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Foretinib (GSK1363089) inhibits growth of gastric cancer cell lines through blockade of inter-receptor tyrosine kinases networks

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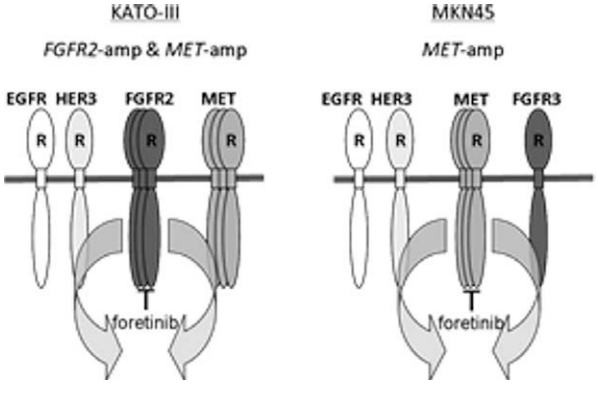
Background: Very few molecularly-targeted agents have been applied to the treatment for gastric cancer. Foretinib (GSK1363089) is an oral multikinase inhibitor targeting MET, RON, AXL, and vascular endothelial growth factor receptors (VEGFRs). The purposes of this study were to determine mechanisms of action of foretinib and to explore possible biomarker to predict sensitivity to the agent in gastric cancer.
Materials and Methods: We evaluated effects of foretinib on cell growth and cell signaling using a panel of gastric cancer cell lines; KATO-III, MKN-1, MKN-7, MKN-45, and MKN-74. All cell lines have been evaluated for copy number of *MET* and fibroblast growth factor receptor 2 (*FGFR2*) genes, and only MKN-45 and KATO-III cell lines are known to have *MET*- and *MET*- and *FGFR2*-amplifications, respectively.
Results: Only MKN-45 and KATO-III were highly sensitive to foretinib (IC_{50}; MKN-45 vs. KATO-III vs. the others, 7 vs. 30 vs. 800 nM<). In MKN-45, 1 μM of foretinib and 1 μM of PHA665752, another MET inhibitor, inhibited phosphorylation of MET and downstream signaling molecules including Akt as expected. However, in KATO-III, inhibition of phosphorylation of MET with PHA665752 did not coincide with the inhibition of phosphorylation of Akt. Instead, 1 μM of foretinib and 1 μM of PD173074, a selective inhibitor of FGFRs, inhibited phosphorylation of FGFR2 and Akt, suggesting that foretinib works through FGFR2 in KATO-III. While activity of foretinib against FGFR2 has not been reported before, we confirmed it in another *FGFR2*-amplified gastric cancer cell line, OCUM-2M. With phospho-receptor tyrosine kinase (RTK) array, we found that in MKN-45 1 μM of foretinib inhibited phosphorylation of epidermal growth factor receptor (EGFR), HER3 and FGFR3 via MET inhibition (figure). Similarly in KATO-III, 1 μM of foretinib inhibited phosphorylation of EGFR, HER3 and MET via FGFR2 inhibition (figure). To explore the role of HER3 and FGFR3 in MKN-45, we knocked down them with SiRNA and found that phosphorylation of Akt and cell growth was partially inhibited.
Conclusions: Foretinib appears effective against cell lines with *MET*- or *FGFR2*-amplified gastric cancer cell lines. Foretinib showed inhibitory effects on MET and FGFR2, and blocked the inter-RTKs signaling driven by *MET* or *FGFR2* gene-amplification in gastric cancer cells.



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Targeting focal adhesion kinase (FAK) in primary human schwannoma

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Neurofibromatosis type 2 (NF2), a dominantly inherited disease, is caused by loss of tumour suppressor protein Merlin. Loss of merlin also causes a variety of spontaneous tumours. NF2 patients normally suffer from multiple non-cancerous nervous system tumours i.e. schwannoma, meningioma and ependymoma. As these tumours are benign, chemotherapy is not effective. Tumour localisation and multiplicity make surgery and radiosurgery very challenging. Thus, a new therapeutic approach is urgently required. Focal adhesion kinase (FAK) is a tyrosine kinase localised in the cytoplasm and focal adhesions acting as a mediator of various signalling pathways. Our previous results revealed that FAK is strongly overexpressed and basally activated in human schwannoma, and autophosphorylated FAK (Y397) colocalises with active ERK1/2 at the focal adhesions in schwannoma.
By using an unique *in vitro* model comprising primary human schwannoma tumour cells and healthy Schwann cells, we tested the hypothesis that FAK is a key regulator of elevated focal adhesion and proliferation in human schwannoma. To target FAK, a small inhibitor PF573228 (Pfizer) and lentivirus containing shRNA against FAK had been applied in this study. We demonstrate that FAK is activated upon stimulation of the overexpressed IGF1−/IGF-IR and integrins/IGFBP-1 leading to the increased proliferation and adhesion. In IGF-IR mediated signalling, FAK recruits ERK1/2 and JNK pathways to regulate proliferation and adhesion. Nuclear localisation of FAK in schwannoma also suggested its potential contribution to proliferation or survival independent of growth factor receptors. Based on these data we suggest that FAK represents a good therapeutic target for the treatment of human schwannoma.

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Endothelin A receptor antagonism with zibotentan (ZD4054) augments androgen ablation-induced inhibition of prostate tumor cell growth

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Background: Endothelin-1 A and B receptors (ET-1 ET_A and ET_B) have emerged as important contributors to the development of castration-resistant prostate cancer (CRPC). Plasma ET-1 and tumor ET_A levels being elevated while ET_B expression is lost, sets the stage for progression to advanced CRPC. The current study focuses on the molecular response of the ET axis to androgen deprivation and effects on ET_A antagonism in the hormone-deprived prostate cancer (PCa) environment.
Materials and Methods: *In vitro,* PCa cell viability was assessed in hormone-depleted conditions with and without specific ET_A antagonist (zibotentan, ZD4054) treatment. *In vivo*, mice bearing established LNCaP xenograft tumors were either castrated or left intact, treated with zibotentan or vehicle, at the time of castration (castrate-immediate [CI]) or 7 days post-castration (castrate-delayed [CD]) and then analyzed for tumor proliferation, vascularization and serum prostate-specific antigen (PSA).
Results: Zibotentan significantly reduced cell viability in androgen-sensitive PCa cells during androgen deprivation. Castration decreased tumor growth rate compared with intact animals and combining castration with zibotentan led to additional reductions in tumor growth, the largest of which was in the CD group (15% lower, $P < 0.05$ vs castrate controls). This latter group also had 60% lower tumor weight vs castrate controls ($P < 0.05$). Time before removal from the study due to maximum allowable tumor volume (survival) was longest in the CI and CD groups, followed by the castrate controls. The intact-vehicle group had no animals remaining in the study by day 42, whereas the intact-zibotentan group still had 20% of animals surviving. Significant reductions in serum PSA were observed in zibotentan-treated castrate mice vs castrate controls (>30%) or intact mice (>100%) and a decrease in proliferation (Ki67) was observed in zibotentan-treated castrate mice vs castrate controls or intact mice.
Conclusion: Zibotentan reduced PCa cell viability and tumor growth in androgen deprived conditions and may provide additional tumor growth inhibition in CRPC through blockade of a cell survival/growth pathway active during hormone depletion.

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Targeting mTOR: a potential therapeutic approach for chondrosarcoma treatment

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Chondrosarcomas are the second most frequent primary malignant type of bone tumor for which no effective systemic treatment is available. If surgical resection remains the most reliable means of cure, this procedure does not restrain the high rates of local recurrence and life threat of chondrosarcoma. Thus, there is a need to develop innovative systemic therapies for the treatment of chondrosarcoma.
The aim of the present study was to determine the effects of Everolimus® (RAD001) on chondrosarcoma tumor progression. RAD001 was tested in vivo (i.p. 1 mg/kg, twice a week) alone or in combination with adriamycine