138

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

O. Soepenberg[1], H. Dumez[2], J. Verweij[1], J. Selleslach[2], J. Ter Steeg[1], S. Assadourian[3], C. Boeuf[3], P. Lefebvre[3], A. Sparreboom[1], A.T. Van Oosterom[2]. [1]*Erasmus Mc - Daniel Den Hoed Cancer Center, Medical Oncology, Rotterdam, The Netherlands;* [2]*University Hospital Gasthuisberg, Medical Oncology, Leuven, Belgium;* [3]*Aventis Pharma, Antony Cedex, France*

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.

139

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

O. Soepenberg[1], L. Scott[2], J. Verweij[1], R. Damji[2], J. ter Steeg[1], D. Mcgovern[3], R. Obach[4], A. Sparreboom[1], C.J. Twelves[2]. [1]*Erasmus Mc-Daniel Den Hoed Cancer Center, Medical Oncology, Rotterdam, The Netherlands;* [2]*Crc-University Of Glasgow, Beatson Laboratories, Glasgow, United Kingdom;* [3]*Beaufour Ipsen Pharma, Berkshire, United Kingdom;* [4]*Beaufour Ipsen Pharma, Barcelona, Spain*

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.

140

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

C.H. Takimoto[1], F. Forero[2], G.H. Schwartz[2], A.W. Tolcher[2], L.A. Hammond[2], A. Patnaik[2], M. Ducharme[3], B. Cooke[4], R. De Jager[4], E.K. Rowinsky[2]. [1]*Univ. of Texas Health Science Center, Medicine/Medical Oncology, San Antonio;* [2]*Cancer Therapy and Research Center, San Antonio, TX, USA;* [3]*MDS Pharma, Montreal, Quebec, Canada;* [4]*Daiichi, Inc., Monvale, NJ, USA*

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.

141

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

G. Abou-Alfa[1], R. Lenzi[2], S. Mani[3], G. Schwartz[1], R. Maki[1], D. Kelsen[1], A. Levin[1], J. Ackerman[4], R. DeJager[4], E. O'Reilly[1]. [1]*Memorial Sloan-Kettering Cancer Center, Gastrointestinal Oncology Service, New York;* [2]*MD Anderson Cancer Center, Houston, TX, USA;* [3]*Montefiore, New York, NY, USA;* [4]*Daiichi Pharmaceuticals, Montvale, NJ, USA*

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)