Inhibition of Focal Adhesion Kinase in Combination With Bevacizumab Reduces the Rate of Tumor Revascularization and Increases Survival in a Pre-clinical Model of Breast Cancer

Abstract

1. Background

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that provides a critical hub for signaling from at least four different classes of cellular sensing mechanisms including growth factor receptors, GPCRs, integrins and mechanical stress forces. By temporal and spatial integration of signals from these sources, FAK plays a central role in cell migration, invasion and proliferation; processes vital for tumorigenesis. The significance of FAK to the function of signal transduction pathways provides a strong rationale for the combination of FAK inhibitors with other targeted agents to achieve improved efficacy against a range of cancers. Others have demonstrated the importance of FAK in angiogenesis and therefore combining a FAKi with anti-VEGF agents is attractive as it employs two complementary mechanisms of suppressing the formation of tumor vasculature.

Vascular Endothelial Growth Factor Receptor 3 (VEGFR3, also known as Flt4) is activated by VEGF-C and -D and under normal physiological conditions in adults is restricted to lymphatic and some fenestrated vascular endothelium. Expression levels of VEGFR3 are significantly increased in sprouting endothelial tip cells of angiogenic blood vessels in tumours and wounds and blocking VEGFR3 signaling has been demonstrated to reduce the number of vessel branches and endothelial sprouts both during development and in tumours. Furthermore, VEGFR3 signaling mediates lymphangiogenesis in tumours and appears to have a significant role in tumour metastasis through the lymphatics. Consequently, inhibition of VEGFR3 could have therapeutic potential in treating lymphomatous and metastatic disease and possibly a subset of patients with advanced cancers. Furthermore, acquired resistance to anti-VEGF treatments such as bevacizumab (bev) have a frequent occurrence. Studies have shown that development of resistance often correlates with a significant increase in the levels of the VEGFR3 ligand, VEGF-C. Therefore, treatment with VEGFR3 inhibitors could be of clinical benefit to patients with acquired resistance to bev.

2. Aim

The aim of this study was to investigate the effect of inhibition of FAK (CTx-0294945) or FAK+VEGFR3 (CTx-0294886) on tumour response to anti-VEGF treatment in an aggressive model of breast cancer. Here we present results from the co-administration of bev, with either CTx-0294945, a highly selective FAKi, or CTx-0294886, a potent inhibitor of FAK and VEGFR3 in an orthotopic model of human breast cancer.

3. Results

CTx-0294945 (FAK) and CTx-0294886 (FAK+VEGFR3) kinase inhibitors suitable for combination therapy

CTx-0294945 reduces rates of tumour growth after cessation of bevacizumab therapy in the MDA-MB-231-LNA breast cancer model

CTx-0294945 may inhibit tumour revascularization and macrophage infiltration in MDA-MB-231-LNA primary tumours following cessation of bevacizumab therapy

Summary

• CTx-0294945 is a potent and selective inhibitor of FAK with excellent developmental potential

• CTx-0294886 is a potent inhibitor of FAK and VEGFR3 with excellent developmental potential

• Our data support the potential clinical utility of combining CTx-0294886 with bevacizumab to enhance anti-tumor effects and increase the durability of response

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