Olaparib (LYNPARZA)
National Drug Monograph Addendum-HRR Gene-Mutated Metastatic Castration-Resistant Prostate Cancer
August 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

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.

Background

- Metastatic castration-resistant prostate cancer has poor outcomes. Up to 30% of castrate-resistant prostate cancer patients have a gene mutation involved in DNA damage repair. One of the repair mechanisms is homologous recombination repair (HRR) involved in double-strand breaks and intra/interstrand crosslinks.
- Loss of function in genes involved in HRR is associated with more aggressive prostate cancer. Gene alterations in the HRR pathway include BRCA1, BRCA2, ATM and others.
- These gene alterations confer sensitivity to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition. PARP is a family of proteins involved in DNA repair via the HRR pathway. Response to PARP inhibition is through inhibition of the enzymatic activity of PARP proteins plus the trapping of PARP which results in the stalling of the DNA replication fork and the formation of double-strand breaks. These same deficiencies in HRR also make cells sensitive to platinum compounds.
- FDA Indication: For the treatment of adult patients with deleterious our suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on FDA-approved companion diagnostic for olaparib.

Other Therapeutic Options

Carboplatin plus docetaxel (based on case series; no randomized trial data available)

Efficacy

Table 1: Olaparib in HRR deficient metastatic castration-resistant prostate cancer

Trial	Inclusion/Exclusion	Patients	Intervention and Comparator	Outcomes
PROfound trial[1] Prospective, R, OL, Phase 3 Cohort A= BRCA1, BRCA2, or ATM Alterations Cohort B= Any of the other 12 genes	Inclusions • Metastatic CRPC that progressed during tx with enzalutamide or abiraterone (for metastatic or nonmetastatic CRPC or for metastatic hormone-sensitive prostate cancer) • Previous taxane chemotherapy allowed • LHRH analogue or surgical castration • Alteration in ≥1 gene with a direct or indirect role in HRR • ECOG 0-2 Exclusions • Previous DNA damaging chemotherapy (mitoxantrone or platinum-based chemo) • MDS/AML • Resting QTc >470 msec or long QT syndrome	Age: 68 Age ≥65 yrs: 67% Gleason ≥8: 67% Alteration in single gene BRCA1: 5% BRCA2: 49% ATM: 37% PSA baseline: 62.2 ECOG 0: 52% 1: 41% 2: 7% Previous therapy Enzalutamide: 42% Abiraterone: 38% Enza and abi: 20% Previous taxane: 65% Cohort A N=245 Cohort B N=142	Olaparib 300 mg twice a day Vs Control: Physician's choice of either enzalutamide 160 mg daily or abiraterone 1000 mg daily plus prednisone 5 mg twice a day	<u>Cohort A</u> Med rPFS: 7.4 vs 3.6 months HR: 0.34 (95%CI 0.25-0.47) ORR: 33 vs 2% OR: 20.86 (95%CI 4.18-379.18) TTPP: HR 0.44 (95%CI 0.22-0.91) Interim Med OS: 18.5 vs 15.1 mos HR 0.64 (95%CI 0.43-0.97) <u>Overall Population (Cohorts A+B)</u> Med rPFS: 5.8 vs 3.5 months HR 0.49 (95%CI 0.38-0.63) ORR: 22 vs 4% OR: 5.93 (95%CI 2.01-25.40) Free from pain progression at 6 months: 85 vs 75% Interim Med OS: 17.5 vs 14.3 mos

	• Concomitant strong or moderate CYP3A inhibitors or inducers • Known brain mets • Spinal cord compression unless clinically stable for 28 days after definitive therapy • Poor risk due to serious, uncontrolled non-malignant medical disorder • Immunocompromised • Known active hepatitis B or C			HR 0.67 (95%CI 0.49-0.93) <u>ATM alteration only</u> <u>rPFS</u> 5.4 vs 4.7 months HR 1.04 (95%CI 0.61-1.87) OS for ATM altered cancers 17.3 vs 17.9 months HR 0.82 (95%CI 0.39-1.88) <u>Cohort B Only (Genes other than BRCA1, BRCA2, and/or ATM)</u> rPFS for Cohort B 4.8 vs 3.3 months HR 0.88 OS for Cohort B 14.2 vs 11.5 months HR 0.73

R=randomized; OL=open label; CRPC=castration-resistant prostate cancer; tx=therapy; HRR=homologous recombinant repair; MDS/AML=myelodysplastic syndrome/acute myelogenous leukemia; rPFS=radiographic Progression-Free Survival; ORR=Objective Response Rate; OR=Odds Ratio; TTPP=time to pain progression; OS=Overall Survival;

- PROfound trial
    - Primary endpoint: radiographic Progression- Free Survival (rPFS) in Cohort A
    - Secondary endpoints: rPFS in Cohorts A+B; Objective Response Rate (RR) in Cohort A; Time to pain progression (TTPP) in Cohort A; Overall Survival (OS) in Cohort A.
    - Median duration of assigned treatment for cohorts A+B was 7.4 months for olaparib and 3.9 months for the control arm.
    - Crossover: 81% of patients in the control group crossed over to Olaparib; median duration olaparib after crossover was 3.5 months.
    - Of the 15 gene alterations evaluated, 97% of patients were randomized based on alterations in 8 of the 15 genes; the other 7 gene alterations had frequencies too low for descriptive statistics
    - Median rPFS by gene subgroups in patients with a single gene alteration (in 8 of 15 genes tested)
        - BRCA2: 10.84 vs 3.48 months
        - CDK12: 5.09 vs 2.20 months (med OS: 14.2 vs 11.5 mos; HR 0.65 (95%CI 0.35-1.25)
        - ATM: 5.36 vs 4.70 months
        - BRCA1: 2.07 vs 1.84 months
        - CHEK2: 5.59 vs 3.35 months
        - PPP2R2A: 2.69 vs NR month
        - RAD51B: 10.89 vs 1.77 months
        - RAD54L: 7.20 vs 2.41 months
    - In Cohort A, the increase in rPFS was driven by alteration in the BRCA2 gene but not BRCA1 or ATM
    - rPFSs Subgroup analysis for prior taxane therapy found olaparib was better than control (point estimate and 95%CI less than 1.00) in patients with or without previous taxane therapy.
    - PSA_{50} response in those who could be evaluated in Cohort A: 43 vs 8%. PSA_{50} in Cohorts A+B: 30 vs 10%.

Safety

Warnings/Precautions

- Myelodysplastic syndrome/Acute Myeloid Leukemia: <1.5%
- Pneumonitis: <1%
- Venous thromboembolic events: 7% in mCRPC
- Embryo-fetal toxicity

Common Adverse Events (≥10%) in mCRPC: nausea, fatigue, anemia, thrombocytopenia, vomiting, diarrhea, decreased appetite, cough, dyspnea,

Serious Adverse Events in mCRPC: anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), urinary tract infection (2%)

Death: 4%; pneumonia (1.4%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), acute cardiac failure (0.4%)

Dose interruption due to AE: 45%
Dose reduction due to AE: 22%
Dose discontinuation due to AE: 18%; anemia (7%)

Table 2: Adverse reactions in ≥10% in PROfound

Event	Olaparib N=256		Enzalutamide or Abiraterone N=130	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Blood				
Anemia	46	21	15	5
Thrombocytopenia	12	4	3	0
GI Disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General				
Fatigue/asthenia	41	3	32	5
Metabolism/nutrition				
Decreased appetite	30	1	18	1
Respiratory				
Cough	11	0	2	0
Dyspnea	10	2	3	0

Conclusions

- Mutation in DNA damage repair (DDR) genes has recently been identified in men with advanced prostate cancer. Among the DDR pathways, defects in homologous recombination repair (HRR) genes BRCA2 associated with more aggressive prostate cancer in patients with localized disease.
- Cancer cells may compensate for mutations in HRR genes by upregulating PARP, an enzyme involved in DNA repair, making them more susceptible to PARP inhibition. In addition, mutations in HRR genes also make cells more susceptible to platinum chemotherapy.
- Phase II trials of the PARP inhibitor olaparib in patients no longer responding to standard therapies who had defects in DNA repair genes showed good response rates.[2,3]
- The phase 3 PROfound trial in men with metastatic castration-resistant prostate cancer that had progressed on enzalutamide or abiraterone with an alteration in ≥1 gene out of 15 involved in HRR compared olaparib to an active control of physician's choice of either enzalutamide or abiraterone. Two cohorts were studied: Cohort A included patients with an alteration in BRCA1, BRCA2 or ATM and Cohort B included patients with an alteration in one of the other 12 genes. The primary endpoint was radiographic Progression-Free Survival (rPFS) in Cohort A. Key secondary endpoints included rPFS in Cohorts A+B, confirmed objective response rate, time to pain progression (TTPP) in Cohort A, and Overall Survival (OS) in Cohort A. The results were statistically significant for the primary endpoint of rPFS in Cohort A [HR 0.34 (95%CI 0.25-0.47)]. In Cohort A, the results for the key secondary endpoints all favored olaparib. For the secondary endpoint of rPFS in Cohorts A+B, the results favored olaparib [HR 0.49 (95%CI 0.38-0.63)].
- Exploratory analyses at the gene level for rPFS found that the rPFS advantage in Cohort A was primarily driven by mutation in BRCA2 with only marginal benefits in patients with BRCA1 or ATM. In Cohort B, rPFS was marginal for some mutations (e.g. CDK12), large for some (e.g. RAD51B) and could not be investigated in others due to the small numbers of patients in those gene subgroups. These differences in response are consistent with other retrospective analyses of

responses by gene mutation.[4,5] Clinical trials with other PARP inhibitors in metastatic castration-resistant prostate cancer also observe low objective responses and PSA responses in men with mutations in HRR genes other than BRCA1/2.

- Place in Therapy
    - Although the FDA gave a broad indication for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), the primary endpoint in the PROfound trial of rPFS was positive in Cohort A in patients with BRCA1, BRCA2, or ATM mutations. Exploratory analysis by gene mutation in PROfound suggests greater benefit in men with BRCA2 mutation than the other HRR genes, and is consistent with other retrospective analyses of response to PARP inhibitors by gene mutation and low response rates in HRR gene mutations other than BRCA1/2 with other PARP inhibitors in clinical trials. PROfound is the only trial to separate out response by BRCA1 and BRCA2, with a lack of benefit in BRCA1 mutations; all other analyses lump BRCA 1 and BRCA2 results, likely due to BRCA1 mutation being a rarer event compared to BRCA2.
    - Use of olaparib in VA should be follow the FDA indication for patients with Homologous Recombination Repair gene-mutated metastatic castration-resistant prostate cancer, based on an FDA approved companion diagnostic, who have progressed on enzalutamide or abiraterone. Patients with non-BRCA2 HRR mutations may consider a clinical trial if available and patient is eligible.

Outcome in clinically significant area	rPFS
Effect Size	HR: 0.34 (95%CI 0.25-0.47)
Potential Harms	High risk (grade 3-4 anemia 21%)
Net Clinical Benefit	Moderate (high benefit, high risk)

[1] de Bono J, Mateo J, Fizazi K, Saad F, et al. Olaparib for metastatic castration-resistant prostate cancer New End J Med 2020;382:2091-102.

[2] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, et al. DNA-repair defects and olaparib in metastatic prostate cancer. New Engl J Med 2015; 373:1697-708.

[3] Mateo J, Porta N, Bianchini D, McGovern UM, Elliott T, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicenter, open-label, randomised, phase 2 trial. Lancet Oncol 2019; 21:162-174.

[4] Marshall CH, Sokolova AO, McNatty AL, Cheng HH, Eisenberger MA, et al. Differential responses to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 versus ATM. Eur Onc 2019;76:452-458.

[5] Antonarakis ES, Isaacsson P, Fu W, Wang H, Agarwal N, et al. CDK12-altered prostate cancer: clinical features and therapeutic outcomes to standard systemic therapies, poly (ADP-ribose) polymerase inhibitors, and PD-1 inhibitors. JCO Precis Oncol 2020;4:370-381.

Prepared August 2020. Contact person: Mark C. Geraci, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)