Talazoparib (TALZENNA)
National Drug Monograph
September 2024
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Talazoparib is a poly(ADP-ribose) polymerase (PARP) inhibitor. PARP enzymes play a role in DNA repair. In cancer cell lines with defects in DNA repair genes, including *BRCA1* and *BRCA2*, talazoparib inhibits PARP enzyme activity resulting in PARP-DNA complexes that result in DNA damage.
Indication Under Review[1]	1. Breast cancer. As a single agent for patients with deleterious germline *BRCA*-mutated (gBRCAm) HER2-negative locally advanced (LA) or metastatic breast cancer (MBC). 2. Prostate cancer. In combination with enzalutamide for treatment of homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC)
Dosage Regimen	1. Breast cancer. Talazoparib dose is 1mg PO once daily 2. Prostate cancer. Talazoparib dose is 0.5 mg PO once daily in combination with enzalutamide
Dosage Forms Under Review	0.1, 0.25, 0.35, 0.5, 0.75 and 1 mg capsules

EFFICACY CONSIDERATIONS

Trial	**EMBRACA (NCT01945775)**	**TALAPRO-2 (NCT03395197)**
Design	Randomized 2:1, Open-label	Randomised, double-blind, phase 3 trial
Population	N=431; LA or MBC, HER2-negative, gBRCAm Prior anthracycline and/or taxane, unless CI; ≤ 2 prior chemo regimens for LA or MBC; ECOG PS 0-1	N=805; Adult men who were receiving ongoing ADT, had asymptomatic or mildly symptomatic mCRPC, ECOG PS 0-1, no prior systemic therapy in mCRPC setting (docetaxel and abiraterone allowed in CSPC setting)
Demographics	mAge 46 yrs (range, 28-84) vs. 51 yrs (24-89); 1 vs. 2% male; 67 vs. 75% white; 11 vs. 11% Asian; 4 vs. 1% Black; 98% ECOG PS 0-1; 56% HR+; 44% TNBC; 15 vs. 14% CNS mets; Median LOT - 1	mAge 71 yrs (range, 65-76); 60 vs. 63% White; 3 vs. 1%, Black, 32 vs. 30% Asian, ECOG 0 64 vs. 67%, prior taxane 21 vs. 23%, HRR gene status 21% deficient; BRCA 1/2 alteration 7 vs. 8%
Intervention	Talazoparib 1mg PO daily	Talazoparib 0.5mg PO daily + enzalutamide 160mg PO daily
Comparator	Provider's choice of chemotherapy: Capecitabine, eribulin, gemcitabine or vinorelbine Stratification: #LOT for MBC, TNBC status, CNS mets	Placebo + enzalutamide 160mg PO daily Stratification: HRR gene status, prior docetaxel or abiraterone or both in castration-sensitive setting
Results	Median follow-up@ 11 months[2] mPFS 8.6 vs. 5.6 months [HR 0.54 (95% CI 0.41-0.71)] p<0.0001 Final overall survival results[3] Median follow-up of 44.9 vs. 36.8 months mOS 19.3 vs. 19.5 months [HR 0.848 (95% CI 0.67-1.07) p=0.17] Improvement in patient-related outcomes[3] Change in baseline EORTC QLQ-C30: Talazoparib +2.1 (95% CI 0.1-4.1) vs. Chemo -5.7 (95% CI -10 to -1.4); p=0.001	Median follow-up 24.9 vs. 24.6 months Median rPFS not reached (27.5 – NR) vs. 21.9 mos (16.6-25.1) [HR 0.63 (95% CI 0.51-0.78) p< 0.0001] Subgroup analysis by HRR gene alteration status: HRR gene-deficient mPFS 27.9 (16.6 – NR) vs. 16.4 (10.9-24.6) rPFS [HR 0.46 (95% CI 0.30-0.70) p=0.0003] HRR gene non-deficient or unknown mPFS NR (27.5-NR) vs. 22.5 (19.1-30.5) rPFS [HR 0.70 (95% CI 0.54-0.89) p=0.0039]
Notes	**NCCN Guidelines Breast Cancer v4.2024:** **1L setting HR+, HER2-negative, endocrine-refractory, recurrent, unresectable locally advanced or MBC, *gBRCAm+***	**NCCN Guidelines Prostate Cancer v4.2024:** **M1 CRPC setting** **No docetaxel or novel hormone:** Preferred regimens (category 1)

Preferred (category 1):
- Olaparib
- Talazoparib

HR-, HER2-negative (TNBC), *gBRCAm+*
1L with platinum agent or 2L
Preferred (category 1):
- Olaparib
- Talazoparib

VA Oncology Clinical Pathway:
Breast Cancer, TNBC, *gBRCAm+*: olaparib
Stage IV ER+ or PR+/HER2-negative, gBRCA 1/2 Pathogenic Variant (PV), sBRCA 1/2 PV or gPALB2 PV: olaparib

- Abiraterone
- Docetaxel
- Enzalutamide

No docetaxel/ PD on novel hormone:
Preferred (category 1)
- Docetaxel
- Olaparib for BRCAm+
- Rucaparib for BRCAm+

Useful in certain circumstances depending on prior therapies include:
Talazoparib/enzalutamide for HRRm+ (cat 1)
Olaparib/abiraterone for BRCAm+ (cat 1)
Olaparib for BRCAm+
Olaparib for HRRm+ (cat 1)
Olaparib for HRRm+ other than BRCA1/2

VA Oncology Clinical Pathway:
Prostate Cancer, 1L mCRPC, no prior ARPI, BRCAm+: Olaparib and abiraterone
Prostate Cancer, 2L, 3L mCRPC, not candidate for docetaxel or cabazitaxel, HRRm+: Olaparib

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) Myelosuppression Embryo-Fetal Toxicity
Top 5 AEs	(≥20%) as monotherapy: decreased hgb, neutrophils, lymphocytes and platelets, fatigue, increased glucose (≥10%) with enzalutamide: decreased hgb, neutrophils, lymphocytes and platelets, fatigue, nausea
Drug Interactions	P-gp Inhibitors. Reduce talazoparib dose with select P-gp inhibitors. Monitor for adverse events. BRCP inhibitors. Monitor for increased adverse events.

VHA PLACE IN THERAPY		

	Potential Use in VHA	• In breast cancer, BRCA1 and BRCA2 mutations have been reported in 5% of patients with metastatic disease.
		  • PARP inhibitor therapy has become the standard in patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA 1/2 mutations after progressing on chemotherapy and endocrine therapy (if hormone-receptor positive disease).
		  • PARP inhibitor therapy is also recommended for patients with metastatic HER2-negative breast cancer with somatic BRCA 1/2 mutations or its germline partner, PALB2 mutations once patients progress on chemotherapy and endocrine therapy (if hormone-receptor positive).
		  • Olaparib is a PARP inhibitor that received FDA-approval prior to talazoparib. VHA Oncology Breast Cancer Pathways include olaparib as the preferred PARP inhibitor due to experience and known safety profile. Talazoparib is a once-daily formulation while olaparib is taken twice-daily, which could impact patient adherence.
		  • Since olaparib in on the VA Breast Cancer Pathway, talazoparib can remain non-formulary for use in breast cancer. Drug should be available via non-formulary processes for patients with adherence issues with olaparib.
		• Homologous recombination repair (HRR) is a DNA repair process for double-strand breaks caused DNA crosslinking, which may result from platinum-based chemotherapy. Cells deficient in HRR have shown sensitivity to PARP inhibitors and platinum-containing chemotherapy. Patients with metastatic castration-resistant prostate cancer who possess a variant in the HRR gene may respond to PARP inhibitor therapy.
		  • Response to PARP inhibitor therapy is highest in patients with germline or somatic BRCA 1/2 mutations.
		  • Genes directly or indirectly involved in the HRR pathway may be sensitive to PARP inhibitors, such as ATM, CHEK2, PALB2, FANCA, RAD51B/C/D, BRIP. It is estimated that ~12% of males with metastatic disease carry a pathogenic germline variant in DNA damage repair; approximately 23% possess somatic alterations.
		  • Olaparib with abiraterone received FDA-approval in BRCA-mutated and HRR-mutated, mCRPC in the 1L setting. It serves as the PARP inhibitor of choice in the VA Oncology Prostate Cancer Pathways in patients who have not received a prior androgen receptor pathway inhibitor (ARPI) in combination with abiraterone in the M1, CRPC, first-line in BRCAm positive patients. Olaparib monotherapy is preferred in subsequent-line settings in patients with HRR-mutated disease. The selection of Olaparib is based on abiraterone as the preferred 1L anti-androgen, FDA-approval of Olaparib with abiraterone and SME experience and familiarity with Olaparib dosing and safety profile.
		  • Talazoparib can remain non-formulary as Olaparib is the preferred agent on the VA Oncology Prostate Cancer Pathway. Use in combination with enzalutamide can be adjudicated at the local level for off-pathway use.

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References

[1] TALZENNA (talazoparib) capsule formulation [prescribing information online]. City, State: Mfr. Month Year. Available at: ——. Accessed Date.

[2] Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018; 379: 753-763.

[3] Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Annals of Oncology 2020; 31: 1526-1535.

[4] Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in med with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomized, placebo-controlled, phase 3 trial. Lancet 2023; Jul 22;402(10398):291-303. doi: 10.1016/S0140-6736(23)01055-3.

[5] US FDA Approval Summary: talazoparib in combination with enzalutamide for treatment of patients with HRR gene-mutated mCRPC. J Clin Oncol 2023; 42: https://doi.org/10.1200/JCO.23.02182.