Systemic anti-tumor immunity and immune memory formation by a novel TLR7/8 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 has the potential to elicit clonal expansion of tumor antigen-specific cytotoxic T cells enabling efficacious anti-tumor immune therapies with durable and specific anti-tumor immune memory formation
- 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 abscessal lesions in multiple preclinical mouse models
- NKTR-262 and NKTR-214 engage non-overlapping immune mechanisms enhancing antigen presentation and anti-tumor T cell response
- NKTR-262 + NKTR-214 combination therapy is being evaluated in select solid tumor indications in a phase 1/2 clinical study (NCT03435640)

RESULTS

NKTR-262 and NKTR-214 combination treatment couples locally initiated tumor antigen release and presentation with systemic CD8 T cell expansion and tumor infiltration

Mice bearing subcutaneous bilateral CT26 tumors were treated in the right flank tumors with NKTR-262 (0.1 µg or 10 µg, IT) on Day 0. NKTR-214 (0.8 mg/kg, IV) was administered on Day 4. Immune cells in blood and both NKTR-262 treated and abscessal left flank tumors (solid and open symbols, respectively) were analyzed by flow cytometry on Day 1 (NKTR-262 single-agent effect) and Day 7 (combination treatment effect). (*, 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 antigen specific T cells

Mice bearing bilateral CT26 tumors were treated in the right flank tumors with 10 µg NKTR-262 (IT) and 0.8 mg/kg NKTR-214 (IV) administered as single agents or in combination. Immune cells in blood and both NKTR-262 treated and abscessal left flank tumors (solid symbols) and untreated left flank (open symbols) tumors were analyzed by flow cytometry at indicated timepoints. Tumor antigen-specific CD8 T cells were labeled with AH1 specific MHC-peptide dextramers. (*, p<0.05, n=3-4, mean ± SEM)

Systemic T cell repertoire modulation in NKTR-262 and NKTR-214 treated tumor-bearing mice – combination treatment increases clonal T cell expansion in blood and tumors and enhances systemic distribution of tumor T cell clones

Fraction of tumor T cell clones found in matched post-treatment blood was measured in bilateral CT26 tumor-bearing mice at indicated timepoints after NKTR-214 (0.8 mg/kg, IV) single agent or combination treatment with NKTR-262 (10 µg, dosed IT into the right flank tumors). TCR usage was determined utilizing ImmunoSEQ platform from Adaptive Biotechnologies

CONCLUSIONS

- 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 results in sustained preferential expansion of CD8 T cells and a substantially larger fraction of tumor antigen-specific CD8 T cells than NKTR-214 monotherapy
- NKTR-262 and NKTR-214 combination demonstrates curative efficacy in multiple syngeneic tumor models and durable anti-tumor immunity in complete responders
- NKTR-262 and NKTR-214 combination treatment increases clonality and enhances clonal expansion of T cell clones in blood and tumors
- 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