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).

404 POSTER

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

W. Kelly[1], D. Petrylak[2], G. Blumenschein[3], U. Lassen[4], P. Buhl Jensen[5], J. DeBono[6]. *[1]Yale University, Medicine, New Haven, CT, USA; [2]Columbia University Medical Center, Medicine, New York, USA; [3]MD Anderson Cancer Center, Medicine, Houston, TX, USA; [4]University Hopsital Rigshospitalet, Medicine, Copenhagen, Denmark; [5]TopoTarget A/S, Drug Development, Copenhagen, Denmark; [6]Royal Marsden Hospital, Medicine, Sutton, United Kingdom*

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.

405 POSTER

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

S.J. Hotte[1], H.W. Hirte[1], P. Moretto[1], A. Iacobucci[1], D. Wong[2], W. Korz[2], W.H. Miller[3]. *[1]Juravinski Cancer Centre, Medical Oncology, Hamilton, Ontario, Canada; [2]Chemokine Therapeutics, Oncology, Vancouver, BC, Canada; [3]Segal Cancer Center at the Lady Davis Insititute for Medical Research Jewish General Hospital McGill University, Oncology, Montreal, PQ, Canada*

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

S. Krishnamurthi[1], P.H.B. Goncalves[2], F. Fox[3], N. Hall[4], E. Rowinsky[5], J. Schwartz[5], H. Youssoufian[5], P. LoRusso[2]. *[1]Case Western Reserve University, Medicine, Cleveland, USA; [2]Karmanos Cancer Institute, Medicine, Detroit, USA; [3]ImClone Systems Incorporated, VP Clinical Pharmacology, Branchburg, USA; [4]ImClone Systems Incorporated, Biostatistics, Branchburg, USA; [5]ImClone Systems Incorporated, Branchburg, USA*

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,