Pts with stable disease (SD) at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. Pharmacokinetics of XL184 will be analyzed in this hepatically impaired patient population.
**Results:** A total of 12 pts have been enrolled with a median age of 65 years (M/F 64%/36%). The median number of prior systemic treatments was 1 with 7 pts having received sorafenib. Of the 7 pts who were evaluable (minimum 12 wks follow up) to date, 2 pts achieved a PR and 5 pts achieved SD with radiological evidence of tumor shrinkage. The overall disease control rate at wk 12 was 88%. One pt previously treated with sorafenib showed a 42% tumor decrease at wk 12. Three pts with SD had an AFP reduction of more than 50% at wk 12. The overall dose reduction rate for pts on study for at least 6 wks was 67%. Most frequently observed adverse events regardless of causality with CTCAE Grade $\geqslant$3 in the Lead-in Stage include diarrhea (n = 2), nausea, fatigue, thrombocytopenia, vomiting, anemia, blister, blood magnesium increased, dehydration, epistaxis, and hypoglycemia (each n = 1).
**Conclusions**: Preliminary results suggest that XL184 is active in pts with advanced HCC, including those previously treated with sorafenib. Updated efficacy and safety results will be presented.

**409** POSTER

**The novel, investigational Nedd8-activating enzyme inhibitor MLN4924 in patients with metastatic melanoma: a phase 1 study**

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**Background:** Metastatic melanoma is associated with poor prognosis; new agents with improved efficacy are needed. The investigational agent MLN4924 is a novel small-molecule inhibitor of Nedd8-activating enzyme (NAE); NAE inhibition prevents the proteasomal degradation of proteins with roles in cell cycle progression (p27), DNA damage (Cdt-1), stress response (Nrf-2), and signal transduction (pI$\kappa$B$\alpha$). MLN4924 is active in preclinical models of several tumor types; in patients, pharmacodynamic responses of elevated Cdt-1 and Nrf-2 levels have been seen in post-treatment skin biopsies (Kauh *et al*, ASCO 2009). The primary objectives of this study were to determine the safety profile and maximum tolerated dose (MTD) of MLN4924 in patients with metastatic melanoma.
**Materials and Methods:** Patients aged $\geqslant$18 years with ECOG performance status 0−2 were treated with 1-hour intravenous infusions of MLN4924 on days 1, 4, 8, and 11 of 21-day cycles. Dose escalation, starting at 50 mg/m$^2$ and using 1.33-fold increments, proceeded via a Bayesian continual reassessment method based on occurrence of dose-limiting toxicities (DLTs) in cycle 1. The primary endpoint included adverse events (AEs). Secondary endpoints included antitumor activity, and the pharmacokinetics (PK) and pharmacodynamics of MLN4924.
**Results:** To date, 12 patients (8 male; median age 55.5 years, range 34−71; median 2 prior therapies, range 0−5) have been enrolled to 5 dose levels: 50 (n = 2), 67 (n = 2), 89 (n = 2), 118 (n = 4), and 157 mg/m$^2$ (n = 2). One DLT, of MLN4924-related grade 3 hypophosphatemia (118 mg/m$^2$ dose level), has been recorded to date; the MTD has not been reached. Patients have received a median of 2 cycles (range 0 to 7+). AEs have been mostly mild/moderate (grade 1/2); the most common include nausea (n = 6), fatigue (n = 5; 2 grade 2), myalgia (n = 4), and diarrhea, pruritus, anorexia, and muscle spasms (each n = 3; 1 grade 2 anorexia). Two grade 3 AEs have been reported of cancer-related pain and transient hypophosphatemia. Six patients have discontinued due to progressive disease (1 died). One patient with brain metastases, who had received 4 prior lines of therapy, remains in stable disease after 7 cycles (67 mg/m$^2$ dose level). Preliminary evidence for shrinkage/softening of subcutaneous nodules has been seen in 2 patients.
**Conclusions:** MLN4924 was well tolerated at the current dosing schedule, and encouraging antitumor activity has been observed. Accrual and dose escalation continues. Updated safety and efficacy data, plus PK and pharmacodynamic data, will be presented.

**410** POSTER

**Vandetanib, docetaxel and carboplatin followed by maintenance vandetanib or placebo in patients with stage IIIB, IV or recurrent non-small cell lung cancer (NSCLC): a randomized phase II study (PrE0502) by PrECOG, LLC (NCT006872970)**

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**Background:** The goal was to determine if vandetanib, a dual inhibitor of the VEGF and EGFR pathways, could improve progression-free survival (PFS) in patients (pts) with NSCLC when given as induction therapy (tx) with docetaxel and carboplatin, followed by maintenance tx, compared to maintenance placebo.
**Materials and Methods:** Pts with advanced stage NSCLC were randomized to receive induction docetaxel (75 mg/m$^2$) + carboplatin (AUC 6) on day 1 of a 21-day cycle and daily vandetanib (100 mg/day po) for 4 cycles, followed by maintenance tx with either daily vandetanib (300 mg/day po) or placebo until progression. The study was designed to demonstrate improvement in PFS with the addition of vandetanib to a median of 6.2 mos, compared to historical control median of 4.5 mos for docetaxel + carboplatin alone. Eligible pts had measurable disease per RECIST, ECOG PS 0 or 1, and no prior cytotoxic or targeted tx for advanced disease. Pts with cardiac conditions including uncontrolled hypertension or history of QT prolongation were ineligible.
**Results:** 162 pts were randomized between May 2008 and December 2009, of whom 158 received tx. 87% of pts had stage IV/recurrent disease; 52% were male. Median age was 63 (range 36−82). A median of 2 cycles of induction tx were given. Sixty pts received maintenance txw/placebo (median 2 cycles). Tx was discontinued primarily for progression (38%/65% for induction and maintenance) and adverse events (AE) (28%/23%). Common AEs included fatigue, dyspnea, diarrhea, dehydration, neutropenia, neutropenic fever, and leukopenia. Death on tx were reported for 19 pts, 11 from progressive disease. Neither arm demonstrated significant improvement over the historical median PFS of 4.5 mos. Median PFS among pts randomized to maintenance vandetanib was 5.3 mos (95% CI, 3.2−6.5 mos), while median PFS among pts randomized to maintenance placebo was 4.6 mos (95% CI, 2.8−4.9 mos, stratified logrank p = 0.04).
**Conclusions:** Although neither arm met the primary endpoint over historical control, pts randomized to vandetanib maintenance had longer PFS compared to pts randomized to placebo maintenance.

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**A phase I trial of the histone deacetylase inhibitor panobinostat (LBH589) and epirubicin in patients with solid tumor malignancies**

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**Background:** Preclinical and clinical data suggest that pre-exposure of cancer cells to a histone deacetylase inhibitor (HDACi) potentiates topoisomerase (topo) inhibitors. The HDACi-induced histone acetylation and chromatin modulation facilitates DNA access and target recruitment for topo II inhibitors. In vitro data further suggest that effective inhibition of HDAC2 is necessary for enhanced epirubicin-induced apoptosis.
**Materials/Methods:** This phase I trial explores the safety, tolerability, and maximum tolerated dose (MTD) of escalating doses of panobinostat given orally on days 1, 3, and 5 followed by epirubicin administered intravenously at 75 mg/m$^2$ on day 5 in 21-day cycles. Histone acetylation and HDAC2 expression are evaluated in pre- and post-treatment peripheral blood mononuclear cells in all patients and in tumor cells of 12 patients treated at the MTD.
**Results:** The trial enrolled 20 patients [5M/15F, median age 49 years (range 24−80)] in 5 panobinostat cohorts: 20, 30, 40, 50, and 60 mg. The MTD was identified as 50 mg panobinostat. Tumor types included melanoma (n = 6), breast (n = 3), sarcoma (n = 3), ovarian (n = 2), lung (n = 2), and one each of neuroblastoma, pancreatic, testicular, and colon cancer. Dose-limiting toxicities included 1/6 patient with a grade 3 atrial fibrillation in the 50 mg cohort and 2/3 patients in the 60 mg cohort with DLT, one with grade 3 fatigue and one with grade 4 thrombocytopenia. Non-dose-limiting grade 3 and 4 toxicities include neutropenia (n = 12, 60%), thrombocytopenia (n = 4, 20%), and anemia (n = 3, 15%). One patient with small cell lung cancer has an unconfirmed partial response, one patient each (melanoma, ovarian, neuroblastoma) demonstrated stable disease for

more than 6 months, out of 18 evaluable patients. The patient with ovarian cancer had progressive disease on liposomal doxorubicin and now on this trial had a 30% drop in her CA125. The patient with neuroblastoma had resolution of her lesions on PET/CT. Patients received a median number of 2 (1−10) treatment cycles. H3 and H4 histone acetylation will be correlated with HDAC2 expression, panobinostat dose, and plasma concentrations.
**Conclusions:** A sequence-specific combination of panobinostat and epirubicin is tolerable and shows early activity. A dose expansion to include mandatory biopsies is being explored at the panobinostat dose of 50 mg.

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**BMS-754807, an oral dual IGF-1R/insulin receptor (IR) inhibitor: initial results from a Phase 1 dose- and schedule-finding study in combination with carboplatin/paclitaxel in subjects with solid tumors**

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**Background:** BMS-754807 is a potent reversible inhibitor of IGF-1R/IR kinase family (IGF-1R, IR; $Ki_{1/2}$ (9−13h), BMS-754807's effects on normal tissues and tumor cell cycle are expected to be different from effects of continuous inhibition by anti-IGF-1R antibodies. This allows exploring continuous and intermittent schedules in chemotherapy combinations for improved safety and efficacy.
**Methods:** CA191005 is an open-label ascending dose study of BMS-754807 combined with carboplatin (C)/paclitaxel (P) in subjects with advanced or metastatic solid tumors. C (AUC = 6 mg/ml min) and P (200 mg/m$^2$) are given on day (D) 1 of 3 week cycles. BMS-754807 is administered orally continuously (D2−21) or in an intermittent schedule. Subjects completing 4 cycles of combination therapy can opt for BMS-754807 monotherapy. Pharmacodynamic (PD) assessments include plasma glucose, insulin, C-peptide and IGF-1 levels. 3′-deoxy-3′-[$^{18}$F]fluorothymidine (FLT)-PET imaging is performed at baseline, D13−15 and D19−21 in cycle 1 to assess anti-tumor activity and explore dependence of anti-proliferative effects on treatment schedule.
**Results**: To date, 11 subjects have been treated with 3-weekly C/P and BMS-754807 at doses of 4, 10, 20 and 30 mg on the continuous schedule. Treatment durations were 21 to 151 days. No dose-limiting toxicity has been observed and dose escalation is ongoing. All subjects had treatment-related AEs, the majority consistent with chemotherapy administration. The most frequent treatment-related Grade 3/4 AE was neutropenia. No AE of fasting hyperglycemia was noted, though subjects experienced post-prandial hyperglycemia most frequently between D2−5, possibly due to steroid use during chemotherapy. Insulin increases 2 hours post dose indicate PD effects on IR, consistent with observations in a monotherapy trial. One subject (small cell lung cancer, chemotherapy failure) had PR after 2 cycles of combination therapy. Data from additional dose levels and updated safety, efficacy, PD and imaging results will be presented.
**Conclusion**: BMS-754807 can be administered safely in combination with C/P at doses that resulted in exposures exceeding preclinical efficacious exposures in a monotherapy trial. Analysis of PD and FLT-PET responses is expected to provide a rational basis for selection of an optimal dose and schedule for BMS-754807 in combination with chemotherapy.

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**Phase II study evaluating the efficacy, safety and pharmacodynamic correlative study of dual anti-angiogenic inhibition using Bevacizumab (B) in combination with Sorafenib (S) in patients (pts) with advanced malignant melanoma**

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**Background:** Melanomas are highly vascular tumors and are known to have high incidence of B-Raf mutations driving tumor proliferation. Inhibition of VEGF signaling at the ligand and receptor level has the potential for enhanced antitumor efficacy. This hypothesis was tested in a NCI-sponsored phase 2 trial of sorafenib (inhibitor of VEGFR and RAS/RAF/MEK/ERK) and bevacizumab in pts with advanced melanoma.
**Methods:** Pts with measurable advanced melanoma, adequate organ function, PS 0−2, $\leqslant$ 2 prior therapies in the advanced setting were eligible; pts with active brain metastases were excluded. S at 200 mg BID days 1−5 q 7 days and B at 5 mg/kg q 14 days on a 28 day cycle. Dose reduction of S permitted, but no dose reduction of B. The primary objective of the study was to determine clinical biological activity (defined as CR + PR+ SD >16 wks). Secondary objectives included safety, tolerability, median time to progression (TTP). Pharmacodynamic (PD) studies analyzing S-100$\beta$ protein, circulating melanoma cells (CMC), endothelial cells (CEC), vascular endothelial growth factor (VEGF) and soluble vascular endothelial growth factor receptor-2 (sVEGFR-2) levels of serum and plasma at baseline, C1D15 and C2D1 were measured using standard ELISA.
**Results:** Final ITT Stage 1 analysis, 14 patients with metastatic melanoma treated (median age 61 years [43−77]; 64% male). No RECIST responses were observed, although 6 (42.9%) patients had SD for more than >16 weeks, 3 of these pts had SD $\geqslant$ 1 year, 5 (35.7%) had PD at or prior to 16 weeks (3/2), 3 unevaluable for tumor response. Median TTP was 18.6 months (95% CI 4.7–32.7 mo). The most frequently reported drug-related adverse events (AEs) were hand-foot skin reaction (HFS) 57.1%, rash 14.2%; fatigue 57.1%, anorexia 28.6%; hypertension (HTN) 64.3%; proteinuria 35.7%; nausea 14.2%, diarrhea 21.4%; bleeding 14.2%. Grade 3/4 drug-related AEs were HTN 14.2%, HFS 7%, proteinuria 7% and thrombocytopenia 7%. Dose reduction of S required in 6 (42.9%) patients (4 due to grade 2/3 HFS, 1 each for HTN and proteinuria). Updated PD analysis and its correlation with clinical activity will be presented.
**Conclusions:** Combined VEGF/VEGFR blockade employing S in combination with B was safe and tolerable. Although objective responses were not observed, 43% of the patients with advanced melanoma had clinical biological activity.

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**Clinical pharmacokinetics and pharmacodynamics of CX-4945, a novel inhibitor of protein kinase CK2: Interim report from the phase 1 clinical trial**

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**Background:** CX-4945 is a potent and selective, first-in-class oral inhibitor of the CK2 protein kinase. CK2 is an essential non-oncogene molecular target that promotes the survival of many cancers. CK2 modulates the PI3K/Akt pathway via phosphorylation of several proteins (Akt and p21), which we have validated as mechanistic biomarkers for CX-4945 activity. In certain tumors CK2 mediates the release of IL-6 and IL-8, and these proteins were evaluated as tumor-based biomarkers for CX-4945 activity. Two different oral dosing schedules have been assessed in a phase 1 clinical trial in order to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) relationships of CX-4945 in humans.
**Materials & Methods:** Eligible patients having advanced solid tumors with progressive disease, or having no available approved therapies, were administered CX-4945 in successive dose escalation cohorts using a standard 3+3 design. Oral doses were administered twice daily (BID) or four times daily (QID) for twenty-one consecutive days of a four week cycle. Plasma samples were evaluated for PK analysis and for IL-6 and IL-8, while peripheral blood mononuclear cells (PBMC) were isolated for PD biomarkers.
**Results:** Twenty-three patients from six dose cohorts have received BID doses, and six patients from two dose cohorts have received QID doses of CX-4945 to date. CX-4945 has been well tolerated, with no dose limiting toxicities observed to date. Plasma exposures at steady state were significantly increased by QID dosing when compared with BID dosing. Evidence of inhibition of CK2 and the Akt pathway, manifested as reduced phosphorylation of Akt (S129) and p21 (T145) in PBMC, was observed in a drug exposure related manner. Stable disease is evident in 26% of patients (6/23) at the time of first evaluation, and in a further 17% of patients (4/23) for at least 6 months, including two patients on treatment for more than 9 months.
**Conclusions:** CX-4945 has been well tolerated on BID and QID dosing schedules. QID dosing provides for substantial increases in plasma