our work has focused on developing approaches to enhance T cell regeneration as a means for targeting minimal residual neoplastic disease. IL7 is a potent immunorestorative which enhances both thymic-dependent and thymic-independent pathways of T cell regeneration in mice. Administration of IL7 to normal primates resulted in dramatic increases in total body T cell number as evidenced by 3-5 fold increases in circulating CD4+ and CD8+ T cell numbers and reversible lymphadenopathy. Further study of these effects revealed that both naive and memory cells increased in IL7 treated monkeys, that there was increased peripheral T cell cycling as evidenced by increased Ki-67 expression and increased BrdU incorporation upon ex vivo culture of cells from IL7 treated primates. Furthermore, TREC levels declined following IL7 therapy. Thus, IL7 therapy induced widespread T cell cycling, a biologic effect which is predicted to result in expansion of antigen specific T cell clones. In order to test whether IL7s effects on T cell cycling could enhance antigen specific responses, we administered IL7 in concert with a dendritic cell based vaccine in a murine model. We observed substantial increases in the numbers of both antigen specific CD8+ cells which responded to both immunodominant and subdominant Class I epitopes and CD4+ cells responding to immunodominant Class II epitopes. IL7 was a more potent vaccine adjuvant than IL2 or IL15. Furthermore, when tumor bearing animals were treated with IL7, we observed enhanced reactivity toward expressed tumor antigens. These results suggest that IL7 may be beneficial in the context of cancer therapy due to its capacity to enhance immune reconstitution, enhance immune reactivity toward weak tumor antigens and potentially to enhance the effectiveness of tumor vaccines.

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TNF revisted: New perspectives for a successful antivascular cancer therapy

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Clinical Program: On the basis of the spectacular results of a multicenter trial in Europe TNF was approved by the EMEA for application of TNF in the Isolated Limb Perfusion (ILP) setting in combination with melphalan for irresectable soft tissue sarcomas of the extremities. In 246 patients limb salvage was achieved in the 71% of patients corresponding to a 76% objective response rate (CR+PR). The procedure is performed in over 30 cancer centers in Europe. It appeared from the clinical studies that a very rapid selective destruction of the tumor-associated vasculature (TAV) was the essential mechanism by which TNF mediates its antitumor effects in combination with melphalan.
Preclinical Models elucidating antitumor mechanisms: A number of crucial observations have been made in new tumor models in Rotterdam: the vasculo-toxic effects of the combination of TNF melphalan lead to haemorrhagic necrosis of the tumors but more importantly we have demonstrated that the addition of high dose TNF to the perfusate results in a 4-6 fold increased uptake by the tumor of the cytostatic drugs. This is true with different tumors in different tumor models and organ settings:
Isolated Liver Perfusion Setting: The same synergy between TNF and melphalan is observed. A very high antitumor response rate of almost 80 percent was observed in studies in patients.
Genetherapy: We have shown that Isolated limb perfusion is an interesting method for new treatment modalities such as adenoviral-vector mediated genetherapy.Other new developments in the field of TNF-based genetherapy have brought very interesting results recently. After intratumoral therapy with the adenoviral vector-TNF-gene construct "TNFerade" (Genvec) in combination with radiotherapy impressive antitumor effects have been observed in various large tumours in a broad phase I program.
Liposomes and New Opportunities for Systemic Application of TNF: We have demonstrated thatlow doses (clnically applicable) of TNF in combination with doxorubicin cointaining liposomes enhanced the uptake of the liposomes in the tumor and the intratumoral drug concentration significantly, resulting in a highly significant antitumor effect This should be the basis to explore the utility of TNF at low doses in combination with liposomes in phase I-II studies.
Conclusions: TNF-based antivascular therapy of cancer is here to stay and its potential needs to be studied further.

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IL-15 mediates good and bad

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Abstract not received.

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First results of a phase I and pharmacokinetic study of SU011248, a novel oral anti-angiogenic agent, in patients with advanced solid tumours

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SU011248 is a novel orally bioavailable indolinone that inhibits VEGFR (Flk-1/KDR), PDGFR alpha and β, Flt3, and c-kit tyrosine kinase activity at nanomolar concentrations. Dose-dependent antitumor activity was measured in a variety of human tumor xenografts in nude mice, and was well tolerated in these studies. In this clinical study, escalating doses of SU011248 were given orally for 28 consecutive days followed by a 2-week rest period to patients (pts) with advanced malignancies not amenable to conventional therapy. Based on preclinical toxicology data, the starting dose was 30mg/m^2 every other day (4 pts), then further escalated to daily 30mg/m^2 (6 pts), 42mg/m^2 (4 pts), and 59mg/m^2 (3 pts). Doses escalations were 100% and 40% in the presence of grade 0-1 and grade 2 toxicity, respectively. Seventeen pts (M/F: 9/8, median age: 53, range 33-73; median PS: 100, range 60-100) were entered including 3 renal cell carcinomas, 2 non-small cell lung cancer, 2 neuro-endocrine tumors, 2 uterine cancer, 2 angiosarcoma, 2 mesothelioma, 1 pancreatic carcinoma, 1 breast cancer, 1 colorectal cancer, 1 undifferentiated nasopharyngeal carcinoma. At the dose of 30mg/m^2 daily, grade 3 edema was observed in 1/6 pts allowing to resume dose escalation. SU011248 was well tolerated up to the dose of 42mg/m^2. At the dose of 42mg/m^2, drug-related toxicities were grade 2 asthenia (4 pts), grade 2 thrombocytopenia (1 pt), grade 2 neutropenia (1 pt), and grade 2 diarrhea (1pt). Grade 2 sore tongue and mouth was observed at the highest doses. Consistent with a high volume of distribution of SU011248, a sustained and dose-dependent tanned gold coloration of the skin was observed in several pts. Progressive hair discoloration was observed in pts with the highest plasma levels, suggesting an effect on tyrosine kinase receptor driven tyrosinase transcription in the hair follicles. Pharmacokinetic data indicate good oral bioavailability with modest intra/inter-patient variability of SU011248 and its metabolite. Target plasma concentrations determined preclinically for activity were achieved in this study. Objective responses were observed in one pt at the first dose level and in 3 pts at the dose of 42mg/m^2 daily, with a prolonged 6-month tumor stabilization in a pt treated at 30mg/m^2 daily. The dose escalation is ongoing at the dose of 59mg/m^2 to define the maximum tolerated dose. The fair toxicity profile and preliminary evidence of activity encourage further exploration of SU011248.

Wednesday 20 November

Poster Sessions

Anthracyclines

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Combination of novel sulfonamide anticancer drug, E7070, with CPT-11 "antitumor effect and synergistic mechanism"

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The novel sulfonamide anticancer drug E7070, N-(-3-chloro-7-indolyl)-1, 4-benzenedisulfonamide, has demonstrated promising antitumor efficacy in pre-clinical models on the basis of its unique mode of action and antitumor spectrum. The phase II studies of E7070 monotherapy have been conducted in Europe and the US. As we reported previously, the combination of E7070 with CPT-11 exhibited synergistic antitumor efficacy in human tumor xenograft models in mice. There was no difference between monotherapy and combination in terms of pharmacokinetic profile of E7070, CPT-11 and SN38 (active metabolite of CPT-11). The synergistic effect of E7070-CPT-11 combination was observed in cultured cells, by the Combination Index method. It has been reported that SN38 treatment causes a transient up-regulation of topoisomerase II alpha mRNA. In our GeneChip analysis, E7070 was shown to decrease topoisomerase II alpha mRNA. Therefore, it was considered that synergism in E7070-CPT-11 combination occurred through the modulation of topoisomerase II alpha amount. To address this

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.