lymphomas and leukemias. IMC 18F1 inhibits tumor proliferation in vitro and in human tumor xenografts in mice. This study will establish the safety profile, MTD, pharmacokinetic (PK)/pharmacodynamic profile, and preliminary antitumor activity of IMC-18F1 in pts with advanced solid tumors.
Methods: Pts in Cohorts 1−4 receive IMC-18F1, administered at doses of 2, 3, 6, and 12 mg/kg weekly. Based on PK data from these cohorts, it was decided to evaluate q2w and q3w regimens; the protocol was amended to include Cohort 5 (15 mg/kg q2w) and Cohort 6 (20 mg/kg q3w). Radiological assessment of tumor response is performed q6w. Pts receive IMC-18F1 until there is evidence of progressive disease (PD) or other withdrawal criteria are met.
Results: 20 pts have been enrolled, including 17 in Cohorts 1−4. All pts in Cohorts 1−4 have discontinued, 16 for reasons related to PD (1 pt discontinued prior to receiving IMC-18F1); 7 remained stable beyond the initial 6-week period (1 for >12 weeks). Three pts have been enrolled and treated in Cohort 5; all are ongoing. No DLTs have been observed. IMC 18F1-related AEs have all been Grade$\leqslant$2, and have included fatigue, nausea, and anemia. Following the final infusion of Cycle 1, as IMC-18F1 dose was escalated from 2 to 3 to 6 to 12 mg/kg the mean t1/2 increased from ~86 h to 205 h. Mean Cmax and AUCinf increased in a greater-than-dose-proportional manner, suggesting nonlinear PK (Cmax = 103, 166, 290 and 800 μg/mL; AUCinf = 9804, 23238, 52988 and 182487 hr*μg/mL for the 2, 3, 6 and 12 mg/kg cohorts, respectively), and mean Cl decreased (0.208–0.07 mL/hr/kg), suggesting near-saturation of elimination. Data from the 2 and 3 mg/kg dose groups suggest VEGF levels increase following infusion of IMC-18F1.
Conclusions: IMC-18F1 has been well-tolerated to date. Initial data suggest that IMC-18F1 is effectively blocking VEGFR-1 ligand binding, with nonlinear PK consistent with saturable clearance mechanisms. The MTD has not yet been reached; enrollment into Cohort 6 (20 mg/kg q3w) is expected prior to disease-directed trials.

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Translational development of the novel kinesin spindle protein (KSP/Eg5) inhibitor SB-743921 (SB-921) in lymphoma: from preclinical models to phase 1 studies

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Background: KSP is a mitotic kinesin essential for cell cycle progression. SB-921, a selective KSP inhibitor, blocks mitotic spindle assembly resulting in cell cycle arrest in mitosis and subsequent cell death. The first-in-humans (FIH) maximum tolerated dose (MTD) was 4 mg/m^2 q21 days (d) = 0.19 mg/m^2/d. Neutropenia was the major dose-limiting toxicity (DLT).
Methods: Cell-Titer Glo cytotoxicity assays evaluated the activity of SB-921 across a panel of lymphomas. KSP levels were measured by Western blot analysis. Given the DLT of neutropenia, a phase I trial to determine an MTD of SB-921 given on a d1/d15 q28 d schedule both without and with G-CSF support in Non-Hodgkin (NHL) or Hodgkin Lymphoma (HL) patients (pts) was initiated. Eligible pts had relapsed or refractory NHL or HL with $\geqslant$ 1 prior chemotherapy regimen and had relapsed and/or were not candidates for transplant. Cohorts of 3 began SB-921 at 2 mg/m^2; escalating by 1 mg/m^2. Expansion to 6 pts if 1/3 pts have DLT.
Results: SB-921 exhibited time-dependent IC50s in the range of high picomolar to low nanomolar (nM) after 72 hrs in a panel of diffuse large B-cell lymphomas (DLBCL). Pulse exposure to the drug for 1 or 3 hrs showed a similar profile in the 1 to 500 nM range. The IC50 is approximately 1 to 1.5 log higher in post-germinal center (ABC) DLBCL compared to germinal center derived (GC) DLBCL. Cytotoxicity assays with T-cell (TCL) and mantle cell lymphomas (MCL) revealed IC50s in the low nM range. SB-921 treatment results in accumulation of KSP to variable levels in most cell lines. Cell cycle analyses demonstrated M-phase arrest and apoptosis in the low nM range. In the phase 1 study, 39 pts received SB-921 doses $\leqslant$ 7 mg/m^2 without G-CSF; 18 had HL; 21 had NHL (10 indolent, 11 aggressive). Neutropenic DLTs occurred in 2/10 pts at 6 mg/m^2 (both with sepsis) and 2/7 pts at 7 mg/m^2. The ([−]G-CSF) MTD was 6 mg/m^2. No neuropathy or alopecia >grade 1 was reported. A partial response (PR) occurred in a HL pt for 2 cycles at 6 mg/m^2; a NHL pt had stable disease for 12 cycles.
Conclusions: SB-921 exhibits activity in the nM range across a broad range of NHL cell lines, including GC and ABC DLBCL, MCL and TCL. It induces M-phase arrest and apoptosis at the same concentrations. SB-921 is well tolerated without G-CSF given d1/d15 q28 d, a substantial increase in dose density from the q21 d MTD in the FIH trial (0.43 vs. 0.19 mg/m^2/d). A PR occurred in a HL pt at 6 mg/m^2. Dose escalation with G-CSF continues.

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Phase 1 study of recombinant human Interleukin-21 (rIL-21) in combination with sunitinib in patients with stage IV renal cell carcinoma

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Background: Sunitinib, a tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor (VEGF) pathway, has shown to prolong progression free survival (PFS) in metastatic clear cell RCC. However, complete responses are uncommon. Immunotherapy is a well-established approach for part of the patients (pts) with metastatic RCC. rIL-21 is a cytokine, which stimulates T cells, B cells and NK cells. Combining sunitinib with rIL-21 may improve anti-tumour responses. The primary objective of the present trial was to investigate the safety and tolerability of increasing doses of rIL-21 in combination with sunitinib and to determine the MTD.
Material and Methods: This isan open-label dose escalation trial evaluating increasing doses of rIL-21 (starting at 3 μg/kg) administered s.c. three times weekly in combination with sunitinib 50 mg orally once daily in the '4 weeks on 2 weeks off'-schedule in pts with intermediate or good risk stage IV RCC. Treatment with sunitinib was initiated 1 week in advance of rIL-21 treatment. Pts were treated with rIL-21 for up to 22 weeks. Thereafter sunitinib treatment could be continued until progressive disease (off study). 3−6 subjects were enrolled at each dose level (DL), dependent on the observed dose-limiting toxicities (DLTs). Pharmacokinetic blood samples were collected. rIL-21 antibodies were determined. Tumour evaluations were performed after 10 weeks and thereafter every 6 weeks.
Results: Nine pts entered the study; five pts at the 3 μg/kg rIL-21 DL and four pts at 10 μg/kg. Two pts were withdrawn at first DL due to sunitinib toxicity, consisting of grade 3 dizziness and grade 3 GGT, each in one pt, and they were replaced. No DLTs were observed at the 3 μg/kg dose level. At the 10 μg/kg rIL-21 dose level two DLTs were observed in four patients: neutropenia grade 4 and thrombocytopenia grade 3. Therefore, it was concluded that 10 μg/kg rIL-21 in combination with sunitinib 50 mg '4 weeks on-2 weeks off' was not tolerable. The most frequently reported AEs were injection site reaction, fatigue, stomatitis, diarrhoea, dysgeusia, and pyrexia. PK data will be presented.
Conclusions: rIL-21 on 10 μg/kg dose is not tolerated in combination with 50 mg sunitinib (4/2 schedule), whereas the previous DL (3 μg/kg) is too low to be therapeutically relevant for further evaluation. For combining rhIL-21 with sunitinib, the dose of sunitinib have to be lower, *e.g.* 37.5 mg which than might be administered in continuous dosing.

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A Phase I clinical trial of the oral PPAR gamma agonist, CS-7017 in patients with advanced malignancies

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Background: Agonists of the peroxisome proliferator activated receptor gamma (PPAR gamma) have been shown to be potent anti-cancer agents in pre-clinical models. CS-7017 is a novel, third generation thiazolidinedione (TZD) that is significantly more potent than the second generation TZDs, such as Rosiglitazone. We conducted a Phase I clinical trial of CS-7017 in patients with advanced malignancies.
Methods: Refractory patients with advanced malignancies and with adequate hepatic and renal function were eligible for enrollment. Patients with pre-existing evidence of fluid retention were excluded. CS-7017 was administered orally twice a day (BID) for six weeks in successive cohorts of at least three patients starting at a dose of 0.1 mg. Patients