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Early evidence of tolerability and clinical activity from a phase 1 study of TRC105 (anti-CD105 antibody) in patients with advanced refractory cancer

L.S. Rosen[1], M.S. Gordon[2], H.I. Hurwitz[3], D.S. Mendelson[2], D. Kleinzweig[1], B.J. Adams[4], C.P. Theuer[4]. [1]*Premiere, Oncology, Santa Monica, CA, USA;* [2]*Premiere Oncology, of Arizona, Scottsdale, AZ, USA;* [3]*Duke University, Medical Center, Durham, NC, USA;* [4]*TRACON Pharmaceuticals Inc., Clinical Development, San Diego, CA, USA*

Background: TRC105 is a human/murine chimeric IgG1 monoclonal antibody that inhibits angiogenesis and tumor growth. TRC105 binds human CD105, a proliferation-associated and hypoxia-inducible protein found on the surface of proliferating vascular endothelial cells. Preclinical studies have demonstrated the safety and antitumor activity of TRC105 in multiple tumor types as monotherapy and in combination with cytotoxic chemotherapy. An ongoing phase 1 trial is evaluating the safety and tolerability of single-agent TRC105 in patients with solid cancers.
Methods: Study patients were required to have advanced refractory cancer, ECOG $\leqslant$ 1, and adequate organ function. Patients with CNS or central thoracic cancers were excluded. TRC105 was administered by 60 minute IV infusion every 2 weeks until progression. Cohorts of 3−6 patients were planned at doses of 0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg.
Results: A total of 12 patients have been enrolled and treated, 3 each at 0.01 and 0.03 mg/kg and 6 at 0.1 mg/kg. Dose escalation is ongoing. One patient at 0.1 mg/kg experienced Grade 4 hemorrhage from a gastric ulcer within 1 week of the first TRC105 infusion. The hemorrhage was considered possibly related to study treatment and a dose limiting toxicity, and responded to nonsurgical supportive care including red cell transfusions. No other Grade 3 or 4 adverse events have been reported. Possibly related grade 1 or 2 adverse events have included grade 2 fatigue, grade 2 dysgeusia, and grade 1 intermittent vaginal bleeding in a premenopausal woman with locally recurrent ovarian cancer. Two patients at 0.01 mg/kg remain on study without progression at month 5: a man with hormone refractory prostate cancer who had a complete PSA response accompanied by marked improvement in his bone scan, and a woman with metastatic ovarian cancer with radiographically stable disease and a 16% decrease in plasma CA125. Immunogenicity and PK analyses are ongoing and will be presented.
Conclusion: TRC105 is well-tolerated at doses that show evidence of clinical activity in advanced refractory cancer.

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A phase I study of enzastaurin (ENZ), an oral PKC inhibitor, in combination with erlotinib (ERL) administered orally daily to patients with advanced solid malignancies

H.A. Wakelee[1], S.K. Padda[1], L. Chhatwani[1], M. San Pedro-Salcedo[1], Y. Krupitskaya[1], L. Musib[2], J.E. Latz[2]. [1]*Stanford University, Medicine Oncology, Stanford, USA;* [2]*Eli Lilly and Company, Oncology, Indianapolis, USA*

Background: ENZ, a serine/threonine kinase inhibitor, targets the PKC and PI3K/AKT pathways to inhibit angiogenesis and tumor cell proliferation and induce apoptosis. This study was conducted to determine the recommended dose (RD) of oral daily (po qd) ENZ in combination with ERL at the standard dose of 150 mg po qd, and to evaluate pharmacokinetics (PK) of the combination in patients (pts) with advanced solid tumors.
Methods: Cohorts of pts received escalating doses of ENZ plus standard ERL. All pts received ERL at 150 mg po qd on an empty stomach. ENZ dose levels of 250 mg (cohort 1) and 500 mg (cohort 2) po qd were studied with Day 1 loading doses of 250 mg bid and 375 mg tid, respectively. ENZ was taken with food. A treatment cycle was 28 days. PK sampling was conducted for all pts.
Results: Sixteen pts were enrolled (age range 46−83 y; 3M/13F; 11 Caucasian, 4 Asian, 1 Hispanic). Pts had NSCLC (n = 10) and 1 each of biliary papillomatosis, sarcoma, GIST, parotid gland tumor, thymoma, hepatocellular carcinoma. Performance status: ECOG 0 (n = 5), ECOG 1 (n = 10), ECOG 2 (n = 1). Pts had received 1 (n = 6), 2 (n = 9) or 3 (n = 1) prior regimens. Eight pts were never-smokers. No DLTs were observed. A pt in cohort 1 expired from rapid disease progression prior to completing 1 cycle and was replaced. The RD was ENZ 500 mg po qd and ERL 150 mg po qd (the established single agent doses of the drugs). Further dose escalation was not attempted. Twelve pts were enrolled in the expanded RD cohort. The majority of pts discontinued due to PD. One pt discontinued due to AEs (diarrhea, nausea/vomiting). One pt discontinued in cycle 1, 11 pts completed 2 cycles (10 with PD, 1 stopped for AEs), 1 pt completed 4+ cycles (ongoing) and 3 pts completed 7+ cycles (2 ongoing). Observed G3 toxicities possibly related to study drug were: diarrhea, deep venous thrombosis, renal insufficiency, hypertension, dizziness, fatigue. The most common AEs included G1/2 rash, diarrhea, and fatigue. Most pts had a red discoloration of urine/feces. One pt had a best response of PR for 11 mo. Three pts had SD for >4 mo including 1 with a 27% reduction in tumor size by RECIST and 1 actively smoking pt with SD for over 10 months. PK analyses are ongoing.
Conclusions: The RD of ENZ in combination with ERL is 500 mg and 150 mg respectively. There were no unexpected toxicities beyond those seen with either drug as a single agent. A phase 2 study of the combination is ongoing in pts with advanced NSCLC.

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A phase I study of gemcitabine, capecitabine and vandetanib in patients with advanced solid tumors with an expanded cohort in biliary and pancreatic malignancies

S. Leong[1], C.L. Obryant[1], W.A. Messersmith[1], S. Diab[1], M.A. Kane[1], S. Nallapreddy[1], C. Weekes[1], J. Spratlin[1], J. Call[1], S.G. Eckhardt[1]. [1]*University of Colorado Cancer Center, Oncology, Aurora, USA*

Background: Vandetanib (V) is a multi-tyrosine kinase inhibitor with the ability to inhibit three key pathways involved in tumor growth: VEGF, EGF, and RET. Both VEGF and EGF pathways are overexpressed in biliary and pancreatic cancers. The objectives of this phase I study are to evaluate the safety profile of V in combination with standard doses of gemcitabine (G) and capecitabine (C); and to determine the maximum tolerated dose (MTD). In the expanded cohort, additional patients with biliary or pancreatic malignancies will be enrolled to further evaluate the safety of the combination and to assess the antitumor activity in this subset of patients.
Methods: Escalating doses of V (200 mg and 300 mg) administered orally for 28 days in combination with G 1000 mg/m^2 intravenously on days 1, 8, 15 and C 1660 mg/m^2/d given orally in divided doses on days 1−21. A cycle (cy) is 28 days. Inclusion criteria: ECOG PS 0−1; adequate hematologic, hepatic, and renal function. Exclusion criteria: infection, use of immunosuppressive agents, prolongation of QTc, and uncontrolled intercurrent illness. Dose Limiting Toxicites (DLT) was defined as >grade 3 (gr) non-hematologic toxicity or >gr 4 hematologic toxicity = 5 days. Response is assessed by RECIST criteria every second cy. Correlative studies: Plasma concentrations of VEGF and soluble VEGFR2 are being evaluated as potential biomarkers in the expanded cohort.
Results: To date, 9 patients have been enrolled in the dose escalation cohort. The median age is 55 (range 35−73); PS 1. All patients were evaluable for toxicity and had received a total of 30 cy (median 3 cy). There was one DLT (grade 4 neutropenia), which occurred in the 200 mg V cohort. Adverse events of gr 2 or above occurring in = 10% of the cy (n = 30) were neutropenia (gr 2 – 1 cy; gr 3 – 7 cy and gr 4 – 1 cy) and diarrhea (gr 2−3 cy). Considering antitumor effects (n = 9), 1 patient had a confirmed PR (metastatic cholangiocarcinoma with 80% tumor reduction, 5+ cy administered) and 5 had stable disease (endometrial, 6 cy; ovarian, 5+ cy; colon, 3+ cy; thymic, 3 cy; and cervical cancer, 3+ cy). Four patients are still on study.
Conclusions: V at 300 mg given orally for 28 days in conjunction with standard doses of G and C was well tolerated. No MTD was identified. Accrual of an expanded cohort of untreated systemic biliary and pancreatic cancer patients has commenced and an update of these patients will be presented at the meeting.

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Clinical responses in highly refractory solid tumor patients with oral MP-470, a multi-targeted tyrosine kinase inhibitor, in combination with standard of care chemotherapy regimens: preliminary report from a multi-institutional phase-1b clinical trial

A.W. Tolcher[1], M. Mita[2], M. Gordon[3], L. Rosen[4], A. Patnaik[1], G.D. Fine[5], G.S. Choy[5], G.I. Berk[5]. [1]*South Texas Accelerated Research Therapeutics, Clinical Research, San Antonio, TX, USA;* [2]*Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX, USA;* [3]*Premiere Oncology of Arizona, Clinical Research, Scottsdale, AZ, USA;* [4]*Premiere Oncology of California, Clinical Research, Santa Monica, CA, USA;* [5]*SuperGen Inc., Clinical Research, Dublin, CA, USA*

Background: MP-470 (MP) is an orally bioavailable multi-targeted tyrosine kinase inhibitor which hits a number of validated tumor targets. MP also sensitizes cancer cells to DNA damaging agents and to radiation therapy, presumably through the suppression of Rad51, a key component to the cellular repair machinery in response to DNA double-strand breaks. Preliminary phase-1 data on MP as a single agent have been presented previously. Results presented here are from a phase-1b trial of MP combined with five standard-of-care (SOC) anticancer therapies.

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

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.

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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

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.

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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,