PARPi (poly [ADP-ribose] polymerase inhibitors) are pharmacologic agents which primarily inhibit the PARP-1 and -2 toxicities of combined PARPi and Top1 inhibitors while improving efficacy. Despite the clear mechanistic rationale, combination of PARPi and irinotecan has been limited clinically, as both agents of PARPi, DNA damage induced by irinotecan is not efficiently repaired, ultimately leading to cell death [7].

Development of PARPi in combination with DNA damage agents has been limited by an increase in toxicities less [1], which may result in a better safety profile. In patients, etirinotecan pegol leads to greatly prolonged plasma SN38 exposure compared to irinotecan [2].

Conclusions: All combinations of etirinotecan pegol and rucaparib are well-tolerated, synergistic, and lead to 100% Prolonged Survival in the BRCA1-Deficient MX-1 Breast Cancer Model

Methods and Study Design

Tumor xenografts were initiated with M1 hormone breast cancer xenografts maintained by serial subcutaneous transplantation in female athymic nude (NCr/Nu) females. 8-week-old mice. On the day tumor implants were tested, mice received either a vehicle (0.2% methylcellulose - saline, 1:1, v:v) subcutaneously in the right flank, mice were randomized into treatment groups. (n=10) and all cohorts received p.o. once daily until all mice were euthanized. Mice were monitored for tumor response every week. Tumor size, weight and volume were measured and calculated. (2000 mg/d) for 2 consecutive weeks. Efficiency was measured by tumor growth delay and regression response rate. Complete regression + tumor volume ≤ 3 mm³ for 3 consecutive measurements.

Tumor-free survival + survival with complete regression at the termination of the study that the lowest doses of both agents.

Doses used in this study provide exposures of etirinotecan pegol (SN38 trough) and rucaparib that are achievable clinically, underscoring the translational relevance of these results. Combination studies of etirinotecan pegol and rucaparib are ongoing in ovarian patient-derived xenograft models in collaboration with Prof. Paul Halauskas at Mayo Clinic and Clinic Oncology. Further studies will assess the full potential of etirinotecan pegol and PARPi inhibitor combinations in additional tumor types.

Table 1. Statistical Results for Groups Treated with vehicle (n=10) or drug doses (n=10). Statistical analysis was performed using Kaplan-Meier survival analysis and log rank (Mantel-Cox) test.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Drug Dose</th>
<th>p-value</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent survival</td>
<td>Low Dose</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Percent survival</td>
<td>High Dose</td>
<td>0.01</td>
<td>0.001</td>
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<tr>
<td>Progression-free survival</td>
<td>Low Dose</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>High Dose</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to tumor-control</td>
<td>Low Dose</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to tumor-control</td>
<td>High Dose</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean tumor weight</td>
<td>Low Dose</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean tumor weight</td>
<td>High Dose</td>
<td>0.001</td>
<td>0.001</td>
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References: