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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

data from a population-based cancer registry. Information on octogenarians and nonagenarians who underwent resection for gastric cancer or colorectal cancer in the period 1987-2000 was retrieved from the Rotterdam Cancer Registry. Postoperative mortality was defined as death within 30 days of operation and proportions were tabulated by tumour site and age-group. Differences between subgroups were evaluated with chi-square testing. This study comprises 2765 patients with colorectal cancer and 424 patients with gastric cancer. For colorectal cancer, postoperative mortality rates increased from 8% in patients aged 80 to 84 years, to 13% in patients aged 85 to 89 years and to 20% in nonagenarians (p

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## Increased bone marrow-derived endothelial cells in Barrett's metaplasia

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**Background:** Barrett's metaplasia represents the first step in a metaplasia-dysplasia-adenocarcinoma sequence. Oesophageal adenocarcinoma is characterized by early vascular invasion and metastasis. Circulating endothelial progenitor cells (EPCs) differentiate into mature endothelial cells in areas of injury and are involved in vasculogenesis and tissue repair. It is reported that these EPCs are mobilized from the bone marrow by various growth factors and cytokines including VEGF and IGF-1. We hypothesized that, circulating progenitor endothelial cells are upregulated in Barrett's metaplasia in response to elevated levels of serum VEGF and/or IGF-1.

**Methods:** Three groups of patients were studied. Group 1 (n=10) were normal controls; Group 2 (n=15) had benign reflux disease; Group 3(n=20) had Barrett's metaplasia. Fresh blood was analysed via flow cytometry using a panel of 3 antibodies: CD146, CD133 and CD45. Serum VEGF and IGF-1 was measure via ELISA. Data was analysed using ANOVA, LSD post-hoc statistics (SPSS software).

**Results:** EPCs were significantly increased in patients with Barrett's metaplasia (3.77 $\pm$ 0.89) versus benign reflux (1.4 $\pm$ 0.4) or controls (0.75 $\pm$ 0.41) ($p<0.5$). Circulating endothelial cells levels was greatest in Barrett's metaplasia but this increase was not significant (3.33 $\pm$ 1.04 vs. 1.9 $\pm$ 0.5 vs. 2 $\pm$ 0.46). Serum levels of VEGF and IGF-1 did not differ significantly between the patient groups.

**Conclusion:** Circulating progenitor cells but not mature endothelial cells were increased in Barrett's metaplasia. Since progenitor cells are pro-vasculogenic they may contribute to tumourigenesis and early microvascular invasion in Barrett's adenocarcinoma.

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## Oxaliplatin plus capecitabine in advanced biliary adenocarcinomas: a multicenter phase II trial

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**Background:** At present, no standard chemotherapy is established for the treatment of advanced adenocarcinomas of the biliary system. Therefore, we determined the efficacy and safety of oxaliplatin combined with capecitabine in patients (pts) with unresectable or metastatic gallbladder carcinoma (GBC) or intra-/ extrahepatic cholangiocarcinoma (CCC).

**Material and methods:** 41 pts (19M, 22F) were included. Median age was 63 yrs (range 28-74). Major eligibility: histologic proven, measurable disease, age $\leq$ 75 yrs, ECOG PS $\leq$2. A total number of 126 cycles (median: 5; range 1-11) of combined oxaliplatin (130 mg/m$^2$, d1) and capecitabine (2000 mg/m$^2$, d 1-14), were administered every 3 weeks for advanced GBC (14 pts), intrahepatic (12 pts) and extrahepatic CCC (15 pts). Pts were assessed for response according to WHO standard criteria initially after 2 cycles, thereafter every 3 cycles. Results: On 24 evaluable pts, 6 (25%) partial responses (PR) were observed; 14 pts (58%) had stable disease (NC); progressive disease (PD) was diagnosed in 4 pts (17%). Median overall survival and median time to progression were not reached. Grade 4 toxicities (WHO) were diarrhea in 1 pt (1% of cycles), peripheral sensory neuropathy in 2 pts (2%), and fever in 1 pt (1%); grade 3 toxicities were: diarrhea in 2 pts (2% of cycles), thrombocytopenia in 2 pts (4%), fever in 1 pt (1%), peripheral sensory neuropathy in 5 pts (12%). One patient was removed from study after six courses for an allergic reaction to oxaliplatin.

**Conclusions:** This phase II study demonstrates that an outpatient protocol of oxaliplatin plus capecitabine for advanced biliary tract adenocarcinomas is highly active (disease control rate: 83%) and well tolerated. Updated results will be presented at the meeting.

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## Outcomes in patients with metastatic colorectal cancer (MCRC) treated with infusional cpt-11/5fu/leucovorin (CFL)under a stringent positive-response dependent protocol: less treatment does not compromise outcome

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**Background:** CPT-11/5FU/leucovorin (CFL) has recently become the new reference regimen in patients with metastatic colorectal cancer (MCRC). However, the optimal duration of therapy with CFL in MCRC is not well defined and many experts recommend continuous treatment until disease progression or intolerance. We designed a study to examine 1) the efficacy of CFL in Chinese patients in the first-line setting 2) the impact on survival outcomes by limiting continuation of therapy only to patients with a positive response.

**Material and methods:** Between 8/2000 and 7/2001, 67 consecutive patients with MCRC and adequate haematological and renal/hepatic functions entered the study conducted in two affiliated institutions. Median age: 56, median ECOG: 0. Previous adjuvant chemotherapy: 30%. No. of organs/sites involved: 1-3 (median 2). Liver metastases: 71.6%. Regimen: fortnightly cycles of CFL: CPT-11 180mg/m2 q2h infusion D1, Leucovorin 200mg/m2 q2h D1+2, 5FU 400mg/m2 bolus/600mg/m2 q20hr infusion D1+2. Imaging evaluation (all CT) was performed after every 4 cycles and continuation of therapy was strictly response-dependent: PD after 4 cycles: stop chemotherapy; SD/PR/CR after 4 cycles: proceed to 8 (stop at 8 if CR after 4); PD/SD after 8 cycles: stop chemotherapy; PR/CR after 8 cycles: proceed to 12 (stop at 12 if CR after 8); PD/SD after 12 cycles: stop chemotherapy; PR/CR after 12 cycles: proceed to 16 (stop at 16 if CR after 12); PD/SD after 16 cycles: stop chemotherapy. No patients will receive >16 cycles regardless of their response status Response status was determined by comparing the latest imaging with the last CT, not the baseline CT, except for after the 4th cycle.

**Results:** 592 cycles of CFL were given. Median follow-up: 15months(m). Median no of cycles: 8. Median duration of treatment:18.4 weeks(w). Dose intensity of CPT-11: 96% and full-dose cycles in 92% of cycles. 62 pts evaluable for response (with >/=4cycles given). Response: Not Evaluable:7.5%, PD:15%, SD:34.3%, PR:34.3%, CR:8.95%. Median duration of response: 11.1m. Median progression-free survival: 9.2m. Median OS: 15.5m. 67 pts were evaluable for toxicities. Grade * neutropenia: 22% of cycles, fever: 1.8% of cycles, neutropenic fever: 7.5% pts and 0.8% of cycles and admission required in 3 pts. Diarrhea of any grade: 15.5% cycles and 64.2% pts. No G3/4 diarrhea but imodium use observed in 10.1% of cycles. Nausea/vomiting: all G1/2 and in 73% of pts and 49.3% of cycles. Salvage chemotherapy (mostly with oxaliplatin) given in 37.3% pts.

**Conclusions:** Compared with large international studies using first-line CFL in MCRC, the present regimen achieved comparable endpoints, especially in OS, with a shorter duration of treatment (e.g. 24.6w, Douillard et al, Lancet 2000; 23.8w Saltz et al, NEJM 2000). This response-dependent policy may have both economic and quality-of-life implications and further studies are warranted to further define the optimal treatment duration of CFL.