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.
- The biologic 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**

- Implant dual flank tumors in BALB/c mice
- Treatment regimen:
  - Vehicle control
  - RT
  - NKTR-214
  - NKTR-262
  - NKTR-214/NKTR-262

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

- CD8+ T cell densities were compared to tumor burden for the treated and vehicle control groups.
- Comparison between the two combination groups using Students T Test.
- NKTR-214/NKTR-262 combination treatment resulted in monocytic cells (CD11b+Ly6C+Ly6G-) with increased iNOS expression, conversion to an exhausted phenotype (PD-1, Tim3, Lag3).
- NKTR-214/NKTR-262 significantly increases the abscopal responses in comparison to other treatment groups.

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

- Data is presented as percent of population or ratio of M1/M2 based on iNOS and Arg1 expression.
- NKTR-214/NKTR-262 combination treatment resulted in monocytic cells with increased expression of M1 markers (CD11b+Ly6C+Ly6G+) and decreased expression of M2 markers (CD11b+Ly6C+Ly6G+).
- Correlation of tumor burden and tumor size was demonstrated by the increased M1/M2 ratio.
- 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 tumor. 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 monocyte ratio in NKTR-214/NKTR-262 treated animals.

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