(>650 fold selectivity over 265 kinases), small molecule inhibitor of MET being co-developed with Hutchison MedPharma. AZD6094 is being developed as a monotherapy or combination therapy in multiple tumor indications including papillary renal cell carcinoma (PRCC) and gastric cancer. AZD6094 in MET sensitive mouse xenograft models (including RCC-43b & RCC-47 for PRCC; MKN-45, SNU-5 & Hs746T for gastric) demonstrates rapid, sustained and extensive inhibition of phosphorylated-MET (pMET) and tumour efficacy. The modelling objectives of this work were to build a generalised quantitative model that can be applied across cell-lines linking drug concentration to pMET to tumour growth inhibition (TGI). The model was then used to explore whether differences in sensitivities to AZD6094 observed across animal models is due to differences in the PK-pMET or pMET-TGI relationships. Additionally, the mouse pMET model was linked to the observed human PK model to simulate pMET inhibition to inform the Phase II dose selection in PRCC patients and select time-points to take tumour samples for pMET measurement. A population PK-PD-efficacy model was developed for mouse consisting of (1) a PK model connected to (2) an Emix model for the inhibition of pMET, driving (3) a variation on the Simeoni model for tumour growth inhibition. It was found that a direct response model for the inhibition of pMET with a single IC50 values best represents the data available across the different xenograft models. Conversely, it was necessary to fit individual IC50 values for each xenograft model for inhibition of the tumour growth. A human population PK model was established from emerging dose escalation Phase I study data. Using the human PK model to drive the human population PK-PD-efficacy model was developed from mouse consisting of (1) a PK model connected to (2) an Emix model for the inhibition of pMET, driving (3) a variation on the Simeoni model for tumour growth inhibition. It was found that a direct response model for the inhibition of pMET with a single IC50 values best represents the data available across the different xenograft models. Conversely, it was necessary to fit individual IC50 values for each xenograft model for inhibition of the tumour growth.

Background: Ceritinib is an ALK inhibitor under phase II clinical trial, and it shows an impressive result in ALK fusion positive patients. To get the excellent ALK inhibitors, we synthesized several ceritinib derivatives.

Materials and Methods: We made small modification in ceritinib especially on piperidine and benzene ring. With the newly synthesized compounds, several IC50 values best represent the data available across the different xenograft models. Conversely, it was necessary to fit individual IC50 values for each xenograft model for inhibition of the tumour growth.

Results: We made a potent ALK inhibitor by small modification of ceritinib. The in vitro efficacy of KRCA-386 is as good as ceritinib, however, KRCA-386 is much better than ceritinib in vivo efficacy.

Conclusion: We made a potent ALK inhibitor by small modification of ceritinib. The in vitro efficacy of KRCA-386 is as good as ceritinib, however, KRCA-386 is much better than ceritinib in vivo efficacy.

394 Sensitivity of acute myeloid leukemia cells to a urokinase-activated anthrax lethal toxin (PrAgU2/LF) is dependent on uPAR expression and phospho-MEK1/2 levels

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In this study, we attempt to target AML cells using a urokinase-activated anthrax lethal toxin (PrAgU2/LF). Anthrax lethal toxin consists of protective antigen (PrAg), the cell binding and internalization (necrotic and lethal factor) (LF) the catalytic moiety. PrAg binds cells through ubiquitously expressed anthrax toxin receptors (ANTX R), is cleaved by furin proteases, oligomerizes, binds 3 to 4 molecules of LF and undergoes endocytosis, releasing LF into the cytosol. LF is a metalloprotease that cleaves all mitogen-activated protein kinase (MAPK) kinases. We have replaced the furin activation site of PrAg with a urokinase activation site (PrAgU2), generating PrAgU2/LF, a dual selective toxin targeting both the urasinase plasminogen activation system (uPA/uPAR) and the MAPK pathway. Potency of PrAgU2/LF was tested on 11 human AML cell lines and on CD4+ progenitor bone marrow blasts using a proliferation inhibition assay, uPAR expression and phospho-MEK1/2 levels were determined by flow cytometry. Cell cycle analysis was carried out by propidium iodide (PI) staining and type of cell death was determined by Annexin V/PI and active caspase staining. PrAgU2/LF was cytotoxic to 5 out of 11 AML cell lines (IC50 = 12–151 pM and percent cell death >75%) and induced cell cycle arrest in the surviving fraction of 3 out of the 5 sensitive cell lines. AnnexinV/PI and caspase staining showed an increase in the percentage of cells stained with both annexin V and PI along with negative staining for active caspases indicating that treatment with PrAgU2/LF leads to caspase-independent, non-apoptotic cell death in AML cells. All five PrAgU2/LF-sensitive cell lines had high levels of phospho-MEK1/2 and uPAR expression while the six resistant cell lines either lacked phospho-MEK1/2 (four cell lines) or lacked uPAR expression (two cell lines). Inhibition of uPAR through co-incubation with an anti-uPAR antibody or desensitization of cells to MEK1/2 inhibition through growth in the presence of U0126 (MEK1/2 inhibitor) blocked toxicity of PrAgU2/LF to sensitive AML cells indicating the absolute requirement for both uPAR expression and MAPK activation for the activity of this toxin. CD4+ progenitor bone marrow blasts lacked uPAR expression, MAPK activation and were resistant to PrAgU2/LF demonstrating the tumor selectivity of this approach.

Results indicate that the urasinase plasminogen activator and the MAPK pathway can be simultaneously targeted in AML using the dual selective, urokinase-activated PrAgU2/LF with cell sensitivity being dependent on uPAR expression and phospho-MEK1/2 levels.

395 cMet: Proof-of-concept clinical trial with volitinib in patients with advanced papillary renal cell cancer (PRCC)

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Met is a receptor tyrosine kinase that is deregulated across multiple cancer types, leading to uncontrolled tumor cell growth, invasion and survival. cMet is amplified in ~5–20% of GC. Met is amplified (~4%) and overexpressed (~50%) in newly diagnosed NSCLC adenocarcinomas. Activating cMet mutations are present in hereditary and a subset of sporadic PRCC cases (up to 21% of type II PRCC). Trisomy of chromosome 7 (containing both cMet and HGF genes) has been reported in 45–75% of sporadic PRCC cases; 81% of type I and 46% of type II PRCC have copy number alterations of cMet. PRCC represents 10–15% of RCC, and is the most common form of non-clear cell RCC.