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Edison Explains

DNA damage repair inhibitors

With PARP inhibitors becoming an established class of drug, what other DNA damage repair inhibitor technologies are in development?

What are PARP inhibitors?

Poly ADP ribose polymerase (PARP) inhibitors reduce the effect of PARPs, a family of 18 proteins involved in cellular DNA repair. Of the 18 PARP proteins, the current generation of inhibitors are most notable for their effect on PARP-1 and PARP -2.

Both proteins are critical elements of base excision repair (BER), whereby single-strand DNA breaks, the result of either spontaneous damage or environmental factors, are fixed. PARP inhibitors, the most advanced drugs in the field of DNA repair inhibition, inhibit the BER pathway.

The result of treatment with PARP inhibitors is an inability to repair single-strand DNA breaks, which eventually lead to double-strand breaks, catastrophically damaging the affected cells. One double-strand break can initiate cell death.

What is synthetic lethality?

In healthy cells, the damage caused by double-strand breaks is repaired by two mechanisms: homologous recombination (HR) and non-homologous end joining (NHEJ).

Together, HR and NHEJ repair double-strand breaks, including those caused by unrepaired single-strand breaks accumulated as a result of PARP inhibition.

However, HR uses two proteins, BRCA1 and BRCA2, when repairing double-strand breaks, with some potential involvement in NHEJ as well. In certain cancers, BRCA1/2 mutations render this pathway ineffective. As a result, the double-strand breaks resulting from PARP inhibitor suppression of single-strand repair kill BRCA1/2 mutated cancers. This is known as synthetic lethality.

HR-deficient (BRCA-mutated) cancers are 100–1,000 times more sensitive to PARP inhibition than normal cells and therefore more likely to die following PARP treatment. One of the key drawbacks that has emerged is the fact that cancers develop resistance to PARP inhibitors relatively quickly.

Which cancers are sensitive to PARP inhibition?

PARP-sensitive BRCA1/2 mutations are present in 15% of ovarian cancers. As ovarian cancer is most often diagnosed in its advanced stages (70–80% of the time), the demand for novel treatments is high. This was one of the reasons for the relatively quick uptake of PARP inhibitors in this indication.

PARP inhibitors have also proved themselves in breast cancer. Around 5–10% of breast cancers have the BRCA1/2 mutation, which makes them PARP sensitive.

Studies are ongoing for a variety of other indications, including stomach and small cell lung cancers.

Which PARP inhibitors are on the market?

So far, four PARP inhibitors have received marketing approval: AstraZeneca's Lynparza, Clovis Oncology's Rubraca, GlaxoSmithKline's/Tesaro's Zejula and Pfizer's Talzenna.

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'The approval and commercial success of the first PARP inhibitors has kick-started interest from the scientific community and large pharma in the DNA damage repair inhibition field. While multiple PARP inhibitors are now in development, few companies are already positioned in this emerging field, with drug candidates employing novel and differentiated mechanisms of action.' Jonas Peciulis, Edison healthcare analyst

Lynparza, Rubraca and Zejula were originally approved for ovarian cancer and Talzenna for breast cancer. Lynparza subsequently gained an additional indication in breast cancer.

Pamiparib, fluzoparib and veliparib are all in advanced Phase III studies.

BeiGene's pamiparib is undergoing trials as a monotherapy in stomach, ovarian and breast cancers, and as a combined treatment with immune checkpoint inhibitor tislelizumab in a Phase Ia/b trial.

Meanwhile, AbbVie's veliparib is being developed for small cell lung cancer, as well as BRCA mutated breast and ovarian cancer. Finally, Jiangsu HengRui Medicine's fluzoparib is in a Phase III trial for ovarian cancer with a

primary completion date of August 2021.

Which other DNA repair inhibitor technologies are in development?

PARP is the most advanced DNA inhibitor pathway in terms of drugs in development, but by no means the only one. Onxeo's lead asset AsiDNA (Phase Ib) is the only oligonucleotide decoy agonist in development that disrupts and exhausts the tumour DNA Damage Response mechanism. So far, AsiDNA has demonstrated broad potential in various cancers, including the unique ability to abrogate resistance to PARP inhibitors.

Large pharma companies are very active in the space, in particular AstraZeneca and Merck KGaA, with several projects investigating ATM and ATR (HR pathways), DNA-PK (an NHEJ pathway) and the WEE1 pathway. The most advanced projects are in Phase II.