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In human tumor xenografts the resistance to ET-743 or to cisplatin can be overcome by giving the two drugs in combination

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ET-743 is a marine-derived antitumour agent isolated from Ecteinascidia turbinata. ET-743 binds to the minor groove of the DNA bending the DNA towards the major groove. In cancer cell lines growing *in vitro* the combination of ET-743 and cisplatin showed an additive or slightly synergistic effect evaluated by isobologram analysis. Instead, in several xenografts the combination was clearly synergistic. Specially, in xenografts that are partially sensitive to both drugs such as H&N (FADU), H-187 melanoma and TE 671 rhabdomyosarcoma, the effect of the combination was significantly better than the one achieved with each drug alone at the optimal dosage-schedule. In xenografts which were resistant either to ET-743 or to cisplatin such as A 2780 (1 A9), SKOV-3, HOC-8 ovarian cancer, LX1 non-small cell lung cancer and SKN-DZ neuroblastoma, the potentiation was clear-cut, suggesting that the combination can overcome the resistance mechanisms. The combination was also tested in the murine M5076 (M5) ovarian reticular cell sarcoma and a subline made resistant to cisplatin by repeated *in vivo* treatments (M5/DDP). Both in M5 and in M5/DDP the combination of ET743 and cisplatin produced a significant increase of the antitumor and antimetastatic effect that were markedly greater than those of each drug alone, although the effects were less marked in the latter resistant tumor. No consistent differences in the antitumor activity were observed when the two drugs were given simultaneously or when cisplatin was given first followed by ET-743 after 1h or in the opposite sequence. The toxicity of the combination, assessed by determining the weight loss, was moderate and reversible but greater than that of each drug alone given at the same dosage. In conclusion these data strongly support the development of the combination of ET-743 and cisplatin in clinic, also for tumors that are not very sensitive to ET-743 or cisplatin given alone.

Prodrugs

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Pharmacological study of CT-2103 (XyotaxTM), a poly(L-glutamic acid)-paclitaxel conjugate administered every 3 weeks or every 2 weeks in a phase I study

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CT-2103 is a water-soluble poly (L-glutamic acid)-paclitaxel conjugate, which has preferential tumour distribution and demonstrated antitumour activity in mice. In a two centre, Phase I, dose escalation study CT-2103 was administered as a thirty minute infusion every three weeks (Phase Ia). When the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) were established, a two-weekly schedule was employed (Phase Ib) with further investigation of the pharmacokinetic profile. Nineteen patients were entered into Phase Ia (30 to 720mg/m^2 CT-2103). Three patients have been treated on Phase Ib (480 mg/m^2 CT-2103, 177mg/m^2 paclitaxel equivalents). Plasma levels of CT-2103 and unconjugated paclitaxel were measured during cycles 1 and 2 of both schedules. In the initial dose-escalation (Phase Ia), DLT was seen in two of six patients (1 neutropaenia, 1 motor neuropathy) at 720mg/m^2 (266mg/m^2 paclitaxel equivalent). 630mg/m^2 (233mg/m^2 paclitaxel equivalent) was subsequently established as the MTD on a 3-weekly schedule. Grade 4 neutropaenia was observed at the 720 and 630mg/m^2 dose levels. Only one other grade 1 sensory neuropathy was observed. Three patients experienced hypersensitivity reactions to treatment. CT-2103 has a long plasma half-life of up to 162hr. The patients at 630 or 720mg/m^2 had prolonged elevated plasma concentrations of paclitaxel (0.35$\pm$0.17μM at 24 hr). A confirmed partial response has been seen after 2 cycles in a patient with mesothelioma at 480mg/m^2 (176mg/m^2 paclitaxel equivalent). This persisted until 2 months following completion of six cycles of treatment. In the Phase Ib study, plasma concentrations of CT-2103 and of paclitaxel were similar to those seen in Phase Ia at the same dose level. Neither CT-2103 nor paclitaxel accumulated in plasma following the second cycle of administration 2 weeks later. Clinical development with CT-2103 is proceeding.

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Enzyme-Catalyzed Therapeutic Activation (ECTA) NB1011 (Thymectacin™) selectively targets thymidylate synthase (TS) - overexpressing tumor cells: preclinical and phase I clinical results

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Resistance to fluoropyrimidine cancer chemotherapy is associated with an increase in expression of TS. NB1011 is a pronucleotide analog converted to (E)-5-(2-bromovinyl)-2'-deoxyuridine-5'-monophosphate (BVdUMP), a known substrate for TS. Enzymatic activation of BVdUMP by TS results in liberation of cytotoxic product(s) resulting in preferential cytotoxicity to TS-overexpressing tumor cells and human colorectal and breast carcinoma xenografts. This activity is associated with induction of p21 and BAX, and is associated with arrest in cell cycle progression (Neuteboom, et al., Mol Cancer Therap 1: 377-384, 2002). To test the hypothesis that NB1011 may be useful in the treatment of fluoropyrimidine-resistant cancers, we have initiated a phase I dose-escalation clinical trial for patients with advanced colorectal cancer with fluoropyrimidine failure within the prior 6 months. The primary endpoint of the study is assessment of safety and pharmacokinetics. Secondary endpoint is assessment of objective clinical response. Thus far, 15 subjects have been dosed with NB1011 (dose range 200mg/m^2 – 1250mg/m^2) given intravenously over 1 hour daily X 5 days (repeat cycles every 28 days for patients with stable or responsive disease). Over this dose range, plasma pharmacokinetics appear linear with mean cycle 1 Cmax = 3495ng/mL at 200mg/m^2 and 10,469ng/mL at 800mg/m^2. Mean AUC at 200mg/m^2 is 2499ng-h/mL and is 9429 ng-h/mL at 800mg/m^2. The half life of NB1011 is just under 1 hour; however half life of metabolite BVDU is ~12 hours with mean BVDU day 1 Cmax = 9190 ng/mL and AUC = 13932 ng-h/mL at 800mg/m^2 dose level. NB1011 is clinically well tolerated at all dose levels tested, without significant hematologic toxicity. The maximum tolerated dose has not yet been established. There have been 7 serious adverse event reports, including: ascites, respiratory distress, vomiting, possible bowel obstruction, surgical procedure (transurethral prostate resection), hyperglycemia, and allergic reaction. One possible DLT event was recorded (pneumonia) at the 800mg/m^2 dose level; however, cohort expansion at this level showed no further DLT events. Four patients with stable disease received multiple cycles of NB1011: one received 5 cycles at 200mg/m^2; two received 2 cycles at 800mg/m^2; one received 3 cycles at 800mg/m^2. Ten patients have discontinued secondary to disease progression; 5 patients remain active on study as of 13/6/2002. NB1011 dose escalation is continuing with cohorts of 3 patients per dose level; updated data will be presented.

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Phase 2 Study of TLK286 (GST P1-1 Activated Glutathione Analog) in patients with platinum and paclitaxel refractory/resistant advanced epithelial ovarian cancer

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Objectives: To determine the objective tumor response rate (ORR), disease stabilization rate, safety and survival of patients with platinum and paclitaxel refractory or resistant ovarian cancer treated with TLK286.
Methods: TLK286 is a glutathione analog activated in cancer cells by glutathione S-transferase P1-1, resulting in apoptosis through the stress kinase pathway. Patients with ovarian cancer resistant or refractory to paclitaxel and platinum-based chemotherapy were to be enrolled in this multicenter, Fleming two-stage design study. TLK286 was given intravenously at 1,000 mg/m^2 once every 3 weeks until tumor progression or unacceptable toxicities. ORR was assessed by RECIST. Toxicity was graded by NCI-CTC. Survival was estimated by Kaplan-Meier Analysis.
Results: Thirty-six patients, ECOG 0-1, prior chemotherapy regimens, median 3 (range 1-7), were enrolled between June 2001 and March 2002. A to-