the combination regimen JANEX-1 plus the standard anti-GVHD drug Methotrexate (MTX) was more effective than JANEX-1 alone or MTX alone. More than half of the C57BL/6 recipients receiving this most effective GVHD prophylaxis remained alive and healthy throughout the 85-day observation period with a cumulative survival probability of 70±10%. Taken together, these results indicate that targeting JAK3 in alloreactive donor lymphocytes with a chemical inhibitor such as JANEX-1 may attenuate the severity of GVHD after BMT.

393 POSTER

A phase II study of OSI-774 given in combination with carboplatin in patients with recurrent ovarian cancer (NCIC IND.149)

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Approximately 50% of ovarian cancers have elevated levels of epidermal growth factor receptor (EGFR) and this overexpression is correlated with a poor prognosis. Preclinical evidence suggests that EGFR tyrosine kinase inhibitors (TKI's), such as OSI-774, may potentiate the antitumour effects of cytotoxic agents, including carboplatin. EGFR TKI's may also beneficially modulate drug resistance, and EGFR may be causal in the development of resistance to platinum. Blocking the EGFR could thus potentially reverse drug resistance.

This study was designed to determine the efficacy of the addition of OSI-774 to carboplatin in patients with recurrent ovarian cancer. Patients enrolled on this study had recurrent ovarian cancer with measurable disease. They may have had up to 2 prior chemotherapy regimens, one of which must have contained platinum, and they must have responded to prior platinum therapy. The patients were treated with OSI-774 150 mg daily on a continuous dosing schedule, and carboplatin at an AUC of 5 every 21 days. Patients were stratified by platinum sensitivity (>6 months from last dose of platinum agent to relapse). The primary objective of the study was to assess the response rate of OSI-774 in patients with recurrent ovarian cancer who were receiving carboplatin.

Fifty patients with recurrent ovarian cancer entered the study, 33 in the platinum sensitive arm and 17 in the platinum-resistant arm. Of patients evaluable for response, there were 16 partial responses (PR) of 24 evaluable for response (67% response rate (RR)) in the platinum-sensitive arm, and 1 PR of 14 evaluable for response (7% RR) (Table 1). The hematologic and biochemical toxicities were those expected with carboplatin and OSI-774. Of 21 patients who had tumour samples tested for EGFR status, 17 (81%) tested positive. A review of the responses is ongoing and the results will be presented.

Table 1. Response rate

Response	Platinum Sensitive (n=24)	Platinum resistant (n=14)
CR	1* (4%)	0
PR	15 (63%)	1
SD	8	10
PD	0	3
Overall RR	67% (95% CI 45–84%)	7% (95% CI 0.2–33.8%)

*CA-125 remains elevated.

The combination of OSI-774 and carboplatin was active in patients with platinum sensitive disease, but not in platinum resistant disease. The toxicities seen were those expected with carboplatin and OSI-774. The majority of patients had EGFR+ tumours. To determine the effect of OSI-774 in enhancing the efficacy of carboplatin in patients with platinum-sensitive disease, a randomized controlled combination study is under development.

394 POSTER

Inhibition of Kit-dependent tumor growth by OSI-930, a novel selective tyrosine kinase inhibitor

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The receptor tyrosine kinase Kit has been implicated in multiple human tumor types. These include GIST and mast cell leukemia in which mutant, constitutively active forms of Kit are thought to play a major role in tumor progression. In addition, in small-cell lung cancer (SCLC) co-expression of wild-type Kit and its ligand (SCF) is thought to provide continuous growth and survival signals that may contribute to tumor growth. We have recently identified a series of 2,3-substituted thiophenes with potent inhibitory activity against Kit, as well as the related tyrosine kinases KDR and PDGFRa/b, and OSI-930 has emerged from this series of compounds as an IND-track clinical candidate. In cell-based assays OSI-930 has been found to inhibit with low nanoMolar potency both the wild-type enzyme found in SCLC cells (H526) and the exon 11 juxtamembrane mutant form of Kit (V560G) found in HMC-1 cells, which is similar to the most common type of mutation identified in tumors from GIST patients. Furthermore, OSI-930 inhibits the growth of both HMC-1 and H526 cell lines in vitro and potently induces apoptosis in HMC-1 cells, where the mutant Kit enzyme appears to provide an essential cell survival signal. These in vitro effects correlated with potent effects of OSI-930 on the phosphorylation state of the downstream signaling effectors Erk1/2, Akt and S6, which are established mediators of cell growth and survival pathways. Following oral dosing of OSI-930 in mice, a reduction in the level of tyrosine phosphorylation of Kit has been observed in extracts prepared from HMC-1 and H526 tumor xenografts, and this effect could be maintained for up to 24h. The ability of OSI-930 to inhibit Kit in vivo correlated with potent anti-tumor activity in both the mutant Kit-expressing HMC-1 model and wild-type Kit-expressing SCLC models (H526, H209 and WBA). These results suggest that OSI-930 may have clinical utility in tumor types that are dependent on Kit tyrosine kinase activity.

395 POSTER

Blocking the interaction between HIF-1alpha and p300 by a 32 amino acid fragment of p35srj inhibits the hypoxia induced transcriptional activity of HIF-1alpha in human U87MG glioma cells

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The Hypoxia Inducible Factor-1α (HIF-1α) is the oxygen- and growth factor-regulated subunit of HIF, an αβ-heterodimer and a transcriptional activator of several genes involved in the regulation of angiogenesis, glycolysis, and tissue invasion. The binding of the carboxyl terminal activation domain of HIF-1α (TAD-C) to the transcriptional co-activator proteins p300 and CBP (CREB-binding protein) is essential for the transcription of HIF target genes and occurs at the cysteine-histidine-rich CH1 domain of p300 and CBP. A 35 kD nuclear protein containing a serine rich junction (p35srj) is constitutively bound via its amino acid residues 224–255 to the CH1 domain of p300, inhibiting the binding of HIF-1α to p300. As p35srj is encoded by a HIF-1 regulated gene, and the binding of p35srj to p300 restricts the access of HIF-1α to p300, it is believed that p35srj is a natural feedback inhibitor of the activation of HIF-1α (Bhattacharya, S., et al. Genes and Development. 13:64–75, 1999). We have confirmed that p35srj (224–255) inhibited the interaction of the TAD-C domain of HIF-1α and the CH1 domain of p300, using an Amplified Luminescence Proximity Homogeneous Assay (AlphaScreen™). Coupling p35srj (224–255) to a cell permeable peptide resulted in a product that inhibited the hypoxia-induced transcriptional activity of HIF-1α, as determined by a reporter gene assay in the human U87MG glioma cell line. We believe that the interaction of HIF-1α with the p300 co-activator protein can be a target for the development of new therapeutic agents that inhibit the hypoxia-induced transcriptional activity of HIF-1α.