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.