Overcoming PARP Inhibitor Resistance in Cancers

Therapy designed to reinvigorate the effectiveness of PARP inhibitors

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Team

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70% of ovarian cancer patients will have recurrence & develop therapeutics-resistant disease

Cancers with BRCA mutation (defective HR repair) are sensitive to PARP inhibitors

Reversion of BRCA mutation to restore HR repair

As PARP Inhibitors become widely used, there will be an increase in patients who develop PARP inhibitor resistant cancers

Recurrent cancers without BRCA mutation are resistant to PARP inhibitors

AsPARP Inhibitors become widely used, there will be an increase in patients who develop PARP inhibitor resistant cancers

\[\text{Adapted from Iglehart JD, Silver DP. N Engl J Med 2009;361:189-191.}\]

Our team has developed DB4, a small molecule drug that inhibits HR repair. **DB4 + Olaparib combo provides effective therapy for cancers without BRCA mutation**

- PARP inhibitors are used for the treatment of ovarian, breast, prostate, and pancreatic cancers.

- The 2017 US PARP inhibitor market for ovarian cancer: $305.5 million. The 2023 market for ovarian, breast, prostate, and pancreatic cancers: **$2.2 billion.**

¶ Trade name: Lynparza®. It is an FDA-approved PARP inhibitor for the treatment of BRCA-mutated advanced ovarian cancer

DB4 demonstrates effectiveness to inhibit HR repair and increase DNA damage in cancers without BRCA mutation.

DB4 inhibits HR repair (HRR) in ovarian cancer cells.

DB4 + Olaparib combo increases DNA damage (γH2AX) in ovarian cancer cells.
DB4 + Olaparib combo inhibits ovarian cancer progression and increases the survival time of CDX tumor-bearing mice

DB4 + Olaparib combo reduces ascitic/abdominal distension

DB4 + Olaparib combo prolongs the survival time of mice
# Competitive Landscape for PARPi vs. PARPi + DB4 for Treatment of Various Cancer Types

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>PARPi</th>
<th>PARPi+DB4</th>
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</thead>
<tbody>
<tr>
<td>BRCA mutation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No BRCA mutation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PARP inhibitor-resistant</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Yes to No†</td>
<td>Yes</td>
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† Likelihood of YES reduces with each cancer recurrence following treatment.

The estimated market opportunity for DB4: $0.5-1 billion
Next Steps: Milestones & Cost for Development of DB4

1. Design and synthesize DB4 analogs for SAR studies to improve potency using cell-based assays (Team+CRO)
   - Cost: $100K
   - Months: 0-10

2. Identify leads and perform large-scale synthesis for PK/PD and toxicity studies in vivo (CRO)
   - Cost: $50K
   - Months: 11-16

3. Conduct efficacy studies using ovarian, breast, prostate cancer PDXs in mouse models (CRO)
   - Cost: $150K
   - Months: 17-24