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