carboplatin/gemcitabine). Therefore, we conducted a limited size (n = 15) single arm Phase II study to evaluate the safety and activity of BelCaP in pts with TCC of the bladder.
Methods: Patients (ECOG PS 0−2, >18 years, ⩽3 prior chemotherapy regimens in the advanced disease setting) with bladder carcinoma were eligible to receive BelCaP; B as a 30-min i.v. infusion once daily (1000 mg/m^2) on days 1−5 with P (175 mg/m^2) administered 2−3 hrs following B on day 3 and C (AUC5) following directly after P (cycles repeated every 3 weeks). Response was evaluated according to RECIST criteria.
Results: 13 pts have been enrolled so far and preliminary data from 8 pts are available. The median age was 60 years (range 43−76), all had at least one prior treatment (7 pts cisplatin/gemcitabine and 1 pt MVAC as first-line) and they received a total of 37 cycles (median = 4; range = 3 to 7) of BelCaP. In the 8 evaluable pts three responses have been observed (one complete and two partial), each occurring after 2 cycles of treatment. In addition, a prolonged stabilization (5.6 months) was reported. Related grade 3 adverse events include neutropenia (1 pt), hypokalemia (1 pt), sensory neuropathy (2 pts), cardiac ischemia (1 pt) and syncope (1 pt). Related grade 4 adverse events included only neutropenia (3 pts).
Conclusions: The BelCaP regimen, which combines the novel HDAC inhibitor belinostat with C and P, has a manageable toxicity and shows promising activity in patients with pretreated TCC of the bladder. Recruitment to the study continues, and updated information will be presented at the meeting.

214 POSTER

AP5346 (ProLindacTM), a pH-dependent polymer-vectorized DACH platinum, is active in borderline potentially platinum-sensitive ovarian cancer (OC) patients: results from an ongoing Phase I/II trial

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Background: We have previously reported findings of an ongoing dose-intensity guided phase I/II trial with AP5346 (ProLindacTM), a novel DACH-platinum, in patients with multi-treated ovarian cancer. In q2w and q3w schedules, treatment at 2 dose intensity levels (300 mg/m^2/wk and 466 mg/m^2/wk) was found to be well tolerated (Campone et al, EORTC-NCI-AACR, 2007). Here we provide updated results from the study, focusing on the most recent dose level (DL +2, DI=560 mg/m^2/wk), in which as of May 2008, 5 patients (pts) have been treated (3 in Arm A, 2 in Arm B – q2w and q3w, respectively).
Material and Methods: Pts having failed 2−4 prior chemotherapy (CT) lines were eligible provided they had ~6 months of platinum-free progression-free interval (PPFI) (potentially platinum-sensitive), adequate organ function and evaluable (Rustin and/or RECIST) disease. Standard anti-emetic prophylaxis and hydration (2L NS with NaHCO3) were given before and after 1-hour ProLindac infusion.
Results: From June 2006 until May 2008, 22 pts were enrolled in the first three dose levels (6 pts in DL0: 300 mg/m^2/wk; 11 pts in DL+1: 466 mg/m^2/wk; 5 pts in DL+2: 560 mg/m^2/wk). Median age: 63 years (range: 45−70), median number of previous CT lines: 3 (2−7), and median PPFI is 17.4 months (6.9–42.6). Median Ca125 levels at baseline were 18.6x upper normal limit (UNL) for DL0, 6.3 UNL for DL+1 pts, and 17.1 UNL for DL+2 pts. Median number of cycles (1 dosing per cycle) was only 2 (2−4) for DL0, since 5/6 pts had outright progression, 3 cycles (1−8) for DL+1, and 6 cycles (2−8) for DL+2 (3 pts ongoing). Safety: no renal toxicity or significant neutropenia or thrombopenia were reported; moderate nausea and vomiting were observed. Clinical delayed cisplatin-like neurotoxicity was seen in 3 pts (one with grade 2, two with grade 3), several weeks after 6, 3 and 3 cycles, respectively. All 4 evaluable pts to date treated in DL+2 (2 treated at q2w, 2 at q3w) have received 4 cycles (4/6/8/8 cycles), with 3/3 consistent Ca125 decreases (1 PR, 2 MR, Rustin criteria) and 1 SD (8 q2w cycles) in a pt with normal Ca125. Expanded accrual at the current DL (+2) is planned, with PK/PD and prospective neurotoxicity evaluation.
Conclusions: The level of activity observed in the first pts of DL +2 compares favourably with published reports with oxaliplatin in the same population. Studies in combination with taxol and gemcitabine in the same clinical setting, and in other indications, are planned for Q4 2008.

215 POSTER

Prospective study of erlotinib comparing chemotherapy-naive non-small cell lung cancer patients having an activating mutatation in EGFR gene with those having wild-type EGFR gene

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Background: Erlotinib demonstrated to significantly improve survival for previously treated NSCLC patients. There is increasing use of first-line erlotinib in specific subgroups of NSCLC based on their clinical or molecular predictors. However, there is no data to support the use of activating mutation in EGFR gene in decision-making process. Therefore, we conducted a prospective study of erlotinib for chemotherapy-naive patients to assess efficacy according to their mutational status of EGFR gene.
Methods: The eligible criteria were as follows; pathologically confirmed stage IIIB or IV, ECOG PS of 0−2, adequate organ functions, measurable lesions. Before starting erlotinib therapy, whether tumors had an activating mutation in exon 19−21 of EGFR gene or not should be identified. Neither prior chemotherapy or targeted therapy nor radiotherapy to measurable disease was allowed. Treatment consisted of erlotinib 100–150 mg orally given once daily till disease progression, unacceptable toxicity or patient's refusal. Objective tumor responses were assessed one month after the commencement of erlotinib and then every two months.
Results: Between 10/2006 and 12/2007, all 23 patients enrolled (median age: 61 years; M/F 7/16; ECOG PS 0/1/2 2/15/6; stage IIIB/IV 1/22; never/former/current smoker 15/5/3; EGFR gene: mutant/wild 11/12) were evaluable for response. A response rate for the 11 patients with an activating somatic mutation in EGFR gene was 81.8% (9/11), while that of the 12 patients with wild-type was 16.7% (2/12) (p = 0.007). Progression-free survival was longer for those with an activation mutation in EGFR gene (not reached yet vs. 1.0 month, p = 0.0026). Overall survival and response rates for subsequent chemotherapy will be presented at the meeting.
Conclusions: An activating EGFR gene mutation is a reliable predictor of response to erlotinib. For chemotherapy-naive NSCLC patients with an activating mutation in EGFR gene, erlotinib might be a treatment of choice.

PI3Kinase

216 POSTER

A phase I dose-escalation study of the safety, pharmacokinetics and pharmacodynamics of XL765, a novel inhibitor of PI3K and mTOR, administered orally to patients with solid tumors

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Background: XL765 is a selective oral inhibitor of Class I PI3K isoforms and the mTOR/Raptor and mTOR/Rictor kinase complexes. XL765 is a potent inhibitor of PI3K pathway signaling in vivo and slows tumor growth or causes tumor regression in multiple human xenograft tumor models.
Methods: Patients (pts) with advanced solid malignancies are enrolled in cohorts of 3 to receive XL765 orally twice daily (BID) or once daily (QD) for cycles of 28 days. Pharmacokinetic (PK) and pharmacodynamic samples are collected. Tumor response is assessed every 8 weeks by RECIST criteria.
Results: To date, 19 pts have been treated with XL765 across 4 dose levels from 15 to 120 mg BID which is the maximum administered dose (MAD) for BID dosing. 60 mg BID is being evaluated as the preliminary MTD. At the MAD, reversible, treatment-related increases in hepatic transaminases have been observed. One pt at the MAD had DLTs of grade 3 anorexia and hypophosphatemia. DLT has not been reported at doses below the MAD. Two pts (colon adenocarcinoma and mesothelioma) have had SD for at least 6 months. Preliminary PK analysis for BID dosing indicates that AUC and C_{max} appear to increase with dose. Median T_{max} is 1−3 hours, and the mean $t_{1/2,\ ss}$ ranges from 3 to 11 hours. Plasma concentrations appear to reach steady state by Day 8. XL765 administration augments food-induced changes in plasma insulin in an exposure-dependent fashion, but has no effect on plasma glucose levels. XL765 administration inhibits PI3K pathway signaling in PBMCs as determined by reductions in phosphorylation of PRAS40 and 4EBP1. Moreover, XL765 administration results in inhibition of PI3K and mTOR in solid tissues, including patient hair bulbs and skin, as determined by reductions in phosphorylation of AKT, PRAS40, 4EBP1 and S6. In a pt with chondrosarcoma, XL765 at

60 mg BID resulted in reductions of 80−90% in phosphorylation of AKT, 4EBP1 and S6, and was associated with a 54% reduction in proliferation as assessed by Ki67 in tumor cells. The pattern of inhibition of PI3K pathway phosphoepitopes suggests that XL765 inhibits PI3K and both mTOR/Raptor and mTOR/Rictor in pts.
Conclusions: In this Phase 1 study, XL765 has been generally well tolerated at doses up to 60 mg BID, and further exploration of this dose as well as a QD regimen is in progress. XL765 demonstrates robust pharmacodynamic activity, as assessed by analysis of multiple PI3K and mTOR dependent readouts in surrogate tissues and tumor.

217 POSTER

Pre-clinical evaluation of efficacy and PK/PD biomarkers of GDC-0941, a potent class 1 PI3K inhibitor

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Background: Constitutive activation of the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway is a frequent event in many types of cancers and results in increased cell growth and survival. We recently discovered GDC-0941, a class 1 PI3K inhibitor currently in phase 1 clinical trials. Pre-clinically, we have demonstrated the potent anti-tumor activity of GDC-0941 *in vitro* and *in vivo*. (Folkes *et al.,* late breaking abstract-146, Friedman *et al.,* late breaking abstract 110, AACR 2008). In this study we evaluate the efficacy, pharmacokinetic (PK) and pharmcaodynamic (PD) markers of GDC-0941 *in vivo*.
Methods: GDC-0941 was dosed up to 200 mg/kg daily by oral gavage in mice bearing breast and prostate cancer xenografts. GDC-0941 plasma PK, tumor PK and tissue PD analysis of downstream PI3K biomarkers (pAKT, PRAS40, pS6, phospho-p70S6K) was evaluated after single dose and multiple daily dose efficacy studies. PD analysis was conducted on *ex vivo* xenograft tumour samples and normal murine tissues using a combination of luminex, mesocale, immunohistochemical and Western blot assays.
Results: GDC-0941 had significant dose dependent *in vivo* efficacy and was well tolerated. In single dose and multiple daily dose efficacy studies GDC-0941 caused rapid downregulation of pAKT, PRAS40, pS6 and phospho-p70S6K in the tumour, consistent with PI3K pathway inhibition. PK analysis of GDC-0941 showed that reduction of pAKT in the tumours was positively correlated to plasma and tumour drug concentrations. There were minimal effects on pAKT in normal murine tissue at 30 min. pAKT knockdown in the tumour was verified and found to be comparable using both luminex and mesocale assays. Imunohistochemical analysis of MDA-MB-361 breast tumours showed heterogenous expression of pAKT and pS6, which was significantly reduced 1hr post dose of GDC-0941. Highly efficacious doses of 75–150 mg/kg GDC-0941 gave prolonged biomarker knockdown, recovering by 24 hrs consistent with the drug exposure.
Conclusions: GDC-0941 had significant anti-tumour activity *in vivo* with concomitant reduction in PI3K signalling in xenograft tumour tissue. These pre-clinical data support the evaluation of pAKT, PRAS40, pS6 and phospho-p70S6K as potential PI3K pathway biomarkers in GDC-0941 clinical studies.

218 POSTER

A phase I dose-escalation study of the safety, pharmacokinetics and pharmacodynamics of XL147, a novel PI3K inhibitor administered orally to patients with advanced solid tumors

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Background: XL147 is a potent, selective, oral inhibitor of Class I PI3 kinases. Administration of XL147 leads to tumor growth inhibition or regression in preclinical cancer models and has been shown to enhance the anti-tumor activity of EGFR-targeted agents and cytotoxic drugs.
Methods: XL147–001 is a Phase 1, non-randomized, open label, dose escalation, safety and pharmacokinetics (PK) study. Patients (pts) with advanced solid tumors are enrolled in successive cohorts to receive XL147 daily on Days 1−21 of 28-day cycles (21on/7off schedule). In Cycle 1, clinical and laboratory data are obtained to assess safety and pharmacodynamics. Tumor response is evaluated by RECIST criteria every 8 wks.
Results: To date, 19 pts have been treated with XL147 across six dose levels from 30 mg to 600 mg daily. At 600 mg daily a DLT of Grade 3 skin rash was observed. At 400 mg daily, one Grade 1 gastritis, and one Grade 1 skin rash were reported possibly related to study drug. There were no SAEs related to XL147. Plasma PK analysis indicated exposure increased with dose. The mean terminal plasma half-life at steady state ranged from 3−6 days, with steady state plasma concentrations achieved between Days 15 and 20. Accumulation was evident, as plasma exposures were 5 to 10-fold higher on Day 21 than on Day 1. XL147 transiently augmented food-induced changes in plasma insulin with a trend suggesting dose- and exposure-dependence. Inhibition of PI3K pathway signaling was demonstrated in pts by reductions in phosphorylation of PI3K pathway components including AKT, PRAS40, and 4EBP1 in PBMCs and hair bulbs. In one example, administration of 120 mg daily resulted in reduced phosphorylation of AKT (32%), PRAS40 (74%), 4EBP1 (46%) and S6 (57%) in hair bulbs. Similar analyses are ongoing in skin and tumor samples from multiple pts. As of May 2008, one pt with basal cell carcinoma has remained on study >10 cycles; three pts with NSCLC and one pt with NHL remained on study >8 cycles; an additional two pts remained on study >4 cycles.
Conclusions: XL147 has been generally well tolerated at doses up to 400 mg daily on the 21on/7off dosing schedule. Inhibition of PI3K signaling has been demonstrated and there are preliminary signs of clinical benefit as assessed by time on study. Cohort expansion at the 600 mg dose level is ongoing to determine the MTD for the 21/7 dosing regimen. In parallel, pts are being enrolled on a continuous daily dosing schedule.

219 POSTER

NVP-BEZ235, a dual pan-PI3K/mTOR kinase inhibitor, is effective in human lung cancer models harboring EGFR mutations

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Background: Mutations in the intracellular kinase domain of the epidermal growth factor receptor (EGFR) are often found in a subset of patients with lung cancer and correlate with therapeutic response to EGFR kinase modulators. Resistance to these targeted anticancer agents invariable develops, and current treatments have limited long-term antitumor efficacy. In this study, we evaluated the effectiveness of a dual PI3K/mTOR kinase inhibitor, NVP-BEZ235, in the treatment of human lung cancer models harboring EGFR mutations.
Materials and Methods: To study the potential use of NVP-BEZ235, which is currently in Phase I clinical trials, in the treatment of lung adenocarcinomas, the compound was tested *in vitro* and *in vivo* in several human lung models that require a functional EGFR for tumor maintenance.
Results: NVP-BEZ235 significantly inhibits the proliferation (GI_{50} <50 nM) of lung tumor cell lines harboring EGFR-activating mutations as well as EGFR tyrosine kinase resistance somatic mutations by specifically blocking the biological function of PI3K signaling components. In animal models, oral treatment with NVP-BEZ235 (35 mg/kg qd) caused tumor stasis ($T/C = 0.04$, $p < 0.05$) in NCI-H1975 xenografts, an EGFR mutant model (Leu858Arg and Thr790Met), which has shown high levels of EGFR tyrosine kinase inhibitor resistance. Moreover, ex-vivo analysis of tumor samples treated with NVP-BEZ235 revealed significant inhibition of pS473-Akt and downstream targets with no inhibition of YP/TP-ERK1/2 at 1 h post last dose. NVP-BEZ235 was well tolerated at the efficacious doses when compared with vehicle treated animals, with no significant difference seen in the body weight. Significant antitumor activity was also observed in a mechanistic c-MET amplified gefitinib resistant model (Hcc827GR), and in an EGFR mutant model sensitive to EGFR kinase inhibitors (Hcc827, ex 19 del).
Conclusions: These preclinical evaluations suggest that NVP-BEZ235 may represent an effective therapeutic strategy for patients with lung cancers harboring drug-sensitive EGFR mutations or those with the novo and acquired resistance to EGFR tyrosine kinase inhibitors.

220 POSTER

Combination of class I PI3K inhibitor, GDC-0941, with standard of care therapeutics results in enhanced anti-tumor responses in human cancer models in vitro and in vivo

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Background: Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that regulate tumor cell growth, migration and survival. We previously reported