Inhibition of KIT In Vivo Modifies Immune Cell Populations to Improve The Efficacy of Checkpoint Inhibitors in Syngeneic Mouse Tumor Models

**Introduction**

- **KTN0158** is a humanized anti-KIT IgG1 monoclonal antibody that binds to the extracellular domain of KIT, and is being developed as a potential therapy for cancer (Phase 1 study; NCT02945016) and other mast cell-related diseases such as neuroinflammation type 1.
- Expression of KIT in immune cell types, including mast cells, suggests the potential for additional roles of KIT in indirect modulation of tumor progression.
- KIT may be involved in modulating the activity of mast cells and MDSCs in tumors (Dannell et al., Cancer Immunol Res. 2015; Saleem et al., J Immunol. 2012; Pan et al., Blood 2016).
- In melanoma patients, prolonged overall survival is associated with lower numbers of monocytic myeloid-derived suppressor cells in peripheral blood prior to treatment with imatinib or nilotinib (Kline et al., Cancer Immunol Res. 2014; Weber et al., Cancer Immunol Res. 2016).
- The ability of anti-KIT mAb treatment to relieve immune suppression and enhance anti-tumor activity of immune checkpoint inhibitors was evaluated in a panel of preclinical tumor models.

**Methods**

- **KIT and SCF Expression in Mouse Tumor Cell Lines**
- **Lack of Effect of SCF and KIT Inhibition on Cell Growth In vitro**
- **No evidence for KIT-dependent proliferation in mouse tumor cell lines in vitro, regardless of KIT or SCF expression levels**

**Results**

- **Anti-KIT Treatment Inhibits KIT Phosphorylation in Mast Cells and Mast Cells Are Present in the Tumor Microenvironment**
- **The potentiation of KIT inhibition in mouse mast cells by AOC2 was comparable to KTN0158 inhibition of KIT in human mast cells**
- **The immune cell content of Colon26 tumors included mast cells identified by ex vivo staining of tumor tissue with toluidine blue and an anti-mast cell tryptase antibody.**

- **The Combination of Anti-KIT and Anti-CTLA-4 Exhibits Anti-Tumor Activity in the Pan02 Mouse Pancreatic Tumor Model**
- **The combination of anti-KIT and anti-CTLA-4 treatment yielded anti-tumor activity in the Pan02 pancreatic tumor model**
- **Anti-CTLA-4 and anti-PD-1 did not exhibit strong anti-tumor activity in the Pan02 model when dosed as single agents or in combination.**

- **Potential Mechanism for Enhanced Efficacy of Immune Checkpoint Inhibitors in Combination with a KIT mAb**
- **Combination of anti-KIT and anti-PD-1, or anti-CTLA-4 and anti-PD-1, yielded additional anti-tumor activity in the CloudmanS91 melanoma model compared to single agent treatments.**

**Conclusions**

- **KTN0158** is a potent humanized anti-KIT mAb in clinical development. Tumor-infiltrating mast cells represent a potential target for anti-KIT antibodies within the tumor microenvironment.
- The combination of an anti-KIT antibody with immune checkpoint inhibitors showed enhanced anti-tumor activity in the Colon26 model, Pan02 and CloudmanS91 models.
- High pre-treatment m-MDSC counts are associated with reduced survival in melanoma patients treated with checkpoint inhibitors.
- Anti-KIT treatment in vivo reduced m-MDSC numbers, which may result in reduced suppression of anti-tumor immunity.
- The data support clinical evaluation of KTN0158 in combination with anti-PD-L1 and/or anti-CTLA-4 for the treatment of cancer.