Olaparib (AZD2281) is one of the first PARP inhibitors. Olaparib (AZD2281, KU0059436) is a selective inhibitor of PARP1 and PARP2 with IC50 of 5 nM and 1 nM, respectively. Olaparib would act against BRCA1 or BRCA2 mutations. Olaparib is not sensitive to tankyrase-1 (IC50 >1 μM). Olaparib could ablate the PARP-1 activity at concentrations of 30-100 nM in SW620 cells. Olaparib is hypersensitive to BRCA1-deficient cell lines (MDA-MB-463 and HCC1937), compared with BRCA1- and BRCA2-proficient cell lines (Hs578T, MDA-MB-231, and T47D). Olaparib is strongly sensitive to KB2P cells due to suppression of base excision repair by PARP inhibition, which may result in the conversion of single-strand breaks to double-strand breaks during DNA replication, thus activating BRCA2-dependent recombination pathways.

**Biological Activity**

**Description**

Olaparib (AZD2281, KU0059436) is a selective inhibitor of PARP1 and PARP2 with IC50 of 5 nM and 1 nM, respectively.

**Targets**

PARP1, PARP2

**IC50**

5 nM, 1 nM

**In vitro**

Olaparib would act against BRCA1 or BRCA2 mutations. Olaparib is not sensitive to tankyrase-1 (IC50 >1 μM). Olaparib could ablate the PARP-1 activity at concentrations of 30-100 nM in SW620 cells. Olaparib is hypersensitive to BRCA1-deficient cell lines (MDA-MB-463 and HCC1937), compared with BRCA1- and BRCA2-proficient cell lines (Hs578T, MDA-MB-231, and T47D). Olaparib is strongly sensitive to KB2P cells due to suppression of base excision repair by PARP inhibition, which may result in the conversion of single-strand breaks to double-strand breaks during DNA replication, thus activating BRCA2-dependent recombination pathways.

**In vivo**

Combining with temozolomide, Olaparib (10 mg/kg, p.o.) significantly suppresses tumor growth in SW620 xenografts.

**Clinical Trials**

Combining with cediranib, Olaparib is currently in Phase II study for treatment of recurrent papillary-serous ovarian, fallopian tube or peritoneal cancer or treatment of recurrent triple-negative breast cancer.

**Features**

Olaparib is one of the first PARP inhibitors.

**Protocol (Only for Reference)**

**Kinase Assay:**

To columns 1 through 10, 1 μL of Olaparib (in DMSO) is added, and 1 μL DMSO only is added to the positive (POS) and negative (NEG) control wells (columns 11 and 12, respectively) of a pretreated FlashPlate. PARP-1 is diluted 1:40 in buffer (buffer B: 10% glycerol (v/v), 25 mM HEPES, 12.5 mM MgCl2, 50 mM KCl, 1 mM DTT, 0.01% NP-40 (v/v), pH 7.6) and 40 μL added to all 96 wells (final PARP-1 concentration in the assay is ~1 ng/μL). The plate is sealed and shaken at RT for 15 min. Following this, 10 μL of positive reaction mix (0.2 μg/μL of double-stranded oligonucleotide (M3M4) DNA per well, 5 μM of NAD+ final assay concentration, and 0.075 μCi 3H-NAD+ per well) is added to the appropriate wells (columns 1-11). The negative reaction mix, lacking the DNA oligonucleotide, is added to column 12 (with the mean negative control value used as the background). The plate is resealed and shaken for a further 60 min at RT to allow the reaction to continue. Then, 50 μL of ice-cold acetic acid (30%) is added to each well to stop the reaction, and the plate is sealed and shaken for a further 60 min at RT. Tritiated signal bound to the FlashPlate is then determined in counts per minute (CPM) using the TopCount plate reader.

**In vitro isolated enzyme assay**

PARP-2 activity inhibition uses a variation of the PARP-1 assay in which PARP-2 protein (recombinant) is bound down by a PARP-2 specific antibody in a 96-well white-walled plate. PARP-2 activity is measured following [3H]-NAD+ DNA additions. After washing, scintillant is added to measure [3H]-incorporated ribosylations. For tankyrase-1, a c-Scan assay is developed in which His-tagged recombinant TANK-1 protein is incubated with biotinylated NAD+ in a 384-well ProxiPlate assay. Alpha beads are added to bind the His and biotin tags to create proximity signal, whereas the inhibition of TANK-1 activity is directly proportional to the loss of this signal.

**Cell Assay:**

**Cell Lines**

Breast cancer cell lines including SW620 colon, A2780 ovarian, HCC1937, Hs578T, MDA-MB-231, MDA-MB-436, and T47D

**Concentrations**

1-300 nM

**Incubation Time**

7-14 days

The cytotoxicity of Olaparib is measured by clonogenic assay. Olaparib is dissolved in DMso and diluted by

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Methods

The cytotoxicity of Olaparib is measured by clonogenic assay. Olaparib is dissolved in DMSO and diluted by culture media before use. The cells are seeded in sixwell plates and left to attach overnight. Then Olaparib is added at various concentrations and the cells are incubated for 7-14 days. After that the surviving colonies are counted for calculating the IC50.

Animal Study[3]

Animal Models
Brca1<sup>−/−</sup>p53<sup>−/−</sup>mammary tumors are generated in K14cre;Brca1<sup>F/F</sup>;p53<sup>F/F</sup> mice.

Formulation
50 mg/mL stocks in DMSO with 10% 2-hydroxy-propyl-β-cyclodextrine/PBS

Doses
50 mg/kg

Administration
Administered via i.p. injection at 10 μL/g of body weight

References

Customer Reviews

, , Dr David Schürmann from University of Basel
Olaparib (AZD2281) purchased from Selleck in vivo suppression of PAR formation by the PARP inhibitor AZD2281 upon induction of DNA damage Primary human lung fibroblast cells (MRC-5) were pre-treated with the indicated concentration of the PARP inhibitor AZD2281 for two hours. Oxidative DNA damage was induced by 500 μM H2O2 for 10 min and cellular PARP activity was measured by immuno-staining of poly(ADP)-ribose (PAR) (right panels). The in vivo effect of PARP inhibition was compared to cells without DNA damage induction and inhibitor (control) and H2O2-treated cells without inhibitor. Average nuclear PAR staining intensities of more than 50 cells were statistically analysed by Kruskal-Wallis and the post-hoc Dunn’s Multiple Comparison tests (left panel). Asterisks indicate highly significant (p<1%) differences to H2O2-treated cells without PARP inhibitor. Thick horizontal bars mark medians and error bars the interquartile range.

, , Dr Xiangbing Meng of University of Iowa
Olaparib (AZD2281) purchased from Selleck
Effect of AZD 2281 on the viability of endometrial cancer cell line Heo50 and Ishikawa and ovarian cancer cell line SKOV3,Caov3 and PA-1 was detected by WST-1 method after 3 days treatment.

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