INTRODUCTION

- Tumor antigen release and T cell priming by antigen presenting cells is a crucial first step for T cell-mediated immune recognition and tumor cell killing.
- Toll-like receptor (TLR) stimulation can induce differentiation of functional antigen presenting cells, plasticity of the tumor microenvironment and reduce suppression of T cell responses.
- 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-reactive T cells.
- Combination treatment with a novel intratumoral TLR7/8 targeting agent NKTR-262 and a systemic CD122-biased IL-2 pathway activator NKTR-214 leads to synergistic activation of innate and adaptive immune response resulting in high efficacy of antitumor activity of these agents when used in combination.

NKTR-262 and NKTR-214 engage non-overlapping immune mechanisms enhancing antigen presentation and antitumor T cell responses.
- Intratumorally delivered NKTR-262 provides localized TLR7/8 agonism triggering effective tumor antigen presentation to T cells.
- Systemically sustained CD122-biased IL-2 pathway activation by NKTR-214 expands and maintains systemic T cell responses.

RESULTS

- Blistered subcutaneous tumor models.
- Single-sided subcutaneous tumor models.
- Intratumorally delivered NKTR-262 provides localized TLR7/8 agonism triggering effective tumor antigen presentation to T cells.
- Systemically sustained CD122-biased IL-2 pathway activation by NKTR-214 expands and maintains systemic T cell responses.

Figures: Right flank tumors in mice bearing subcutaneous bilateral CT26 tumors were intratumorally treated with NKTR-262 (0.1 µg kg⁻¹, 5X q2d). Tumor volume was measured in the unilateral tumor at days 5, 7, 9, 11, and 13 relative to vehicle.

MECHANISM OF ACTION OF NKTR-262 AND NKTR-214 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.

NKTR-262 and NKTR-214 combination reduces PD-1 expression levels in PD-1 and checkpoint receptor expressing regulatory T cells.

NKTR-262 and NKTR-214 combination optimally couples localized innate immune activation to systemic CD8 T cell expansion enhancing cytotoxic T cell infiltration.

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 relaxing 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.
- Combination NKTR-262 with NKTR-214 increases tumor CD11c+ and CD11c– tumor associated macrophage populations with substantial lung and liver infiltration.
- NKTR-262 and NKTR-214 induce T cell cytostimulatory ligands and receptors on dendritic cells and T cells respectively leading to coordinated CD8 T cell infiltration in combination treatments.
- 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 combination increases M1 to M2 macrophage ratio in treated tumors and activates iNOS expression in intratumoral macrophages.
- NKTR-262 and NKTR-214 combination increases M2 macrophage population in tumors and activates iNOS expression in intratumoral macrophages.
- NKTR-262 and NKTR-214 combination activates systemic immune responses to systemic CD8 T cell expansion enhancing T cell infiltration and activity in tumor lesions.

Nektar Therapeutics, San Francisco, CA, USA