Talazoparib is an investigational anticancer drug called a PARP (poly ADP ribose polymerase) inhibitor, which is being evaluated in breast cancer patients with germline BRCA (gBRCA) mutations, as well as other cancer types with deficiencies in DNA damage repair (DDR). Talazoparib has not been approved by any Regulatory Authorities for the treatment of any disease.

MECHANISM OF ACTION BASED ON PRECLINICAL DATA

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 DNA breaks (DSBs). BRCA mutations can be hereditary (germline) or occur spontaneously (sporadic) – and are deficient in a key DNA DSB repair pathway.

This 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 trapping may prevent DNA damage repair by leading to heightened cell death, based on in vitro preclinical experiments.\(^3,4\)

As a dual-mechanism PARP inhibitor, talazoparib is believed to both inhibit and trap the PARP enzyme, which may lead to heightened cell death.\(^5,6\)

TALAZOPARIB AS A DUAL-MECHANISM PARP INHIBITOR

**PARP Enzyme Inhibition\(^2,6,7\)**

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

**PARP Trapping\(^6,8,9,10\)**

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.
CLINICAL STUDIES

- The Phase 3 EMBRACA trial is an open-label, randomized, parallel, 2-arm study designed to evaluate once-daily talazoparib versus protocol-specified physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine), in gBRCA+ locally advanced and/or metastatic breast cancer patients who have received zero to three prior chemotherapy regimens for advanced disease.

- The Phase 2 ABRAZO trial is an open-label, 2-stage, 2-cohort study designed to evaluate the safety and efficacy of talazoparib as a single agent in patients with locally advanced or metastatic breast cancer with a gBRCA1/2 mutation.

- The Phase 1 PRP-001 trial is a single-arm, open-label study to assess the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of talazoparib in patients with advanced tumors with DNA-repair pathway deficiencies. The study consisted of two parts (dose escalation, dose expansion) and has been completed.

REFERENCES