PARP-1 Inhibitor (Poly(ADP-ribose) Polymerase-1 Inhibitor)

Overview PARP-1 inhibitors are a class of drugs that target **poly(ADP-ribose) polymerase 1 (PARP-1)**, an enzyme involved in DNA repair, particularly the **base excision repair (BER) pathway**. These inhibitors are used primarily in the treatment of cancers with **defective homologous recombination repair (HRR)**, such as **BRCA1/2-mutated ovarian, breast, prostate, and pancreatic cancers**.

Mechanism of Action PARP-1 inhibitors work by **trapping PARP on damaged DNA** and preventing the repair of single-strand DNA breaks. This leads to the accumulation of DNA damage, which, in HRR-deficient cancer cells, results in **synthetic lethality** and cell death.

1. **PARP Inhibition** – Blocks the enzymatic activity of PARP-1. 2. **PARP Trapping** – Causes PARP-1 to remain bound to DNA, preventing its repair. 3. **Synthetic Lethality** – In cells with BRCA1/2 mutations, failure to repair DNA leads to **double-strand breaks (DSBs)**, triggering apoptosis.

Clinical Applications PARP-1 inhibitors are FDA-approved for multiple cancers, including: - **Ovarian cancer** (especially BRCA-mutated and platinum-sensitive cases) - **Breast cancer** (HER2-negative, BRCA-mutated) - **Prostate cancer** (HRR-deficient) - **Pancreatic cancer** (BRCA-mutated)

Examples of PARP-1 Inhibitors

Drug	Brand Name	Indications
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Olaparib	Lynparza	Ovarian, breast, prostate, pancreatic cancer
Rucaparib	Rubraca	Ovarian, prostate cancer
Niraparib	Zejula	Ovarian cancer
Talazoparib	Talzenna	Breast cancer
Veliparib (investigational)	-	Various cancers (clinical trials)

Side Effects Common side effects include: - **Fatigue** - **Nausea and vomiting** - **Anemia** - **Thrombocytopenia** - **Neutropenia** - **Myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML)** (rare but serious)

Future Directions PARP inhibitors are being explored in: - **Combination therapies** with immune checkpoint inhibitors, chemotherapy, and radiotherapy. - **Expanding indications** beyond BRCA-mutant cancers. - **Targeting PARP resistance mechanisms** to enhance efficacy.