NKTR-214 synergizes with radiotherapy to drive tumor regression

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BACKGROUND

-Interleukin-2 (IL-2) is a cytokine that activates tumor killing lymphocytes, but also activates suppressive T regulatory cells. NKTR-214 is an IL-2 receptor-based cytokine agonist conjugated with multiple re-leaseable chains of polyethylene glycol.
-NKTR-214 is designed to provide sustained signaling through the heterodimeric IL-2 receptor (IL-2Rβγ), which preferen-tially activates effector CD8 T and NK cells over regulatory CD4 T cells.
-NKTR-214 is being evaluated in phase I/II dose escalation trials as a single agent and as a combination with anti-PD-1 (nivolumab) in collaboration with Bristol-Myers Squibb.
-NKTR-214 has a favorable safety and tolerability profile.

-We evaluated the pharmacodynamic effects and therapeutic efficacy of NKTR-214 plus radiation therapy (RT).
-We hypothesized that RT would induce the release of tumor-specific antigens, leading to more effective T cell responses following NKTR-214.

EXPERIMENTAL DESIGN

Model

CT26 (colon carcinoma) or MCA-205 (sarcoma)

CT26 (BALB/c; n=14) and MCA-205 tumor-bearing mice were treated with NKTR-214+/-RT. Eight days later, peripheral blood, lymph nodes, and tumor were harvested and the extent of Nur77-GFP expression in CD4 and CD8 T cells was determined by flow cytometry. In additional cohorts of mice, the frequency of tumor-specific AH1-A5 tetramer+ CD8 T cells was determined by flow cytometry. Graphs represent the mean+/-SD of n=3 (LN/tumor) or n=17 (PBL) per group.

PERIPHERAL ACTIVATION

TUNOR-SPECIFIC RESPONSES

Figure 2. NKTR-214/RT synergizes to elicit tumor-reactive CD8 T cells. CT26 tumors were implanted into wild-type or Nur77-GFP Tg (BAlb/c) reporter mice on day 0. Ten days later, tumor-bearing mice received NKTR-214+/-RT as in Figure 1. Eight days later, peripheral blood, lymph nodes, and tumor were harvested and the extent of Nur77-GFP expression in CD4 and CD8 T cells was determined by flow cytometry. In additional cohorts of mice, the frequency of tumor-specific AH1-A5 tetramer+ CD8 T cells was determined by flow cytometry. Graphs represent the mean+/-SD of n=3 (LN/tumor) or n=17 (PBL) per group.

TUMOR ENVIRONMENT REMODELLING

Figure 3. Leukocyte distribution following NKTR-214/RT. CT26 tumor-bearing mice were treated with NKTR-214+/-RT. Eight days later, the frequency of the indicated cell populations was determined by flow cytometry. Graphs depict the mean+/-SD of n=1/group.

Figure 4. Whole tumor transcriptome following NKTR-214/RT treatment. Eight days following treatment (as described above), whole tumors were harvested from CT26 tumor-bearing mice and mRNA isolated for gene expression analysis with Affymetrix Mouse 430 2.0 arrays (n=3 biological replicates per group). Graphs represent the change in gene expression (Log2) relative to control (vehicle) treated tumors.

Figure 5. Effects of NKTR-214/RT on tumor growth and survival. MCA-205 (left) or CT26 (right) tumor-bearing mice were treated with NKTR-214+/-RT as described previously. Tumor growth (area; mm²) was determined every 2-3 days. Graphs depict the survival (top) or individual tumor growth curves (n=6/group).

CONCLUSIONS

-Single dose NKTR-214 (0.8 mg/kg) induced robust peripheral T cell proliferation (Ki-67), differentiation (GzmA), CD122 (IL-2Rb) expression, and upregulation of the immune checkpoints PD-1 and TIM-3, while the addition of RT (20 Gy x 1) did not affect many of these parameters in the peripheral blood.

-Combined therapy increased the frequency of tumor-reactive CD8 T cells in the target (irradiated) tumors as measured by increased TCR ligation (Nur77-GFP+) and AH1-A5 tetramer staining.

-Transcriptional profiling of the target (irradiated) tumors revealed significant changes in T cell recruitment, differentiation, and signaling following NKTR-214 and/or RT. NKTR-214 treatment significantly increased Gzmd-GzmG and may alter the frequency of lymphatic endothelial cells (LYVE1).

-A single dose of NKTR-214+RT exhibited significant therapeutic efficacy in MCA-205 tumor-bearing mice, but efficacy was limited in the CT26 model.

-Multi-dose studies of NKTR-214 and radiation are underway.

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