CLINICAL UPDATE

Brand Name	Talzenna®
Generic Name	talazoparib
Drug Manufacturer	Pfizer Laboratories Div Pfizer Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strengths

FDA APPROVAL DATE

June 20, 2023

LAUNCH DATE

June 21, 2023

REVIEW DESIGNATION

New Drug Application (NDA): 211651

TYPE OF REVIEW

Priority

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Talzenna® is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for:

Breast Cancer

As a single agent, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for Talzenna®.

HRR Gene-mutated mCRPC

In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

MECHANISMS OF ACTION

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA1 and BRCA2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis. Talazoparib anti-tumor activity was observed in patient-derived xenograft breast cancer models bearing mutated BRCA1 or mutated BRCA2 or wild type BRCA1 and BRCA2.

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DOSAGE FORM(S) AND STRENGTH(S)

Capsules: 0.1 mg, 0.25 mg, 0.35 mg, 0.5 mg, 0.75 mg, and 1 mg.

DOSE & ADMINISTRATION

Breast cancer: 1 mg orally once daily.

Renal Impairment:
For moderate renal impairment (CLcr 30 – 59 mL/min), the recommended dose is 0.75 mg orally once daily.
For severe renal impairment (Clcr 15 – 29 mL/min), the recommended dose is 0.5 mg orally once daily.

Prostate cancer: 0.5 mg taken orally once daily in combination with enzalutamide.

Renal Impairment:
For moderate renal impairment (CLcr 30 – 59 mL/min), the recommended dose is 0.35 mg orally once daily.
For severe renal impairment (Clcr 15 – 29 mL/min), the recommended dose is 0.25 mg orally once daily.

EFFICACY

Deleterious or Suspected Deleterious Germline BRCA-mutated HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA was an open label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive Talzenna®1 mg or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior lines of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status [triple-negative breast cancer (TNBC) versus non-TNBC], and history of central nervous system (CNS) metastasis (yes versus no).

Patients received no more than 3 prior cytotoxic chemotherapy regimens for their metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. Patients with prior platinum therapy for advanced disease were required to have no evidence of disease progression during platinum therapy. No prior treatment with a PARP inhibitor was permitted. Of the 431 patients randomized in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical trial assay; out of which 354 (82%) were confirmed using the BRAC Analysis CDx®. BRCA mutation status [breast cancer susceptibility gene 1 (BRCA1)-positive or breast cancer susceptibility gene 2 (BRCA2)-positive] was similar across both treatment arms.

The median age of patients treated with Talzenna® was 46 years (range 28 to 84) and 51 years (range 24 to 89) among patients treated with chemotherapy. Among all randomized patients, 1% versus 2% were males, 67% versus 75% were White; 11% versus 11% were Asian, and 4% versus 1% were Black or African American in the Talzenna® and chemotherapy arms, respectively. Almost all patients (98%) in both arms had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Approximately 56% of patients had estrogen receptor-positive and/or progesterone receptor-positive disease; 44% of patients had triple-negative disease, and the proportions were balanced across both treatment arms. Fifteen percent (15%) of patients in the Talzenna® arm and 14% of patients in the chemotherapy arm had a history of CNS metastases. Ninety-one percent (91%) of patients in the Talzenna® arm had received prior taxane therapy, and 85% had received prior anthracycline therapy in any setting. Sixteen percent (16%) of patients in the Talzenna® arm and 21% of patients in the chemotherapy arm had received prior platinum treatment in any setting. The median number of prior cytotoxic

regimens for patients with advanced breast cancer was one; 38% received no prior cytotoxic regimens for advanced or metastatic disease, 37% received one, 20% received two, and 5% received three or more prior cytotoxic regimens.

The major efficacy outcome measure was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by blinded independent central review (BICR). A statistically significant improvement in PFS was demonstrated for Talzenna® compared with chemotherapy. A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. Consistent PFS results were observed across patient subgroups defined by study stratification factors (prior lines of chemotherapy, TNBC status, and history of CNS metastases).

HRR Gene-mutated mCRPC

The efficacy of Talzenna® in combination with enzalutamide was evaluated in TALAPRO-2 (NCT03395197), a randomized, double-blind, placebo-controlled, multi-cohort trial in which 399 patients with HRR gene-mutated (HRRm) mCRPC were randomized 1:1 to receive enzalutamide 160 mg daily plus either Talzenna®0.5 mg or placebo daily until unacceptable toxicity or progression. All patients received a GnRH analog or had prior bilateral orchiectomy and needed to have progressed on prior androgen deprivation therapy. Prior treatment with a CYP17 inhibitor or docetaxel for metastatic castration-sensitive prostate cancer (mCSPC) was permitted. Mutation status of HRR genes was determined prospectively using solid tumor tissue or circulating tumor DNA (ctDNA)-based next generation sequencing assays. Patients were required to have a mutation in at least one of 12 genes involved in the HRR pathway (*ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2,* or *RAD51C*).

Randomization was stratified by previous treatment with a CYP17 inhibitor or docetaxel (yes/no).

The median age was 70 years (range: 41 to 90); 100% were male; 68% were White, 21% Asian, 2.8% Black, 0.8% Other, 7% unknown/not reported; 12% were Hispanic/Latino; and baseline ECOG performance status was 0 (62%) or 1 (38%). Thirty-nine percent of patients had bone-only disease; 15% had visceral disease. In the mCSPC setting, 29% percent of patients had received docetaxel and 9% had received a prior CYP17 inhibitor. The most commonly mutated HRR genes (>5%), including co-occurring mutations,
were: *BRCA2* (34%), *ATM* (22%), *CDK12* (19%), *CHEK2* (18%), and *BRCA1* (6%).

The major efficacy outcome measure was radiographic progression-free survival (rPFS) evaluated according to RECIST, version 1.1 and Prostate Cancer Working Group (PCWG3) (bone) criteria, assessed by BICR. An additional efficacy outcome measure was OS.

A statistically significant improvement in rPFS was demonstrated at the pre-specified interim analysis in patients randomized to Talzenna® in combination with enzalutamide compared with placebo in combination with enzalutamide. Consistent rPFS results were observed in patients who received or did not receive a prior CYP17 inhibitor or docetaxel. The OS data were not mature at the time of the rPFS analysis (24% of patients had died).