Combination of CTX-0294945 a highly selective inhibitor of focal adhesion kinase with bevacizumab in pre-clinical models of breast cancer

**Abstract # LB-308**

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that provides a critical hub for signalling 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 development 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 a FAK inhibitor with anti-VEGF agents is attractive as it employs two complementary mechanisms of suppressing the formation of tumor vasculature. Here we present results from the administration of CTX-0294945, a highly selective FAK, and bevacizumab (bev) in an orthotopic model of human breast cancer.

**Background**

**Aim**

The aim of this study was to investigate the effect of inhibition of FAK, using the proprietary small molecule, CTX-0294945 on the response to bevacizumab (bev).

**Methods**

MDA-MB-231-LNA cells were implanted into the right mammary fat pad of Balb/c SCID mice. Once tumors were palpable (day 14), the mice were randomized into groups of 8 to receive drug vehicle alone (vehicle; black), 80 mg/kg CTX-0294945 po once daily (red), 12.5 mg/kg bev twice weekly (blue) or the two drugs in combination (purple) for a period of 14 days (day 14 – 28). Bars represent the mean ± S.E.M of 8 mice per treatment group.

**Results**

- **Figure 1:** CTX-0294945 augments MDA-MB-231-LNA tumor growth inhibition in combination with bev
- **Figure 2:** CTX-0294945 inhibits pY<sup>FAK</sup> in primary tumors
- **Figure 3a-d:** CD31 blood vessel staining
- **Figure 4:** F4/80 macrophage staining

**Discussion**

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

**Summary**

- CTX-0294945 is a potent and selective FAK inhibitor with good development potential
- Bevacizumab is widely used in the clinic but efficacy can be limited and clinical benefit is often short-lived
- Inhibition of FAK by CTX-0294945 increases the duration of Avastin response in an aggressive orthotropic model of triple negative breast cancer
- Our data suggest the potential utility of combining a selective FAK inhibitor with bevacizumab to prevent tumor progression and enhance the durability of response