Modeling Suggests Synergistic Treatment Effect Following Combination Therapy of NKTR-214 and NKTR-262 in Tumor Bearing Mice

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Background: NKTR-214 is a CD122-biased agonist designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand effector CD8+ T and NK cells over T regulatory cells in the tumor microenvironment. NKTR-262 is a small molecule agonist that targets toll-like receptors (TLRs) found on innate immune cells in the body. NKTR-262 potently synergizes with NKTR-214 by creating an immuno-competent environment within the tumor in addition to increasing proliferation and infiltration of CD8+ T cells. The objective is to build a model to describe the efficacy (tumor volume) in mice administered with combination treatment of NKTR-214 and NKTR-262.

Methods: Mice bearing established CT26 tumors of ~100 mm3 volume are treated with vehicle, NKTR-214, NKTR-262, or combination of NKTR-262 and NKTR-214. Modeling is conducted using NONMEM 7.

Results: A 1-compartmental model describes PK of NKTR-214 and a 2-compartmental model describes PK of NKTR-262. Transit compartment with indirect response model captures proliferation of CD8 T-cells. Tumor growth inhibition (TGI) model with intrinsic tumor growth rate (KGR) and reduction of tumor via immune clearance (KDT) captures tumor volume profile. Only KGR is estimated for vehicle group whereas KGR and KDT are estimated for treatment group as the treatment could potentially effect either of them by altering tumor milieu. Preliminary estimates of KGR is 0.177 day-1, 0.0427 day-1, 0.0312 day-1, and 0.00177 day-1 for vehicle, NKTR-214, NKTR-262, and NKTR-214/NKTR-262 combination treatment groups respectively. Preliminary estimates of KDT are 0.00336 %CTL·day-1, 0.0000399 %CTL·day-1, and 0.0108 %CTL·day-1 for NKTR-214, NKTR-262, and NKTR-214/NKTR-262 combination treatment groups respectively.

Conclusion: TGI model demonstrates synergy in efficacy for combination of NKTR-214 with NKTR-262. The model could be used to help estimate efficacious doses for human clinical trials.