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Phase I and pharmacokinetic study of oral Irinotecan (CPT-11) on a daily-times 5 schedule every 3 weeks in combination with evaluation of food effect

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CPT-11, administered intravenously, is registered for the treatment of advanced colorectal cancer and has shown clinical activity against several other types of solid tumors. Topoisomerase-I-inhibitors showed more pronounced antitumor efficacy with prolonged exposure at low concentrations due to their S-phase specific cytotoxic behavior. Oral drug administration is a more convenient and cost effective method to reach this purpose. In this Phase I study, CPT-11 was administered orally as new semi-solid matrix (SSM) capsules once daily for 5 consecutive days every 3 weeks in fasted condition. For the first administration at day 1 of cycle 1 or 2, for which patients were randomly assigned, patients took the drug in the fed state after a FDA-standardized high-fat breakfast. Dose levels tested include: 70 mg/m^2/day (dose level I, n=20) and 80 mg/m^2/day (dose level II, n=5). A total of 25 patients (10 male / 15 female (median age 53 years (range, 31 - 76), median WHO-PS 1 (0 - 2), with a variety of refractory solid tumors was included, of which 16 patients were evaluable for food effect. The worst hematological toxicities (CTC grading) were: grade 3 neutropenia (n=1), grade 2 leucopenia (n=3), grade 2 thrombocytopenia (n=1), and grade 2 anemia (n=3). At dose level 80 mg/m^2/day, three patients received DLT due to grade 3 diarrhea, grade 3 nausea and/or vomiting, fever without neutropenia. Other non-hematological toxicities were mild to moderate and included: anorexia, fatigue, alopecia, skin rash and taste changes. MTD was defined at a dose level of 70 mg/m^2/day. One confirmed partial remission and 12 stable diseases were observed. To evaluate CPT-11 and SN-38 pharmacokinetics, an extensive sampling scheme was applied on day 1 and 5 of the 1st course and day 1 of the 2nd course. The day 5 to day 1 AUC ratios for CPT-11 and SN-38 were 1.6$\pm$1.2 and 1.2$\pm$1.0, respectively, indicating no relevant accumulation of the active metabolite. The SN-38 to CPT-11 AUC ratio was dose-independent with an overall mean value of 0.13$\pm$0.13, which suggests extensive presystemic biotransformation. A 1.4-fold, but statistically not significant increase in exposure to CPT-11 and SN-38 was observed after a high fat meal. Overall, this study confirms that oral administration of CPT-11 is feasible at 70 mg/m^2 daily-times 5 q.3 wks. and may have improved pharmacokinetic characteristics, with only a limited or no effect of food intake.

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Phase I and pharmacologic study of diflomotecan (BN80915) administered intravenously daily for 5 consecutive days every 3 weeks in patients with solid tumors

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Diflomotecan (BN89015) is an E-ring modified camptothecin derivative. This topoisomerase-I-inhibitor bears a novel 7-membered β-hydroxylactone ring structure characterized by a more stable lactone form. As a result it showed a greater plasma stability, which potentially can enhanced antitumor activity. In this abstract interim results are presented from a current Phase I study. Diflomotecan was administered once daily as a 20-minute IV infusion for 5 consecutive days every 3 weeks. Dose levels tested include: 0.05 mg/m^2/day (dose level I, n=3), 0.1 mg/m^2/day (dose level II, n=4), and 0.15 mg/m^2/day (dose level III, n=6). Currently, 13 patients (6 male / 7 female; median age, 55 years (range, 42 - 73), median WHO-PS 1 (0 - 2), with a variety of refractory solid tumors are included. The worst hematological toxicities (CTC grading) were grade 4 neutropenia (n=3), grade 3 leucopenia (n=2), grade 3 thrombocytopenia (n=3), and grade 3 anemia (n=1). At dose level 0.15 mg/m^2/day, two patients experienced DLT due to grade 4 (febrile) neutropenia, and grade 3 diarrhea, stomatitis and fatigue. Other non-hematological toxicities were mild to moderate and included anorexia, fatigue, myalgia, stomatitis, alopecia, skin rash. Of 12 assessable patients, 4 had disease stabilisation after 2 courses. To evaluate the pharmacokinetics of BN89015, blood samples were taken up to 96 h post infusion and analysed from 11 patients. At dose level III, the mean half-life of the terminal disposition phase was 3.35 $\pm$ 1.78 h, with a time to peak concentration (Cmax) of 0.37 $\pm$ 0.04 h and a Cmax of 4.84 $\pm$ 1.79 ng/ml. Across all dose levels, the area under the plasma concentration versus time curve (AUC) increased proportionally with dose, suggesting that BN80915 delineates a linear pharmacokinetic behavior. No substantial drug accumulation was observed as measured by the day 4 to day 1 AUC0-24 ratio (mean, 1.12 $\pm$ 0.362). The mean overall BN80915 plasma clearance of 20.2 $\pm$ 20.0 l/h/m^2 (range, 7.3 - 78.6 l/h/m^2) was dose-independent, and demonstrated a significant degree of interindividual variability (coefficient of variation, 99%). The relatively short half-life of BN80915 in combination with the lack of accumulation provide a pharmacokinetic rationale for the tested regimen in order to optimize antitumor activity.

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A phase I and pharmacokinetic study of DE-310 administered as a 3 hour infusion every 4 weeks (wks) to patients (pts) with advanced solid tumors or lymphomas

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DE-310 is a large (~340 kDa) water soluble conjugate of DX-8951 (Exatecan), linked by a peptidyl spacer to a carboxymethyldextran polyalcohol polymer. About 1/15 of DE-310 by weight is DX-8951, which is slowly released in cells by cathepsins. In preclinical studies, DE-310 is preferentially retained in tumors due to an enhanced permeability and retention effect. It is active against a broad range of human colon and lung cancer xenografts. Study objectives were to determine the recommended dose of DE-310 given as a 3 hr infusion every 4 wks, to determine the toxicity profile, and to define drug pharmacokinetics. As of April 2002, 16 pts (median age 60 yrs, range 43-73 yrs, 10 male/6 female) were treated with 35 courses over 5 dose levels. Tumor types included colorectal (5), gastric (3), hepatic (2), non-small cell lung (2), and pancreas, breast, cholangial, and unknown primary cancers. The dose of DE-310 (in DX-8951 equivalents) was escalated in cohorts of 3 pts. The number of new pts (# courses) was 3(10) at 1.0 mg/m^2, 3(5) at 2.0, 3(7) at 4.0, 6(12) at 6.0, and 1(1) at 7.2 mg/m^2. At 6 mg/m^2 the cohort was expanded because of grade 4 neutropenia and death occurring in 1 pt during cycle 2, however, 5 other pts tolerated this dose without substantial toxicities. At 6 mg/m^2, grade 3/4 myelosuppression included anemia in 3 pts, thrombocytopenia in 2 pts, and neutropenia in 1 pt. Myelosuppressive nadirs were generally dose related and tended to occur in cycle 2. One pt was decreased from 7.2 to 6 mg/m^2 in cycle 2 as a precaution after pts at lower dose levels were observed to have delayed toxicities. However, this pt tolerated DE-310 without problems. Other toxicities seen at all dose levels included reversible liver transaminitis and easily managed mild nausea, vomiting, anorexia, and fatigue. The best responses in 12 pts were stable disease in 3 and progressive disease in 9. Both conjugated DX-8951 and free DX-8951 concentrations increased linearly with dose and plasma drug concentrations were sustained for several weeks. At 6 mg/m^2 (n=5), the mean (CV%) Cmax for DE-310 in the form of conjugated DX-8951 was 3267 (20.6%) ng/mL and the apparent terminal plasma half-life (t1/2) was 262 (41.8%) hrs. Free plasma DX-8951 was much lower with a mean Cmax of 3.0 (38.6%) ng/mL and a t1/2 of 178.2 (19%) hrs. Currently, accrual continues at 7.5 mg/m^2. DE-310 is easily administered, generates sustained systemic exposures to DX-8951, and thus far has been well tolerated.

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A phase I/II Study of DX-8951f and gemcitabine in advanced solid tumour malignancies

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DX-8951f is a hexacyclic, water soluble camptothecin with broad-spectrum activity. *In vitro* data has demonstrated pre-clinical synergy for a combination of DX-8951f and gemcitabine. A phase I study of DX-8951f and gemcitabine was conducted to determine (1) the MTD of DX-8951f and gemcitabine, (2) to define the dose-limiting and non-dose-limiting toxcities, (3)

to assess for pharmacokinetic (PK) interactions when DX-8951f is given concurrently with gemcitabine, (4) to identifiy, preliminarily, evidence of antitumor activity, and specifically in a cohort of patients with pancreatic cancer. Between 5/00 and 10/01, 70 patients were enrolled at 3 academic centers. 36 men (51%), 34 women (49%). Median age, 58 years, range 26-81, Median ECOG 1, range 0-2. 67% of patients had no or up to one prior chemotherapy regimen (minimally pretreated, MP). 33% were deemed to be heavily pretreated (HP), having had significant prior chemotherapy or radiation exposure. Patients were accrued seperately to MP and HP cohorts. 39 (56%) had pancreatic cancer, 11 (16%) colon cancer, and the remainder a variety of other solid tumors. In the MP cohort, dose-limiting toxicity was identified at the 2.5 mg/m^2 DX-8951f and gemcitabine 1,000 mg/m^2 cohort. Myelosuppression,(neutropenia more than thrombocytopenia), was the principal toxicity. There were 10 episodes of fever and neutropenia. There was one treatment-related death. Grade 3-4 non-hematologic toxicities were uncommon, while the Grade 1-2 included fatigue, nausea, and vomiting. In general, the combination was well-tolerated and both drugs could be given at full dose intensity. The recommended combination doses are 2.0 mg/m^2 DX-8951f and gemcitabine 1,000 mg/m^2. Significant antitumor activity was seen at all dose levels, including, partial and complete responses in pancreatic cancer and heavily pretreated ovarian and GE junction cancers. In the pancreatic cohort (N=39), there were 2 CR's (5%), 4 PR's (10%), 2 MR's (5%) and 19 (49%) with stable disease. In 27 patients with previously untreated pancreatic cancer, the median time to progression and median survival time were 6.3 and 8.4 months respectively. The combination of DX-8951f is active, safe and very tolerable. Complete PK, toxicity and response data will be presented. An ongoing phase III trial is comparing the combination (DX-8951f 2.0 mg/m^2, gemcitabine 1,000 mg/m^2) to gemcitabine alone in advanced pancreatic cancer.

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Open label phase II study on RFS 2000 in advanced/metastatic urothelial tract tumors

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Background: RFS 2000 is a direct, highly potent inhibitor of the DNA-religating activity of topoisomerase-I. The aims of this study were to evaluate the activity and safety profile of RFS 2000 as a second line chemotherapy in patients with advanced /metastatic urothelial tract tumors.
Patients and methods: Eligible patients were to have failed first line treatment for advanced/metastatic disease (MVAC or other treatment). Patients received RFS 2000 as one daily oral intake at the dose of 1.5 mg/m^2/day according to a 5 days on/2 days off schedule continuously. One cycle was arbitrarily defined as a 3 week period. Patients were required to have adequate oral hydration to prevent cystitis previously described in phase I trials with RFS2000. Gehan design was used for sample size determination. Drug activity was evaluated according to the RECIST criteria and toxicity according to CTC version 2.
Results: A total of 21 patients (pts) were entered from June 2000 to September 2001, and all pts received treatment. Male/female/no data: 14/5/2 with median age 67 years (range: 43-78). 8, 11, and 2 patients had performance status 0, 1, 2 respectively. Data are validated for 19 patients who received 50 cycles (median 2; range 1-8). Safety profile: 8 patients developed neutropenia Grade (G) 3-4 which was complicated with febrile neutropenia in 3 patients and lead to treatment interruption in 2 of them, 4 thrombocytopenia G3-G4 and 4 anemia G3-4. Other G 3-4 adverse reactions were: 4 fatigue, 5 diarrhea, 2 nausea and 2 vomiting. 1 hematuria G3 was considered partially related to tumor progression and to RFS 2000 toxicity. To date, among 19 patients documented for activity data, 1 confirmed partial remission (5.2%, 95%CI: [0.1-26]%) and 6 stable disease were reported. 16 patients stopped treatment for progressive disease and 3 patients for hematological toxicity.
Conclusion: RFS 2000 administered orally as a 5 days on/2 days off schedule continuously shows modest activity in patients with advanced/metastatic urothelial tract tumors who failed first line therapy. Hematological toxicity requires careful monitoring and the occurrence of diarrhea G3-4 confirms similar observations in other studies. This trial is now closed and full data analysis will be available at the time of presentation.

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Conserved mechanism of CDC45 function in protecting yeast and human cells from DNA damage

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Camptothecin (CPT) reversibly stabilizes a covalent intermediate formed between DNA topoisomerase I (Top1) and a 3' phosphoryl end of DNA. Replication fork collisions with CPT-Top1-DNA complexes produce the DNA lesions that induce cell cycle arrest and cell death. As cellular pathways that recognize and repair Top1-DNA lesions are poorly understood, a yeast genetic screen was designed to isolate temperature sensitive mutants with enhanced sensitivity to a self-poisoning Top1T722A mutant that mimics the cytotoxic mechanism of CPT (Reid R et al, 1999 PNAS 96:11440-5). A novel set of TAH genes were defined that function to protect yeast cells from CPT-induced lethality, including the essential CDC45 gene whose function is required for the initiation of DNA replication. The cdc45-10 mutant exhibits a partial loss of function- DNA replication initiation appears to be unaffected, but processive replication is delayed in early S-phase. Viability is unaffected in the absence of DNA damage; however, cdc45-10 mutant cells exhibit enhanced sensitivity to hydroxyurea and UV (independent of Top1) and to CPT (in a Top1-dependent manner). Thus, alterations in processive DNA replication potentiate Top1 poison toxicity. To address the conservation of Cdc45 function, human hCDC45 was PCR amplified from untransformed human IMR90 fibroblast cDNA and expressed in yeast. Constitutive expression of hCDC45 failed to complement cdc45-10 cell hypersensitivity to DNA damaging agents, yet galactose-induced overexpression of hCDC45 restored cdc45 deletion cell viability. This suggests that the essential function of Cdc45 in replication initiation is distinct from the defect in cdc45-10 cells that enhance CPT toxicity. hCDC45 function in modulating cell sensitivity to Top1 poisons was addressed using siRNA to down regulate hCDC45 levels in IMR90 cells. At sub lethal topotecan concentrations, CDC45 siRNA induced a dramatic S-phase arrest and a decrease in cell number. No alterations in cell cycle distribution or cell number were observed in drug-treated cells without siRNA. This mirrors the response of yeast cdc45-10 cells, supporting a conserved mechanism of CDC45 protection against CPT-induced DNA lesions. As deletion of the RAD9 DNA damage checkpoint exacerbates the cdc45-10 mutant phenotype, future studies will focus on hCDC45 down-regulation in the absence of the p53 checkpoint in isogenic IMR90 cell lines. This work is supported by NIH grant CA70406 and ALSAC.

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Antiangiogenic potential of the novel camptothecin ST1481

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Camptothecins are potent cytotoxic agents and their antitumor activity has been ascribed to stabilization of a covalent DNA-topoisomerase I complex. In addition to the direct cytotoxic effect, camptothecins have been described for possessing antiangiogenic effects. ST1481 is a new lipophilic camptothecin active by oral route, which, based on its favorable preclinical profile, is currently in clinical development. Aim of the study was to investigate the antiangiogenic effects of ST1481, delivered by oral route, in a subcutis growing human tumor xenograft, the A549 NSCLC, which is only moderately sensitive to the agent delivered by an intermittent schedule (q4dx4, MTD 2 mg/kg), but sensitive to a prolonged daily low-dose (0.5 mg/kg) treatment. A tumor volume inhibition of 67 and 83% was achieved by ST1481 administered q4dx4 or daily, respectively ($p < 0.05$, by Student's t test). Immunohistochemical analysis showed a reduced number of microvessels (CD31+ cells) in tumors of both treated groups versus controls, and a significantly higher reduction in the daily versus the q4dx4-treated tumors ($P < 0.0001$, by Student's t test). In our experimental model, microvessel density and tumor volumes were related ($r = 0.738$, by Spearman rank test). ST1481 resulted more potent than topotecan in inhibiting endothelial cells growing *in vitro*. In conclusion, the study showed that ST1481 has a significant antiangiogenic potential in *in vivo* systems and that such effect is enhanced with a daily prolonged administration of low drug doses.