Nonclinical Evaluation of Rucaparib in Tumors with Mutations in Non-BRCA1/2 Homologous Recombination Repair (HRR) Genes

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Rucaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved for treatment of patients with recurrent ovarian cancer or metastatic castration-resistant prostate cancer (mCRPC). Rucaparib treatment causes PARP inhibition, resulting in genome instability and tumor cell death.

HRR genes were included in this analysis to explore tumorigenic potential in other contexts. Additional methods can be found in the supplementary material. 

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Figure 3. Rucaparib Demonstrates Potent Activity in Tumors with Genetic or Epigenetic Alterations

**Rucaparib tumor growth inhibition (TGI) for BRCA1/2mutated or hypermethylated models (A)**

**BRCA1/2 tumors demonstrated increased TGI compared to wild type (WT) tumors across all models.**

- **Model BR1180**: Maximal TGI observed with Rucaparib 150 mg/kg BID. A 10-fold decrease in volume compared to baseline was observed after six weeks of treatment.

- **Model BRIP1**: Maximal TGI observed with Rucaparib 50 mg/kg QD. A 28-fold decrease in volume compared to baseline was observed after six weeks of treatment.

- **Model RAD51C hypermethylation**: Maximal TGI observed with Rucaparib 50 mg/kg QD. A 14-fold decrease in volume compared to baseline was observed after six weeks of treatment.

**Equivalent Rucaparib Responses in PDX Tumor Models with BRCA1/2 Genetic or Epigenetic Alterations**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Tumor-bearing tissues</th>
<th>TGI of Rucaparib (μM)</th>
<th>TGI of PARP Inhibitors (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td><strong>0.0001</strong></td>
<td><strong>0.001</strong></td>
<td><strong>0.1</strong></td>
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<tr>
<td>BAK</td>
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