cytotoxic drugs (carboplatin, cisplatin, gemcitabine, fluorouracil, etoposide and doxorubicin). Three cell lines (H28, MSTO211H and LO68) were screened against 1524 JHCCL compounds. SYBR(R) Green I- fluorometric assay was used to measure compound activity.
Results: All lines were sensitive to doxorubicin and gemcitabine except MM05 and H226, which were resistant to gemcitabine. MSTO211H was chemosensitive to carboplatin and etoposide and H226 was resistant to flurouracil.
50 drugs (9 antineoplastic, 10 antheminithic, 14 antiseptic, 5 antibiotics, 3 antidote, 3 antihistaminic, 2 antihyperlipidemic, 2 antimalarial, 3 carditonic, 2 dermatologic, 2 progestogen, and other include aesthetic, antifungal, antiparkinsonian, antiprotozoal, antipsychotic, diagnostic aid, hemostatic) have been short listed after first screening with 10uM of each drug of JHCCL. Compound activity was analysed by comparison to an arbitrary point within the dynamic range defined by assay controls (e.g. representing 50% cell death). A five-log range of final concentrations from 100 uM to 1 nM was tested and IC50 was determined. The results ranged within 0.7 uM−10 uM.
Conclusions: Active compounds were identified from a panel of agents with history of clinical use. The anti-mesothelioma action of several candidates active *in vitro* at levels below PPC now requires validation in vivo or in clinical settings.
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Oral Presentations (Mon, 26 Sep, 09:00−10:55)
Drug Development

1200 ORAL

RP5237- a Novel, Selective, and Potent Inhibitor of PI3Kdelta With Therapeutic Potential in B-cell Lymphomas

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Background: Pan-PI3K inhibitors currently in development have been associated with adverse side-effects such as insulin resistance, thus necessitating the need to develop isoform specific inhibitors of PI3K. Because expression of PI3Kδ isoform is limited to blood cells, it serves as an ideal target against cancers associated with dysfunctional expansion of hematopoietic cells. Herein, we describe the biological and pharmacokinetic properties of RP5237, a novel and small molecule PI3Kδ inhibitor with scope to be further developed as a clinical candidate for B-cell lymphomas.
Material & Methods: Activity of RP5237 on individual PI3K isoforms was determined by a Homogenous Time Resolved Fluorescence assay (Millipore, Billerica, MA) with modifications. Potency of the compound on the delta isoform was further corroborated in FcεR1 induced CD63 expression studies using human whole blood and anti-IgM induced human B-cell proliferation assays. Anti-tumour efficacy of the compound was confirmed *via* cell viability and apoptosis assays besides testing for inhibition of pAkt, a downstream kinase regulating cell survival and growth. Metabolic stability of the compounds was evaluated in liver microsomes. Pharmacokinetic parameters were estimated in plasma from mice and rat.
Results: RP5237 demonstrated significant potency against PI3Kδ (**13.8 nM**) with several fold selectivity over the α (**>1000**), β (**>50**), and γ (**>9**) isoforms. Additionally, the compound inhibited B-cell proliferation (**32.2 nM**) and FcεR1 induced CD63 expression in human whole blood basophils (**48.9 nM**) indicating specificity towards the delta isoform. Viability assays demonstrated that the compound caused a dose-dependent inhibition in growth of B-cell mediated cancerous cell lines such asTHP-1, TOLEDO, HL-60, and Raji. Reduction in viability was accompanied by a reduction in pAKT along with a significant increase in apoptosis manifested by an induction of caspase-3 activity in the cell lines tested. Pharmacokinetic studies in mice and rat indicated good oral absorption with favourable peak plasma concentrations.
Conclusions: Results demonstrate the therapeutic potential of RP5237 in B-cell mediated cancers *via* the PI3Kδ pathway. *Ex vivo* studies using blood obtained from naive lymphoma patients are currently underway to determine the efficacy of the compound in different tumour sub-sects. Additionally, the compound shall be tested in mouse xenograft models of haematological malignancies.

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Early Studies of the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Anti-tumour Activity of the Humanized Monoclonal Antibody (huMAb) Anti-EGFL7 (MEGF0444A) Alone and in Combination With Bevacizumab (Bev) With and Without Paclitaxel (Pac) in Patients (pts) With Advanced Cancer

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Background: Epidermal growth factor-like domain 7 (EGFL7) is a vascular-restricted, tumour-enriched, extracellular matrix protein that forms perivascular tracks and promotes endothelial cell adhesion and survival. Anti-EGFL7 (MEGF0444A) is a huMAb that inhibits the activity of EGFL7 and reduces vascular density and perfusion in murine tumour models. Anti-EGFL7 as a single agent (SA) has limited anti-tumour activity, but it significantly enhances the anti-tumour activity of anti-VEGF in multiple murine tumour models.
Materials and Methods: A standard 3+3 dose escalation was used to study safety, PK, PD, and anti-tumour activity of MEGF0444A in 2 serial Phase I trials. In a Phase Ia study, 30 pts were treated with SA MEGF0444A in 21-day cycles at doses ranging from 0.3 to 15 mg/kg. In a subsequent 2-arm Phase Ib study, 40 pts were enrolled. In Arm A, MEGF0444A was given at doses of 2, 5, or 10 mg/kg along with Bev at 10 mg/kg on Days 1 and 15 of each 28-day cycle; in Arm B, pts additionally received Pac (90 mg/m^2) on Days 1, 8, and 15 of each cycle. PD biomarkers including circulating progenitor cells (CPCs) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) were assessed.
Results: In the Phase Ia trial, the highest planned dose of 15 mg/kg was reached without dose-limiting toxicities. MEGF0444A was well tolerated with no attributed Grade ⩾3 serious adverse events (AEs). There were no responses. In the Phase Ib study, the combination of MEGF0444A and Bev with or without Pac did not appear to exacerbate Bev-related AEs. Five partial and 2 minor responses were observed in multiple tumour types in the Phase Ib trial. In both studies, MEGF0444A had linear PK typical of an IgG1 huMAb. Enumeration of CPCs showed a decrease in a subset of pts within 15 days of MEGF0444A therapy. DCE-MRI results were suggestive of anti-angiogenic activity in select pts. Five mg/kg q2weeks (w) was chosen as the recommended Phase II dose.
Conclusions: MEGF0444A has favorable PK and is well tolerated as a SA and in combination with Bev and Bev/Pac. Changes in CPC levels and DCE-MRI parameters are consistent with MEGF0444A anti-angiogenic and anti-vascular activity. Study data support a Phase II dose of 5 mg/kg q2w (equivalent to a flat dose of 400 mg q2w or 600 mg q3w). Phase II trials of MEGF0444A with chemotherapy/Bev are planned.

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A Phase I Study of the Potent AKT Inhibitor MK-2206 in Combination With Carboplatin and Paclitaxel, Docetaxel or Erlotinib in Patients With Advanced Solid Tumours

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Background: MK-2206 is a novel allosteric inhibitor of all 3 isoforms of AKT, which are targets implicated in malignant progression and resistance to anti-cancer therapies. *In vitro*, MK2206 demonstrated synergistic or additive anti-cancer effects when combined with C+P, D and E.
Material and Methods: Pts with advanced solid tumours, ECOG PS ⩽1 were recruited to a 3-arm phase I study of MK2206 QOD (days 1, 3, 5, 7) or Q3W with carboplatin (C) (AUC6) and paclitaxel (P) (200 mg/m^2) (Arm 1), or docetaxel (D) (60 & 75 mg/m^2) (Arm 2) or QOD (alternate days continuous) and QW with erlotinib (E) (100 and 150 mg) OD (Arm 3). The primary objectives were to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of MK2206 in combination with C+P, D or E. Secondary objectives were to determine preliminary activity