NKTR-214 (CD122-biased agonist) and NKTR-262 (TLR7/8 agonist) combination treatment pairs local innate immune activation with systemic CD8+ T cell expansion to enhance anti-tumor immunity

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Introduction
The abscopal effect refers to the ability of localized radiation to trigger systemic anti-tumor effects. However, with radiation therapy (RT) alone, the abscopal effect is exceedingly rare.

Combining local RT with immunotherapy such as NKTR-214, a CD122-biased cytokine agonist conjugated with releasable polyethylene-glycol (PEG) chains, increases abscopal response rates, but still leaves room for improvement.

The biological mechanism driving the abscopal response is yet to be fully understood, but immunosuppression is thought to contribute to low abscopal response rates.

Toll-like receptor (TLR) signaling can induce APC differentiation and reduce tumor microenvironment immune suppression.

We hypothesized that combination treatment with a novel TLR7/8 targeting agent, NKTR-262, with NKTR-214 will activate innate and adaptive anti-tumor immune responses that will increase abscopal tumor responses.

Finally, comparison of NKTR-214 combined with either RT or NKTR-262, will reveal mechanisms driving abscopal responses.

Methods

**1 NKTR-214/NKTR-262 treatment improves abscopal responses through a CD8 T cell dependent mechanism**

- **Vehicle control**
- **RT**
- **NKTR-214**
- **NKTR-262**
- **NKTR-214/NKTR-262**
- **NKTR-214/NKTR-262 aCD4**
- **NKTR-214/NKTR-262 aCD8**

**2 Peripheral blood CD8 T cell responses correlate with overall tumor burden**

- **Vehicle control**
- **NKTR-214**
- **NKTR-214/RT**
- **NKTR-214/NKTR-262**

**3 Intratumoral CD8 T cell responses correlate with tumor burden**

- Data presented as percent of population (top row) and cell density (bottom row).
- Statistical significance was determined using Students T test between the two combination groups.
- Cell densities were compared to tumor burden for the treated and abscopal tumor (heat map below).
- CD8 T cell responses correlate strongly with abscopal tumor size.
- Spearman correlation of tumor burden 7 dpt vs TIL cells/mm².

**4 NKTR-214/NKTR-262 induces less exhausted and more active CD8 T cell responses**

- NKTR-214/NKTR-262 combination treatment resulted in CD8 T cells with reduced expression of exhaustion markers PD-1, Tim3, and Lag3.
- NKTR-214 also had reduced expression of PD-1. N=4-8 from two independent experiments.
- Statistical significance was determined using Students T test between the two combination groups.
- Naïve T cells (CT26 tumors treated with NKTR-214/NKTR-262) had a greater tumor CD8+ Nur77+ cell density, which also expressed increased GzmA levels.
- NKTR-214/NKTR-262 induces more functional cells, which is represented by a relationship between those cells and tumor size in the NKTR214/NKTR-262 treated mice. N=4 from one experiment.

**5 NKTR-214/NKTR-262 TME favors M1 monocytes**

- Data presented as percent of population or a ratio of M1/M2 based on iNOS and Arg1 expression. N>4 from one experiment.
- NKTR-214/NKTR-262 combination treatment resulted in monocytic cells (CD11b+Ly6C+Ly6G-) with increased iNOS expression.
- Data is presented as percent of population or a ratio of %M1/%M2 based on iNOS and Arg1 expression. N>4 from one experiment.
- The effect. N>10 from two independent experiments.
- Statistical significance was determined using a 1-way ANOVA comparing all groups against NKTR-214/NKTR-262, with a p-value cutoff of 0.05.
- The data suggests that NKTR-262 may alter the TME to be less suppressive, thereby supporting a more effective adaptive response.

Conclusions

- NKTR-214/NKTR-262 significantly increases the abscopal responses in comparison to NKTR-214/RT combination therapy in a CD8 T cell dependent manner.
- Across all treatment groups, peripheral CD8 T cells correlate with tumor burden 7 days post treatment.
- NKTR-214/NKTR-262 combination treatment results in an increased density of CD8 T cells in both the treated and abscopal tumors. These CD8 T cells have increased GzmA expression and reduced conversion to an exhausted phenotype (PD-1, Tim3, Lag3).
- These active CD8 T cells are supported by a less suppressive tumor microenvironment, demonstrated by the increased M1/M2 monocytic ratio in NKTR-214/NKTR-262 treated animals.

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