### INTRODUCTION

- **RP12146** is an orally bioavailable, potent inhibitor of PARP 1/2 and showed growth inhibitory activity in solid tumor cell lines. In a rat in vivo model, myelosuppression/neutropenia was not seen due to the relatively lower distribution of RP12146 into the bone marrow (AACR 2022).
- Based on promising preclinical data, a Phase I dose escalation study to assess safety and PK was conducted in patients likely to harbour HRR mutations. The dose expansion part aims to establish proof of concept of clinical activity in patients enriched with HRR defects.

### PHASE I STUDY

#### Pre-Clinical Activity

<table>
<thead>
<tr>
<th>In-Vitro studies</th>
<th>PARP1</th>
<th>PARP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic potency, IC50 (nM)</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>GI50 in U87.MG cell line (µM)</td>
<td>1.47</td>
<td></td>
</tr>
</tbody>
</table>

**PARP Trap assay**

Figure 1. PARP Trapping effect on the DNA binding activities of recombinant human PARP1 and PARP2 enzymes.

**Erythroid surface marker**

Figure 2. Effect on growth of erythroid progenitors manifested by erythroid surface markers on human CD34+ bone marrow cells.

**Pre-Clinical Activity**

- **RP12146** demonstrated more potent PARP trapping for PARP1 compared to PARP2.
- **RP12146** showed lower potency in inhibiting growth of erythroid progenitors as compared to Olaparib.

### METHODS

- Open-label, two-part study to assess the safety, PK and efficacy in patients with locally advanced or metastatic solid tumors. RP12146 was given orally in a 28-day cycle until disease progression. (NCT0002668).
- Part 1 was a dose-escalation, 3+3 design, MTD determination study and enrolled pts who have tumors which are known to harbour DNA repair deficiencies. Retrospective HRR mutation testing was done using tumor biopsy and blood.
- Part 2 was dose expansion at the MTD (or optimal dose) and enrol ovarian, breast cancer, and prostate cancer pts with a confirmed deleterious HRR mutation in at least 1 of 15 pre-specified genes as confirmed by the central genomics laboratory.
- Study objectives were safety, PK, and investigators assessed ORR, CBR, and PFS.

### RESULTS

- **Baseline Characteristics and Patient Demographics**
  - As of 10 Aug 2022, 9 pts were enrolled at 3 dose levels (100 mg QD, 200 and 400 mg BID) in the dose escalation part and one patient (mCRPC) in dose expansion. Cohort 2 of 200mg QD was skipped based on PK data from the 100mg QD cohort.
  - Tumor types included colorectal (n=3), ovarian (n=2), ovarian (n=2), breast (n=1) and biliary tract (n=1) cancers.
  - Seven (78%) of 9 patients had Stage IV/IV disease with 3 median prior therapies.
  - Out of 9 patients enrolled in dose escalation, one ovarian cancer patient had a known CDK12 mutation.
  - mCRPC patient enrolled in dose expansion part, had a germline CHEK2 mutation.

### CONCLUSIONS

- **RP12146** exhibited pre-clinical anti-tumor potential as a single agent and in combination with Gemcitabine in OVCAR-3 xenograft model.
- In the Phase I study, **RP12146** was well tolerated across dose levels. Majority of the reported TEAEs were mild to moderate in severity.
- There were no DLT or any Grade 3 AE related to RP12146.
- No changes were seen in any of the hematological parameters.
- 400 mg BID dose was considered as recommended Phase 2 dose for expansion part.

### SAFETY

- **RP12146** was well tolerated across dose levels.
- Majority of the reported TEAEs were mild to moderate in severity.
- No related TEAEs were reported except mild events of neuropathy (n=1) and proteinuria (n=1).
- There was no DLT or any Grade 3 AE related to RP12146.
- No changes were seen in any of the hematological parameters.
- 400 mg BID dose was considered as recommended Phase 2 dose for expansion part.

### PHARMACOKINETICS

- **RP12146** showed rapid absorption achieving maximum concentrations in 1 hr, with an elimination half-life between 4.7-5.3hrs.
- No accumulation was observed at C2D1.

### TARGET ENGAGEMENT

**RP12146 treatment increased levels of γH2AX in patient’s PBMC samples confirming target engagement**

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**Pre-clinical and Early Clinical Assessment of the Safety and Anti-tumor Activity of RP12146, a PARP1/2 inhibitor in solid tumors**

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