Poster #3755

Comprehensive Antitumor Immune Activation by a Novel TLR 7/8 Targeting Agent NKTR-262 Combined With CD122-Biased Immunostimulatory Cytokine NKTR-214

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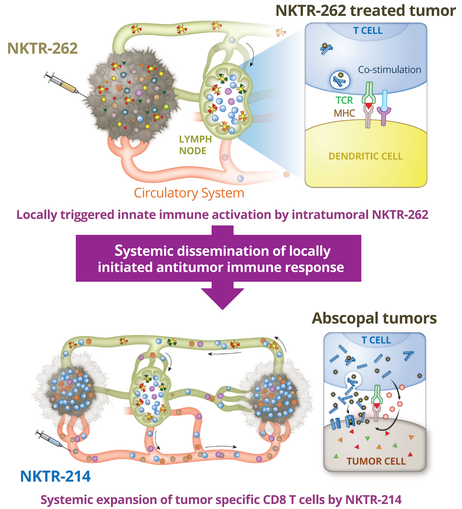
INTRODUCTION

- 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-biased agonist NKTR-214 leads to synergistic activation of innate and adaptive anti-tumor immune response resulting in highly efficacious growth inhibition of NKTR-262 treated and abscopal lesions in multiple preclinical mouse tumor models
- NKTR-262 and NKTR-214 engage non-overlapping immune mechanisms enhancing antigen presentation and anti-tumor T cell response
  - Intratumorally delivered NKTR-262 provides localized TLR7/8 agonism triggering effective tumor antigen presentation to T cells
  - Systemic sustained CD122-biased IL-2 pathway activation by NKTR-214 expands and maintains tumor reacting CD8$^+$ T cell clones

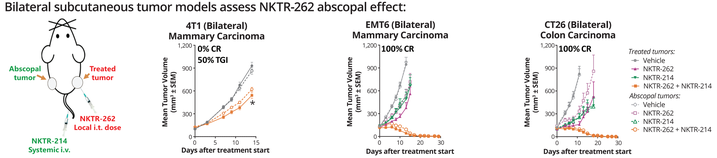
MECHANISM OF ACTION OF NKTR-262 AND NKTR-214 COMBINATION TREATMENT



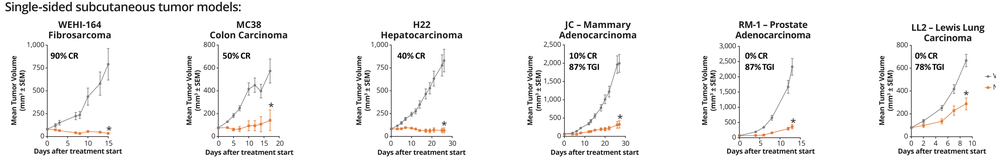
RESULTS

Effective tumor growth inhibition by combining NKTR-262 with NKTR-214 in multiple syngeneic mouse tumor models

Bilateral subcutaneous tumor models assess NKTR-262 abscopal effect:

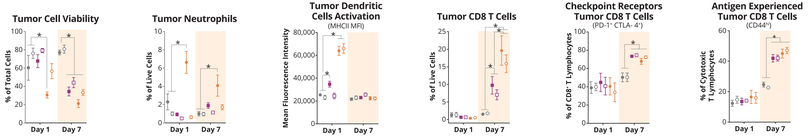


Single-sided subcutaneous tumor models:

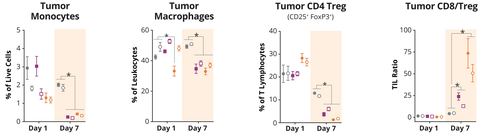


A single NKTR-262 dose (20 µg) combined with NKTR-214 (0.8 mg/kg, i.v., q9d x 3 doses) inhibits tumor growth in syngeneic mouse tumor models. Only the right flank tumor was treated with NKTR-262 in bilateral models to assess abscopal efficacy in the untreated left flank tumors (*, p<0.05 relative to vehicle).

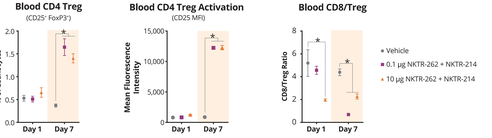
NKTR-262 and NKTR-214 combination treatment couples locally initiated intratumoral antigen release and presentation with systemic expansion and infiltration of cytotoxic tumor reactive CD8 T cells



NKTR-262 + NKTR-214 combination treatment leads to relative decrease of immune suppressive cells in tumors

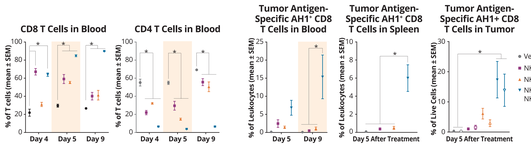


Regulatory T cells are expanded selectively in blood

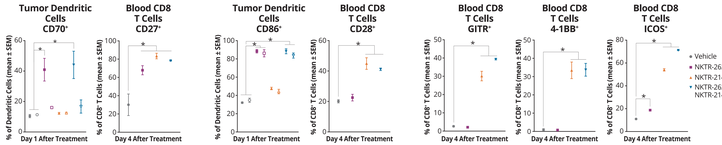


Right flank tumors in mice bearing subcutaneous bilateral CT26 tumors were intratumorally treated with NKTR-262 (0.1 µg or 10 µg) on Day 0. NKTR-214 (0.8 mg/kg) was administered IV on Day 4. Immune cells in blood and in both NKTR-262 treated and abscopal tumors (solid and open symbols, respectively) 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, n=4, mean ± SEM)

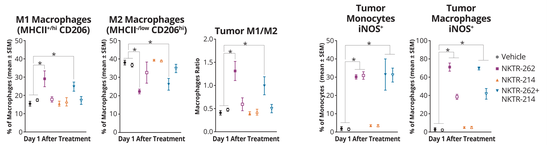
NKTR-262 and NKTR-214 combination selectively expands CD8 T cells and systemically sustains tumor specific T cells



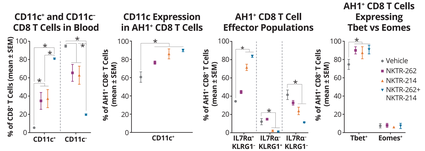
T cell costimulatory ligands and receptors are induced by NKTR-262 and NKTR-214 respectively coupling innate and adaptive immune signals in combination treatment



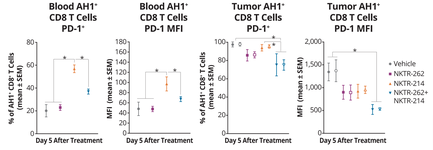
NKTR-262 increases M1 to M2 macrophage ratio in treated tumors and activates iNOS expression in intratumoral monocytes and macrophages



NKTR-262 and NKTR-214 driven efficacy in CT26 model correlates with expansion of tumor specific CD8 T cells with Tbet$^+$ IL7Rα$^+$ CD11c$^+$ effector phenotype in blood



NKTR-262 and NKTR-214 modulate PD-1 expression in tumor antigen specific CD8 T cells in blood and tumors



Right flank tumors in mice bearing subcutaneous bilateral CT26 tumors were intratumorally treated with 10 µg NKTR-262 and intravenously administered 0.8 mg/kg NKTR-214 as single agents or in combination. Immune cells in blood and in both NKTR-262 treated (solid symbols) and untreated (open symbols) tumors were analyzed by flow cytometry at indicated timepoints post treatment. Tumor antigen specific CD8 T cells were labeled with AH1 tumor antigen specific MHC-peptide dextramers. (*, p<0.05 with bars indicating comparisons, n=3-4, mean ± SEM)

CONCLUSIONS

- NKTR-262 and NKTR-214 combination demonstrates efficacy in a broad range of syngeneic tumor models with diverse histologies
- Intratumoral NKTR-262 treatment concurrently induces tumor antigen release and activation of antigen presenting cells enhancing CD8 T cell tumor infiltration
- NKTR-262 and NKTR-214 combination reduces relative levels of macrophages and monocytes in tumors potentially relieving intratumoral immune suppression
- NKTR-262 and NKTR-214 combination reduces relative levels of Tregs in tumors while selectively expanding Tregs in periphery potentially restricting CD8 T cell activity to tumor lesions
- Combining NKTR-262 with NKTR-214 expands and sustains substantially larger fraction of tumor antigen specific CD8 T cells than NKTR-214 monotherapy
- NKTR-262 and NKTR-214 induce T cell costimulatory ligands and receptors on dendritic cells and T cells respectively leading to coordinated CD8 T cell costimulation in combination treatment
- NKTR-262 increases M1/M2 macrophage ratio in treated tumors and induces iNOS expression in macrophages and monocytes potentially facilitating T cell extravasation from tumor vasculature
- NKTR-262 and NKTR-214 combination favors generation of tumor specific effector cells with memory precursor phenotype
- NKTR-262 and NKTR-214 combination reduces PD-1 expression levels in PD-1$^+$ tumor infiltrating CD8 T cells suggesting reduced negative feedback in combination treatment
- NKTR-262 and NKTR-214 combination optimally couples localized innate immune activation to systemic CD8 T cell expansion enhancing cytotoxic T cell infiltration and activity in tumor lesions

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