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

C.P. Hart[1], M. Borad[2], S.P. Chawla[3], J.R. Infante[4], K.N. Ganjoo[5], V.K. Langmuir[6], S. Kroll[6], J.G. Curd[6]. *[1]Threshold Pharmaceuticals, Discovery, Redwood City CA, USA; [2]Mayo Clinic, Clinical, Scottsdale AZ, USA; [3]Sarcoma Oncology Center, Clinical, Santa Monica CA, USA; [4]Sarah Cannon Research Institute, Clinical, Nashville TN, USA; [5]Stanford University Medical Center, Clinical, Stanford CA, USA; [6]Threshold Pharmaceuticals, Clinical, Redwood City CA, USA*

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

M. Macpherson[1], D. Bissett[2], B. Tait[3], L.M. Samuel[2], J. MacDonald[4], A.L. Barnett[5], C.R. Wolf[5], C.R. Elcombe[5], A. Jeynes-Ellis[6], T.R.J. Evans[1]. *[1]University of Glasgow, Centre for Oncology and Applied Pharmacology, Glasgow, United Kingdom; [2]Aberdeen Royal Infirmary, Dept of Medical Oncology, Aberdeen, United Kingdom; [3]Beatson West of Scotland Cancer Centre, Clinical Trials Unit, Glasgow, United Kingdom; [4]Beatson West of Scotland Cancer Centre, Clinical Research Unit, Glasgow, United Kingdom; [5]CXR Biosciences Ltd., CXR Biosciences Ltd., Dundee, United Kingdom; [6]The Jeynes-Ellis Partnership, Pitcairlie House, Auchtermuchty, United Kingdom*

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

S. Oizumi[1], Y. Ando[2], K. Kitagawa[2], S. Morita[2], Y. Komatsu[3], S. Yuki[3], Y. Fujiwara[4], N. Kiyota[4], K. Kobayashi[5], H. Minami[4]. *[1]Hokkaido University School of Medicine, First Department of Medicine, Sapporo, Japan; [2]Nagoya University Hospital, Department of Clinical Oncology and Chemotherapy, Nagoya, Japan; [3]Hokkaido University Graduate School of Medicine, Department of Gastroenterology and Hematology, Sapporo, Japan; [4]Kobe University Hospital & Graduate School of Medicine, Medical Oncology/Hematology Department of Medicine, Kobe, Japan; [5]Novartis Pharma KK, Oncology Translational Medicine, Tokyo, Japan*

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

tissue (1) and sinonasal (1). Dose-limiting toxicities (DLTs) were assessed in 12 patients (2 pts at 20 mg/m^2 were excluded due to skipping of the second dose). 1 DLT (Gr 3 gamma-GTP increased for >7d) occurred at 20 mg/m^2. All patients experienced thrombocytopenia, and in 3 patients, it reached Gr 4 (1 at 15 mg/m^2 and the others at 20 mg/m^2) in cycle $\geqslant$2, and 2 pts required platelet transfusion. Generally, platelet counts recovered quickly without any special treatment, and almost grade 3 or 4 events recovered to grade 1 or less within 8 days. Pts enrolled at the 20 mg/m^2 cohort with baseline platelet counts <200K/mm^3 required dose delay or interruption during cycle 1, but those with higher baseline platelet counts did not. Other common toxicities were leukopenia, neutropenia, fatigue, and anorexia. PK was almost linear within the dose range examined with $T_{1/2}$ of 20 to 40 hr and systemic clearance of 40 to 60 L/hr. As efficacy outcome, SD was seen in 7/14 patients. The longest duration of exposure was 408d for the tongue cancer pt. Additional exploratory correlation analyses between the platelet reduction ratio on d7 as compared to baseline with LBH589 dose and PK parameters were performed. It was suggested that the platelet reduction ratio might be positively correlated with initial LBH589 dose, C_{max} and AUC.

Conclusions: By the time the 20 mg/m^2 cohort was completed in this trial, the parallel Western trial had established that a dose of 25 mg/m^2 was not tolerable. Therefore, in the interests of patient safety, the decision was made not to explore doses higher than 20 mg/m^2, and to declare 20 mg/m^2 the recommended phase II starting dose for Japanese pts. Pts with low baseline platelet counts should be closely monitored and considered for dose interruption and reduction as indicated.

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Phase I pharmacokinetics and pharmacodynamics of GDC-0152, a novel IAP protein antagonist, administered to patients with locally advanced or metastatic malignancies

W. Fairbrother[1], P. LoRusso[2], A. Wagner[3], N. Budha[4], W. Darbonne[5], Y. Shin[6], H. Wong[6], I. Chan[7], J. Ware[4], S.G. Eckhardt[8]. [1]*Genentech Inc., Protein Engineering, South San Francisco, USA;* [2]*Karmanos Cancer Institute, Departments of Medicine and Pharmacology, Detroit, USA;* [3]*Dana-Farber Cancer Institute, Ludwig Center for Cancer Research, Boston, USA;* [4]*Genentech Inc., Clinical Pharmacology, South San Francisco, USA;* [5]*Genentech Inc., Oncology Biomarker Development, South San Francisco, USA;* [6]*Genentech Inc., Drug Metabolism and Pharmacokinetics, South San Francisco, USA;* [7]*Genentech Inc., Clinical Sciences, South San Francisco, USA;* [8]*University of Colorado, Division of Medical Oncology, Denver, USA*

GDC-0152 is a small molecule that selectively antagonizes the inhibitor of apoptosis (IAP) proteins. IAP antagonists promote cell death via effects on both intrinsic and extrinsic pathways of apoptosis. Study IAP4050g is a phase Ia, open-label, multicenter, standard dose-escalation study (3 + 3 design) of GDC-0152 in patients with locally advanced or metastatic solid malignancies or non-Hodgkin's lymphoma without leukemic phase. The study has evaluated nine GDC-0152 doses, 0.049, 0.1, 0.2, 0.28, 0.39, 0.54, 0.76, 1.06 and 1.48 mg/kg, administered by 30-minute IV infusion once every 14 days. Plasma samples were collected at predetermined serial time points during the first two cycles. PK profiles have been obtained for the 36 evaluable patients enrolled in the first 9 cohorts. The plasma concentration-time data were analyzed using non-compartmental PK analysis (WinNonlin®, Pharsight Inc.,Mountain View, CA). The plasma concentrations of GDC-0152 declined tri-exponentially with a mean terminal elimination half-life of 4 hours. Exposures (AUC_∞) of 2580 ng·hr/mL (n = 3) and 3400 ng·hr/mL (n = 1) were achieved at doses of 1.06 mg/kg and 1.48 mg/kg, respectively. The between-patient variability in the key PK parameters, clearance and distribution volume was moderate (33.2% and 40.6%, respectively). In general, the exposures (AUC) increased in proportion to the dose during the studied dose range (0.049–1.48 mg/kg). Plasma samples were also collected for exploratory cytokine/chemokine protein analysis for identification of a potential pharmacodynamic biomarker. The plasma samples were analyzed by Luminex® human antigen multi-analyte profile assay (Rules Based Medicine, Austin,TX). To date, no-dose-dependent increases in plasma MCP-1, a chemokine elevated in plasma from preclinical studies with higher drug exposure, have been observed in a subset of patients through cohort 9. In summary, GDC-0152 exhibited dose-proportionality in exposure and no effect on the PD biomarker in the tested dose range.

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A phase I dose escalation and pharmacological study of the novel class I selective histone deacetylase inhibitor CHR-3996, in patients with advanced or treatment refractory solid tumours

F. Eskens[1], L. van Doorn[1], D. Papadatos-Pastos[2], P. Debnam[3], M. Tall[4], M. Toal[3], L. Hooftman[3], J. Verweij[1], U. Banerji[2]. [1]*Erasmus University Medical Center, Medical Oncology, Rotterdam, The Netherlands;* [2]*Royal Marsden Hospital, Drug Development Unit, Sutton, United Kingdom;* [3]*Chroma Therapeutics Ltd, Drug Development, Oxford, United Kingdom;* [4]*Institute of Cancer Research, Research, Sutton, United Kingdom*

Background: CHR-3996 is an orally bioavailable HDACi that inhibits HDAC 1, 2 and 3 at low nanomolar concentrations, with pleiotropic activity against a range of human cancer cells *in vitro*. The efficacy of CHR-3996 has been established in xenograft (mouse) models of colorectal (HCT116, LoVo) and pancreatic (MiaPaCa) cancer.

Methods: This was a dose escalation study of once daily orally administered CHR-3996 (5–160 mg) in a standard 3 + 3 design in patients (PS $\leqslant$ 2) with histologically confirmed advanced solid tumors refractory to standard therapy. Patients were treated for 28 days (the dose finding phase) and could remain on therapy until evidence of PD or unacceptable toxicity. PK samples were taken from all patients on Day 1 and Day 28 of the first cycle. Acetylated lysine in PBMCs from all patients was measured using an ELISA, while histone acetylation in hair follicles was assessed with confocal microscopy.

Results: 29 patients (median age 56 years [range 24−77], 21M/8F) have been enrolled. Dose levels studied were 5, 10, 20, 40, 80, 160 and 120 mg (in 3, 4, 3, 7, 4, 5 and 3 patients respectively). At 160 mg DLT was observed consisting of two episodes of short lasting and uncomplicated thrombocytopenia G4. At 120 mg DLT has been observed in a single patient (inability to tolerate a complete cycle of treatment), and 3 additional patients are being enrolled at 120 mg. Observed drug related toxicities (all grades) included fatigue (44%), nausea (44%), vomiting (26%), anorexia (15%), and thrombocytopenia (11%). 22 patients continued CHR-3996 after day 28. PK parameters (Cmax and AUC0-t) showed dose proportionality across the range 5 − 160 mg. A partial response was seen at 160 mg in one patient with an acinar pancreatic carcinoma, and stable disease for $\geqslant$ 3 months (range 3−10 months) was observed in 7 other patients.

Conclusions: Once daily oral CHR-3996 was well tolerated and MTD is currently defined at 160 mg. Plasma concentrations of CHR-3996 achieved in this trial exceed the concentrations required for anti-tumor efficacy in preclinical models, in the absence of significant toxicity. Assessment of histone acetylation as a pharmacodynamic biomarker in PBMCs and hair follicles confirmed intracellular drug activity in most patients. 29 subjects have been treated to date, with one partial response and 7 stable diseases recorded, hinting at clinical activity of CHR-3996.

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MGCD265, an orally active Met/VEGFR multitargeted kinase inhibitor, in combination with erlotinib: clinical and preclinical experience

A. Patnaik[1], J. Besterman[2], A.W. Tolcher[1], M. Mehran[2], M. Drouin[2], C. Maroun[2], C. Bonfils[2], M. Beeram[1], R. Martell[3], K. Papadopoulos[1]. [1]*South Texas Accelerated Research Therapeutics, Start, San Antonio, USA;* [2]*MethylGene, Clinical Research, St-Laurent, Canada;* [3]*Tufts Medical Center Cancer Center, Neely Center for Clinical Cancer Research, Boston, USA*

Background: MGCD265 is an oral multitargeted receptor tyrosine kinase (RTK) inhibitor that targets Met, VEGFR 1/2/3, Tie-2, and Ron. Although Met can be an oncogenic driver on its own, its functional interactions with other key RTKs such as EGFR, has become central to oncogenesis. Met and EGFR are coexpressed and functionally cooperate to amplify activating signals in cancer cells. Moreover, in NSCLC, Met gene amplification or overexpression of HGF was identified as a molecular mechanism through which tumors escape EGFR inhibition. These data provide a compelling rationale for concomitantly inhibiting Met and EGFR.

Material and Methods: The anti-tumor activity of MGCD265 in combination with erlotinib was evaluated in multiple xenograft models. In addition, a phase I study (as part of a phase II NSCLC program) using the 3 + 3 design is currently ongoing to evaluate the safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK) and potential benefit of MGCD265+erlotinib in patients with advanced tumors.

Results: Improved anti-tumor activity was observed when MGCD265 was combined with erlotinib in several human xenograft models including a NSCLC model resistant to erlotinib (EGFR T790M mutation). To date, in the ongoing clinical trial, 19 patients have been enrolled. MGCD265 daily doses ranged from 96 mg/m^2 to 144 mg/m^2 in combination with erlotinib at 100 to 150 mg daily. Safety evaluations indicate that MGCD265 can be combined with full dose of erlotinib. Nine patients (47%) were on study