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THE HEART OF MEDICAL EDUCATION

GU CONNECT
ANIMATED VIDEO

CLINICAL IMPLEMENTATION OF TESTING AND PARPis IN COMBINATION WITH NHAs, AND THE PATIENT JOURNEY FOR PROSTATE CANCER PATIENTS

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UPDATED NOVEMBER 2023

NHA, novel hormonal agents; PARPi, poly-ADP ribose polymerase inhibitor

EDUCATIONAL OBJECTIVES

1. Recognise the **efficacy and safety** profiles of PARP inhibitors, know their differences and understand their place in the treatment landscape for patients with mCRPC
2. Understand the **data of combination studies** with PARP inhibitors and novel hormonal agents (NHAs) in mCRPC, the **rationale** & **MoA** of the combination, its appropriate implementation and impact on clinical practice
3. Understand the **role of testing** for assessment of HRRm status and subsequent decision making for treatment with PARP inhibitors in combination with NHAs

HRRm, homologous recombination repair mutation; mCRPC, metastatic castration-resistant prostate cancer; MoA, mechanism of action; PARP, poly-ADP ribose polymerase

CLINICAL TAKEAWAYS

- PARP inhibitors are effective drugs as monotherapy in mCRPC patients with HRR alterations
- Genetic testing is important to inform on prognosis, help with treatment decision making and for understanding inherited risk
- *BRCA* mutations are associated with poor outcomes in mCRPC patients
- Patients with tumours harbouring *BRCA1/BRCA2* alteration appear to derive the greatest clinical benefit from PARP inhibitor monotherapy, but patients with other HRR alterations also derive benefit
- PARP inhibitors combined with novel hormonal agents are also effective as a first line treatment option for mCRPC patients with a HRR mutation. Certain combinations such as olaparib plus abiraterone and talazoparib plus enzalutamide have also shown benefit in patients regardless of their HRR status

BRCA1/2, breast cancer gene 1/2; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly-ADP ribose polymerase

DEVELOPED BY GU CONNECT

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Expert Disclaimers:

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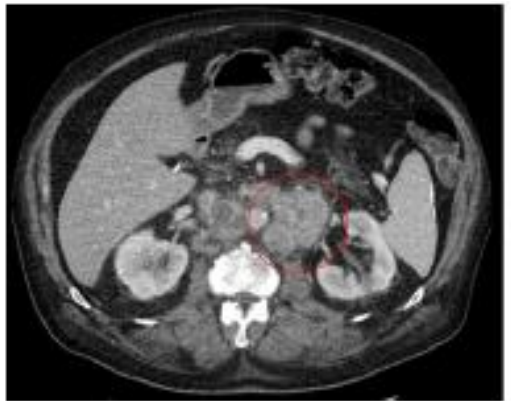
INTRODUCING THE PATIENT CASE AND TREATMENT OPTIONS

PATIENT CASE: *DE NOVO* HIGH VOLUME mHSPC

Patient: 66 year old
Presents with: mild fatigue
Medical history:

- Well-controlled hypertension and hyperlipidaemia
- +FH of breast cancer in sister, age 56



ADT/docetaxel x 6 → ADT

12 months

18 months

24 months

PSA 110

PSA nadir 0.2

PSA 1.6

PSA 14.4

Initial Presentation

Biopsy: 9 / 12 cores; Adenocarcinoma Gleason 4+4

Staging: T3 by DRE and mpMRI, N1 M1b, high volume mHSPC

Imaging: bone and CT scan

- Metastases in hip, lumbar spine and ribs (five)
- Multiple pelvic & retroperitoneal lymph nodes between 2-4 cm

Current situation
Slight discomfort in lumbar spine

Imaging:

- Progression of bone and lymph node metastases
- Haemoglobin: 11 g/dL

ADT, androgen deprivation therapy; CT, computed tomography; DRE, digital rectal exam; FH, family history; mHSPC, metastatic hormone sensitive prostate cancer; mpMRI, multi-parametric magnetic resonance imaging; PSA, prostate-specific antigen; T, N, M, tumour, nodes, metastasis

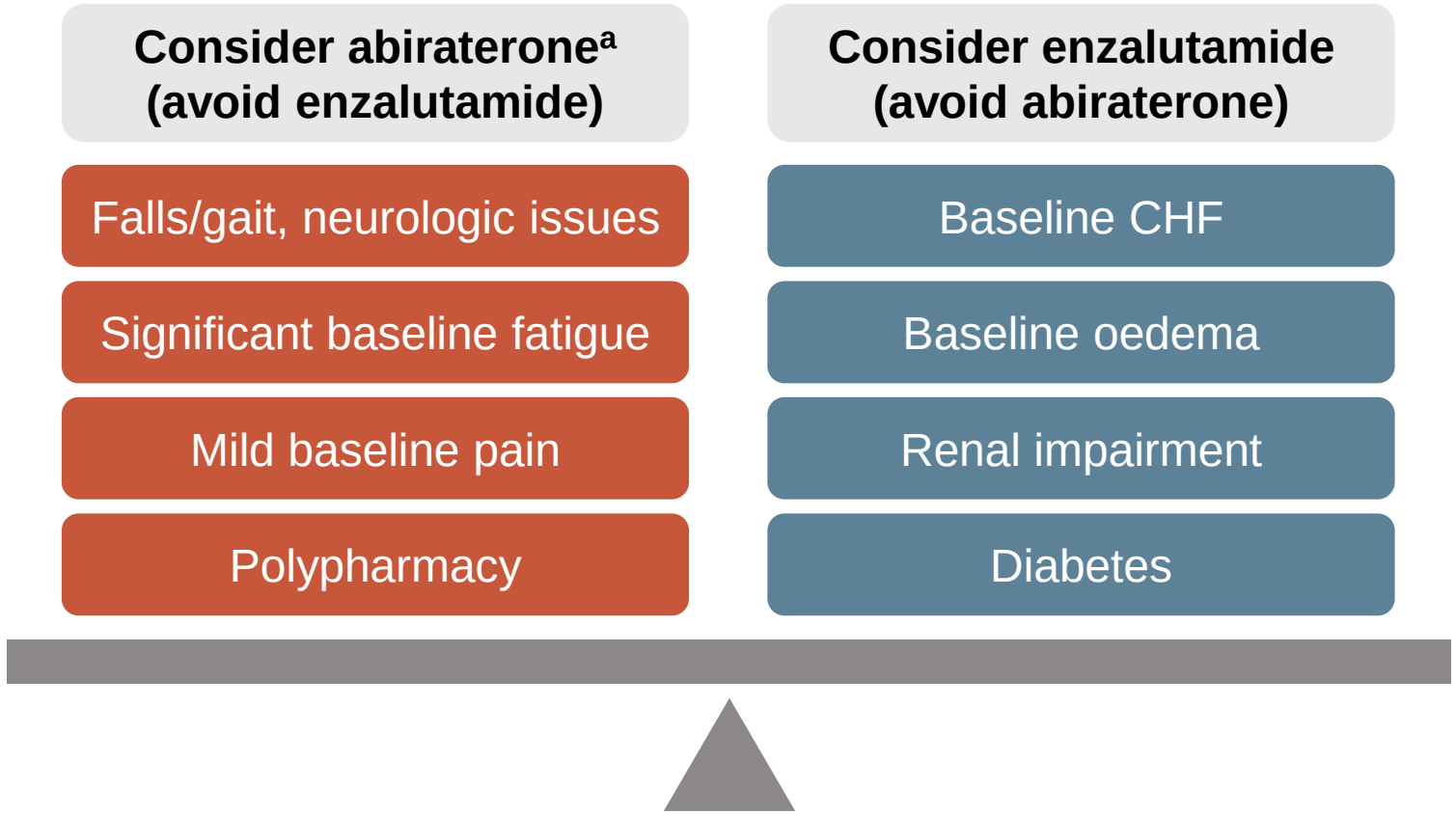
TIMING AND SELECTION OF SECONDARY AR-DIRECTED THERAPIES

- Choice of abiraterone vs. enzalutamide cannot be dictated based on differences in efficacy
  - Similar OS, PFS from cross-trial comparisons
  - Enzalutamide has been evaluated in men with visceral metastases in the chemo-naïve setting
  - Both considered level 1 evidence in NCCN guidelines based on improved PFS and overall survival

- Therefore, choice is based on differential toxicity, costs, drug interactions, and other patient factors
  - Abiraterone acetate in men who are seizure-prone, frail/elderly (>75 yrs) at high risk for falls, men for who drug-drug interactions is a potential issue
  - Enzalutamide for men with significant CV risk factors, contraindications to prednisone, brittle diabetes and metabolic syndrome, contraindications to prednisone

AR, androgen receptor; CV, cardiovascular; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival; yrs, years

SELECTING ABIRATERONE VS ENZALUTAMIDE



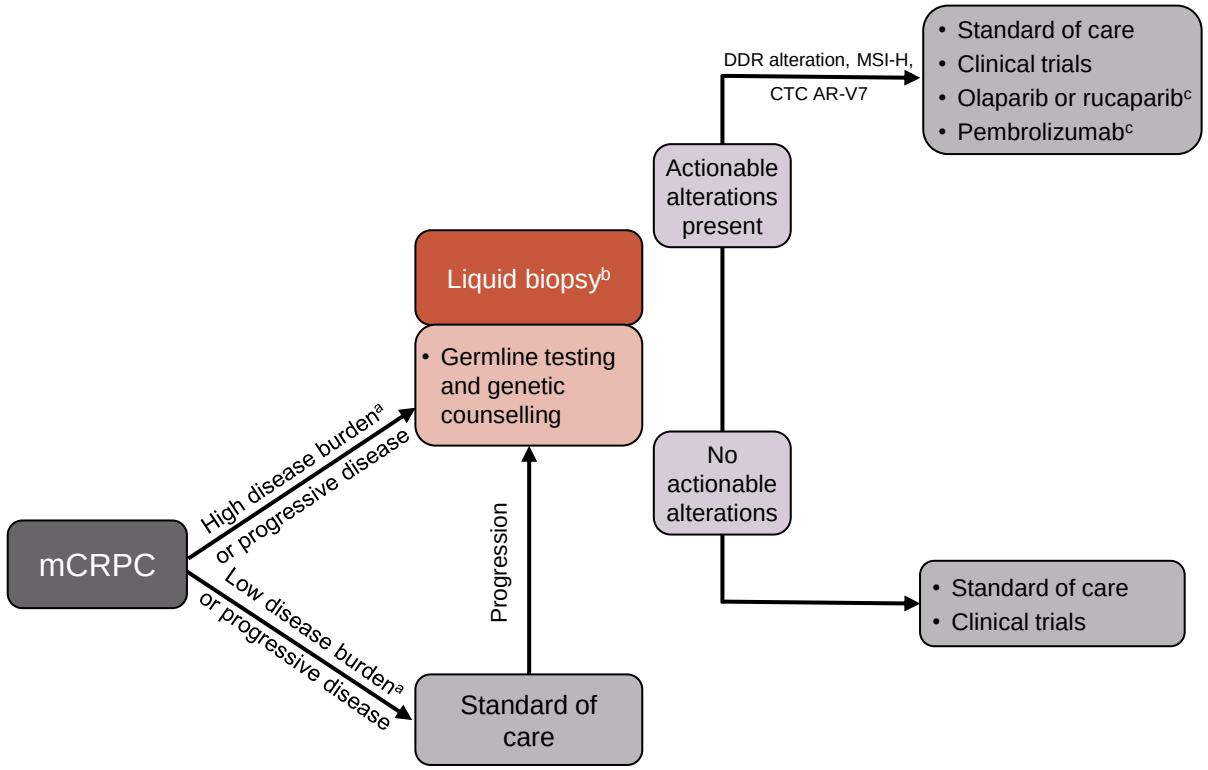
[a]Keep in mind that the steroids used with abiraterone are not supra-physiologic

CHF, congestive heart failure

THE RELEVANCE OF GENETIC TESTING

PRECISION MEDICINE TESTING: WHY?

1. **Inform treatment decisions to improve survival, clinical benefit, and chance of remission**
   - DNA: HRR mutation→PARPi,
   - MSI-high mCRPC→pembrolizumab
   - RNA: AR-V7 and AR therapy resistance
   - Histology/Phenotype:
     - small cell transformation→ platinums;
     - PSMA expression→Lu^{177}
2. **Inform hereditary cancer risk, family counselling and risk reduction**
   - DNA/RNA: *BRCA2, ATM*, Lynch Syndrome, HOXB13, other DNA repair enzymes
3. **Assess for clinical trial eligibility (research)**
   - PTEN loss, PI3K/Akt mutations, CDK12 mutation, PSMA expression, TP53/RB1 loss

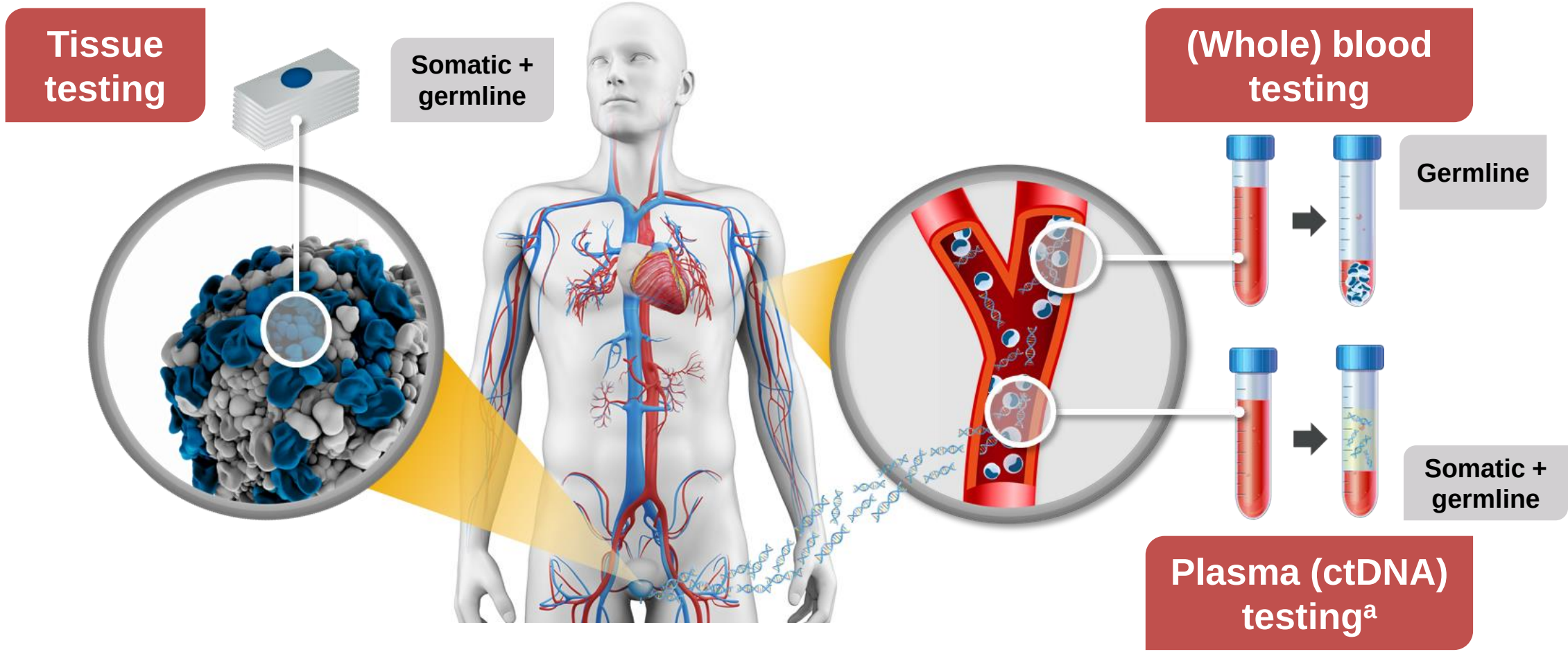


[a] High disease burden based on the presence of known adverse prognostic factors in men with mCRPC, such as visceral metastases, high volume of bone metastases, anaemia, rapid PSA kinetics, high circulating tumour cell count, high LDH or alkaline phosphatase, pain, and progression despite multiple prior therapies. [b] If tumour biopsy is not available/inadequate or remote. Liquid biopsy can include ctDNA and/or CTC biomarkers such as AR-V7 testing. [C]Timing of these treatments dependent on product labels

AR(-V7), androgen receptor variant 7; ARSi, androgen receptor signalling inhibitor; ATM, ataxia-telangiectasia gene; BRCA2, breast cancer gene 2; CDK12, cyclin dependent kinase 12; CTC, circulating tumour cell; ctDNA, circulating tumour DNA; DDR, DNA damage response; LDH, lactate dehydrogenase; Lu, lutetium; mCRPC, metastatic castration resistant prostate cancer; MSI, microsatellite instability; PARPi, poly-ADP ribose polymerase inhibitor; PI3K, phosphoinositide 3-kinase; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma tumour suppressor gene

Adapted from: Hawkey N, Armstrong A. Clin Cancer Res. 2021;27(11):2961-3

THERE ARE SEVERAL WAYS TO IDENTIFY *BRCA* / HRR MUTATIONS IN PROSTATE CANCER

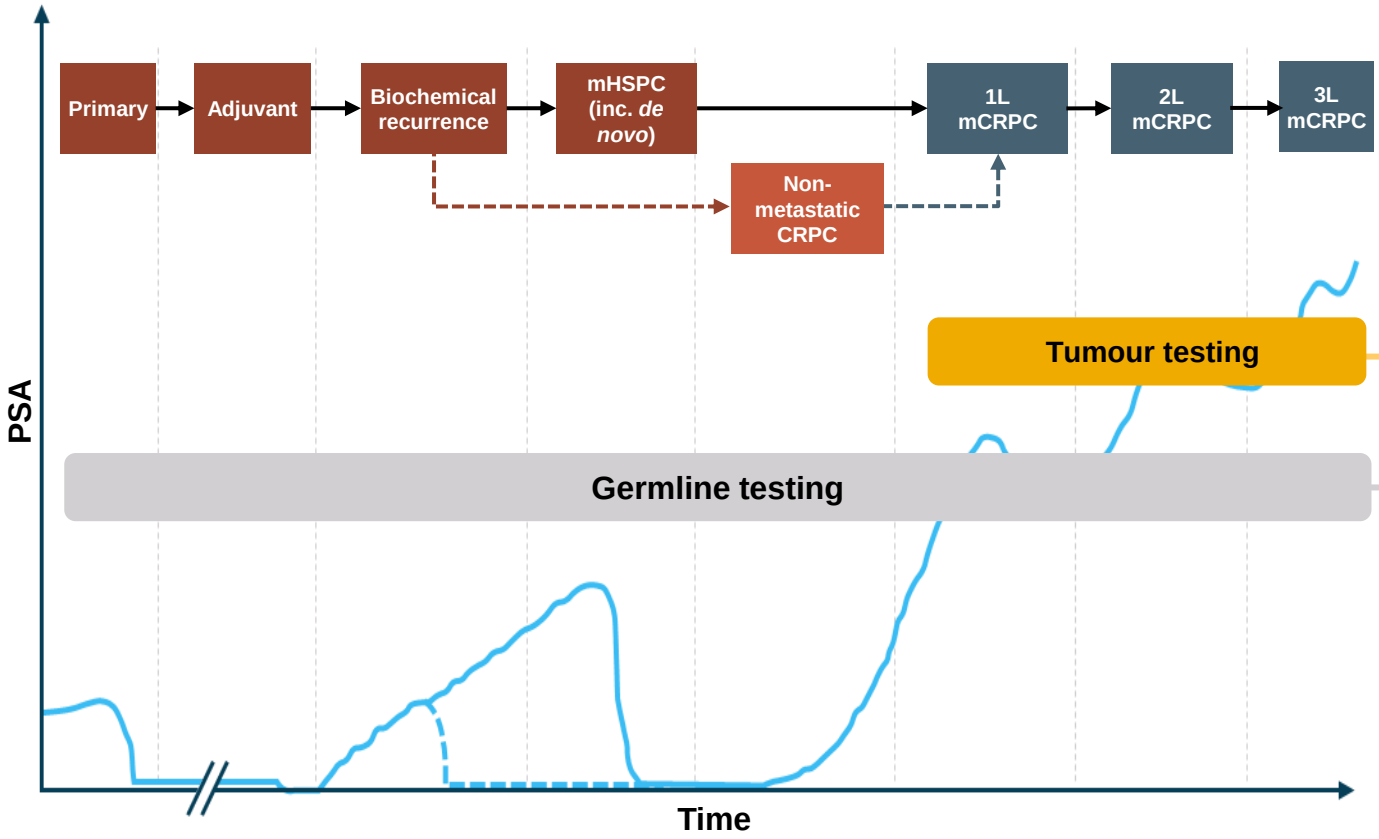


[a]Tumour cells shed DNA into the circulation through necrosis or apoptosis. ctDNA can be isolated from a plasma sample

BRCA, breast cancer gene; ctDNA, circulating tumour DNA; HRR, homologous recombination repair

1. Cheng HH, et al. J Natl Compr Canc Netw. 2019;17:515-21; 2. Haber DA, Velculescu VE. Cancer Discov. 2014;4:650-61

CONSIDERATIONS FOR WHEN TO TEST FOR *HRR*m ARE INCLUDED IN INTERNATIONAL GUIDELINES



Based on Scher et al, 2016

ESMO[1,2]

- Recommended for ***BRCA2*** and other **DDR genes** associated with cancer predisposition in patients with family history of cancer
- Should be considered in all patients with metastatic prostate cancer
- **Consider HRRm** and **MSI dMRR** testing in patients with **mCRPC**

EAU/EANM/ESTRO/ESUR/ISUP/SIOG[3]

- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age <60 years;
- Men with multiple family members diagnosed with csPCa at age <60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.
- **Consider HRRm** and **dMRR** testing in all patients with **mPC**

NCCN[4]

- Metastatic, regional (node positive), very-high-risk localised, or high-risk localised PCa
- Family history of certain cancers
- Known family history of familial cancer risk mutation
- Personal history of breast cancer
- Recommend **HRRm** testing in patients with **mPC.** Consider for regional PC
- Recommend testing for **MSI-H, dMMR for mCRPC.** Consider for regional or CSPC
- Consider **TMB** testing for **mCRPC**

AUA/SUO[5]

- Testing for **DDR, MSI dMMR, TMB** and other potential mutations **in mCRPC** patients
- Consider for **mHSPC patients**
- Testing for **DDR, MSI dMMR, TMB and other potential mutations in mCRPC** patients
- Consider for **mHSPC patients**

1L/2L/3L, first/second/third line; BRCA2, breast cancer gene 2; CRPC, castration-resistant prostate cancer; csPCa, clinically significant PCa; DDR, DNA damage repair; dMMR, mismatch repair damage; HRRm, homologous recombination repair mutation; mCRPC, metastatic CRPC; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; MSI, microsatellite; PCa, prostate cancer; PSA, prostate-specific antigen; TMB, tumour mutational burden

1. Parker C, et al. Annals of Oncology 2020; 31(9): 1119-34; 2. Fizazi K, et al. Annals of Oncology 2023 https://doi.org/10.1016/j.annonc.2023.02.015 ; 3. Mottet N, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf (d56bochluxqnz.cloudfront.net) Accessed May 2023); 4. National Comprehensive Cancer Network. Prostate Cancer (Version 4.2023). prostate.pdf (nccn.org). Accessed Nov 2023; 5. Lowrance W, et al. J Urol. 2023; 209(6):1082-1090; 6. Scher HI, et al. J Clin Oncol 2016; 34 (12): 1402-1418

PATIENT CASE

Patient: 66 year old
Presents with: mild fatigue
Medical history:

- Well-controlled hypertension and hyperlipidaemia
- +FH of breast cancer in sister, age 56

Germline *BRCA2* mutation detection which is pathogenic.
Consider patient for treatment with a PARPi

Initial Presentation

Biopsy: 9 / 12 cores; Adenocarcinoma Gleason 4+4
Staging: T3 by DRE and mpMRI, N1 M1b, high volume mHSPC
Imaging: bone and CT scan

- Metastases in hip, lumbar spine and ribs (five)
- Multiple pelvic & retroperitoneal lymph nodes between 1-3 cm

Current situation
Slight discomfort in lumbar spine
Imaging:

- Progression of bone and lymph node metastases
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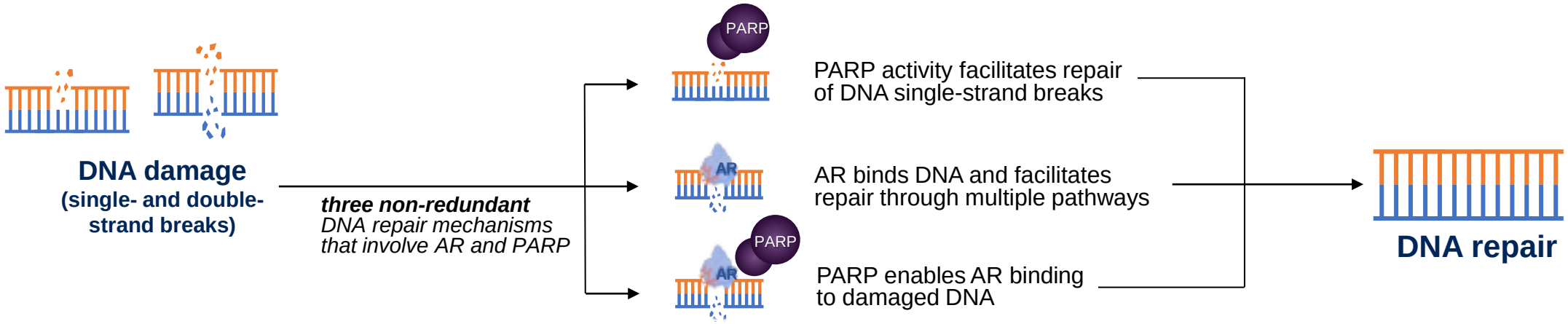
ADT, androgen deprivation therapy; CT, computed tomography; DRE, digital rectal exam; FH, family history; mHSPC, metastatic hormone sensitive prostate cancer; mpMRI, multi-parametric magnetic resonance imaging; PSA, prostate-specific antigen; T, N, M, tumour, nodes, metastasis

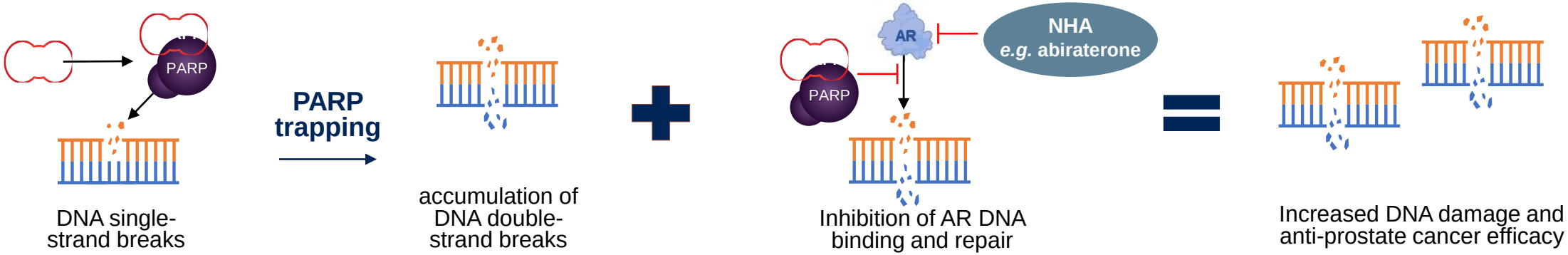
RATIONALE FOR COMBINING PARP AND AR INHIBITORS

PRECLINICAL RATIONALE FOR A COMBINED EFFECT OF PARP AND AR INHIBITION

PARP and AR are important for DNA repair in prostate cancer



Inhibition of PARP and AR in combination results in more DNA damage in AR-driven cancer cells



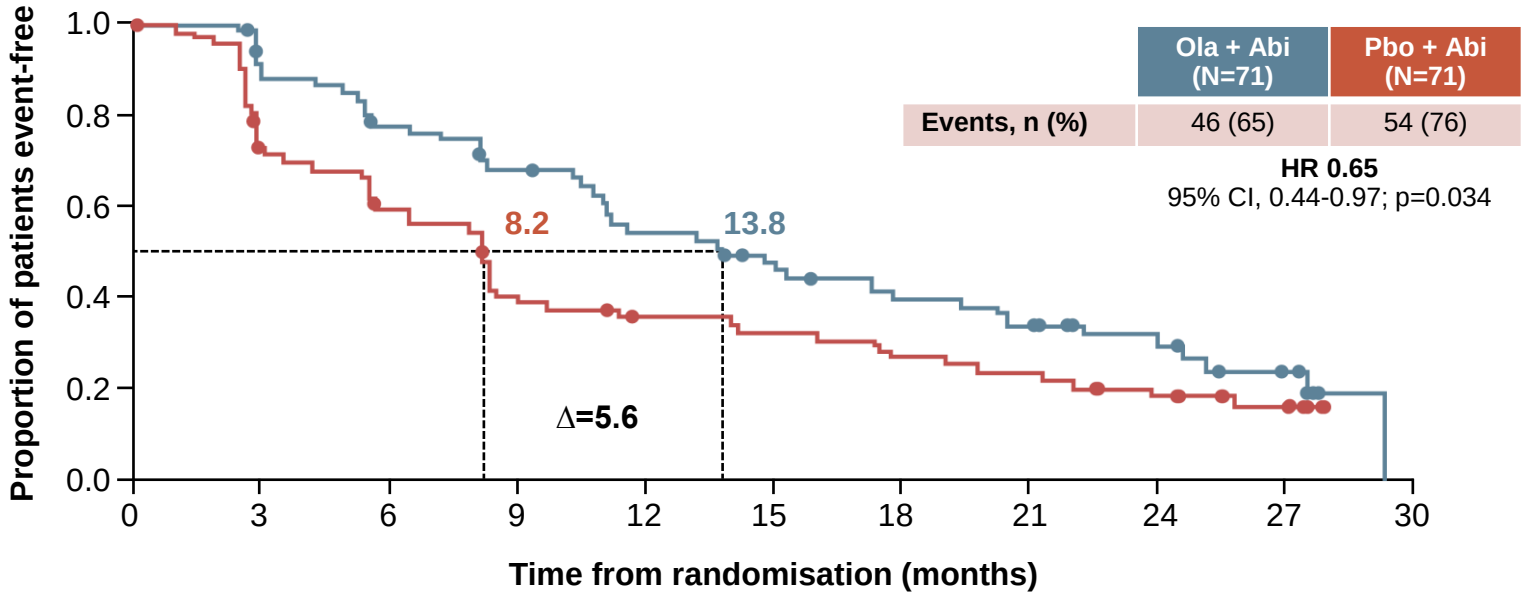
AR, androgen receptor; DNA, deoxyribonucleic acid; NHA, novel hormonal agent; PARP, poly(ADP-ribose) polymerase

1. Chaudhuri AR, et al. Nat Rev Mol Cell Biol. 2017;18:610-21; 2. Polkinghorn WR, et al. Cancer Discov. 2013;3:1245-53; 3. Lord CJ, et al. Science 2017;355:1152-8;
4. Pommier Y, et al. Sci Transl Med 2016;8:p362ps17; 5. Schiewer MJ, et al. Cancer Discov. 2012;2:1134-49; 6. Asim M, et al. Nat Commun. 2017;8:374;
7. Li L, et al. Sci Transl Med. 2017;10:10.1126/scisignal.aam7479

PROpel: CLINICAL RATIONALE FOR COMBINATION OF OLAPARIB WITH ABIRATERONE

- In a phase 2 trial (NCT01972217), **abiraterone + olaparib prolonged rPFS vs abiraterone + placebo in biomarker-unselected patients with mCRPC**, who had received docetaxel[1,2]

INVESTIGATOR-ASSESSED rPFS



Abi, abiraterone; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; Ola, olaparib; Pbo, placebo; rPFS, radiographic progression-free survival

1. Clarke N, et al. Lancet Oncol. 2018;19:975-86; 2. Carr TH, et al. Cancers. 2021;13:5830

KEY TRIAL DATA

PROpel: STUDY DESIGN

A GLOBAL, RANDOMISED, DOUBLE-BLIND PHASE 3 TRIAL

Key eligibility criteria

- First-line mCRPC
  - Docetaxel allowed at mCSPC stage
  - No prior abiraterone
  - Other NHAs allowed if stopped ≥12 months prior to enrolment
  - Ongoing ADT
  - ECOG PS 0 or 1

Stratification Factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mCSPC: yes vs no

NCT03732820

Randomise 1:1

Olaparib 300 mg BID + abiraterone 1,000 mg QD[a] (n=399)

Full dose of abiraterone and olaparib used

Placebo + abiraterone 1,000 mg QD[a] (n=397)

Full dose of abiraterone used

Primary endpoint:

- rPFS by investigator assessment (sensitivity analysis by BICR)

Key secondary endpoint:

- OS (alpha control)

Additional endpoints:

- TFST, ORR, PFS2
- HRR gene mutation[b] status (by tissue and ctDNA testing)
- Health-related quality of life
- Safety and tolerability

Analysis timeline:

DCO1: 30 July 21 rPFS (primary)

DCO2: 14 March 22 OS (interim)

DCO3: 12 October 22 OS (final pre-planned OS)

First patient randomized: Nov 2018; last patient randomised: Mar 2020

Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS; if the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS

[a] abiraterone used in combination with prednisone or prednisolone 5 mg BID; [b] HRR mutation, including 14-gene panel, using the FoundationOne®CDx test and FoundationOne®Liquid CDx test

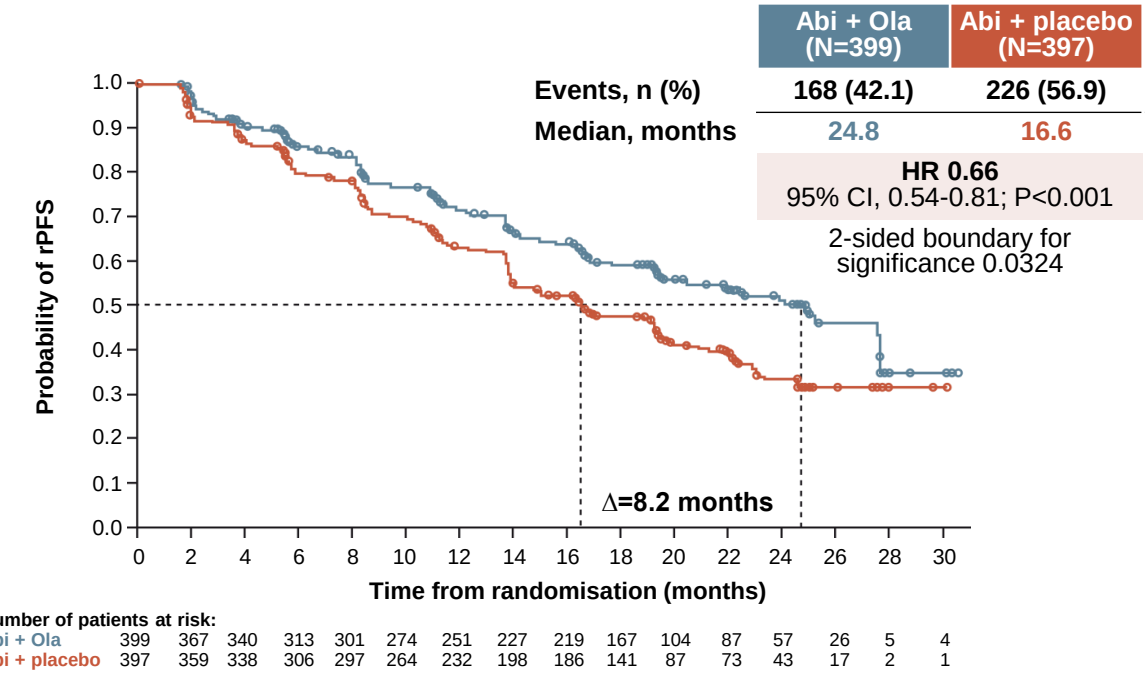
ADT, androgen-deprivation therapy; BID, twice daily; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NHA, novel hormonal agent; ORR, objective response rate; OS, overall survival; PFS2, time to second progression; QD, per day; rPFS, radiographic progression-free survival; TFST, time to first subsequent therapy or death

1. Clarke NW, et al. J Clin Oncol. 2019;37 Suppl: TPS340; 2. https://clinicaltrials.gov/ct2/show/NCT03732820; 3. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation)

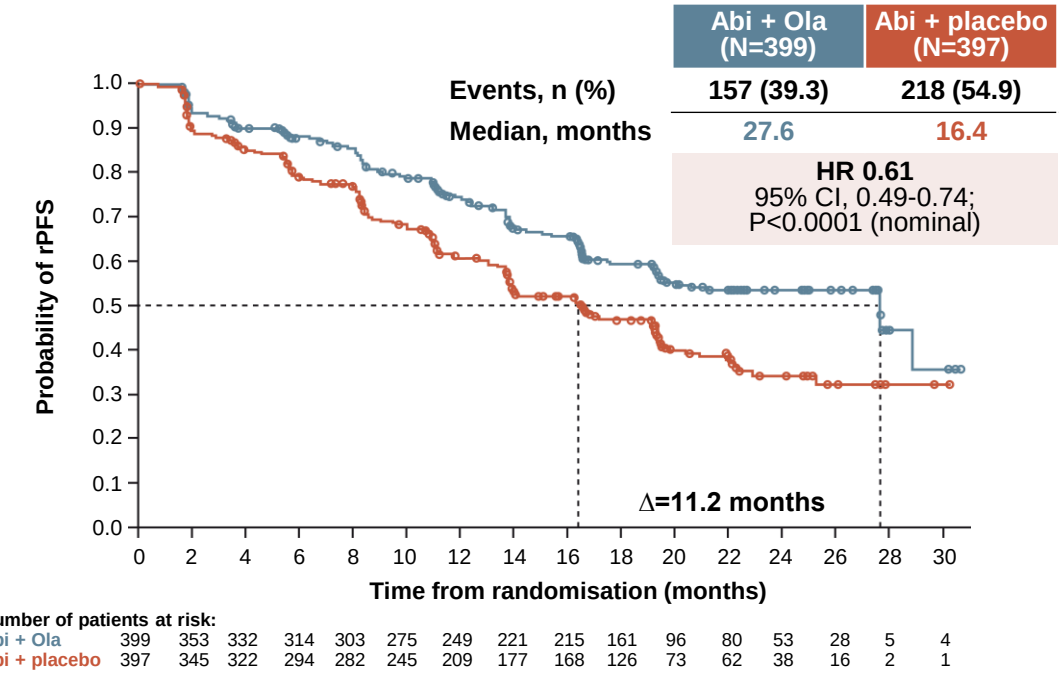
PROpel: PRIMARY rPFS RESULTS (DCO1)[1]

ABIRATERONE + OLAPARIB SIGNIFICANTLY PROLONGED rPFS VS ABIRATERONE + PLACEBO IN THE ITT POPULATION

rPFS by investigator assessment (INV)



rPFS by blinded independent central review (BICR)



DCO1: 30 July 2021

Median duration of follow-up for investigator-assessed rPFS for censored patients was 19.3 months in the abiraterone and olaparib arm, and 19.4 months in the abiraterone and placebo arm (19.3 and 19.2 months, respectively, for BICR)

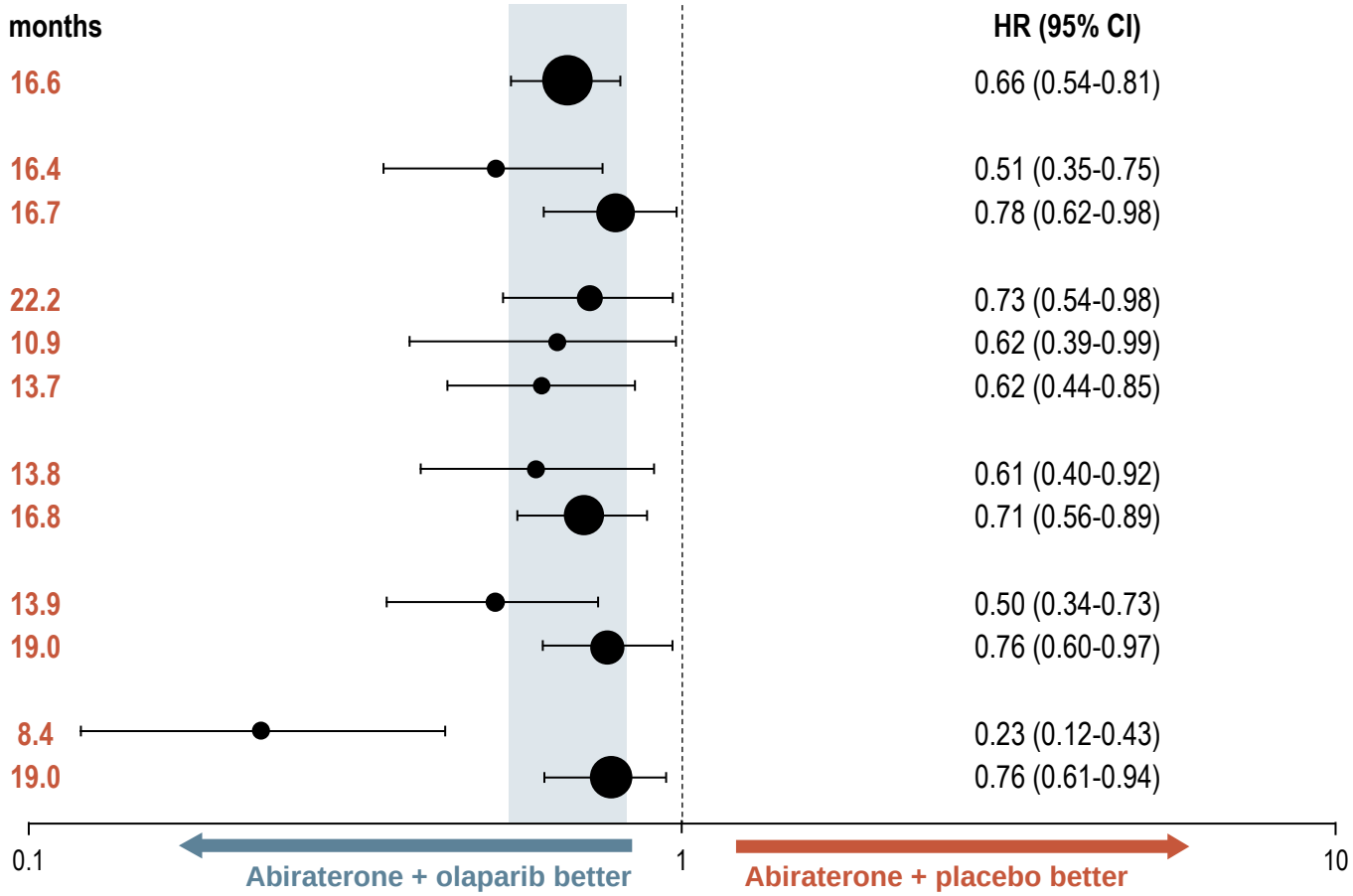
Abi, abiraterone; CI, confidence interval; DCO1, first data cut-off; HR, hazard ratio; ITT, intention-to-treat; Ola, olaparib; rPFS, radiographic progression-free survival

Clarke N, et al. NEJM Evidence 2022;1(9): doi: https://doi.org/10.1056/EVIDoa2200043; Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation)

PROpel: SUBGROUP ANALYSIS OF rPFS

AN rPFS BENEFIT WAS OBSERVED ACROSS ALL PATIENT SUBGROUPS, INCLUDING PATIENTS WITH AND WITHOUT HRRm (DCO1)

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54-0.81)
Age at randomisation, years				
<65	227	NR	16.4	0.51 (0.35-0.75)
≥65	569	22.0	16.7	0.78 (0.62-0.98)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54-0.98)
Visceral	105	13.7	10.9	0.62 (0.39-0.99)
Other	257	20.5	13.7	0.62 (0.44-0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40-0.92)
No	607	24.8	16.8	0.71 (0.56-0.89)
HRRm status[a]				
HRRm	226	NR	13.9	0.50 (0.34-0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60-0.97)
***BRCA*m status[a]**				
*BRCA*m	85	NR	8.4	0.23 (0.12-0.43)
*Non-BRCA*m	693	24.1	19.0	0.76 (0.61-0.94)



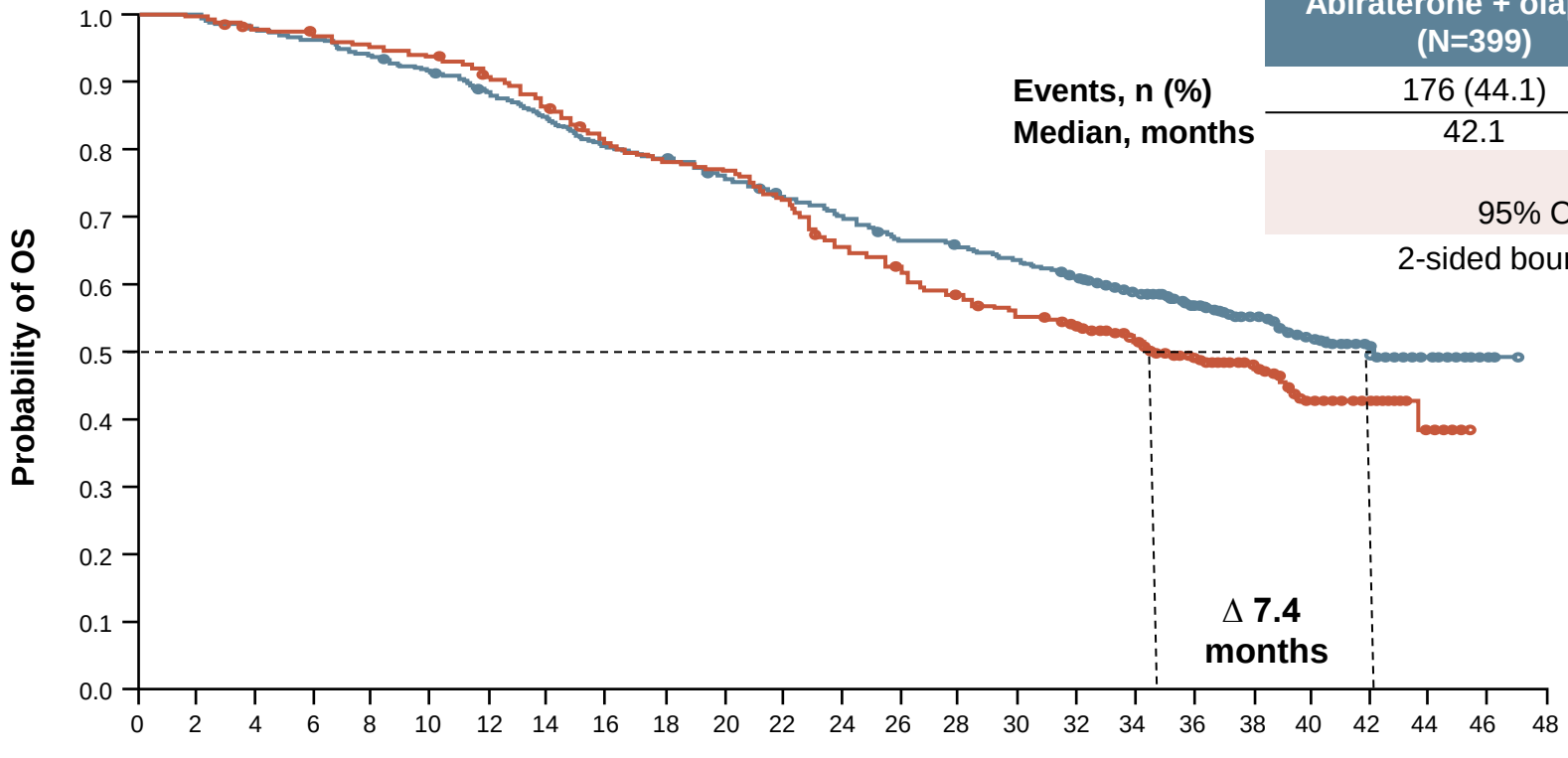
[a] The HRRm and BRCAm status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and/or plasma ctDNA HRRm tests. Aggregate HRRm and *BRCA*m subgroup analyses are post-hoc exploratory analyses. Results shown are by investigator assessment

*BRCA*m, breast cancer gene mutation; CI, confidence interval; ctDNA, circulating tumour DNA; DCO1, first data cut-off; HR, hazard ratio; HRRm, homologous recombination repair mutation; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; rPFS, radiographic progression-free survival

Saad F, et al. Ann Oncol. 2022;33 (suppl_7): S616-S652 (ESMO 2022 oral presentation); Clarke N, et al. NEJM Evidence 2022;1(9): doi: https://doi.org/10.1056/EVIDoa2200043

PROpel: OS AT FINAL ANALYSIS (DCO3)

IN THE ITT POPULATION, MEDIAN OS WAS >7 MONTHS LONGER IN THE ABIRATERONE + OLAPARIB ARM



	Abiraterone + olaparib (N=399)	Abiraterone + placebo (N=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7

HR 0.81
95% CI, 0.67-1.00; P=0.0544

2-sided boundary for significance 0.0377

47.9% maturity

Number of patients at risk:

Abiraterone + olaparib	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
Abiraterone + placebo	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.
Median (range) duration of follow-up for censored patients at DCO3 was 36.6 months (8.3–47.0) in the abiraterone + olaparib arm and 36.5 months (2.9–45.3) in the abiraterone + placebo arm.

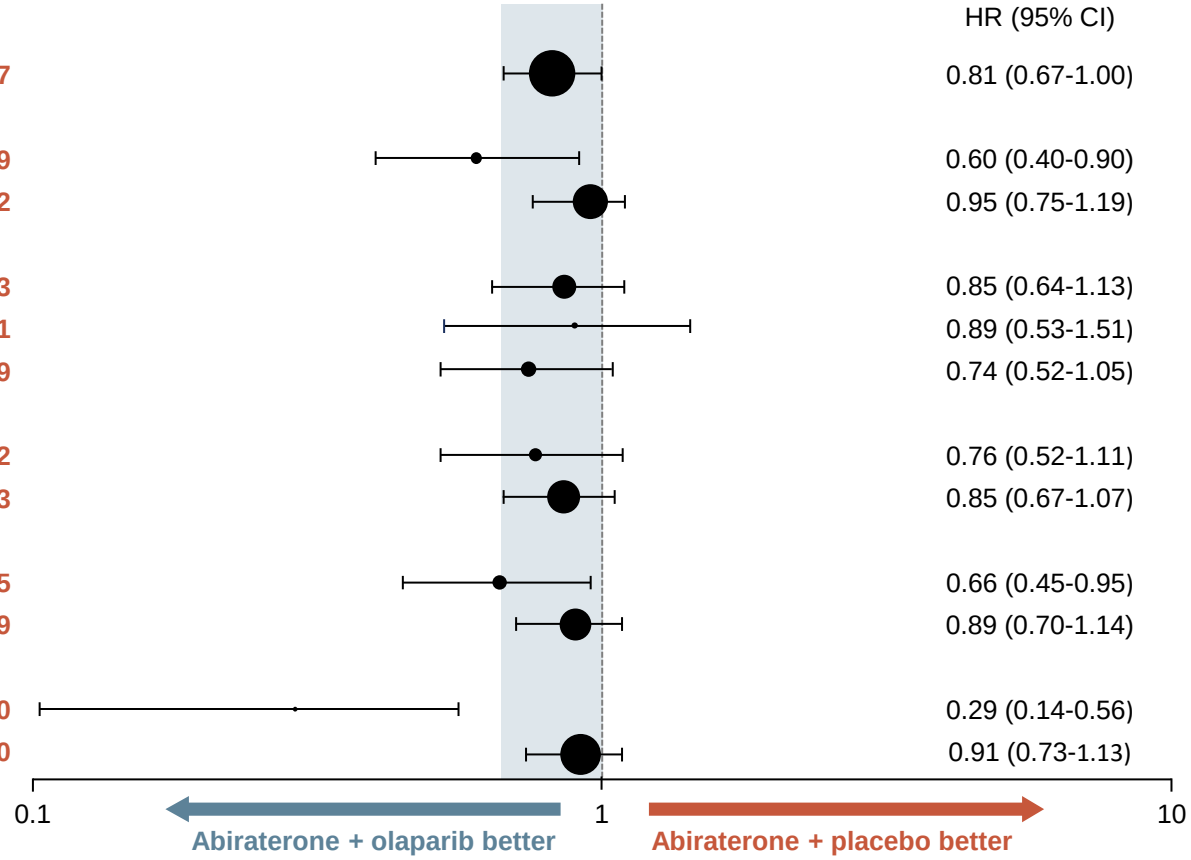
CI, confidence interval; DCO3, third data cut-off; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); Saad F, et al. Lancet Oncology 2023;24: 1094-1108

PROpel: OS IN SUBGROUPS (DCO3)

RESULTS ACROSS SUBGROUPS WERE GENERALLY CONSISTENT WITH THE ITT POPULATION

	Events/ Number of patients, n	Median OS, months		HR (95% CI)
All patients	381/796	42.1	34.7	0.81 (0.67-1.00)
Age at randomization, years				
<65	93/227	NR	33.9	0.60 (0.40-0.90)
≥65	288/569	35.9	36.2	0.95 (0.75-1.19)
Site of distant metastases				
Bone only	198/434	NR	38.3	0.85 (0.64-1.13)
Visceral	56/105	34.0	26.1	0.89 (0.53-1.51)
Other	127/257	40.4	31.9	0.74 (0.52-1.05)
Docetaxel treatment at mHSPC stage				
Yes	107/189	38.8	27.2	0.76 (0.52-1.11)
No	274/607	NR	38.3	0.85 (0.67-1.07)
HRRm status[a]				
HRRm	117/226	NR	28.5	0.66 (0.45-0.95)
Non-HRRm	255/552	42.1	38.9	0.89 (0.70-1.14)
*BRCA*m status[a]				
*BRCA*m	38/85	NR	23.0	0.29 (0.14-0.56)
*Non-BRCA*m	334/693	39.6	38.0	0.91 (0.73-1.13)



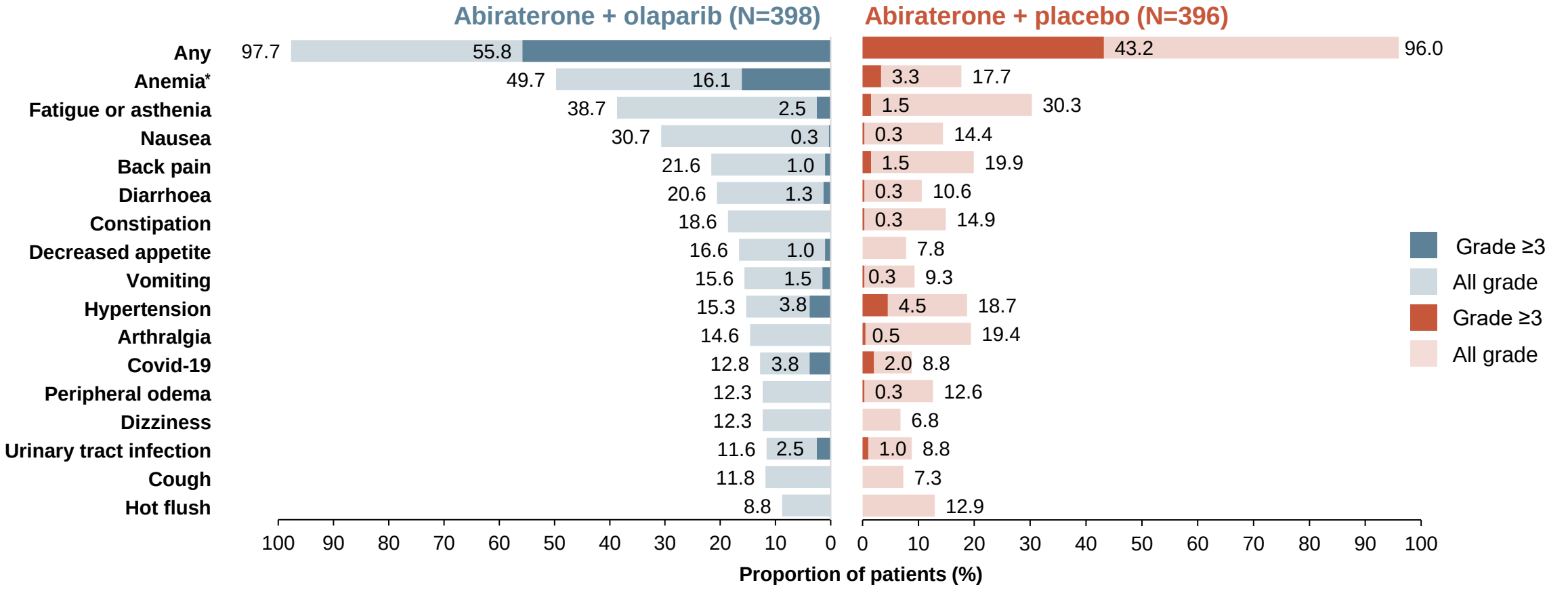
DCO3: 12 October 2022.
a HRRm and *BRCA*m status was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA tests. Aggregate subgroup analyses are post hoc and exploratory.

BRCAm, breast cancer gene mutation; CI, confidence interval; ctDNA, circulating tumour DNA; DCO3, third data cut-off; HR, hazard ratio; HRRm, homologous recombination repair mutation; ITT, intention-to-treat; mHSPC, metastatic hormone sensitive prostate cancer; NR, not reached; OS, overall survival

Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); Saad F, et al. Lancet Oncology 2023;24: 1094-1108

PROpel: MOST COMMON AEs (>10% PATIENTS; DCO3)

CONSISTENT WITH THE KNOWN SAFETY PROFILES OF ABIRATERONE AND OLAPARIB



Pulmonary embolism (7.3% vs 2.3%) and cardiac failure events (1.8% vs 1.8%) were similar to earlier data cut-offs

DCO3: 12 October 2022. Safety was assessed through the reporting of AEs according to NCI CTCAE v4.03 and laboratory assessments. *Grouped term 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.

AEs, adverse events; DCO3, third data cut-off

Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); Saad F, et al. Lancet Oncology 2023;24: 1094-1108

TALAPRO-2: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Patient population:
- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors:
- Prior abiraterone[a] or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)

R 1:1

(N=805)

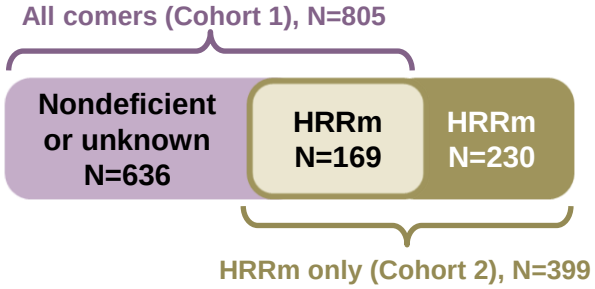
Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily

(n=402)

(*0.35 mg daily if moderate renal impairment)

Placebo + enzalutamide 160 mg, once daily

(n=403)



Primary endpoint:
Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

Key secondary endpoint:
- Overall survival (alpha protected)

Other secondary endpoints:
- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment[b]
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cut-off: August 16, 2022)

Samples prospectively assessed for HRR gene alterations (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MOH1*, *MRE11A*, *CDK12*) using FoundationOne®CDx and/or FoundationOne®Liquid CDx

Results are repoprted only from the all-comers cohort of men unselected for HRR gene alterations

To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in the hierarchical stepwise procedure to preserve the overall type I error

[a] Two patients in each treatment arm received prior orteronel

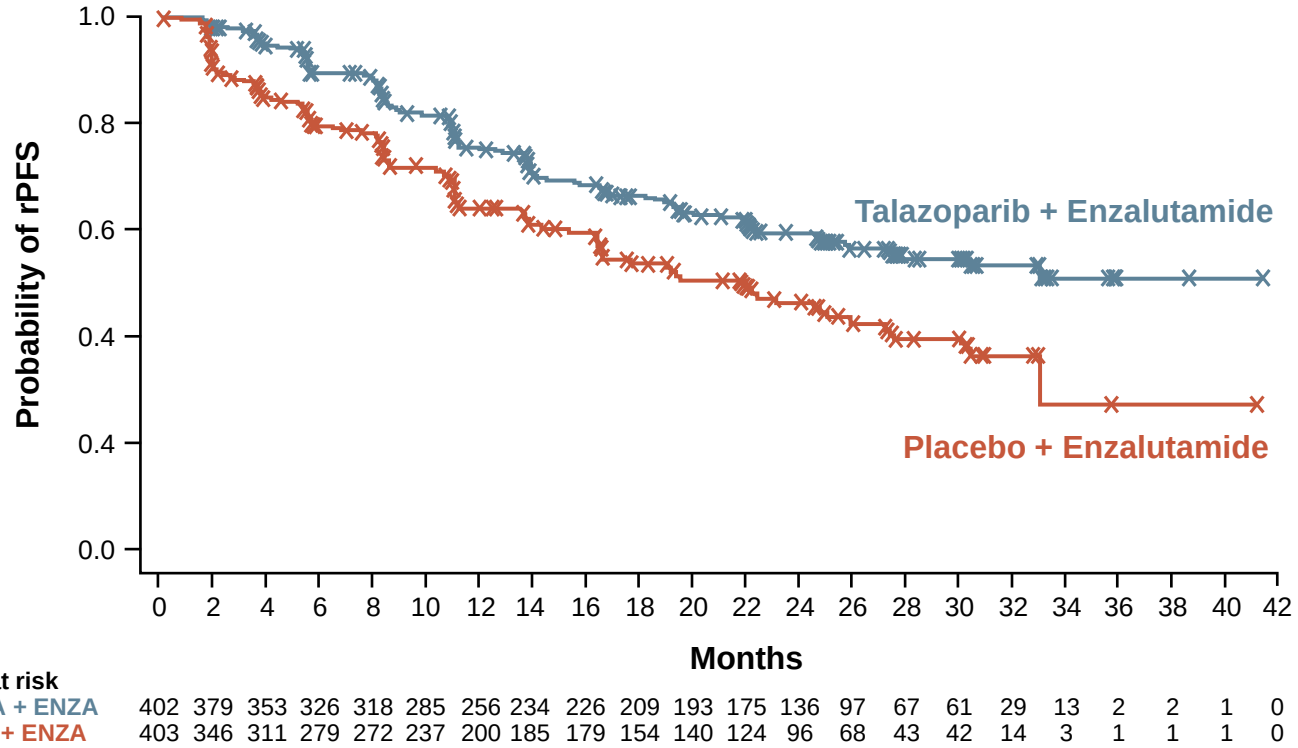
[b] Time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first

ATM, ataxia-telangiectasia gene; ATR, ataxia telangiectasia and Rad3 related; BICR, blinded independent central review; BRCA, breast cancer gene; CDK12, cyclin dependent kinase 12; CHEK2, checkpoint kinase 2; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; HRRm, HRR mutation; NBN, nibrin; ORR, objective response rate; PALB2, partner and localizer of BRCA2; PFS2, time to second progression; rPFS, radiographic progression-free survival

Agarwal N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation)

TALAPRO-2 PRIMARY ENDPOINT: rPFS BY BICR

TREATMENT WITH TALAZOPARIB PLUS ENZALUTAMIDE RESULTED IN A 37% REDUCED RISK OF PROGRESSION OR DEATH



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	NR (27.5-NR)	21.9 (16.6-25.1)
HR 0.63 95% CI, 0.51-0.78; P<0.001		

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50-0.81); P<0.001

Stratified hazard ratios (HRs) and 2-sided p values are reported throughout this presentation unless otherwise stated

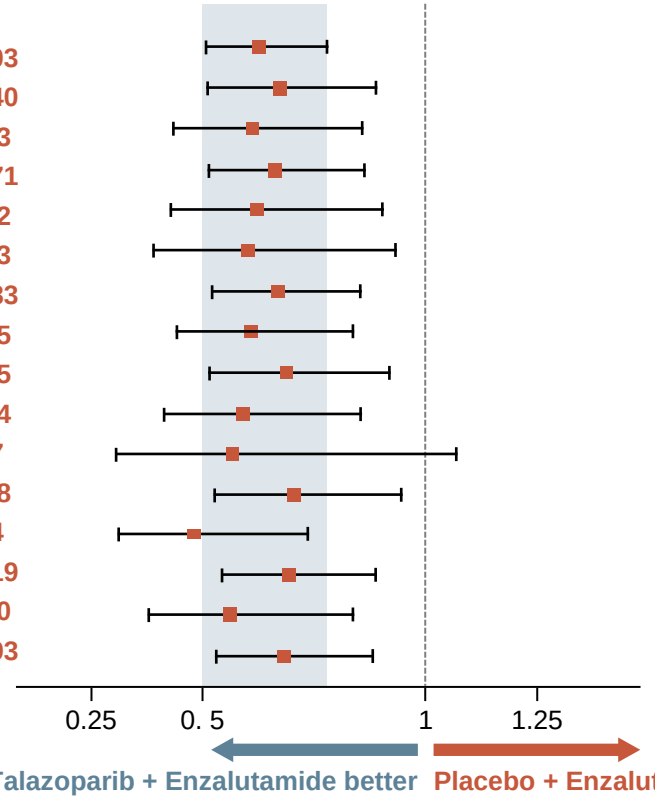
BICR, blinded independent central review; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; rPFS, radiographic progression-free survival; TALA, talazoparib

Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

TALAPRO-2: SUBGROUP ANALYSIS OF rPFS BY BICR

A CONSISTENT TREATMENT EFFECT WITH TALAZOPARIB PLUS ENZALUTAMIDE WAS SEEN IN PRESPECIFIED SUBGROUPS

Subgroup		Talazoparib + Enzalutamide Events/N	Placebo + Enzalutamide Events/N	HR (95% CI)	2-sided p value
Overall		151/402	191/403	0.63 (0.51-0.78)	<0.001
Age, years	≥70	93/240	109/240	0.67 (0.51-0.89)	0.005
	<70	58/162	82/163	0.61 (0.44-0.86)	0.004
ECOG PS	0	100/259	130/271	0.67 (0.51-0.86)	0.002
	1	51/143	61/132	0.62 (0.43-0.90)	0.01
Gleason score	<8	34/117	49/113	0.60 (0.39-0.93)	0.02
	≥8	115/281	137/283	0.67 (0.52-0.86)	0.001
Stage at diagnosis	M0	64/172	92/185	0.61 (0.44-0.84)	0.002
	M1	86/226	98/215	0.69 (0.51-0.92)	0.01
Site of metastasis	Bone only	52/169	63/154	0.59 (0.41-0.86)	0.005
	Soft tissue only	15/48	29/57	0.57 (0.30-1.07)	0.07
	Bone and soft tissue	82/180	98/188	0.71 (0.53-0.95)	0.02
HRR status	Deficient	37/85	49/84	0.48 (0.31-0.74)	<0.001
	Non-deficient/unknown	114/317	142/319	0.69 (0.54-0.89)	0.004
Prior abiraterone[a] or docetaxel	Yes	42/109	58/110	0.56 (0.38-0.83)	0.004
	No	109/293	133/293	0.68 (0.53-0.88)	0.003



The HR for all patients was based on a Cox model stratified by the randomisation stratification factors. For all subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate

[a] Includes two patients in each treatment arm who received prior orteronel

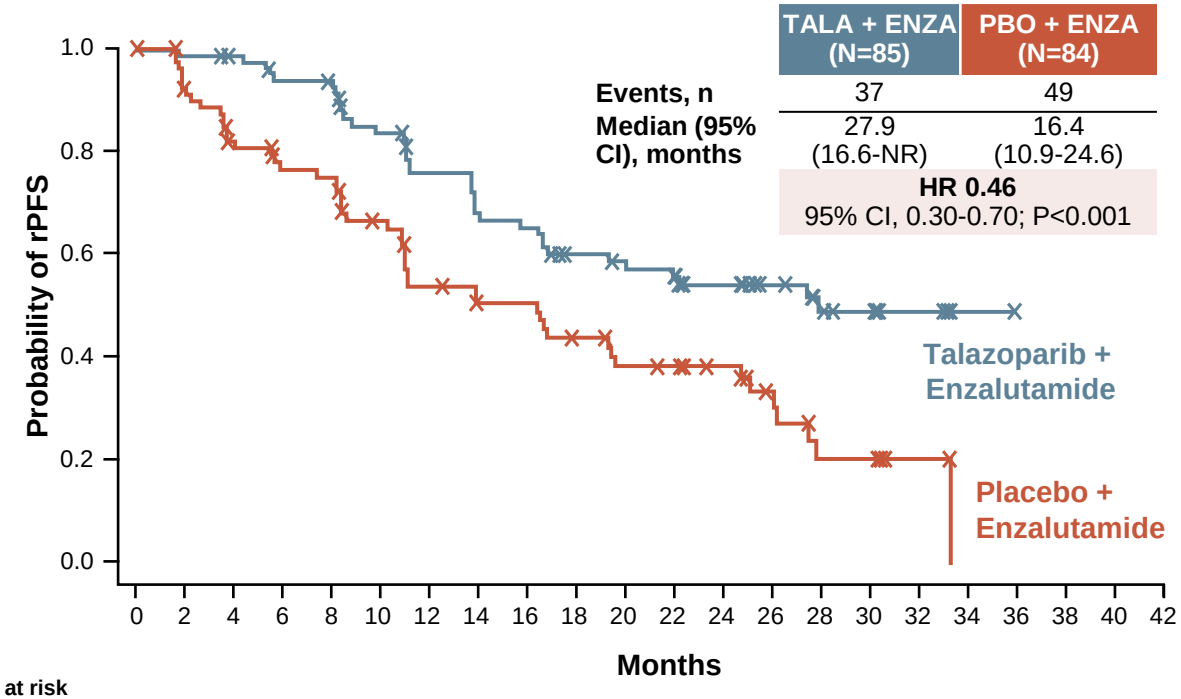
BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HRR, homologous recombination repair; rPFS, radiographic progression-free survival

Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

TALAPRO-2: rPFS BY BICR BY HRR STATUS

A CLINICALLY MEANINGFUL REDUCTION IN RISK OF PROGRESSION OR DEATH WAS SEEN REGARDLESS OF HRR STATUS

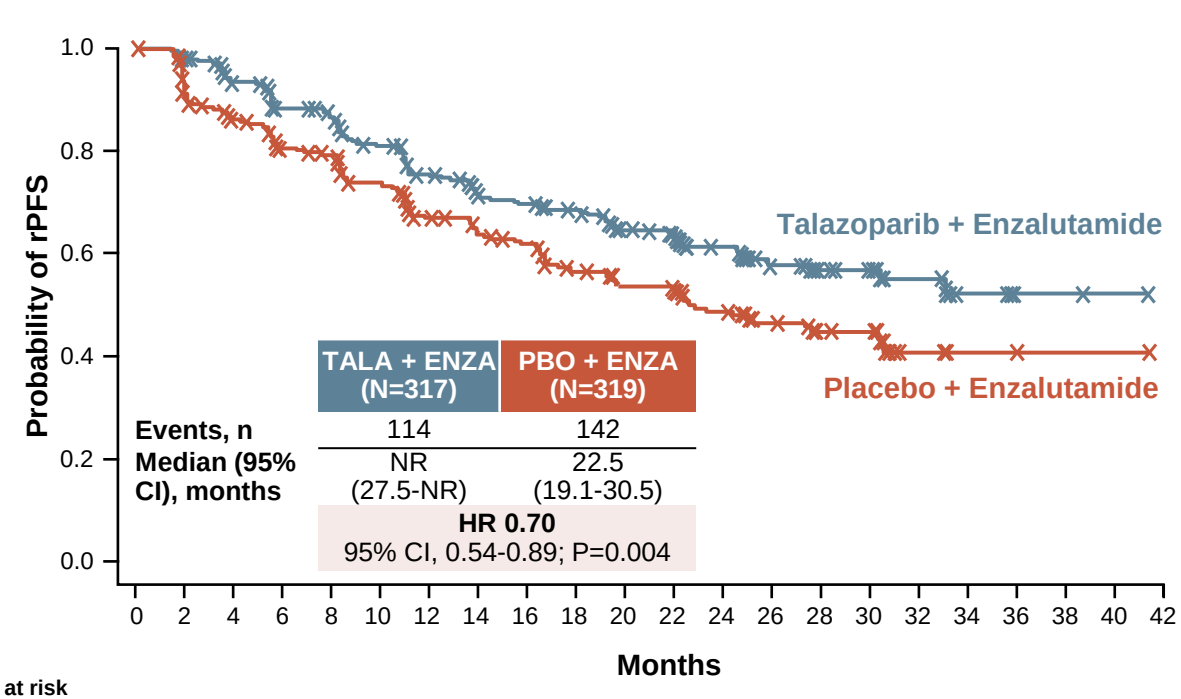
HRR-deficient



No. at risk

TALA + ENZA	85	83	81	76	75	65	57	51	49	42	40	37	30	23	17	15	6	3	0	0	0	0
PBO + ENZA	84	72	61	55	54	43	34	30	30	25	21	20	17	11	6	6	2	0	0	0	0	0

HRR-nondeficient or unknown



No. at risk

TALA + ENZA	317	296	272	250	243	220	199	183	177	167	153	138	106	74	50	46	23	10	2	2	1	0
PBO + ENZA	319	274	250	224	218	194	166	155	149	129	119	104	79	57	37	36	12	3	1	1	1	0

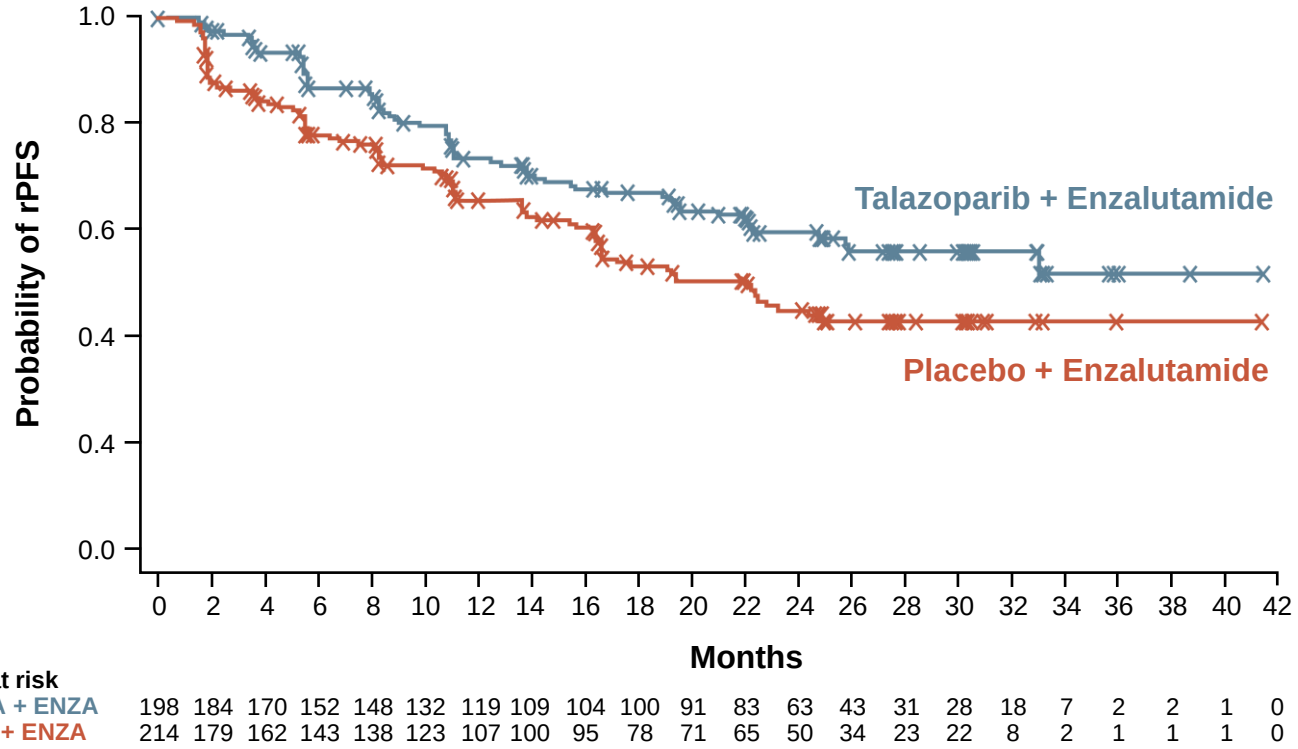
HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor

BICR, blinded independent central review; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; NR, not reached; PBO, placebo; rPFS, radiographic progression-free survival; TALA, talazoparib

Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

TALAPRO-2: rPFS BY BICR IN HRR-NONDEFICIENT BY PROSPECTIVE TUMOUR TISSUE TESTING

34% RISK REDUCTION IN PATIENTS WITHOUT HRR GENE ALTERATIONS DETECTED BY PROSPECTIVE TUMOUR TISSUE TESTING



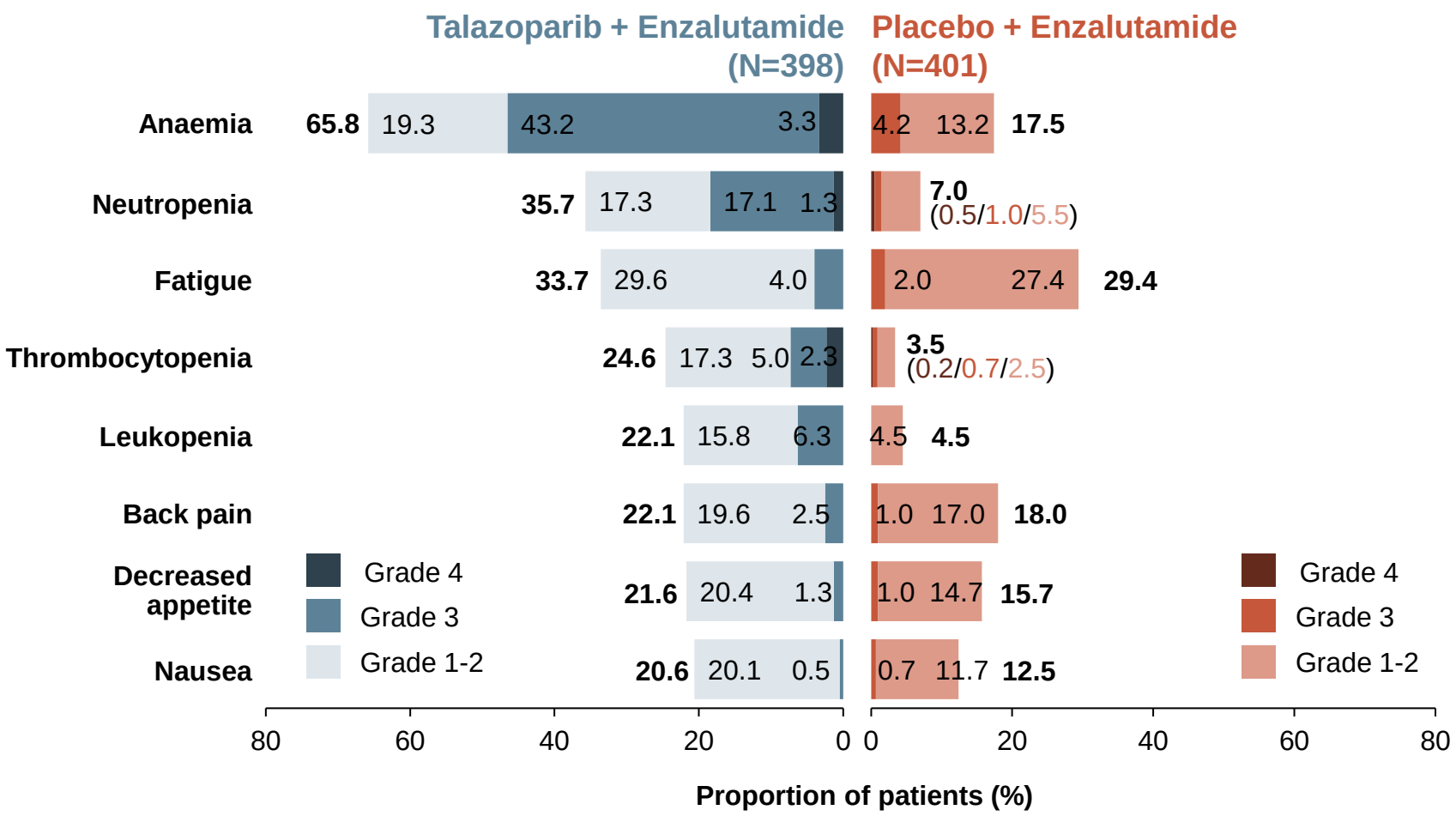
	TALA + ENZA (N=198)	PBO + ENZA (N=214)
Events, n	70	96
Median (95% CI), months	NR (25.8-NR)	22.1 (16.6-NR)
	HR 0.66 95% CI, 0.49-0.91; P=0.009	

Exploratory endpoint analysis based on HRR gene alteration status derived from the clinical database (unstratified analysis)

BICR, blinded independent central review; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; NR, not reached; PBO, placebo; rPFS, radiographic progression-free survival; TALA, talazoparib

Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

TALAPRO-2: MOST COMMON ALL-CAUSE TEAEs



In the talazoparib arm:

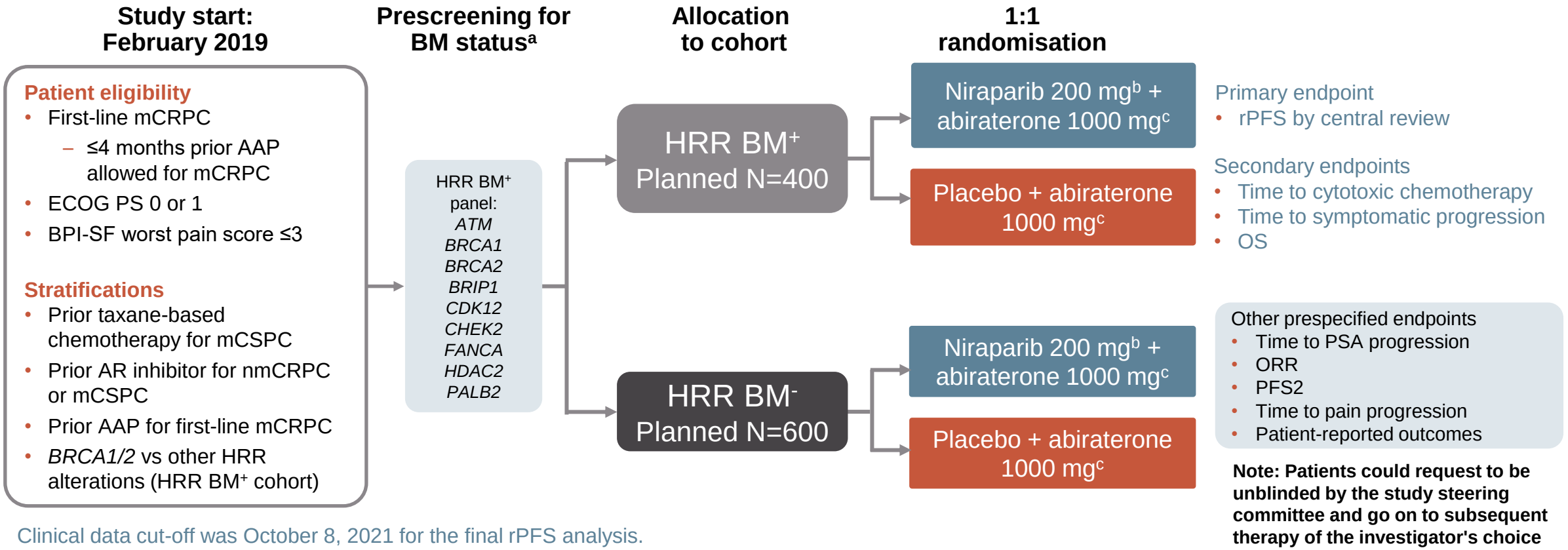
- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anaemia (43.2%)
  - Neutropenia (15.1%)
  - Thrombocytopenia (5.5%)
- 49.0% had grade 1-2 anaemia at baseline
- Grade 3-4 anaemia
  - Median time to onset was 3.3 months
  - Reported in 46.5% of men
- 8.3% discontinued talazoparib due to anaemia
- The median relative dose intensity of talazoparib remained >80%

TEAEs, treatment emergent adverse events

Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

MAGNITUDE: RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

BIOMARKER COHORTS SELECTED PRIOR TO RANDOMISATION DESIGNED TO TEST HRR BM$^+$ AND HRR BM$^-$



Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

[a] Tissue and plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (ctDNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel
[b] Dose of niraparib used was lower than the usual monotherapy dose as a result of data obtained from the BEDIVERE trial
[c] Abiraterone given in combination with prednisone or prednisolone 5 mg BID

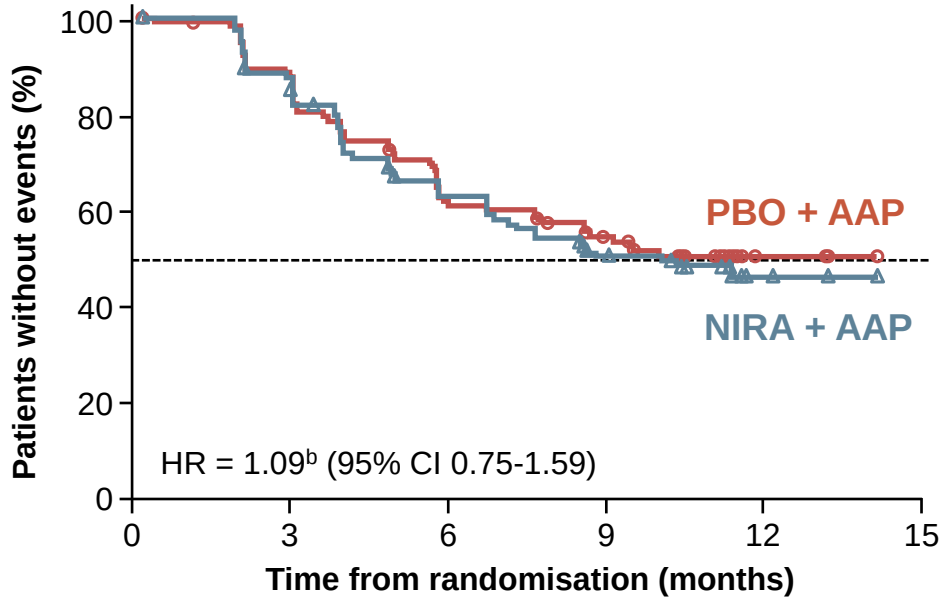
AAP, abiraterone acetate and prednisone/prednisolone; AR, androgen receptor; ATM, ataxia-telangiectasia gene; BID, twice daily; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase 2; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HDAC2, histone deacetylase 2; HRR, homologous recombination repair; mCRPC, metastatic CRPC; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic CRPC; ORR, overall response rate; OS, overall survival; PALB2, partner and localiser of BRCA2; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation); https://clinicaltrials.gov/ct2/show/NCT03748641

MAGNITUDE HRR BM$^-$: PRESPECIFIED EARLY FUTILITY ANALYSIS

NO BENEFIT OF NIRA + AAP IN HRR BM$^-$ PATIENTS

Composite progression endpoint[a]



No. at risk						
NIRA + AAP	117	92	68	51	4	0
PBO + AAP	116	91	68	56	8	0

- Additional grade 3/4 toxicity was observed using NIRA + APP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM$^-$ mCRPC, the IDMC recommend stopping enrolment in this cohort

[a] Composite endpoint: rPFS or PSA progression, whichever occurred first
[b] Breakdown of composite endpoint events: 83 PSA events (HR = 1.03, 95% CI 0.67-1.59); 65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

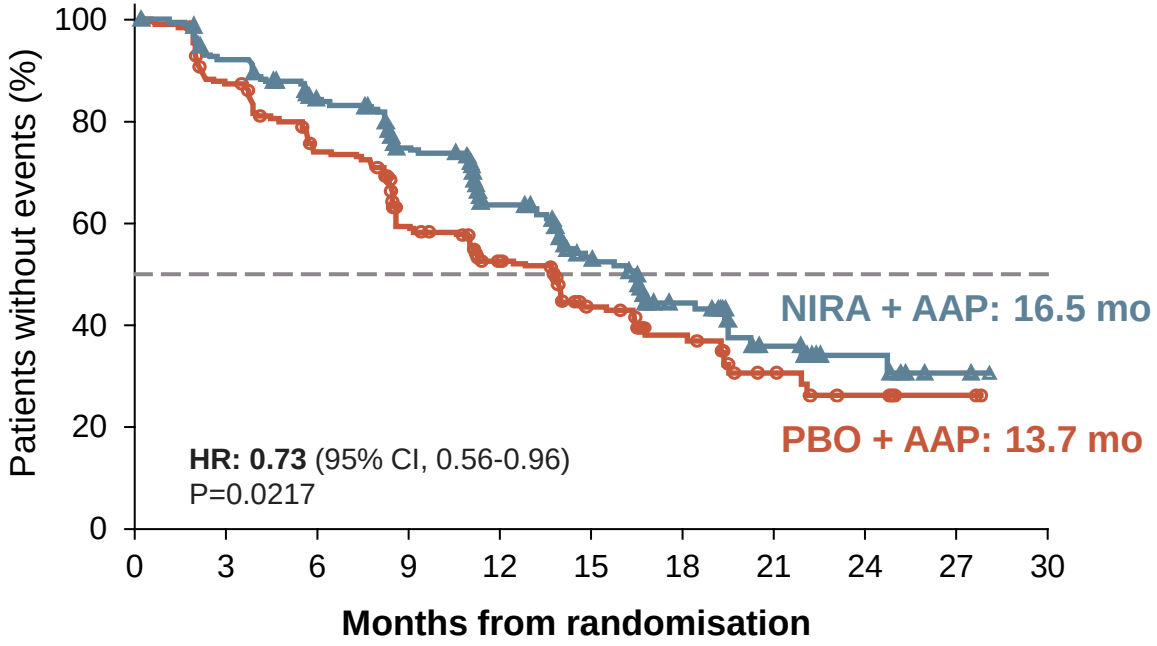
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate antigen; rPFS, radiographic progression free survival

Chi K, et al. J Clin Oncol 2022; 40, (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE: PRIMARY ENDPOINT rPFS (BICR)

rPFS WAS 2.8 MONTHS GREATER FOR ABIRATERONE + NIRAPARIB VERSUS ABIRATERONE + PLACEBO in HRR BM+ PATIENTS

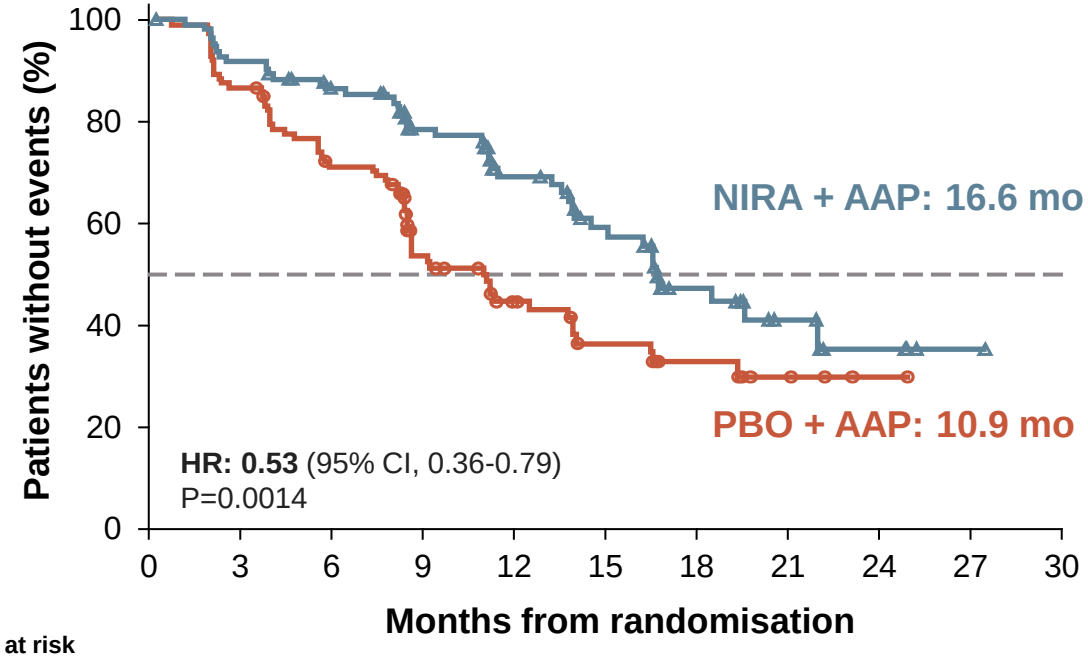
All HRR BM+ patients



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

Median follow-up 18.6 months

BRCA1/2-Mutated patients



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

Median follow-up 16.7 months

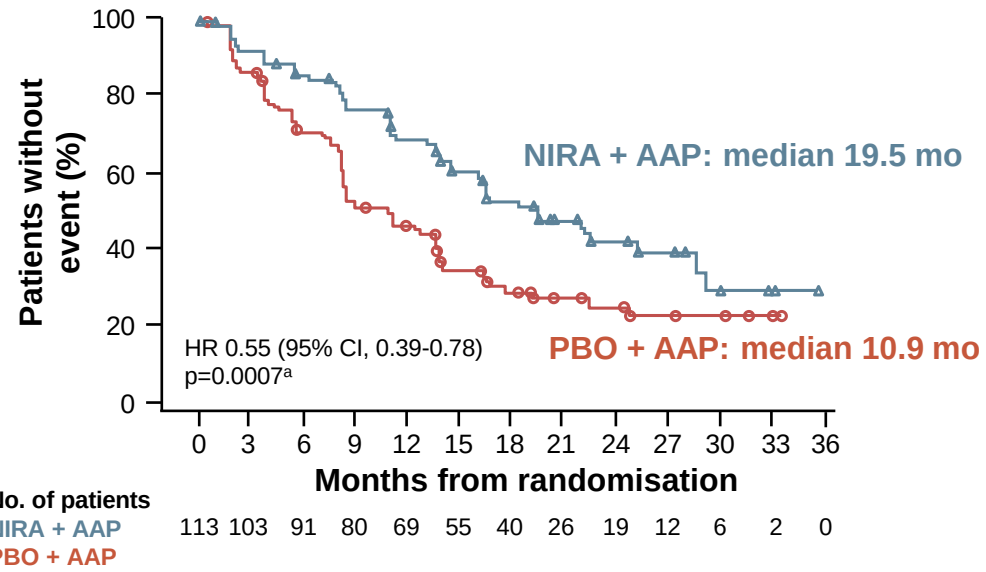
AAP, abiraterone acetate + prednisone/prednisolone; BICR, blinded independent central review; BM, biomarker; BRCA1/2, breast cancer gene 1/2; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE *BRCA* PATIENTS: NIRA + AAP IMPROVED rPFS AND TIME TO SYMPTOMATIC PROGRESSION IN THE *BRCA* SUBGROUP

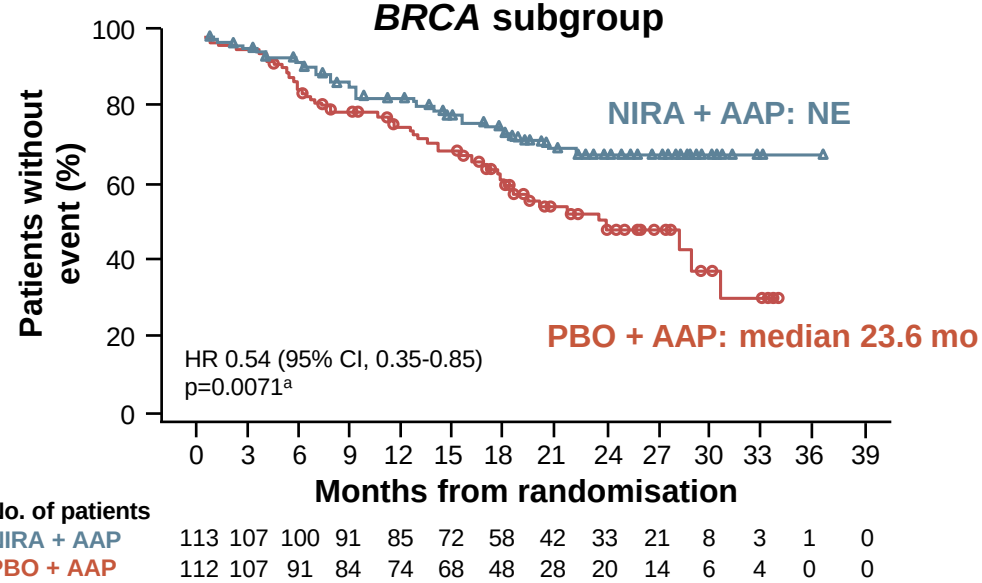
With additional 8 months follow-up

rPFS by central review in the *BRCA* subgroup



- rPFS by central review demonstrated a consistent and clinically meaningful treatment effect favouring niraparib + AAP, with a median rPFS of 19.5 months at IA2 compared with 10.9 months for placebo + AAP
- **Investigator Assessed HR (95% CI) 0.46 (0.32-0.67)**

Time to symptomatic progression in the *BRCA* subgroup



- A strong improvement in time to symptomatic progression (TSP) was observed in patients who received niraparib + AAP compared with placebo + AAP

NIRA + AAP reduced the risk of progression or death by 45% in patients with *BRCA* mutations, extending rPFS by >8 months

Results are descriptive. No formal statistical testing was performed. Consistent results were observed for rPFS assessed by investigator for both the *BRCA* subgroup and HRR+ population

[a] Nominal P value

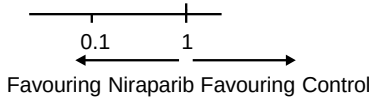
AAP, abiraterone acetate with prednisone; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRR+, homologous recombination repair positive; IA2, second interim analysis; mo, months; NE, not estimable; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

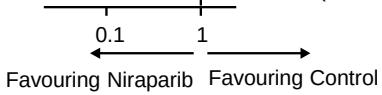
Efstathiou E, et al. J Clin Oncol 41, 2023 (suppl 6; abstr 170) (ASCO GU 2023 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE ALL HRR BM+: SUBGROUP ANALYSIS OF rPFS

rPFS BENEFIT WAS SIMILAR ACROSS ALL PATIENT SUBGROUPS

Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
All HRR+ patients	All	16.5	13.7	0.74 (0.57–0.97)	100/212	117/211
Age group	<65	13.9	13.9	1.01 (0.61–1.66)	32/61	30/62
	≥65-74	19.4	13.6	0.58 (0.38–0.89)	34/88	57/100
	≥75	16.4	10.9	0.76 (0.46–1.24)	34/63	30/49
Race group	Asian	22.0	10.9	0.48 (0.22–1.05)	9/29	22/41
	White	14.4	13.8	0.83 (0.61–1.13)	82/160	83/153
	Other	18.4	9.0	0.47 (0.20–1.14)	9/23	12/17
Baseline ECOG performance status	0	19.5	13.9	0.65 (0.46–0.92)	53/130	76/146
	1	13.1	10.5	0.84 (0.55–1.28)	47/82	41/65
Baseline BPI-SF#3 Score	0	16.7	16.8	0.75 (0.51–1.12)	47/108	53/103
	1 to 3	13.9	10.5	0.78 (0.52–1.17)	46/88	50/86
	>3	13.7	13.7	0.68 (0.26–1.79)	6/14	14/22
Region	Asia Pacific	19.5	13.8	0.64 (0.35–1.17)	17/43	27/52
	Europe	14.4	13.7	0.82 (0.58–1.14)	68/128	71/120
	North and South America	16.6	16.4	0.60 (0.30–1.18)	15/41	19/39
Past taxane–based chemotherapy	Yes	13.4	10.9	0.89 (0.48–1.66)	20/40	21/41
	No	16.6	13.8	0.71 (0.53–0.96)	80/172	96/170
Past androgen receptor-targeted therapy[a]	Yes	NE	4.3	0.19 (0.03–1.23)	2/8	3/4
	No	16.5	13.8	0.76 (0.58-1.00)	98/204	114/207
Prior AAP use[b]	Yes	13.9	14.6	0.95 (0.54–1.67)	23/47	26/45
	No	16.7	12.7	0.71 (0.52–0.96)	77/165	91/166
Presence of visceral metastases	Yes	11.0	8.1	1.03 (0.60–1.77)	34/51	22/39
	No	19.4	13.8	0.64 (0.47–0.87)	66/161	95/172
Bone only metastasis at entry	Yes	19.4	15.4	0.72 (0.45–1.14)	32/78	41/85
	No	14.8	10.9	0.73 (0.53–1.02)	68/134	76/126
Number of bone lesions at baseline	≤10	19.4	15.4	0.76 (0.53–1.10)	54/127	65/128
	>10	13.8	8.4	0.69 (0.47–1.04)	46/85	52/83
Baseline PSA above median	Yes	15.7	8.3	0.58 (0.40–0.82)	56/110	66/101
	No	16.7	18.2	0.93 (0.62–1.40)	44/102	51/110
Gene mutation type	BRCA	16.6	10.9	0.55 (0.38–0.81)	45/113	64/112
	Other HRR	14.8	16.4	0.99 (0.68–1.45)	55/99	53/99





[a] Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide

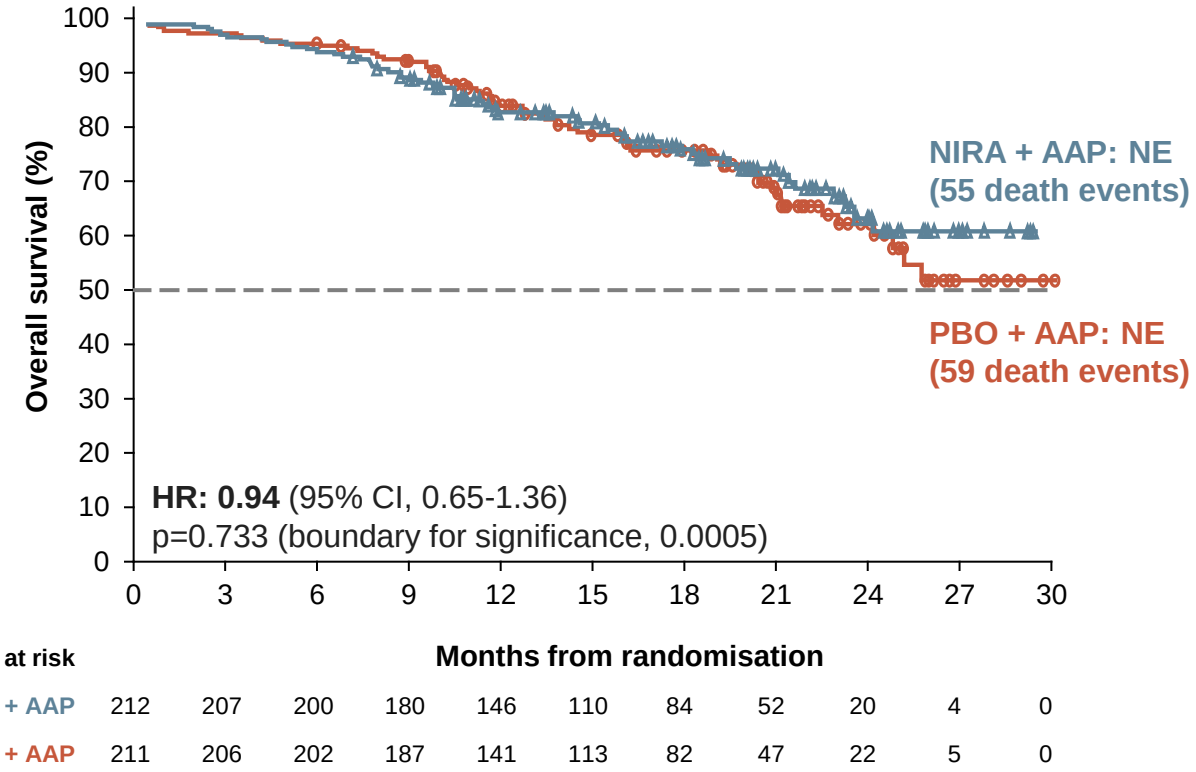
[b] Prior AAP use was up to 4 months prior to study start

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; BRCA, breast cancer gene; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE ALL HRR BM+: OVERALL SURVIVAL

NO STATISTICALLY SIGNIFICANT IMPROVEMENT IN OS AT THE TIME OF THIS ANALYSIS



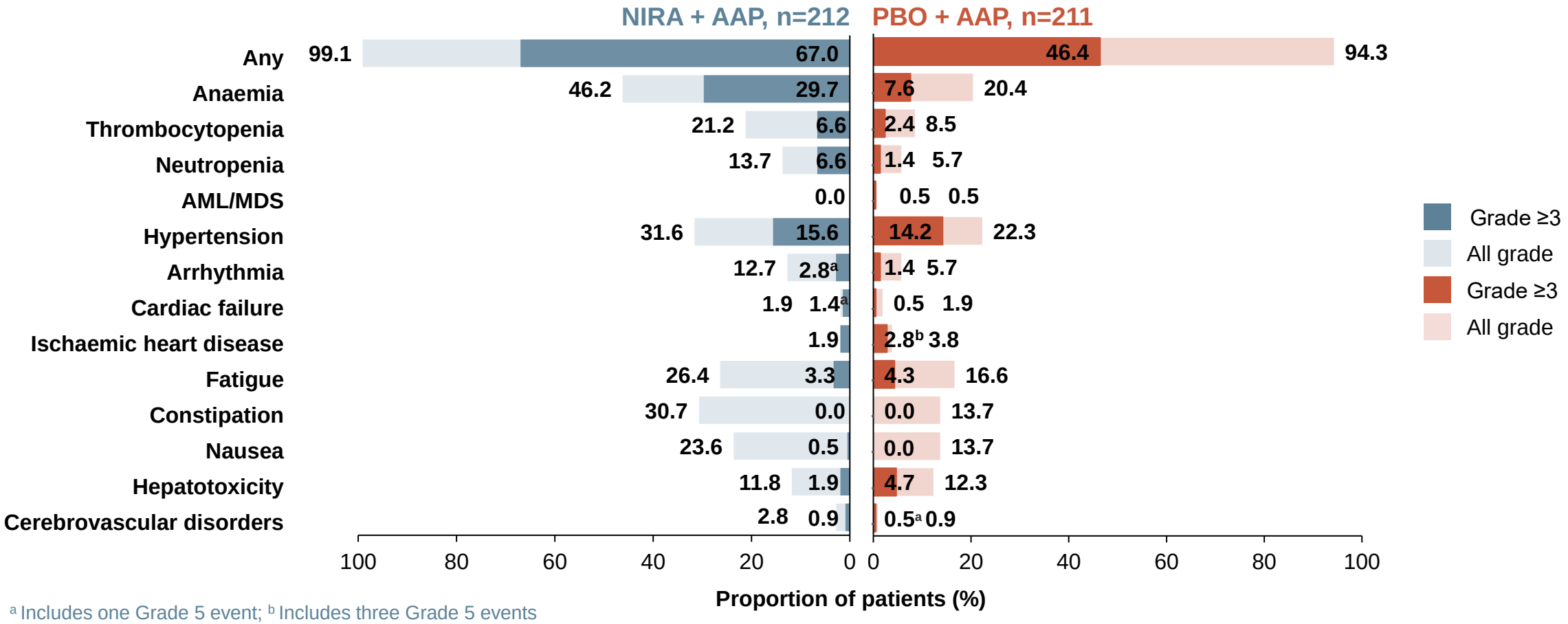
46.3% of the required death events for the final analysis observed and thus overall survival data are immature

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; NIRA, niraparib; OS, overall survival; PBO, placebo

Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE: HRR BM+ TEAEs OCCURRING AT >20% IN NIRA ARM OR OF CLINICAL INTEREST

TEAEs CONSISTENT WITH THE KNOWN SAFETY PROFILE FOR EACH THERAPY



[a] Includes one Grade 5 event; [b] Includes three Grade 5 events

AAP, abiraterone acetate + prednisone / prednisolone; AML, acute myeloid leukaemia; BM, biomarker; HRR, homologous recombination repair; MDS, myelodysplastic syndrome; NIRA, niraparib; PBO, placebo; TEAE, treatment-emergent adverse event

Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

CONSIDERATIONS FOR TREATMENT SELECTION

PATIENT CASE

Patient: 66 year old
Presents with: mild fatigue
Medical history:

- Well-controlled hypertension and hyperlipidaemia
- +FH of breast cancer in sister, age 56

Germline *BRCA2* mutation detection which is pathogenic.
Consider patient for treatment with a PARPi

Initial Presentation

Biopsy: 9 / 12 cores; Adenocarcinoma Gleason 4+4
Staging: T3 by DRE and mpMRI, N1 M1b, high volume mHSPC
Imaging: bone and CT scan

- Metastases in hip, lumbar spine and ribs (five)
- Multiple pelvic & retroperitoneal lymph nodes between 1-3 cm

Current situation
Slight discomfort in lumbar spine
Imaging:

- Progression of bone and lymph node metastases
- Haemoglobin: 11 g/dL

ADT, androgen deprivation therapy; CT, computed tomography; DRE, digital rectal exam; FH, family history; mHSPC, metastatic hormone sensitive prostate cancer; mpMRI, multi-parametric magnetic resonance imaging; PSA, prostate-specific antigen; T, N, M, tumour, nodes, metastasis

rPFS ACROSS AR-PARP INHIBITOR COMBINATION TRIALS (PRIMARY ENDPOINT)

		TALAPRO-2 (BICR)[1]		PROpel (invest. review)[2,3]		Magnitude (BICR)[4]	
		TALA+ ENZA	Placebo+ ENZA	OLA+ ABI	Placebo+ ABI	NIRA+ ABI	Placebo+ ABI
All comers/unselected	n	402	403	399	397	Not applicable	
	Median rPFS, mo	Not reached	21.9	24.8	16.6		
	HR	**0.63**		**0.66**			
HRR deficient	n	85	84	111	115	212	211
	Median rPFS, mo	27.9	16.4	Not reached	13.9	16.5	13.7
	HR	**0.46**		**0.50**		**0.73**	
HRR non-deficient[a]	n	198	214	279	273	117	116
	Median rPFS, mo	Not reached	22.1	24.1	19.0	NA	NA
	HR	**0.66**		**0.76**		**(1.09)**	
*BRCA*m	n	27	32	47	38	113	112
	Median rPFS, mo	Not reported	Not reported	Not reached	8.4	16.6	10.9
	HR	**0.23**		**0.23**		**0.53**	
Non-*BRCA*m	n	58	52	343	350	99	99
	Median rPFS, mo	Not reported	Not reported	24.1	19.0	14.8	16.4
	HR	**0.66**		**0.76**		**0.99**	

[a]in TALAPRO-2 determined by prospective tumour tissue testing.

Please note that these studies cannot be directly compared. The data are presented for information purposes only

ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3; 2. Clarke N, et al. NEJM Evidence 2022; 1(9): DOI: 10.1056/EVIDoa2200043; 3. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); 4. Chi K, et al. J Clin Oncol 2023: DOI: 10.1200/JCO.22.01649

rPFS ACROSS AR-PARP INHIBITOR COMBINATION TRIALS (BY BICR)

		TALAPRO-2 (BICR)[1]		PROpel (BICR)[2,3,a]		Magnitude (BICR)[4]	
		TALA+ ENZA	Placebo+ ENZA	OLA+ ABI	Placebo+ ABI	NIRA+ ABI	Placebo+ ABI
All comers/unselected	n	402	403	399	397	Not applicable	
	Median rPFS, mo	Not reached	21.9	27.6	16.4		
	HR	**0.63**		**0.61**			
HRR deficient	n	85	84	111	115	212	211
	Median rPFS, mo	27.9	16.4	28.8	13.8	16.5	13.7
	HR	**0.46**		**0.45**		**0.73**	
HRR non-deficient[b]	n	198	214	279	273	117	116
	Median rPFS, mo	Not reached	22.1	27.6	19.1	NA	NA
	HR	**0.66**		**0.72**		**(1.09)**	
*BRCA*m	n	Not reported		47	38	113	112
	Median rPFS, mo			NR	8.4	16.6	10.9
	HR			**0.18**		**0.53**	
Non-*BRCA*m	n	Not reported		343	350	99	99
	Median rPFS, mo			27.6	16.6	14.8	16.4
	HR			**0.72**		**0.99**	

[a]BICR is sensitivity analysis of PROpel primary endpoint
[b]Determined by prospective tumour tissue testing in TALAPRO-2
Please note that these studies cannot be directly compared. The data are presented for information purposes only

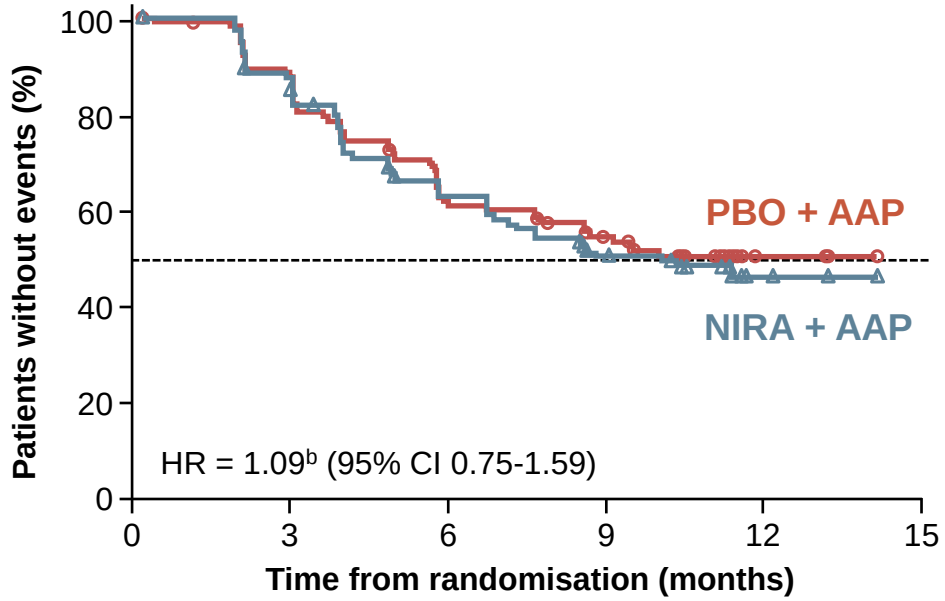
ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); 2. Clarke N, et al. NEJM Evidence 2022; 1(9): DOI: 10.1056/EVIDoa2200043 (supplementary appendix); 3. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation, data supplement); 4. Chi K, et al. J Clin Oncol. 2023; 41 (18): 3339-3351

MAGNITUDE HRR BM$^-$: PRESPECIFIED EARLY FUTILITY ANALYSIS

NO BENEFIT OF NIRA + AAP IN HRR BM$^-$ PATIENTS

Composite progression endpoint[a]



No. at risk						
NIRA + AAP	117	92	68	51	4	0
PBO + AAP	116	91	68	56	8	0

- Additional grade 3/4 toxicity was observed using NIRA + APP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM$^-$ mCRPC, the IDMC recommend stopping enrolment in this cohort

[a] Composite endpoint: rPFS or PSA progression, whichever occurred first
[b] Breakdown of composite endpoint events: 83 PSA events (HR = 1.03, 95% CI 0.67-1.59); 65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

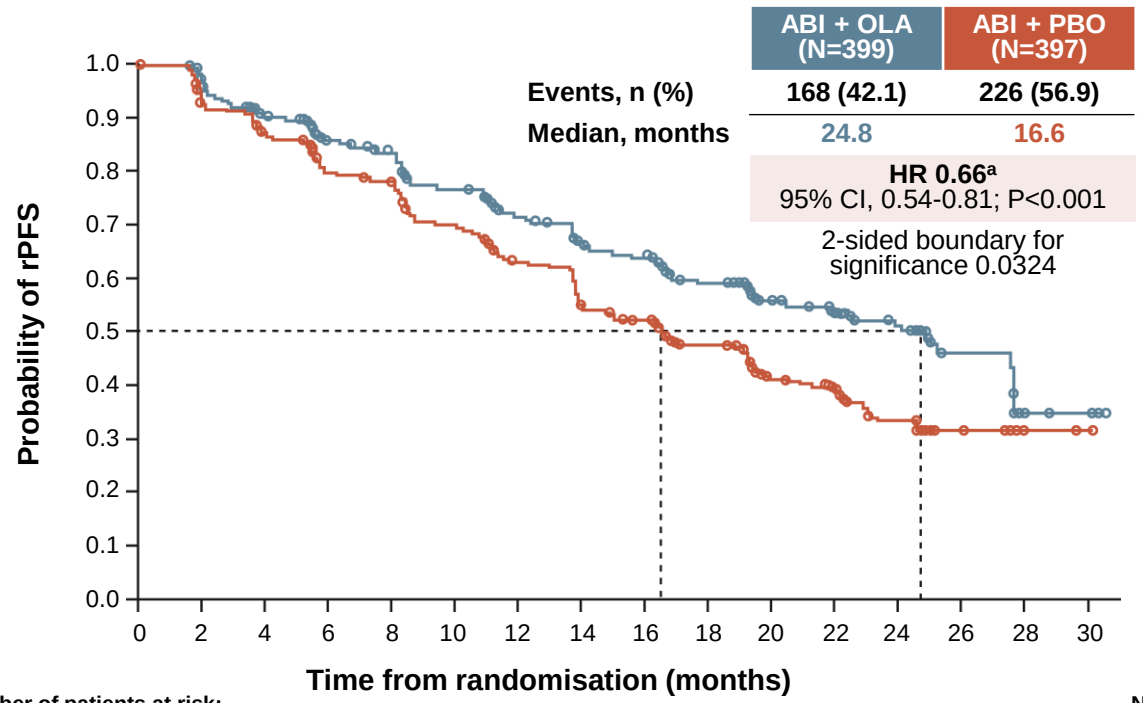
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate antigen; rPFS, radiographic progression free survival

Chi K, et al. J Clin Oncol 2022; 40, (suppl 6; abstr 12) (ASCO GU 2022 oral presentation)

rPFS IN AN ALL-COMER POPULATION (PRIMARY ENDPOINT)

PROpel[1,2]

rPFS by investigator assessment (INV)

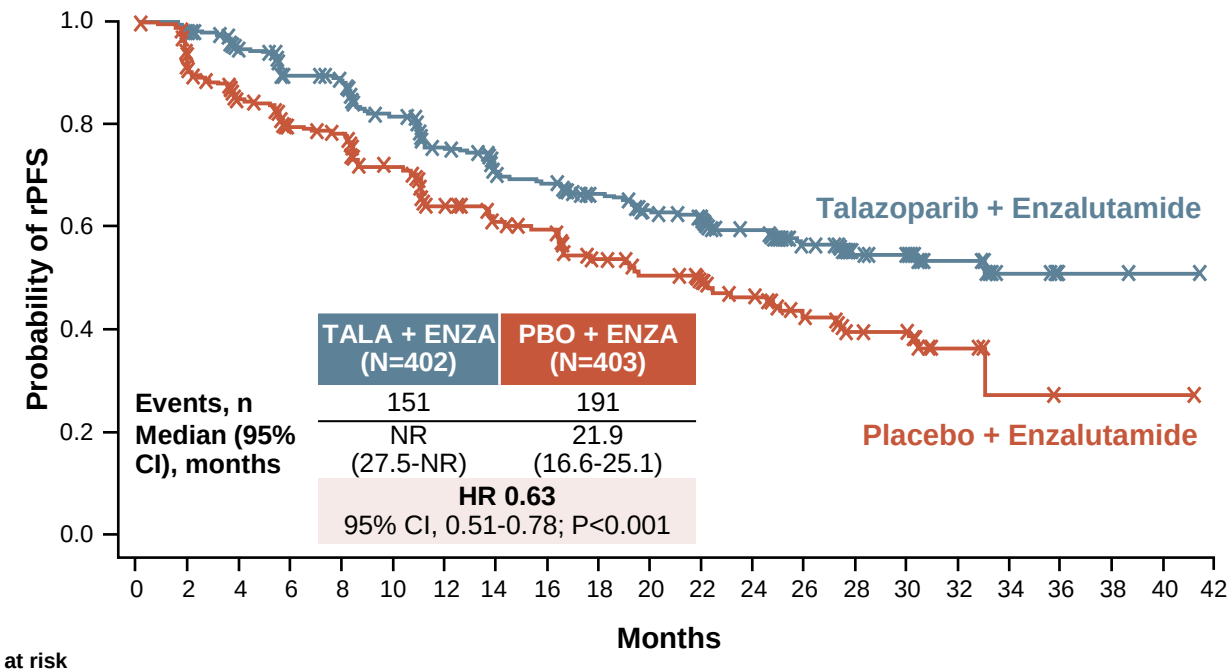


Number of patients at risk:

ABI + OLA	399	367	340	313	301	274	251	227	219	167	104	87	57	26	5	4
ABI + PBO	397	359	338	306	297	264	232	198	186	141	87	73	43	17	2	1

TALAPRO-2[3]

rPFS by blinded independent central review (BICR)



No. at risk

TALA + ENZA	402	379	353	326	318	285	256	234	226	209	193	175	136	97	67	61	29	13	2	2	1	0
PBO + ENZA	403	346	311	279	272	237	200	185	179	154	140	124	96	68	43	42	14	3	1	1	1	0

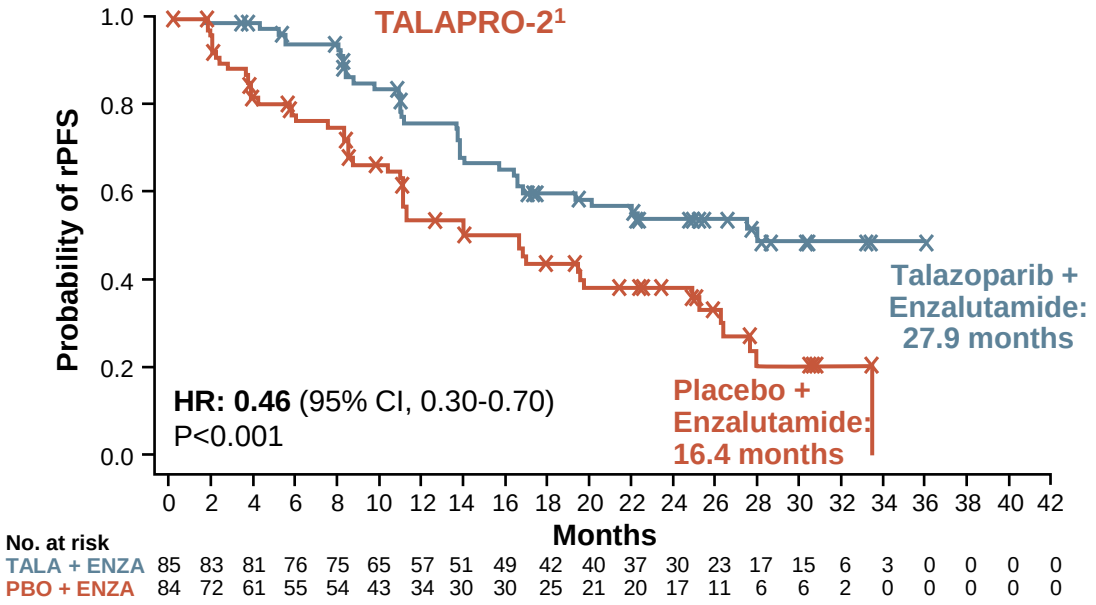
[a]HR for rPFS by BICR in pre-defined sensitivity analysis is 0.61

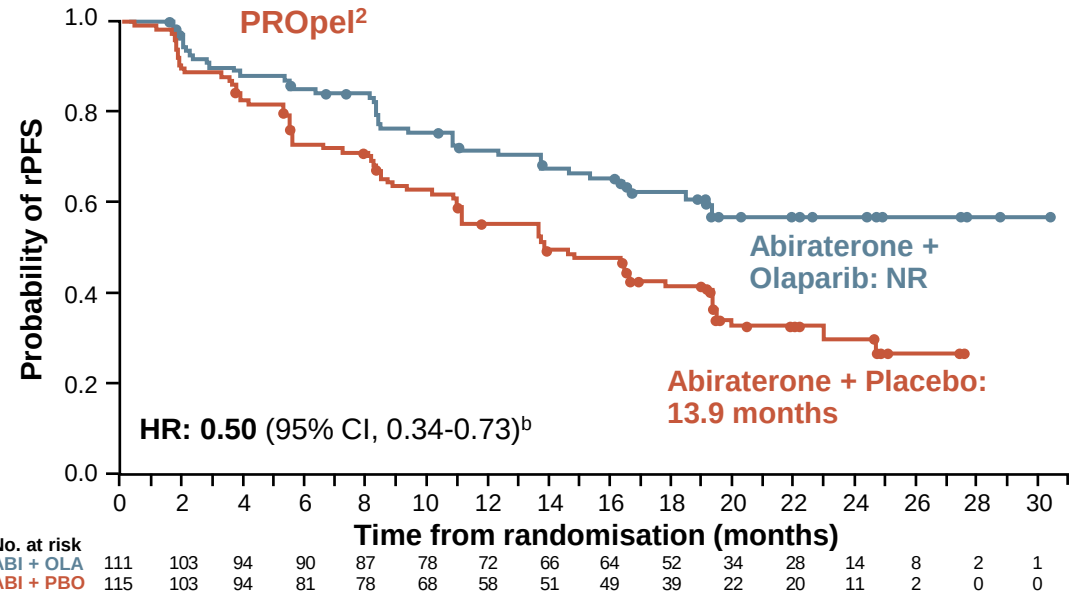
Please note that these studies cannot be directly compared. The data are presented for information purposes only

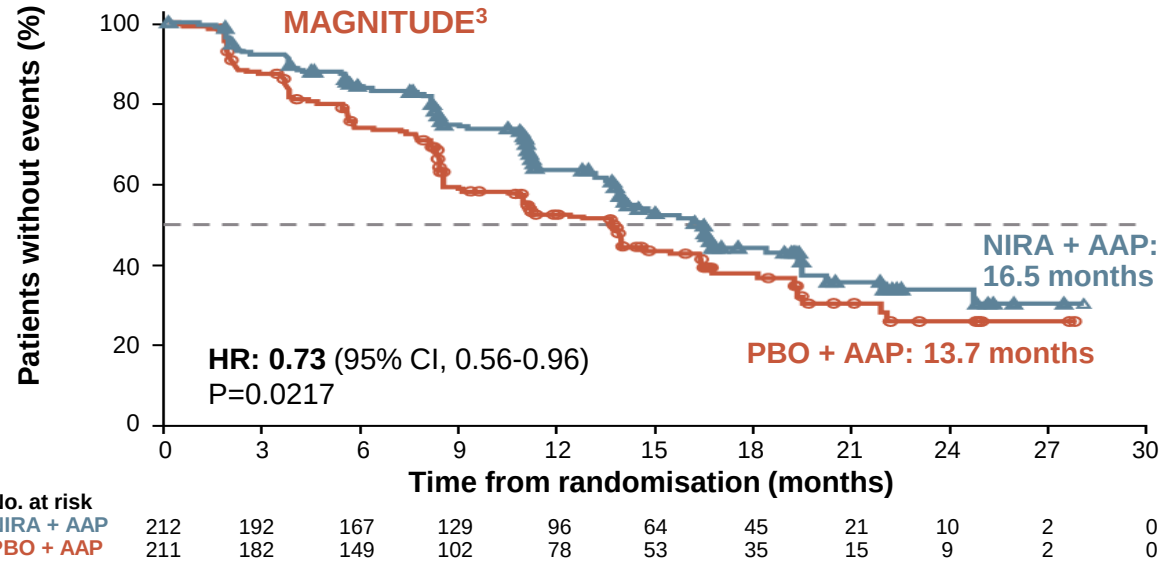
Abi, abiraterone acetate; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; Ola, Olaparib; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Clarke N, et al. NEJM Evidence 2022;1(9): doi: https://doi.org/10.1056/EVIDoa2200043; 2. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); 3. Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation)

rPFS[a] IN HRRm PATIENTS







Please note that these studies cannot be directly compared. The data are presented for information purposes only

[a]rPFS by BICR for TALAPRO-2 and MAGNITUDE studies and by investigator assessment in PROpel; [b]*post hoc* exploratory analysis

AAP, abiraterone acetate + prednisone/prednisolone; Abi, abiraterone acetate; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NIRA, niraparib; NR, not reached; Ola, Olaparib; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); 2. Clarke N, et al. NEJM Evidence 2022;1(9): doi: https://doi.org/10.1056/EVIDoa2200043; 3. Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation)

mOS ACROSS AR-PARP INHIBITOR COMBINATION TRIALS

		TALAPRO-2 (BICR)[1]		**PROpel** (invest. review)[2]		**Magnitude** (BICR)[3,4]	
		TALA+ ENZA	**Placebo+ ENZA**	**OLA+ ABI**	**Placebo+ ABI**	**NIRA+ ABI**	**Placebo+ ABI**
All comers/unselected	n	402	403	399	397	Not applicable	
	Median OS, mo	36.4	Not reached	42.1	34.7		
	HR	**0.89** *(31% mature)*		**0.81** *(47.9% mature)*			
HRR deficient	N	Not reported		111	115	212	211
	Median OS, mo			Not reached	28.5	Not reached	Not reached
	HR			**0.66**		**0.94** *(46.3% mature)*	
HRR non-deficient	n	Not reported		279	273	Not reported	
	Median OS, mo			42.1	38.9		
	HR			**0.89**			
*BRCA*m	n	Not reported		47	38	113	112
	Median OS, mo			Not reached	23.0	29.3	28.6
	HR			**0.29**		**0.88**	
Non-*BRCA*m	n	Not reported		343	350	Not reported	
	Median OS, mo			39.6	38.0		
	HR			**0.91**			

Please note that these studies cannot be directly compared. The data are presented for information purposes only

ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NA, not applicable (not reported); NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3 (Data supplement); 2. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); 3. Chi K, et al. J Clin Oncol 2023: DOI: 10.1200/JCO.22.01649; 4. Efstathiou E, et al. J Clin Oncol 41, 2023 (suppl 6; abstr 170) (ASCO GU 2023 oral presentation);

CYTOPENIAS (≥10% OF PTS) ACROSS AR-PARP INHIBITOR COMBINATION TRIALS

Frequency of cytopenias – All grade (Grade ≥3), %	TALAPRO-2[1]		PROpel[2]		Magnitude[3, a]	
	TALA+ ENZA	Placebo+ ENZA	OLA+ ABI	Placebo+ ABI	NIRA+ ABI	Placebo+ ABI
Anaemia[b]	66 (46)	17 (4)	46.0 (15.1)	16.4 (3.3)	46.2 (29.7)	20.4 (7.6)
Thrombocytopenia	25 (7)	3 (1)	NR	NR	21.2 (6.6)	8.5 (2.4)
Neutropenia	36 (18)	7 (1)	NR	NR	13.7 (6.6)	5.7 (1.4)
Leukopenia	22 (6)	4 (0)	NR	NR	10.4 (1.9)	2.4 (0.5)
Lymphopenia	11 (5)	5 (1)	NR	NR	NR	NR

Please note that these studies cannot be directly compared. The data are presented for information purposes only.
AEs reported if > 10% in TALAPRO-2 and MAGNITUDE and ≥ 10% in PROpel in combination arms

AEs highlighted in blue if value ≥20%; [a] safety presented for HRR+ cohort; [b] In PROpel: grouped term 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

ABI, abiraterone acetate; AE, adverse event; AR, androgen receptor; ENZA, enzalutamide; HRR, homologous recombination repair; NIRA, niraparib; NR, not reported; OLA, olaparib; PARP, poly-ADP ribose polymerase; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3; 2. Clarke N, et al. NEJM Evid 2022;1(9): DOI: 10.1056/EVIDoa2200043; 3. Chi K, et al. J Clin Oncol. 2023; 41 (18): 3339-3351

MOST COMMON TEAEs (≥10% OF PTS) ACROSS AR-PARP INHIBITOR COMBINATION TRIALS

Frequency of AEs – All grade (Grade ≥3)	TALAPRO-2[1]		PROpel[2]		Magnitude (HRR+)[3]	
	TALA+ ENZA	Placebo+ ENZA	OLA+ ABI	Placebo+ ABI	NIRA+ ABI	Placebo+ ABI
Fatigue	34 (4)	29 (2)	37.2 (2.3)[a]	28.3 (1.5)[a]	26.4 (3.3)	16.6 (4.3)
Nausea	21 (<1)	12 (<1)	28.1 (0.3)	12.6 (0.3)	23.6 (0.5)	13.7 (0)
Constipation	18 (<1)	17 (<1)	17.3 (0)	13.9 (0.3)	30.7 (0)	13.7 (0)
Diarrhoea	14 (<1)	14 (0)	17.3 (0.8)	9.3 (0.3)	NR	NR
Decreased appetite	22 (1)	16 (1)	14.6 (1.0)	5.8 (0)	14.2 (0.5)	6.2 (0.5)
Back pain	22 (3)	18 (1)	17.1 (0.8)	18.4 (1.0)	14.6 (2.4)	20.9 (0.9)
Hypertension	14 (5)	15 (7)	12.6 (3.5)	16.4 (3.3)	31.1 (14.6)	20.9 (12.3)
Fall	18 (2)	15 (2)	NR	NR	5.2 (0.9)	12.3 (2.8)
Arthralgia	15 (<1)	20 (<1)	12.8 (0)	17.7 (0.5)	13.2 (0.5)	9.5 (0.5)
Asthenia	14 (3)	9 (<1)	NR	NR	15.6 (1.0)	9.0 (0.5)
Dizziness	12 (1)	6 (<1)	10.8 (0)	6.3 (0)	11.3 (0.5)	5.7 (0)
Hot flush	12 (0)	13 (0)	NR	NR	NR	NR
Oedema peripheral	11 (0)	6 (0)	10.3 (0)	11.4 (0.3)	NR	NR
Dyspnoea	10 (<1)	6 (<1)	NR	NR	16.0 (1.9)	5.7 (0.9)
Decreased weight	10 (<1)	8 (<1)	NR	NR	NR	NR
Hypokalemia	NR	NR	NR	NR	13.7 (2.8)	9.5 (2.8)
Vomiting	NR	NR	13.1 (1.0)	9.1 (0.3)	13.2 (0.5)	6.6 (0.5)
Insomnia	NR	NR	NR	NR	10.4 (0)	3.8 (0)
Bone pain	NR	NR	NR	NR	9.9 (1.4)	11.4 (0.5)
Urinary tract infection	NR	NR	10.3 (2.0)	7.8 (1.0)	NR	NR

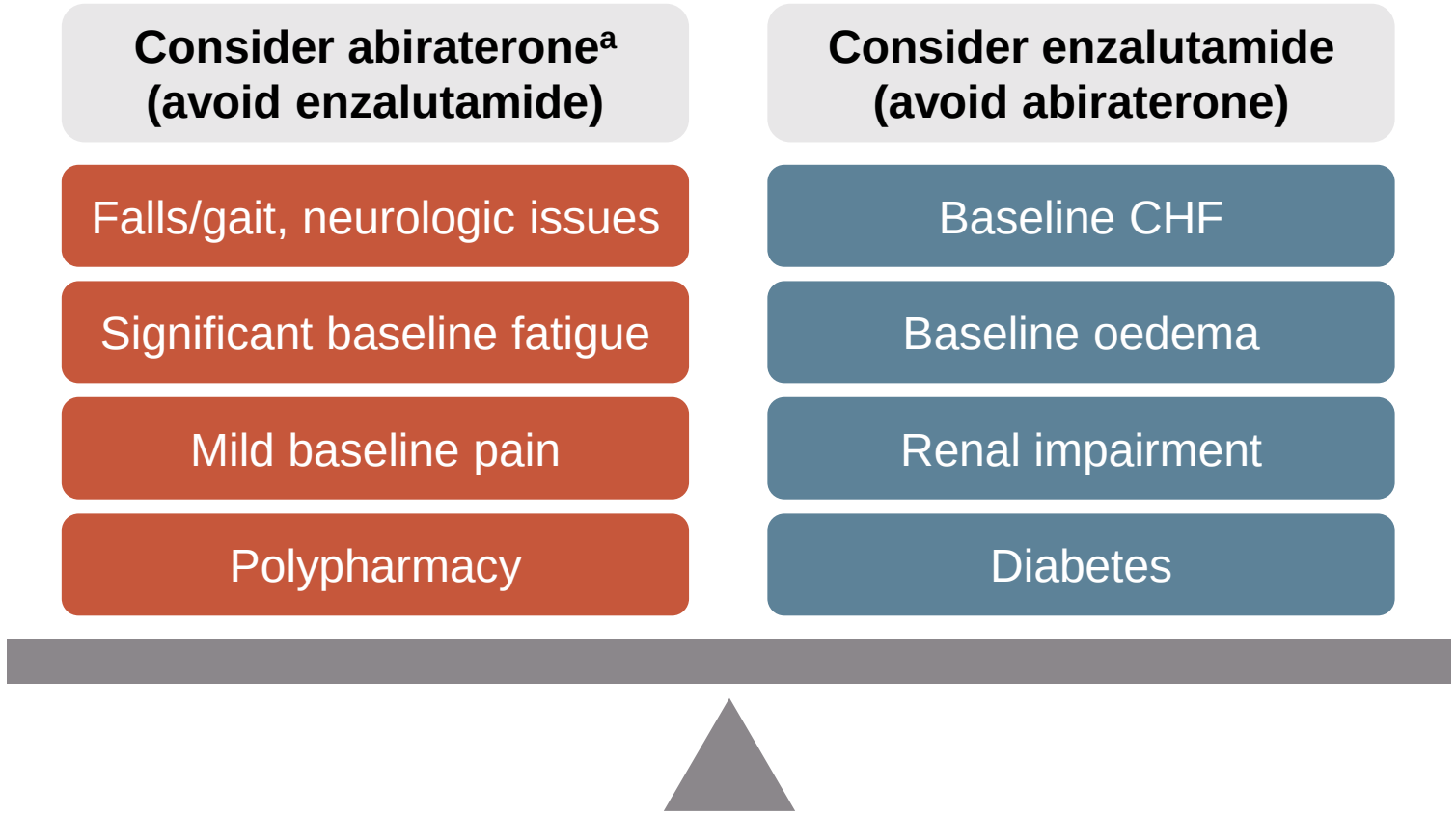
Please note that these studies cannot be directly compared. The data are presented for information purposes only.

AEs highlighted in blue if value ≥20%; [a]Fatigue and asthenia as grouped term

ABI, abiraterone acetate; AE, adverse event; AR, androgen receptor; ENZA, enzalutamide; HRR, homologous recombination repair; NIRA, niraparib; NR, not reported; OLA, olaparib; PARP, poly-ADP ribose polymerase; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3; 2. Clarke N, et al. NEJM Evid 2022;1(9): DOI: 10.1056/EVIDoa2200043; 3. Chi K, et al. J Clin Oncol. 2023; 41 (18): 3339-3351

SELECTING ABIRATERONE VS ENZALUTAMIDE



[a]Keep in mind that the steroids used with abiraterone are not supra-physiologic

CHF, congestive heart failure

CONSIDERATIONS FOR SELECTION OF PARP INHIBITOR

- Both **talazoparib plus enzalutamide and olaparib plus abiraterone,** have demonstrated efficacy **in men with mCRPC** in the first line setting, no prior ARSi use, and **irrespective of HRR mutation detection**
  - Improvements in rPFS similar, with greater benefits seen in HRRm and *BRCA*m populations
- Differences in discontinuation rates, severe anaemia, dosing, and AR inhibitor partner may better inform on choice
- With either choice, patients should be followed regularly for adverse events, particularly anaemia requiring transfusion, GI intolerance, fatigue
  - Dose holds and reductions are not uncommon and may be needed for optimal individualised care
  - CBC every 2-4 weeks especially in first 3-4 months is reasonable
- **Niraparib and abiraterone is also associated with longer rPFS** than abiraterone alone in first line mCRPC. However, this occurred **in patients with *BRCA* mutations only**

AR, androgen receptor; ARSi, androgen receptor signalling inhibitor; BRCAm, breast cancer gene mutation; CBC, complete blood count; GI, gastrointestinal; HRR, homologous recombination repair; HRRm, HRR mutation; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival

PARP INHIBITORS ARE APPROVED IN PROSTATE CANCER

Olaparib FDA-approved indication[1]

- Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and **HRRm**, who have **progressed** on enzalutamide or abiraterone acetate
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with ***BRCAm*** **mCRPC**

Niraparib FDA-approved indication[3]

- Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone for the treatment of adult patients with ***BRCAm*** **mCRPC**

Rucaparib FDA-approved indication[5]

- Indicated as **monotherapy** for the treatment of adult patients with ***BRCAm*** **mCRPC** who have **progressed on** AR-directed therapy and a **taxane[a]**

Talazoparib FDA-approved indication[6]

- In combination with enzalutamide for the treatment of adult patients with HRRm **mCRPC[b]**

Olaparib EMA-approved indication[2]

- Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and a ***BRCAm***, who have **progressed** on prior therapy, including an **NHA**
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with **mCRPC in whom chemotherapy is not clinically indicated**

Niraparib EMA-approved indication[4]

- Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone or prednisolone for the treatment of adult patients with **mCRPC and *BRCA1/2* gene mutations** (germline and/or somatic) **in whom chemotherapy is not clinically indicated**

[a]Rucaparib has no current approval in prostate cancer in Europe

[b]Talazoparib has no current approval in prostate cancer in Europe

AR, androgen receptor; BRCAm, breast cancer gene mutation; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PARP, poly-ADP ribose polymerase

1. Lynparza (olaparib) US prescribing information (Sep-2023); 2. Lynparza (olaparib) summary of product characteristics (Mar 2023); 3. FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer | FDA; 4. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate; 5. Rubraca (rucaparib) US prescribing information (Jun 2022); 6. Talzenna (talazoparib) summary of product characteristics (Jun 2023)

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