presence secondary antibody or FcR-expressing effector cells. The KMTR2 antibody formed supracomplexes with soluble recombinant and membrane-anchored TRAIL-R2 and enhanced clustering of TRAIL-R2 on the surface of cell without crosslinking. The KMTR2 antibody was dramatically efficacious in reducing establish human xenograft tumors in vivo when compared to other anti-TRAIL-R2 antibodies of similar isotype and affinity suggesting the agonistic anti-tumor activity is independent of host effector function. These results indicate that this monoclonal agonist antibody can direct antibody-dependent oligomerization of TRAIL-R2 and initiates efficient apoptotic signaling and tumor regression.

311 POSTER

Anti-cancer efficacy of a functional monoclonal antibody targeting melanoma-associated chondroitin sulfate proteoglycan

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Melanoma-associated chondroitin sulfate proteoglycan (MCSP) is a glycoprotein-proteoglycan complex present on the surface of melanoma cells, and some other cancers, either as a free glycoprotein or modified by the addition of chondroitin sulfate. MCSP has been purported to have a role in cancer progression by enhancing adhesion and invasion of melanoma cells through multiple mechanisms. AR11BD-2E11–2 is a functional monoclonal antibody that targets MCSP, which was discovered using the ARIUS FunctionFIRST™ platform. Mice were immunized with human breast cancer cells. The functional screening process identified a hybridoma that produces an antibody that is cytotoxic to breast and ovarian cancer cells but not to normal cells. AR11BD-2E11–2 was evaluated *in vivo* in order to further examine its anti-cancer effects. In a xenograft MCF-7 breast cancer model, AR11BD-2E11–2 suppressed tumor volume by 80% compared to isotype control-treated mice, and conferred a significant survival benefit. In a second xenograft model, the increase in body weight due to ascites was used as a marker of OVCAR-3 ovarian cancer progression. The mice in the control-treated group showed a 60% tumor-related weight gain, while the AR11BD-2E11–2 treated mice showed a significantly lower weight gain of 40%, and had a significantly longer mean survival time. Antigen characterization was carried out using immunoprecipitation followed by mass spectrometry. The identity of the target antigen for AR11BD-2E11–2 was determined to be MCSP. The IHC staining pattern of the epitope recognized by AR11BD-2E11–2 on frozen human breast cancer sections was found to be highly specific for malignant cells. On a panel of frozen human normal tissues, staining with AR11BD-2E11–2 was generally restricted to the smooth muscle fibers of blood vessels. The generation of a functional anti-cancer antibody that recognizes MCSP has confirmed the relevance of this antigen as a target for cancer therapy, and has demonstrated its potential as a target in ovarian and breast cancer.

312 POSTER

Pilot study of the use of Infliximab for fatigue in advanced cancer

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Background: Many patients with advanced cancer experience fatigue, some with cachexia. There is evidence that the pro-inflammatory cytokine Tumour Necrosis Factor alpha (TNF-α) may be a mediator[1].
Infliximab (Remicade®) is a chimeric monoclonal antibody to TNF-α licensed for the treatment of Crohn's disease and rheumatoid arthritis. We investigated whether Infliximab used in advanced cancer would improve measurable fatigue.
Method: Seventeen patients with advanced cancer (various solid tumours, age range 42–82 years) scoring over the threshold on the Fatigue Severity Scale (FSS) (Stone et al[2]) were recruited from a Specialist Palliative Care Unit in London (patients with specific risk factors were excluded[3]). Subjects received 5mg/kg Infliximab intravenously, repeated at 4 weekly intervals so long as there was clinical improvement. On each visit measures of fatigue, appetite, body mass, performance status, quality of life, depression, pain, serum TNF-α and leptin levels were recorded. Serum will be analyzed for the presence of TNF-α gene promoter polymorphisms. Treatment with Infliximab was discontinued if any intolerable adverse effects were reported or when clinical benefit ceased.
Results: Six patients reported subjective clinical benefit. Four patients showed greater than 20% reduction in fatigue severity score (primary outcome) 4 weeks after first treatment [Figure 1].
Four patients died during the study, 1 due to disease progression, 1 possibly due to adverse effects of treatment (acute infection) and 2 from causes probably unrelated to treatment (cerebral infarct and myocardial infarction). 8 treated patients died from disease progression after completing the study. 5 treated patients remain alive.
Secondary outcome measures (change in appetite, body mass, mood, pain, QOL, serum TNF-α and leptin) showed no emerging pattern.

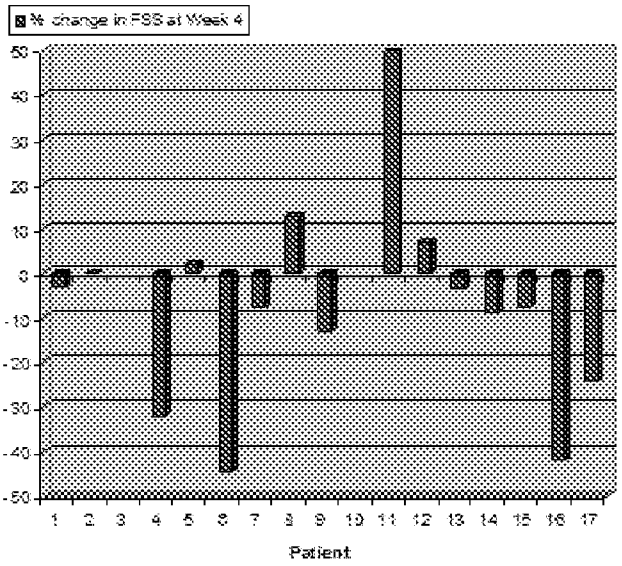

Figure 1: Percentage change in FSS 4 weeks after first treatment.

Note: a negative change in FSS score indicates decreasing fatigue
Conclusions: Numbers in this pilot study are small and the results therefore are descriptive. A few patients showed clinical benefit but initial data are inconclusive. There may be an improvement in fatigue in a selected group of patients with advanced cancer. It is hoped that further data analysis may determine future research questions in this area.

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313 POSTER

Mono- and combination-therapeutic activity of panitumumab (ABX-EGF) on human A431 epidermoid and HT-29 colon carcinoma xenografts: correlation with pharmacodynamic parameters

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Background: Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor. Overexpression has been correlated with aggressiveness and poor prognosis in many tumor types including colon. Panitumumab, a fully human antibody, binds to the EGFR with high affinity ($5x10^{-11}$ M) preventing ligand-induced autophosphorylation resulting in arrest of tumor cell proliferation and increased apoptosis in some cases [1,2]. The purpose of this study was to examine the effects of panitumumab as a monotherapy and in combination with irinotecan in the HT-29 xenograft tumor model of colon cancer.
Methods: Inhibition of ligand-induced autophosphorylation was determined *in vitro* and *in vivo*. *In vitro*, A431 and HT-29 cells were treated with 0.5, 2, and 10 μg/ml of panitumumab for one hour prior to 100 ng/ml EGF stimulation. *In vivo*, tumor-bearing mice were treated with 100 ng of *rh*EGF 30 minutes prior to removing the tumor and measuring the phosphorylation of EGFR. To measure efficacy, tumor bearing were treated twice per week with panitumumab at 100, 200 or 500 μg/mouse, or panitumumab in combination with 100 mg/kg irinotecan once per week. Immunohistochemistry was performed to evaluate the extent of panitumumab penetration into tumors and changes in pMAPK and Ki67 staining as a result of panitumumab administration.
Results: *In vitro,* panitumumab treatment resulted in a dose-dependent cytostatic effect in both A431 and HT-29 carcinoma cells and a concomitant reduction in ligand-induced phosphorylation of EGFR both *in vitro* and *in vivo*. Immunohistochemistry demonstrated dose-dependent tumor