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Precision Medicine Matters

Idience: developing selective and potent PARP inhibitor IDX-1197 for solid tumors

Oncology-focused company Idience enters phase 1b/2a clinical trials of IDX-1197 in multiple cancer types

The first wave of PARP inhibitors has improved outcomes in people with a variety of solid tumors. However, Idience has identified opportunities to improve the efficacy of existing drugs and overcome resistance. The company plans to target homologous recombination repair-proficient patients with a clinical-phase PARP inhibitor that is now available for licensing.

Ildong Holdings, a major pharmaceutical company in Korea, established Idience in May 2019 to support its global oncology development ambitions. Led by innovative pharmaceutical experts with vast global experience, Idience is leveraging its clinical and business advantages to realize the value of new drugs discovered by Ildong and third parties.

Developing a better PARP inhibitor

Idience's focus on anticancer drugs that could transform patient quality of life is exemplified by its lead asset IDX-1197, a PARP inhibitor that is currently in a phase 1b/2a basket study with additional studies planned in gastric and ovarian cancers.

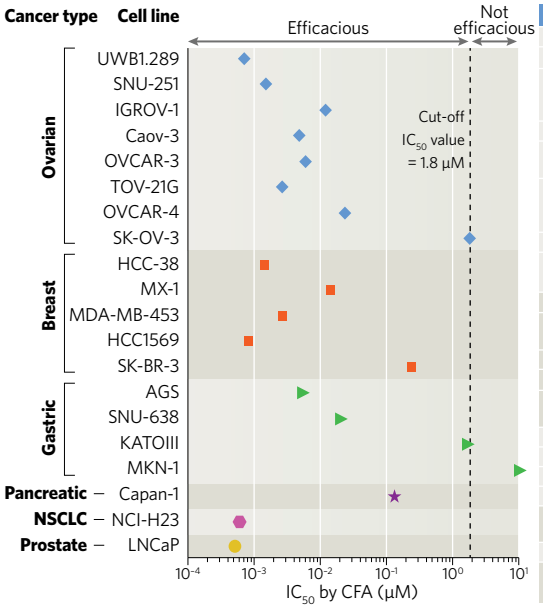
PARP (poly ADP-ribose polymerase) is an enzyme central to the repair of DNA replication errors known as single-strand breaks (SSBs). By inhibiting PARP, IDX-1197 stops cancer cells from repairing SSBs and drives the conversion of SSBs into double-strand breaks.

In doing so, IDX-1197 triggers a phenomenon known as synthetic lethality, which is defined by cell death resulting from the simultaneous perturbation of two genes without damaging normal cells. IDX-1197 is primarily aimed at treating homologous recombination deficient (HRD) patients.

Other PARP inhibitors have validated the mechanism of action in cancers of the ovary, breast, prostate and pancreas. IDX-1197 has several key advantages over those commercially available PARP inhibitors.

Notably, IDX-1197 has a particularly strong trapping effect, meaning it is more effective at trapping PARP1 and PARP2 enzymes on damaged DNA. The trapping effect is critical to the cytotoxicity of PARP inhibitors, so this may boost the efficacy of IDX-1197 over similar compounds. Early studies suggest IDX-1197 shows both strong PARylation blockade power and trapping effect at similar mole concentration. A wider safety margin indicates IDX-1197 is likely to be used in various types of combination therapy.

Researchers have demonstrated the potency of IDX-1197 in in vitro and in vivo studies that have also shown the molecule has favorable pharmacological properties and is highly selective for PARP1 and PARP2. Moreover, IDX-1197 showed promising efficacy beyond BRCA in HRD and platinum-resistant and PARP-resistant models.



Cell line	Genetic status
UWB1.289	*BRCA1* null
SNU-251	*BRCA1* (p.W1815*)
IGROV-1	*BRCA1* (K654Sfs*47), *ARID1A* (G276Efs*87, D1850Gfs*4), *PTEN* (Y155C, T319*)
Caov-3	*ATM* (S1905Ifs*25)
OVCAR-3	*BRCA2, ATM, ARID1A, BLM, CHEK1, PALB2, CDK12* (HOMDEL)
TOV-21G	*ARID1A* (Y551Lfs*72, Q758Rfs*75), *NBN* (R466Gfs*18), *PTEN* (K267Rfs*9, G143Afs*4)
OVCAR-4	-
SK-OV-3	*ATM* (X1413_splice), *ARID1A* (Q586*), *CHEK2*, PTEN (HOMDEL)
HCC-38	*CHEK1* (HOMDEL)
MX-1	*BRCA1* (33636delGAAA), *BRCA2* (p.N991D)
MDA-MB-453	*BRCA1, RAD51, FANCC* (HOMDEL)
HCC1569	*BRCA2* (V1862*), *PTEN* (K267Rfs*9)
SK-BR-3	*BRCA1, BAP1, BRIP1, RAD51C, FANCA, PTEN* (HOMDEL)
AGS	low ATM
SNU-638	low ATM
KATOIII	*ARID1A* (HOMDEL)
MKN-1	*BRIP1* (X700_splice)
Capan-1	*BRCA2* (V1532Sfs*2), *FANCA* (E1196*), *RAD50* (HOMDEL)
NCI-H23	*ATM* (p. Q1919P)
LNCaP	*ATM* (Q912*), *ARID1A* (G285Efs*78), *BRIP1* (X306_splice), *PTEN* (HOMDEL)

Fig. 1 | Clinical potential of IDX 1197 (left) using the colony formation assay, based on the various cancer cell lines (right).

Based on the encouraging data, Idience's parent company Ildong and National OncoVenture began studying IDX-1197 in humans.

Validating IDX-1197 in humans

Ildong initiated a phase 1a clinical trial of IDX-1197 in patients with advanced solid tumors in 2017 (Fig. 1). The study reported clinical responses and good tolerability, with no dose-limiting myelosuppression until the last cohort of the study. These findings indicated that a wider safety margin and tolerability profile could differentiate IDX-1197 from other PARP inhibitors.

The results informed the design of an ongoing phase 1b/2a clinical trial that Idience started in 2019. Idience is enrolling up to 310 patients with homologous recombination repair mutated solid tumors in the basket trial to assess the effects of IDX-1197 as a monotherapy. The study will enable Idience to confirm clinical effectiveness and target those tumor types treated with chemotherapy alone, or with fewer standard of care options.

Idience aims to conduct a phase 2 gastric cancer clinical trial in combination with chemotherapy to get accelerated approval from the US Food and Drug Administration. Additionally, an ovarian cancer study is being planned as a monotherapy. Given the applicability of PARP inhibition to a wide range of cancers, Idience sees opportunities to increase the value of IDX-1197 through clinical trials that expand its indications, both as a monotherapy and in combination with other anti-cancer agents. Its safety profile will allow for more efficacious combination therapies.

Partnering to advance cancer drugs

So far, Idience has pursued IDX-1197 R&D without partners with a view to filing for approval in the US in 2025. It hopes to make a co-development or licensing deal with leading global pharmaceutical companies.

Idience is also planning to build on the success of IDX-1197 by in-licensing additional cancer drugs. Reflecting its translational research expertise, Idience is looking for innovative candidates in the late stages of preclinical development that it can take through clinical value-inflection points.

By advancing IDX-1197 and the in-licensed assets, Idience stands to deliver on its mission to realize the value of innovative oncology drugs that address major medical needs.

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