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-100β 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