ABSTRACT
Blockade of tumor inflammation has potential for cancer therapy, both as a primary mechanism to counter tumor growth but also in combination with other therapeutics. IL-1R signaling has been observed previously to be important in tumor development and progression to metastasis, and we have shown previously that an IL-1Ra receptor-antagonist antibody (3A9) can inhibit tumor growth and reduce lung metastasis in a mouse breast cancer xenograft model. Here we demonstrate that administration of 3A9 in vivo can significantly reduce expression of the tumor microenvironment and in an immune competent setting, an antibody towards mouse IL1RAP was generated. This antibody potently blocks mouse IL-1R signaling (Kd = 8 pM), leads to IL-1Ra protein, with high affinity (Kd = 0.25 nM), leads to IL-1B expressing cells and can be administered in mice with good pharmacokinetics. In vivo imaging showed that the antibody is not generally distributed in tissues but localizes to tumor sites after injection. Treatment of mice with orthotopically implanted 4T1 breast cancer cells did not reduce primary tumor growth significantly but reduced both the number of 4T1 RAP+ and IL-6+ and size of lung metastases. Interestingly, 4T1 tumors express low levels of IL1RAP and were not responsive to 3A9 blockade, but the effects instead relied on effects on the tumor microenvironment, particularly in addition to inducing AREG of tumor cells and block their response to IL-1, also inhibit metastases by affecting the tumor microenvironment.

STUDY OBJECTIVES
• To generate data supporting translational research around CAN04, a fully humanized antibody against IL1RAP in phase I/II clinical development
• To develop a surrogate antibody to the human-specific clinical candidate CAN04 for studies in mice
• To contribute to development of IL-1R targeting of non-tumor cells in tumor development and metastasis

RESULTS
The 3A9 antibody binds to murine IL1RAP and inhibits IL-1 signal

CONCLUSIONS
• A surrogate antibody to the clinical candidate CAN04 was developed, the antibody binds to murine IL1RAP and inhibits IL-1 signaling
• This surrogate antibody, 3A9, accumulates in tumors and spleen of 4T1 tumor-bearing mice which recognizes myeloid cell populations
• Treatment of 4T1 tumor-bearing mice with 3A9 inhibits metastasis of tumor cells to the lungs.
• The effects mediated by 3A9 are consistent with an effect on tumor-growth-regulating myeloid cells to counter tumor metastasis

REFERENCES