1205 ORAL

A first-in-human Phase I study to evaluate the pan-PI3K inhibitor GDC-0941 administered QD or BID in patients with advanced solid tumours

D.D. Von Hoff[1], A.J. Wagner[2], P.M. LoRusso[3], R. Tibes[1], J. Jin[4], J.A. Ware[4], Y. Yan[5], M.K. Derynck[6], M.V. Dolezal[6], G.D. Demetri[2]. *[1]Translational Genomics Research Institute, Clinical Translational Research, Phoenix, USA; [2]Dana-Farber Cancer Institute, Medical Oncology, Boston, USA; [3]Karmanos Cancer Institute, Oncology, Detroit, USA; [4]Genentech Inc., Clinical PK/PD, South San Francisco, USA; [5]Genentech Inc., Pharmacodynamic Biomarkers Development, South San Francisco, USA; [6]Genentech Inc., Oncology Clinical Science, South San Francisco, USA*

Background: The PI3K-PTEN-AKT signaling pathway is deregulated in a wide variety of cancers. GDC-0941 is a potent and selective oral pan-inhibitor of the class I PI3K, with 3 nM IC50 for the p110-alpha subunit in vitro and 28 nM IC50 in a cell-based pAKT assay, and demonstrates broad activity in breast, ovarian, lung, and prostate cancer in vitro and in vivo (xenograft) models.
Materials and Methods: A Phase I dose-escalation study (GDC4255 g, sponsored by Genentech) using a 3+3 design was initiated in patients (pts) with solid tumors to evaluate the pharmacokinetic (PK), pharmacodynamic (PD), and safety characteristics of GDC-0941. GDC-0941 was given on Day 1, followed by a 1-week (wk) washout to study single-dose PK and PD markers. GDC-0941 was then administered QD on a 3-wks on, 1-wk off, schedule. Steady-state PK and PD were evaluated after 1 wk of continuous dosing. A separate concurrent dose-escalation arm with BID dosing was initiated after the third QD cohort.
Results: Twenty-five pts have been enrolled in 6 successive dose-escalation cohorts in the QD arm, with dose levels up to 100 mg daily. Thirteen pts have been enrolled in 3 cohorts in the BID arm at total daily doses (TDD) of 60, 80, and 100 mg. Day 1 and Day 15 PK data suggest GDC-0941 is rapidly absorbed and displays dose-proportional increases in mean C_{max} and AUC_{inf}, with a mean apparent half-life that supports either QD or BID dosing regimens. The most frequently reported drug-related adverse events were Grade 1–2 nausea, fatigue, diarrhea, peripheral edema, dysgeusia, and dry skin. Two dose-limiting toxicities have been reported in separate cohorts: Grade 3 headache at 80 mg QD and Grade 3 pleural effusion at 50/30 mg BID (80 mg TDD). Potential signs of anti-tumor activity have been observed in 2 ovarian pts, the first (30 mg BID) on-study >253 days with a 22% decrease in measured disease and 2.8-fold decrease in CA-125 (now within normal limits) and the second (60 mg QD) on-study >200 days with stable disease. Archival tissue analysis for PI3K pathway alterations (including P13K amplification, mutation, PTEN loss) is ongoing.
Conclusions: GDC-0941 is generally well tolerated, with potential signs of anti-tumor activity. Preliminary PK data suggest dose-proportional increases in exposure over the dose levels evaluated. Dose-escalation on both schedules continues with updated data to be presented.

1206 ORAL

Phase I study of Pazopanib (PAZ) in Hepatocellular Carcinoma (HCC): evaluation of clinical activity, Pharmacokinetics (PK), and Dynamic Contrast Enhanced MRI (DCE-MRI)

C.C. Yau[1], P. Chen[2], C. Curtis[3], P. Murphy[3], G. Parker[4], A. Suttle[3], T. Arumugham[3], J. Hodge[3], M. Dar[3], R. Poon[5]. *[1]Queen Mary Hospital, University Department of Medicine, Hong Kong, China; [2]National Taiwan University Hospital, Research and Development, Taipai, Taiwan; [3]GlaxoSmithKline, Research and Development Oncology, North Carolina, USA; [4]University of Manchester, Research and Development Oncology, Manchester, United Kingdom; [5]University Department of Medicine, Queen Mary Hospital, Hong Kong, China*

Background: HCC is a highly vascular tumor with increased levels of VEGF and VEGFR. PAZ is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, & c-Kit. A correlation between a trough plasma PAZ concentration (C24) of $\geqslant$15 μg/ml and markers of pharmacodynamic activity has been demonstrated in previous studies. DCE-MRI is a noninvasive imaging technique that can provide indices related to blood flow & vascular permeability. A Phase I study was conducted to determine the MTD as well as evaluate safety, PK, DCE-MRI changes, & clinical activity of PAZ in pts with locally unresectable or advanced HCC.
Methods: Eligibility criteria included HCC with at least 1 target lesion, recovery from prior therapy, PS 0 or 1, Child-Pugh A, & adequate organ function. PAZ was escalated from 200 to 800 mg QD. DCE-MRI was performed to determine Ktrans (contrast transfer coefficient) & IAUC60 (initial area under the contrast enhancement curve), at baseline & Day 22. PAZ PK, including C24, was determined on Day 15 of Cycle 1.
Results: 17 of 28 Asian pts successfully completed both baseline & day 22 DCE-MRI. Median (range) values for PK, DCE-MRI, & clinical activity parameters are provided below by dose level.

	PAZ Dose (mg)			
	200	400	600	800
C24 μg/mL	15.4 (13, 26)	24.5 (10.5, 31.1)	21.8 (1.63, 36.8)	30.6 (24.6, 30.9)
Ktrans % change	−36.3 (−70.0, −22.9)	−18.3 (−63.3, −9.47)	−44.6 (−45.6, −4.19)	−74.4 (−86.2, −37.5)
IAUC % change	−17.3 (−24.7, −11.7)	−19.3 (−48.7, −12.5)	−39.4 (−56.0, 13.4)	−60.4 (−78.4, 10.8)
# Days on Study	133.5 (43, 757)	55 (14, 275)	106 (4, 289)	169 (9, 274)

Median C24 was >15 mg/mL at all doses evaluated. Median changes in Ktrans & IAUC were negative in all dose groups with the greatest median decline at 800 mg. Decreases in IAUC60 were correlated with Cmax and trough concentration. At the MTD of 600 mg QD, median decline from baseline in imaging markers was ~40%; 67% of pts achieved C24 $\geqslant$15 ug/mL. Of 10 pts who received 600 mg QD for the largest number of days on study, 7 demonstrated clinical benefit (6 with SD $\geqslant$ 4 mo & 1 with confirmed PR). The 2 pts with confirmed PRs (1 each at 600 mg & 800 mg QD) both achieved C24 >25 ug/mL. 1 pt with PR & imaging data achieved >60% declines in Ktrans & IAUC relative to baseline.
Conclusions: In pts with HCC, the recommended Phase II dose for PAZ of 600 mg QD achieved target trough concentrations associated with clinical benefit & demonstrated meaningful changes in imaging markers.

1207 ORAL

Results of study PX-171–007 a phase 1b/2 study of carfilzomib, a selective proteasome inhibitor, in patients with selected advanced metastatic solid tumors

M. Gordon[1], J. Infante[2], K.P. Papadopoulos[3], P. Lee[4], E. Sausville[5], D. Mendelson[6], A.F. Wong[7], M. Vallone[8], P.J. Rosen[4], H. Burris[2]. *[1]Premiere Oncology of Arizona, Clinical Trials, Scottsdale, USA; [2]Sarah Cannon Research Institute, Hematologic Malignancy Research, Nashville, USA; [3]South Texas Oncology and Hematology, Medical Oncology and Hematology, San Antonio, USA; [4]Tower Cancer Research Foundation, Clinical Research Services, Beverly Hills, USA; [5]University of Maryland Medical Center, Greenebaum Cancer Center, Baltimore, USA; [6]Premiere Oncology, Division of Hematology-Oncology, Scottsdale, USA; [7]Proteolix Inc., Clinical Development, South San Francisco, USA; [8]Proteolix Inc., Clinical Operations, South San Francisco, USA*

Background: Carfilzomib (CFZ) is a novel proteasome inhibitor of the peptide epoxyketone class that exhibits a high level of selectivity for active sites within the proteasome. This phase 1/2 study assessed the maximum tolerated dose (MTD), safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of CFZ in patients (pts) with advanced metastatic solid tumors.
Material and Methods: Pts failing $\geqslant$2 prior treatments were enrolled in the phase 1 3+3 dose escalation study. Pts received CFZ 20 mg/m^2 IV Day (D) 1, 2, 8, 9, 15 and 16 every 28 d for up to 12 cycles (C) Cycle 1 D1, D2 dosing in all cohorts was at 20 mg/m^2. Subsequent doses were escalated to 20, 27 or 36 mg/m^2 in a stepped up regimen. At 20/36 mg/m^2, 1 pt had a DLT (Grade 3 fatigue) and established the phase 2 dose. Phase 2 is designed as a Simon 2 stage of 70 pts split into 5 subgroups (small cell lung [SCLC], non-small cell lung [NSCLC], ovarian, renal, and other cancers) to estimate the ORR, defined as CR+PR+SD, to 16 wks of CFZ.
Results: 14 pts in phase 1 and 51 pts in phase 2 (23M/28F, mean age 61 yrs) received a total of 154.5 cycles of CFZ. Median cycles administered was 1.7 (range 1 to 12). To date, in stage 1 of phase 2 there were 6 SCLC, 10 NSCLC, 11 ovarian, 6 renal, and 18 other cancer patients enrolled. Efficacy of SD or better is detailed in the table below:

		Tumor type	Prior chemotherapy regimens	Duration of response
Phase 1b, n = 14	SD	Mesothelioma	4	5.1 months[1]
	PR	Renal cell (clear cell)	3	11 months +
		SCLC	6	10 months +
Phase 2, n = 50	SD	NSCLC	3	6.6 months +
		Renal (clear cell)	6	5.2 months[1]
		Renal (clear cell)	3	5.9 months +
		Ovarian	4	4.0 months +
		Endometrial	3	4.6 months +

[1] Discontinued for progression; + Continues on study.

The most common AEs included fatigue headache, diarrhea, nausea and constipation. Notable was the absence of painful peripheral neuropathy