Material and Methods: Treatment arms/SOC regimens: paclitaxel/carboplatin (PC); carboplatin/etoposide (CE); topotecan (T); docetaxel (D); and erlotinib (E). MP is administered daily during 21-day cycles of SOC. Each arm follows a 3+3 design where MP is escalated based on modified Fibonacci sequence until MTD of MP in combination with SOC agent(s) is reached. RESCIST and CTCAE for response and safety assessments, respectively.
Results: Across all 5 arms, 22 of 39 pts have received $\geqslant$ 2 cycles of treatment. Grade-3/4 AEs are similar to those expected with SOC therapy. Four heavily pretreated pts show encouraging response. Case 1: a 25 yo male with a malignant neuroendocrine tumor participating in PC arm and receiving MP at 100 mg/d. Prior lines of treatment were 4 cycles CDDP/VP-16 and 2 cycles T. PR noted after Cycle 2 included marked decrease in size of liver, reduction in extent of liver metastases, and complete resolution of an FE cardiac lymph node. Response was durable through Cycle 4. Patient is continuing on study; now out to Cycle 6 without apparent clinically significant toxicities. Case 2: a 65 yo male with metastatic SCLC participating in the CE arm and receiving MP at 100 mg/d. Five prior lines of treatment (>10 total cycles) included 3 cycles of prior CE. Pt had PR after Cycle 2 with marked overall improvement in mediastinal adenopathy and improvement and stability of multiple liver lesions with no new evidence of disease. Cases 3 and 4: One pt in PC arm and one in E arm receiving MP at 100 and 200 mg/d, respectively, have SD with >15% decrease in sum of longest diameters of target lesions at end of Cycle 2 and Cycle 4, respectively.
Conclusions: MP combined with standard regimens of DNA damaging agents and EGFR inhibitors may promote tumor regression and MP may also sensitize/resensitize tumors to the anticancer effects of such agents. Toxicity is similar to that known for SOC agent(s).

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A phase I study of oral administration of the histone deacetylase (HDAC) inhibitor belinostat in patients (pts) with advanced solid tumors

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Background: Belinostat is a class I and II hydroxamate HDAC inhibitor with broad anti-neoplastic activity in vitro and in vivo. IV belinostat is well-tolerated at a dose of 1000 mg/m^2 daily x5, q3-weekly.
Methods: Pts had advanced solid tumors refractory to standard therapy. Objectives were safety and tolerability, pharmacokinetics (PK) and anti-tumor efficacy. Pts were dosed in cohorts of 3−6 pts evaluating continuous and intermittent dosing schedules administered once or twice daily. PK studies on day (d) 1 (fasting) and d7 (non-fasting) were performed along with serial ECGs.

	Continuous schedule			Schedule d1−14, q3w				
Cohort	A	B	C	D	E	F	G	H
	QD	QD	BID	QD	QD	QD	QD	BID
Daily dose (mg)	250	500	250+250	500	750	1000	1250	500+250
# pts	20	6	19	3	6	7	2	7
DLTs	0	2	0	0	1	1	2	3

Results: 70 pts, median age 60 (range 32−80) have so far been treated according to the table. Most common cancer types were colorectal (n = 17), prostate (n = 12), and bladder (n = 10). In cohort B, 2 pts developed dose limiting toxicity (DLT) of grade (gr) 3 dehydration and gr 3 fatigue and the MTD for continuous once a day dosing was therefore 250 mg QD. Dose escalation from cohort C was deferred and MTD set at 250 mg BID. On d1−14 schedules the following DLTs were noted (cohort): gr 3 fatigue (E), gr 2 nausea/vomiting/diarrhea (F), gr 3 atypical chest pain (G), gr 3 elevated creatinine (G), gr 3 atrial fibrillation (H), gr 3 hypokalemia (H), gr 3 fatigue (H). Based on an overall evaluation of tolerability and DLTs, the MTD was set at 750 mg QD for d1−14 dosing, with the option to include intra-pt dose escalation if no or limited toxicity. The most frequent related adverse events (AEs) were fatigue (55%), nausea (47%), anorexia (38%), vomiting (28%), diarrhea (25%), and weight decrease (21%). Fatigue was the only related grade 3/4 AE experienced by more than one pt. To date, 29 pts have SD, 10 pts $\geqslant$ 4 months duration; longest treatment durations in pts with adenoidcycstic (+20 mo), RCC (15.9 mo), rectal (6.8 mo), and prostate (6.0 mo) carcinoma. The exposure of belinostat in plasma correlates with dose (d1 AUC_{all} vs dose R^2= 0.8129). Exposure from d1 to d7 increased on average 25±17%. The $t_{1/2}$ of QD oral belinostat ranged from 1.3 to 2.7 hours (h). T_{max} ranged from 1.5 to 4.7 h d1 and 2.0 to 6.1 h d7 indicating a possible effect of food.
Conclusions: MTDs for continuous QD and BID dosing, and d1−14, q3-weekly, QD dosing has been established for oral belinostat. Dose escalation is currently ongoing at 1250 mg QD in a d1−5, q3-weekly schedule.

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Final results of a Phase I/II study of CTCE-9908, a novel anticancer agent that inhibits CXCR4, in patients with advanced solid cancers

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Introduction: CTCE-9908 is a 17 amino acid peptide CXCR4 antagonist targeting the CXCR4 / CXCL12 (SDF-1) pathway, which is critical in the metastatic process. CXCR4 receptors are expressed on over 23 malignant cell types. SDF-1, the CXCR4 ligand is produced in large amounts by organs representing the first sites of metastasis for these malignant cell types. CTCE-9908 is expected to be effective against a wide range of cancer types that express CXCR4 by inhibiting the metastatic process as well as interfering with the recruitment of hemangiocytes critical to vasculogenesis. This study was designed to determine the maximal tolerated dose (MTD), toxicity profile, pharmacokinetics and antitumor activity of CTCE-9908 in patients (pts) with refractory solid tumors.
Patients and Methods: CTCE-9908 was administered to eligible pts using an accelerated titration design with escalating dose levels (DLs). Dosing was performed via 30 minute daily intravenous infusions during week days for 20 doses per cycle. Five DLs from 0.25 mg/kg to 5.0 mg/kg were planned. Twenty-six pts were enrolled in 5 cohorts and 25 pts received drug: DL 1 (0.25) – 1 pt; DL 2 (0.5) – 1 pt; DL 3 (1.0) – 4 pts; DL 4 (2.5) – 2 pts; DL 5 (5) – 17 pts. DL 5 was expanded to obtain more information on toxicity and efficacy. Pts with ovarian, breast, prostate and 'other' cancers were eligible. Pts with SD or better after cycle 1 were eligible to receive further cycles. Median age was 56 years (range, 30−84), 60% were female. Primary tumor types were breast (8 pts), melanoma (3 pts), ovarian (3 pts), lung (3 pts), colorectal (3 pts), others (5 pts).
Results: No pt had DLT. Most common drug-related toxicity consisted of fatigue (7 pts), grade 2 phlebitis (3 pts), grade 2 gingivitis (2 pts) and grade 3 GGT elevation (2 pts). Most AEs occurred at the highest DL. Responses were: PD (17), SD (5), N/A (3). Six pts entered the continuation phase after cycle 1. One pt with a breast and ovarian cancer primary (1.0 mg/kg group) had a decrease in CA-125 from 657 to 303 after 1 cycle with a decrease in baseline target lesions but was found to have brain mets, which was unfortunately not assessed at baseline. One pt with CRC had a 34.5% decrease in CEA at Day 26 (5.0 mg/kg group). One pt with small bowel cancer had SD after 7 cycles. PK analysis showed that the majority of pts had plasma levels of CTCE-9908 below the lower limit of detection at the 45min post-dose mark.
Conclusions: CTCE-9908, an anticancer agent with a novel mechanism of action, is well tolerated and has shown preliminary signs of efficacy. Further studies in a targeted population are warranted and planned. It would be of interest to assess the PK in tumor tissues, and the kinetics of the reduction of CXCR4 activity to determine if they differ from the plasma PK.

406 POSTER

IMC-18F1, a recombinant human monoclonal antibody (MAb) against the vascular endothelial growth factor receptor-1 (VEGFR-1), in the treatment of patients (pts) with advanced solid malignancies: A Phase 1 study

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Background: VEGFR-1 plays a dual role in tumor growth by regulating malignant angiogenesis and directly mediating proliferative signaling in cancer cells. IMC-18F1 is a MAb that exhibits high-affinity binding to VEGFR-1 and blocks VEGFR-1 ligand binding and downstream signaling in endothelial and VEGFR-1-expressing cancer cells, including carcinomas of breast, colon, pancreas, lung, head and neck, prostate, and ovary,

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