High dose IL-2 has been used in treatment of metastatic melanoma and renal cell carcinoma. However, physiologic toxicities associated with IL-2 treatment, limited its use in anti-cancer therapies. Interleukin-2 (IL-2) is a cytokine that activates and expands tumor killing lymphocytes, but also potently activates suppressive T regulatory cells (Tregs) by binding to the heterotrimeric IL-2Rαβγ. NKTR-214 is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol and 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 Tregs.

**Objectives**

- To assess the therapeutic synergy of NKTR-214 with CTLA-4 and PD-1-based checkpoint blockade therapy or with peptide-vaccination in CT26 colon carcinoma and B16 melanoma models.
- To investigate impact of treatment on proliferation and apoptosis of effector CD8+ T cells and immunosuppressive CD4+Foxp3+ Tregs, as well as effector cytokines and chemokines in tumor and peripheral tissues.
- To identify mechanisms by which NKTR-214 mediates depletion of intratumoral Tregs while preserving them in periphery.

**Results**

**NKTR-214 synergizes with checkpoint blockade**

**NKTR-214 enhances proliferation and survival of CD8+ T effector cells while depleting intratumoral Tregs**

**NKTR-214 treatment induced cytokines and chemokines**

**NKTR-214 -induced CD8+ T-derived IFN-γ and TNF-α mediate selective depletion of intratumoral Tregs**

**Conclusions**

NKTR-214 synergizes with checkpoint blockade as well as with vaccination to improve the survival, proliferation and tumor infiltration of effecter CD8+ T cells while promoting selective intratumoral depletion of Tregs to establish effective anti-tumor immunity.