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

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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.

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

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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

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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

and severe hematologic toxicities. Final results of the PK and PD will be reported.
Conclusions: CFZ is active as a single agent in relapsed solid tumors demonstrating PR in both renal (clear cell) and SCLC; and SD >16 wks in mesothelioma, ovarian, renal and NSCLC. The 20/36 mg/m^2 QDx2 dose schedule was well tolerated and lacks severe myelosuppression, hepatotoxicity and neuropathy which make CFZ an attractive agent to combine with traditional or novel targeted agents. In addition, further dose escalation is underway.

Poster presentations (Mon, 21 Sep, 09:00–12:00)
Drug development – Preclinical

1208 POSTER

Toxicity of systemic administration of blank and paclitaxel-loaded lipid nanocapsules in mice

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Background: Lipid nanocapsules (LNCs) are very promising nanocarriers (size ranging from 25 to 100 nm) containing lipophilic drugs such as paclitaxel or etoposide. The authors describe the first blank and paclitaxel-loaded LNCs preclinical toxicological studies in mice.
Materials and Methods: The study was performed on 55 nm-diameter LNCs on female Swiss mice (7 weeks; 20–22 g). LNCs formulations or saline serum were slowly injected in the lateral tail vein during a short inhalational anaesthesia induced by isoflurane. The experimental protocols were approved by the Pays-de-la-Loire ethic committee. Repeated dose toxicity studies corresponding to 12 mg/day from Day 1 to Day 5 were performed in 3 groups: blank LNCs, paclitaxel-loaded LNCs and saline serum. At Day 12, gross or histological analyses of vital organs such as liver, spleen, kidneys and lungs, complete blood counts, biological analysis (ion counts, ALAT, total bilirubin, creatinine and C-Reactive protein) were performed. Maximum tolerated dose (MTD) and 50% lethal dose (DL50) were assessed for high concentration blank LNCs and paclitaxel-loaded LNCs (12, 24, 48, 96, 192 and 288 mg/kg) in comparison with Taxol® (commercial formulation diluted at 1.2 mg/ml in saline) and saline serum in accordance with Irwin Test.
Results: No mortality was observed in repeated dose toxicity studies. Weight increase was similar in both groups. At Day 12, no abnormality was observed during autopsy. The mean weight of the organs of interest was similar ($p > 0.05$). Histological studies revealed that the livers, spleens and kidneys were normal. Complete blood counts, natremia, kaliemia, chloremia, ALAT, total bilirubin, serum creatinine and C-Reactive protein in serum were similar in both groups ($p > 0.05$). For Taxol®, MTD and DL50 were equal to 12 mg/kg and 19.5 mg/kg, respectively. MTD and DL50 of paclitaxel-loaded LNCs was equal to 96 mg/kg and 216 mg/kg. MTD of blank LNCs was equal or superior to 288 mg/kg.
Conclusion: This study demonstrates for the first time the good tolerance of systemic administration of blank and paclitaxel-loaded LNCs in mice. A five-day i.v. injection schedule does not induce any histological or biochemical significant abnormality in Swiss mice. In comparison with paclitaxel-solvent formulation Taxol®, the paclitaxel-loaded LNCs dispersion tolerance in mice was increased such that the LD50 and MTD were eightfold and eleven fold than the commercial formulation, respectively. The entrapment of paclitaxel in LNCs induces an improvement of its therapeutic index in comparison with Taxol®.

1209 POSTER

SU14813 induces mitotic catastrophe in a wide-spectrum of tumour models independently of the expression of active receptor tyrosine kinase targets

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Background: Receptor Tyrosine Kinases (RTKs) have emerged as clinically valuable drug target molecules for treating different types of cancer such as Chronic Myeloid Leukemia, Gastrointestinal Stromal Tumors and Metastasic Renal Cell Carcinoma among others. SU14813 is a novel broad-spectrum receptor tyrosine kinase inhibitor for multiple membrane RTKs such as FLT-3, VEGFR, KIT, EGFR or PDGFR, derived from the same molecular library than Sunitinib®. This new molecule has shown potent antiangiogenic and antitumoral properties, however the complete molecular mechanisms involved in its antitumoral activity, in vivo and in vitro, still remains unclear.
Methods: After incubating A549, SK-UT-1 and Jurkat cells for 24–72 hours with 1–100 μM of SU14813, western blotting, flow cytometry and citotoxicity assays were performed in order to address the possible mechanism of action associated to SU14813.
Results: SU14813 induces in multiple cell lines the formation of huge cells with numerous micronucleus. This morphological event is accompanied by an increased percentage of cell death in time. This process has been already defined as the failure of the cells to go through a complete mitosis or mitotic catastrophe, after DNA damage. In this context the cell cycle deregulation induced by SU14813 is associated with significant changes on the expression of pivotal proteins that control cellular mitosis such as cdc2, Cyclin B1 and Retinoblastoma (Rb). Moreover we show in this study how cells with defective p53 or Rb are more sensitive to SU14813-induced mitotic catastrophe and or cell death.
Conclusion: We present, to our knowledge, SU14813 as the first Tyrosine Kinase Inhibitor (TKI) that induces mitotic catastrophe (1–100 μM) in different tumor models in vitro. This cellular event is associated with changes in the activity of mitotic regulators and could play an essential role in the antitumoral activity observed in "in vivo" models treated by this compound. Moreover we do not discard that another TKIs may also act by deregulating mitotic exit depending on the dose. This work opens the possibility of combining SU14813 with inhibitors of Aurora Kinase B.

1210 POSTER

Novel nanoparticle fusion protein achieves normal P21 delivery to p53/p21 mutated tumors resulting in their eradication

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Background: Novel applications of nanotechnology present us with new opportunities and the potential to design new as well as enhance the effectiveness of current cancer treatments.
Material and Methods: We report here the creation and application of a nanoparticle fusion protein driven by the Antennapedia protein as a "Trojan horse" able to penetrate the cell membrane and intracellular compartments of cancer cells in order to deliver normal p21 to the nucleus, a known tumor suppressor protein. The fusion protein has been validated in multiple tumor models in nude mice.
Results: The fusion protein (TR1), consisting of Antennapedia and normal p21 has the ability to interfere with the cell cycle, and more specifically to antagonize and block the interaction between cyclins and cyclin-dependent kinases. TR1, has been validated in multiple tumor models *in vivo* and has demonstrated its therapeutic potential. Additionally, it is non-immunogenic and nontoxic.
Cell-based studies have shown its effectiveness in a range of human tumor types, whilst iv administration resulted in a time- and dose-dependent uptake into all tissues including regions of restricted drug delivery and access, such as the brain.
Restoration of p21 function in tumors devoid of endogenous activity resulted in growth arrest and, in combination with conventional chemotherapy, in complete tumor eradication.
Conclusions: Evaluation of this novel strategy is currently being initiated in a phase I clinical trial designed to determine, pharmacokinetics, safety profile and as to whether it has an anticancer effect in humans as it has in mice.