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Preliminary results from a Phase II Trial of EPO906 in patients with advanced refractory ovarian cancer

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EPO906 is a newly developed microtubule stabilizer that inhibits cell growth in a broad range of human cancer cell lines *in vitro*, including those that are resistant to taxanes such as paclitaxel. Phase I trials identified diarrhea as the primary toxicity, with objective responses seen in colon, ovarian, breast, NSCL and carcinoid cancers. An open-label multi-center Phase II study is in progress to evaluate the efficacy and safety of EPO906 in patients with advanced refractory ovarian cancer whose disease progressed during or within six months of completing first-line therapy with carboplatin/taxol. EPO906 was administered at a dose of 2.5mg/m^2 intravenously as a 5-minute bolus infusion repeated every week for 3 weeks, followed by a 1-week rest period until progressive disease [PD] or unacceptable toxicity occurred. A total of 25 patients have been enrolled so far. Of the 17 evaluable patients to date, a partial response by RECIST criteria was observed in 2/17 [12%], stable disease was observed in 5/17 [29%], and discontinuation due to PD occurred in the remaining 10 patients. Of the 5 SD patients, all of whom are still on study, falling CA-125 values have been seen in four in association with variable degrees of radiologic response. Overall, toxicity has been modest. Only two grade 3/4 adverse events [diarrhea, constipation] have been reported to date. Grade 1 and 2 toxicities attributed to study drug have included diarrhea, nausea, vomiting, anorexia and fatigue. These interim results suggest that EPO906 is well-tolerated and has activity in patients with advanced refractory ovarian cancer. Additional accrual and response data will be presented.

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OXI 4503 a novel vascular targeting agent: Effects on bloodflow and antitumor activity in comparison to Combretastatin A-4 phosphate

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Oxi 4503 which is the diphosphate prodrug of Combretastatin A1 is a novel vascular targeting agent from the combretastatin family. Another member of thsi family Combretastatin A-4 phosphate (CA4P) is a well characterised vascular targeting agent already beeing evaluated in clinical trials. Oxi 4503 induced the shutdown of tumor blood vessels in a dose-dependent pattern with an ED50 at 3 mg/kg in contrast to 43 mg/kg of CA4P. Quantitative flurescence microscopy showed that Oxi 4503 increased the spatial heterogeneity in tumor blood flow. Oxi 4503 affected peripheral tumor regions less than central regions, although nort as pronounced as seen with CA4P where opnly central regions were affected. The vascular shutdown induced by administration of Oxi 4503 at a dose of 6 mg/kg resulted in extensive cell loss 24 hours following treatment which translated into a significant effect on tumor growth. Tumor growth was completely repressed at doses above 12.5 mg/kg of Oxi 4503, and doses above 25 mg/kg showed tumor regression and even complete regression in some animals. These results are promising for the use of Oxi 4503 as a tumor vascular trageting agent. Moreover the potent antitumor effect when administered as a single agent suggest a different activity profile than CA4P.

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Combination of IDN5390, an orally active taxane, with paclitaxel in a human tumor xenograft: improvement in antitumor efficacy without increase of toxicity

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Taxanes are tubulin-binding agents, that appear to exert their antitumor activity via a dual mechanism, as they have a direct cytotoxic effect on tumor cells and antiangiogenic activity. This study was designed to exploit both mechanisms using a combination of paclitaxel (PTX) and a novel C-seco analog, IDN 5390. The rationale of the study was based on the use of cytotoxic dose levels of PTX, by an intermittent treatment schedule, and on the favorable profile of tolerability of IDN 5390, which allowed a prolonged daily treatment by oral route. IDN 5390 was originally selected on the basis of its potent antimotility activity on endothelial cells and ability to down-regulate angiogenesis-related growth factors (VEGF and bFGF), in spite of a reduced cytotoxic potency. According to the selected treatment schedules, the MTDs were 54 mg/kg and 120 mg/kg for i.v. PTX and oral IDN 5390, respectively. Combination of suboptimal doses of each agent against an ovarian carcinoma xenograft (A2780/DDP) resulted in a clear increase of antitumor efficacy in terms of tumor weight inhibition (higher than additive) and rate of PR (6/20 in the two-drugs treated vs 2/36 in the single-drug treated mice). A therapeutic advantage was also achieved when, after an optimal regimen of PTX (54 mg/kg, i.v., q4dx4) which induced PR in all mice, the regrowing tumors were treated daily with oral IDN 5390 (90 mg/kg qdx5/week) for 4 weeks. In mice receiving both drugs, the improvement in activity over PTX was documented by the LCK values (4.7 vs 3.4, respectively). IDN 5390 treatment did not add toxicity, neither in terms of body weight loss, nor of lethal toxicity. In conclusion, combination of two taxanes, in a human tumor xenograft, allowed a superior antitumor efficacy to be achieved, without increase of toxicity. The good tolerability of IDN 5390 and the lack of overlapping toxicity with PTX could be exploited for consolidation therapy after PTX-based treatment.

Topoisomerase inhibitors

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NQO1*2 genotype predicts poor survival in NSCLC patients receiving radiation and chemotherapy as part of E3590

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Introduction: E3590 was a randomized, prospective trial of adjuvant radiation alone (Arm A) or radiation plus chemotherapy (Arm B) with etoposide and cisplatin in patients with resected II or IIIA NSCLC. NQO1 is a two-electron reductase, with a characteristic polymorphism (NQO1*2) that results in an inactive enzyme. Since NQO1 may be important in predicting chemosensitivity and toxicity, the influence of the NQO1*2 polymorphism on toxicity and overall survival in patients in E3590 was evaluated.
Methods: Genomic DNA isolated from primary lung tumor was evaluated for the NQO1*2 polymorphism by pyrosequencing, an automated sequencing method based on primer extension chemistry. Patients were designated as *1/*1, *1/*2, or *2/*2. Overall survival for these three groups was compared using Kaplan-Meier survival analysis with two-sided log rank tests.
Results: There were 78 tumor samples available for analysis in Arm A, 54% of samples were *1/*1, 29% of samples were *1/*2, 16% of samples were *2/*2. There were 74 tumor samples available for analysis in Arm B, 55% of samples were *1/*1, 30% of samples were *1/*2, 15% of samples were *2/*2. In patients receiving radiation + chemotherapy (Arm B), NQO1 *2/*2 was a strong independent predictor of poor survival, with a median survival of 41.8 months for the *1/*1, 39.8 months for the *1/*2, and 16.2 months of the *2/*2. The median survival in patients receiving just radiation (Arm A) was 40.2 months for the *1/*1, 45.2 months for the *1/*2, and 53.4 of the *2/*2. The estimated hazard ratio comparing NQO1*2 in Arm B with NQO1*2 in Arm A was 3.6, with 95% confidence interval (1.4,9.2) p=0.028.
Conclusion: NQO1*2 predicts poor survival in NSCLC patients receiving radiation and chemotherapy. This genotype may help individualize cancer therapy, by predicting poor responders who may benefit from alternative therapies.