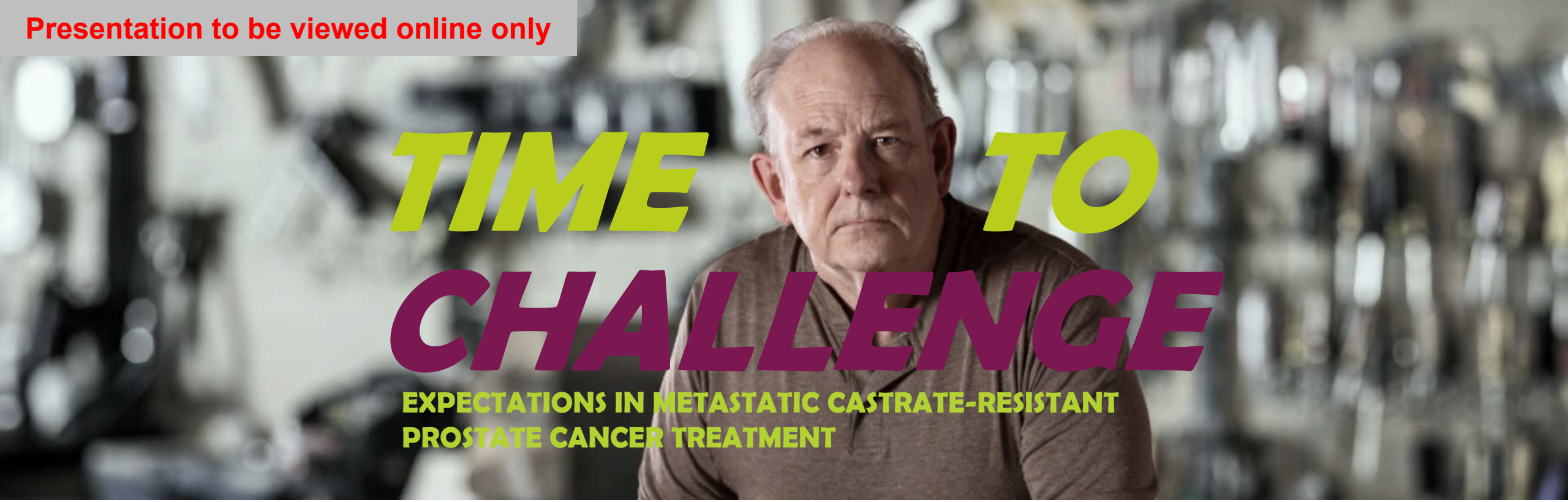
Presentation to be viewed online only



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EXPECTATIONS IN METASTATIC CASTRATE-RESISTANT PROSTATE CANCER TREATMENT

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 01992 467272) and AstraZeneca (UK) by visiting https://contactazmedical.astrazeneca.com/ or by calling 0800 783 0033.

FOR HEALTHCARE PROFESSIONAL USE ONLY.

Prescribing information and adverse event reporting for Great Britain can be found here.

Prescribing information and adverse event reporting for Northern Ireland can be found here.

This promotional asset has been fully developed and funded by AstraZeneca and MSD.

JBN: GB-48038
DOP: August 2023

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LYNPARZA© (olaparib) tablets mCRPC indications

LYNPARZA© (olaparib) tablets

Prostate cancer indications[1]

NICE/SMC approved[2] **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 medicines

mCRPC=metastatic castrate resistant prostate cancer.

1. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed June 2023); 2. Final appraisal document: Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer. April 2023. Available at: https://www.nice.org.uk/guidance/gid-ta11314/documents/final-appraisal-determination-document (Accessed June 2023).

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LYNPARZA is the first PARPi reimbursed for the treatment of NHA-treated, BRCAm relapsed mCRPC

LYNPARZA monotherapy is recommended for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults[1]

LYNPARZA + abiraterone combination therapy (PROpel trial) is not currently reimbursed by the NHS

BRCA1/2m=BRCA1/2 mutation; mCRPC=metastatic castrate resistant prostate cancer; NHA=novel hormonal agents.

1. NICE Guideline TA887 - Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer. Available from: https://www.nice.org.uk/guidance/TA887 (Accessed June 2023).

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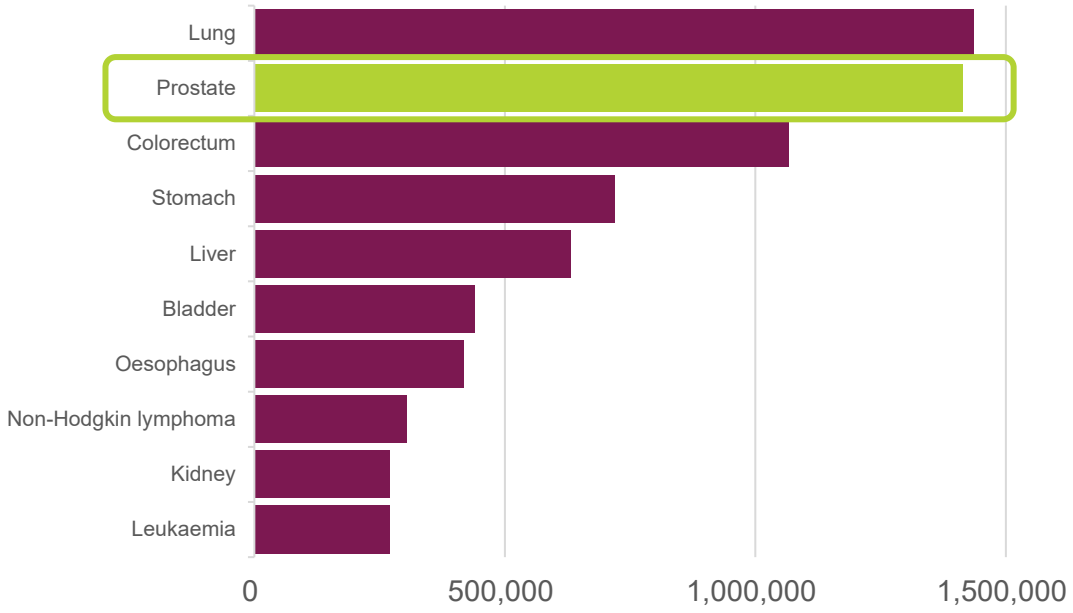
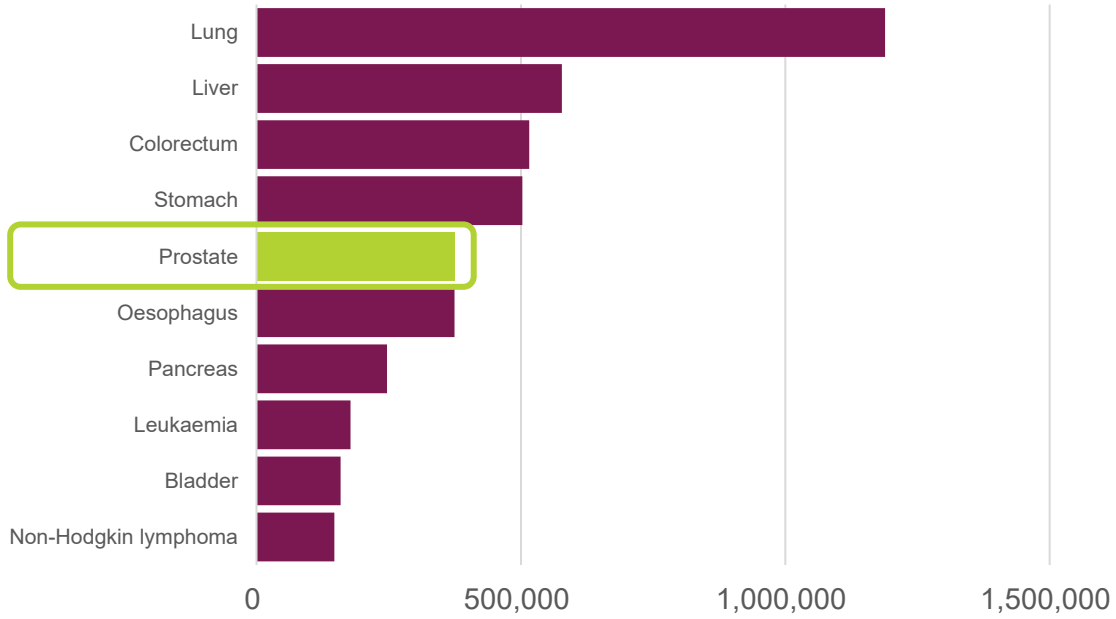
Prostate cancer is the fifth leading cause of cancer-related deaths amongst males globally[1]

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(2):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 June 2023); 2. Prostate Cancer UK. Available at: https://prostatecanceruk.org/prostate-information/about-prostate-cancer (Accessed June 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 June 2023); 5. Cancer Research UK. Available at: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/survival (Accessed June 2023); 6. Holm M, et al. *BMC Palliat Care*. 2018;17:126.

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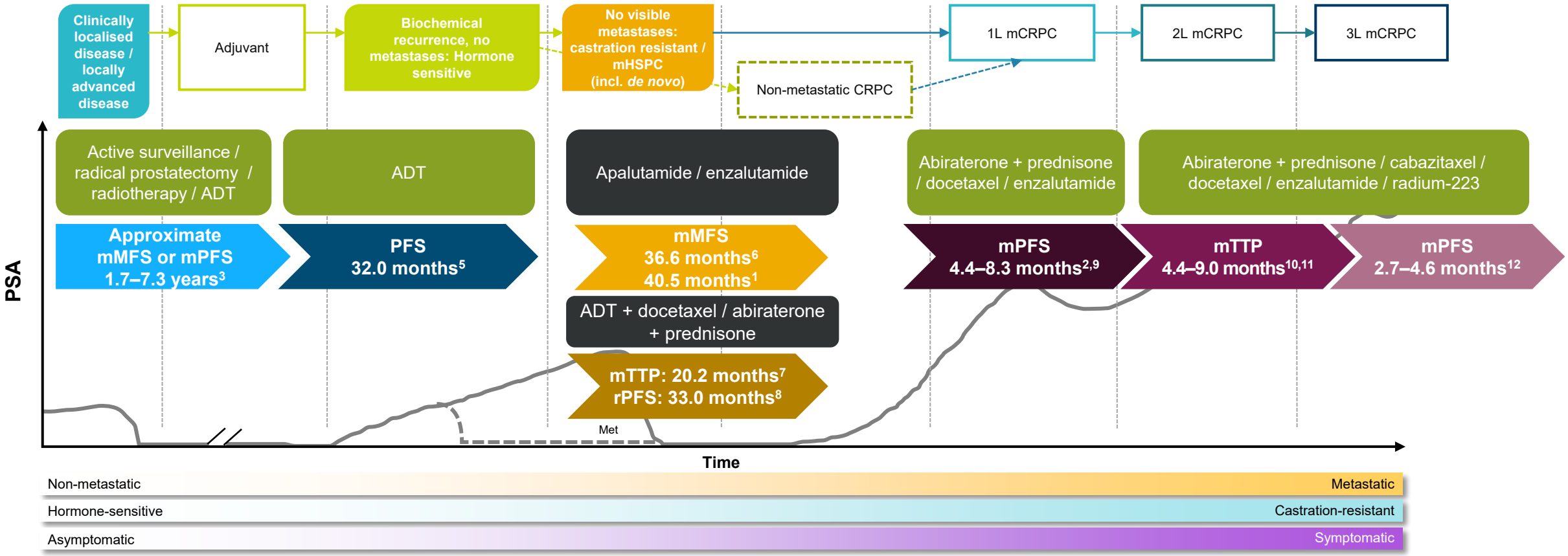
Despite advances in mCRPC treatment, clinical outcomes for patients remain poor[1–4]



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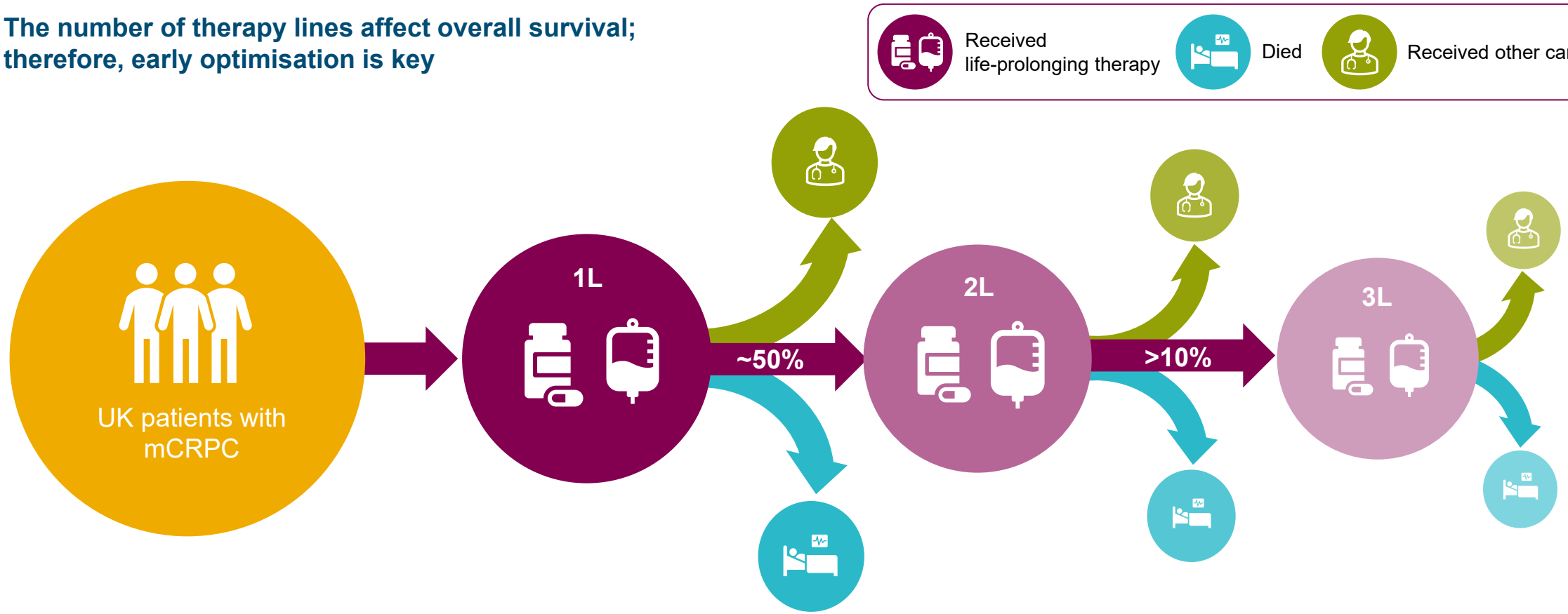
Approximately one half of UK patients with mCRPC receive more than one line of therapy[1]

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 June 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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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]

MHRA 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 June 2023); 2. Prostate Cancer UK. Olaparib. Available at: https://prostatecanceruk.org/prostate-information-and-support/treatments/olaparib (Accessed June 2023); 3. Be BRCA Aware. Available at: https://www.bebrcaware.com/what-is-brca/brca-testing-basics.html (Accessed June 2023; 4. Abida W, et al. *JCO Precis Oncol* 2017;2017:PO.17.00029.

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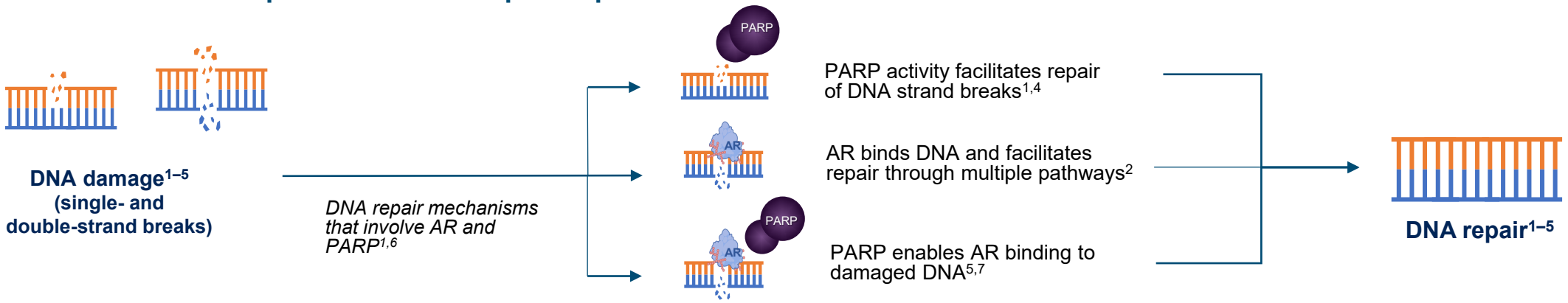
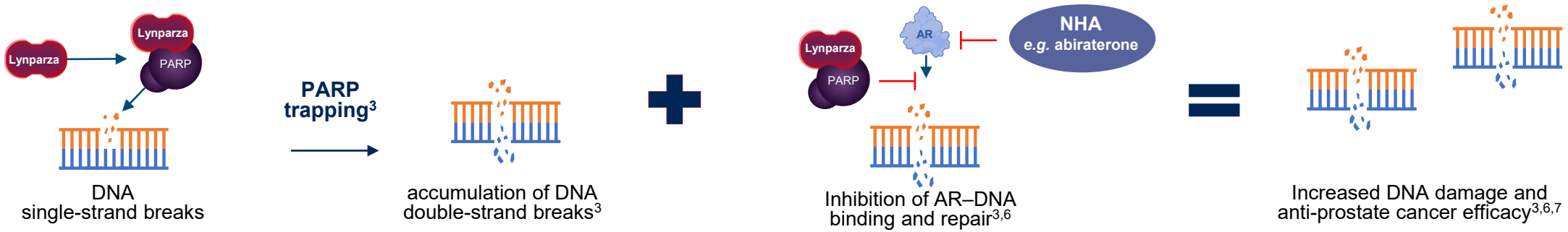
The interaction between PARP- and AR-signalling may explain the combined effect of LYNPARZA + abiraterone[1–7]

This is a hypothetical mechanism for the pharmacological rationale for the efficacy of the combination. Extrapolation of pre-clinical experimental evidence to clinical efficacy of the combination in patients cannot be made. The role of the addition of prednisolone or prednisone corticosteroid treatment to the pharmacological and genetic effects of the combination is unknown.

PARP and AR are important for DNA repair in prostate cancer[1–6]



Inhibition of PARP and AR in combination results in more DNA damage[2,3,6,7]



AR=androgen receptor; NHA=novel hormonal agent.

1. Chaudhuri AR, Nussenzweig A. *Nat Rev Mol Cell Biol.* 2017;18:610–621; 2. Polkinghorn WR, et al. *Cancer Discov.* 2013;3:1245–1253; 3. Lord CJ, Ashworth A. *Science.* 2017;355:1152–1158; 4. Pommier Y, et al. *Sci Transl Med.* 2016;8:362ps17; 5. Schiewer MJ, et al. *Cancer Discov.* 2012;2:1134–1149; 6. Asim M, et al. *Nat Commun.* 2017;8:374; 7. Li L, et al. *Sci Signal.* 2017;10:eaam7479.

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LYNPARZA cannot be combined with strong CYP3A4 inducers, such as enzalutamide, due to expected reduced exposure and hence reduced efficacy of LYNPARZA[1–4]

Hepatic cytochrome P450 enzymes CYP3A4 and CYP3A5 are predominantly responsible for the **metabolic clearance of LYNPARZA*[1]**

Strong CYP3A4 inducers could **reduce plasma levels** of **LYNPARZA,** potentially **affecting efficacy** (e.g. co-administration of a strong CYP inducer, such as rifampicin, decreases the exposure to LYNPARZA)[1]

Enzalutamide is a strong CYP3A4 inducer and therefore expected to **reduce exposure of LYNPARZA** and hence cannot be co-administered with LYNPARZA[1–4]

*Hypothesis based on experimental models.
CYP=cytochrome P450.
1. Dirix L, et al. *Clin Ther*. 2016;38:2286–2299; 2. Gibbons JA, et al. *Clin Pharmacokinet*. 2015;54:1057–1069; 3. Xtandi (enzalutamide). EU Prescribing Information. Available at: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf (Accessed June 2023) ; 4. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed June 2023).

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The recommended Phase II dose of LYNPARZA was identified through the open-label safety run-in study of the randomised Phase II trial - Study 8

Cohort 1

(n=3–6)

LYNPARZA 200 mg* PO BID,
abiraterone 1000 mg OD†

Recruited to Cohort 2

Cohort 2

Group 1 (n=6)

LYNPARZA 300 mg* BID

Group 2 (n=6)

Abiraterone 1000 mg OD†

Monotherapy pharmacokinetic sampling

LYNPARZA 300 mg* PO BID,
abiraterone 1000 mg OD†

Combination therapy pharmacokinetic sampling

No patients reported dose limiting toxicities
Selected RP2D = LYNPARZA 300 mg* PO BID + abiraterone 1000 mg OD†

*In tablet formulation. The recommended dose of Lynparza in combination with abiraterone and prednisone or prednisolone for prostate cancer is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.[2]
†Plus prednisone or prednisolone 5 mg BID. If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.
BID=twice a day; RP2D=recommended Phase II dose; OD=once daily

1. Clarke NW, et al., *Lancet Oncol*. 2018; 19(7): 975–986 (suppl. appx.); 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed June 20230.

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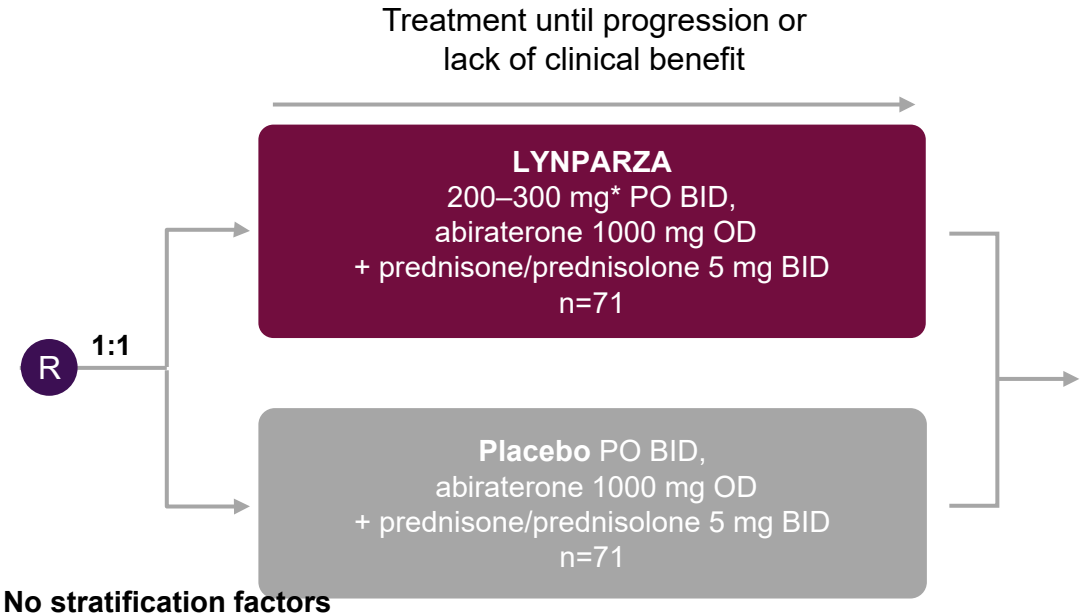
Study 8 provided clinical evidence supporting the addition of abiraterone to LYNPARZA in mCRPC

Study 8 was a Phase II randomised trial assessing the combination of LYNPARZA + abiraterone vs. placebo + abiraterone in patients with mCRPC who had received docetaxel[1]

Eligibility criteria

- Histologically or cytologically proven mCRPC
- Candidate for abiraterone therapy
- ECOG PS 0–2
- ≤2 prior lines of chemotherapy for metastatic disease
- Received docetaxel for treatment of mCRPC
- No prior treatment with second generation antihormonal drugs (including abiraterone or enzalutamide) or LYNPARZA



No stratification factors

Trial endpoints

Primary endpoint
- rPFS (RECIST v1.1 and/or PCWG2)†

Secondary endpoints
- Proportion of patients with rOR,† DoR and malignant soft tissue OR (RECIST v1.1)
- PFS2
- TFST
- TSST
- OS
- Biomarker analysis (PSA/CTC)
- Safety and tolerability

Exploratory analysis
- rPFS by HRRm status by tumour and ctDNA‡
- HRQoL

*In tablet formulation; 200 mg starting dose, 300 mg if well tolerated (≤1 dose-limiting toxicity). The recommended dose of Lynparza in combination with abiraterone and prednisone or prednisolone for prostate cancer is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.[2]
†Plus prednisone or prednisolone 5 mg BID. If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.
†Defined according to RECIST v1.1 (for soft tissue disease) and/or PCWG-2 criteria (for bone disease).
‡Loss-of-function mutations were assessed in 15 HRR genes: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*,and *RAD54L*.
BID=twice daily; CTC=circulating tumour cell; ctDNA=circulating tumour DNA; ECOG=Eastern Cooperative Oncology Group; HRQoL=health related quality of life; HRRm=homologous recombination repair gene mutation; mCRPC=metastatic castrate resistant prostate cancer; OD=once daily; OS=overall survival; PARPi=poly (ADP-ribose) polymerase inhibitor; PO=orally; PFS2=time to second progression or death; PSA=prostate specific antigen; R=randomisation; RECIST=Repsonse Evaluation Criteria in Solid Tumors; (r)OR=radiographic objective response; rPFS=radiographic progression free survival; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy.
1. Clarke NW, et al. *Lancet Oncol.* 2018;19(7):975–986; 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed June 2023).

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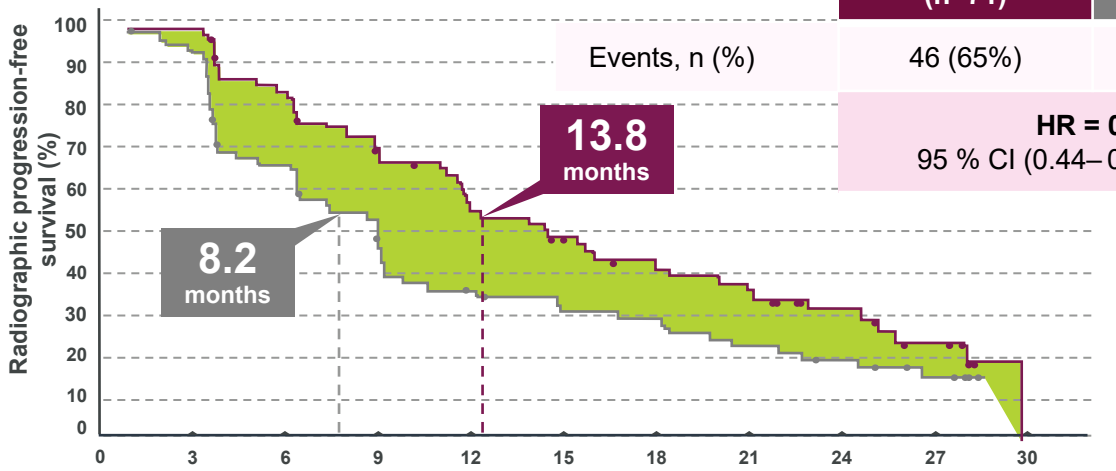
Study 8: The addition of LYNPARZA significantly prolonged rPFS vs. abiraterone + prednisone/ prednisolone alone, irrespective of HRRm status[1]

Investigator-assessed rPFS (ITT)[1]

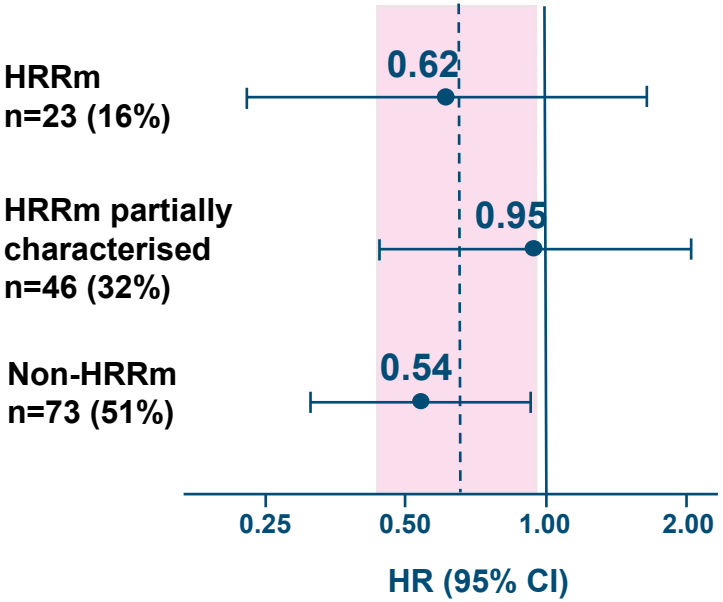
	LYNPARZA + abi + prednisone/ prednisolone (n=71)	Placebo + abi + prednisone/ prednisolone (n=71)
Events, n (%)	46 (65%)	54 (76%)
	HR = 0.65 95 % CI (0.44– 0.97) **p=0.034**	



Number of patients at risk (censored)

LYNPARZA + abi + pre	71(0)	58(5)	50(6)	42(8)	33(9)	26(12)	21(13)	18(13)	13(17)	8(19)	0(25)
Placebo + abi + pre	71(0)	48(3)	39(4)	25(5)	21(7)	19(7)	16(7)	14(7)	10(8)	7(10)	0(17)

rPFS by HRRm subgroup* (final analysis)†[2]



DCO: 22 September 2017.

*Dashed line and shaded area show HR and 95% CI, respectively, for the intent to treat population. †Patients without a HRRm detected in the tumour tissue test and no HRRm detected by any other assay, and patients with ctDNA fraction estimated to be ≥5% of ctDNA, and no HRR gene mutation detected in a plasma test.[2]

Abi=abiraterone; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; HRRm=homologous recombination repair gene mutation; ITT=intent-to-treat; pre=prednisolone/prednisone; rPFS=radiographic progression free survival.

1. Clarke NW, et al. *Lancet Oncol* 2018;19(7):975–986; 2. Carr TH, et al. *Cancers* 2021;13(22):5830.

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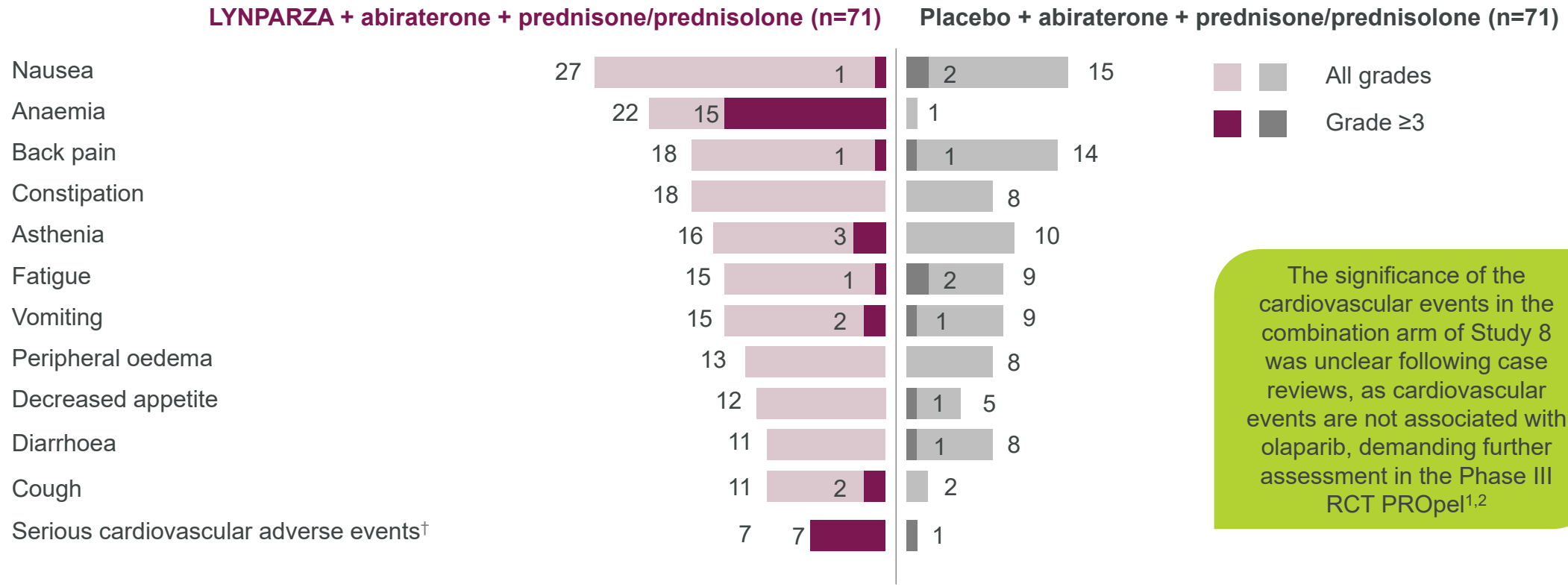
Study 8: Adverse events associated with LYNPARZA + abiraterone + prednisone/prednisolone were generally recognised for the individual agents[1]

Adverse events experienced by >10 combination arm patients*

Median treatment duration was 309 days for LYNPARZA compared with 253 days for placebo[1]



The significance of the cardiovascular events in the combination arm of Study 8 was unclear following case reviews, as cardiovascular events are not associated with olaparib, demanding further assessment in the Phase III RCT PROpel[1,2]

*Numbers inside bars indicate Grade ≥3 adverse events.
†Experimental group: Myocardial infarction, n=4; fatal cardiac failure, n=1; chronic cardiac failure, n=1; fatal ischemic stroke, n=1. Placebo and abiraterone group; thrombotic stroke, n=1.
RCT=randomised clinical trial.
1. Clarke NW, et al. *Lancet Oncol*. 2018;19:975–986; 2. Clarke NW, et al. *NEJM Evid*. 2022;1(9):1–16.

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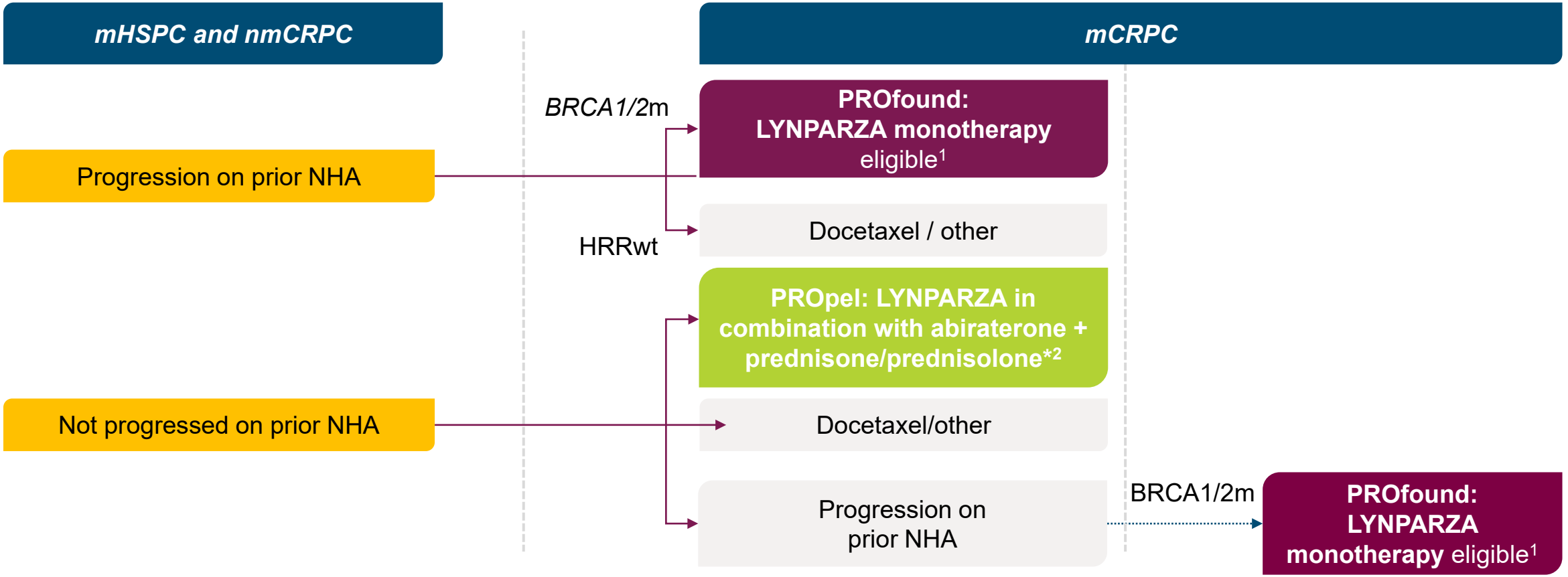
PROpel expands the opportunities for LYNPARZA in mCRPC

PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER



*LYNPARZA in combination with abiraterone has MHRA approval in this indication, but is not yet reimbursed.[3]
1L=first line; 2L=second line; ASCO=American Society of Clinical Oncology; EMA=European Medicines Agency; GU=genitourinary; HRRm=homologous-recombination-repair gene mutation; HRRwt=homologous recombination repair wild-type; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=novel hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer.

1. de Bono J, et al. *N Engl J Med*. 2020;28;382(22):2091–2102; 2. Saad F, et al. Presented at ASCO GU 2022. 17–19 February. San Francisco, CA. Oral Abstract 1; 3. AstraZeneca. LYNPARZA in combination with abiraterone approved in the EU as 1st-line treatment for patients with metastatic castration-resistance prostate cancer. Available at: https://www.astrazeneca.com/media-centre/press-releases/2022/LYNPARZA-approved-in-eu-for-prostate-cancer.html (Accessed June 2023).

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PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

PROpel trial

TIME TO CHALLENGE

LYNPARZA + abiraterone + prednisone/prednisolone. The first and only PARPi-based combination therapy for first-line mCRPC patients not previously treated with an NHA, irrespective of biomarker status[1]

Please note this indication has not been reviewed by NICE or the SMC

mCRPC=metastatic castrate resistant prostate cancer; NHA=novel hormonal agent; NICE=National Institute for Health and Clinical Excellence; SMC=Scottish Medicines Consortium.

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

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PROpel studied LYNPARZA combination therapy in 1L mCRPC with any HRR mutation status[1,2]

PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

PROpel trial design

Key eligibility criteria

- Histologically or cytologically confirmed prostate adenocarcinoma with ≥1 metastatic lesion
- No prior 1L treatment for mCRPC
- Docetaxel during neoadjuvant / adjuvant treatment for localised prostate cancer and mHSPC was permitted
- Other NHAs permitted if treatment was stopped more than 12 months prior to randomisation*
- ECOG performance status 0–1

*Treatment was initiated with **full doses** of both LYNPARZA and abiraterone, maximising the effectiveness of the combination*

R
1:1
N=796

LYNPARZA
300 mg BID +
abiraterone 1000 mg OD +
prednisone/prednisolone 5 mg BID
n=399

Placebo +
abiraterone 1000 mg OD +
prednisone/prednisolone 5 mg BID
n=397

Stratification factors:
- Metastases (bone only vs. visceral vs. other)
- Docetaxel treatment at mHSPC stage (yes vs. no)

Trial endpoints

Primary endpoints:
- Imaging-based PFS by investigator assessment†
- Pre-specified sensitivity analysis of imaging-based PFS by BICR

Key secondary endpoint:
- OS

Additional endpoints:
- TFST
- PFS2
- ORR
- HRR mutation prevalence (pre-defined, post-randomisation testing)
- Health-related QoL (FACT-P)
- Safety and tolerability
- Time to an SSRE
- Time to opiate use
- Pharmacokinetics

*Except abiraterone.
†Imaging-based PFS assessed by investigator per RECIST v1.1 (soft tissue) and PCWG-3 (bone) criteria.
1L=first-line; BICR=blinded independent central review; BID=twice daily; ECOG=Eastern Cooperative Oncology Group; FACT-P=Functional Assessment of Cancer Therapy - Prostate; HRR=homologous recombination-repair; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=novel hormonal agent; OD=once daily; ORR=objective response rate; OS=overall survival; PCWG-3=Prostate Cancer Working Group-3; PFS=progression-free survival; PFS2=time to second progression or death; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumours; SSRE=symptomatic skeletal-related event; TFST=time to first subsequent treatment.
1. Clinicaltrials.gov. NCT03732820. Available at: https://clinicaltrials.gov/ct2/show/NCT03732820 (Accessed June 2023); 2. Clarke NW, et al. *NEJM Evid.* 2022;1(9):1–16.

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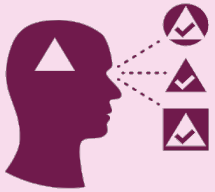
In PROpel, molecular testing to determine HRRm status was not done prospectively[1]



Prevent bias

- HRRm status determination for all study eligible patients is complicated by sample and testing challenges
- Requiring determination of HRRm status pre-enrolment risks biasing patient enrolment to those with sufficient tumour, and/or detectable ctDNA

Ensure balanced patient prevalence

- It was anticipated that due to the size of the study, the population baseline factors would be balanced
- Therefore, retrospective patient assignment to biomarker subgroups was expected to give balanced representation of HRR subgroups in the study arms

ctDNA=circulating tumour DNA; HRR(m)=homologous recombination repair (gene mutation).

1. Clarke NW, et al. *NEJM Evid*. 2022;1(9):1–16.

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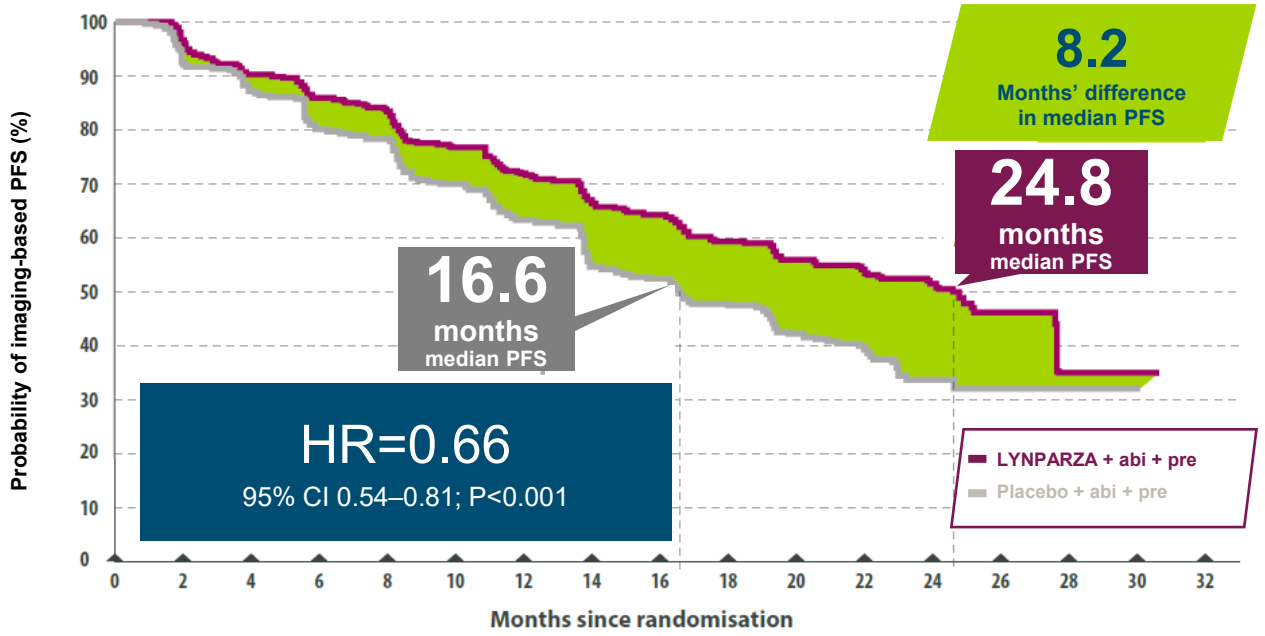
Primary endpoint: At primary analysis, PROpel demonstrated a median 8.2-month improvement in rPFS vs. abiraterone

P<0.001[1,2]

PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Investigator-assessed imaging-based PFS in the ITT population at the primary analysis[1,2]



No. at risk																	
LYNPARZA + abi + pre	399	367	340	313	301	274	251	227	219	167	104	87	57	26	5	4	0
Placebo + abi +pre	397	359	338	306	297	264	232	198	186	141	87	73	43	17	2	1	0

Adapted from Clarke NW, et al. 2022[1]

DCO1: 30 July 2021.
Events: 394; Maturity 49.5% at DCO1.[1]
*In combination with prednisone or prednisolone.
Abi=abiraterone; ASCO=American Society of Clinical Oncology; CI=confidence interval; GU=genitourinary; HR=hazard ratio; PFS=progression-free survival; pre=prednisolone/prednisone; SOC=standard of care.
1. Clarke NW, et al. *NEJM Evid*. 2022;1(9); 2. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16

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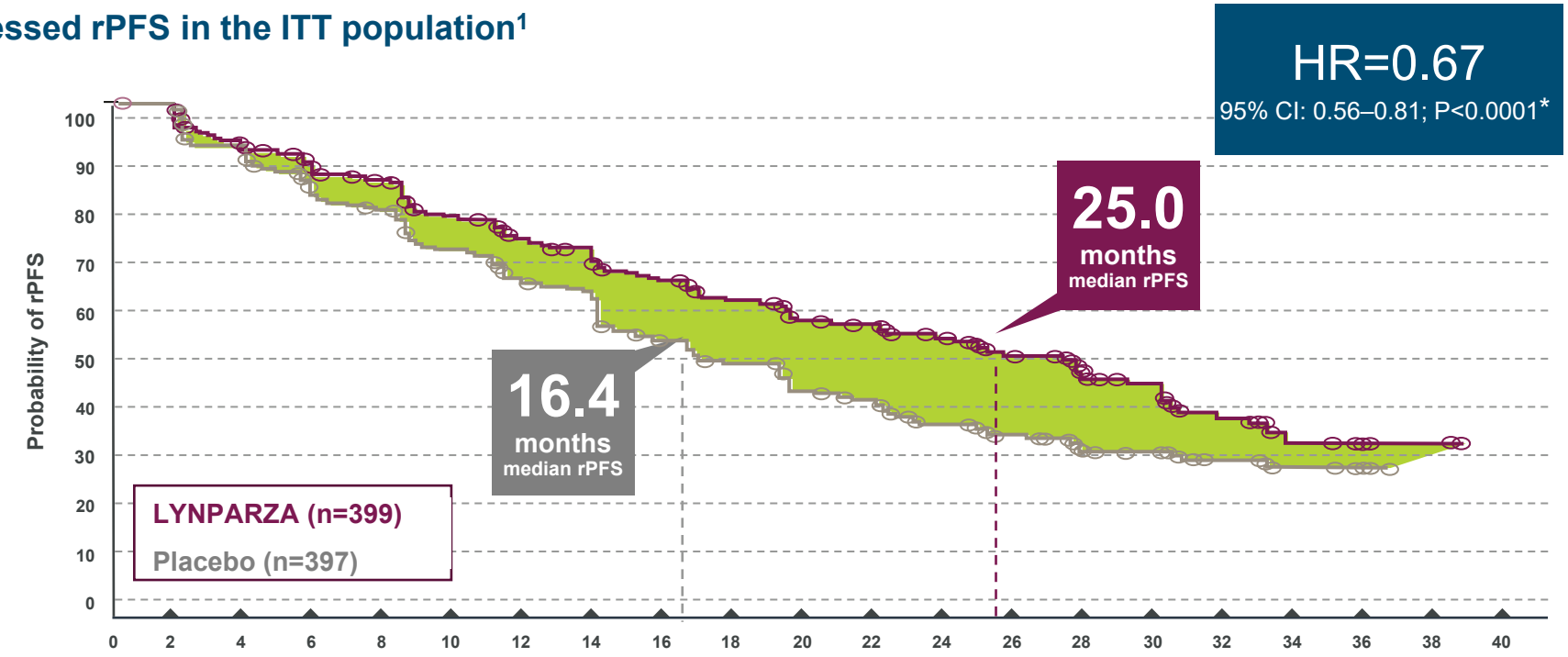
The experimental arm increased rPFS by 8.6 months vs. the control arm at DCO2[1]

*P<0.0001 (nominal)**

PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Investigator-assessed rPFS in the ITT population[1]



Number of patients at risk

LYNPARZA + abi + pre	399	367	340	313	301	274	251	228	220	220	184	174	158	110	62	58	33	15	5	3	0
Placebo + abiraterone + pre	397	359	338	297	297	264	232	199	187	169	145	135	117	84	51	48	30	8	3	0	0

Adapted from Saad F et al. 2022[1]

DCO2: 14 March 2022.
Median duration of follow-up for censored patients at DCO2 was 24.9 months (range 0.03–38.8) in the LYNPARZA arm and 27.4 months (range 0.03–36.76) in the placebo arm.
*Nominal.
Abi=abraterone; CI=confidence interval; DCO=data cut-off; ESMO=European Society for Medical Oncology; HR=hazard ratio; ITT=intent-to-treat; pre=prednisolone/prednisone; rPFS=radiographic progression-free survival.
1. Saad F, et al. Presented at ESMO Annual Congress 2022. 9–13 September. Paris, France. Abstract #13570.

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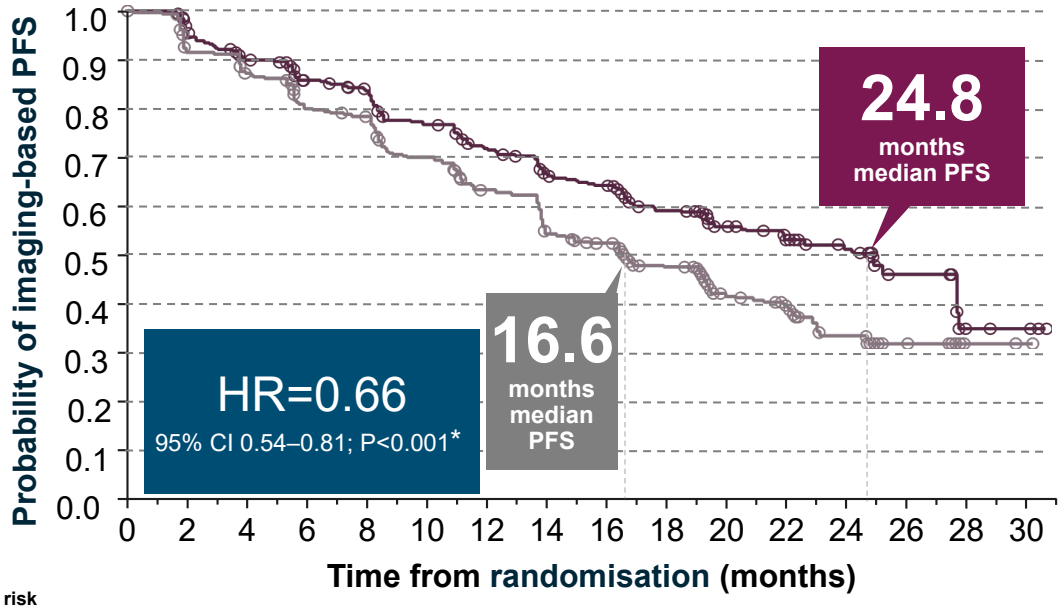
Primary endpoint: At the primary analysis, imaging-based PFS by BICR supported the findings of investigator-assessed rPFS[1,2]

Sensitivity analysis of primary endpoint

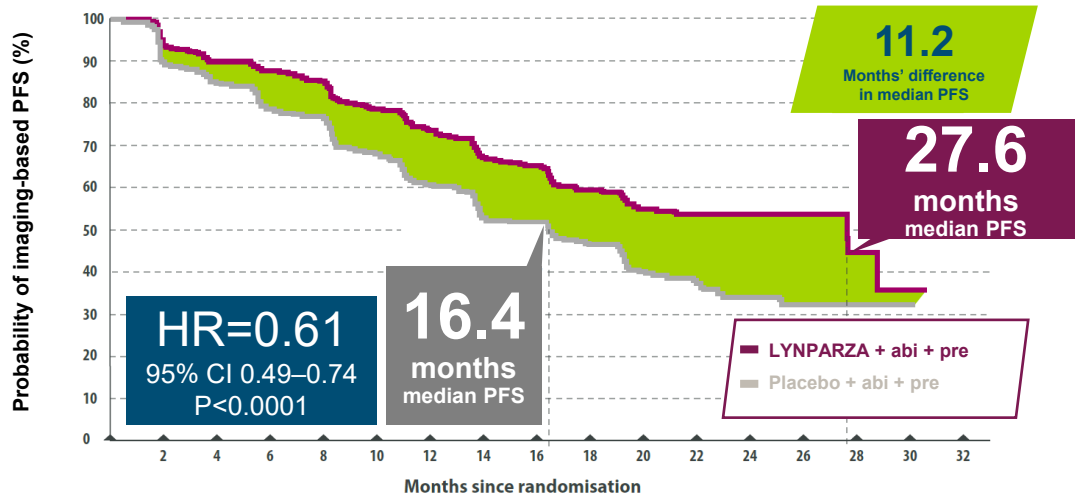
Investigator assessed imaging-based PFS in the ITT population[1,2]



No. at risk																
LYNPARZA + abi + pre	399	367	340	313	301	274	251	277	219	167	104	87	57	26	5	4
Placebo + abi + pre	397	359	338	306	297	264	232	198	186	141	87	73	43	17	2	1

Adapted from Clarke NW, et al. 2022[1]

BICR-assessed imaging-based PFS in the ITT population[1,2]



No. at risk																	
LYNPARZA + abi + pre	399	353	332	314	303	275	249	221	215	161	96	80	53	28	5	4	0
Placebo + abi + pre	397	345	322	294	282	245	209	177	168	126	73	62	38	16	2	1	0

Adapted from Clarke NW, et al. 2022[1]

DCO1: 30 July 2021.[2]

*Pre-specified 2-sided alpha: 0.0324.[2]

abi=abiraterone; ARR=absolute risk reduction; BICR=blinded independent central review; CI=confidence interval; ESMO=European Society for Medical Oncology; HR=hazard ratio; ITT=intent-to-treat; pre=prednisolone/prednisone; PFS=progression-free survival.

1. Clarke NW, et al. *NEJM Evid*. 2022;1(9):1–16; 2. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16.

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Secondary endpoint: mOS in the LYNPARZA arm was 42.1 months vs. 34.7 months in the placebo arm[1]

Final OS analysis; P=0.0544 (not statistically significant)*

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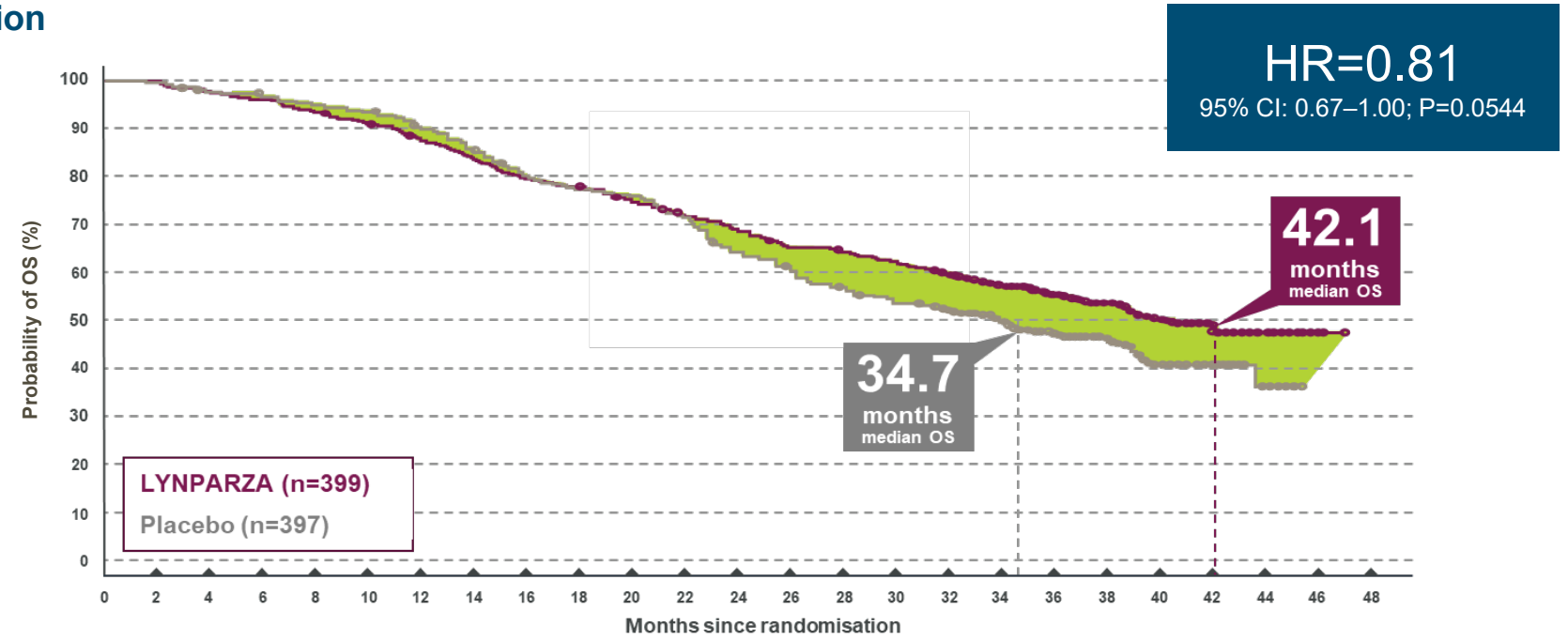
mOS in the ITT population



Adapted from Clarke NW et al. 2023[1]

Number of patients at risk																									
LYNPARZA + abi + pre	399	399	391	385	374	364	349	334	318	312	298	283	273	258	253	246	226	192	135	96	63	29	10	2	0
Placebo + abi + pre	397	395	388	383	376	370	355	337	316	305	301	282	254	241	225	213	201	157	119	84	53	25	7	0	0

DCO3: 12 October 2022; 47.9% data maturity.
*2-sided boundary for significance: 0.0377.
Median duration of follow-up for censored patients at DCO3 was 36.6 months (range 8.3–47.0) in the LYNPARZA arm and 36.5 months (range 2.9–45.3) in the placebo arm.
Abi=abiraterone; ASCO=American Society of Clinical Oncology; CI=confidence interval; DCO=data cut-off; GU=genitourinary; HR=hazard ratio; ITT=intent-to-treat; mOS=median overall survival; OS=overall survival; pre=prednisolone/prednisone.

1. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16.

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Secondary endpoint: OS benefit across subgroups was generally consistent with the ITT population[1]

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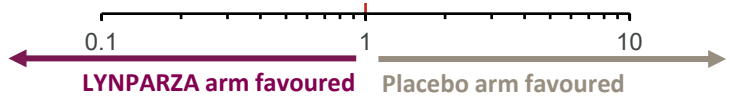
Subgroup		Number of patients, n	HR (95% CI)	Median OS, months	
				LYNPARZA + abi + pre	Placebo + abi + pre
	All patients	796	0.81 (0.67–1.00)	42.1	34.7
AGE	Age at randomisation <65	227	0.60 (0.40–0.90)	NR	33.9
	Age at randomisation ≥65	569	0.95 (0.75–1.19)	35.9	36.2
METASTASIS	Metastasis: bone only	434	0.85 (0.64–1.13)	NR	38.3
	Metastasis: visceral	105	0.89 (0.53–1.51)	34.0	26.1
	Metastasis: other	257	0.74 (0.52–1.05)	40.4	31.9
DOCETAXEL	Docetaxel treatment at mHSPC stage	189	0.76 (0.52–1.11)	38.8	27.2
	No docetaxel treatment at mHSPC stage	607	0.85 (0.67–1.07)	NR	38.3
HRRm STATUS*	HRRm	226	0.66 (0.45–0.95)	NR	28.5
	non-HRRm	552	0.89 (0.70–1.14)	42.1	38.9
BRCAm STATUS	BRCAm	85	0.29 (0.14–0.56)	NR	23.0
	non-BRCAm	693	0.91 (0.73–1.13)	39.6	38.0



DCO3: 12 October 2022.
No p values were presented for this subgroup analysis.
*The HRRm and BRCAm status of patients in PROpel was determined by prespecified HRRm testing conducted after randomisation, and before primary analysis, using tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumour tissue or ctDNA test and were excluded from the subgroup analysis.
Abi=abiraterone; ASCO=American Society of Clinical Oncology; BRCAm=BRCA mutation; CI=confidence interval; DCO=data cut-off; GU=genitourinary; HR=hazard ratio; HRRm=homologous recombination repair mutation; ITT=intention-to-treat; mHSPC=metastatic hormone-sensitive prostate cancer; NR=not reached; OS=overall survival; pre=prednisolone/prednisone.
1. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16.

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Safety: The toxicity profiles remain consistent with those of the individual drugs and the primary analysis[1]

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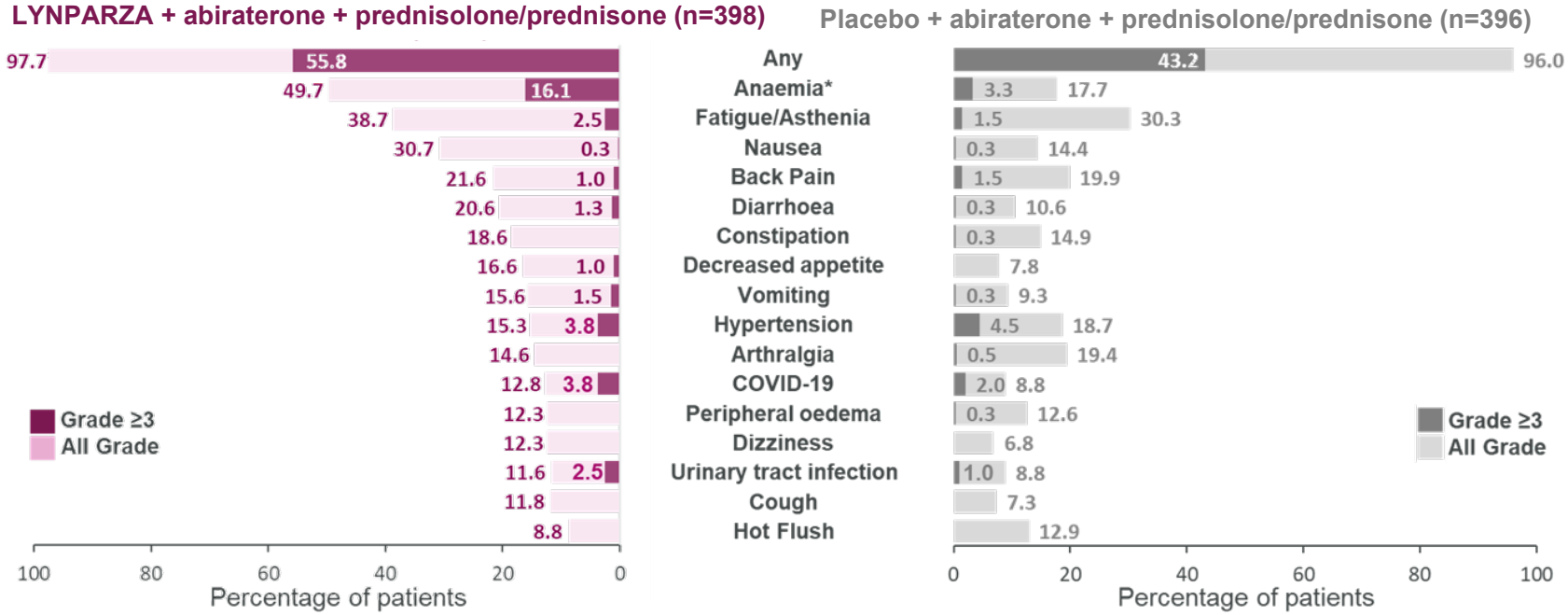
Most common AEs (in ≥10% patients)[1]



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[2]

- More pulmonary embolisms were observed in the LYNPARZA arm in PROpel, consistent with other observations in other PARPi studies in mCRPC[3]
- The majority of pulmonary embolism events were asymptomatic and incidental on imaging[1]

DCO3: 12 October 2022.
Safety was assessed through the reporting of AEs according to the NCI CTCAE v4.03 and laboratory assessments.
*Anaemia category includes anaemia, decreased haemoglobin level, decreased red cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia.
ASCO=American Society of Clinical Oncology; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; DCO=data cut-off; GU=genitourinary; mCRPC=metastatic castration-resistant prostate cancer; NCI=National Cancer Institute; PARPi=poly (ADP-ribose) polymerase inhibitor.
1. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16; 2. LYNPARZA (olaparib). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9488/smpc (Accessed June 2023); 3. Clarke NW, et al. *NEJM Evid*. 2022;1(9):1–16.

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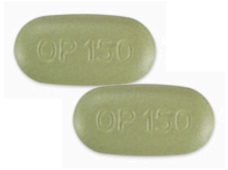
LYNPARZA + abiraterone + prednisolone/prednisone therapy is simple to administer via oral dosing[1]

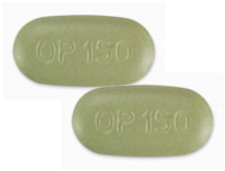
2 LYNPARZA tablets 2 times per day
(with or without food)

AM



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

PM



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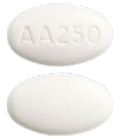

Abiraterone
Two 500 mg tablets once daily (total 1000 mg daily)

+

Prednisone/ prednisolone
One 5 mg tablet twice daily (total 10 mg daily)

Dose adjustments and reductions

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia, and dose reduction can be considered

- **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.

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

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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.

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

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PROpel is a Phase III trial that has led to the approval of LYNPARZA + abiraterone + prednisone/ prednisolone in patients with mCRPC[1]

PROpel
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

- LYNPARZA + abiraterone + prednisolone/prednisone met the primary endpoint for PROpel, demonstrating a statistically significant 8.2-month improvement in imaign-based PFS vs. placebo + abiraterone + prednisolone/prednisone[2]
- An OS difference (non-significant) was also observed in patients treated with LYNPARZA + abiraterone + prednisolone/prednisone vs. placebo + abiraterone + prednisolone/prednisone, and was sustained at the final pre-specified analysis[2–4]

Median imaging-based PFS[2] DCO: 30 July 2021	Median OS[4] DCO: 12 October 2022: 47.9% maturity
HR=0.66 (95% CI: 0.54–0.81; P<0.001) LYNPARZA arm 24.8 months Placebo arm16.6 months	**HR=0.81 (95% CI: 0.67–1.00; P=0.0544)*** LYNPARZA arm 42.1 months Placebo arm 34.7 months

- LYNPARZA + abiraterone + prednisolone/prednisone is a generally well-tolerated combination prescribed at the full monotherapy dose for each individual drug,[3] with a consistent and generally manageable safety profile

*2-sided boundary for significance: 0.0377.[4]

ASCO=American Society of Clinical Oncology; CI=confidence interval; ESMO=European Society for Medical Oncology; GU=genitourinary; HR=hazard ratio; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; PFS=progression-free survival.

1. AstraZeneca. Lynparza in combination with abiraterone EU approval. Available at: https://www.astrazeneca.com/media-centre/press-releases/2022/lynparza-approved-in-eu-for-prostate-cancer.html (Accessed June 2023); 2. Clarke NW, et al. *NEJM Evid.* 2022;1(9):1–16; 3. Saad F, et al. Presented at ESMO Annual Congress 2022. 9–13 September. Paris, France. Abstract #13570; 4. Clarke NW, et al. Presented at ASCO GU 2023. 16–18 February. San Francisco, US. Abstract #LBA16.

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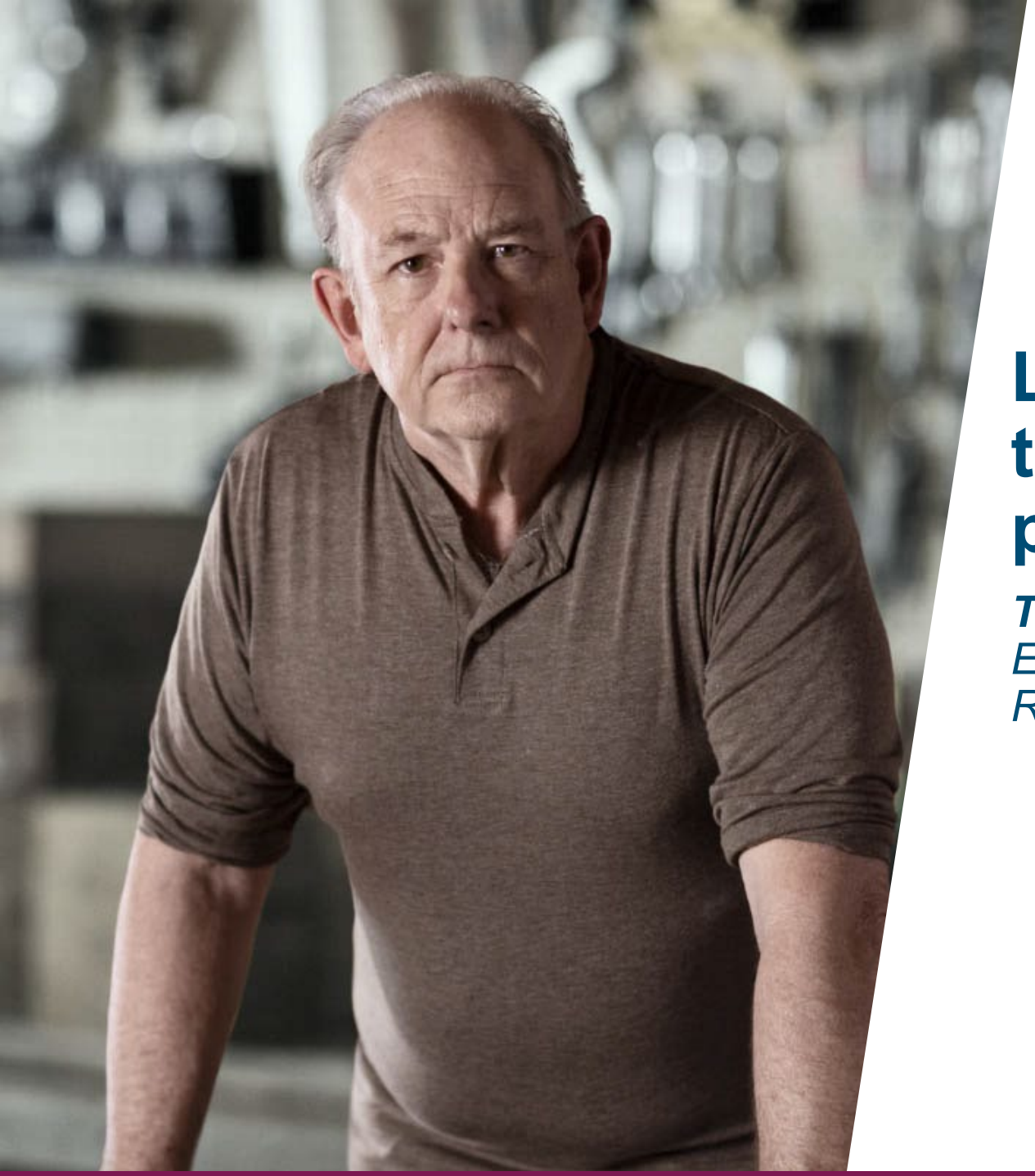

LYNPARZA combination therapy for your NHA naive patients with mCRPC

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

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