Rucaparib is a small molecule poly(ADP-ribose) polymerase (PARP) inhibitor and has demonstrated activity in A431 ovarian cancer tumors through synthetic lethality.\(^1\) Rucaparib has also been shown to synergize with checkpoint inhibitors by increasing DNA damage, intratumoral CD8+ 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 deleterious 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 is currently being evaluated for the treatment of prostate, bladder, breast, pancreas, and other cancers.\(^3\)

**Abstract**

**Efficacy and Immune Modulation of the Tumor Microenvironment with the Combination of the PARP Inhibitor Rucaparib and CD122-Biased Agonist NKTR-214**

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**Background**

Ongoing, Phase 2 clinical trials with the PARP inhibitor rucaparib,\(^1\) 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 deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies,\(^3\) are showing clinical activity in these settings.\(^3\)

**Objectives**

The current study was designed to assess the efficacy of rucaparib monotherapy and in combination with the CD122-biased agonist NKTR-214,\(^2\) in genetically relevant ovarian cancer models. The rationale for this study was based on recent findings showing that NKTR-214 is preferentially activating CD8+ T and natural killer (NK) cells.\(^2\)

**Methods**

**In Vivo Studies**

Orthotopic cancer models were established in FVB\(^1\)/BR5FVB1 (TP53\(^−/−\)) mice.\(^1\) Rucaparib (150 mg/kg days 1–5, 2018) or vehicle control was administered to these mice, followed by 214 Combination Therapy (days 6–21). Tumor volumes and body weights were assessed. Haematoxylin and eosin (H&E) stained sections were evaluated. Immunohistochemistry (IHC) was performed on formalin-fixed, paraffin-embedded (FFPE) tissues. The expression level of CD8+ T cells, NK cells, and the NK cell receptor NKG2D was investigated. The IFN-γ and IL-2 levels were measured using enzyme-linked immunosorbent assay (ELISA). The tumor-infiltrating lymphocytes (TILs) were also assessed using flow cytometry.

**Results**

Rucaparib + 214 Combination Therapy Induces Immune-Related Gene Expression Profiles in Tumors

- **Gene Expression Analysis**
  - **CD8 + T cell infiltration**
  - **NK cell infiltration**
  - **NKG2D expression**
  - **IL-2 and IFN-γ production**

**Conclusions**

The combination of rucaparib with NKTR-214 preferentially activates CD8+ T and NK cells, and reduces tumor growth in genetically relevant ovarian cancer models.