KTN0158, a Humanized Anti-KIT Monoclonal Antibody, Demonstrates Antitumor Activity in Dogs with Mast Cell Tumors

Clinical benefit of KTN0158 was observed in dogs with MCTs at KTN0158 binds the IgG1 constant domain of the KIT extracellular domain and blocks KIT homodimerization and ligand binding. KTN0158 is a more potent inhibitor of SCF-dependent M0/7e cell proliferation than imatinib or nilotinib.

KTN0158 inhibits Dog KIT Activation In Vitro and Decreases Mast Cell Numbers in Skin In Vivo

Results

Best Tumor Response in Dogs with Evaluable MCTs

- All dogs treated with KTN0158 experienced clinical benefit

Lack of Neoplastic Mast Cells in a Subset of Primary Tumors and Metastatic Lymph Nodes after KTN0158 Treatment

- No degranulation in primary human mast cells in vitro at KTN0158 concentrations up to 1000 nM with or without IgE crosslinking
- KTN0158 did not induce KIT phosphorylation in cells expressing endogenous or exogenous KIT

Methods

- Mutation analysis in primary human mast cell lines at KTN0158 concentrations up to 1000 nM with or without IgE crosslinking
- Clinical Study

KTN0158 Does Not Have Agonist Activity In Vitro

- No degranulation in primary human mast cells in vitro at KTN0158 concentrations up to 1000 nM with or without IgE crosslinking
- KTN0158 did not induce KIT phosphorylation in cells expressing endogenous or exogenous KIT

Conclusions

- Clinical benefit of KTN0158 was observed in dogs with MCTs at all dosing levels and in tumors with and without activating KIT mutations
- 5 dogs with partial responses and 7 dogs with stable disease
- Hematopoietic stem cell transplantation showed a lack of neoplastic cells in primary tumors and/or lymph node samples from a total of 4 dogs
- Reversible hematologic and biochemical effects were observed in dogs receiving 10 and 30 mg/kg/dose of KTN0158 with the MTD established at 10 mg/kg
- In contrast to findings in dogs, IND enabling toxicity studies in cynomolgus monkeys revealed no significant findings after repeat dosing of KTN0158 with a no observed adverse event level (NOAEL) of 75 mg/kg, the highest dose tested
- Overall, nonclinical toxicology demonstrates a favorable safety profile supporting planned clinical testing in human phase 1 studies in 2016 in GISTs and other solid tumors

Adverse Events in Dogs with MCTs after KTN0158 Treatment

- Dose-limiting toxicities observed at 30 mg/kg in dogs; however, no significant toxicological findings were observed in multiple studies in cynomolgus monkeys after repeat dosing of KTN0158 with a NOAEL of 75 mg/kg (exposure similar to 30 mg/kg in dogs)
- Maximum tolerated dose (MTD) = 10 mg/kg
- Two dogs experienced anaphylaxis during the second infusion which may have been due to the development of anti-KTN0158 antibodies
- All study related adverse events were transient and recovered fully by study completion

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In Vitro Assays

- Human mast cell lines (human and canine) were derived from patient mast cell tumors and cultured as described previously. All experiments were performed with cells in log phase growth.
- Pharmacology: The human mast cell line was obtained from DSMZ GmbH. The canine mast cell line was obtained from CCBRC GmbH. Cytotoxicity and proliferative assays were performed as described previously.
- Dog mast cell line: Human and canine mast cell lines were freshly isolated from patient mast cell tumors and engineered to express the human or canine KIT receptor. The cell lines were maintained under standard cell culture condition and used for all experiments. KIT phosphorylation was measured using an anti-human KIT receptor antibodies.

Overall, nonclinical toxicology demonstrates a favorable safety profile supporting planned clinical testing in human phase 1 studies in 2016 in GISTs and other solid tumors.