurrent small cell lung cancer (SCLC).

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Background: Patients (pts) with advanced (adv) SCLC after first-line platinum-basedchemotherapy have limited options. Nivolumab, a programmed death-1 (PD-1) immune checkpointinhibitor, is approved for previously treated metastatic NSCLC in the US and for squamous NSCLC inthe EU. Nivolumab + ipilimumab, a cytotoxic T-lymphocyte antigen-4 immune checkpoint inhibitor, has shown durable responses in multiple tumor types. CheckMate 032 was designed to evaluate nivolumab +/- ipilimumab in adv tumors including SCLC. **Methods:** AdvSCLC pts with progressivedisease (PD) after ≥1 platinum-based chemotherapy, regardless of platinum sensitivity or tumorPD-1 ligand 1 (PD-L1) expression, were eligible. Pts received nivolumab ([mg/kg] N3 Q2W) or nivolumab + ipilimumab combination (N1 + I3 or N3 + I1 Q3W for 4 cycles then N3 Q2W). Primaryendpoint was objective response rate (ORR). Additional endpoints were safety, overall survival (OS), progression-free survival (PFS), and biomarkers. **Results:** 180 pts were enrolled (n=80, N3; n=47, N1 + I3; n=53, N3 + I1). Among 127 pts in the N3 and N1 + I3 cohorts, 56% received ≥2 prior regimens and 30% were platinum resistant. Efficacy data are shown (Table). Responses were observed independent of platinum sensitivity and PD-L1 expression. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 11% of pts in N3 and 32% of pts in N1 + I3; 5% and 13% discontinued due to TRAEs, respectively. One TR death due to myasthenia gravis occurred (N1 + I3 arm). **Conclusions:** Nivolumab and nivolumab + ipilimumab showed durable objective responses and manageable safety profiles, with possibly higher toxicities observed with the combination, in previously treated SCLC pts. Updated efficacy including OS by prior lines of therapy, safety, and biomarkers will be presented for the N3 and N1 + I3 cohorts. Efficacy and safety for the N3 + I1 cohort will be presented. [footer] [a]15 pts had <6 weeks minimum follow-up [b]Minimumfollow-up = 120 days [c]25 pts in N3 and 2 pts in N1 + I3 were non-evaluable for tumor response DOR = duration of response[/footer]

Abstract ID: 3003 (170754)

Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology.

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Background: Mismatch repair deficiency (MRD) is feature of many cancers at a frequency of approximately 1 in 30 patients independent of tumor histology. Tumors with MRD are deficient in the repair of specific DNA replication errors and as a result accumulate hundreds to thousands of mutations per tumor genome. The high number of somatic mutations increase the chances for at least one of these mutations to result in a highly immunogenic neo-antigenic protein that can trigger a potent anti-tumor immune response in the presence of PD-1 blockade. **Methods:** To further test this hypothesis, we conducted a phase 2 study to evaluate the activity of pembrolizumab (pembro), a programmed death-1 (PD-1) antibody in MRD tumors independent of tumor histology using a basket design. Pembro was administered at 10 mg/kg every 14 days inpatients with > 1 prior therapy. The co-primary endpoints were response and progression-free survival rate at 20 weeks. Secondary endpoints included disease control rate (DCR = CR+PR+SD), PFS, overall survival (OS) and safety. **Results:** A total of 29 patients were enrolled and treated on this study, including the following histologies: (endometrial: 9; pancreatic: 4; ampullary: 4; biliary: 3; small bowel: 3; gastric: 3; thyroid: 1; prostate: 1; sarcoma: 1). Median follow up time is 8.1 mos. Objective response and disease control rates were 48% (14/29, 95% confidence interval: 29-67%) and 72% (21/29), respectively. Twenty of 29 patients remain on treatment due to clinical benefit. Median overall Survival (OS) and progression-free survival (PFS) were 21 months and not reached (NR). The OS and PFS rates at 12 months were 79% and 54%, respectively, which support the durability of clinical benefit. Among the patients with an objective response, only 3 have developed secondary resistance to pembro with a median time to progression of 5 months. **Conclusions:** Independent of tumor histology, patients with advanced MRD cancers receive durable clinical benefit with Pembro. (NCT01876511)

Abstract ID: 3001 (163524)

CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC.

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Background: Nivo + ipi is approved in adv melanoma and has demonstrated clinical activity and manageable safety in various solid tumors. CheckMate 012 is a phase I study of nivo monotherapyor combined with other therapies in 1L adv NSCLC; we report updated results, including tumor growth dynamic (TGD) modeling, from N+I dosing schedules explored to optimize safety and permit synergistic activity. **Methods:** Patients ([pts] N=148, any NSCLC histology) received N+I(mg/kg) across 4 dose cohorts (Table). Primary objective was safety; secondary objectives were ORR (RECIST v1.1) and 24-wk PFS rate; exploratory endpoints were OS and efficacy by tumor programmed death ligand 1 (PD-L1) expression. The effect of N+I dosing was assessed by TGD modeling generated using individual tumor assessments; model-predicted tumor shrinkage at wk12 was compared across cohorts. **Results:** Treatment-related (TR) adverse events (AEs) and select TRAEs were manageable (Table). TRAEs leading to discontinuation (DC) were comparable to nivo alone (10%), with no TR deaths. Across cohorts, ORRs ranged from 13%–39% (Table), and median duration of response was not reached. Responses were noted regardless of PD-L1 expression, with a higher magnitude of benefit in tumors that expressed PD-L1. TGD modeling predicted enhanced tumor shrinkage for N3 + I1 schedules compared with nivo alone or any N1-containing schedule. Based on integrated efficacy/safety/TGD data, N3 Q2W + I1 Q6W was proposed for further evaluation. **Conclusions:** 1L therapy with N+I demonstrates clinical activity and a manageable safety profile. Updated safety and efficacy across cohorts (by histology, EGFR, smoking status, PD-L1 expression) and TGD modeling data will be presented. [footer]NC = not calculated; Gr = grade. [/footer]