The adoptive cell transfer (ACT) of genetically engineered T cells expressing cancer-specific TCR in combination with high dose interleukin-2 (IL-2) is able to induce effective anti-tumor response. However, tumors frequently relapse after an initial effective response and the known toxicities of IL-2 further limit use of this therapy. 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-2 receptor αβγ pathway to preferentially activate and expand effector CD+ T and NK cells over Tregs in the tumor.

NKTR-214 is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol (PEG), designed to provide sustained signaling through the IL-2Rαβγ pathway to preferentially activate and expand effector CD+ T and NK cells over Tregs in the tumor. NKTR-214 is being evaluated in an outpatient setting in a Phase 2 expansion trial. NKTR-214 has a favorable safety and tolerability profile.

Here we evaluated the tumor immunology, biodistribution of CD8 T cells by immuno-imaging and anti-tumor activity of NKTR-214 in the pre-clinical model of pmel-1 ACT in the B16F10 tumor melanoma model.

NKTR-214 provides significant anti-tumor growth delay in combination with ACT compared to IL-2 and ACT+

Increased T cell expansion in the spleen and homing to and persistence in the tumor is associated with NKTR-214 treatment.

NKTR-214 elicits a marked upregulation of polyfunctionality in Thy1.1 specific T cells in either spleen or tumor infiltrate compared to IL-2. The persistent and tumor-specific induction of cytotoxic T cells provided by NKTR-214 supports its combination with cell-based therapies.

Results

**NKTR-214 provides significant anti-tumor growth delay in combination with ACT compared to IL-2**

**NKTR-214 elicits a marked upregulation of polyfunctionality in Thy1.1 specific T cells in either spleen or tumor infiltrate compared to IL-2**

**NKTR-214 increases expression of genes associated with T cell cytotoxicity and memory**

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**NKTR-214 promotes persistent proliferation of tumor-specific Thy1.1 T cells, but not Tregs in tumor**

**NKTR-214 increases expression of genes associated with T cell cytotoxicity and memory**

**Conclusion**

- ACT+NKTR-214 is well tolerated and provides a robust anti-tumor response in the aggressive B16F10 melanoma.
- Treatment with NKTR-214 enhances antigen-specific CD8 T cells into the tumor but not regulatory T cells. The CD8 T cells in tumor durably persist. Peripheral tissue (kidney, liver) are relatively spared of CD8+ T cells.
- The persistent and tumor-specific induction of cytotoxic T cells provided by NKTR-214 supports its combination with cell-based therapies.
- In the clinic, NKTR-214 is dosed administered in an outpatient setting and provides an activated TIL phenotype in human tumors, similar to these observations in the immune modeling.

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