Table 1 presents the models' predictions from the relationship between SB-715992 dose and ANC for a selected subset of doses.

Table 1. Predicted response as a function of dose

Dose (mg/m^2)	Decrease ANC (%) (Emax model) with 90% CI	Probability (%) of Gr 4 neutropenia (ordinal model) with 90% CI
10	63.4 (54.4, 72.4)	1.9 (0.3, 12.5)
12.5	73.2 (64.8, 81.6)	7.9 (2.0, 26.2)
18	85.2 (77.2, 93.1)	68.7 (49.1, 83.3)
21	88.7 (81.3, 96.1)	92.8 (78.4, 97.9)

Conclusion: Exploratory PK/PD analysis suggests that dose (mg/m^2), total dose (mg), and AUC (log transformed) or Cmax (log transformed) are important independent predictors of a decline in ANC when evaluated separately. Dose is the most predictive of ANC decrease after SB-715992 administration. The Emax model and ordinal models are useful to predict ANC response after SB-715992 doses are administered once every 21 days.

56 POSTER

Hsp90-targeted therapy for small cell lung cancer

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Nearly all small cell lung cancer (SCLC) cell lines and tumors demonstrate functional inactivation of the retinoblastoma gene (RB). As all normal cells in the body express functional Rb, a drug that specifically targets cells with mutationally inactive or deleted Rb would represent a potential targeted approach for patients with SCLC. Cells with defective Rb treated with an Hsp90 inhibitor progress normally though G1 and arrest in mitosis. The mitotic block is unstable and leads to massive apoptosis. While these data suggest that Hsp90 inhibitors may be of clinical utility in patients with SCLC, 17AAG is relatively inactive in these cells. As the doses required for anti-tumor effects in SCLC cell lines appear greater that those achievable without toxicity in patients in the ongoing phase I studies, these data suggest that while Hsp90 may be an appropriate target in patients with SCLC, 17AAG is a poor choice for use in these patients. In contrast, the novel Hsp90 inhibitor PU24FCl retains activity in SCLC cells. PU24FCl binds tightly to Hsp90 found in SCLC cells, while its affinity for normal cell-Hsp90 is at least 10 – (brain, pancreas and lung) to 50 – (heart, kidney and liver) fold lower. We evaluated the in vitro growth inhibitory properties of PU24FCl against two SCLC cell lines, NCI-H69 and NCI-N417. PU24FCl inhibits cell proliferation and appears to be cytotoxic in these cells. By contrast to transformed cells, normal prostate epithelial cells (PrEC) and human renal proximal tubular epithelial (RPTEC) are 1-log more resistant to the effects of PU24FCl on growth. The effects of PU24FCl on growth correlate with its effects on Hsp90-client proteins (i.e. cMet, Raf-1, Akt) thought to be involved in the dysregulated growth, survival and metastatic potential of SCLC cells. SCLC cells are blocked in mitosis by PU24FCl; the mitotic block is unstable and leads to apoptosis with a significant increase in the number of apoptotic nuclei observed (i.e. 35% in NCI-N417, 65% in NCI-H526 at 10 uM, 72 hr post-treatment). PU24FCl maintains its activity in vivo as it is demonstrated by increased apoptosis and reduced proliferative potential of NCI-N417 xenografted tumors treated with the agent. In conclusion, our results define a novel strategy for the treatment of SCLC patients by specific inhibition of tumor Hsp90.

57 POSTER

The facilitative glucose transporter Glut-1 as a target for novel anti-cancer agents

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Rapidly proliferating tumour cells outgrow their blood supply, which results in hypoxia. Hypoxia is a problem for the treatment of cancer because it is associated with chemo- and radioresistance, increased malignancy and poor prognosis. Tumour cells exposed to hypoxia survive by switching to anaerobic glycolysis. Expression of the facilitative glucose transporter Glut-1 is induced in response to hypoxia to satisfy the increased cellular demand for glucose. Glut-1 has been reported to be over-expressed in virtually all solid tumours, and has been shown to correlate with hypoxia in cancers of the head and neck and cervix (Airley *et al*., 2001; Oliver *et al*., 2004) and with prognosis in a wide variety of solid tumours. *In vitro* and *in vivo* studies using antisense down regulated Glut-1 have also shown the importance of Glut-1 overexpression to tumour growth. Therefore Glut-1 may prove to be an excellent therapeutic target for potential anticancer agents against chemo- and radioresistant cells within solid tumours.
In an effort to identify prospective drugs that may mediate toxicity through interaction with the Glut-1 transporter, we have recently carried out a COMPARE analysis of the correlation between Glut-1 expression in the NCI 60 cell line panel and the toxicity caused by standard agents and those agents from the BEC database of NCI compounds. To confirm that the action of agents that show a statistically significant positive correlation with Glut-1 expression, i.e. COMPARE "hits" is Glut-1-dependent, we are carrying out toxicity studies using stable clones that constituently over-express Glut-1, which we have derived from PC-3 (human prostate adenocarcinoma) and HT1080 (human fibrosarcoma) cell lines. To identify a possible relationship between the subcellular location of Glut-1 and its effect on tumour growth or Glut-1-mediated toxicity in hypoxic conditions, we have also transfected the HT1080 cell line with a vector carrying the cDNA for a Glut-1/EGFP fusion protein and have generated stable clones that constitutively over-express this gene product. Using fluorescence microscopy, we have established that like Glut-1, this fusion protein is located in discrete compartments in the cytoplasm and within the cell membrane.

58 POSTER

Pharmacodynamic responses to a novel histone deacetylase inhibitor, PXD101, in mice and humans

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PXD101 is a novel hydroxamate type inhibitor of histone deacetylase (HDAC) activity. Previously, we have shown that treatment of nude mice bearing human ovarian and colon tumour xenografts with PXD101 (10–40mg/kg/day i.p.) daily for 7 days causes a significant dose-dependent growth delay with no obvious signs of toxicity to the mice (Plumb et al, 2003, Mol Cancer Ther 2; 721). This evidence of efficacy without apparent toxicity suggests that pharmacodynamic assessment of drug activity will be important in determining the optimal dose and drug schedule in patients. A marked increase in acetylation of histone H4 was detected in mouse blood 1 and 2 hours after i.p. treatment with PXD101. Levels of acetylation in both blood and tumour increased with dose (10–40mg/kg). As part of an ongoing Phase I trial of PXD101 we have determined levels of histone acetylation in peripheral blood mononuclear cells (PBMCs) in blood taken from patients treated with PXD101. Patients received PXD101 (150–600mg/m^2) as a 30 minute intravenous infusion on days 1–5 and blood samples were taken on day 1 before the infusion and at various times from the end of the infusion (0–6hours). Histones were extracted from PBMCs and acetylated histones detected by Western blotting with antibodies specific for the acetylated form. All samples from an individual patient were run on the same gel and the level of acetylation was quantified by densitometry. To allow comparison of acetylation levels between patients each blot contained an internal standard of histones prepared from cell line A2780 exposed to PXD101 (0.2 μM) for 1 hour. For all patients acetylation of histone H4 was low in the pre-treatment sample but was markedly increased at the end of the infusion to levels comparable to that observed for the internal control. At the lowest dose (150mg/m^2) levels showed a clear decrease by 30 minutes and had returned to basal by 2 hours post-infusion. The rate of decrease of acetylation levels was slower at the higher doses. At the highest dose studied so far (600mg/m^2) levels remained elevated after 2 hours and then showed variable rates of decrease such that in some patients levels were still elevated after 6 hours. Although this is an ongoing Phase I trial we have shown that the HDAC inhibitor PXD101 at these starting doses can induce histone acetylation in PBMCs in patients. Our results show that these effects are transient but are more sustained with increasing dose of PXD101.

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Comparison of the efficacy of MS-275, CI-994 and SAHA in vivo in various experimental tumor models after oral application

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Background: Histone deacetylases (HDACs) are a family of enzymes that are involved in the epigenetic regulation of gene expression. The inhibition of HDACs is a new potential therapeutic option in cancer treatment