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.