Talazoparib

TALAZOPARIB (PARP INHIBITOR) IN BREAST CANCER

Talazoparib is an investigational, once-daily, oral, anti-cancer medicine called a PARP (poly ADP ribose polymerase) inhibitor that is currently in Phase 3 development for advanced germline (inherited) BRCA-mutated (gBRCAm) breast cancer. Talazoparib is also being evaluated in early triple negative breast cancer (TNBC), DNA damage repair (DDR)-deficient prostate cancer and in combination with immunotherapy in various solid tumor types.

Talazoparib has not been approved by any regulatory authorities for the treatment of any disease.

THE ROLE OF PARP IN BRCA-MUTATED CELLS

PARP and BRCA proteins are important components of normal DNA damage repair. All cells experience constant DNA damage, including single-strand breaks (SSBs) and double-strand breaks (DSBs). BRCA mutations can be hereditary (germline) or occur spontaneously (somatic) – and cells with gBRCA mutations are deficient in a key DNA DSB repair pathway. This deficiency leads to an overreliance on PARP enzymes to repair damaged DNA.[1,2]

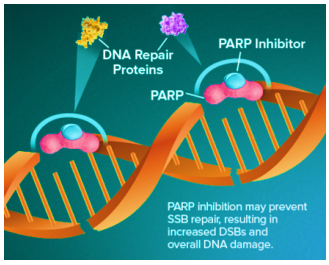
PARP repair of SSBs enables DNA replication and tumor cell survival. PARP enzyme inhibition and PARP trapping may selectively target cells with DNA repair deficiencies, such as BRCA mutations, to lead to cancer cells death.[3,4]

TALAZOPARIB MECHANISM OF ACTION

Preclinical studies suggest that talazoparib is highly potent and has a dual mechanism of action, with the potential to induce tumor cell death by blocking PARP enzyme activity and trapping PARP on the sites of DNA damage.

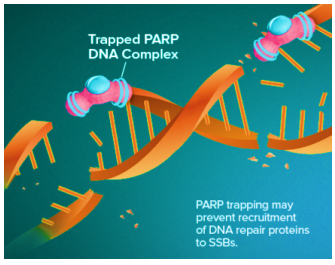
PARP Enzyme Inhibition [1,5 6]

Talazoparib is believed to disrupt the enzymatic activity of SSB repair in BRCAm tumor cells by inhibiting the PARP enzyme, which may lead to detrimental DSBs and ultimately, tumor cell death.



PARP Trapping [3,5,7,8]

Talazoparib is believed to trap the PARP enzyme on SSBs, preventing dissociation from damaged DNA. This trapping mechanism may prevent other DNA repair proteins from completing the DNA repair process.



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CLINICAL STUDIES

- The Phase 3, randomized EMBRACA trial evaluated once-daily talazoparib compared to physician's choice chemotherapy (capecitibine, eribulin, gemcitabine or vinorelbine) in 431 patients with an inherited BRCA1/2 mutation and locally advanced or metastatic TNBC or hormone receptor-positive (HR+)/HER2- breast cancer.[9]
  - The study met its primary endpoint, demonstrating superior progression-free survival (PFS) with talazoparib versus chemotherapy [HR: 0.54 (95% CI: 0.41, 0.71), p<0.0001]. This represents a 46% reduction in the risk of disease progression.[9]
  - The PFS benefit was consistent across prespecified subgroups, including those who had a history of brain metastases, patients previously treated with chemotherapy, TNBC patients and those with HR+ disease.[9]
  - The most common adverse events (AEs) observed with talazoparib (all grades, in at least 15% of patients) were anemia (52.8%), fatigue (50.3%), nausea (48.6%), neutropenia (34.6%), headache (32.5%), thrombocytopenia (26.9%), alopecia (25.2%), vomiting (24.8%), diarrhea (22%), constipation (22%), decreased appetite (21.3%), back pain (21%) and dyspnea (17.5%).
  - The incidence of serious AEs was 31.8% in the talazoparib arm and 29.4% in the chemotherapy arm. Discontinuations due to AEs occurred in 7.7% of patients in the talazoparib arm and 9.5% of patients in the chemotherapy arm.[9]
  - The primary results were presented at the 2017 San Antonio Breast Cancer Symposium.[9]
- The Phase 2 ABRAZO trial is an open-label, 2-stage, 2-cohort trial designed to evaluate the safety and efficacy of talazoparib as a single agent in patients with locally advanced or metastatic breast cancer with a germline BRCA 1/2 mutation. The study's primary endpoint was objective response rate (ORR) by independent radiology review.[10]
  - Patients who previously responded to platinum-based chemotherapy and had disease progression showed an ORR of 21% (95% CI: 10 - 35).[10]
  - Patients who received and progressed on at least three lines of non-platinum-based chemotherapy regimens showed an ORR of 37% (95% CI: 22 - 55).[10]
  - The most common adverse events (AEs) observed in at least 20% of patients consisted of anemia (51.8%), thrombocytopenia (32.5%), neutropenia (26.5%), fatigue (44.6%), nausea (42.2%), diarrhea (32.5%), decreased appetite (24.1%), dyspnea (24.1%), alopecia (21.7%), back pain (21.7%) and vomiting (20.5%).[10]
  - Results were presented at the 2017 Annual Meeting of the American Society of Clinical Oncology (ASCO).[10]
- The Phase 1 PRP-001 trial is a single-arm, open-label trial to assess the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of talazoparib in patients with advanced tumors with DNA-repair pathway deficiencies. The trial consisted of two parts (dose escalation, dose expansion) and has been completed.[11]

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