Abstract # 4842

A comparative preclinical study of PARP inhibitors demonstrates superb properties for IDX-1197

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Background

Currently approved poly (ADP-ribose) polymerase (PARP) inhibitors are not priced in alignment with benefits, except for olaparib in recurrent *BRCA*-mutant ovarian cancer[1]. Also, their clinical applications are mainly focused on *BRCA*-mutant ovarian cancer so far[2]. For example, olaparib demonstrated comparatively low efficacy in *BRCA*-wild type patients[3].

In spite of these limitations, application of PARP inhibitors is expected to expand toward the fields of *BRCA*-wild type patients, as combination with standard chemo/immunotherapies would be available and mutations in repair genes other than *BRCA*1/2 were recently revealed[2]. Thus, improvement on efficacy is needed to overcome the limitations of approved PARP inhibitors and to expand the application.

IDX-1197 is a novel, potent, selective, and orally bioavailable PARP inhibitor with enzymatic IC_{50} of 1.4, 1.0, and >10,000 nM for PARP-1, -2, and -5, respectively. IDX-1197 demonstrated antitumor activities in numerous preclinical models[4]. *In vitro* & *in vivo* studies were conducted to evaluate the superior efficacy of IDX-1197 to olaparib.

Methods

- **Colony formation assays**

The inhibitory effects of IDX-1197 on the colony formation were assessed using cancer cell lines.

- **PARP1 Trapping assay**

PARP1 Trapping was determined by western blot analysis of chromatin-bound fractions from drug-treated DU145 cells. DU145 cells were treated by either IDX-1197 or olaparib for 4 hours. Blots were probed with PARP1 and histone H3 antibodies. Histone H3 was used as a positive marker for chromatin-bound fractions and as a loading control.

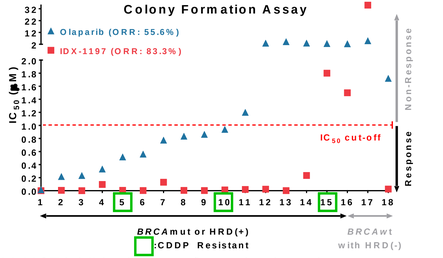
- ***In vivo* animal models**

In vivo efficacy of IDX-1197 against growth of *BRCA*-mutant or *BRCA*-wild type tumors was evaluated using patient-derived xenograft or cancer cell line xenograft models. Statistical analysis was performed with non parametric Mann-Whitney test.

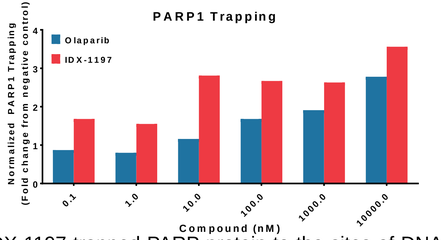
The PAR levels in tumors obtained from xenograft studies were measured biochemically with PARP *in vivo* Pharmacodynamic Assay II Kit (Trevigen®). The concentrations of IDX-1197 in plasma were determined using LC-MS/MS method.

Results

In vitro efficacy

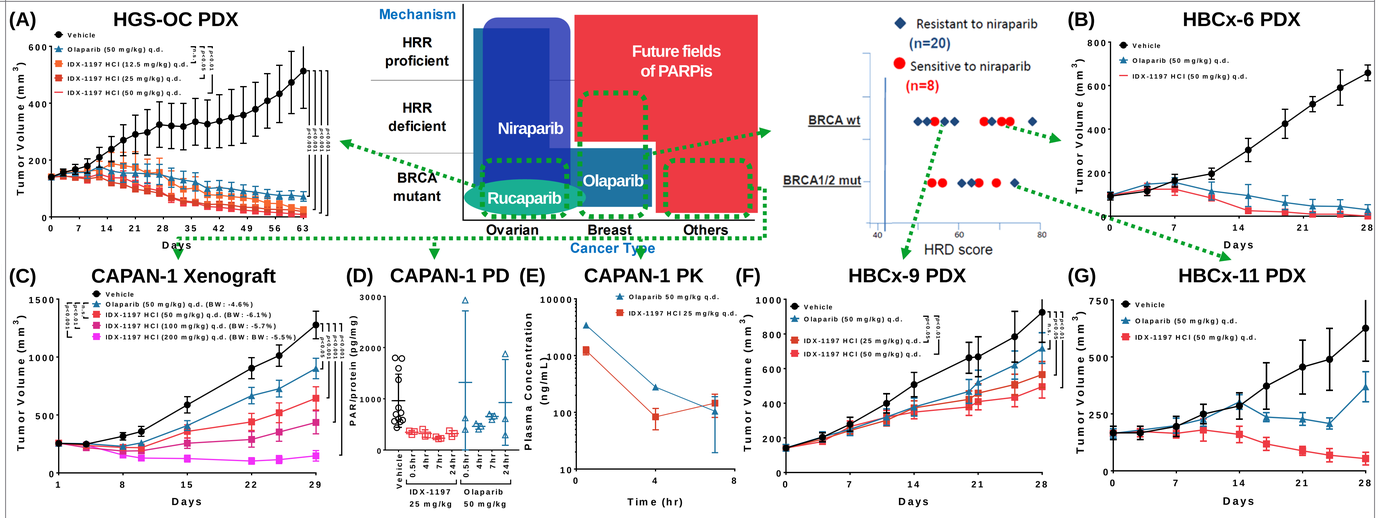


- IDX-1197 inhibited colony formation in various cancer cell lines, with higher overall response ratio than olaparib.



- IDX-1197 trapped PARP protein to the sites of DNA damage at sub-nanomolar concentrations (≥0.1 nM), in MMS-treated DU145 prostate cancer cells.

In vivo efficacy



- IDX-1197 demonstrated superior antitumor activity to olaparib in PDX model of (A)
- IDX-1197 has greater inhibitory effects on (C) tumor growth, (D) PARylation at (E) lower plasma drug concentrations than olaparib, in *BRCA*-mutant pancreatic adenocarcinoma xenograft model.
- IDX-1197 is expected to expand its indication toward 'Future Fields of PARP inhibitors' beyond current indications, based on these results.

Conclusions

- IDX-1197 administration induces potent antitumor activities in multiple preclinical models. The potent antitumor activity induced by IDX-1197 is consistent with its PK/PD.
- These preclinical data demonstrate the efficacy of IDX-1197, which has the potential for a best-in-class profile.
- Based on these findings, IDX-1197 is under clinical Phase 1 trials in Republic of Korea.
- Clinical exposure of IDX-1197 has reached effective exposure determined in preclinical models without significant adverse events, and the dose escalation is currently ongoing.

Acknowledgements

Ovarian model experiments: Asan Medical Center / TNBC PDX model experiments: XenTech

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References

1. ICER, PARP Inhibitors for Ovarian Cancer: Effectiveness and Value 2017
2. *Onco Targets Ther* 2017;10: 5195-5208
3. *Biodrugs* 2015; 29(2): 143-150
4. *Mol Cancer Ther* 2018; 17(1 Suppl) Abstract nr A106
5. *Cancer Res* 2015; 74 (19 Suppl) Abstract nr 2742