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