Rucaparib is a small molecule poly(ADP-ribose) polymerase (PARP) inhibitor and has demonstrated activity in BRCA-mutated tumors through synthetic lethal[1]. Rucaparib has also been shown to synergize with checkpoint inhibitors by increasing intratumoral CD1 T-cell infiltration and activating the STING pathway[2]. Oral twice daily (BID) rucaparib is approved by the U.S. Food and Drug Administration for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and for the treatment of adult patients with germline or somatic BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies[3]. Rucaparib, currently being evaluated for the treatment of prostate, bladder, breast, pancreas, and other cancers.

**Background**

**Rucaparib**

- Rucaparib is a small molecule poly(ADP-ribose) polymerase (PARP) inhibitor and has demonstrated activity in BRCA-mutated tumors through synthetic lethal[1].
- Rucaparib has also been shown to synergize with checkpoint inhibitors by increasing intratumoral CD1 T-cell infiltration and activating the STING pathway[2].
- Oral twice daily (BID) rucaparib is approved by the U.S. Food and Drug Administration for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and for the treatment of adult patients with germline or somatic BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies[3].

**NKTR-214**

- Interleukin-2 (IL-2) is a cytokine that activates and expands tumor-destroying lymphocytes, but also activates suppressive regulatory T cells (Tregs) through the heterodimeric IL-2R complex. In addition, a high dose of IL-2 (10 million in all experiments) is required.
- NKTR-214, a bispecific agent that targets the IL-2 pathway, provides sustained signaling through the heterodimeric IL-2 receptor (IL-2Rβ) and preferentially activates and expands natural killer (NK) and effector CD8 T cells over Tregs in the tumor microenvironment.
- NKTR-214 is currently in multiple phase 1 and 2 clinical trials in combination with checkpoint inhibitors (NCT02853045, NCT02319389). NKTR-214 is dosed once every 4 weeks in an outpatient setting.

**Rucaparib + NKTR-214**

- The goal of these studies was to evaluate the antitumor activity of the combination of a targeted therapy (rucaparib) and a direct T-cell stimulator (NKTR-214) in mouse models of cancer.

**METHODS**

**Rucaparib + NKTR-214 Combination Therapy Produces Tumor-Free Mice in a BRCA2- Synergistic Ovarian Cancer Model**

**Rucaparib + NKTR-214 Combination Therapy Results in Differential Immune-Related Gene Expression Profiles in Tumors**

**CONCLUSIONS**

- **Rucaparib + NKTR-214** provided enhanced survival as compared to either agent alone in BRCA1 (ID8 F3) and BRCA2 (BR5FVB1) ovarian cancer models.
- **NKTR-214** increased also intratumoral immune cell infiltration and enhanced the expression of genes involved in multiple immune-stimulating pathways over either agent alone.
- **NKTR-214** induced highly specific gene expression related to T-cell activation, proliferation, and increased intratumoral treatment-immune pathways. Combining both drugs synergized and enhanced the antitumor effects.
- The enhanced antitumor activity and survival observed with this combination treatment may be due to activation of immune cells and their penetration through the tumor microenvironment.
- The top figure shows genes in the infiltrating immune population that were differentially upregulated in rucaparib, NKTR-214, or the combination relative to vehicle. T-test significance was assessed with the gene expression data. The expression of each gene was significantly different between the monocytic and combination treatment groups. 15 genes were up-regulated, 7 were down-regulated, and 10 were not significantly different.
- **The results of the studies presented here provide strong support for evaluating the combination of rucaparib and NKTR-214 in patients.**