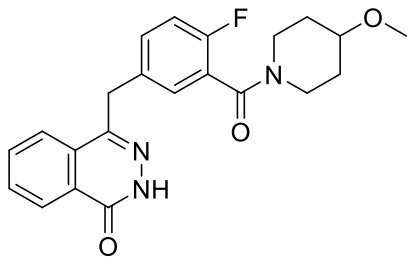
Product data sheet

MedKoo Cat#: 204530 Name: AZD-2461 CAS#: 1174043-16-3 Chemical Formula: $C_{22}H_{22}FN_3O_3$ Exact Mass: 395.16452 Molecular Weight: 395.43	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
AZD2461 is a novel and potent PARP inhibitor with lower affinity to P-glycoprotein. AZD2641 is currently in Phase I clinical study. The study is being conducted to see how it may work to treat solid tumors. The main purpose is to establish a safe dosage of the drug and provide additional information on any potential side effects this drug may cause. The study will also assess the blood levels and action of AZD2461 in the body over a period of time and will indicate whether the drug has a therapeutic effect on solid tumors.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	55.0	139.09
Ethanol	24.0	60.69

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.53 mL	12.64 mL	25.29 mL
5 mM	0.51 mL	2.53 mL	5.06 mL
10 mM	0.25 mL	1.26 mL	2.53 mL
50 mM	0.05 mL	0.25 mL	0.51 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Sargazi S, Saravani R, Zavar Reza J, Zarei Jaliani H, Galavi H, Moudi M, Abtahi NA. Novel Poly(Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibitor, AZD2461, Down-Regulates VEGF and Induces Apoptosis in Prostate Cancer Cells. Iran Biomed J. 2019 Sep;23(5):312-23. doi: 10.29252/.23.5.312. Epub 2019 May 18. PMID: 31102368; PMCID: PMC6661129.
2. Węsierska-Gądek J, Heinzl S. Interactions Between Ataxia Telangiectasia Mutated Kinase Inhibition, Poly(ADP-ribose) Polymerase-1 Inhibition and BRCA1 Status in Breast Cancer Cells. J Cancer Prev. 2014 Jun;19(2):125-36. doi: 10.15430/JCP.2014.19.2.125. PMID: 25337581; PMCID: PMC4204161.

In vivo study

1. Jaspers JE, Kersbergen A, Boon U, Sol W, van Deemter L, Zander SA, Drost R, Wientjens E, Ji J, Aly A, Doroshow JH, Cranston A, Martin NM, Lau A, O'Connor MJ, Ganesan S, Borst P, Jonkers J, Rottenberg S. Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov. 2013 Jan;3(1):68-81. doi: 10.1158/2159-8290.CD-12-0049. Epub 2012 Oct 25. PMID: 23103855; PMCID: PMC7518105.
1. Henneman L, van Miltenburg MH, Michalak EM, Braumuller TM, Jaspers JE, Drenth AP, de Korte-Grimmerink R, Gogola E, Szuhai K, Schlicker A, Bin Ali R, Pritchard C, Huijbers IJ, Berns A, Rottenberg S, Jonkers J. Selective resistance to the PARP

inhibitor olaparib in a mouse model for BRCA1-deficient metaplastic breast cancer. Proc Natl Acad Sci U S A. 2015 Jul 7;112(27):8409-14. doi: 10.1073/pnas.1500223112. Epub 2015 Jun 22. PMID: 26100884; PMCID: PMC4500240.

7. Bioactivity

Biological target:

AZD-2461 is a potent PARP inhibitor, with IC50s of 5 nM, 2 nM and 200 nM for PARP1, PARP2 and PARP3, respectively.

In vitro activity

In the presented study the anti-proliferative and pro-apoptotic action of AZD2461, a novel PARP inhibitor already under clinical evaluation, were examined in human MCF-7 and SKBr-3 breast cancer cells. Interference with PARP-1 activity using AZD2461 was cytotoxic to both the SKBR-3 line and (less strongly) MCF-7 line, reducing numbers of viable cells in a concentration- and time-dependent manner (Fig. 2). The finding that AZD2461 induced synthetic lethality in both cell lines, previously shown to be NU1025-resistant, indicates that even BRCA1/2-deficient or mutant breast cancer cells have differing sensitivity to pharmacological PARP-1 inhibitors. PARP-1 inhibition by AZD2461 increased proportions of MCF-7 cells in the G2 phase at the expense of proportions in the S-phase, and had similar (but weaker) effects on SKBr-3 cells (Fig. 3). Both apoptotic, mitotic and G2-arrested SKBr-3 cells were detected in the samples after treatment with AZD2461 (Fig. 5). Concurrent inhibition of ATM kinase and PARP-1 caused much more pronounced reduction in the cell density. The results show that both MCF-7 and SKBr-3 cells are sensitive to AZD2461, a new PARP-1 inhibitor that is under clinical investigation. AZD2461 induced synthetic lethality in both tested breast cancer cell lines that are insensitive to the PARP-1 inhibitor NU1025 even at higher doses (up to CE = 200 μM)

Reference: J Cancer Prev. 2014 Jun; 19(2): 125–136. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204161/

In vivo activity

Short-term AZD2461 treatment in mice with KB1P tumors was first studied, using daily dosing for 28 consecutive days, as the same was done for olaparib. Although mice treated with AZD2461 clearly showed increased survival compared with olaparibtreated mice ($P = 0.0061$), all mice eventually developed relapsing tumors that were refractory to PARPi treatment (Fig. 6C and Supplementary Fig. S9C). Three of 12 AZD2461-resistant KB1P tumors also showed loss of 53BP1 expression (Fig. 6D). In the AZD2461-resistant tumor KB1P2, a deletion of 94 base pairs was found in exon 21 of Trp53bp1 (Fig. 6E and Supplementary Fig. S9D), which leads to a stop-codon in this exon. A deletion of 34 base pairs was also identified on the boundary of intron 24 and exon 25 of Trp53bp1 in AZD2461-resistant tumor KB1P8 (Fig. 6F and Supplementary Fig. S9E). When the AZD2461 treatment was increased to 100 consecutive days, it was found that 8 of 9 mice engrafted with fragments from 3 individual KB1P tumors did not develop refractory tumors within 300 days after treatment start (Fig. 7A and Supplementary Fig. S10A–S10C). The tumor that acquired AZD2461 resistance during the first treatment cycle had an epithelial-to-mesenchymal transition phenotype (Supplementary Fig. S10D), which is frequently linked to drug resistance. Long-term AZD2461 treatment was well tolerated and doubled the median relapse-free survival from 64 to 132 days $P < 0.0001$, Fig. 7B). As one strategy to minimize the risk of developing PARPi resistance, continuous treatment with the novel PARPi AZD2461 is presented.

Reference: Cancer Discov. 2013 Jan; 3(1): 68–81. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7518105/