CLINICAL UPDATE

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

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength

FDA APPROVAL DATE

September 21, 2021

LAUNCH DATE

February 24, 2022

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 1 - New Molecular Entity, New Drug Application (NDA): 211651

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

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

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 BRCA 1 and BRCA 2, 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 human patient-derived xenograft breast cancer tumor models bearing mutated BRCA 1 or mutated BRCA 2 or wild-type BRCA 1 and BRCA 2.

DOSAGE FORM(S) AND STRENGTH(S)

Capsules: 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg

DOSE & ADMINISTRATION

- The recommended dose of Talzenna® is 1 mg taken as a single oral daily dose, with or without food.

- Patients should be treated until disease progression or unacceptable toxicity occurs.
- For adverse reactions, consider dosing interruption or dose reduction.
- For patients with moderate renal impairment (CLcr 30 – 59 mL/min), the recommended dose of Talzenna® is 0.75 mg once daily.
- For patients with severe renal impairment (Clcr 15 – 29 mL/min), the recommended dose of Talzenna® is 0.5 mg once daily.

EFFICACY

Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer.

EMBRACA (NCT01945775) 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 BRACAnalysis 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.

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).

Table 1. Summary of Efficacy Results – EMBRACA Study

	TALZENNA	Chemotherapy
PFS by BICR	N=287	N=144
Disease Progression or Deaths, n (%)	186 (65)	83 (58)
Median months (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI)[a]	0.54 (0.41, 0.71)	
p-value[b]	p<0.0001	
Patients with Measurable Disease by Investigator[c]	N=219	N=114
ORR, % (95% CI)[d]	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Median[e] DOR months (95% CI)	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)
OS	N=287	N=144
Deaths, n (%)	216 (75)	108 (75)
Median months (95% CI)	19.3 (16.6, 22.5)	19.5 (17.4, 22.4)
Hazard ratio (95% CI)[a]	0.85 (0.67, 1.07)	
p-value[b]	p=0.1693	

Abbreviations: BICR=blinded independent central review; CI=confidence interval; DOR=duration of response; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

[a] Hazard ratio is estimated from a Cox proportional hazards model stratified by prior use 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 by history of central nervous system metastasis (yes versus no) and was relative to overall chemotherapy with <1 favoring talazoparib.

[b] P-values (2-sided) from the log-rank test stratified by number of prior cytotoxic chemotherapy regimens, triple negative status and history of central nervous system metastasis.

[c] Conducted in ITT population with measurable disease at baseline.

[d] Response rate based on confirmed responses.

[e] Median estimated from Kaplan-Meier probabilities.