Methods: This phase 1 study evaluates safety, tolerability, pharmacokinetics/-dynamics and anti-tumor effects of MT110 in pts with advanced solid tumors expressing EpCAM. A dose escalation with 3−6 pts per cohort is used to determine the maximum tolerated dose (MTD). Starting dose was 1 μg/d given as continuous i.v. infusion for 1 or more 28-day cycles.
Results: To date, a total of 14 pts (3 gastric, 9 CRC, 1 NSCLC, 1 SCLC; up to 7 previous chemotherapies) have been treated in 4 cohorts up to 10 μg/d. Overall, MT110 was very well tolerated with few clinical adverse events. All but 1 of the treated pts completed at least 4 wks of therapy. Besides initial lymphopenia, an increase in liver enzymes, up to grade 3/4, was the most frequent laboratory abnormality. These events were transient in nature and not found to impact on liver synthesis nor were any abnormal results seen in imaging (ultrasound, CT scan, and/or MRI of the liver). The increase in liver enzymes did not occur on re-exposure to MT110. Concomitant corticosteroids were found to mitigate increases in liver enzymes and further optimization of the treatment schedule is currently ongoing. As observed with blinatumomab, MT110 caused a rapid redistribution of lymphocytes shortly after start of infusion. Signs of T cell expansion/-activation were seen in pts with clinical benefit after 4 wks. Disease stabilization according to RECIST was confirmed in 6 of 13 pts, lasting 12 wks in median. In one patient, a lung metastasis was resected 11 wks after initiation of MT110 treatment. Immunohistochemistry revealed tumor cell necrosis and a massive T cell infiltration as possible evidence of MT110 activity. None of the pts developed antibodies against MT110.
Conclusion: First signs of biological activity of MT110 in pts with advanced EpCAM-expressing tumors have been observed at clinically well tolerated doses. Optimization of the treatment schedule and evaluation of BiTE antibody MT110 at higher doses is currently ongoing.

References

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1255 POSTER

Clinical and preclinical development of 4SC-201, a new oral histone deacetylase (HDAC) inhibitor

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Background: 4SC-201 is a new, specific, potent, pan-HDAC inhibitor under evaluation as mono or combination therapy for solid and haematological malignancies.
Methods: Preclinical studies of anti-cancer activity of 4SC-201 alone or in combination with other cancer drugs in cell lines and in xenograft models were performed. In a First-in-Man (FIM) study, patients (pts) with advanced refractory solid tumours were dosed once daily, d1−5, in a 14-day cycle in sequential cohorts. Objectives included determination of safety, tolerability, pharmacokinetics (PK), pharmacodynamics, maximum tolerated dose and anti-cancer activity.
Results: In preclinical studies 4SC-201 demonstrated potent activity across a broad range of tumour cell lines originated from different cancers. Xenograft studies revealed strong dose-dependent anti-tumour activity and good tolerability. 4SC-201 enhanced the anti-tumour activity of a variety of approved cancer drugs when tested in combination. In a FIM study, 18 pts were treated at dose levels of 100 mg, 200 mg, 400 mg, 600 mg (3 pts each) and 800 mg (6 pts). Grade 3 DLT of nausea and vomiting occurred in 1 pt dosed at 800 mg. Most common adverse events included nausea, vomiting and fatigue. 8 of 9 pts treated at the two highest dose levels had stable disease during the main phase of the study (4 cycles). A patient with metastatic thymoma (minor response) continued treatment until cycle 18 and stopped without evidence of progressive disease. Another patient with liposarcoma remains on treatment for over a year. Following single oral administration high plasma exposure of 4SC-201 was obtained indicating good bioavailability with a dose-proportional PK profile and low inter-individual variability for all dose levels. Biomarker assays revealed that HDAC inhibition in PBMC ranged from 50 to 100% and was dose-dependent.
Conclusions: In summary, preclinical studies testing 4SC-201 alone or in combination with several cancer drugs showed substantial synergistic anti-tumour activity. Phase I data confirmed the favorable oral drug profile and good tolerability of 4SC-201. Efficient target modulation and anti-tumour activity were observed. Consequently, phase II development will be initiated aiming for clinical proof-of-concept in specific tumour indications, including combination studies with e.g. STIs such as sorafenib or chemotherapeutic agents.

1256 POSTER

Phase I trial of oral Deforolimus in combination with Bevacizumab in patients with advanced solid tumours

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Background: Deforolimus (DF) is a unique inhibitor of mammalian target of rapamycin (mTOR). One of mTOR's many functions is to regulate vascular endothelial growth factor (VEGF) secretion and VEGF receptor (VEGFR) signaling in endothelial target cells. Combination of bevacizumab (BV), a humanized monoclonal antibody that inhibits VEGF, with DF would be expected to diminish VEGF production and VEGFR signaling, and offer a promising therapeutic approach. The goal of the study was to identify an optimal phase 2 dose of DF combined with each of the two approved BV regimens.
Methods: Three dose combinations were tested in this phase 1, dose-escalation design in adult patients with advanced solid cancers (Clinical Trials ID: NCT00781846). The 3 dose combinations were: Cohort 1, DF 30 mg PO daily for 5 days/week (QD×5/wk) with BV 10 mg/kg IV every 2 weeks (4 wk cycles); Cohort 2a: DF 40 mg PO QD×5/wk and BV 10 mg/kg IV Q2 wks (4 wk cycles); and Cohort 2b: DF 40 mg PO QD×5/wk and BV 15 mg/kg IV Q3 wks (3 wk cycles). DLTs were protocol-defined events related to study drug that occurred during cycle 1.
Results: Seventeen patients (10F, 7M) were enrolled and treated; 16 were evaluable for DLTs (3 in Cohort 1; 6 in Cohort 2a; 7 in Cohort 2b). Median age was 60 years (range 24−72). Patients had 12 solid tumor types: 3 had ovarian carcinoma, 2 leiomyosarcoma, 2 pancreatic cancer, 2 colorectal carcinoma, 2 uterine carcinoma, and 6 had other distinct tumor types. No DLTs were noted in the 3 cohorts. One patient had 2 SAEs (G2 abdominal wall abscess and a G2 colonic fistula) related to BV per the investigator's assessment. Ten patients experienced treatment related AEs. The most common AEs were stomatitis, mucosal inflammation, neutropenia, thrombocytopenia, proteinuria, and headache. In this heavily pre-treated population, the median duration of treatment is currently 7 wks (range 2.3−24 wks). Six patients have discontinued treatment (4 for PD and 2 for unrelated SAEs) and 11 remain on treatment. Two patients have had stable disease for more than 4 months (1 patient with pancreatic cancer had a 13% reduction in tumor for more than 6 months and a patient with ovarian carcinoma that has been stable for 4+ months).
Conclusions: DF 40 mg QDx5/wk combined with two approved dosages and schedules (10 mg/kg q2 wks & 15 mg/kg q3 wks) of BV is feasible, well tolerated, and shows potential anti-tumor activity. The combination of DF/BV warrants further investigation in phase 2 trials.

1257 POSTER

Retrospective analysis of unplanned hospital admissions: an early surrogate indicator of patient (pt) attrition in phase-I trials

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Background: We have previously reported a high Royal Marsden Hospital (RMH) prognostic score (RPS) of 2−3 predicts 90-day mortality and reduced overall survival (Arkenau et al BJC & EJC 2008). In this study, we explored the significance of unplanned hospital admissions (UHA) as a potential surrogate indicator of poor clinical outcome.
Methods: All pts admitted to RMH Phase I Unit, UK, during 2-month intervals over 3 consecutive years were included in this analysis (2005–2007). We collated pt baseline characteristics, demographic and laboratory profiles, reasons for hospital admissions and relevant clinical trial data.
Results: A total of 172 pts accounting for 310 admissions were seen on the Phase I unit during the stipulated time periods (amounting to 6 months in total). Median age: 61 years (range: 19−84); male to female admissions ratio 1.3:1. Pts were on trials of single-agent targeted therapies (69%), cytotoxic combinations (26%), vaccine/viruses (3%) and hormonal modulation (2%). Reasons for planned admissions (n = 246) included treatment commencement, PK/PD sampling, paired pre/post treatment biopsies and insertion of central lines. 20.6% (64/310) of overall admissions were unplanned: 50 (78%) were due to disease-associated symptoms/complications and 14 (22%) treatment-related toxicities (TRT). 71% of pts with TRT were on cytotoxic combination trials. Median duration of UHA was 2 days (range:1−20) and there was no relation between length of stay and predicted outcome. 78% of pts in the UHA cohort had a high RPS of 2−3 (i.e. poor outcome) vs 43% in patients whose admission was