Harnessing the innate and adaptive immune system to eradicate treated and distant untreated solid tumors

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**INTRODUCTION**

- Tumor antigen release and T cell priming by antigen presenting cells is a critical first step for tumor growth inhibition by the adaptive immune system
- Toll-like-receptor (TLR) stimulation can induce differentiation of functional antigen presenting cells in the tumor environment and reduce immune suppression in tumors facilitating T cell priming
- Pharmacological induction of tumor antigen presentation combined with sustained in vivo expansion of tumor specific CD8 T cells can potentially increase diversity and numbers of tumor killing cytotoxic T cells enabling efficacious anti-tumor immune therapies
- Combination treatment with a novel intratumoral TLR7/8 targeting agent NKTR-262 and a systemic CD122-based agonist NKTR-214 leads to synergistic activation of innate and adaptive anti-tumor immune response resulting in highly efficacious growth inhibition of treated and abscopal lesions in multiple preclinical mouse tumor models
  - Intratumorally delivered NKTR-262 provides local sustained release of TLR7/8 agonist with minimal systemic exposure
  - Systemic sustained CD122-based IL-2 pathway activation by NKTR-214 expands and maintains tumor infiltrating CD8+ T cell clones

**NKTR-262 and NKTR-214 engage non-overlapping immune mechanisms enhancing antigen presentation and anti-tumor T cell response**

**RESULTS**

Complete anti-tumor immune response cascade induction by NKTR-262 and NKTR-214 – combination treatment optimally couples locally initiated intratumoral innate immune activation with systemic expansion and infiltration of cytotoxic tumor reactive CD8 T cells

The injected tumors exhibit extended exposure to TLR7/8 agonist with minimal systemic exposure after local NKTR-262 administration

Right flank tumors in mice bearing subcutaneous bilateral CT26 tumors were treated intratumorally with 10 µg of NKTR-262 (0.1 µg or 10 µg) on Day 0, NKTR-214 (0.8 mg/kg) was administered IV on Day 4. Immune cells in blood and in both treated and abscopal tumors were analyzed by flow cytometry on Day 1 (NKTR-262 single agent activity) and Day 7 (NKTR-262 + NKTR-214 combination activity), *(p<0.05 with bars indicating comparisons)*

Right flank tumors in mice bearing subcutaneous bilateral CT26 tumors were treated intratumorally with NKTR-262 (10 µg). NKTR-262 and released TLR7/8 agonist concentrations were measured from both treated and abscopal left flank tumors and from plasma at indicated timepoints after treatment.

Rapid and transient activation of TLR7 pathway and type I interferon response genes in NKTR-262 treated tumors

**CONCLUSIONS**

- Intratumoral NKTR-262 treatment simultaneously induces tumor antigen release and activation of antigen presenting cells
- NKTR-262 and NKTR-214 combination treatment relieves immune suppression selectively in tumor environment facilitating CD8 T cell activity
- NKTR-262 design enables TLR7/8 agonist release and induction of proinflammatory cytokines at the injection site reducing systemic exposure
- NKTR-262 and NKTR-214 combination treatment optimally couples localized innate immune activation to systemic CD8 T cell expansion enhancing cytotoxic T cell infiltration and activity in tumor lesions