483P

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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INTRODUCTION

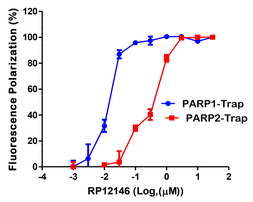
- RP12146 is an orally bioavailable, potent inhibitor of PARP 1/2 and showed growth inhibitory activity in solid tumor cell lines. In a rat *in-vivo* model, myelosuppression/ leucopenia was not seen due to the relatively lower distribution of RP12146 into the bone marrow (AACR 2022).
- Based on promising 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.

PRE-CLINICAL ACTIVITY

In-Vitro studies	PARP1	PARP2
Enzymatic potency, IC_{50} (nM)	0.6	0.5
GI_{50} in UWB.1 cell line (µM)	1.47	

PARP Trap assay

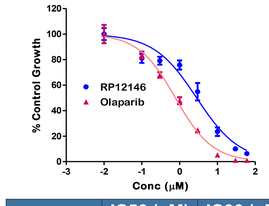
Figure 1. PARP Trapping effect on the DNA binding activities of recombinant human PARP1 and PARP2 enzymes



	PARP1 Trap	PARP2 Trap
EC_{50} (nM)	13	273

Erythroid surface marker

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

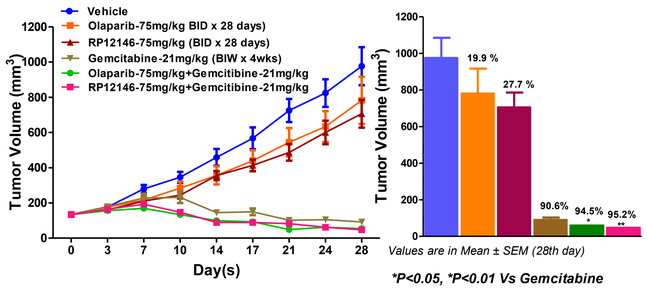


	IC50 (µM)	IC90 (µM)
Olaparib	0.8	8.5
RP12146	2.8	28.8

- 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.

XENOGRAFT STUDY

Figure 3. Anti-tumor activity in OVCAR-3 Xenograft in Female Nude Mice



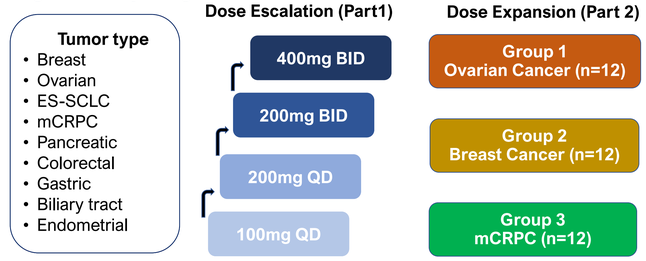
Values are in Mean ± SEM (28th day)

P<0.05, *P<0.01 Vs Gemcitabine

- RP12146 showed anti-tumor activity with TGI of 27.7% as a single agent and 95.2% in combination with Gemcitabine.

PHASE I STUDY

Figure 4: Study Design



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. (NCT05002868).
- 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 enroll 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.

15 HRR gene panel		
CDK12	CHEK1	RAD54L
RAD51C	RAD51B	BRIP1
BRCA1	RAD51D	ATM
BRCA2	CHEK2	FANCL
PPP2R2A	BARD1	PALB2

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), prostate (n=2), ovarian (n=2), breast (n=1) and biliary tract (n=1) cancers.
- Seven (78%) out of 9 patients had Stage III/IV disease with 3 median prior therapies.
- Out of 9 patients enrolled in dose escalation, one ovarian cancer patient had a somatic CDK12 mutation.
- mCRPC patient enrolled in dose expansion part, had a germline CHEK2 mutation.

SAFETY

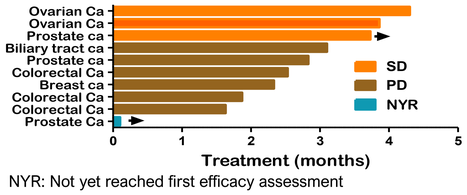
- RP12146 was well tolerated across dose levels.
- Majority of the reported TEAEs were mild to moderate in severity.
- No related TEAEs were reported except mild events of neuropathy (n=1), nausea (n=1) and proteinuria (n=1).
- There was no DLT or any Grade 3 AE related to RP12146.
- No changes were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

Figure 5. Treatment emergent adverse events (Causality-All)

TEAE	Any grade, n (%)	Grade≥3 , n (%)
Urinary tract infection	2 (22)	1 (11)
Hypokalemia	1 (11)	1 (11)
Escherichia coli Infection	1 (11)	1 (11)
Increase in blood pressure	1 (11)	1 (11)
AST increased	1 (11)	-
ALT Increased	1 (11)	-
Neuropathy	1 (11)	-
Vaginal spotting	1 (11)	-
Otitis	1 (11)	-
Nausea	1 (11)	-
Proteinuria	1 (11)	-
Vomiting	1 (11)	-
Bleeding with clots post catheterization	1 (11)	-

TUMOR RESPONSE

Figure 6. Duration of treatment and Tumor response



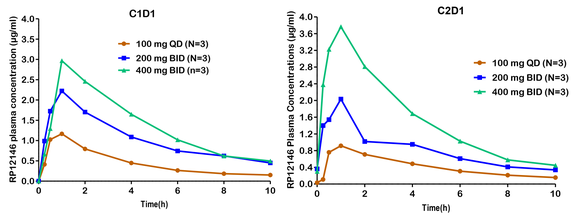
NYR: Not yet reached first efficacy assessment

- Three patients (2 pts from 200 mg BID cohort and 1 pts from 400 mg BID cohort) showed stable disease.
- Two patients (one from dose escalation and one from dose expansion) are ongoing, 8 patients were discontinued to due to disease progression.
- Median duration of treatment in dose escalation part was 2.83 months (range: 1.63-4.3+).

PHARMACOKINETICS

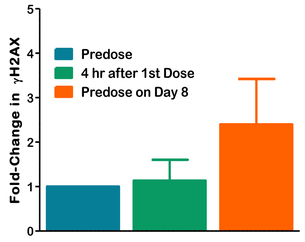
- RP12146 showed rapid absorption achieving maximum concentrations in 1 hr, with an elimination half-life between 4.7-5.3hrs.
- No accumulation was observed at C2D1

Figure 7. Plasma concentrations of RP12146



TARGET ENGAGEMENT

Figure 8. Effect on γ-H2AX expression in PBMCs



- RP12146 treatment increased levels of γH2A.X in patient's PBMC samples confirming target engagement

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 (100 mg QD-400 mg BID). There we no events of anemia or cytopenias reported so far. Lower impact on erythroid progenitor cells and decreased PARP2 trapping could potentially be the reason behind this translation.
- Unlike other PARP inhibitors which have a common class effect of anemia and cytopenias, which typically occur during the first couple of cycles, early data showed that RP12146 was devoid of any hematological toxicities in patients treated as long as 4.3 months.
- RP12146 showed rapid absorption and dose dependent exposures without any accumulation.
- Favourable safety profile supports the combinations of RP12146 with SOC for the management of various cancers with HRR defects

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