The most common tumor types were lung (n = 11), breast (n = 11), and ovary (n = 5).
Cohort I is completed, the median number of cycles was 6 (range 1−9) and the RD is Ob20/C75/D75 mg/m^2. Two DLTs (febrile neutropenia and pulmonary embolism) were reported at cycle 1 of DL 25/75/75 mg/m^2.
Cohorts II, III and IV are under evaluation.
Other clinically significant gr 3/4 study drug related adverse events were: diarrhea, asthenia, drug hypersensitivity (2 pts each), transaminase increase, hypocalcemia, vomiting, nausea, peripheral neuropathy (1 pt each). Related cardiovascular events consisted on: gr 2 thrombo-phlebitis (3 pts), gr 2 left ventricular function decrease, gr 3 peripheral ischemia, gr 3 troponin increase and gr 2 hypertension (1 pt each).
Hematotoxicity was typical for T and PS combinations.
Objective responses were observed: one complete response (pt with triple negative breast cancer), 7 partial responses (3 lung including one pt with squamous histology, 3 breast and 1 ovarian cancer) and 21 pts had stable disease.
Preliminary results of PK and biomarkers studies will be provided.
Conclusion: Combinations of Ob with T and PS are feasible and well tolerated, with preliminary encouraging evidence of anti-tumor activity. Further studies in specific tumor types are planned.

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First-in-human study of PF-05212384, a small molecule intravenous dual inhibitor of PI3K and mTOR in patients with advanced cancer: preliminary report on safety and pharmacokinetics

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Background: The PI3K/mTOR pathway regulates cell growth, proliferation, glucose metabolism and survival. It has been implicated in many human cancers by mutational activation of PI3Kα, loss of function of PTEN and/or activation of upstream receptor tyrosine kinases. PF-05212384 is an intravenous dual-specificity inhibitor of PI3K and mTOR that has potent and selective activity in *in vitro* and xenograft models. A first-in-human phase 1 dose-escalation study is ongoing.
Methods: PF-05212384 is administered intravenously to adult patients with advanced solid tumors once weekly; the starting dose was 10 mg. Endpoints include safety (NCI CTC AE v4.0), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity. A modified continual reassessment method (CRM) targeting a 25% DLT rate is employed for the dose escalation phase. Patients have been enrolled in cohorts of 2 to 4 with dose assignment based on the adverse event profile of the previous cohorts; increments may range from 20% to 107%. PD assessments include blood glucose and insulin. Antitumor activity is assessed per RECIST version 1.1.
Results: As of 29 May 2010, 12 patients have been dosed at 10, 21, and 43 mg. Median age 54, median ECOG PS 1. Represented tumor types have included CRC (3), NSCLC (2), sarcoma (2), breast, pancreatic, esophageal, RCC, and salivary gland (1 each). PF-05212384 has been well tolerated, with the most common treatment-related AEs being nausea, hyperglycemia, and fatigue. Treatment-related AEs have all been mild to moderate (CTC AE grade 1−2). No patients have experienced DLT and dose escalation is ongoing. Preliminary PK data indicate that PF-05212384 is eliminated with a half-life of approximately 16 hours, with low clearance and a relatively high volume of distribution. At steady state, plasma concentrations exceed those estimated to be required for suppression of phosphorylation of PI3K/mTOR pathway substrates and induction of apoptosis, based on preclinical predictions. Changes in blood glucose and insulin have been observed in some but not all patients. No objective tumor responses have been observed.
Conclusions: Weekly administration of PF-05212384 is safe and tolerable in early dose levels. Nausea, hyperglycemia, and fatigue of mild to moderate severity are the most frequently reported treatment-related AEs. To date no DLTs have been reported and dose escalation continues. Updated data for safety, PK, PD and antitumor activity will be presented.

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Imetelstat sodium (GRN163L), a telomerase inhibitor: tolerability, pharmacokinetics and pharmacodynamic activity using an intermittent once every four weeks dosing schedule in patients with advanced solid tumors

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Background: Telomerase is upregulated in tumor cells and particularly cancer progenitor cells where it is required for maintenance of telomere length and limitless replication. GRN163L is a potent, lipidated 13-mer oligonucleotide inhibitor of telomerase and is the first agent in clinical trials to target telomerase. Previous reports showed that intermittent dosing (MTD 9.4 mg/kg) on days 1 and 8 of a 21 day schedule was better tolerated than weekly dosing (MTD 3.2 mg/kg). In order to further understand the effects of dose and dosing frequency on tolerability we now report on the use of a once every 28 day schedule in a phase I study in cancer pts.
Methods: Pts with advanced solid tumors received GRN163L as a single agent at a dose of 9.4 mg/kg or 11.7 mg/kg IV over 2 hrs on day 1 of a 28 day cycle. A formal MTD was defined by dose-limiting toxicities during the first cycle. Telomerase activity was measured in blood mononuclear cells 24 hours after dosing as an exploratory end-point.
Results: As of June 15, 2010, 16 pts were treated (9.4 mg/kg, n = 3; 11.7 mg/kg, n = 13), with 11 pts evaluable. Median age was 65 yrs and median number of prior therapies was 4. Current status of patients is: 3 pts on study, 7 pts PD, 1 pt withdrawn due to toxicity. Of the 5 patients who received a 2nd cycle, 2 were delayed due to cytopenia. No significant toxicity was observed at 9.4 mg/kg. At 11.7 mg/kg, 2/8 pts developed neutropenia (grade 2, n = 1; grade 3, n = 1) and 7/8 pts developed thrombocytopenia (all grade 1). Nadirs were observed between 21 and 57 days after dosing at the higher dose. Related AEs included mild GI toxicity (nausea, vomiting, diarrhea, n = 1) and mild to moderate anorexia (n = 4). One pt had an infusion reaction resulting in withdrawal from the study. Due to hematologic toxicity and delayed dosing of C2, the maximum administered dose was 11.7 mg/kg. Although there was significant interindividual pharmacokinetic variability at this dose level, (Cmax, 190$\pm$69 ug/ml; AUC 1698$\pm$617 ug.hr/ml), this did not correlate with toxicity. Telomerase activity in leukocytes was inhibited by 33−72% in 3 pts studied to date.
Conclusions: GRN163L at a dose of 11.7 mg/kg given every 28 days is well tolerated, and results in excellent exposure and inhibition of telomerase activity in leukocytes. Further dose-escalation was considered undesirable due to cytopenias and the potential for delays in subsequent dosing. This alternate schedule remains an option for administration of GRN163L.

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A phase I study evaluating the pharmacokinetics (PK) and pharmacodynamic (PD) activity of the dual PI3K/mTor inhibitor GDC-0980 administered QW

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Background: The PI3K-AKT-mTOR signaling pathway is deregulated in a wide variety of cancers. GDC-0980 potently inhibits tumor growth of xenografts and has shown activity in preclinical models bearing PI3K mutant, PTEN-null, K-ras mutant, as well as PI3K pathway wild-type tumors in vitro and in vivo.
Methods: A phase I dose escalation study using a 3+3 design has been initiated in patients (pts) with advanced solid tumors or non-Hodgkin's lymphoma. Treatment is once weekly (QW) dosing with GDC-0980 in 4-week cycles. The objectives are to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD), evaluate PK and PD effects, and describe any observed anti-tumor activity of GDC-0980 on this schedule. PD assessments include pAKT levels in platelet-rich plasma (PRP), changes in pS6 in paired tumor biopsies, changes in FDG uptake via PET imaging, and changes in tumor vasculature via DCE-MRI. Archival tumor tissue is being evaluated for markers of PI3K pathway modulation.
Results: Seventeen pts have been enrolled in 4 successive cohorts of 6 to 50 mg GDC-0980 administered QW. GDC-0980 was generally well-tolerated with no Grade 3 or higher drug-related adverse events (AEs) or DLTs reported to date. The most common drug-related AEs reported to date include nausea, fatigue, lethargy, myalgia, vomiting, weight loss, pain, peripheral edema, stomatitis, and dry skin. Preliminary analyses of

PK data suggest dose-proportional increases in fasting mean Cmax and AUC. pAKT levels in PRP were inversely correlated with GDC-0980 plasma concentrations. Decreases in pS6 staining of >50% have been observed in tumor biopsies at ⩾6 mg GDC-0980. Signs of biologic activity have been observed in a pt with leiomyosarcoma (PTEN negative by IHC) treated at 25 mg GDC-0980. The pt had a 46% decrease in tumor FDG avidity and continues on study treatment with stable disease after 16 weeks. Evaluation of DCE-MRI data and correlation of PI3K pathway alterations with tumor response to GDC-0980 are underway.
Conclusions: GDC-0980 is generally well-tolerated when administered QW up to 50 mg with potential signs of anti-tumor activity. Reduction in pAKT levels in PRP and decreases in pS6 staining in paired tumor biopsies are consistent with downstream modulation of the PI3K pathway. Dose-escalation continues and updated PK/PD data will be presented.

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TH-302, a tumor selective hypoxia activated prodrug, complements and enhances chemotherapy treatment with gemcitabine, docetaxel, pemetrexed, and doxorubicin

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Background: TH-302, a metabolically inert prodrug, is selectively activated in deep hypoxic subregions of the tumor microenvironment. TH-302 was designed and selected to be relatively inert to hepatic metabolism and enzymatic inactivation, and is not a substrate for efflux-based resistance pumps. TH-302 binds weakly to albumin, exits the vascular system quickly *in vivo* with a $T_{1/2}$ of 45 minutes, and penetrates deeply in tissues. Upon activation in deep hypoxia TH-302 releases a bis nitrogen mustard which subsequently alkylates DNA.
Methods: TH-302 was assessed in multiple translational studies and in ongoing clinical studies in over 300 advanced cancer patients.
Results: Extensive translational studies of the mechanisms of action for TH-302 in animal models of cancer demonstrated that TH-302 complements the standard chemotherapy by penetrating into the severely hypoxic vessel-distal subregions of xenografts, adding to the activity of the chemotherapy. These findings were observed with all four chemotherapies in multiple models.
TH-302 is active as a single agent and is essentially non-myelosuppressive in humans, even at doses which produce dose limiting toxicities in the skin and mucosa. In combination with full doses of four chemotherapies in animals, TH-302 added significantly to the activity observed with each alone and was well tolerated. In cancer subjects the MTD, DLT, and activity of combinations of TH-302 were determined using full doses and approved schedules for gemcitabine (71 subjects), for docetaxel (50 subjects), for pemetrexed (36 subjects), and for doxorubicin (45 subjects). TH-302 was tolerated at 40−60% of the MTD for TH-302 alone in all combinations. The DLTs were primarily hematologic. The activity of the combinations by RECIST was 24% PR for all evaluable patients and clinical benefit (PR and SD) was observed in 79% across multiple tumor types. Selected expansions in 1st line pancreatic ca, recurrent NSCLC, castrate resistant prostate ca, and first line soft tissue sarcoma (STS) demonstrated RECIST PR rates of 26%, 26%, 20% (73% PSA response), and 23%, respectively. In addition to RECIST activity, the median progression free survival observed was encouraging in pancreatic ca, refractory NSCLC, and STS, suggesting durability.
Conclusions: The human studies of safety and activity of TH-302 alone and in combination with gemcitabine, docetaxel, pemetrexed, and doxorubicin are consistent with the novel design and characterization of TH-302. Animal and human studies indicate that selective targeting of tumor hypoxia can significantly improve the responses to chemotherapy. Taken together the studies suggest that TH-302 is a novel approach for the treatment of solid tumors.

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A phase I clinical trial of CXR1002 in patients (pts) with advanced cancer

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Background: CXR1002, an ammonium salt of perfluorooctanoic acid, is a lipid mimetic that causes ER stress and inhibits PIM kinases. CXR1002 exhibits anti-cancer activity in multiple xenograft models. Aims of this first-in-man study were to assess the tolerability, safety and pharmacokinetics (PK) and to identify the recommended phase II dose of CXR1002 administered orally once weekly.
Methods: Sequential cohorts of pts with advanced refractory solid tumors were enrolled. Cohort 1 received a single dose of CXR1002 followed by once weekly dosing commenced 6 weeks (wks) later. Subsequent cohorts received CXR1002 once wkly. Dose escalation followed a standard 3 + 3 design until dose-limiting toxicity (DLT) was observed in ⩾2/6 pts. Plasma levels of CXR1002 were determined by LC-MS/MS at the following time-points: pre-dose, 2, 3, 4, 24 hours post-dose for the first 6 weeks then 6 weekly. Exploratory PD analyses included: serum leptin; plasma lipids, glucose and insulin.
Results: 28 pts have been enrolled (16M/12F); median age 64.5 (range 36−75); PS ⩽ 2; colorectal (n = 14); pancreatic (n = 3); other (n = 11). CXR1002 was administered at 7 dose levels [mg (pts entered/evaluable)]: 50 (4/3), 100 (3/3), 200 (3/3), 300 (4/3), 450 (3/3), 600 (8/6), 750 (3/3). Median duration of therapy was 9 wks (range 0−40). DLT (grade 5 renal failure/grade 4 transaminitis; possibly drug-related) occurred in 1 pt at the 600 mg dose. Common (⩽ grade 2) cumulative drug-related toxicities were: nausea, vomiting, lethargy, and diarrhea. Cmax was reached 1.5 hours after administration of a single dose of CXR1002 and maintained at a constant level over a 6 wk sampling period. CXR1002 was cumulative with wkly dosing with increased exposure seen with increasing dose level and duration. 8 pts demonstrated stable disease ⩾12 wks including pts with anaplastic thyroid (40 wks), pancreatic (35 wks), and cervical cancer (34 wks).
Conclusions: CXR1002 has demonstrated a favorable toxicity profile up to doses of 750 mg once weekly and evaluation of higher dose levels is ongoing. Unusual PK were demonstrated with an extremely long $t_{1/2}$. Exposure to CXR1002 levels exceeding those efficacious in xenograft models has been achieved.

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A phase IA, dose-escalating study of LBH589 administered intravenously in adult patients with advanced solid tumors

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Background: Panobinostat (LBH589) is a pan-deacetylase inhibitor which has been shown to have anti-tumor activity against various tumor types in pre-clinical models and demonstrated promising clinical efficacy in Western patients. The purpose of this study was to evaluate the safety, tolerability, pharmacokinetic (PK) profile and preliminary antitumor activity of i.v. LBH589 in Japanese patients.
Material and Methods: A "3 + 3" design was employed. Patients (pts) with advanced solid tumors refractory to available standard therapies, or for whom no conventional therapies exist, were enrolled. 3 dose levels (10, 15, and 20 mg/m^2 LBH589 i.v. on d1 and d8 of a 21-day cycle) were assessed. Blood samples for PK analysis were obtained on d1 and d8. PK parameters were calculated by non-compartmental analysis as implemented in WinNonLin.
Results: 14 pts were enrolled as follows: 10 mg/m^2 (3), 15 mg/m^2 (3), and 20 mg/m^2 (8). Primary sites were colon (3), stomach (2), tongue (2), esophagus (1), peritoneum (1), lung (1), gall bladder (1), ovary (1), soft