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

exposures when compared with BID dosing. Moreover, mechanistic and tumor biomarker analyses in patients demonstrates that CX-4945 inhibits CK2 activity. This phase I trial will continue to seek the maximum tolerated dose of CX-4945 while preparing for additional clinical trials as a single agent and in combination with other targeted agents as well as conventional chemotherapy.

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A phase I study evaluating the safety profile and pharmacokinetics of CS-1008 (Tigatuzumab), humanized monoclonal antibody targeting death receptor 5 (DR5), in Japanese patients with advanced solid tumours

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Background: CS-1008 (Tigatuzumab) is an IgG1 agonistic humanized monoclonal antibody targeting the human death receptor 5 (DR5). CS-1008 triggers apoptosis after binding to DR5 resulting in death of targeted tumor cells. This is a phase I, open-label, dose-escalating study evaluating the safety profile and pharmacokinetics (PK) of CS-1008 in Japanese patients (pts) with advanced solid tumors. In addition, evaluation of anti-CS-1008 antibody (HAHA), preliminary anti-tumor effects, DR5 protein expression, and potential CS-1008 biomarker activity were performed.
Methods: Pts with advanced solid tumors having no available standard therapy were enrolled. CS-1008 is administered over 30 minutes intravenously once every week at doses of 2 mg/kg (level 1), 4 mg/kg (level 2), and 6 mg/kg (level 3); once every 2 weeks at a dose of 8 mg/kg (level 4); and once every 3 weeks at a dose of 10 mg/kg (level 5).
Results: Three pts were enrolled in each level (total 15 pts); median age was 57 years. Pts had pancreatic cancer (4), esophageal carcinoma (3), sarcoma (3), thymic carcinoma (2), breast cancer (1), non-small cell lung cancer (NSCLC) (1), intrahepatic cholangiocarcinoma (1). There was no dose-limiting toxicity observed. The most frequent ($\geq$6 patients) adverse events (AEs) were AST increase, serum albumin decrease and fever. Grade 3/4 drug-related AEs were not observed. Two pts had serious AE (fever and esophagostenosis), but all of them related to the disease progression. Neither infusion reaction nor HAHA was observed. PK results demonstrated a half-life of 166$\pm$10 hr (mean$\pm$SD) to 237$\pm$38 hr. At level 1, 2, 3, 4 and 5, the exposures (level 1, 2, 3: $AUC_{168,}$ level 4: $AUC_{336,}$ level 5: AUC_{504}) were 4031$\pm$376 μg·hr/mL (mean$\pm$SD), 6317$\pm$1702 μg·hr/mL, 14085$\pm$3702 μg·hr/mL, 26577$\pm$8134 μg·hr/mL, and 40041$\pm$10579 μg·hr/mL, respectively. PK was similar to those in the study conducted in the United States. Three pts (pancreatic cancer, NSCLC, intrahepatic cholangiocarcinoma) had stable disease, and 12 pts had progressive disease.
Conclusions: CS-1008 is well tolerated up to 10 mg/kg in Japanese pts with advanced solid tumors. Clinical trials of CS-1008 in combination with chemotherapy for the treatment of DR5 positive tumors have been implemented.

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The oral HDAC inhibitor SB939 shows activity in in vitro and in vivo models of acute myeloid leukemia

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Background: SB939 is an orally active HDAC inhibitor with a very favorable pharmacological, pharmacokinetic, pharmacodynamic and safety profile that is currently in phase Ib clinical trials in AML and MDS.
Methods: Blasts from primary AML cells (obtained from AllCells; Emeryville, CA) were expanded using a StemSpan® medium and a cytokine cocktail (FLT3 ligand, SCF, IL-3 and IL-6) as recommended by the manufacturer (StemCell Technologies). Effects of SB939 on cell proliferation were assessed in leukemic cell lines as well as in primary AML cells. The anti-tumor activity was tested against MV4−11 or HEL92.1.7 tumors grown *s.c.* in nude mice, and against HL-60-induced leukemia, induced after *i.v.* injection into SCID mice. Mice were dosed with SB939 either with 25−50 mg/kg *q.d*. or 75 or 125 mg/kg *q.o.d* or three times per week in the different animal models. Tissues from the AML *in vivo* model or PBMCs from phase I patients were analyzed for target efficacy by using a validated Western blot assay to measure acetylated histone H3 (acH3) levels. Cytokines from AML cell lines or AML patients treated with SB939 were measured using the Milliplex® cytokine multiplex assay (Millipore).
Results: Leukemia cell lines were the most sensitive cell lines towards SB939 amongst 30 liquid and solid cell lines tested, with IC_{50} between 70 and 170 nM. Primary cells from patients with relapsed/refractory AML were significantly more sensitive to SB939 than those of newly diagnosed patients with IC_{50} of 0.70$\pm$0.36 μM (n = 8) *versus* 1.28$\pm$0.47 μM (n = 8), respectively. SB939 was highly efficacious in the xenograft models: MV4−11 (116% TGI) and HEL92.1.7 (55% TGI) after dosing at 50 mg/kg *q.d.* and 125 *q.o.d.* respectively. In the HL-60 leukemia model white blood counts were reduced by 73% and the onset of severe paralysis or death was delayed for at least 18 days. Maximal acH3 levels were measured 3 h after dosing in tissues as well as patient PBMCs. AcH3 values in normal tissues decreased after 15 days, but increased in diseased tissues, showing a selectivity of SB939 for diseased tissues. Levels of several cytokines important in AML (VEGF, TNFα, PDGF AA and MCP-1), were significantly reduced in AML cell lines after treatment with SB939.
Conclusion: SB939 is highly efficacious on AML cell lines *in vitro* and also on primary cells from AML patients, with higher activity *in vitro* on cells from patients with relapsed/refractory AML compared to cells from newly diagnosed patients. SB939 was highly efficacious in mouse models of AML, where target efficacy was confirmed by detection of increased acH3 levels in diseased tissue. Target efficacy was also demonstrated in PBMCs from patients. The influence of HDACi on cytokines may be an additionally benefit during AML treatment. These findings indicate a therapeutic potential of SB939 for treating relapsed/refractory AML.

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Human biotransformation of olaparib (AZD2281) an oral poly(ADP-ribose) polymerase (PARP) inhibitor

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Background: Olaparib (AZD2281) has demonstrated activity and acceptable toxicity as an oral monotherapy in patients with advanced breast or ovarian cancer who are *BRCA* mutation carriers, and acceptable toxicity as monotherapy in patients with advanced solid tumours.
Material and Methods: A single oral radiolabelled dose of olaparib (100 mg; 120 μCi of ^{14}C-labelled drug) was administered to patients (n = 6) with advanced or metastatic solid tumours in an open-label, non-randomized, single-centre study. A single radiolabelled dose of olaparib was also administered to male and female Han Wistar rats (15 mg/kg, 200 μCi/kg) to provide samples which could be used to compare the biotransformation between humans and the toxicology species. Samples of plasma, urine and faeces were obtained for metabolite identification purposes from both studies. Metabolite profiles of samples were generated by high performance liquid chromatography coupled to radiochemical detection (HPLC-RAD) and metabolite characterization was performed on selected samples by HPLC with mass spectrometry ($HPLC\text{-}MS^n$).
Results: In plasma, olaparib accounted for 70% of the radioactivity present in human plasma, and 70% or 100% in male and female rats, respectively. Olaparib was also the major component in human excreta, accounting for ca. 21% of the dosed radioactivity; comprising ~15% in the urine and ~6% in the faeces. In addition to the parent compound, 36 metabolites were identified in human excreta, the major ones accounting for up to 11% of the dosed radioactivity. Of the 36 metabolites observed in human excreta, 17 were specific to urine. All of these urine specific metabolites were of low abundance; six of which accounted for slightly more than 1% of the dose whilst the remainder accounted for less than 1% of the dose (or were detectable by HPLC-MS only). Metabolites observed in human samples were present in similar proportions to those in rat. Only three metabolites were identified in human that were not identified in rat samples, these non-rat metabolites each accounted for less than 1% of the dosed radioactivity. The main site of metabolism was the piperazine carboxycyclopropyl moiety, although, to a lesser extent, both the fluorophenyl and the phthalazinone ring systems were subject to metabolism. The majority of the metabolism can be attributed to two main pathways, dehydrogenation and oxidation. There were a number of components that were further metabolized by the glucuronide or sulphate conjugation.
Conclusions: The metabolic fate of olaparib is similar in the toxicology species and humans, with metabolism and urinary excretion being important clearance pathways.