Conclusions: BI 811283 was well tolerated overall; dose-limiting neutropenia was the most common high grade AE observed. 125 mg was defined the MTD. There was some evidence of pharmacodynamic effect as demonstrated by a reduction of histone H3 phosphorylation at higher doses, consistent with inhibition of Aurora B kinase.

497 POSTER

Combination therapy with an Aurora B kinase inhibitor AZD1152 and AraC, shows enhanced tumouricidal activity in a preclinical model of acute myeloid leukaemia (AML)

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Abstract: Acute myeloid leukaemia (AML) is characterized by an overproduction of immature, abnormal hematopoietic cells in the bone marrow and peripheral blood. Intrinsic resistance or treatment-induced acquired resistance is one of the major obstacles to the effective treatment of patients with AML, and underlies the continuing need to develop new treatments for AML. The Aurora kinases (AK) play a critical role in mitosis and have been suggested as promising targets for cancer therapy due to their frequent overexpression in a variety of tumours. Several AK inhibitors are advancing in various stages of development including AZD1152, a selective Aurora B kinase inhibitor, with a novel anti-tumour mechanism of action, inducing endoreduplication, apoptosis and inhibition of cytokinesis, leading to prolonged anti-tumour activity in solid and haematological preclinical cancer models (Wilkinson et al. Clin Can Res. 2007; Oke et al. Can Res. 2009). Cytarabine (cytosine arabinoside, Ara-C) is widely used as a therapy in clinical management of AML to induce remission and also for post remission therapy.
In the present study, we treated SCID mice bearing subcutaneous human AML tumour (HL60) xenografts with AZD1152 (25 mg/kg once daily i.p. for 4 consecutive days) or AraC (25 mg/kg twice daily i.p. for 2 consecutive days) as monotherapies or together in two overlapping combination schedules [either AZD1152 (Day 1−4) plus AraC (Day 1−2) (SCHEDULE 1) or AZD1152 (Day 1−4) plus AraC (Day 3−4) (SCHEDULE 2)]. Both treatments, when dosed as monotherapy, produced significant tumour growth inhibition (TGI) compared to vehicle-control animals (Maximum TGI of 31.7% & 48.3% for AraC & AZD1152 respectively, both $p < 0.05$). When dosed in combination, both sequences of dosing produced enhanced anti-tumour activity compared to vehicle-control (Maximum TGI of 110.9% for SCHEDULE 1 & 76.2% for SCHEDULE 2, both $p < 0.05$), as well as the monotherapy groups. Additionally, the data suggest that the combination SCHEDULE 1 was more effective in inhibiting tumour growth compared to combination SCHEDULE 2. Histological analysis of tumour sections showed a decrease in mitotic cells and an increase in apoptotic cells in drug treated tumours compared to vehicle-control treated tumours. Additionally, there was an increased level of apoptosis in tumours treated with SCHEDULE 1 compared to tumours treated with SCHEDULE 2, in concordance with the effects on tumour growth.
These data indicate a promising therapeutic strategy of combining AZD1152 and AraC for the treatment of AML, and suggest that the schedule of drug administration may have a consequence on the overall anti-tumour efficacy. AZD1152 is currently in phase II trials.

498 POSTER

In vivo evaluation of TAK-960, a novel, orally bioavailable inhibitor of Polo-like kinase 1

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Background: Polo-like kinase 1 (PLK1) plays an essential role in mitosis, including chromosome segregation, centrosome maturation, bipolar spindle formation, regulation of anaphase-promoting complex, and execution of cytokinesis. Human PLK1 has been shown to be overexpressed in various human cancers, and has been associated with poor prognosis. TAK-960 is a novel, highly selective inhibitor of PLK1 that demonstrates nanomolar activity *in vitro*. TAK-960 is currently being investigated in phase I clinical trials.
Materials and Methods: Nude mice or SCID mice ($n = 5$) were inoculated subcutaneously with human cancer cell lines and treated PO using various dosing schedules. Antitumor activity was evaluated by the ratio of treated to control (T/C) tumor volume on day 14 or 21 and response criteria modeled after the clinical standards. In PK/PD studies, mitotic index (pHistone H3 ELISA) and TAK-960 concentrations in tumor and plasma were evaluated in HT-29 xenograft tumor tissues after a single PO or IV administration.
Results: Once daily (QD) administration of TAK-960 potently inhibited the tumor growth of HT-29 colorectal xenograft model in a dose-dependent manner with T/C values of −7.59, −20.2 and −20.3% at 6.25, 10 and 12.5 mg/kg, respectively. Complete regression (CR) was observed in 4/5 mice in 10 and 12.5 mg/kg groups. TAK-960 also resulted in regression in two hematological malignancy models, MV4−11 (AML, 10 mg/kg of TAK-960 QD for 2 weeks, 4 partial responses (PRs) in 5 mice) and KARPAS299 (NHL, 10 mg/kg of TAK-960 QD for 3 weeks, 1CR and 2PRs in 5 mice). In addition, 10 mg/kg of TAK-960 QD $\times$ 6/week for 2 weeks resulted in a significant T/C of 4.7% against K562ADR xenograft model, which was established as doxorubicin-resistant cell line from K562 (CML). In the PK/PD studies, TAK-960 is distributed preferentially into tumor tissue compared to the circulating plasma levels, irrespective of the dosing routes. AUE (area under the effect-versus-time curve) for pHistone H3 appears to have a linear correlation with exposure of TAK-960 in HT-29 tumor xenografts.
Conclusions: TAK-960 showed the potent antitumor activity against various xenograft models including MDR1-expressing tumors, by oral administration. TAK-960 induced PD responses, which correlated with preferential retention of TAK-960 in tumor tissues. Taken together, these preclinical data indicate the therapeutic potential of TAK- 960 in the treatment of diverse human malignancies.

499 POSTER

Metastatic lung cancer proliferation is inhibited by Caveolin-1 silencing

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Background: Caveolin-1 (cav-1) is an essential structural constituent of caveolae implicated in mitogenic signalling, oncogenesis, angiogenesis, neurodegenerative diseases and senescence. Its role as an oncogene or as a tumour suppressor gene seems to strictly depend on cell type and tumour stage/grade. The high expression of caveolin-1 in some tumours *in vivo,* amongst which lung adenocarcinoma, is associated with increased tumour aggressiveness, metastatic potential and suppression of apoptosis. The aim of the present study was to investigate the role of caveolin-1 in metastatic lung cancer proliferation.
Materials and Methods: Human cell lines RAL and SCLC-R1 were obtained by us from metastatic lesions of lung adenocarcinoma and of small cell lung carcinoma respectively and grown in H/H medium supplemented with 10% foetal bovine serum (FBS). Inhibition of Cav-1 expression was performed by the use of small interfering RNA (siRNA). Cell growth inhibition was determined by Trypan Blue Dye Exclusion test and protein expression by Western Blotting analysis.
Results: Results indicate that lung RAL and SCLC-R1 metastatic cells express high levels of cav-1 protein; a siRNA-mediated down-regulation of cav-1 expression is evident in SCLC-R1 (100%) and RAL (80%) cells; cav-1 knockdown causes arrest of cell growth in both cell lines, maintained up to 72 h after transfection; cav-1 inhibition affects the expression of cell cycle regulatory proteins (cyclin-D1, Cdk2, Cdk4, phosphoRb) and thereby cell cycle progression, by a novel molecular pathway that we describe here.
Conclusions: A growing body of evidence links elevated cav-1 expression to an aggressive malignant and metastatic phenotype in several tumors. This has been recently reported in lung adenocarcinoma. The present data indicate for the first time that lung RAL and SCLC-R1 cell lines express high levels of cav-1 and demonstrate that cav-1 knock-down arrests metastatic growth either in small cell lung carcinoma or in adenocarcinoma in vitro by a novel molecular pathway.
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500 POSTER

A novel pyrazolo[4,3-d]pyrimidine inhibitor of cyclin-dependent kinases: antiproliferative and proapoptotic effects

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Background: Cyclin-dependent kinases (CDK) are a group of enzymes involved in many cellular processes including regulation of the cell cycle and transcription. Deregulation of the cell cycle connected with CDK hyperactivity is a common feature of tumor cells and provides a rationale for the development of specific CDK inhibitors. We have recently prepared a novel class of purine bioisostere CDK inhibitors based on the pyrazolo[4,3-*d*]pyrimidine skeleton. This work is focused on the biological and biochemical characterization of a new 3,5,7-trisubstituted pyrazolo[4,3-*d*]pyrimidine, LGR1492.