PARP INHIBITORS ARE EFFECTIVE DRUGS AS MONOTHERAPY IN mCRPC PATIENTS WITH HRR ALTERATIONS

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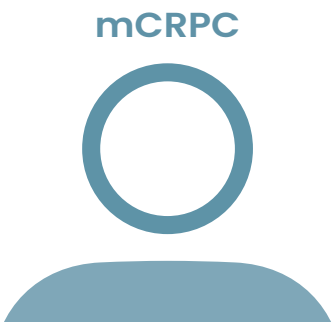

In mCRPC patients, up to **one third** harbour somatic HRR mutations[1]

Up to 10% are of germline origin[1]

BRCA1/2 **and** ***ATM*** **gene mutations are most common but there are others**[1]

PARP inhibitors are a treatment option for patients with HRR mutations, as they trigger cell death in HRR-deficient cells

Trial name	**Olaparib** **PROfound**[2,3] *Approved in*[a,b]	**Rucaparib** **TRITON2**[4,5] *Approved in*[c]
Phase	3	2
Dose	300 mg bid	600 mg bid
Required prior therapy	Progression on NHA for mPC and/or nmCRPC	1 taxane-based regimen AND ≥1 NHA for mCRPC
Comparator	Physician's choice (enzalutamide or abiraterone)	Not applicable
Primary endpoint	rPFS by BICR in Cohort A (*BRCA1*, *BRCA2*, or *ATM* mutations)	ORR
Key results	**Median rPFS (months)** *BRCA1/2* or *ATM*: Olaparib: 7.4 Comparator: 3.6 HR (95% CI): 0.34 (0.25-0.47) **Median OS (months)** *BRCA1/2* or *ATM* Olaparib: 19.1 Comparator: 14.7 HR (95% CI): 0.69 (0.50-0.97)	**ORR (IRR)** 43.5% (95% CI, 31.0 - 56.7%; n=27/62) **ORR (IA)** 50.8% (95% CI, 38.1 - 63.4%; n=33/65)
Most common Grade 3+ AEs	**Olaparib arm** Anaemia: 23% Fatigue/asthenia: 3 % Nausea: 2%	Anaemia: 25% Fatigue/asthenia: 9% Thrombocytopenia: 10%

a. Olaparib FDA-approved indication: indicated as monotherapy for the treatment of adult patients with mCRPC and HRRm, who have progressed on enzalutamide or abiraterone acetate, selected using an FDA-approved Lynparza companion diagnostic. **b.** Olaparib EMA-approved indication: indicated as monotherapy for the treatment of adult patients with mCRPC and a *BRCAm*, who have progressed on an NHA. Determine *BRCAm* status with a validated test method. **c.** Rucaparib FDA-approved indication: indicated as monotherapy for the treatment of adult patients with *BRCAm* mCRPC who have progressed on AR-directed therapy and a taxane.

AE, adverse event; ATM, ataxia telangiectasia mutated; BICR, Blinded Independent Central Review; bid, twice a day; ***BRCA***(1/2), breast cancer (type 1/2) susceptibility protein; CI, confidence interval; CRPC, castration-resistant prostate cancer; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HR, hazard ratio; HRD, homologous repair defects; HRR, homologous recombination repair; HRRm, homologous recombination repair gene mutation; IA, investigator assessed; IRR, independent radiological review; m, mutated; mCRPC, metastatic castration-resistant prostate cancer; mPC, metastatic prostate cancer; NHA, novel hormonal agent; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; rPFS, radiographic progression-free survival

1. Robinson D, et al. Cell. 2015;161:1215-28; **2.** de Bono J, et al. N Engl J Med. 2020;382:2091-2102; **3.** Hussain M, et al. N Engl J Med. 2020;383:2345-57; **4.** Abida W, et al. J Clin Oncol. 2020;38:3763-72; **5.** Abida W, et al. Clin Cancer Res. 2020;26:2487-96; **6.** Lynparza (olaparib) US prescribing information (Aug-2022); **7.** Lynparza (olaparib) summary of product characteristics (Sep 2022); **8.** Rubraca (rucaparib) US prescribing information

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