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.

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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.

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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.

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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.

Materials and Methods: Eligible patients (pts) had ECOG ⩽1, advanced or metastatic solid tumors, at least one target lesion by RECIST, and acceptable hematologic, liver and renal function. A modified accelerated titration design was used. TH-302 was administered intravenously over 30 minutes on Day 1, 8 and 15 of a 28-day cycle. CT scans were obtained after every 2 cycles. Detailed pharmacokinetic (PK) sampling was performed during Days 1 and 15. The objectives of this study were to determine the maximum tolerated dose and dose limiting toxicity (DLT) and to evaluate the safety, PK and preliminary efficacy of TH-302 in advanced solid tumors.
Results: Seventeen pts have enrolled to date at 3 sites. Median age: 65. ECOG 0/1 in 11/6 pts. Primary tumor: prostate (5), colorectal (4), NSCLC (2), SCLC (2), other (4). Pts received 1−8 cycles (median 2;1−22 doses) at 7.5–480 mg/m^2. Twelve pts have discontinued: progressive disease (PD; 9), PSA PD (1; SD by RECIST) and adverse event (AE; 2; unrelated to TH-302). No DLT has occurred to date. Grade 1 or 2 study drug-related AEs have been reported in 10 of 17 pts treated at doses up to 480 mg/m^2 including fatigue in 4 pts (2 grade 1 and 2 grade 2 at 30 and 480 mg/m^2) and grade 1 nausea in 3 pts (7.5, 7.5 and 120 mg/m^2). One pt treated at 7.5 mg/m^2 with pre-existing cyclic neutropenia had intermittent grade 2 neutropenia not considered due to TH-302. Six subjects developed worsening or new lymphopenia (4 grade 2, 3 grade 3) but none were reported as clinically significant. Four pts had worsening or new anemia (2 grade 1, 2 grade 2). Seven of 14 evaluable pts had a best response of stable disease, one of whom (NSCLC; dose level 7.5 mg/m^2) had PET metabolic response with 35% and 36% declines in maximum SUV following cycles 2 and 4. PK Cmax and AUC for TH-302 and Br-IPM increased linearly over the range of doses evaluated to date (7.5–240 mg/m^2) with no accumulation at Day 15. Half-life ranged from 0.5−1 h. The ratio of TH-302 to Br-IPM is higher than in rats or dogs but the Cmax and AUC for Br-IPM are similar to dogs at comparable doses.
Conclusions: TH-302 administered as a weekly dose is well tolerated to date. There is early evidence of clinical activity. Preclinical toxicology in rats and dogs predicted hematologic toxicity and xenograft studies predicted efficacy at doses over 100 mg/m^2. Dose escalation is continuing. Studies of TH-302 combined with other therapies are planned.

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A phase I dose escalation study of oral SB939 when administered thrice weekly (every other day) for 3 weeks in a 4-week cycle in patients with advanced solid malignancies

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Background: SB939 is a potent competitive inhibitor of Class 1 and 2 histone deacetylase (HDAC). This study was designed to assess the safety, maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics, pharmacodynamics and preliminary efficacy of SB939 in patients with advanced solid malignancies.
Methods: SB939 was administered orally every other day 3 times a week for 3 consecutive weeks, in a 4-week cycle. Cohorts of patient were treated with escalating doses of SB939 starting from 10 mg; first cycle DLT were used in dose escalation decisions.
Results: Twenty patients (10 males, 10 females; mean age 55.6 yrs, range 41−74) were treated with the following dose levels: 10 mg, 20 mg, 40 mg and 80 mg with 3, 3, 8, and 6 patients in each cohort, respectively. DLTs were observed at the highest 2 dose levels (40 mg, n = 1 of 8 and 80 mg, n = 3 in 6). DLTs were grade 3 fatigue (1 patient at 40 mg and 80 mg each), asymptomatic QT prolongation (1 patient, at 80 mg) and troponin T elevation (1 patient, at 80 mg). Grade 3 anaemia and thrombocytopenia (1 patient each) were observed in the 80 mg cohort. Other adverse events included nausea (5 patients), vomiting (7 patients) and diarrhoea (3 patients). SB939 was rapidly absorbed reaching Tmax between 1−3 h after ingestion, and mean elimination half-life and oral clearance of SB939 were 8 hrs and 50.2 L/h respectively. Cmax and AUC (0-∞) were dose-proportionally increased over the range studied. There was no substantial accumulation of SB939 following repeated dosing. The mean plasma concentrations of SB939 were above its HDAC enzyme IC50 (T>IC50) for 12 and 24 h in 40 and 80 mg cohorts, respectively. Of the 13 patients evaluable for response, stable disease was seen in 1 patient with follicular thyroid carcinoma and 1 patient with hepatocellular carcinoma for 51 and 164 days, respectively.
Conclusion: SB939 has a manageable toxicity profile. The 80 mg dose was the highest dose tested in this study and was not tolerated by 3 out 6 patients. Patients are currently being enrolled at a 60 mg dose to further define the recommended phase II dose.

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A phase I, open-label, dose escalation study of the humanized monoclonal antibody (HuMAb) TRC093, an inhibitor of angiogenesis that binds to cleaved collagen, in patients with locally advanced or metastatic solid tumors

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Background: TRC093 is a HuMAb that binds cleaved collagen to inhibit angiogenesis and tumor growth. Preclinical studies confirm safety and antitumor activity of the agent in multiple solid tumors as monotherapy and in combination with cytotoxic and targeted agents. We performed a phase 1 trial to evaluate the safety and tolerability of TRC093 in patients with solid tumors.
Methods: Patients were required to have advanced refractory cancer, ECOG ⩽ 2, and adequate organ function including proteinuria and hematuria ⩽ 1+. TRC093 was administered by 90 minute IV infusion on days 1 and 15 of each 28-day cycle until progression. Cohorts of 3 patients were planned at doses of 0.5, 1.5, 5, 12 and 24 mg/kg.
Results: A total of 16 patients have been treated to date, 3 at each of the 0.5, 1.5, and 5 mg/kg dose levels, 6 at the 12 mg/kg and 1 at the 24 mg/kg dose levels without the development of dose-limiting toxicity. The 12 mg/kg dose level was expanded and considered the maximal feasible dose (rather than the top dose level of 24 mg/kg) due to limited drug supply. The most common adverse event (all grade 1 or 2) felt to be possibly drug-related was fatigue. Related grade 3 or 4 AEs and infusion reactions have not been observed. One patient with non-small-cell lung cancer treated at the 1.5 mg/kg dose, a patient with malignant hemangiopericytoma treated at the 5.0 mg/kg dose and a patient with metastatic cervical cancer treated at the 12.0 mg/kg dose had stable disease for 2 months, 6 months (ongoing) and 2 months respectively. In addition, one patient with granulosa cell carcinoma of the ovary with progressive disease had a mixed response in the liver after 2 months of treatment. Biomarker, immunogenicity and PK analyses are ongoing and will be presented.
Conclusion: TRC093 is well-tolerated when administered by 90 minute IV infusion every 2 weeks. Phase 1b and 2 trials based on preclinical studies will evaluate this novel agent in combination with other targeted and standard cytotoxic therapies.

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Dosing strategies for MLN8054, a selective Aurora A kinase inhibitor, based on pharmacokinetic modeling and simulations

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Background: MLN8054, an oral selective small-molecule inhibitor of Aurora A kinase, is being developed as an anti-mitotic agent for the treatment of cancer. MLN8054 binds to the $GABA_A$-alpha1 benzodiazepine receptors and causes CNS adverse effects, such as somnolence. A pharmacokinetic (PK) model was developed to simulate PK profiles in order to find a dosing regimen to reduce peak concentrations (C_{max}) thereby potentially minimizing CNS adverse effects, while maximizing steady-state concentrations to increase the likelihood of Aurora A kinase inhibition.
Materials and Methods: MLN8054 was evaluated in two Phase I trials in patients with advanced solid tumors. Serial blood samples were collected to measure plasma concentrations of MLN8054 using LC/MS/MS methods. PK parameters of MLN8054 were estimated using non-compartmental analyses. A two-compartment model was developed to characterize the PK of MLN8054 based on the PK data obtained from the first 10 patients enrolled. The model was then used to simulate PK profiles for testing various dosing regimens. WinNonlin® was applied to non-compartmental PK analyses and compartmental PK modeling/simulations.
Results: MLN8054 was evaluated for 7 to 21 days of dosing in 104 patients and 12 dose levels between 5 and 80 mg. The drug was rapidly absorbed