COMBINING BEMPEGALDESLEUKIN (CD122-PREFERENTIAL IL-2 PATHWAY AGONIST) AND NKTR-262 (TLR7/8 AGONIST) PAIRS LOCAL INNATE ACTIVATION WITH SYSTEMIC CD8+ T CELL EXPANSION TO ENHANCE ANTI-TUMOR IMMUNITY

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Background Tumor cell death caused by radiation therapy (RT) can trigger anti-tumor immune responses in part because dying cells release adjuvant factors that amplify and sustain DC and T cell responses. We previously demonstrated that bempegaldesleukin (BEMPEG; NKTR-214, a first-in-class CD122-preferential IL-2 pathway agonist), significantly enhanced the anti-tumor efficacy of RT through a T cell-dependent mechanism. Because RT can induce either immunogenic or tolerogenic cell death, depending on a multitude of factors (radiation dose, cell cycle phase, and tumor microenvironment), we hypothesized that providing a specific immunogenic adjuvant, like intratumoral NKTR-262, a novel toll-like receptor (TLR) 7/8 agonist, to the tumor site would further improve systemic tumor-specific immunity by promoting synergistic activation of local immunostimulatory innate immune responses. Therefore, we evaluated whether intratumoral NKTR-262, combined with systemic BEMPEG treatment would result in improved tumor-specific immunity and survival compared to BEMPEG combined with RT.

Methods Tumor-bearing mice (CT26; EMT6) received BEMPEG (0.8 mg/kg; iv), RT (16 Gy x 1), and/or intratumoral NKTR-262 (0.5 mg/kg). Flow cytometry was used to evaluate CD4+ and CD8+ T cell activation status in the blood and tumor (7 days post-treatment). The contribution of specific immune subsets was determined by depletion of CD4+, CD8+, or NK cells. CD8+ T cell cytolytic activity was determined in vitro with an Incucyte assay. Data are representative of 1–2 independent experiments (n=5–14/group) and statistical significance was determined by 1-way ANOVA (p-value cut-off of 0.05).

Results BEMPEG/NKTR-262 resulted in significantly improved survival compared to BEMPEG/RT. Both combination therapies were CD8+ T cell dependent. However, response to BEMPEG/NKTR-262 was characterized by a significant expansion of activated CD8+ T cells (GzmA+; Ki-67+; ICOS+; PD-1+) in the blood, which correlated with reduced tumor size (p<0.05). In the tumor, BEMPEG/NKTR-262 induced higher frequencies of GzmA+ CD8+ T cells exhibiting reduced expression of suppressive molecules (PD-1+, TIM-3+), compared to BEMPEG/RT. Additionally, CD8+ T cells isolated from BEMPEG/NKTR-262-treated tumors had greater cytolytic capacity than those from BEMPEG/RT-treated mice.

Conclusions Combining BEMPEG with NKTR-262 lead to a more robust expansion of activated CD8+ T cells compared to the BEMPEG/RT combination. Enhancement of the activated CD8+ T cell response in mice treated with NKTR-262 in combination with BEMPEG suggests that intratumoral TLR stimulation provides superior antigen presentation and costimulatory activity compared to RT. A clinical trial of BEMPEG/NKTR-262 for patients with metastatic solid tumors is in progress (NCT03435640).

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