**Abstract**

**Rucaparib Induces IFN Type 1 Regulated Genes and Enhances Immune-Associated Tumor Suppression**

**Background**

The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib effectively kills homologous recombination (HR) deficient cells through inhibiting DNA repair causing DNA damage and apoptosis. Detection of cytotoxic DNA by the stimulator of interferon genes (STING) pathway mediates interferon (IFN) signaling and activates the immune system. Following rucaparib treatment, the accumulation of damaged DNA in HR-deficient tumors may elicit an immune response through STING signaling, and enhance rucaparib activity as a single agent or in combination with immune checkpoint blockade. To test this hypothesis, the efficacy and mechanism of rucaparib were evaluated using BRCA deficient syngeneic ovarian carcinoma models.

**Methods**

In vivo studies: Studies in the syngeneic ovarian cancer BRCA mouse models revealed that rucaparib treatment significantly reduced tumor burden. Treatment was initiated by established subcutaneous implantation of 1×10^6 BRCA cells and, rucaparib was administered by oral gavage at 200 mg/kg BID for 7 days. Tumor growth was monitored on the daily basis of Day 0 to Day 15. After the completion of treatments, tumors were harvested, weighed, and used for subsequent analyses. Flow cytometry and IHC analysis: Flow cytometry was performed using a BD FACScanto II flow cytometer interfaced with an automatic cell dispenser. For flow cytometry and IHC analysis, tumor tissue was fixed in 10% phosphate buffered formalin solution and embedded into paraffin. Anti-Cd4 depletion study: Anti-Cd4 antibody was used to deplete tumor-infiltrating CD4+ T cells. Anti-Cd4 was administered through intraperitoneal injection of 0.25 mg Q3D. The anti-Cd4 antibody was administered on Day 0, 3, and 6.

**Results**

Rucaparib demonstrates potent antitumor efficacy mediated through tumor infiltrating CD8 T cells

**Conclusions**

Rucaparib treatment in BRCA ovarian carcinoma cells, and at a combination concentration in BRCA+ cells, triggers IFN signaling through the STING pathway and induces expression of the chimeric Csf1 and Cxcl10 in vitro. The single agent efficacy of rucaparib in vivo is mediated through the activation of immune cells including CD8+ T cells and induction of IFN inducible genes. Rucaparib enhances the antitumor activity of the combination regimen and checkpoint inhibitors in the syngeneic tumor model. The combination rucaparib plus checkpoint blockade is currently being evaluated in prostate cancer xenograft and high-risk neuroblastoma xenograft models (NCT01108180).

**References**