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Preliminary results of a Phase II study of picoplatin in combination with 5-fluorouracil and leucovorin (FOLPI) as a potential neuropathy-sparing first-line therapy for colorectal cancer (CRC)

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Background: Picoplatin (Pico) is designed to overcome platinum resistance. FOLFOX (5-FU, LV and oxaliplatin) treatment for advanced CRC has significant oxaliplatin-related neurotoxicity. The incidence of grade 3−4 neurotoxicity with Pico in previous studies was <2%, suggesting that Pico may provide a neuropathy-sparing alternative to oxaliplatin. The Phase I study identified the MTD at 150 mg/m^2 when Pico was infused Q4W with Q2W FU and LV. The present study was designed to evaluate the efficacy and safety of Pico when administered Q4W with FU and LV (FOLPI) vs. modified FOLFOX-6 (85 mg/m^2 oxaliplatin) in a randomized Phase II trial.
Methods: Each patient (pt) received LV and infusional FU per modified FOLFOX-6 (m-FOLFOX-6) Q2W. Fifty-one pts with no prior chemotherapy for advanced CRC received Pico every 4 wks at a dose of 150 mg/m^2, and 51 pts were treated with Q2W oxaliplatin at a dose of 85 mg/m^2. Tumor response was assessed by RECIST using CT scans. Neuropathy was assessed using the FACT-Neurotoxicity questionnaire and by a neurologist who was blinded to treatment.
Results: Between 16 Nov 2007 and 30 Apr 2008, 102 pts were randomized (51 to FOLPI and 51 to m-FOLFOX-6) and have received a total of 455 two-week cycles of FOLPI or m-FOLFOX-6 (maximum = 11, median = 4; 225 cycles of FOLPI and 230 cycles of m-FOLFOX-6) as of 21 May 2008. Forty-two pts have each received more than 8 weeks of treatment. To date, based on early data from 51 pts, 25 FOLPI pts have had 2 PR, 15 SD and 2 PD; 6 are not evaluable, and 26 m-FOLFOX-6 pts have had 2 PR, 17 SD and 2 PD; 5 are not evaluable. 51 pts (26 FOLPI and 25 m-FOLFOX-6) are too early to evaluate response. Most frequent adverse events were neutropenia, thrombocytopenia, nausea, and anorexia. Three pts had neuropathy in the m-FOLFOX-6 arm (one Grade 3) and none in the FOLPI arm. Confirmed response rates, dose intensity and adverse event data will be updated in the presentation.
Conclusions: FOLPI with Q4W Pico is well-tolerated and may have comparable efficacy to m-FOLFOX-6. Additional data are expected with continued follow-up of this ongoing Phase II study.

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Results of a phase II study of picoplatin with docetaxel and prednisone in chemotherapy-naive patients with metastatic hormone refractory prostate cancer (HRPC)

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Background: Picoplatin (Pico) is designed to overcome platinum resistance. In HRPC, a PSA response rate of 25% was observed when Pico monotherapy was infused at 120 mg/m^2 Q3W (N = 20). A 34-pt Phase I study was performed to investigate the safety and efficacy of Pico in combination with docetaxel (D) + prednisone (pred) in patients with metastatic HRPC. Picoplatin therapy was well-tolerated and 20 of 31 evaluable pts (65%) achieved confirmed PSA responses. 120 mg/m^2 Pico with D 75 mg/m^2 and pred was determined to be the MTD, and supported this dose level for the Phase II study to evaluate safety and efficacy of Pico with D and pred.
Methods: Pts with chemotherapy-naive HRPC and disease progression received Pico (120 mg/m^2) and D (75 mg/m^2) Q3W with pred 5 mg po bid for up to 10 cycles. PSA responses were defined as a reduction from baseline of at least 50% maintained for at least 4 weeks. CT and bone scans are also evaluated by RECIST criteria.
Results: 32 pts were enrolled and have received 1−10 cycles; 7 remain on treatment. One pt had no baseline PSA data. Of the 31 pts with baseline PSA (median 341, range 6–6682), 3 had no follow-up PSA. 19 (68%, 95% CI 49−82%) of the remaining 28 pts had PSA decreases to <50% of their baseline, and in 6 of these (21% of the evaluable population) PSA reached normal levels (<4). Based on CT/bone scan data, there were 23 pts (72%) with SD by RECIST criteria, 5 (16%) with PD, and 4 (12%) were not evaluable. The most common adverse events were neutropenia, alopecia, anemia and asthenia. In comparison to Pico monotherapy, thrombocytopenia was less severe and less frequent. No neurotoxicity >grade 1 has been reported.
Conclusions: Picoplatin at 120 mg/m^2 can be safely administered with 75 mg/m^2 docetaxel and prednisone. PSA and RECIST response data indicate that this novel combination may be efficacious in the first-line treatment of patients with HRPC.

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A phase II study of the KIT inhibitor XL820 in patients with advanced gastrointestinal stromal tumors (GIST) resistant to or intolerant of imatinib and/or sunitinib

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Background: XL820 is an orally bioavailable, small molecule inhibitor of both wild-type and mutationally-activated KIT, VEGFR2, and PDGFR. Mutations in KIT, particularly in the juxtamembrane domain, are common in GIST. XL820 potently inhibits both the ATP-binding region and activation loop classes of resistance mutations, which are associated with imatinib and sunitinib resistance.
Methods: This is a Phase 2, randomized, open-label, multi-center trial with Simon optimal two-stage design. Patients (pts) with metastatic GIST who have progressed after prior imatinib and/or sunitinib treatment are eligible. Up to 60 pts will be enrolled to receive XL820 at 800 mg once daily or 300 mg twice daily. Tumor response is being assessed by RECIST and Choi criteria at baseline, 4 weeks (wks), 8 wks, and every 8 wks thereafter. 18FDG (fluoro-2-deoxyglucose)-PET (positron emission tomography) scans are obtained at study baseline and approximately 4 wks following the first dose of XL820. Plasma samples for pharmacokinetics (PK) and pharmacodynamic samples including plasma, PBMCs, hair and buccal mucosa are being collected.
Results: Ten pts have enrolled to date, ranging in age from 21 to 80 years. All pts had ECOG of 0/1. Nine pts received 2 prior treatments and one pt imatinib only. Seven pts were evaluable at 4 wks. With FDG-PET, 4 pts had $\geqslant$20% reduction in SUV max (−38%, −38%, −27%, −20%) and 3 pts had increased SUV max (+73%, +8%, +8%). After 4 wks, 5 pts had stable disease (SD) by RECIST (2 pts had partial response by Choi), and 2 pts had progressive disease (PD). Four pts continue to have SD at wk 8. One pt died at 2 wks from bowel perforation (possibly related to treatment). Most frequent possibly related grade 1/2 adverse events were fatigue (6 pts), diarrhea (4 pts), nausea (4 pts), and neutropenia (3 pts); grade 3 toxicities possibly related to treatment included fatigue (1 pt), leucopenia (1 pt), and urticaria (1 pt).
Conclusions: XL820 is generally well tolerated and appears to have biological activity in pts with advanced GIST: decreased FDG-PET activity was observed in 4/7 evaluable pts at 4 wks; 2 PRs by CHOI criteria were observed and pt enrollment and follow-up continue.

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Phase II multicenter trial of belinostat (PXD101) in combination with carboplatin and paclitaxel (BelCaP) for patients (pts) with transitional cell carcinoma (TCC) of the bladder

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Background: Treatment options for patients with metastatic transitional cell carcinoma of the bladder are limited. Belinostat (PXD101) is a low molecular weight class I and II HDAC inhibitor of the hydroxamate class. In preclinical models, belinostat (B) displayed single agent anti-tumor activity, enhanced by the combination with carboplatin (C) and paclitaxel (P). Phase I data in pts with pretreated advanced solid tumors showed B with standard doses of C + P (BelCaP) to be well-tolerated and clinically active, including bladder carcinoma (disease control during 14 months of treatment in a pt previously treated with cisplatin/gemcitabine and