ANV419 is a novel CD122-biased IL-2/anti-IL-2 fusion protein showing increased efficacy in combination with checkpoint inhibitors and treatments acting through antibody dependent cellular cytotoxicity

Background ANV419 is an antibody-cytokine fusion protein with natural affinity to the heterodimeric IL-2Rβ/γ, but no affinity for IL-2Rα/β/γ. As a result, ANV419 preferentially stimulates CD8 T cells and NK cells over regulatory T cells. ANV419 is currently being investigated in a phase I dose finding study in patients with solid tumors. The goal of this study is to evaluate the activity of ANV419 on NK and CD8 T cells and investigate the potential synergy of ANV419 with complementary immune-activating mechanisms. We also evaluated pharmacological combination partners enhancing the therapeutic potential of ANV419.

Methods The signaling properties of ANV419 were compared to recombinant hIL-2 and hIL-15 in human PBMCs. NK cell killing was analyzed in combination with trastuzumab. Mechanistic studies were performed to test the combination of ANV419 with checkpoint inhibitors using the H22 syngeneic tumor mouse model. The impact of checkpoint inhibitor combination on safety was tested in human whole blood.

Results To assess the impact of ANV419 treatment, human PBMCs were analyzed. NK and CD8 T cells showed comparable STAT5 phosphorylation kinetics upon treatment with ANV419, hIL-2 and hIL-15. Combination of ANV419 with the antibody-dependent cellular cytotoxicity (ADCC) inducing anti-HER2 antibody trastuzumab showed additive effects in NK cell killing compared to single trastuzumab treatment supporting clinical combination of ANV419 with treatments promoting NK cell mediated killing.

To assess the role of ANV419 in indications where T cells are involved in tumor resolution, ANV419 combination with the checkpoint inhibitors anti-PD1 or anti-CTLA4 was tested and showed additive effects in inducing tumor growth retardation in mice bearing H22 tumors compared to mice treated with single agents. Analysis of tumor infiltrating lymphocytes indicated intra-tumoral accumulation of NK and CD8 T cells. Treatment of whole blood with a combination of ANV419 and pembrolizumab (anti-PD1) or ipilimumab (anti-CTLA4) induced only slightly increased cytokine secretion compared to ANV419 alone and is therefore considered to have a reasonable safety profile.

Conclusions The data presented here further elucidate the in vitro and in vivo effects of ANV419 and support the rationale for clinical development in indications where NK and CD8 T cells are involved in tumor resolution as well as in combination with ADCC inducing treatments or checkpoint inhibitors.