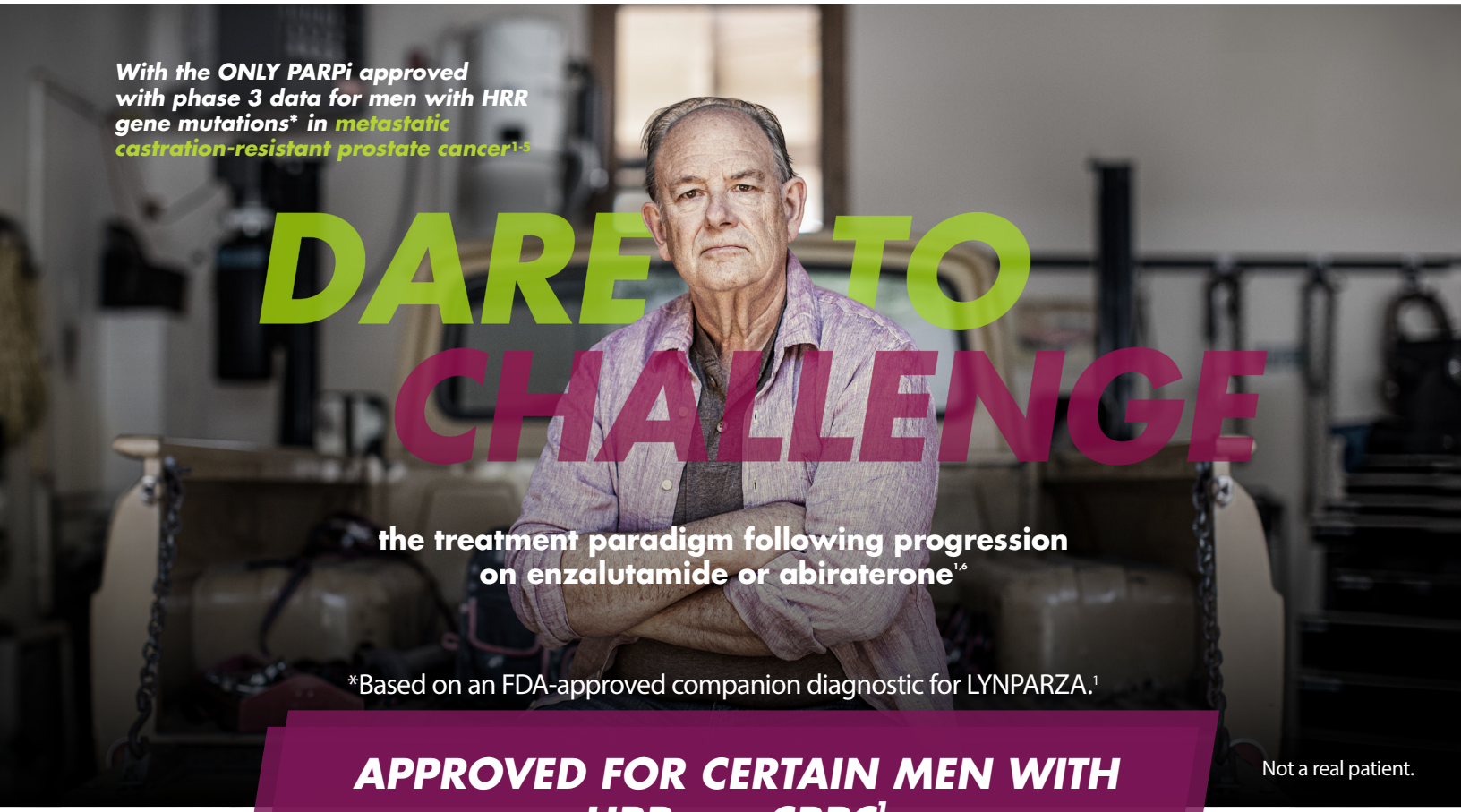
Lynparza®
olaparib
tablets 150 mg



APPROVED FOR CERTAIN MEN WITH HRRm mCRPC[1]

INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or 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 an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Please see Important Safety Information throughout, and click here for complete Prescribing Information, including Patient Information (Medication Guide).

HRR=homologous recombination repair; PARPi=poly (ADP-ribose) polymerase inhibitor.

Among men with BRCA1/2- or ATM-mutated mCRPC following progression on enzalutamide or abiraterone

In the PROfound trial, LYNPARZA more than doubled median rPFS vs retreatment with enzalutamide or abiraterone[1]

PROfound TRIAL DESIGN[1,5]

- The PROfound trial was a prospective, multicenter, randomized, open-label, phase 3 trial of LYNPARZA in patients with HRRm mCRPC
- Key eligibility criteria: Metastatic castration-resistant prostate cancer; progression on prior enzalutamide or abiraterone treatment for metastatic prostate cancer and/or CRPC; a tumor mutation in at least 1 of 15 genes* involved in the HRR pathway
- Patients were divided by mutation: ***BRCA1/2* or *ATM* gene mutation (Cohort A [n=245]†‡) and other HRR gene mutations (Cohort B [n=142]‡§)**, and randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1
- Each cohort was randomized 2:1 to receive LYNPARZA (tablets, 300 mg per dose, twice daily) or an active comparator (retreatment with investigator's choice of enzalutamide or abiraterone)

*HRR gene mutations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and/or *RAD54L*) were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory. No patients were enrolled who had mutations in 2 of the 15 prespecified HRR genes: *FANCL* and *RAD51C*.
†Patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.
‡All patients received a GnRH analog or had prior bilateral orchiectomy.
§*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
Although patients with *PPP2R2A* gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit ratio.

PRIMARY ENDPOINT: RADIOLOGICAL PROGRESSION-FREE SURVIVAL (rPFS)[1,5]

LYNPARZA more than doubled median rPFS vs retreatment with enzalutamide or abiraterone **in Cohort A**

LYNPARZA median rPFS (n=162)

7.4 MONTHS (95% CI: 6.2–9.3)

Retreatment with enzalutamide or abiraterone median rPFS (n=83)

3.6 MONTHS (95% CI: 1.9–3.7)

>2x median rPFS

66% relative risk reduction of disease progression or death
HR=0.34, 95% CI: 0.25–0.47, *P*<0.0001

- rPFS in Cohort A was determined by BICR using RECIST version 1.1 and PCWG3 (bone) criteria
- Consistent results were observed in exploratory analyses of rPFS:
  - For patients who received or did not receive prior taxane therapy
  - For those with germline *BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS)[1,5]

LYNPARZA demonstrated an OS benefit and reduced risk of death by 31% vs retreatment with enzalutamide or abiraterone **in Cohort A**

LYNPARZA median OS (n=162)

19.1 MONTHS (95% CI: 17.4–23.4)

Retreatment with enzalutamide or abiraterone median OS (n=83)

14.7 MONTHS (95% CI: 11.9–18.8)

31% **reduced risk of death**
HR=0.69, 95% CI: 0.50–0.97, *P*=0.0175

PROfound was powered to evaluate OS in Cohort A within a hierarchical statistical analysis.

SECONDARY ENDPOINTS[1,5]

- **LYNPARZA significantly improved confirmed ORR by BICR vs retreatment with enzalutamide or abiraterone for patients with measurable disease at baseline in Cohort A:** 33% (n=28) with LYNPARZA (95% CI: 23–45, *P*<0.0001; n=84) vs 2% (n=1) with enzalutamide or abiraterone retreatment (95% CI: 0–12, *P*<0.0001; n=43)
- **LYNPARZA improved median rPFS vs retreatment with enzalutamide or abiraterone (Cohorts A+B):** 5.8 months median rPFS with LYNPARZA (95% CI: 5.5-7.4; n=256) vs 3.5 months median rPFS with enzalutamide or abiraterone retreatment (95% CI: 2.2–3.7; n=131)

rPFS in Cohorts A+B was assessed by BICR.

PROfound was powered to evaluate secondary endpoints within a hierarchical statistical analysis.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Please see Important Safety Information throughout, and click here for complete Prescribing Information, including Patient Information (Medication Guide).

BICR=blinded independent central review; CI=confidence interval; CRPC=castration-resistant prostate cancer; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; HRRm=homologous recombination repair gene–mutated; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.

Among men with HRRm mCRPC following progression on enzalutamide or abiraterone

Safety data from the phase 3 trial

Lynparza® olaparib tablets 150 mg

ADVERSE REACTIONS* REPORTED IN ≥10% OF PATIENTS IN COHORTS A+B IN PROfound[1]

LYNPARZA (n=256) | Retreatment with enzalutamide or abiraterone (n=130)

Adverse reactions	Grades 1–4 (%)	Grades 3–4 (%)
Blood and lymphatic disorders		
Anemia†	46 / 15	21 / 5
Thrombocytopenia‡	12 / 3	4 / 0
Gastrointestinal disorders		
Nausea	41 / 19	1 / 0
Diarrhea	21 / 7	1 / 0
Vomiting	18 / 12	2 / 1
General disorders and administration-site conditions		
Fatigue (including asthenia)	41 / 32	3 / 5
Metabolism and nutrition disorders		
Decreased appetite	30 / 18	1 / 1
Respiratory, thoracic, and mediastinal disorders		
Cough	11 / 2	0 / 0
Dyspnea	10 / 3	2 / 0

*Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
†Includes anemia and hemoglobin decreased.
‡Includes platelet count decreased and thrombocytopenia.

- **Fatal adverse reactions** occurred in 4% of patients treated with LYNPARZA. These included pneumonia (1.2%), 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%), and acute cardiac failure (0.4%)
- **Serious adverse reactions** occurred in 36% of patients receiving LYNPARZA. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%)
- **Venous thromboembolic events,** including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study

LABORATORY ABNORMALITIES REPORTED IN ≥25% OF PATIENTS IN COHORTS A+B IN PROfound[1]

LYNPARZA (n=256)§ | Retreatment with enzalutamide or abiraterone (n=130)§

Laboratory parameter‖	Grades 1–4 (%)	Grades 3–4 (%)
Decrease in hemoglobin	98 / 73	13 / 4
Decrease in lymphocytes	62 / 34	23 / 13
Decrease in leukocytes	53 / 21	4 / 0
Decrease in absolute neutrophil count	34 / 9	3 / 0

§This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‖Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

DOSE MODIFICATIONS AND DISCONTINUATIONS IN PROFOUND (n=256)

>8 out of 10 men remained on LYNPARZA without discontinuing due to ARs[1]

- 45% of men on LYNPARZA had dose interruptions due to an AR of any grade
- 22% of men on LYNPARZA had dose reductions due to an AR
- 18% of men discontinued LYNPARZA due to an AR

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-Fetal Toxicity (Cont'd)

Females
Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males
Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

Please see Important Safety Information throughout, and click here for complete Prescribing Information, including Patient Information (Medication Guide).

AR=adverse reaction; HRRm=homologous recombination repair gene–mutated; mCRPC=metastatic castration-resistant prostate cancer.

With the ONLY PARPi approved with phase 3 data for men with HRR gene mutations in metastatic castration-resistant prostate cancer*[1]

DARE TO CHALLENGE

the treatment paradigm following progression on enzalutamide or abiraterone[1,6]

*Based on an FDA-approved companion diagnostic for LYNPARZA.[1]

Test to inform your treatment decisions[1,7]

RECOMMENDED

Test all patients with advanced prostate cancer for HRR gene mutations at metastatic diagnosis or upon progression with enzalutamide or abiraterone[7]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend tumor testing for HRRm for any patient with mCRPC.[7]

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Venous Thromboembolic Events: Including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving LYNPARZA and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA for **PROfound** were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for **PROfound** were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Please see Important Safety Information throughout, and click here for complete Prescribing Information, including Patient Information (Medication Guide).

You may report side effects related to AstraZeneca products by clicking here. If you prefer to report these to the FDA, either visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Visit LYNPARZAhcp.com for additional data

HRR=homologous recombination repair; HRRm=homologous recombination repair gene–mutated; mCRPC=metastatic castration-resistant prostate cancer; NCCN=National Comprehensive Cancer Network; PARPi=poly (ADP-ribose) polymerase inhibitor.

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** Zejula® (niraparib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2021. **3.** Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020. **4.** Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2020. **5.** de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102. **6.** Teo MY, Rathkopf DE, Kantoff P. Treatment of advanced prostate cancer. *Annu Rev Med*. 2019;70:479-499. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 13, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org.

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