Presentation to be viewed online only

Time to challenge the treatment paradigm for patients with BRCAm metastatic castration-resistant prostate cancer following novel hormonal agent progression

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DOP: November 2023

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LYNPARZA© (olaparib) tablets mCRPC indication

LYNPARZA© (olaparib) tablets

Prostate cancer indications[1]

LYNPARZA tablets are indicated as monotherapy for:

The treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a novel hormonal agent

LYNPARZA tablets are indicated in combination with abiraterone and prednisone or prednisolone for:

The treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated

Always refer to the Summary of Product Characteristics before prescribing to minimise the risks associated with the use of this medicine

mCRPC=metastatic castration-resistant prostate cancer.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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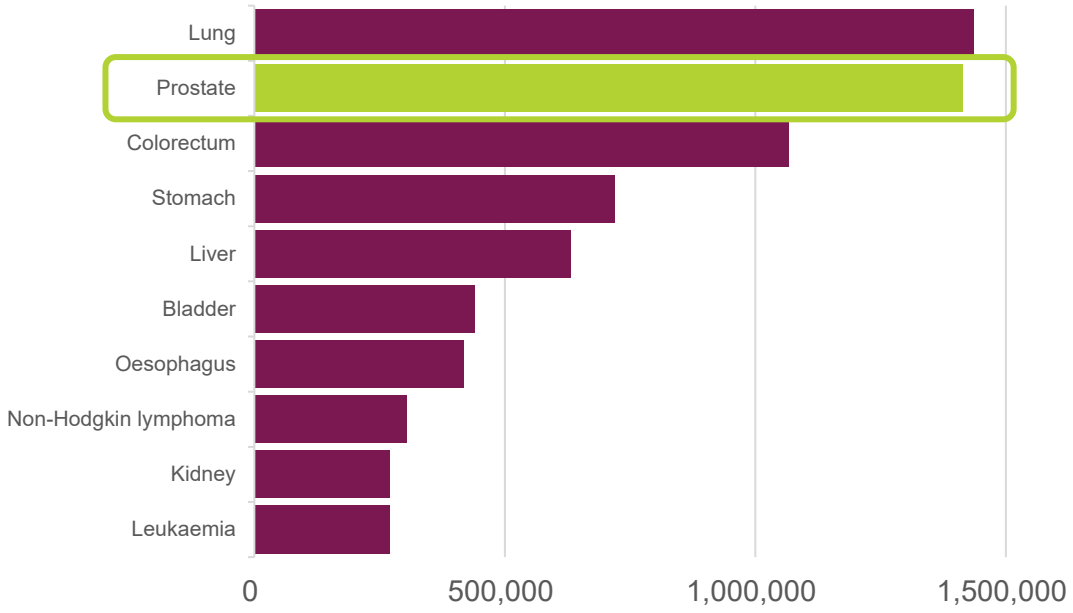
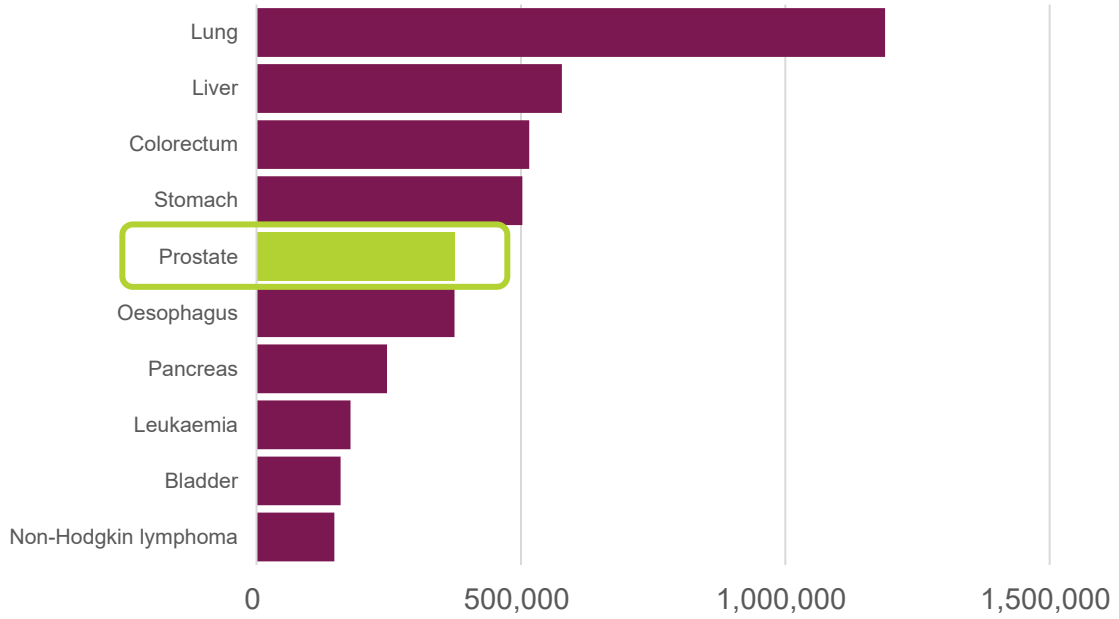
Prostate cancer is the fifth leading cause of cancer-related deaths amongst males globally[1]

In 2020, there were an estimated 1.4 million new cases and 375,000 deaths related to prostate cancer[1]

Estimated number of **incident cases** worldwide, males, all ages in 2020[1]



Estimated number of **deaths** worldwide, males, all ages in 2020[1]



The number of patients predicted to die from prostate cancer is expected to **double** in the **next 20 years**[2]

Figures adapted from GLOBOCAN.[1]

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209–249; 2. Rawla P. *World J Oncol*. 2019;10:63–89.

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The treatment of metastatic prostate cancer poses a significant challenge in the UK

Approximately one in three men with prostate cancer are diagnosed with metastatic disease in **Scotland**,* though this is reduced to one in eight men in **London**†[1]

Prostate cancer is a common and complex disease

- Prostate cancer is the most common cancer in men in the UK, with over **52,000** cases diagnosed every year ‡[2]
- Over **12,000** patients will die of prostate cancer per year ‡[2]

Metastatic prostate cancer is a considerable clinical challenge

- Advanced prostate cancer is incurable, commonly progresses and is often fatal[3,4]
- The 5-year survival for patients with metastatic disease is ~50% in the UK[5]
- Patients with metastatic prostate cancer report low QoL due to exacerbated symptoms and adverse events from life-prolonging therapies[6]

*Data collected between 2014–2018. †Data collected between 2015–2019. ‡Data last updated in June 2022.
QoL=quality of life.

1. Prostate Cancer UK. Available at: https://prostatecanceruk.org/about-us/news-and-views/2023/01/huge-north-south-divide-in-prostate-cancer-diagnoses (Accessed November 2023); 2. Prostate Cancer UK. Available at: https://prostatecanceruk.org/prostate-information/about-prostate-cancer (Accessed November 2023); 3. Sartor O, et al. *N Engl J Med.* 2018;378:645–657; 4. Prostate Cancer UK. Available at: https://prostatecanceruk.org/prostate-information/just-diagnosed/advanced-prostate-cancer (Accessed November 2023); 5. Cancer Research UK. Available at: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/survival (Accessed November 2023); 6. Holm M, et al. *BMC Palliat Care*. 2018;17:126.

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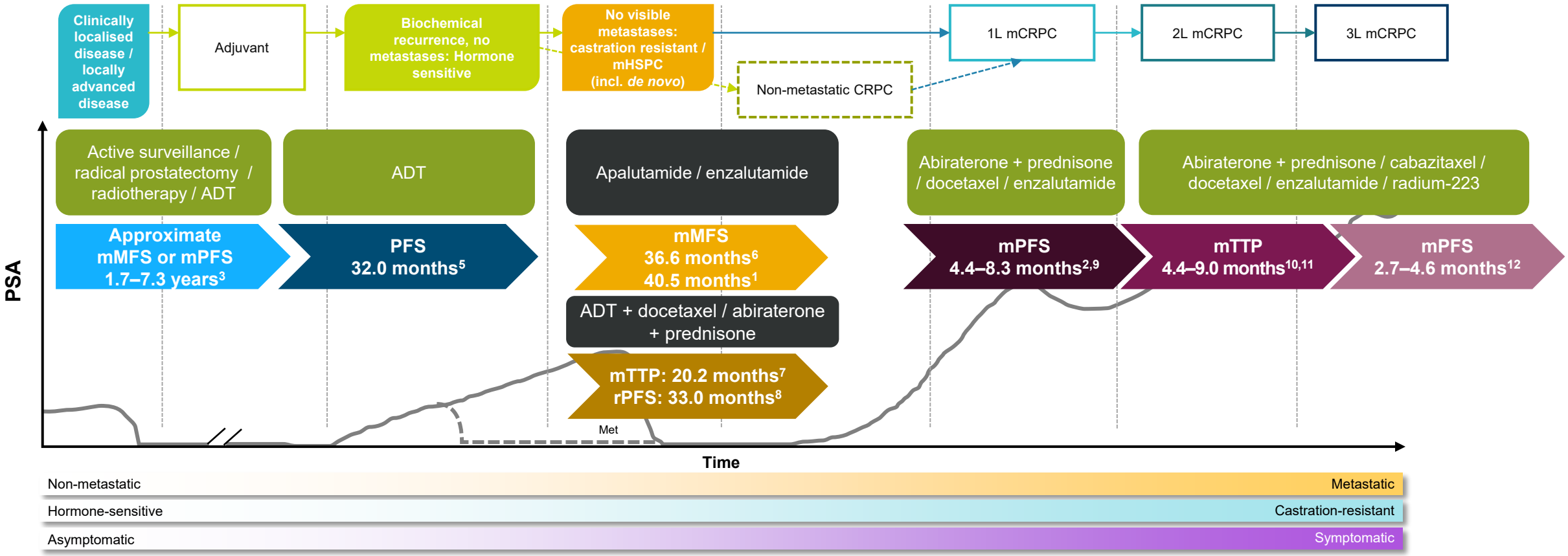
Despite advances in mCRPC treatment, clinical outcomes for patients remain poor[1–4]



1/2/3L=first/second/third-line; ADT=androgen deprivation therapy; (m)CRPC=(metastatic) castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; mMFS=median metastases-free survival; (m)PFS=(median) progression-free survival; mTTP=median time-to-progression; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival.

1. Smith MR, et al. *N Engl J Med*. 2018;378:1408–1418; 2. Fang M, et al. *Prostate Cancer*. 2017;2017:8560827; 3. Barayan GA, et al. *BJU Int*. 2014;114:E99–E104; 4. Tourinho-Barbosa R, et al. *Int Braz J Urol*. 2018;44:14–21; 5. Carrie C, et al. *Lancet Oncol*. 2016;17:747–756; 6. Hussain M, et al. *N Engl J Med*. 2018; 378:2465–2474; 7. Sweeney CJ, et al. *N Engl J Med*. 2015;373:737–746; 8. Fizazi K, et al. *N Engl J Med*. 2017;377:352–360; 9. Oudard S, et al. *J Clin Oncol*. 2017;35:3189–3197; 10. Morris MJ, et al. *J Clin Oncol*. 2017;34:Abstract 5075; 11. Chowdhury S, et al. *J Clin Oncol*. 2017;35:Abstract 5028; 12. Caffo O, et al. *Eur Urol*. 2015;68:147–153.

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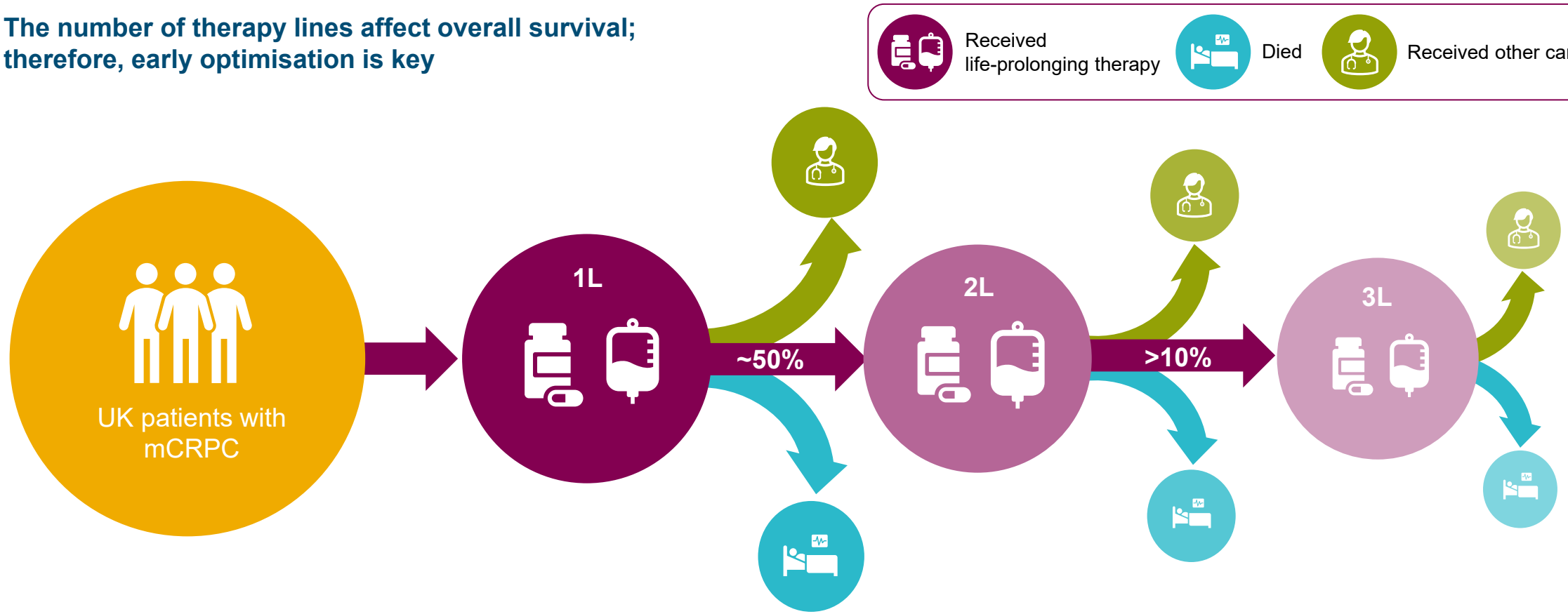
Approximately one half of UK patients with mCRPC receive more than one line of therapy[1]

The number of therapy lines affect overall survival; therefore, early optimisation is key



1/2/3L=first/second/third-line; mCRPC=metastatic castration-resistant prostate cancer.

1. Leith A, et al. *Adv Ther*. 2022;39:2236–2255.

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What considerations may impact treatment choice in 1L mCRPC?

Treatment decision[1–5]

Patient-related factors[1–4]

- Life expectancy
- Comorbidities
- Concomitant medications
- Performance status
- Presence of symptoms
- Social supports
- Preferences and beliefs

Cancer-related factors[1,3]

- Extent of metastatic disease
- De novo vs. recurrent
- Prior treatments
- Molecular features

Clinician-related factors[4]

- Experience with treatment options
- Comfort with AE management
- Interpretation of clinical data
- Preferences and beliefs

Treatment-related factors[1,2,5]

- Therapy availability
- Schedule of treatments and monitoring
- Cost
- Expected efficacy
- Expected toxicity

1L=first-line; AE=adverse event; mCRPC=metastatic castration-resistant prostate cancer.

1. Morgans AK, Beltran H. *J Clin Oncol*. 2022;40:818–824; 2. Anido-Herranz U, et al. *Clin Transl Oncol*. 2019;21:249–258; 3. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 4. Glatzer M, et al. *Oncology*. 2020:98(6):370–378; 5. Turco F, et al. *Res Rep Urol*. 2022;14:339–350.

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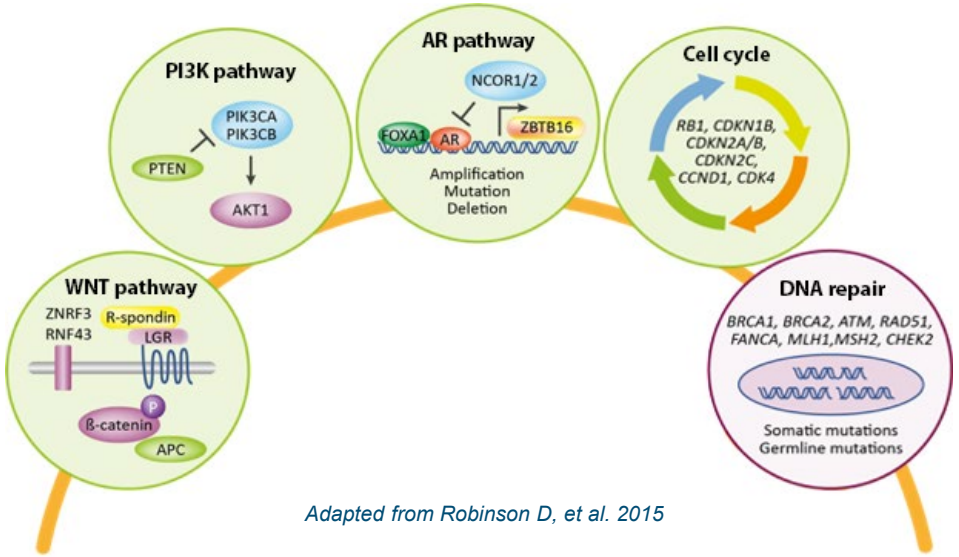
Metastatic prostate cancer is biologically heterogeneous

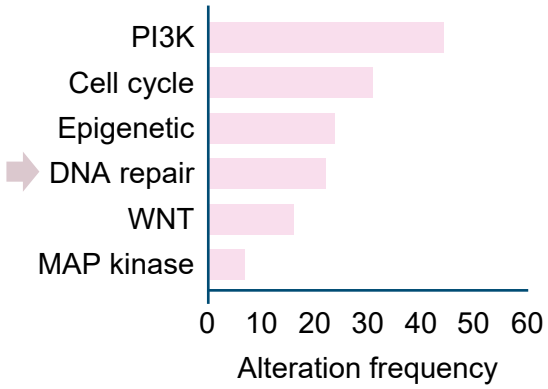
~90% of mCRPC patients have genomically aberrant pathways involving AR, PI3K, DDR, WNT and cell cycle-related signalling[1,2]

Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



Adapted from Robinson D, et al. 2015

Over 20% of patients with mCRPC have alterations associated with DNA repair pathways*[2]



Adapted from Abida W, et al. 2019[2]

Homologous recombination repair (HRR) is a key mechanism for DNA repair[3,4]

*In a multi-institutional study profiling 444 tumours from 429 patients with mCRPC.
AKT=protein kinase B; APC=antigen-presenting cell; AR=androgen receptor; DDR=DNA damage repair; LGR=leucine-rich repeat-containing G-protein coupled receptor; mCRPC=metastatic castration-resistant prostate cancer; PI3K=phosphoinositide 3-kinase; PTEN=phosphate and tensin homologue; WNT=wingless integration.

1. Robinson D, et al. *Cell*. 2015;161:1215–1228; 2. Abida W, et al. *PNAS*. 2019;116:11428–11436; 3. Lord CJ, Ashworth A. *Nature*. 2012;481:287–293; 4. O'Connor MJ. *Mol Cell*. 2015;60:547–560.

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Mutations in DNA repair pathways can lead to genetic instability and drive tumour growth[1,2]

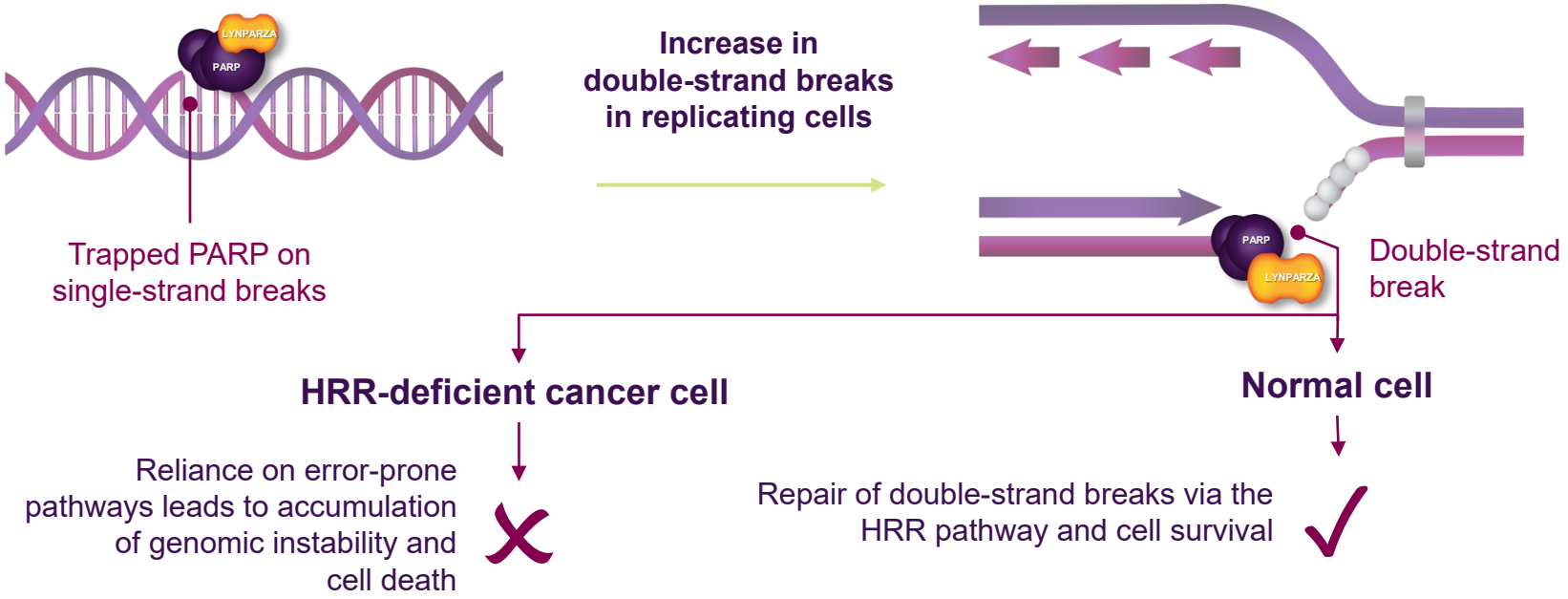
Mechanisms proposed are based on experimental evidence and may not be applicable in a clinical setting

In HRR-deficient cancer cells, double-strand breaks rely on error-prone pathways, such as NHEJ, which ultimately leads to cell death.[1] Therefore, HRR mutations (such as BRCAm) confer sensitivity to PARP inhibition[3,4]

HRR gene alterations, such as BRCAm, can be derived from germline or somatic origin.[5–7]

- **Germline:** inherited from a parent. Non-tumour cells have monoallelic gene loss* and somatic mutation causes biallelic loss in tumour cells
- **Somatic:** non-inherited. Non-tumour cells retain both alleles

In both cases, tumours have biallelic gene loss.†



Adapted from O'Connor MJ. 2015[8]

*Either *BRCA1* or *BRCA2;* †Loss of function can also result from epigenetic and other non-genomic mechanisms. [5]
BRCAm=BRCA mutation; HRR=homologous recombination repair; NHEJ=non-homologous end joining; PARP=poly(ADP-ribose) polymerase.

1. Lord CJ, Ashworth A. *Nature.* 2012;481:287–293; 2. Roy R, et al. *Nat Rev Cancer.* 2012;12:68–78; 3. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 4. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102; 5. Jonsson P, et al. *Nature.* 2019;571:576–579; 6. Warner EW, et al. *BJU Int.* 2019;123:769-776; 7. Mateo J, et al. *Eur Urol.* 2017;71:417–425; 8.O'Connor MJ. *Mol Cell.* 2015;60:547–560.

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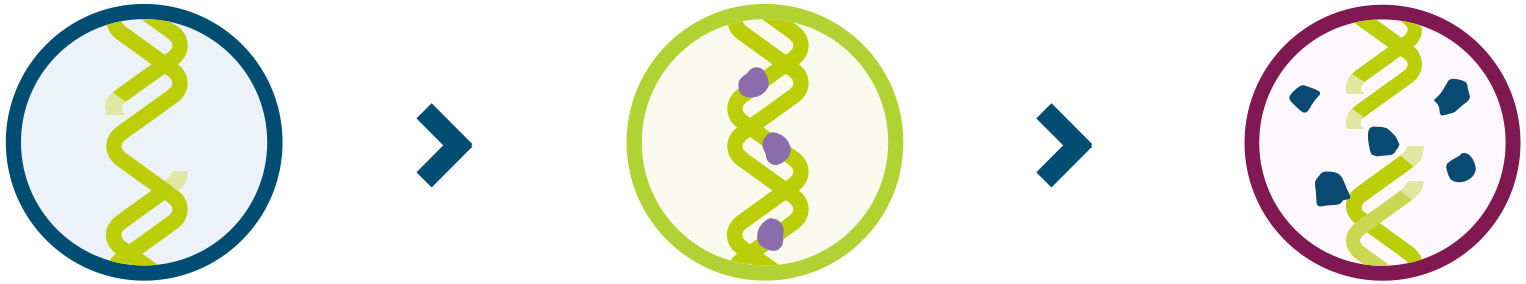
LYNPARZA targets PARP, causing a lethal response in HRRm tumour cells[*1–3]*

Mechanisms proposed are based on experimental evidence and may not be applicable in a clinical setting

LYNPARZA inhibits PARP by:[†]

- Increasing the formation of trapped PARP-DNA complexes[1–3]
- Inhibiting enzymatic activity[1]



As tumour cells proliferate, they accumulate DNA damage[2]

Tumour cells survive by repairing damaged DNA via the PARP enzyme and other cellular processes, such as HRR[3]

Disrupting DNA repair with a PARPi may help drive cell death in HRR-mutated tumours[*2,3]

*Healthy cells may also be affected by LYNPARZA; [†]Based on pre-clinical data; the exact mechanism of action of LYNPARZA remains the subject of research.
HRR(m)=homologous recombination repair gene mutant; PARP(i)=poly (ADP-ribose) polymerase (inhibitor).

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. O'Connor MJ. *Mol Cell*. 2015;60:547–560;
3. Lord CJ, Ashworth A. *Science*. 2017;355:1152–1158.

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Practicalities of introducing LYNPARZA into UK practice

TIME TO CHALLENGE
EXPECTATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER TREATMENT

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LYNPARZA provides a treatment option for patients regardless of HRRm status[1]

Where does LYNPARZA fit into the mCRPC pathway?[1–3]

First line

Optional taxane*

LYNPARZA + abiraterone + prednisone/prednisolone
mCRPC regardless of HRRm

Second line

NHA
(i.e. abiraterone or enzalutamide)

Disease progression

LYNPARZA monotherapy
BRCA-mutated mCRPC

Subsequent treatment(s)

LYNPARZA (tablet formulation) is indicated as monotherapy for the treatment of adult patients with mCRPC and BRCAm (germline and/or somatic) who have progressed following a prior NHA[1]

*Some patients may have received taxane therapy prior to NHA treatment, as reflected in the PROfound trial.[4]
BRCAm=BRCA mutation; HRRm=homologous recombination repair gene mutant; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. XTANDI (enzalutamide). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/10318/smpc (Accessed November 2023); 3. ZYTIGA (abiraterone acetate). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2381/smpc (Accessed November 2023); 4. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102.

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Approximately 10% of patients with mCRPC screened for inclusion in the PROfound trial had a BRCAm[1]

- Both germline and somatic BRCAm have been found in prostate cancer tumour cells[2]
- In a population of patients with advanced prostate cancer, approximately half of those with a germline mutation were identified as having a BRCAm[2]

Germline BRCAm

Germline:
Originates in germinal cells and are transmitted at conception to the individual's offspring - they are present in every cell of the body[3]

Somatic BRCAm

Somatic:
Acquired during an individual's life and are only present in cells descended from the cell in which the mutation originated - they are not heritable[3]

BRCAm=BRCA mutation; ESMO=European Society for Medical Oncology; mCRPC=metastatic castration-resistant prostate cancer.

1. de Bono J, et al. Poster presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Poster 847PD; 2. Abida W, et al. *JCO Precis Oncol.* 2017;2017:PO.17.00029; 3. Milani DA, Chauhan PR. Genetics, Mosaicism. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559193/ (Accessed November 2023).

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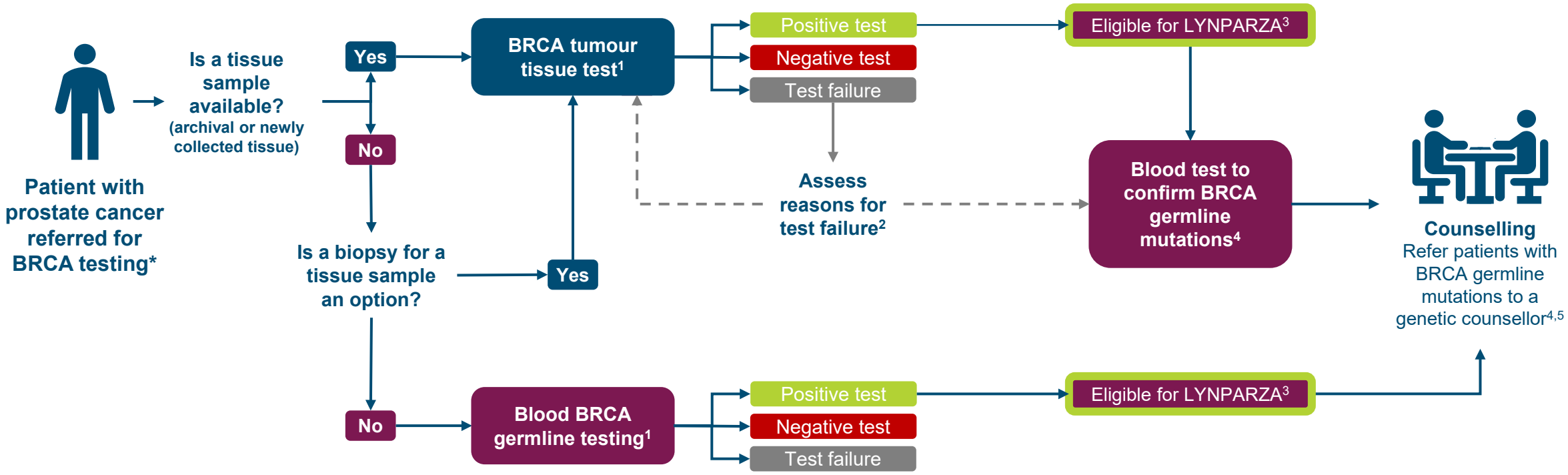
Tumour tissue testing is the current gold standard for cancer diagnosis[1]

Potential testing pathway:



*For patients who have unknown BRCA germline mutation status.
ESMO=European Society for Medical Oncology.

1. Boerrigter E, et al. *Exp Rev Mol Diagn.* 2020;20:219–230; 2. de Bono J, et al. Poster presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Poster 847PD; 3. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 4. Gillessen S, et al. *Eur Urol.* 2020;77:508–547; 5. Parker C, et al. *Ann Oncol.* 2020;31:1119–1134.

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A failed BRCA tumour test is not the same as a negative test result[1]

1. Tumour tissue BRCA test

In case of tissue test failure:

- Assess the reason for test failure – consider repeating the test if tissue is available[1,2]
- Consider a re-biopsy for acquisition of a new sample
- Consider following up with a germline BRCA test (or ctDNA test, if available)[3]

2. BRCA germline test

In case of germline test failure:

- Consider repeating the germline test

ctDNA=circulating tumour DNA; ESMO=European Society for Medical Oncology.

1. de Bono J, et al. Poster presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Poster 847PD; 2. Yadav S, et al. Fam Cancer. 2017;16(3):319–328; 3. National Cancer Control Programme. BRCA test FAQ. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/brca%20test%20faq.pdf (Accessed November 2023).

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Genomic testing involves the coordinated expertise of an MDT

MDT meeting[1]

Discussion on cases referred to the unit[1]

MDT will propose appropriate management options[1]

Qualified MDT member

Consent for tumour test[2]*

Urologist / Radiologist / Pathologist[1,3]

Sourcing of archival tissue sample[4]

OR

Performs biopsy[4]

Histopathology[3,5]

- Histology analysis
- Determination of Gleason score / ISUP grading
- H&E staining
- Delimitation of tumour area
- Calculate tumour content

Molecular pathology[3,6]

Tissue testing

- Macro / microdissection
- Deparaffinisation
- DNA extraction
- Library preparation
- Sequencing
- Analysis and interpretation

Successful tissue test

Unsuccessful tissue test

Clinical oncology

Clinical decision informed by outcome of all successful tests

Consent for germline testing†[2,3]

Consent for germline testing†[2,3]

Nursing / phlebotomy

Blood drawn

Molecular pathology

ctDNA testing[7,8]‡

Blood centrifugation, plasma isolation, DNA extraction, library preparation, sequencing analysis, interpretation

Successful ctDNA test

Unsuccessful ctDNA test

Clinical genetics

Germline testing to determine whether the mutation is somatic or germline and inform familial risk[3,9,10]

Blood testing[11,12]

Buffy coat isolation, DNA extraction, library preparation, sequencing, analysis, interpretation

Successful blood test

Unsuccessful blood test

Genetic counsellor

Genetic counselling for germline tests only[3,9]

Effective communication among the different disciplines is essential to align on **who**, **what** (tissue, blood, ctDNA) and **when** to test, address sample adequacy issues, satisfy genetic counselling needs, minimise turnaround times and ensure test results are available for clinical decision-making

*Consent for tumour testing may be given verbally and should be documented in patients' medical records[2]; †Consent for genetic testing is a more formal process than consent for tumour testing and requires written consent from the patient[2]; ‡ctDNA may be offered to some patients in the UK in private practice. It is currently not available in the National Genomic Test Directory.
ASCO=American Society of Clinical Oncology; BAGP=British Association of Gynaecological Pathologists; BGCS=British Gynaecological Cancer Society; ctDNA=circulating tumour DNA; GU=genitourinary; H&E=haematoxylin and eosin; ISUP=International Society of Urologic Pathologists; MDT=multidisciplinary team.

1. Sciarra A, et al. *Am J Clin Exp Urol*. 2013;1:12–17; 2. BAGP. BAGP/BGCS consensus recommendations for BRCA testing in ovarian cancer. Available at: https://www.thebagp.org/bagp-bgcs-consensus-recommendations-for-brca-testing-in-ovarian-cancer/ (Accessed November 2023); 3. Capoluongo E, et al. *Semin Oncol*. 2017;44:187–197; 4. Hussain M, et al. Poster presented at ASCO GU 2020. 13–15 February. San Francisco, US. Poster J9; 5. Humphrey PA, et al. *Cold Spring Harb Perspect Med*. 2017;7:a030411; 6. Myriad myChoice Technical Information. Available at: https://myriad-web.s3.amazonaws.com/myChoiceCDx/downloads/myChoiceCDxTech.pdf (Accessed November 2023); 7. Volckmar AL, et al. *Gene Chromosome Canc*. 2018;57:123–139; 8. Foundation Medicine. FoundationOne®Liquid CDx. Available at: https://www.foundationmedicine.com/test/foundationone-liquid-cdx (Accessed November 2023); 9. Cheng HH, et al. *J Natl Compr Canc Netw*. 2019;17:515–5211; 10. Veyseh M, et al. *Front Oncol*. 2018;8:259; 11. Mychaleckyj JC. *J Transl Med*. 2011;9:91; 12. BRACAnalysis CDx Technical Information. Available at: https://myriad-library.s3.amazonaws.com/technical-specifications/BRACAnalysis_CDx_Tech_Specs.pdf (Accessed November 2023).

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LYNPARZA combination / monotherapy are the first approved PARPi therapy options for mCRPC in the UK[1]

- Patients are selected for LYNPARZA monotherapy using a tumour tissue test.[2] *BRCA1/2* mutation status should be determined by an experienced laboratory using a validated test method[1]
- No genomic testing is required prior to using LYNPARZA in combination with abiraterone and prednisone or prednisolone for the treatment of patients with mCRPC[1]

UK indication[1]

LYNPARZA is indicated as monotherapy for the treatment of adult patients with mCRPC and ***BRCA1/2* mutations** (germline and/or somatic) who have progressed following prior therapy that included a novel hormonal agent

LYNPARZA is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated

Biomarker	Sample type[3]	
	Tumour	Blood
s*BRCA1/2*m	X	
g*BRCA1/2*m	X	X

Since about half of *BRCA1/2* mutations are somatic, solely testing for germline BRCA mutations could miss 50% of the mutated population. It is vital to be aware of which test is most appropriate[4]

BRCA1/2m=BRCA1/2 mutation; EMC=Electronic Medicines Compendium; g=germline; mCRPC=metastatic castration-resistant prostate cancer; MHRA=Medicines and Healthcare products Regulatory Agency; s=somatic.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. Prostate Cancer UK. Olaparib. Available at:https://prostatecanceruk.org/prostate-information-and-support/treatments/olaparib (Accessed November 2023); 3. Be BRCA Aware. Available at: https://www.bebrcaware.com/what-is-brca/brca-testing-basics.html (Accessed November 2023;
4. Abida W, et al. *JCO Precis Oncol* 2017;2017:PO.17.00029.

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profound
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

PROfound trial

TIME TO CHALLENGE
EXPECTATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER TREATMENT FOR PATIENTS WITH A BRCAm

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Early studies have previously confirmed activity of LYNPARZA in biomarker-selected mCRPC[1,2]

Mechanisms proposed are based on experimental evidence and may not be applicable in a clinical setting

LYNPARZA monotherapy → PARP inhibition **AND** trapping to block DNA repair pathways in cells harbouring HRR defects[1] → **Antitumour activity**

STUDY 42[1]

Phase II trial (single arm), gBRCAm advanced solid tumours
LYNPARZA capsules

Included patients with gBRCAm mCRPC (N=8)

Study 42 demonstrated tumour responses in patients with gBRCAm advanced prostate cancer

TOPARP[2,3]

Phase II trial (single arm), mCRPC post-docetaxel
LYNPARZA tablets

TOPARP-A*
All-comers mCRPC, retrospective biomarker analyses (tumour)†

Activity in patients with DDR defects including HRR vs. wild-type mCRPC

TOPARP-B
Prospectively recruited patients mCRPC + DDR defects (tumour)

Validated TOPARP-A study findings of activity in biomarker-selected mCRPC (incl. HRR gene defects)†

*TOPARP-A was set up before the tablet dosing had been established and 400 mg is above the recommended dose for LYNPARZA; †Biomarker studies from both germline and somatic DNA included exome and transcriptome sequencing in order to elucidate the genomic aberrations associated with sensitivity to PARPi in mCRPC.[2]
DDR=DNA damage repair; gBRCAm=germline BRCA mutation; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; PARPi=poly(ADP-ribose) polymerase inhibitor.

1. Kaufman B, et al. *J Clin Oncol.* 2015;33:244–250; 2. Mateo J, et al. *N Engl J Med*. 2015;373:1697–1708; 3. Mateo J, et al. *Lancet Oncol.* 2020;21:162–174.

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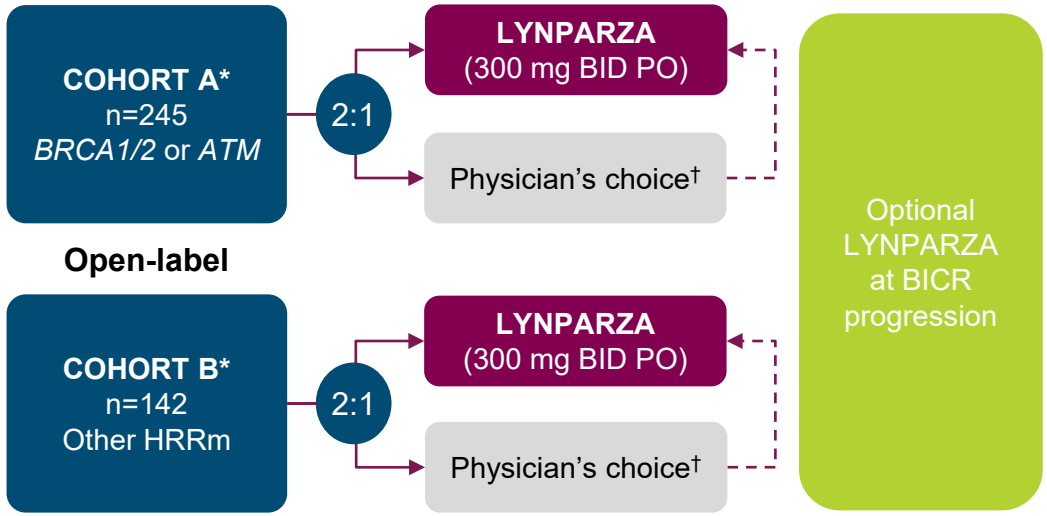
PROfound was the first randomised Phase III study evaluating the efficacy and safety of LYNPARZA vs. NHAs in patients with HRRm mCRPC[1,2]

HRR mutations, such as BRCAm, are known as 'founder effect mutations'[3] as they are as prevalent in primary tumours as in metastases; hence the name PROfound

Eligibility criteria[1,4]

- Documented evidence of mCRPC
- Qualifying HRRm in tumour tissue (central review)
- Progression on NHA for mPC and/or CRPC
- Radiographic progression at study entry while on ADT (or after bilateral orchiectomy)
- ECOG PS 0–2
- No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer



Stratification factors
- Prior taxane therapy (yes vs. no)
- Measurable disease at baseline (yes vs. no)

Treatment until disease progression or until the occurrence of unacceptable toxicity

Trial endpoints

Primary endpoint
- Imaging-based PFS by BICR in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoints
- BICR-confirmed ORR (Cohort A)
- Imaging-based PFS by BICR (Cohort A+B)
- Time to pain progression (Cohort A)
- OS (Cohort A)
- Safety and tolerability

LYNPARZA (tablet) is indicated as monotherapy for the treatment of adult patients with mCRPC and BRCAm (germline and/or somatic) who have progressed following a prior NHA.[2]

*Cohort A included patients with *BRCA1*, *BRCA2* or *ATM* mutations; Cohort B included patients with *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L* mutations;†Prespecified physician's choice of either enzalutamide or abiraterone plus prednisone/prednisolone.

ADT=androgen deprivation therapy; BICR=blinded independent central review; BID=twice daily; BRCAm=BRCA mutation; (m)CRPC=(metastatic) castration-resistant prostate cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; HRRm=homologous recombination repair gene mutation; mPC=metastatic prostate cancer; NHA=novel hormonal agent; ORR=objective response rate; OS=overall survival; PARPi=poly(ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PO=orally; RECIST=Response Evaluation Criteria in Solid Tumors.

1. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102; 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 3. Agalliu I, et al. *Clin Cancer Res.* 2009;15:1112–1120; 4. ClinicalTrials.gov. NCT02987543. Available at: https://clinicaltrials.gov/ct2/show/NCT02987543 (Accessed November 2023).

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Patients characteristics were balanced between treatments arms in PROfound[1]

Characteristic		All patients (Cohorts A+B*)[1]		Patients with BRCAm†[2]	
		LYNPARZA (n=256)	Physician's choice‡ (n=131)	LYNPARZA (n=102)	Physician's choice‡ (n=58)
Median age (range), years		69 (47–91)	69 (49–87)	68	67
ECOG PS 0 or 1, n (%)		243 (95)	126 (96)	95 (93)	54 (93)
Site of metastases, n (%)	Bone only	86 (34)	38 (29)	91 (89)	50 (86)
	Visceral (lung/liver)	68 (27)	44 (34)	-	-
	Lung	-	-	23 (23)	9 (16)
	Liver	-	-	12 (12)	10 (17)
	Other	88 (34)	41 (31)	63 (62)	41 (71)
Measurable disease at baseline, n (%)		149 (58)	72 (55)	59 (58)	32 (55)
Prior NHA, n (%)	Enzalutamide	105 (41)	54 (41)	42 (41)	29 (50)
	Abiraterone	100 (39)	54 (41)	38 (37)	21 (36)
	Abiraterone + enzalutamide	51 (20)	23 (18)	20 (20)	8 (14)
Previous taxane use, n (%)	Yes	170 (66)	84 (64)	72 (71)	35 (60)
	Docetaxel	115 (45)	58 (44)	-	-
	Cabazitaxel	3 (1)	0 (0.0)	-	-
	Docetaxel + cabazitaxel	51 (20)	26 (20)	-	-
	Paclitaxel only	1 (<1)	0		

LYNPARZA (tablet forumulation) is indicated as monotherapy for the treatment of adult patients with mCRPC and BRCAm (germline and/or somatic) who have progressed following a prior NHA.[2]

*Cohort A included patients with *BRCA1*, *BRCA2* or *ATM* mutations; Cohort B included patients with *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L* mutations; †The study was not powered for gene-by-gene analysis; ‡Physician's choice of either enzalutamide or abiraterone.

BRCAm=BRCA mutation; ECOG PS=Eastern Cooperative Oncology Group performance status; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent.

1. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102; 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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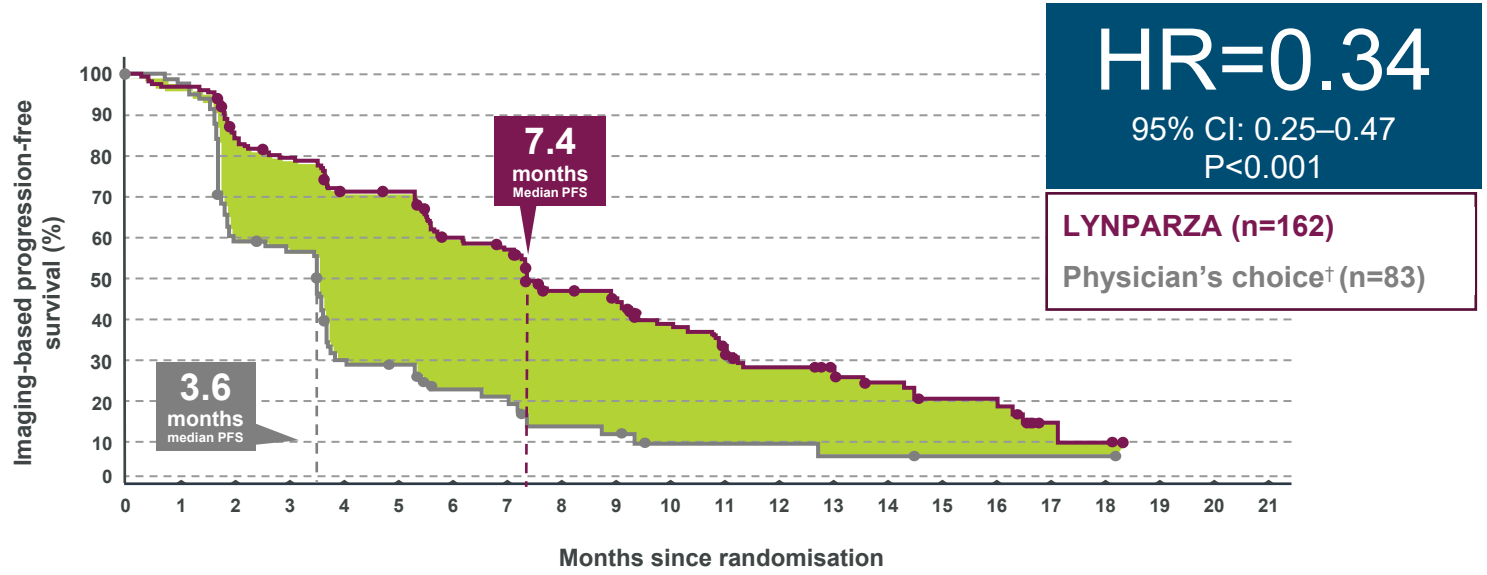
Primary endpoint: LYNPARZA reduced the risk of progression or death by 66% vs. physician's choice in Cohort A[1]

P <0.001

profound

Imaging-based PFS by BICR in patients with alterations in *BRCA1*, *BRCA2* or *ATM* (Cohort A)



Number of patients at risk

LYNPARZA	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice†	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

A small number of patients were censored in the imaging-based PFS analysis because they were lost to follow-up/withdrew consent.* As the numbers of patients who were lost to follow-up were small, comparisons are challenging to make, and there are no clear differences between these sub-populations.

An exploratory sensitivity analysis was conducted to consider the impact of censoring these patients on imaging-based PFS

Adapted from de Bono J, et al. 2020

Data cut-off date: 4 November 2019; Data maturity=71%.
*This included patients that missed two consecutive soft tissue or bone assessment appointments and experienced disease progression or death; †Physician's choice of either enzalutamide or abiraterone.
BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; mCRPC=metastatic castration-resistant prostate cancer; PFS=progression-free survival.
1. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102.

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Exploratory analysis: In patients with BRCAm, median imaging-based PFS was 9.8 months in the experimental arm vs. 3.0 months in the control arm[1,2]

P not tested

Number of patients at risk

LYNPARZA	87	83	78	77	67	66	48	45	36	33	23	22	16	8	8	2	2	0
Physician's choice†	30	27	10	10	6	5	4	3	1	1	1	0	0	0	0	0	0	0

Adapted from de Bono J, et al. 2020 (Suppl)

Data cut-off: 4 November 2019.
*The PROfound study was not powered for gene-by-gene analysis; †Physician's choice of either enzalutamide or abiraterone.
BRCAm=BRCA mutation; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.
1. de Bono J, et al. *N Engl J Med*. 2020;382:2091–2102; supplementary data; 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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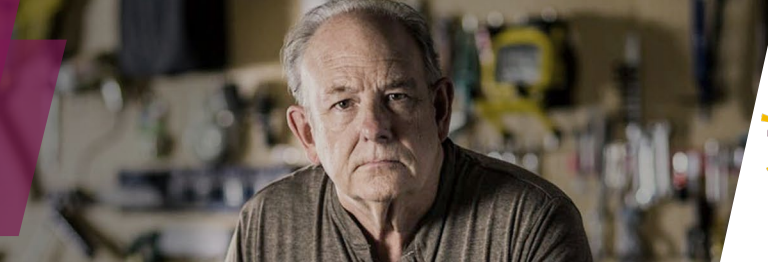
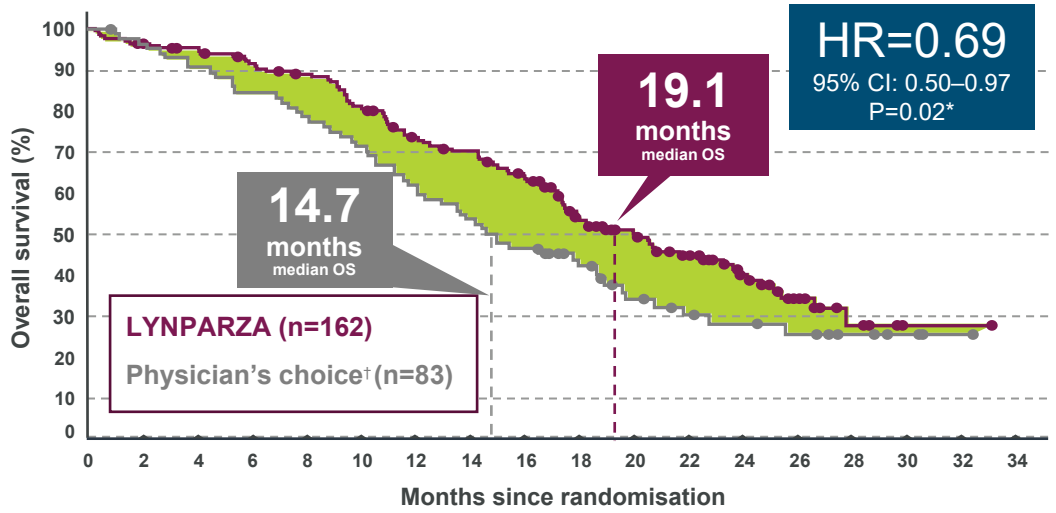
Secondary endpoint: LYNPARZA significantly increased OS in Cohort A vs. physician's choice[1]

*P=0.02**



*Despite **substantial crossover (67%) of control-arm patients to receive LYNPARZA**, LYNPARZA reduced the risk of death in Cohort A by 31% compared with physician's choice treatment*

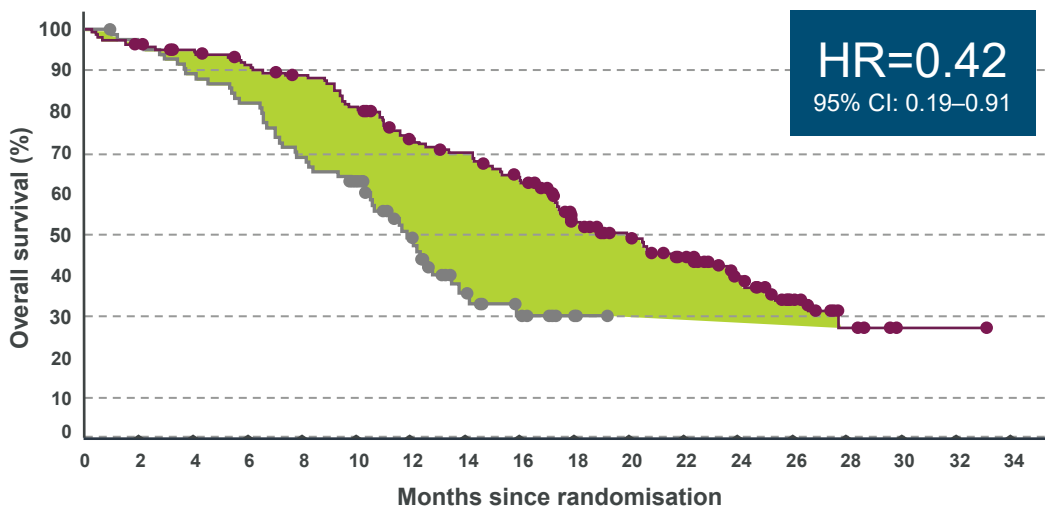
Final OS in patients with alterations in *BRCA1*, *BRCA2* or *ATM* (Cohort A)



Number of patients at risk

LYNPARZA	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice†	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

Cohort A with adjustment for crossover‡



Number of patients at risk

LYNPARZA	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice†	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

Adapted from Hussain M, et al. 2020

Data cut-off: 20 March 2020; Data maturity=60%.
*0.047 alpha spent at the final OS analysis, 2-sided p-value; †Physician's choice of either enzalutamide or abiraterone; ‡Re-censored; conducted using RPSFTM to demonstrate the impact on OS of crossover of patients from the control arm to receive LYNPARZA as a first subsequent anticancer therapy.
CI=confidence interval; HR=hazard ratio; OS=overall survival; RPSFTM=rank preserving structural failure time model.
1. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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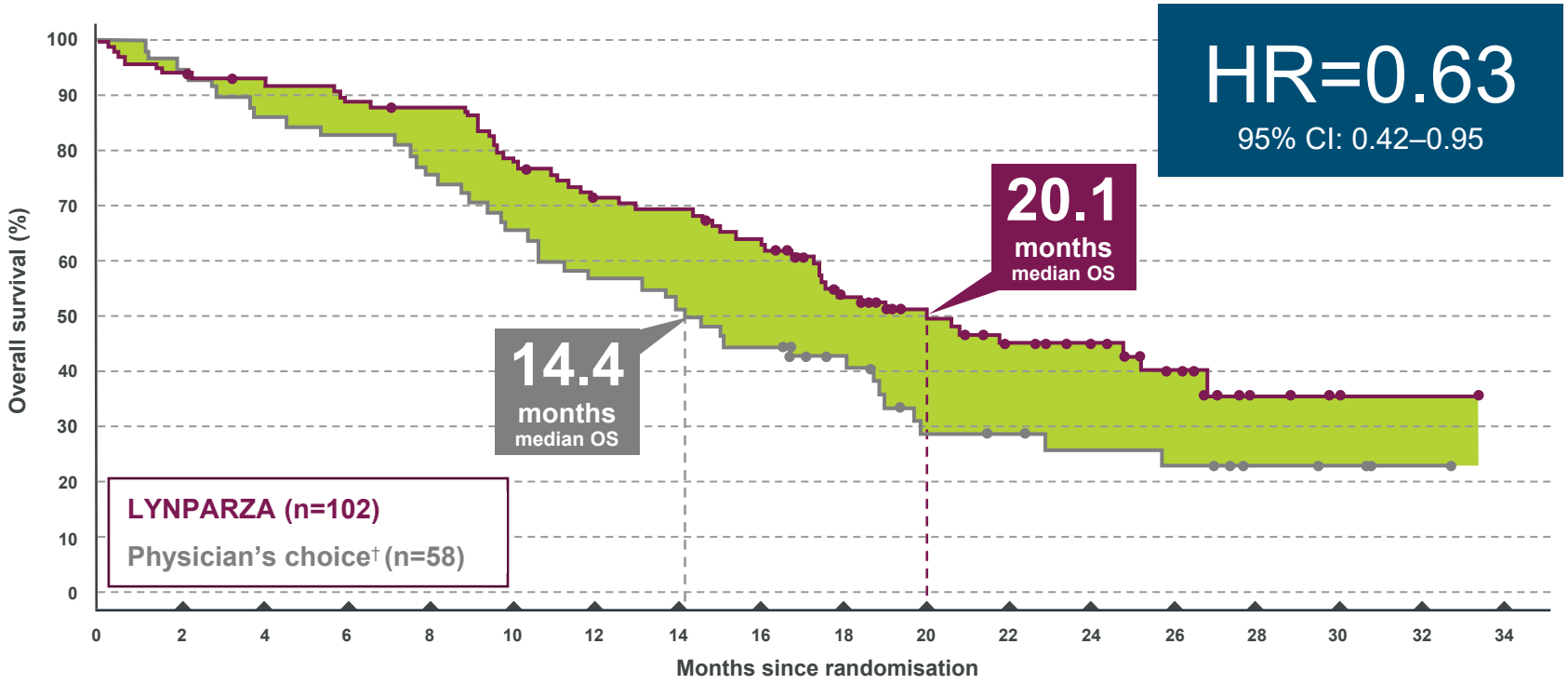
*Exploratory analysis: mOS for patients with a BRCAm was approximately 20 months*1*

P not tested



Number of patients at risk

LYNPARZA	102	96	93	89	87	78	68	66	60	46	35	27	22	12	4	2	1	0
Physician's choice†	58	55	50	48	44	38	33	30	26	20	12	11	9	8	5	3	1	0

Adapted from LYNPARZA SmPC

Data cut-off: 20 March 2020.

*The PROfound study was not powered for gene-by-gene analysis; †Physician's choice of either enzalutamide or abiraterone.

BRCAm=BRCA mutation; CI=confidence interval; HR=hazard ratio; (m)OS=(median) overall survival.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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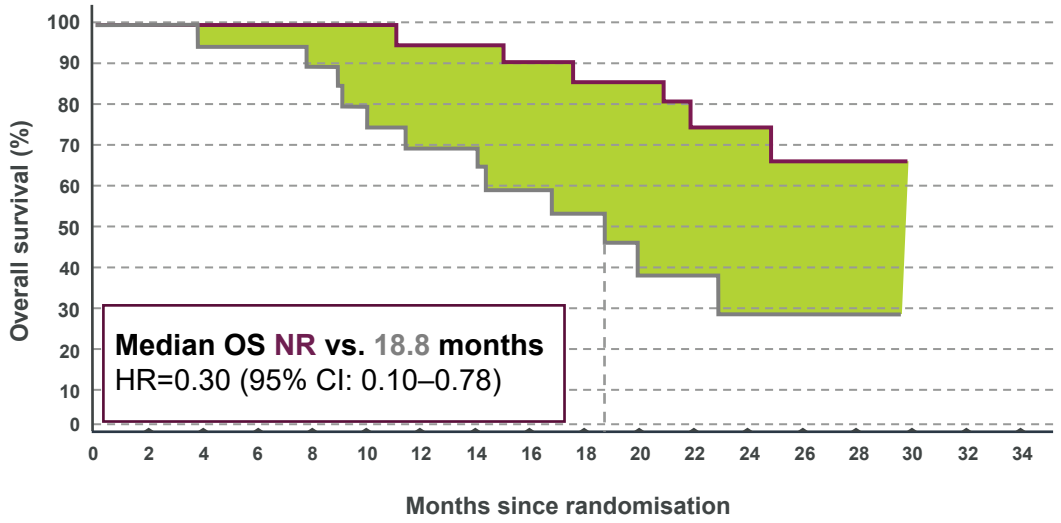
Exploratory analysis: OS in patients with BRCAm according to prior taxane exposure[*1]

P not tested

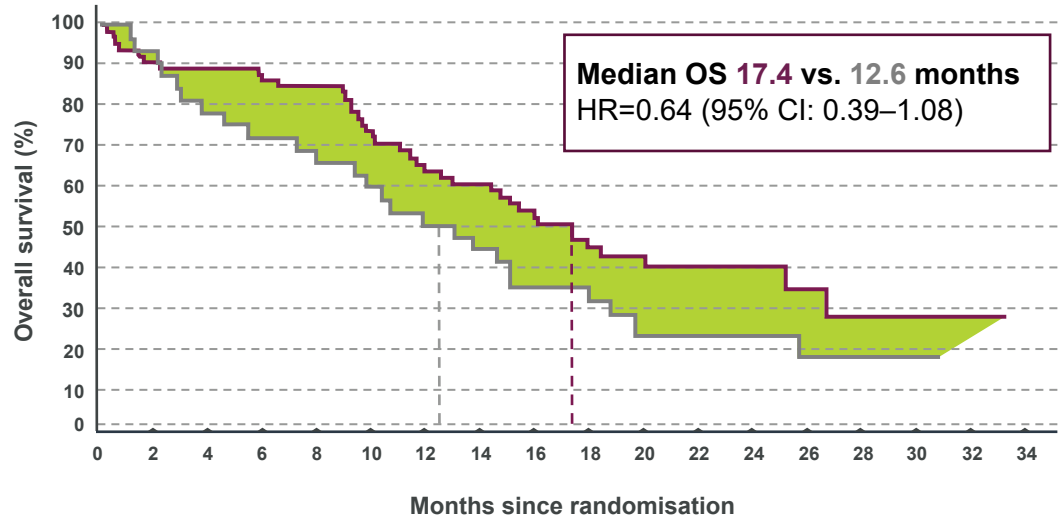
No prior taxane



Number of patients at risk

LYNPARZA	23	23	23	23	23	23	21	21	20	18	16	10	10	5	2	0	0	0
Physician's choice†	20	20	19	19	18	15	14	13	12	7	5	4	3	3	1	0	0	0

Prior taxane



Number of patients at risk

LYNPARZA	66	60	57	55	53	46	38	36	32	23	16	15	11	6	2	2	1	0
Physician's choice†	32	29	25	23	21	19	16	14	11	10	5	5	4	3	3	3	0	0

Adapted from Hussain M, et al. 2020

Data cut-off: 20 March 2020.

*The PROfound study was not powered for gene-by-gene analysis; †Physician's choice of either enzalutamide or abiraterone.
BRCAm=BRCA mutation; CI=confidence interval; HR=hazard ratio; NR=not reached; OS=overall survival.

1. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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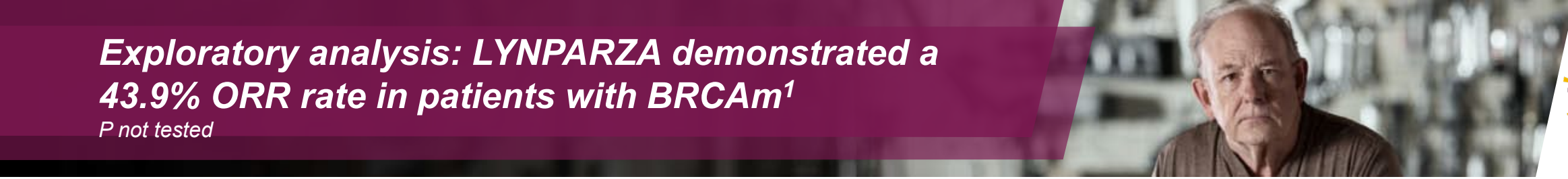
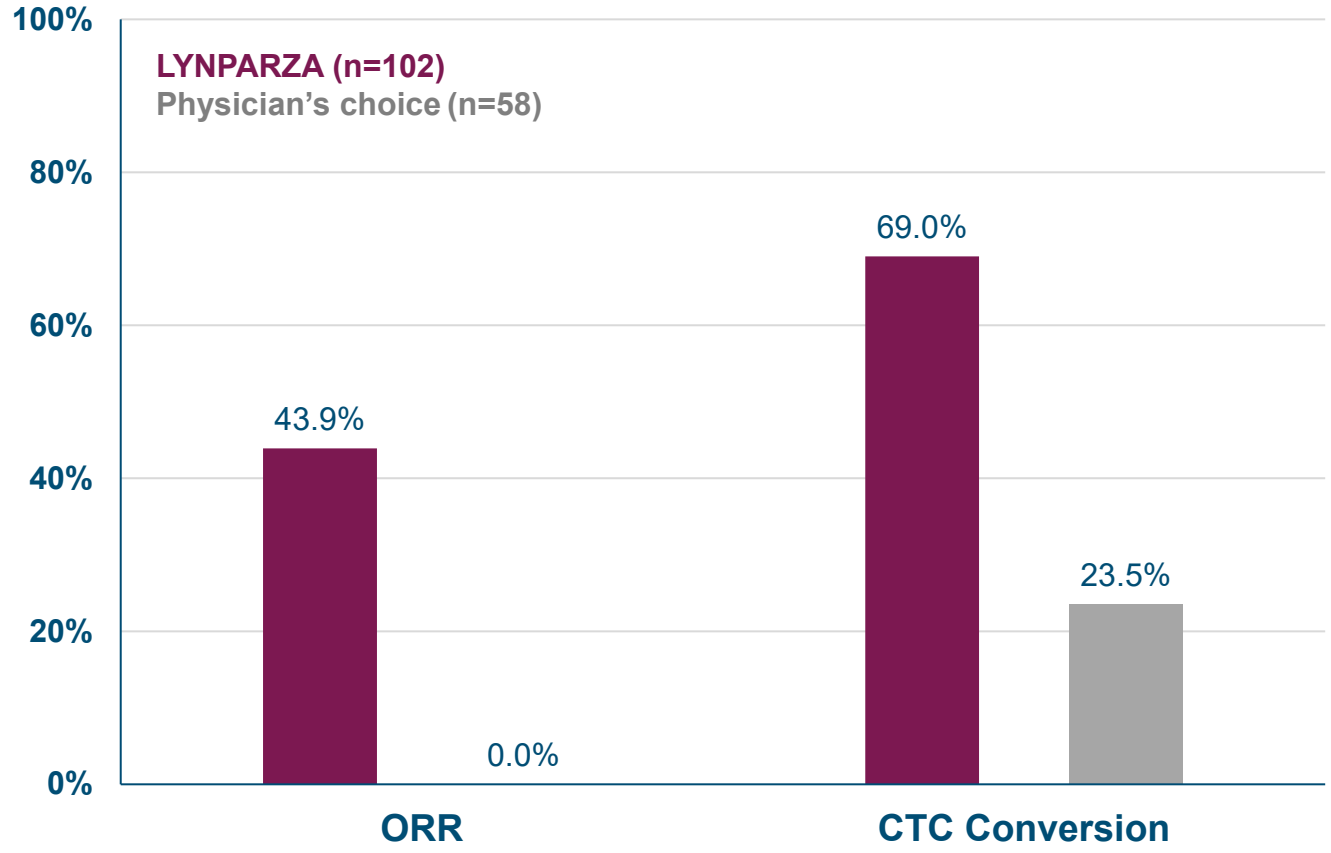
Exploratory analysis: LYNPARZA demonstrated a 43.9% ORR rate in patients with BRCAm[1]

P not tested





Adapted from de Bono J, et al. 2021

Data cut-off: 4 June 2019.[2]

ASCO=American Society of Clinical Oncology; BRCAm=BRCA mutation; CTC=circulating tumour cell; GU=genitourinary; ORR=objective response rate.

1. de Bono J, et al. Presented at ASCO GU Virtual Meeting 2021. 11–13 February. Poster 126; 2. de Bono J, et al. *N Engl J Med.* 2020;382:2091–2102.

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The safety profile for LYNPARZA from the PROfound study is similar to that observed in the previous prostate studies and safety data of LYNPARZA from other tumour types[1–4]

The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥10%) were nausea, fatigue/asthenia, anaemia, vomiting, diarrhoea, decreased appetite, headache, neutropenia, dysgeusia, cough, leukopenia, dizziness, dyspnoea and dyspepsia.[5]

AE (any grade ≥20%), %	Prostate PROfound[1]	Ovarian SOLO-1[2]	Breast OlympiAD[3]	Pancreatic POLO[4]
Anaemia	50	39	40	27
Nausea	43	77	58	45
Fatigue and Asthenia	42	64	30	60
Decreased appetite	31	20	-	25
Arthralgia	-	25	-	-
Diarrhoea	21	34	21	29
Anorexia	-	-	-	-
Dyspnoea	-	-	-	-
Back pain	-	-	-	-
Vomiting	20	40	32	20
Constipation	-	28	-	23
Dysgeusia	-	26	-	-
Neutropenia	-	23	27	-
Abdominal pain	-	25	-	29
Headache	-	23	21	-
Dizziness	-	20	-	-

AE=adverse event.

1. Hussain M, et al. *N Engl J Med*. 2020;383:2345–2357; 2. Moore K, et al. In: Presidential Symposium 2, Abstract #LBA7_PR. Munich, Germany; 2018; 3. Robson ME, et al. *Ann Oncol*. 2019;30:558–566;
4. Golan T, et al. *N Engl J Med*. 2019;381:317–327; 5. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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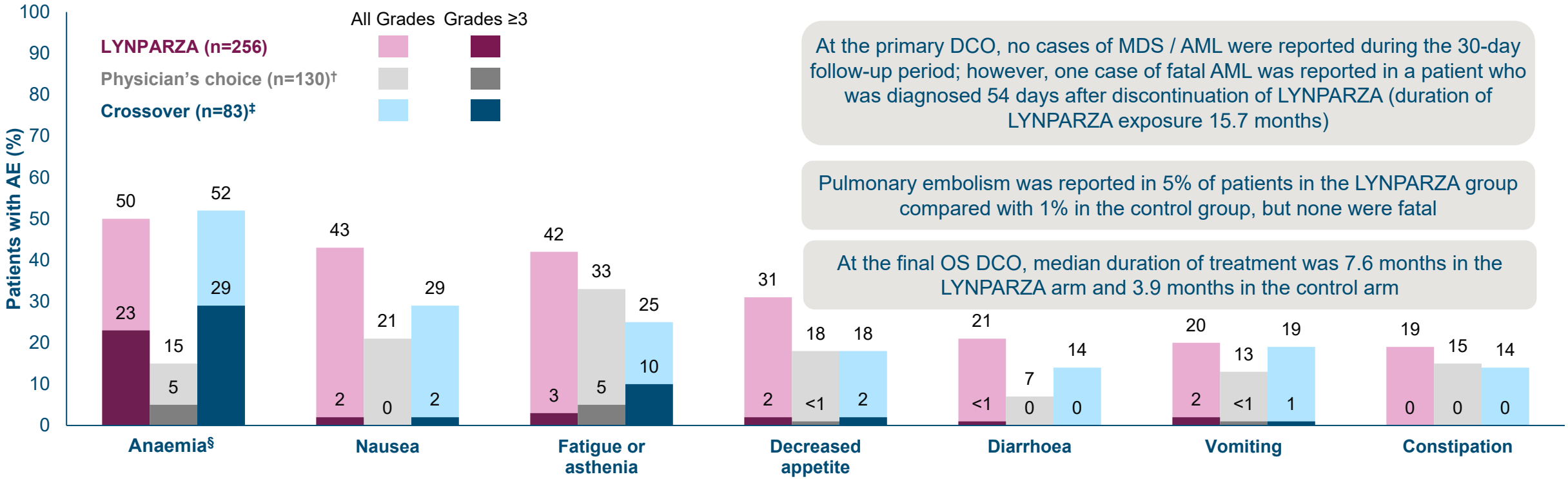
Safety: The most common AEs in the overall population were anaemia, nausea and fatigue or asthenia*

Most common AEs in the overall population (≥15% of patients)[1]



At the primary DCO, no cases of MDS / AML were reported during the 30-day follow-up period; however, one case of fatal AML was reported in a patient who was diagnosed 54 days after discontinuation of LYNPARZA (duration of LYNPARZA exposure 15.7 months)

Pulmonary embolism was reported in 5% of patients in the LYNPARZA group compared with 1% in the control group, but none were fatal

At the final OS DCO, median duration of treatment was 7.6 months in the LYNPARZA arm and 3.9 months in the control arm

Adapted from Hussain M, et al. 2020

Data cut-off: 20 March 2020.
*Patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L*; †Physician's choice of either abiraterone or enzalutamide; ‡Patients in the physician's choice group were allowed to cross over to receive LYNPARZA after disease progression in accordance with the protocol; §Grouped term including includes anaemia, decreased haemoglobin level, decreased red-cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia and normocytic anaemia.
AE=adverse event; AML=acute myeloid leukaemia; DCO=data cut-off; MDS=myelodysplastic syndrome; OS=overall survival.
1. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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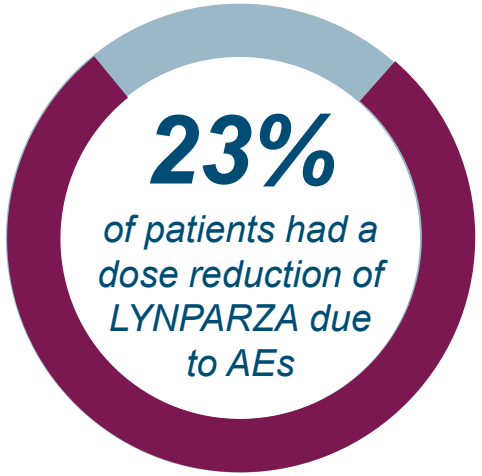
Safety: 77% of patients remained on the full dose of LYNPARZA without a dose reduction due to AEs[1]

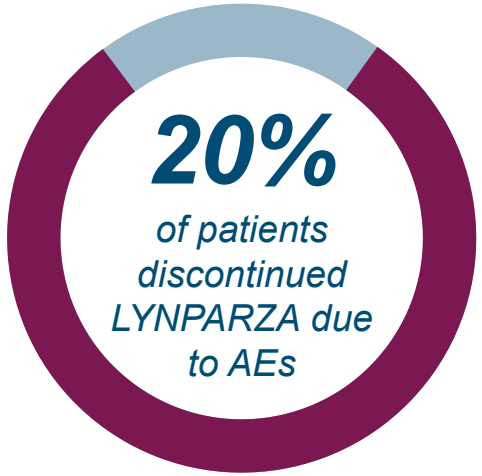
Dose reduction



77%

of patients remained on the full dose of LYNPARZA without needing a dose reduction due to AEs

Discontinuation



80%

of patients remained on LYNPARZA without discontinuing due to AEs

Data cut-off: 20 March 2020.
AE=adverse event.
1. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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LYNPARZA is generally well tolerated across tumour types[1,2]

Although there was an increased rate of pulmonary embolism events with LYNPARZA vs. placebo, no causal association was established. Multiple factors made the results difficult to interpret[1]

Increased baseline risk of a thromboembolic event[1]

x2

Almost two-fold exposure in the LYNPARZA group[1]

Short duration follow-up available[1]

Higher incidence of venous thromboembolic events may be attributed to:

- Patients being at an advanced stage of the disease[2]
- Patients having received treatment with ADT prior to the trial and receiving continuous ADT during the trial[3]
- Some patients being administered erythropoiesis-stimulating agents for cancer-associated anaemia[4]

ADT=androgen deprivation therapy; AE=adverse event.

1. Roubaud G, et al. *Eur J Cancer.* 2022;170:73–84; 2. Razak NBA, et al. *Cancers (Basel).* 2018;10:380; 3. O'Farrell S, et al. *BJU Int.* 2016;118:391–398; 4. Zhan P, et al. *Chin Clin Oncol.* 2012;1:19.

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*Despite treatment crossover, incidence of Grade ≥3 events remained similar between treatment arms*1*

Event, n (%)	LYNPARZA (n=256)	Physician's choice† (n=130)	Crossover‡ (n=83)
Any AE	246 (96)	115 (88)	77 (93)
Any AE of CTCAE Grade ≥3	133 (52)	52 (40)	49 (59)
Interruption of intervention due to AE	119 (46)	25 (19)	44 (53)
Dose reduction due to AE	60 (23)	7 (5)	27 (33)
Discontinuation due to AE	51 (20)	11 (8)	11 (13)
Death due to AE	10 (4)	6 (5)	3 (4)

At final OS data cut-off, patients in the LYNPARZA arm received treatment for nearly twice as long as those in the physician's choice arm
(**median treatment duration: 7.6 months vs. 3.9 months**)

Data cut-off: 20 March 2020.
*Patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L;* †Physician's choice of either abiraterone or enzalutamide;
‡Patients in the physician's choice group were allowed to cross over to receive LYNPARZA after disease progression in accordance with the protocol.
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.
1. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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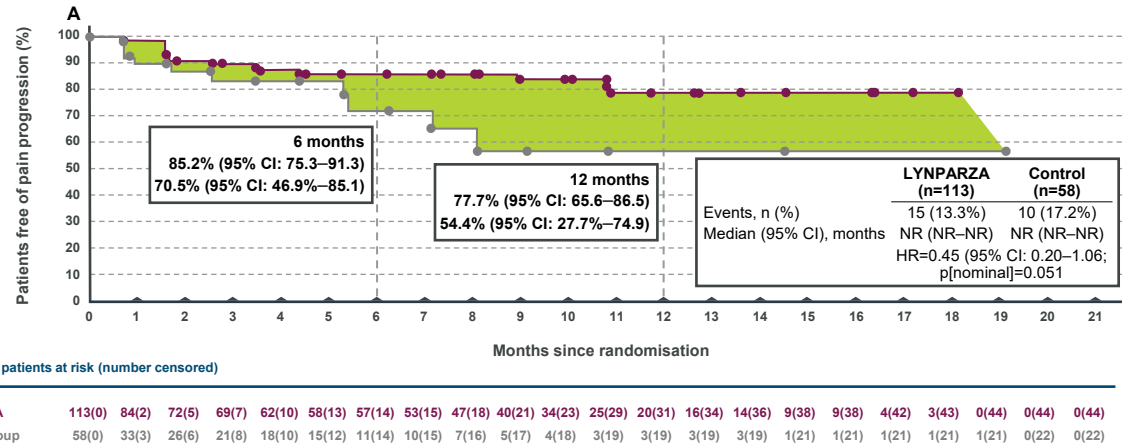
Secondary endpoint: At 12 months, an estimated 77.7% of patients receiving LYNPARZA remained free of pain progression

P=0.051

Time to pain progression for patients in Cohort A who had not used opiates at baseline*[1]

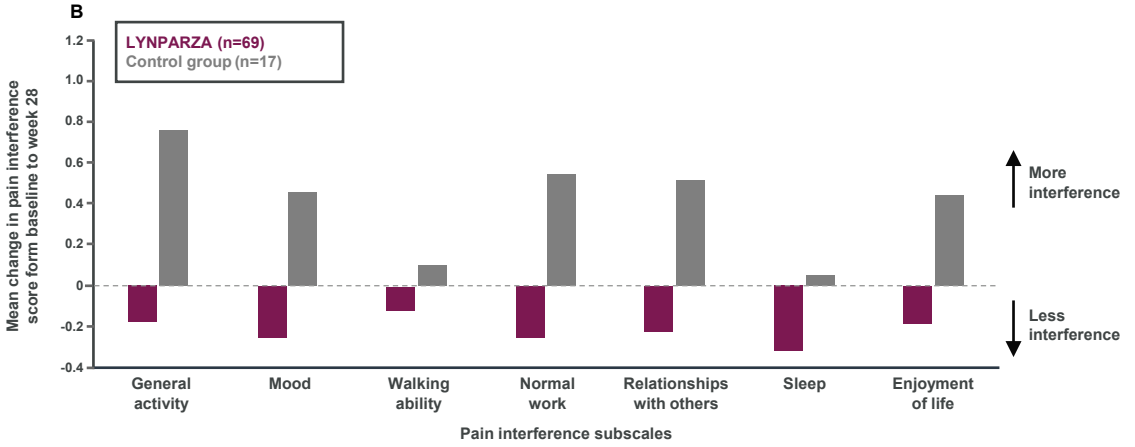


Number of patients at risk (number censored)

LYNPARZA	113(0)	84(2)	72(5)	69(7)	62(10)	58(13)	57(14)	53(15)	47(18)	40(21)	34(23)	25(29)	20(31)	16(34)	14(36)	9(38)	9(38)	4(42)	3(43)	0(44)	0(44)	0(44)
Control group	58(0)	33(3)	26(6)	21(8)	18(10)	15(12)	11(14)	10(15)	7(16)	5(17)	4(18)	3(19)	3(19)	3(19)	3(19)	1(21)	1(21)	1(21)	1(21)	1(21)	0(22)	0(22)

At 12 months, an estimated 77.7% of patients in the LYNPARZA group and 54% of patients in the physician's choice group were free of pain progression

Change in BSI-SF pain interference subscales scores in overall study population‡[1]



Delayed time to pain progression and less interference with QoL as measured by BSI-SF pain scores

*Cohort A included patients with *BRCA1, BRCA2* or *ATM* mutations; †Physician's choice of either abiraterone or enzalutamide; ‡Overall study population includes cohort A and B, patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L*.
BPI-SF=Brief Pain Inventory – Short Form questionnaire; CI=confidence interval; HR=hazard ratio; NR=not reached; QoL=quality of life.
1. Thiery-Vuillemin A, et al. *Lancet Oncol.* 2022;23:393–405.

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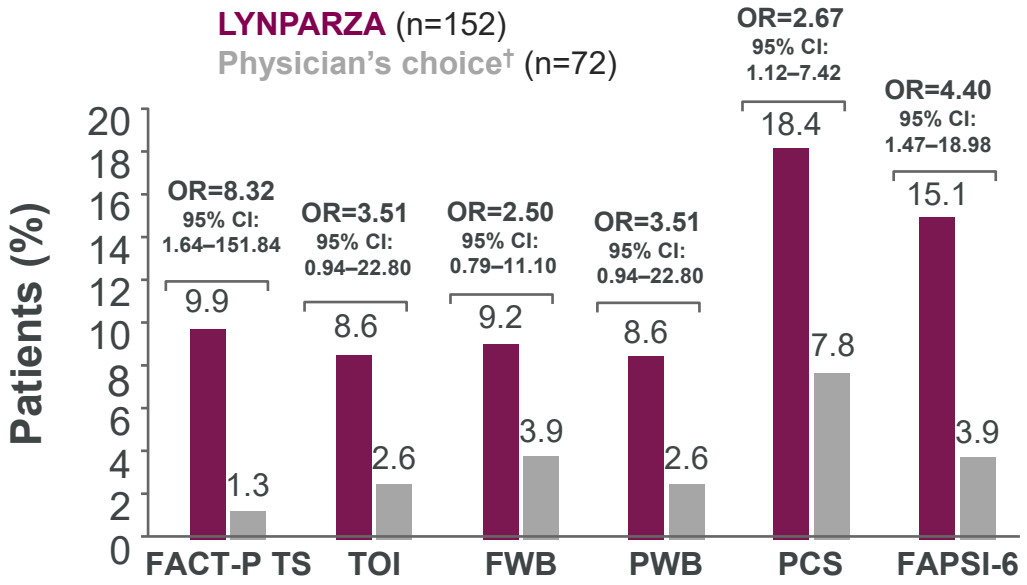
*Secondary endpoint: Numerically more cohort A patients reported HRQoL improvements with LYNPARZA vs. physician's choice**

P not significant

Patient-reported improvements in HRQoL after treatment in Cohort A vs. control*[1]



Time to deterioration in Cohort A*[1]

	Events		Median time to deterioration, months (95% CI)		HR (95% CI)	p value (nominal) 2-sided
	Olaparib group (n=162)	Control group (n=83)	Olaparib group	Control group		
FACT-P total score	67	25	5·55 (3·61–9·13)	3·65 (2·20–7·23)	0·85 (0·54–1·40)	0·49
TOI	60	23	7·29 (4·14–9·20)	3·75 (3·61–7·23)	0·85 (0·52–1·43)	0·49
FWB	69	26	3·68 (3·61–5·78)	3·65 (2·20–5·45)	0·88 (0·56–1·42)	0·54
PWB	63	23	6·24 (3·61–9·20)	3·75 (2·96–9·13)	0·95 (0·59–1·59)	0·78
PCS	66	25	5·78 (3·61–9·13)	3·71 (2·20–5·39)	0·88 (0·55–1·44)	0·53
FAPSI-6*	51	21	9·20 (6·24–17·22)	3·75 (2·96–NR)	0·74 (0·44–1·27)	0·25
FACT-G total score	71	27	3·61 (2·27–5·78)	3·61 (1·97–4·57)	0·87 (0·56–1·40)	0·51

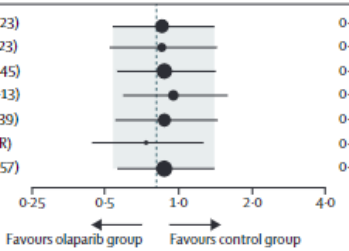


Figure 4: **Time to deterioration in health-related quality of life (FACT-P total and subscale scores, and FACT-G total score)**
The size of the circle is proportional to the number of events. The grey band represents the 95% CI for the FACT-P Total Score. FACT-G=Functional Assessment of Cancer Therapy–General. FACT-P=Functional Assessment of Cancer Therapy–Prostate. FAPSI-6=Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index. FWB=functional wellbeing. HR=hazard ratio. NR=not reached. PCS=prostate cancer subscale. PWB=physical wellbeing. TOI=Trial Outcome Index. *FAPSI-6 is derived from six FACT-P items: pain (three items), fatigue (one item), weight loss (one item), and concerns about worsening condition (one item).

Differences between the LYNPARZA and physician's choice groups for time to deterioration was not statistically significant

*Cohort A included patients with *BRCA1, BRCA2* or *ATM* mutations; †Physician's choice of either enzalutamide or abiraterone.
ASCO=American Society of Clinical Oncology; CI=confidence interval; FACT-G=Functional Assessment of Cancer Therapy – General; FACT-P TS=Functional Assessment of Cancer Therapy – prostate total score; FAPSI-6 FACT Advanced Prostate Symptom Index 6; FWB=functional wellbeing; HR=hazard ratio; GU=genitourinary; HRQoL=health-related quality of life; OR=odds ratio; PCS=prostate cancer subscales; PWB=physical wellbeing; TOI=Trial Outcome Index.

1.Thiery-Vuillemin A, et al. *Lancet Oncol*. 2022;23:393–405; Supplemental data.

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PROfound summary

- An exploratory analysis from the PROfound trial showed a potential benefit from LYNPARZA vs. physician's choice of NHA* for patients with BRCAm
- In the PROfound trial, for patients with BRCAm:†[1]

Median imaging-based PFS by BICR DCO 04 November 2019	Median OS DCO 20 March 2020
HR=0.22 (95% CI: 0.15–0.32); p not tested LYNPARZA 9.8 months Physician's choice of NHA* 3.0 months	**HR=0.63 (95% CI: 0.42–0.95); p not tested** LYNPARZA 20.1 months Physician's choice of NHA* 14.4 months

- Patients treated with LYNPARZA reported less deterioration in HRQoL functioning over time compared with patients treated with physician's choice of NHA[2]
- In the PROfound study, 80% of patients remained on LYNPARZA without discontinuing due to AEs[3]
- The most common (≥30% of patients) AEs associated with LYNPARZA were anaemia, nausea, fatigue/asthenia and decreased appetite[3]

*Physician's choice of either enzalutamide or abiraterone; †The PROfound study was not powered for gene-by-gene analysis.
AE=adverse event; BRCAm=BRCA mutation; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; HRQoL=health-related quality of life; NHA=novel hormonal agent; OS=overall survival; PFS=progression-free survival.
1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. Thiery-Vuillemin A, et al. *Lancet Oncol.* 2022;23:393–405;
3. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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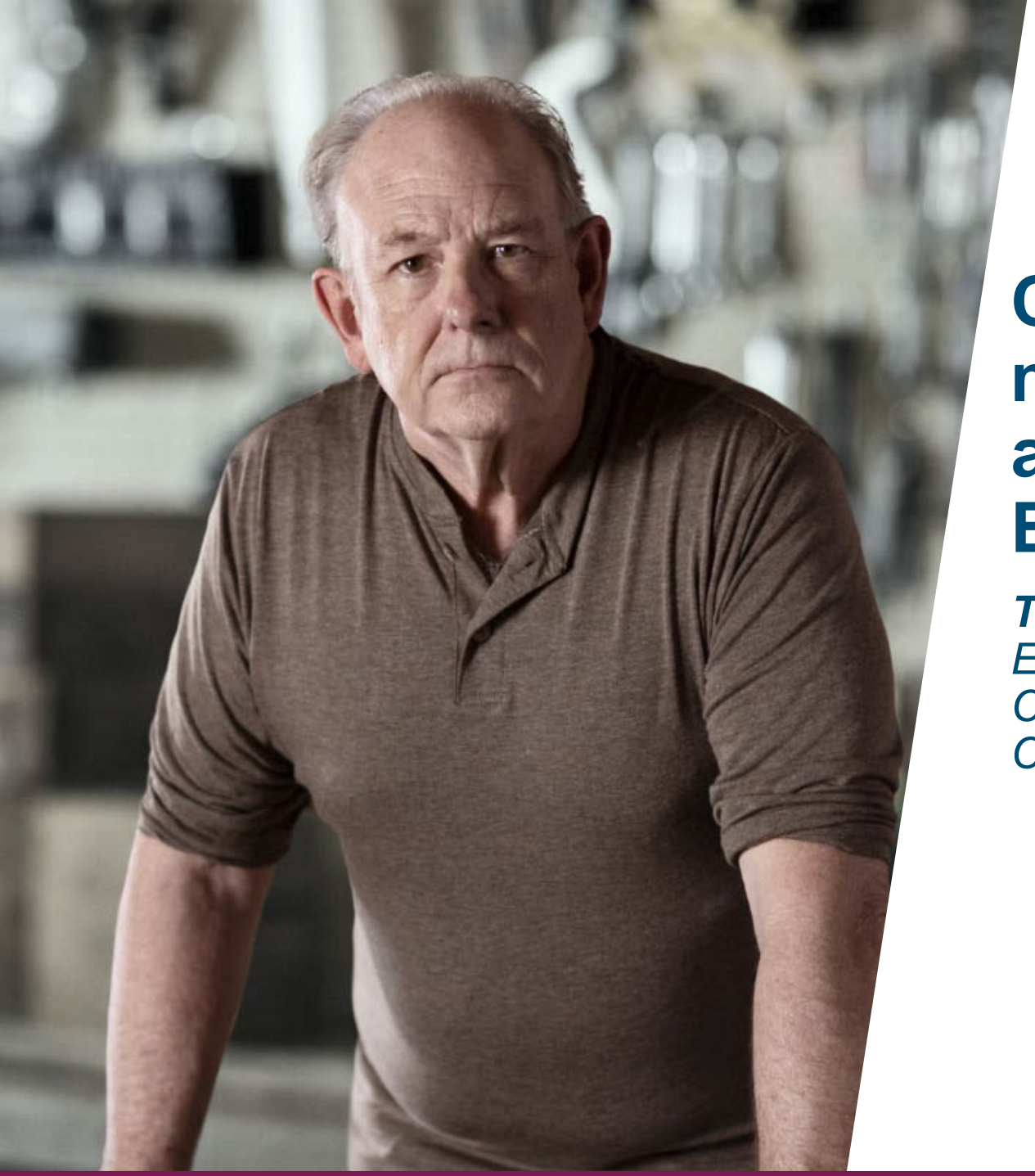


Choose LYNPARZA monotherapy for your appropriate patients with BRCAm mCRPC

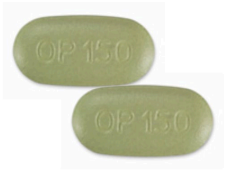
TIME TO CHALLENGE
EXPECTATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER TREATMENT

Lynparza®
olaparib
tablets 150 mg

LYNPARZA is simple to administer orally, twice daily dosing[1]

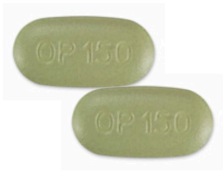
Two tablets
Twice per day
(with or without food)

AM



The recommended dose of LYNPARZA is 300 mg (2 × 150 mg tablets) taken orally, twice daily, with or without food (total 600mg daily)

PM



Dose adjustments and reductions

Dose adjustments are recommended in patients with moderate renal impairment (200mg twice daily); concomitant use of strong (100mg twice daily) or moderate (150mg twice daily) CYP3A4 inhibitors; or those who experience AEs (see below). Lynparza is not recommended for use in patients with severe renal impairment/end-stage renal disease or severe hepatic impairment. Please consult the SmPC for further information.

- **Initial reduction**: 250 mg (1 x 150 mg tablet and 1 x 100 mg tablet) taken twice daily (total 500 mg daily)
- **Final reduction:** 200 mg (2 x 100 mg tablet) taken twice daily (total 400 mg daily)

It is recommended that treatment is continued until progression of the underlying disease or unacceptable toxicity.
Medical castration with an LHRH analogue should be continued during treatment in patients not surgically castrated.
AE=adverse event; CYP3A=cytochrome P450 3A; LHRH=luteinising hormone-releasing hormone.
1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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In patients with BRCAm LYNPARZA demonstrates non-significant difference vs. physician's choice and a manageable safety profile

Testing

- Patients must test positive for a BRCAm to be eligible for treatment with LYNPARZA[1]
- Tumour tissue testing can detect both germline and somatic mutations[2]
- The tissue used for BRCA tumour genetic testing must be of reasonable quality to accurately identify mutations[3]

Efficacy

- In the PROfound trial, patients with BRCAm:*

DCO 04 November 2019: Median imaging-based PFS by BICR[1]

HR=0.22 (95% CI: 0.15–0.32); p not tested

LYNPARZA 9.8 months
Physician's choice NHA retreatment 3.0 months

DCO 20 March 2020: Median OS[1]

HR=0.63 (95% CI: 0.42–0.95); p not tested

LYNPARZA 20.1 months
Physician's choice NHA retreatment 14.4 months

ORR[1]

LYNPARZA 44% (25/57)
Physician's choice NHA retreatment 0% (0/33)

P not tested

Tolerability

- Patients receiving LYNPARZA monotherapy reported less deterioration of HRQoL vs. physician's choice in the PROfound trial (p not significant)[4]
- In PROfound, 80% of patients remained on LYNPARZA monotherapy without discontinuing due to AEs[5]
- Common AEs associated with LYNPARZA monotherapy are often mild / moderate[5–10]
- Refer to the Summary of Product Characteristics for a full list of AEs and associated recommendations, if applicable[1]

*The PROfound study was not powered for gene-by-gene analysis.

AE=adverse event; BRCAm=BRCA mutation; CI=confidence interval; DCO=data cut-off; ESMO=European Society for Medical Oncology; HR=hazard ratio; HRQoL=health-related quality of life; NHA=novel hormonal agent; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. Capoluongo E, et al. *Semin Oncol.* 2017;44:187–197; 3. de Bono J, et al. Poster presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Poster 847PD; 4. Thiery-Vuillemin A, et al. *Lancet Oncol.* 2022;23:393–405; 5. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357; 6. Moore N, et al. *N Engl J Med.* 2018;379:2495–2505; 7. Poveda A, et al. *Lancet Oncol.* 2021;22:620–631; 8. Tutt ANJ, et al. *N Engl J Med.* 2021;384:2394–2405; 9. Robson M, et al. *N Engl J Med.* 2017;377:523–533; 10. Golan T, et al. *N Engl J Med.* 2019;381:317–327.

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Management of anaemia associated with LYNPARZA treatment[1]

Advise patients that:

- Anaemia is one of the most common side effects reported in clinical studies with LYNPARZA
- Management strategies exist to aid in the alleviation of the symptoms of anaemia
- Regular blood tests are necessary to monitor for adverse haematological reactions, including anaemia
- There is a possibility that a blood transfusion may be required
- Communication with their care team may inform their experience on therapy

Advise patients to:

- Contact their HCP if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, low blood cell counts or a need for blood transfusions. This may be a sign of haematological toxicity or a more serious uncommon bone marrow problem (MDS or AML) which have been reported in patients treated with LYNPARZA
- Immediately report any signs or symptoms of thromboembolism, such as pain or swelling in an extremity, shortness of breath, chest pain or tachycardia

AML=acute myeloid leukaemia; HCP=healthcare professional; MDS=myelodysplastic syndrome.

LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023).

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Choose LYNPARZA monotherapy for patients with BRCA-mutated mCRPC following progression on NHA[1]*

Median OS was 20.1 months with LYNPARZA vs. 14.4 months with physician's choice NHA†[1]
Data cut-off: 20 March 2020

LYNPARZA	*Physician's choice†*
20.1	***14.4***
months	*months*

HR=0.63 (95% CI: 0.42–0.95); p not tested

The imaging-based PFS by BICR observed in the experimental arm was **more than triple** the imaging-based PFS in the control arm†[1]
Data cut-off: 04 November 2019

LYNPARZA	*Physician's choice†*
9.8	***3.0***
months	*months*

HR=0.22 (95% CI: 0.15–0.32); p not tested

80% Of patients in the PROfound trial **remained on LYNPARZA** without discontinuing due to AEs[2]

Test patients with advanced prostate cancer for BRCAm

*The PROfound study was not powered for gene-by-gene analysis; †Physician's choice of either enzalutamide or abiraterone.[1]
AE=adverse event; BRCAm=BRCA mutation; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; OS=overall survival; PFS=progression-free survival.
1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. Hussain M, et al. *N Engl J Med.* 2020;383:2345–2357.

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Choose LYNPARZA now for the future of your appropriate patients with mCRPC

LYNPARZA is indicated:

- As **monotherapy** for the treatment of adult patients with mCRPC and **BRCAm** (germline and/or somatic) who have progressed following prior therapy that included an NHA[1]
- **In combination** with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom **chemotherapy is not clinically indicated**[1]

LYNPARZA has a generally consistent tolerability profile and showed activity in patients with BRCAm and mCRPC

- In PROfound, **imaging-based PFS** and **mOS** were numerically higher (not significant) in the LYNPARZA arm vs. the control arm in patients with BRCAm[1–3]
- Numerically, patients treated with LYNPARZA **reported less deterioration in HRQoL functioning** over time vs. patients treated with physician's choice[4]
- The safety profile of LYNPARZA was found to be similar to previous analyses and the safety profile of LYNPARZA in other tumour types[3,5–7]

BRCA testing is essential for informed treatment decisions

- Patients **must test positive for a BRCAm** to be eligible for LYNPARZA monotherapy[1]
- Tumour tissue testing can detect both germline and somatic mutations[8]
- The tissue used for BRCA tumour genetic testing must be of reasonable quality to accurately identify mutations[9]

BRCAm=BRCA mutation; HRQoL=health-related quality of life; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; OS=overall survival; PFS=progression-free survival.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed November 2023); 2. de Bono J, et al. *N Engl J Med*. 2020;382:2091–2102; 3. Hussain M, et al. *N Engl J Med*. 2020;383:2345–2357; 4.Thiery-Vuillemin A, et al. *Lancet Oncol*. 2022;23:393–405; 5. Moore K, et al. In: Presidential Symposium 2, Abstract #LBA7_PR. Munich, Germany; 2018; 6. Robson ME, et al. *Ann Oncol*. 2019;30:558–566; 7. Golan T, et al. *N Engl J Med*. 2019;381:317–327; 8. Capoluongo E, et al. *Semin Oncol*. 2017;44:187–197; 9. de Bono J, et al. Poster presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Poster 847PD.

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