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.

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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.

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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

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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