PARP inhibitors for metastatic castration-resistant prostate cancer: Enhancing patient–practitioner conversations

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Current PARP inhibitor indications

Agent	FDA indication			EMA indication		
	Regimen	Mutation status	Other therapies	Regimen	Mutation status	Other therapies
Olaparib	(2L) Monotherapy	Germline/somatic HRR-mutations†	Progressed on enzalutamide or abiraterone[4]	(2L) Monotherapy	Germline and/or somatic *BRCA1/2* mutations	Progressed following prior therapy that included new hormonal agent[1]
	(1L) Combination with abiraterone and prednisone*	*BRCA*-mutated,† as determined by FDA-approved test[4]		(1L) Combination with abiraterone and prednisone*		Where chemotherapy not clinically indicated[1]
Talazoparib	(1L) Combination with enzalutamide	HRR-mutated[5]		(1L) Combination with enzalutamide		Where chemotherapy not clinically indicated[2]
Niraparib	(1L) Niraparib and abiraterone acetate fixed-dose combination plus prednisone*	*BRCA*-mutated,† as determined by FDA-approved test[6]		(1L) Niraparib and abiraterone acetate fixed-dose combination plus prednisone*	Germline and/or somatic *BRCA1/2* mutations	Where chemotherapy not clinically indicated[3]
Rucaparib	(3L) Monotherapy	Deleterious germline and/or somatic *BRCA* mutation, as determined by FDA-approved test	Prior androgen receptor-directed therapy and a taxane-based chemotherapy[7]	Not approved		

*Or prednisolone; †Deleterious or suspected deleterious mutation. 1L, first line; 2L, second line; 3L, third line; BRCA, BReast CAncer gene; FDA, Food and Drug Administration; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase. 1. EMA. Olaparib SmPC. Available from: www.ema.europa.eu/en/documents/overview/lynparza-epar-medicine-overview_en.pdf; 2. EMA. Talazoparib SmPC. Available from: www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf; 3. EMA. Niraparib + abiraterone acetate SmPC. Available from: www.ema.europa.eu/en/documents/product-information/akeega-epar-product-information_en.pdf; 4. FDA. Olaparib PI. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf; 5. FDA. Talazoparib PI. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2024/211651s012lbl.pdf; 6. FDA. Niraparib + abiraterone acetate PI. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf; 7. FDA. Rucaparib PI. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf; All references accessed 11 December 2024.

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Guideline recommendations for PARPi in mCRPC

NCCN[2]

No prior docetaxel & no prior novel hormone therapy
OR Progression on docetaxel & no prior novel hormone therapy

Useful in certain circumstances:
- Olaparib/abiraterone or niraparib/abiraterone for *BRCA* mutation
- Talazoparib/enzalutamide for HRR mutation

Progression on novel hormone therapy & no prior docetaxel

Preferred regimens:
- Olaparib for *BRCA* mutation
- Rucaparib for *BRCA* mutation

Useful in certain circumstances:
- Talazoparib/enzalutamide for HRR mutation

Progression on docetaxel and novel hormone therapy

Useful in certain circumstances:
- Olaparib for HRR mutation
- Rucaparib for *BRCA* mutation

EAU-EANM-ESTRO-ESUR-SIOG[1]

Base the choice of treatment on:
Performance status, symptoms, comorbidities, location and extent of disease, genomic profile, patient preference, previous treatment for hormone-sensitive metastatic disease

Previously untreated with HRR or *BRCA* mutation:
- Olaparib/abiraterone*

Previously untreated with *BRCA* mutation:
- Niraparib/abiraterone*

Previously untreated with HRR mutation:
- Talazoparib/enzalutamide*

Pre-treated with relevant DNA repair mutations:
- Offer PARP inhibitor

*If patient is fit for both agents. BRCA, BReast CAncer gene; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Radiotherapy and Oncology; ESUR, European Society of Urogenital Radiology; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NCCN, National Comprehensive Cancer Network; PARPi, poly(ADP-ribose) polymerase inhibitor; SIOG, Society of Geriatric Oncology.

1. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Available from: uroweb.org/guidelines/prostate-cancer/chapter/diagnostic-evaluation (accessed 12 December 2024); 2. NCCN guidelines version 1.2025 prostate cancer. Available from: www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed 12 December 2024).

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Profile of patient with mCRPC

- 72-year-old man
- Prostate cancer diagnosed 9 years ago
- Previous therapy: docetaxel, ARPI
- Bone metastases recently discovered
- Family history of breast and ovarian cancer
- **What are the next steps?**

ARPI, androgen receptor pathway inhibitors; mCRPC, metastatic castration-resistant prostate cancer.

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Relevant* molecular testing recommended in mCRPC

Association	Germline	Tumour
NCCN[1]	• Recommended	• Recommended to guide treatment decision-making • Testing for HRR genes recommended: *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12* • Metastatic biopsy strongly recommended • When unsafe or unfeasible, ctDNA assay is an option
ESMO[2]	• Testing for *BRCA2* and other DNA damage repair mutations recommended in patients with family history of cancer • Consider in all patients	• Consider testing for HR genes
EAU-EANM-ESTRO-ESUR-SIOG[3]	• Recommended	• Recommended • Metastatic sample recommended, primary tumour tissue or ctDNA assay also an option
AUA-SUO[4]	• Recommended to inform prognosis, familial risk, and select targeted therapies	• Recommended to inform prognosis, familial risk, and select targeted therapies

*Molecular testing guidelines for prostate cancer are more extensive than shown on slide, focus is on most relevant guidelines to guide PARP inhibitor use. AUA, American Urological Association; BRCA, BReast CAncer gene; ctDNA, circulating tumour DNA; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; ESTRO, European Society for Radiotherapy and Oncology; ESUR, European Society of Urogenital Radiology; mCRPC, metastatic castration-resistant prostate cancer; NCCN, National Comprehensive Cancer Network; SIOG, Society of Geriatric Oncology; SUO, Society of Urologic Oncology. 1. NCCN guidelines version 1.2025 prostate cancer. Available from: www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed 12 December 2024); 2. Parker C, et al. *Ann Oncol*. 2020;31:1119–34; 3. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Available from: uroweb.org/guidelines/prostate-cancer/chapter/diagnostic-evaluation (accessed 12 December 2024); 4. Lowrance W, et al. *J Urol*. 2023;209:1082–90.

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Structured approach to shared decision-making

EDUCATE

- Communicate big picture of treatment plan early
- Remind of next steps as they approach
- Share timely, up-to-date information with patients and caregivers
  - For example, specific information about therapy options, MoA and side effects

EMPHASIZE

- Communicate that PARP inhibitors work differently than traditional chemotherapy…
- …and have unique actions and side effects
- Encourage patients to report AEs early
- Assess and document AEs consistently at each clinic visit

EQUIP

- Provide patients with AE ‘toolkits’ specific to treatment plan phase:
  - Handout/wallet card to grade AEs
  - Supportive care medications including anti-diarrhoeal medications, stool softeners or anti-nausea medications
- Encourage early reporting, give patients permission to call

AE, adverse event; MOA, mechanism of action; PARP, poly(ADP-ribose) polymerase.

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