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MEN4901/T-0128: a new camptothecin derivative-carboxymethyldextran conjugate with potent anti-tumor activities in a panel of human tumor xenografts in nude mice

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MEN4901/T-0128 is a polysaccharide conjugate prodrug comprising 10-(3'-aminopropyloxy)-7-ethyl-(20S)-camptothecin (T-2513) bound to carboxymethyldextran via a triglycine spacer. Previous experiments on the pharmacokinetics of MEN4901/T-0128 in tumor-implanted BALB/c nude mice have demonstrated that MEN4901/T-0128 had an extended circulation time and accumulation in the tumor tissue with sustained tumor levels of T-2513. In the present study, the anti-tumor activity of MEN4901/T-0128 was evaluated in BALB/cA Jcl nude mice bearing human lung (Mqnu-1, H-74), colon (H-110), liver (H-181), esophagus (H-204), gastric (H-81) and pancreatic (H-48) cancer lines, which have been serially transplanted subcutaneously and maintained in nude mice. Groups of 7 animals with almost equal mean tumor sizes and standard errors were treated with either MEN4901/T-0128 or irinotecan (CPT-11) intravenously once a week for 4 weeks and sacrificed 4 weeks after the initiation of chemotherapy. The tumor was removed from each mouse, weighed and processed for histological evaluation. MEN4901/T-0128 was found to demonstrate a remarkable anti-tumor activity in each of these tumor models. At 1/3 of its MTD (maximum tolerated dose), MEN4901/T-0128 produced tumor shrinkage or suppression in the models of Mqnu-1, H-74, H-110, H48 and H-81 carcinoma with tumor growth inhibition rates (IR) of 99.7, 90.7, 98.5, 98.8 and 97.5%, respectively, as compared with untreated controls. MEN4901/T-0128 at its MTD also produced tumor shrinkage in the models of H-181 and H-204 carcinomas. On the other hand, CPT-11 (60 mg/kg, q7d x 4) was less effective in these models with IR ranging from 36.8 to 85.9%. The histological changes induced by MEN4901/T-0128 were extensive and much severer than those obtained with CPT-11. In our previous many experiments, the chemotherapy responses in xenografted mice showed good correlation with those in original patients. Therefore, the findings provide direct support that MEN4901/T-0128 is a broad-spectrum anti-tumor agent, demonstrate that it is more efficacious than CPT-11 and show that it is an excellent candidate for clinical trials for the treatment of solid tumors.

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Safety and efficacy of CPT11/FA/5-FU (ILF) versus ELF in previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction

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Combinations of CPT11 with folinic acid/5-fluorouracil (FA/5-FU) (ILF) have shown promising activity in advanced or metastatic colorectal and gastric cancer (AGC). Therefore, we evaluated prospectively toxicity and efficacy of ILF versus ELF (Etoposide/FA/5-FU) in AGC. As ELF was not inferior to FAMTX or cisplatin/5-FU in a recent EORTC trial, ELF served as internal control arm to avoid selection bias. Eligibility: Metastatic or locally advanced adenocarcinoma of the stomach or gastroesophageal junction; PS 0-2; no prior chemotherapy. Patients (pts) were randomized to ILF (CPT11 80 mg/m2, FA 500 mg/m2, 24h-5-FU 2000 mg/m2, d 1,8,15,22,29,36, q7w) or to ELF (E 120 mg/m2, FA 300 mg/m2, 5-FU 500 mg/m2, d1-3+22-24, q6w).

Results: Accrual is ongoing in this Phase II study. To date, 104 pts have been randomized. The median cycles were 3 for both arms (range 1-14). Toxicity (% of pts, worst grade) was evaluable for 45 (ILF) and 44 pts (ELF), respectively: Grade 1/2 for ILF/ELF: nausea 64%/52%, emesis 56%/30%, diarrhea 64%/23%, asthenia 38%/23%, neutropenia 29%/11%, alopecia 20%/41%, stomatitis 16%/29%, hand-foot syndrome 9%/2%. Grade 3/4 ILF/ELF: neutropenia 11%/36%, neutropenic fever 7%/9%, thrombopenia 2%/7%, alopecia 4%/20%, diarrhea 11%/0%, nausea 18%/7%, emesis 9%/2%, subileus 4%/0%, asthenia 2%/5%, thrombosis 2%/4%, 1 death occurred in ILF after 5 days diarrhea due to pts incompliance, 1 cerebrovascular ischemia during ELF. For response (% of pts) after 7 weeks, 58 pts (ILF/ELF 34/24) were evaluable: CR 3%/0%, PR 32%/17%, NC 41%/37%, PD 24%/38%; tumor control rate (CR+PR+NC) 76%/54%.

Conclusion: These preliminary results show, that ILF is at least as tolerable as ELF in advanced or metastatic gastric cancer. ILF can safely be given in an outpatient setting. Furthermore, ILF seems to be more effective than ELF against AGC. Study sponsor: Aventis, Germany

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A randomized, multinational phase III study in first line metastatic and locally recurrent gastric cancer (MGC): CPT-11 plus 5-Fluorouracil (5-FU)/Leucovorin (LV) versus Cisplatinum (CDDP) plus 5-FU

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CPT-11 is active as a single agent and in combination in gastro-intestinal cancer including in MGC. A previous randomized phase II part of this study (CPT-11/5-FU/LV vs CPT-11/CDDP) selected the CPT-11/5-FU/LV as the experimental arm for the phase III part. The following data on this arm were published: response rate 40% on per protocol population (60 patients (pts)), time to progression 6.5 months and overall survival 10.7 months on full analysis population (74 pts). The main objective of the phase III part was to compare time to progression (TTP) between CPT-11/5-FU/LV and CDDP/5-FU.

Pts and method: pts with gastric adenocarcinoma (diffuse, intestinal, linitis), including esophagogastric junction, measurable (M) and/or evaluable (E) metastatic or locally recurrent disease with at least 1 mesurable lesion, Karnofsky performance status (KPS) > 70, no prior palliative chemotherapy (CT), adjuvant CT allowed if ended more than 12 months before relapse. Biased-coin randomization accounted for center, liver involvement (yes/no), disease type (M/E), gastrectomy (yes/no) and weight loss (WL) ($\leq$5% vs > 5%).

Treatment: test arm, CPT-11 80 mg/m^2 day (D) 1, LV 500 mg/m^2 D1 and 5-FU 2000 mg/m^2 D1, weekly 6/7 weeks, and control arm CDDP 100 mg/m^2 D1, 5-FU 1000 mg/m^2/D D1 to D5, q4w. From June 2000 to March 2002, 337 pts were randomized.

Pt characteristics on treated population (333 pts): M/F = 70%/30%, median age 59 years (y), with 30% of pts e 65y, KPS median = 90 [70-100], 62% of pts with KPS = 100/90, 61% of pts with WL $\leq$ 5% (WL > 10% = 11% of pts), metastatic disease as per investigator 325 pts (98%), median number of organs involved 2, lymph nodes 219 pts (66%), liver 176 pts (53%), peritoneum 62 pts (19%), prior surgery 135 pts (curative 83 pts, palliative 52 pts). Nineteen pts had hemoglobin < 10g/dL before first infusion, 15 out of 19 did not have previous surgery on primary tumor. Safety and efficacy results including survival will be presented at the meeting.

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Postoperative mortality after surgery for gastro-intestinal cancer in octogenarians and nonagenarians

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As a result of the ageing of the general population, the number of elderly patients with cancer is increasing rapidly in Europe. In the Netherlands, 16% of male patients and 18% of female patients are 80 years or older at diagnosis. Survival is generally worse at higher age, mainly due to more advanced disease at diagnosis or due to less intensive treatment. Especially surgery is withheld, out of concern for postoperative morbidity and mortality. To support decisions about the option of surgical treatment in elderly patient with gastro-intestinal cancer, we studied postoperative mortality rates using