hypothesis, we checked the topoisomerase II alpha amount in tumors of mice given E7070 25 mg/kg alone, CPT-11 62.5mg/kg alone and their combination. In tumors treated with CPT-11 62.5mg/kg alone, topoisomerase II alpha amount increased more than 2-fold as compared to that in control tumor. E7070 25mg/kg in combination suppressed completely the increase of topoisomerase II alpha induced by CPT-11. The similar result was obtained in cultured cells. From these data, we consider that E7070 enhances cytotoxicity of CPT-11 by suppressing topoisomerase II alpha up-regulation to compensate for topoisomerase I inhibition by CPT-11.

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CB300919, a quinazoline-based antitumour agent with high activity in the CH1 human ovarian tumour xenograft

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CB300919 is a water-soluble analogue of CB30865, a quinazoline-based compound with an undefined mechanism of action. CB30865 displays a number of unusual properties including the induction of delayed, non-phase specific cell cycle arrest at 18 to 24h and non-cross resistance with other anticancer agents (Skelton et al, Brit J Cancer, 79, 1999). Further studies were continued with CB300919, an analogue considerably more water-soluble that could be evaluated *in vivo*. Properties include, 1) potent inhibition of several human tumour cell lines (IC_{50} ~1nM), 2) weak inhibition of the catalytic activity of the 26S proteasome (IC_{50} ~3000nM), and 3) concentrative uptake into cells (~1000nM after exposure to 10nM for 24h). Data suggests that the proteasome may not be the primary locus of action for the compound although non-classical, modulatory effects have not been ruled out (Allan et al, Proc Amer Assoc Cancer Res, 2002). CB300919 has been evaluated in the human CH1 ovarian tumour. The continuous exposure (96h) growth inhibition IC_{50} for these cells is 2nM. After short-exposures (4, 18 and 24h) the IC_{50}s (measured at 96h) are 23nM, 18nM and 4nM respectively. CB300919 induces a non-phase specific inhibition of the cell cycle between 16 and 24h in these cells. At ~24h the nuclear morphology changes, with the chromatin condensing around the nuclear membrane in a manner distinguishable from apoptosis, which was not induced (similar effects seen with CB30865). CB300919 has good pharmacokinetic properties in mice with a single i.p. dose of 10mg/kg giving plasma levels of 100nM at 6h and ~30nM at 24h (close to the limit of detection by HPLC. Nude mice bearing established CH1 tumours s.c. (~5x5mm) were treated (days 0 and 6) with CB300919; 3mg/kg had minimal effects but 6mg/kg was highly active (median growth delay >32 days). The 6mg/kg dose induced transient bodyweight loss (up to 10%). 9/12 mice treated with a single 6mg/kg i.p injection of CB300919 had no detectable tumour after 42 days (controls reached a median relative volume of ~24 by day 12). There was a 34 day median growth delay in the other tumours. In conclusion, CB300919 displays an exceptionally high level of activity against the CH1 ovarian carcinoma suggesting that the compound should be explored further for its activity in other tumour types, its toxicity profile and mechanism of action. This work has been sponsored by Cancer Research UK.

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A phase II study of MEN-10755 in patients with advanced or metastatic ovarian cancer

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Background: MEN 10755 is a third generation anthracycline which possesses a broader spectrum of antitumoral activity with respect to doxorubicin in gynecologic, lung, and prostate human tumors xenografted in nude mice.
Methods: The aim of the present study was to evaluate the activity and safety profile of MEN 10755 in patients (pts) with locally advanced or metastatic ovarian cancer failing 1st line platinum and/or taxane based chemotherapy, or relapsing < 6 months after prior chemotherapy. Eligible pts received MEN 10755 at the dose of 80 mg/m^2 (dose level 0) every 3 weeks over 30 minutes. Dose was escalated to 90 mg/m^2 (dose level 1) after 1st cycle in case of grade 0-1 toxicity. Response was assessed every 2 courses according to WHO criteria. Toxicity was graded according to CTC version 2.0. Blood and urine samples were taken at 1st cycle for pharmacokinetic (PK) analysis. Gehan's design was used for sample size determination.
Results: As of May 2002, 18 pts have been accrued. Baseline characteristics are available for 17 pts. Median age was 63 (range 45-75); 2 pts had PS 0, 10 pts had PS 1, 5 pts had PS 2. All pts had previously received surgery and systemic therapy. A total of 54 courses have been administered up to now. Drug related hematologic toxicity was moderate. In fact, only 6 episodes of G3-4 leukopenia, 1 episode of G3 febrile neutropenia, 10 episodes of uncomplicated G3-4 neutropenia, and 2 cases of G3 anemia occurred. Other at least possibly drug related G3-4 toxicities were: fatigue (four cases), stomatitis, general health deterioration, anorexia, nausea, vomiting, abdominal pain, hyponatremia (one case each). One pt had a confirmed partial response to treatment, 8 pts had stable disease, 5 pts had disease progression. Three pts were formally not evaluable for response, since one of them died of malignancy immediately after second course, another had no measurable lesions at re-evaluation, while the third had an early death, which was judged as possibly treatment-related, due to G4 stomatitis in presence of clinical signs of disease progression.
Conclusion: These early data indicate that MEN 10755 is feasible and active in this poor prognosis pt population. The study continues up to at least 15 evaluable pts. Final clinical and PK data will be presented at the meeting.

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A multicenter, phase I/II trial of hepatic intra-arterial delivery of doxorubicin hydrochloride adsorbed to magnetic targeted carriers in patients with hepatocellular carcinoma

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Purpose: To test the safety, maximum tolerated dose (MTD), pharmacokinetic profile, and preliminary tumor response following selective arterial infusion of doxorubicin hydrochloride adsorbed to Magnetic Targeted Carriers (MTC-DOX) under magnetic guidance.
Materials and Methods: A phase I/II dose escalation study was undertaken in 32 patients. MTC-DOX was delivered to the tumor via selective arterial catheterization. An external magnet with field strength of 5 kilogauss was positioned over the tumor to capture and then extravasate the material into the selected tumor parenchyma. Delivery to the targeted tumor was confirmed by magnetic resonance imaging (MRI). A range of tumor sizes was treated (cross-sectional areas of 4 to 222 cm^2). Hepatic computed tomography imaging (CT) was obtained prior to and * 28 days following therapy and analyzed for tumor response in accordance to NCI criteria. Patients were followed for survival and data was censored as of May 2002.
Results: Localization of MTC-DOX to the tumor was achieved in 30/32 patients (n=24 single treatment, n=6 two treatments, n=2 three treatments). An MTD has been defined as 60 mg DOX (total dose) and 600 mg MTC localized to the tumor area. The dose is limited by diminished arterial flow. Pharmacokinetic measurements show minimal evidence of DOX in systemic circulation. The most common adverse event is gastrointestinal and abdominal pain (64%). Preliminary response data (NCI criteria, measured at longest available follow up post final MTC-DOX treatment) in 20 lesions (17 patients) treated at doses $\geq$ 0.4 mg/cm^2 have been 1 complete response, 2 partial response, 7 minor response, 5 stable disease, and 5 progressive disease. Median survival in this same patient group is 11.5 months.
Conclusion: Intra-arterial administration of MTC-DOX in either single or multiple treatment cycles has no clinically significant toxicities, and warrants further clinical investigation in patients with hepatocellular carcinoma. Following studies will use dosing based on tumor area ($\geq$ 0.4 mg doxorubicin/cm^2) and multiple dosing cycles.