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.

407 POSTER

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.

408 POSTER

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.

409 POSTER

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

who demonstrated stable disease (SD) continued study treatment without interruption. Pharmacodynamic samples were collected from patient's serum and from peripheral blood monocytes, and pharmacokinetic samples were collected at day 1 and day 22.
Results: 25 patients (16 male, 9 female; age range 40−72) have been treated at doses ranging from 0.1 to 0.75 mg BID. The most common tumor type was colorectal cancer (N = 10) followed by liposarcoma (N = 5), and leiomyosarcoma (N = 2). CS-7017 was extremely well tolerated. Most patients experienced some peripheral edema, often requiring diuretics (17/25). Two DLTs, both related to fluid retention have been observed, one in cohort 1 at 0.1 mg, and one in cohort 3 at 0.25 mg (increase in pleural effusion and peripheral edema, respectively), though the maximally tolerated dose (MTD) has not yet been reached. 24 patients were evaluable for response. There were no CRs or PRs. 9 patients had SD at one time point and in 5 cases SD persisted for at least 11 weeks (range 11−42 weeks). Extensive pharmacodynamic testing was performed. We are currently analyzing the biomarker data, and the results will be reported in the final presentation. Final pharmacokinetic analysis will also be presented.
Conclusions: While the MTD has not been reached, CS-7017 is a novel anti-cancer therapy that is well tolerated and demonstrates evidence of disease stabilization. Further disease specific testing and combination trials with cytotoxic and targeted therapies are planned.

410 POSTER

Phase I pharmacodynamic (PD) and pharmacokinetic (PK) analysis of the sorafenib (S) and erlotinib (E) combination in patients with advanced solid tumors

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Background: S and E are potent, orally administered receptor tyrosine kinase inhibitors with antiproliferative and antiangiogenic activities. We previously have shown in the dose escalation part of this phase I targeted combination trial that both agents could be given at their full-approved dose (Duran et al, Clin Cancer Res 2007). The present study, based on the expansion cohort of this trial, aimed to correlate clinical outcome with PK and PD markers.
Material and Methods: S at 400 mg BID was administered alone for a 1-week run-in period, and then E is added at 150 mg QD, with both drugs then given together continuously in 28-day cycles. EGFR expression by immunohistochemistry was measured in archival tumor specimens. p-ERK was analyzed on fresh tumor tissues prior to study start, before starting E, and between day 15 and 22 of cycle 1. PK samples were obtained 2 days before starting E and on day 15 of the combination. PET scans were performed prior to study start and at the end of cycle 1. EGFR H-score (% staining x intensity), pre- and post-treatment changes in the product of the mean integrated optical density and labeled fraction area (obtained by image analysis for p-ERK), and changes in the standard uptake value (SUV) of FDG uptake on PET, were correlated with clinical outcome.

Pt	Smoking status	Mean Cmax of S (μg/mL)	Mean AUC of S (μg.h/mL)	EGFR H-score	Δp-ERK (%)	ΔSUV (%)	RECIST	No. of cycles	TTP (mo)
1	No	6.2	58.3	140	−63%	−29%	SD	4	3.9
2	No	9.0	53.0	0	–	+11%	SD	9	8.4
3	No	3.8	29.0	0	−33%	−38%	SD	5	4.4
4	**No**	**10.7**	**72.2**	**80**	**−94%**	**−45%**	**SD**	**10**	**10**
5	No	8.0	84.5	60	−4%	−8%	SD	6	5.9
6	Yes	6.9	51.1	5	+15%	+18%	SD	5	4.9
7	No	15.6	129.2	–	–	−8%	SD	4	2.5
8	Yes	16.7	149.8	20	−18%	–	NE	1	0.5
9	No	4.5	33.8	10	−8%	–	NE	1	0.9
10	Yes	11.0	70.1	10	−80%	−21%	SD	2	3.7
11	No	8.6	52.2	0	−31%	+12%	SD	4+	NR

Results: Demographics of 11 patients treated in the expansion cohort were: median age = 51 (range 38−69); ECOG 0:1 = 8:3; prior regimens 0:1:2+ = 3:4:4; tumor types: cholangiocancer (5), hepatoma (2), others (4). A total of 51 cycles were given, with a median of 4 and range of 1–10. Only 4 patients could receive full dose of both drugs for the entire study course. For E, 6 and 2 patients tolerated full and reduced doses respectively, while 3 stopped drug due to toxicity. For S, 4 and 7 tolerated full and reduced doses respectively. Median time-to-progression (TTP) was 4.8 months. Given the small sample size, no clear correlation could be drawn between EGFR expression, changes in p-ERK or SUV of FDG uptake and clinical outcome. Nevertheless, the patient with the longest TTP (10 months) had the greatest decreases in p-ERK level (−94%) and SUV of FDG uptake (−45%). PK analysis revealed no significant effect of E and smoking status on the PK profile of S.
Conclusion: Combination of S with E demonstrated prolonged cytostatic activity in various tumor types. In one case, changes in tumor pERK expression and FDG-PET response correlated with clinical outcome, but generalization cannot be made based on the small sample size.

411 POSTER

A phase I, open-label, dose-escalation study of the safety and pharmacology of MetMAb, a monovalent antagonist antibody to the receptor c-Met, administered IV in patients with locally advanced or metastatic solid tumors

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Background: The Met/hepatocyte growth factor (HGF) pathway has been strongly linked to oncogenic potential and represents an attractive target for therapeutic intervention in many tumors. Bivalent antibodies targeting the Met receptor can be agonistic, accelerating tumor growth in xenograft models. MetMAb was uniquely engineered as a recombinant, humanized, monovalent (one-armed) monoclonal antibody to act as an antagonist of HGF-induced Met signaling. MetMAb was active in a variety of non-clinical HGF-driven tumor models, including both autocrine and paracrine, and especially when dosed in combination with angiogenesis and/or EGFR inhibitors (separate submission); lending support to clinical development.
Materials and Methods: A 3+3 phase I dose escalation trial testing 1, 4, 10, 20, and 30 mg/kg has been initiated. Patients receive MetMAb IV on day 1 of a 3 week cycle. Pre- and post-dose serum is being collected for evaluation of pharmacodynamic (PD) biomarkers that could be affected by inhibition of Met signaling.
Results: Eighteen patients have been treated to date. A single Gr3 and dose-limiting toxicity (DLT) of pyrexia was observed at 4 mg/kg, 2 drug-related Gr2 findings (both of fatigue) were also observed in this cohort. No other Gr2 or higher drug related adverse events (AEs) have been reported at doses up to 30 mg/kg. No objective responses have been observed; 1 patient (melanoma) had stable disease through 8 cycles of therapy, and the majority of patients progressed prior to cycle 5 (n = 12). MetMAb has a half-life and clearance approximating 10 days and 8 mL/kg/day respectively, and pharmacokinetics (PK) are linear in the range of 4−30 mg/kg. Extensive pre-clinical PK/PD modeling (separate submission) was used to identify a therapeutic dose of 15 mg/kg IV every 3 weeks, which will be studied in the expansion stage. Analysis of serum, to identify possible biomarkers of MetMAb activity, is underway and will be updated at the time of the presentation.
Conclusions: This phase I study represents a first-in-human trial of a full-length, one-armed monovalent Ab. Thus far the data suggests that MetMAb is safe and well tolerated as a single agent and may, therefore, be well-suited for clinical studies that test combinations with other anti-tumor agents.

412 POSTER

A first-in-man phase I study of TH-302, a hypoxia-activated cytotoxic prodrug

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Background: TH-302 is a 2-nitroimidazole prodrug of the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, TH-302 is relatively inactive but in hypoxic conditions and in the presence of certain reductases, TH-302 is reduced and Br-IPM is released. In xenograft models, TH-302 was active as a single agent and in combination with chemotherapy resulted in complete responses.