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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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**AUGUST 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 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

**This programme is developed by GU CONNECT, an international group of experts in the field of genitourinary oncology.**

**Acknowledgement and disclosures:**

This GU CONNECT programme is supported through an independent Educational Grant from AstraZeneca.
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**Expert Disclaimers:**

**Dr Andrew Armstrong** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:

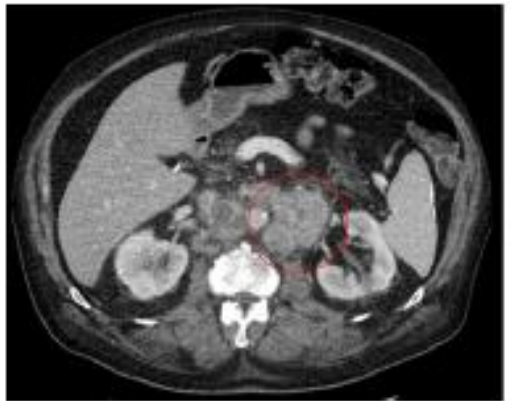
- Amgen, Astellas, AstraZeneca, Bayer, BMS, Celgene, Clovis, Dendreon, Epic Sciences, Exact Sciences, Exelixis, Forma, GoodRx, Janssen, Merck, Myovant, Novartis, Pfizer

# 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

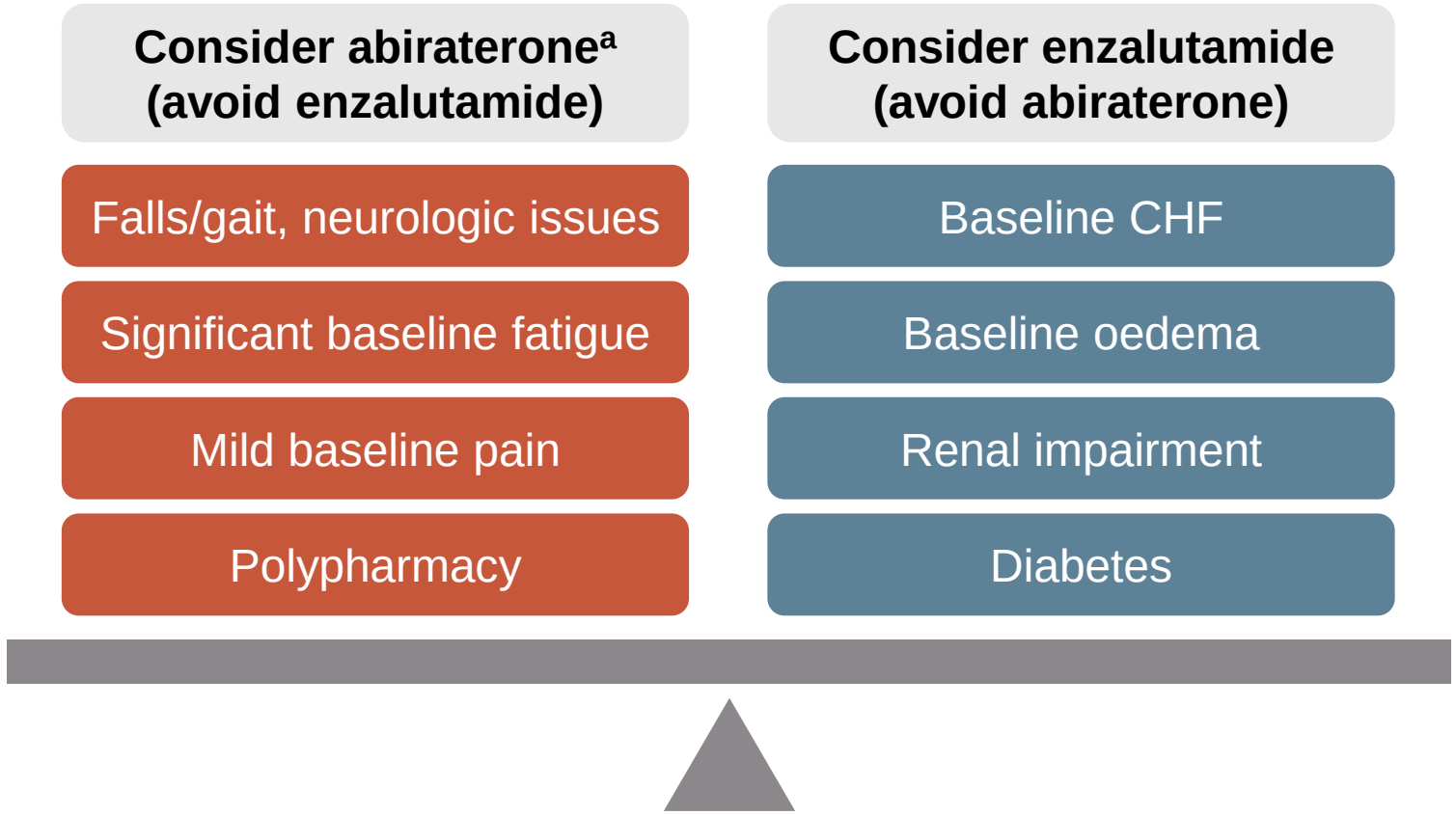
# TIMING AND SELECTION OF SECONDARY AR-DIRECTED THERAPIES

- 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



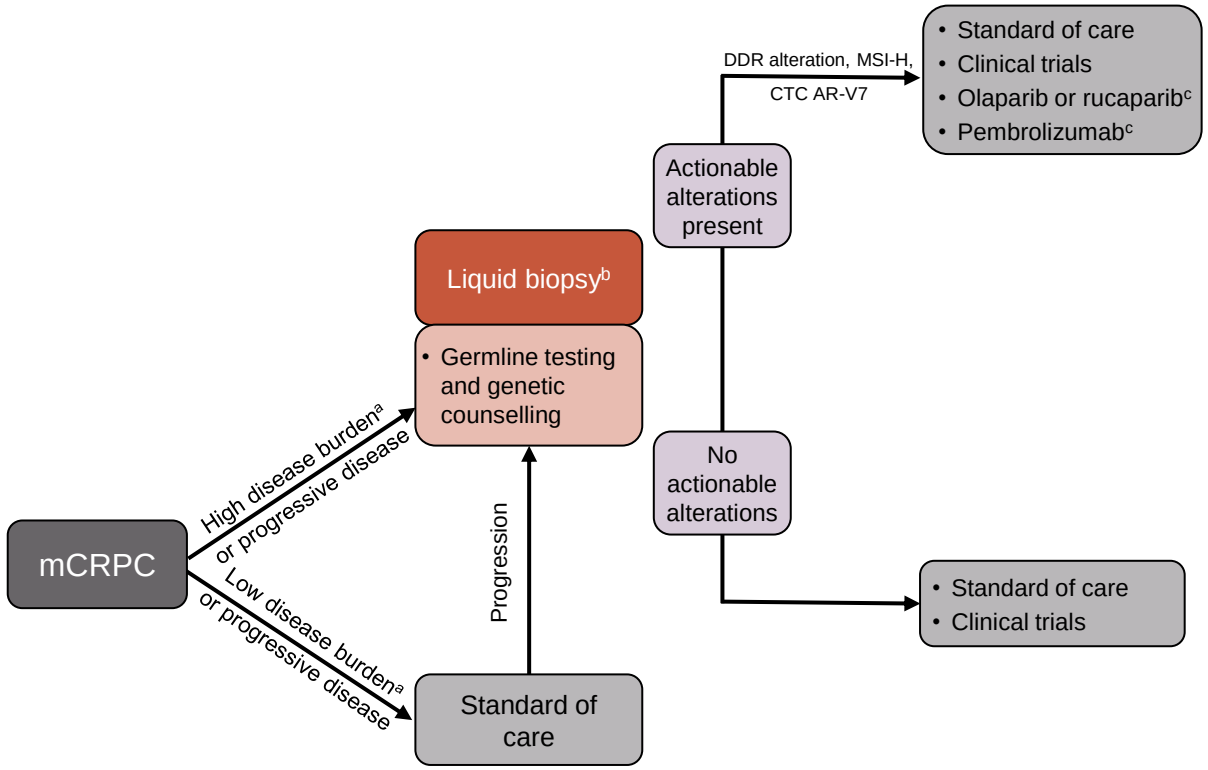

[a]Keep in mind that the steroids used with abiraterone are not supra-physiologic

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

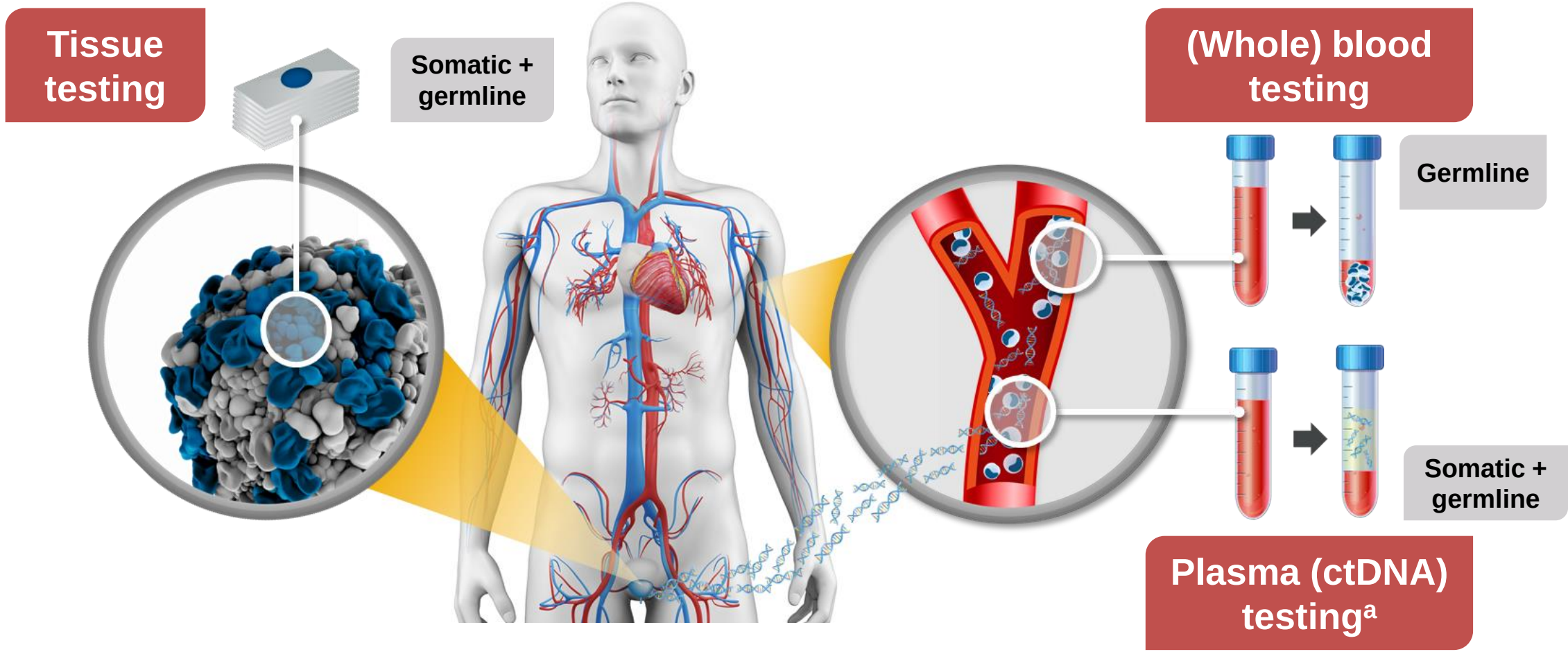



[a] High disease burden based on the presence of known adverse prognostic factors in men with mCRPC, such as visceral metastases, high volume of bone metastases, anaemia, rapid PSA kinetics, high circulating tumour cell count, high LDH or alkaline phosphatase, pain, and progression despite multiple prior 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

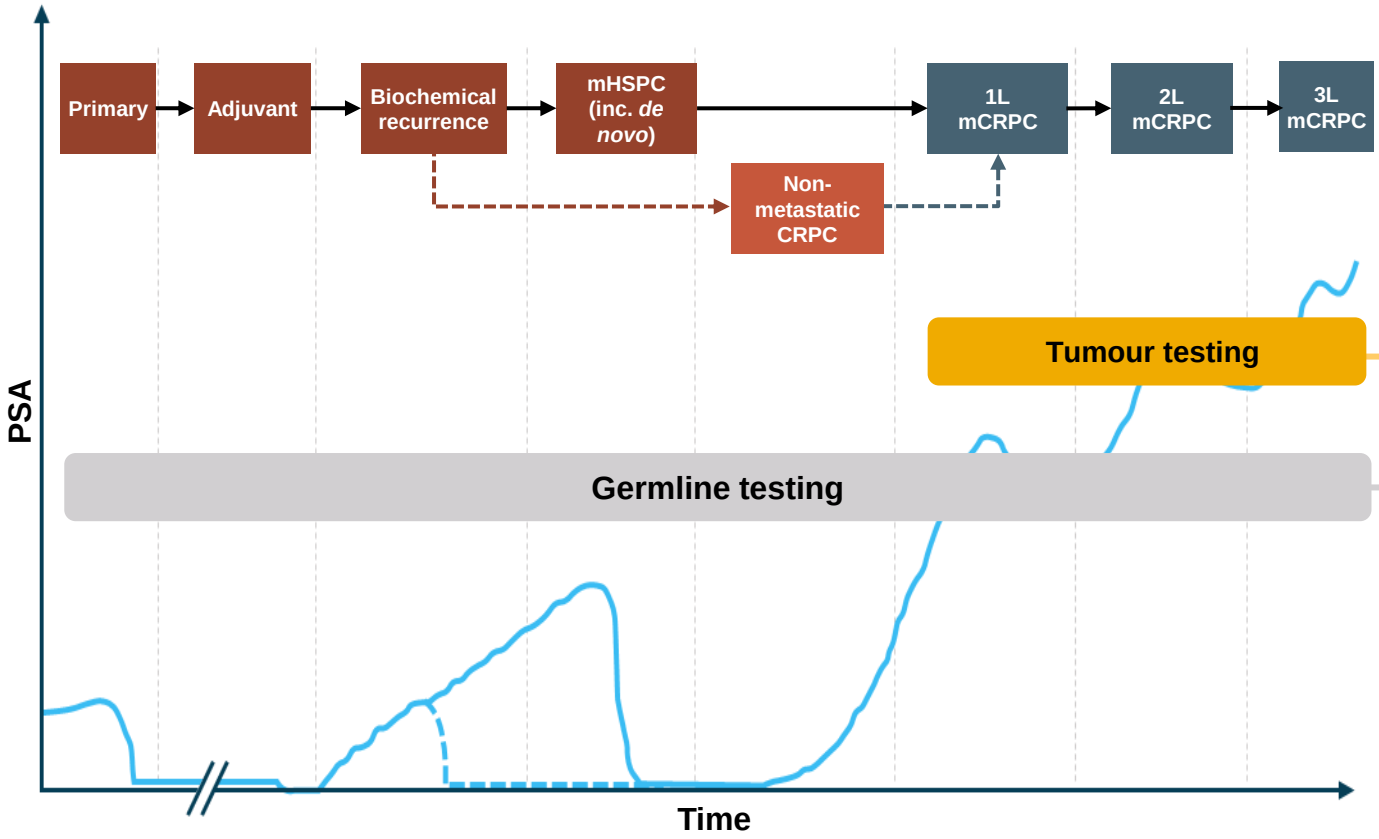



[a]Tumour cells shed DNA into the circulation through necrosis or apoptosis. ctDNA can be isolated from a plasma sample

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

- **Consider HRRm** testing in patients with **mPC**

## 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 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed May 2023; 5. Lowrance W, et al. J Urol. 2023; 209(6):10.1097/JU.0000000000003452; 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:**

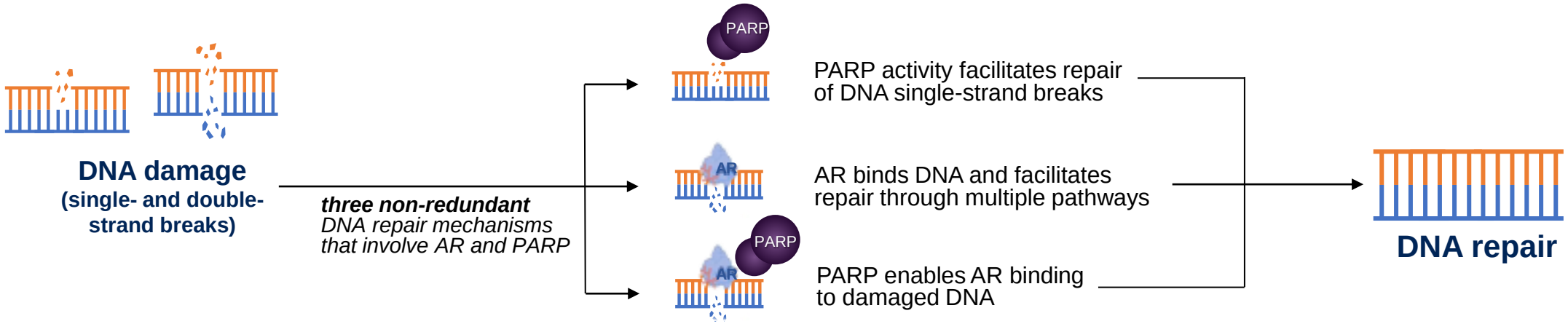
- Progression of bone and lymph node metastases
- Haemoglobin: 11 g/dL

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

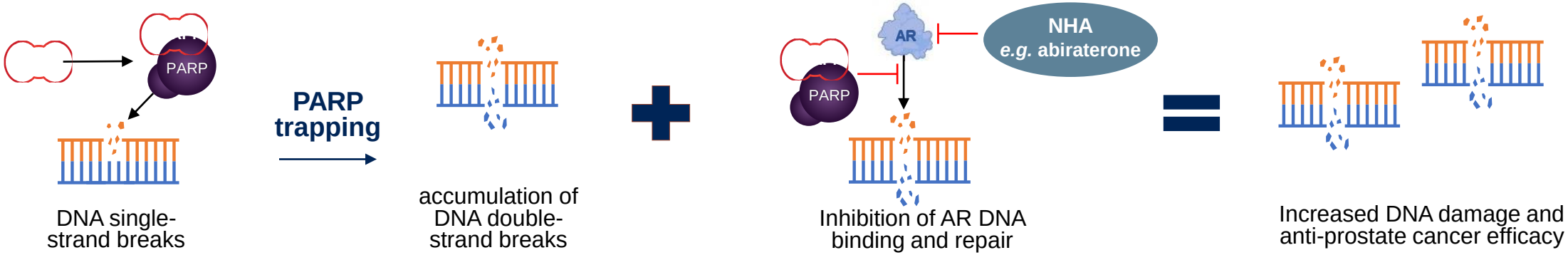
# RATIONALE FOR COMBINING PARP AND AR INHIBITORS

# 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



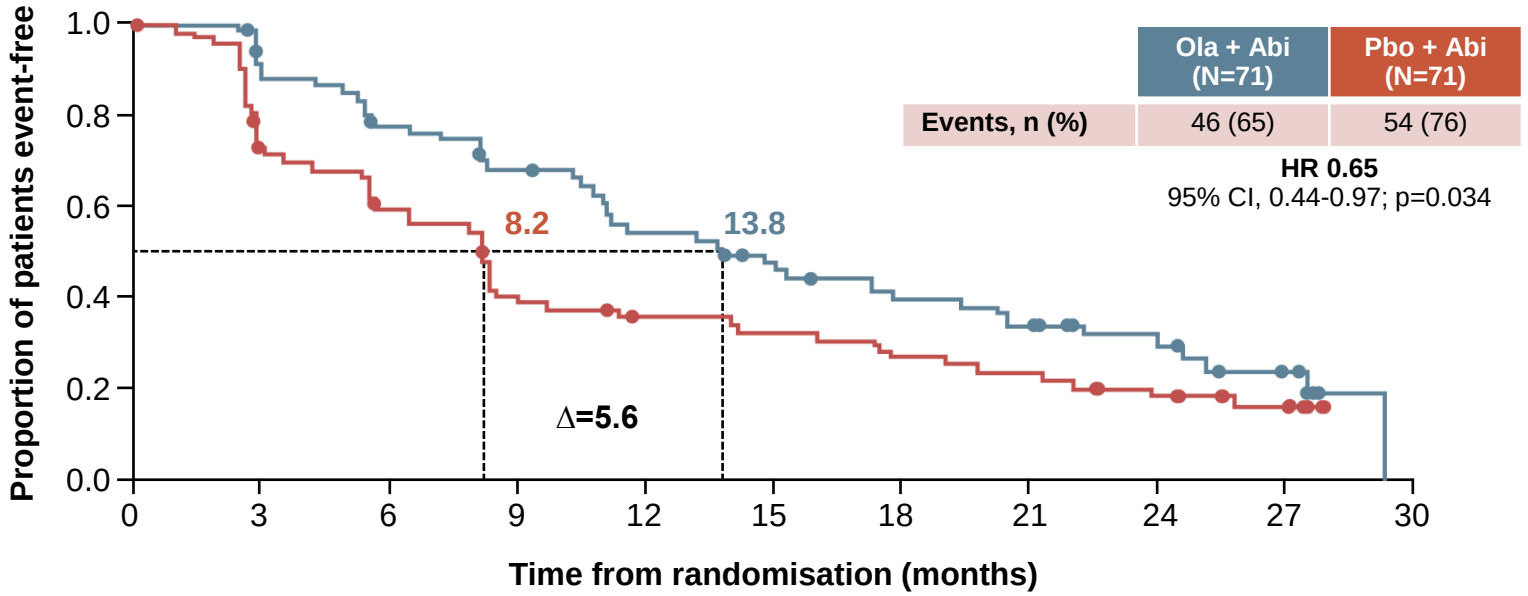

AR, androgen receptor; DNA, deoxyribonucleic acid; NHA, novel hormonal agent; PARP, poly(ADP-ribose) polymerase

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

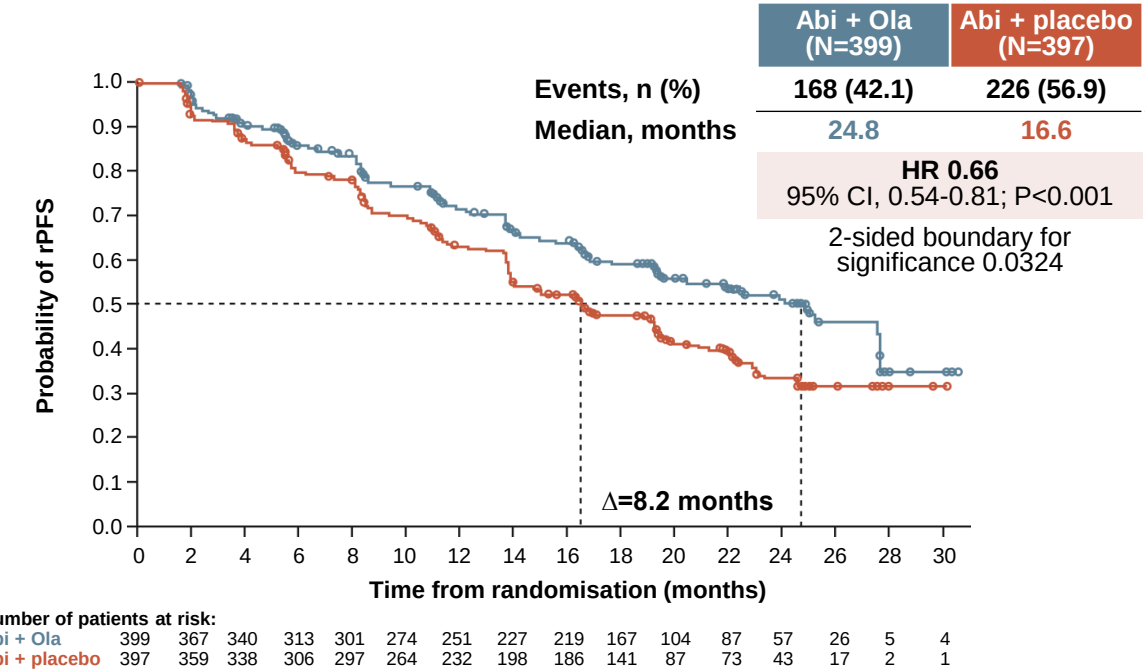
ADT, androgen-deprivation therapy; BID, twice daily; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate 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)

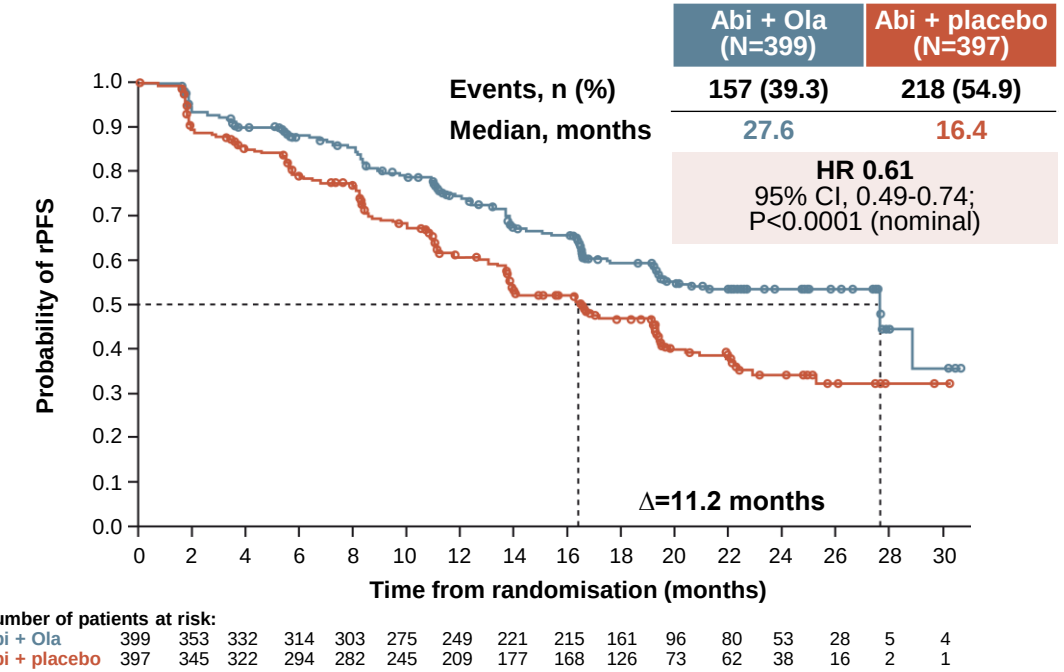
# PROpel: PRIMARY rPFS RESULTS (DCO1)[1]

## 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)

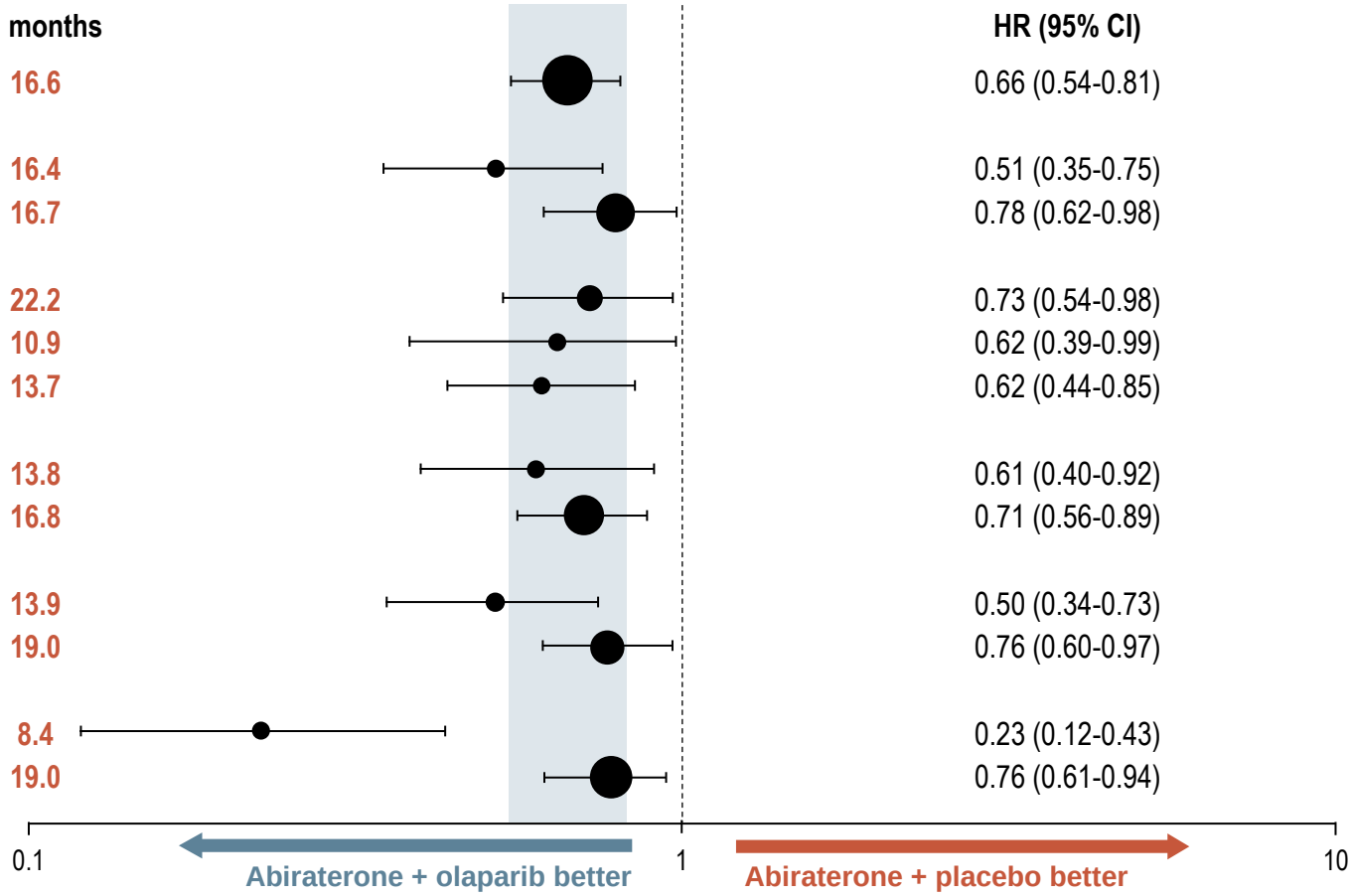
Abi, abiraterone; CI, confidence interval; DCO1, first data cut-off; HR, hazard ratio; ITT, intention-to-treat; Ola, olaparib; rPFS, radiographic progression-free survival

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) |



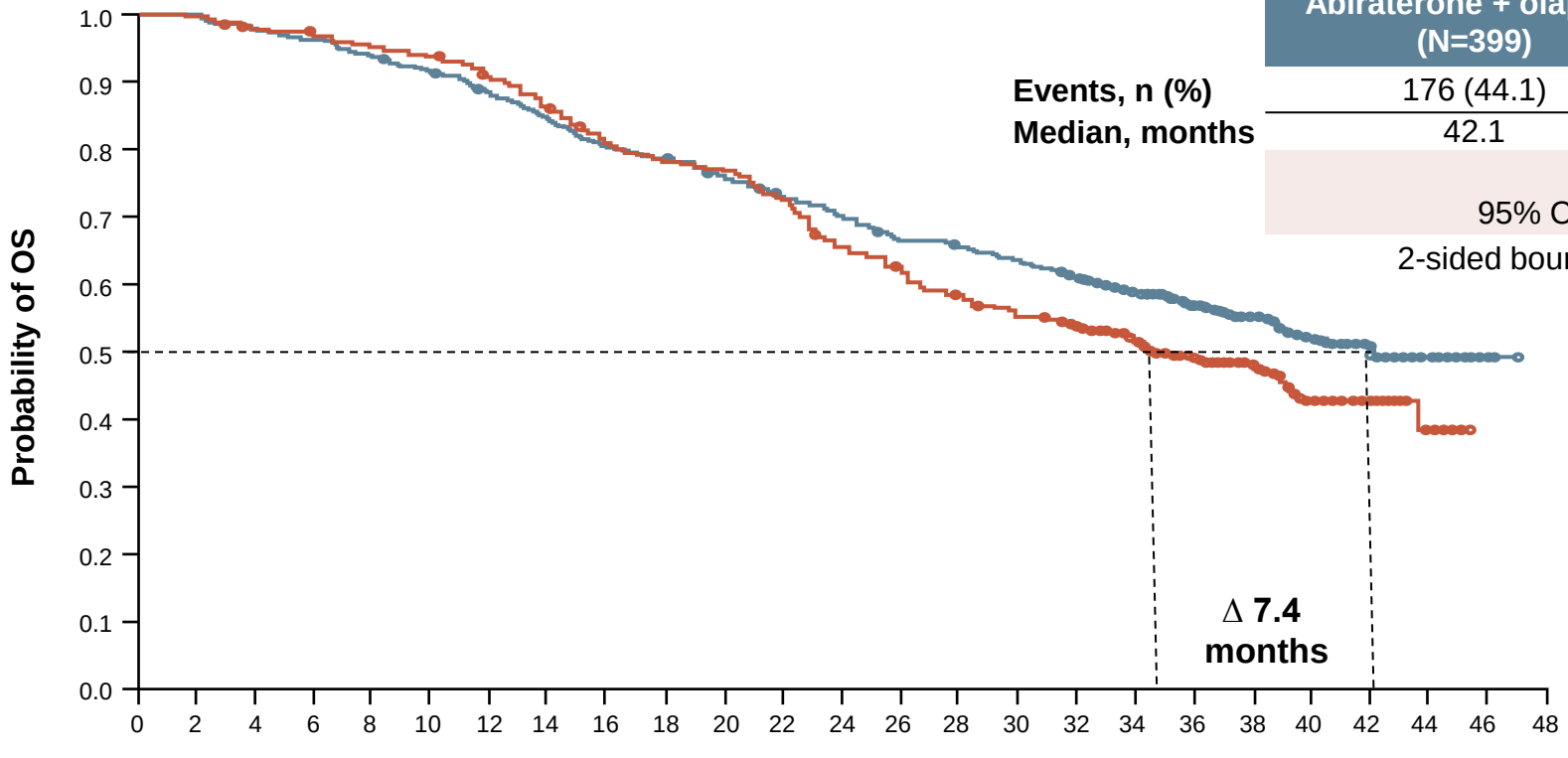

[a] The HRRm and BRCAm status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and/or plasma ctDNA HRRm tests. Aggregate HRRm and *BRCA*m subgroup analyses are post-hoc exploratory analyses. Results shown are by investigator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

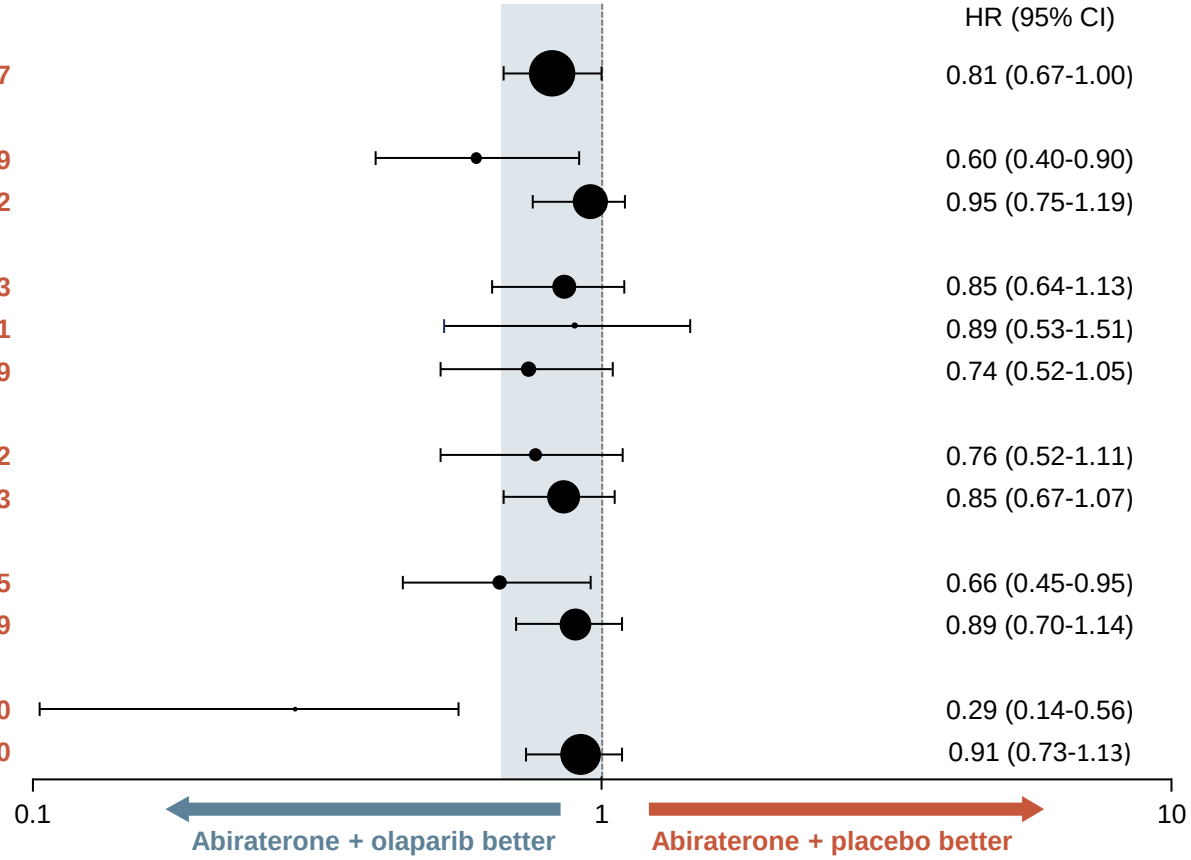
CI, confidence interval; DCO3, third data cut-off; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation)

# 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) |



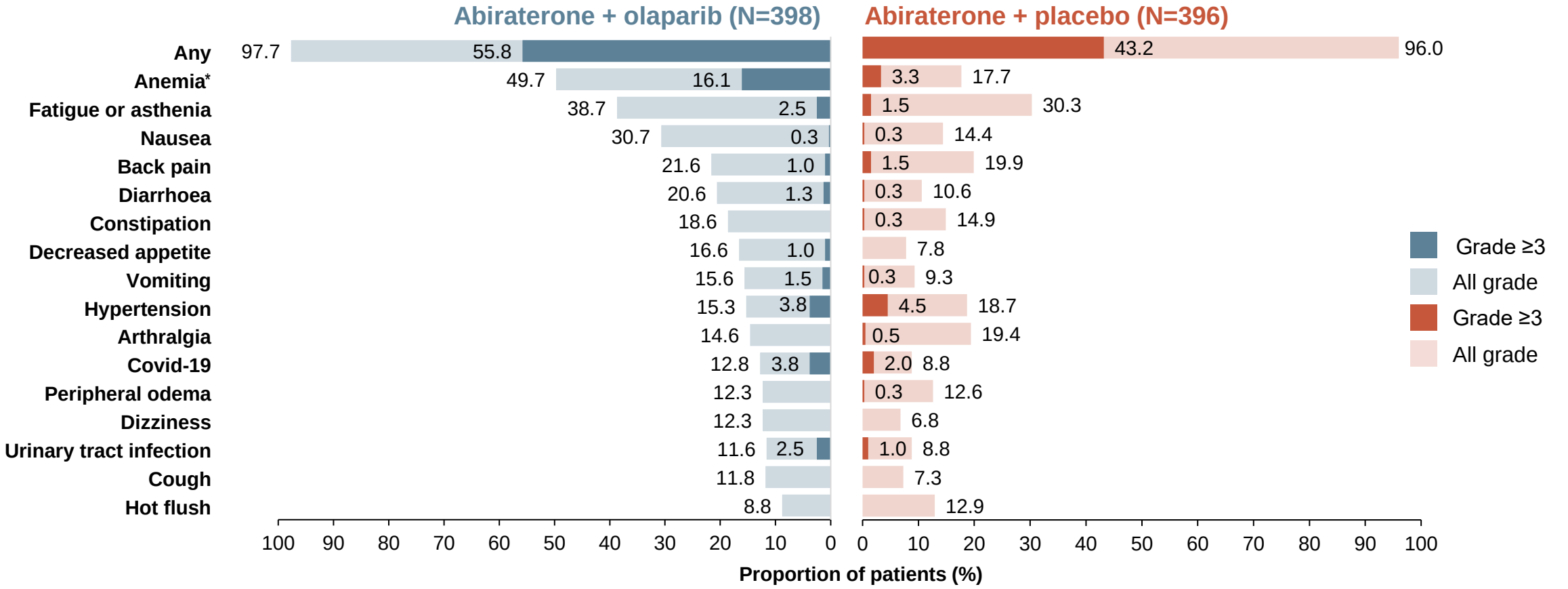

DCO3: 12 October 2022.
a HRRm and *BRCA*m status was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA tests. Aggregate subgroup analyses are post hoc and exploratory.

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)

# 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)

# 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)

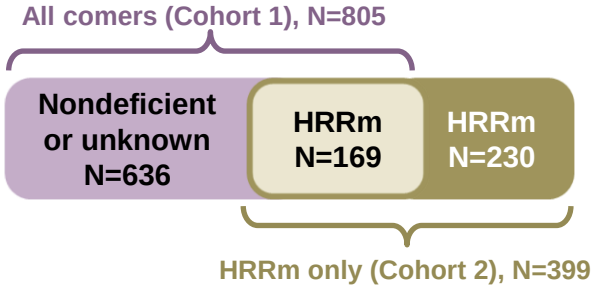
**Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily**

**(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

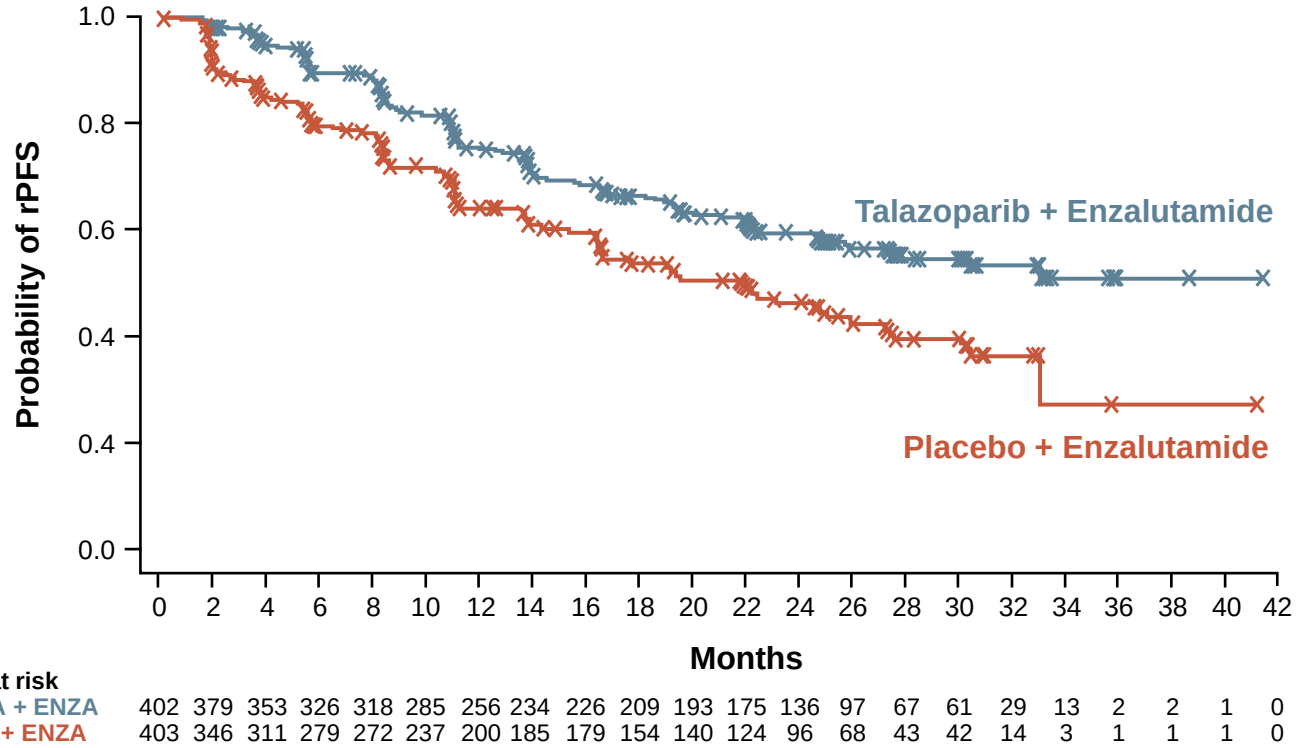
[b] Time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first

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

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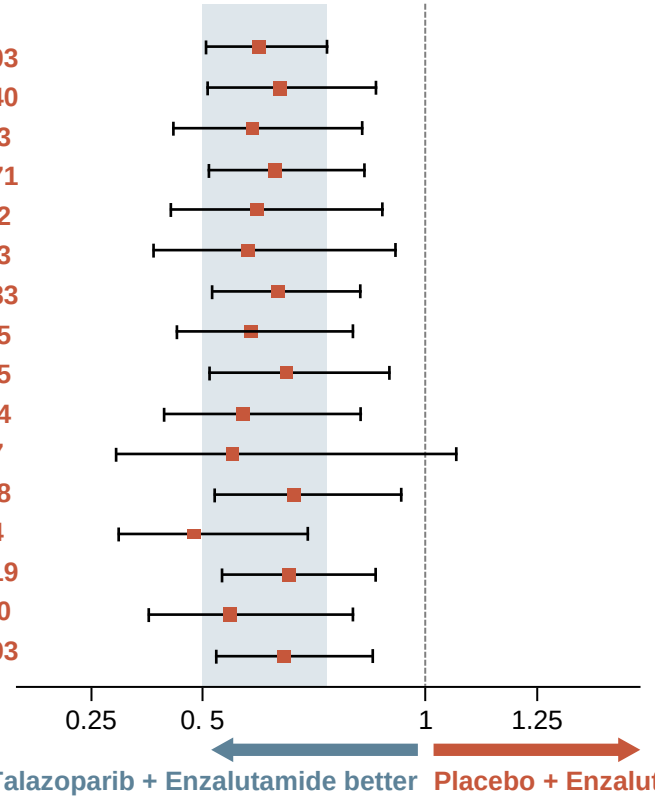
# TALAPRO-2: SUBGROUP ANALYSIS OF rPFS BY BICR

## 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

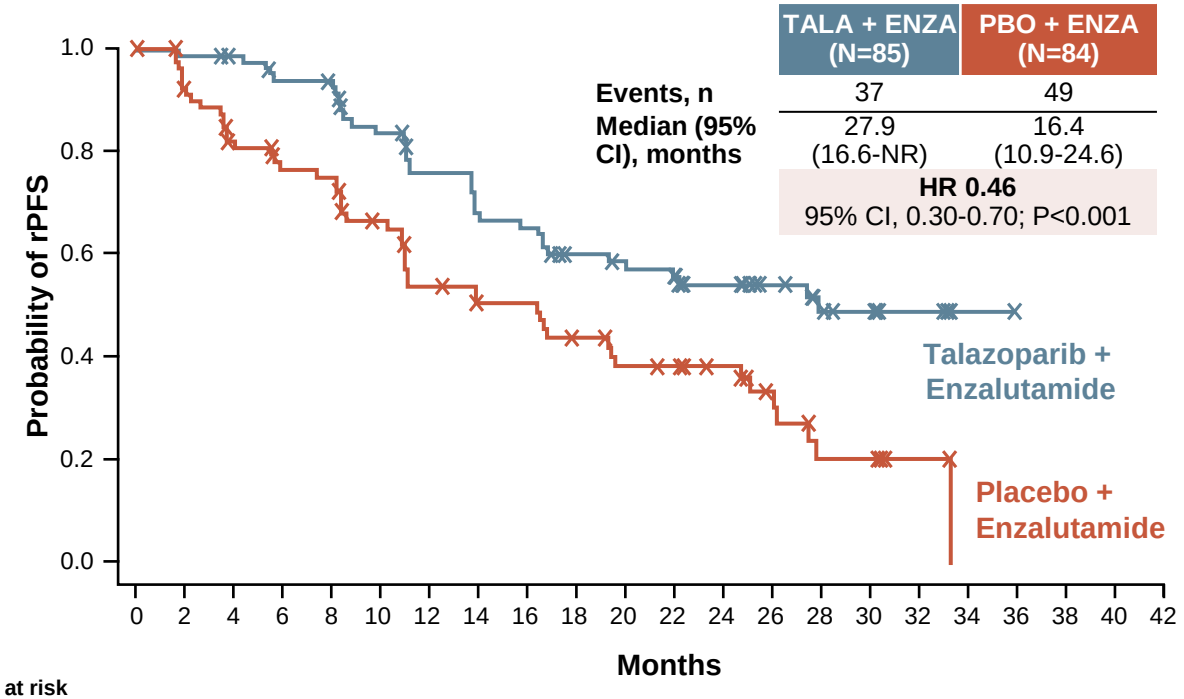
BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HRR, homologous recombination repair; rPFS, radiographic progression-free survival

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

# TALAPRO-2: rPFS BY BICR BY HRR STATUS

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

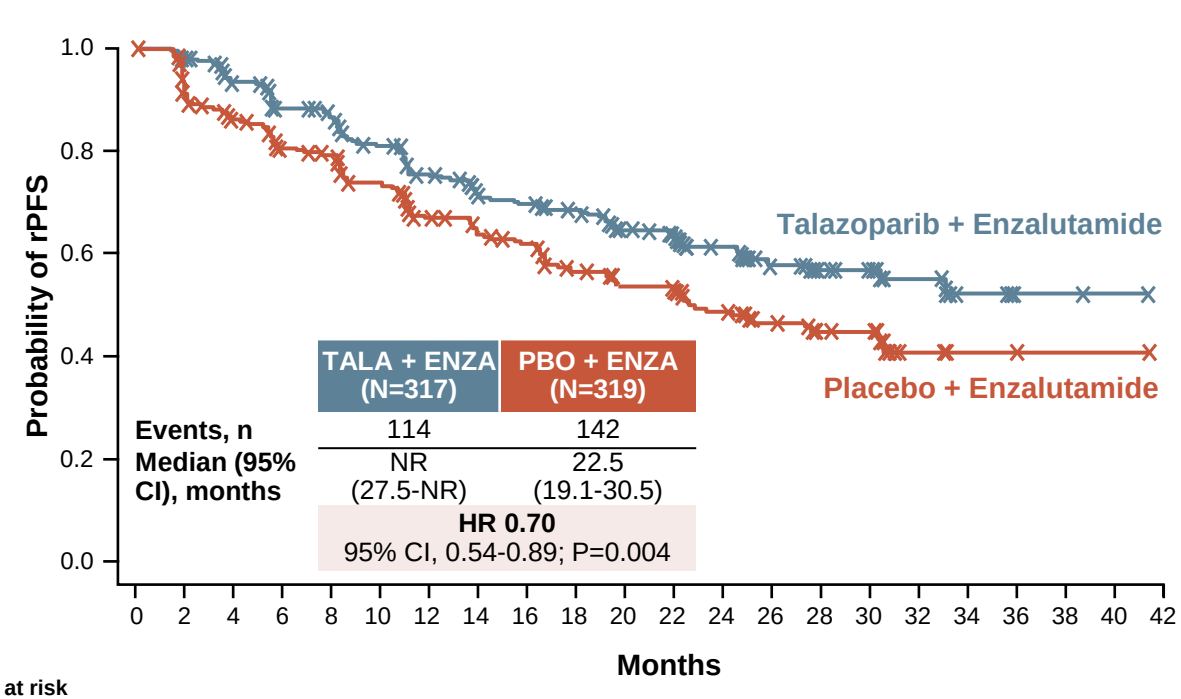
### HRR-deficient




| | TALA + ENZA (N=85) | PBO + ENZA (N=84) |
|---|---|---|
| Events, n | 37 | 49 |
| Median (95% CI), months | 27.9 (16.6-NR) | 16.4 (10.9-24.6) |
| | HR 0.46 95% CI, 0.30-0.70; P<0.001 | |

| 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




| | TALA + ENZA (N=317) | PBO + ENZA (N=319) |
|---|---|---|
| Events, n | 114 | 142 |
| Median (95% CI), months | NR (27.5-NR) | 22.5 (19.1-30.5) |
| | HR 0.70 95% CI, 0.54-0.89; P=0.004 | |

| 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 |

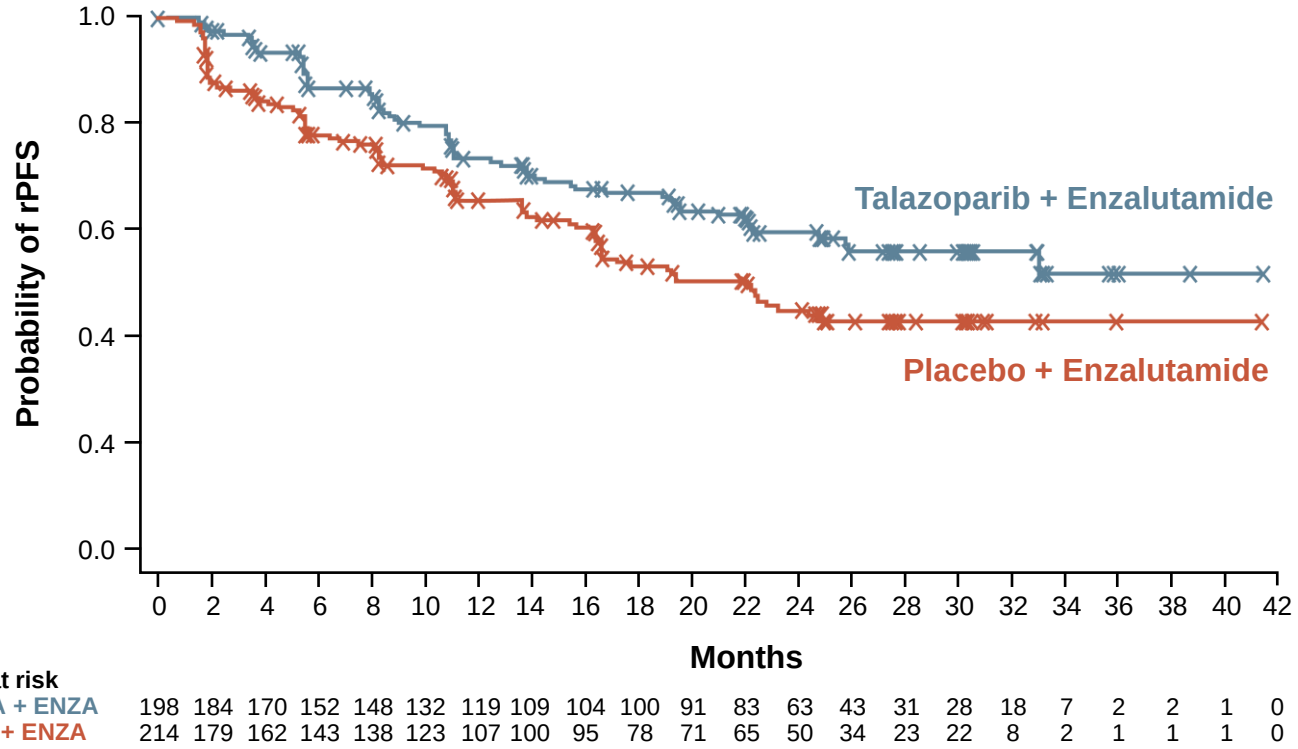
**HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor**

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)

# 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

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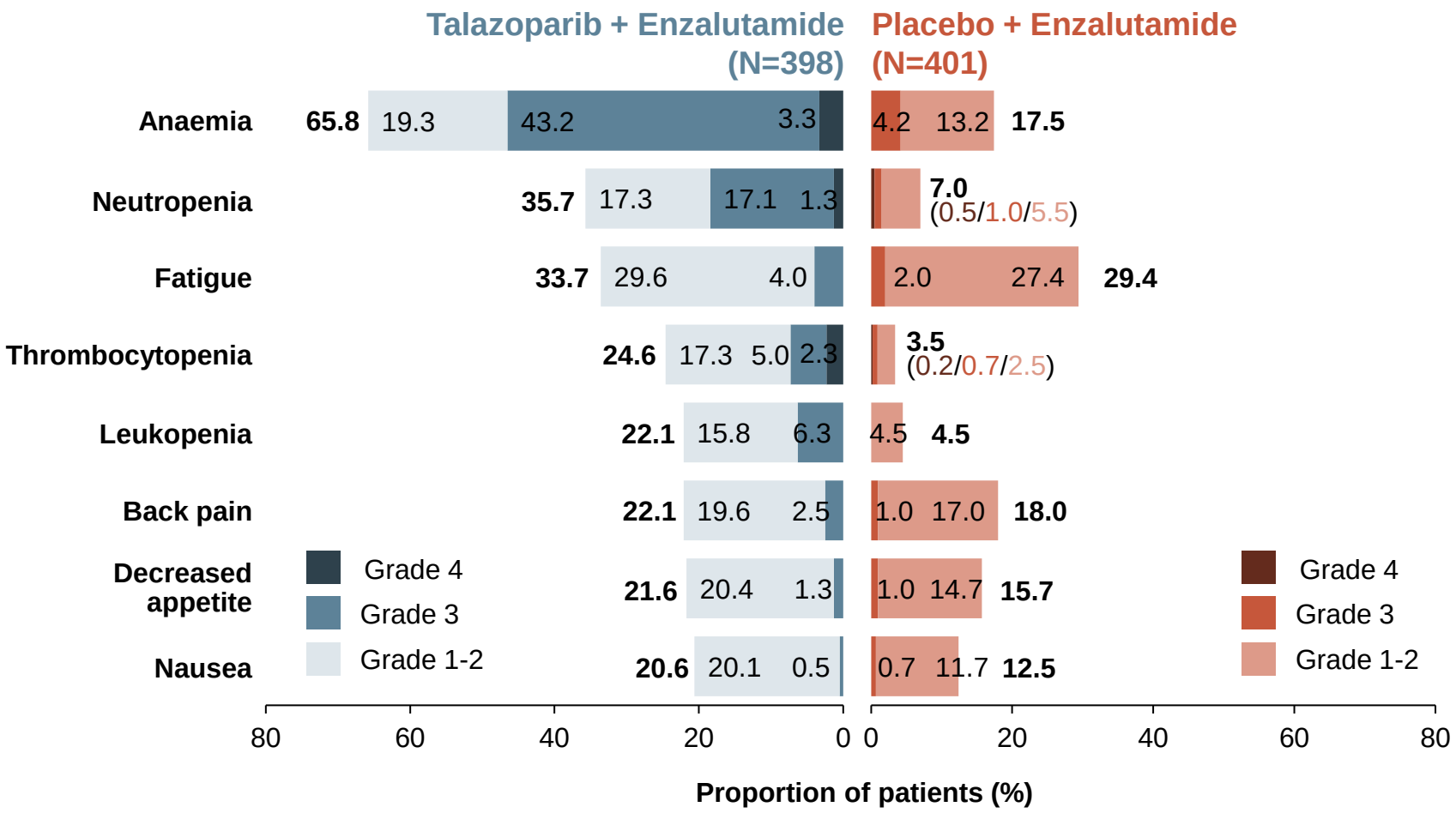
# TALAPRO-2: MOST COMMON ALL-CAUSE TEAEs




**In the talazoparib arm:**

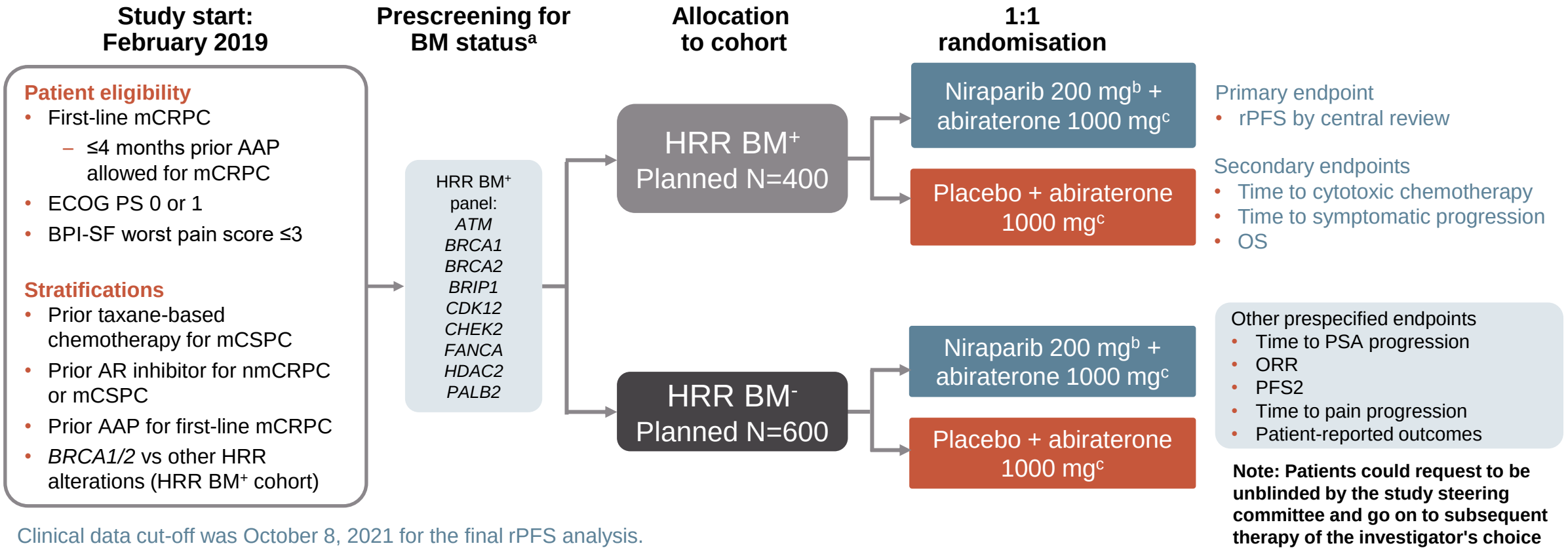
- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anaemia (43.2%)
  - Neutropenia (15.1%)
  - Thrombocytopenia (5.5%)
- 49.0% had grade 1-2 anaemia at baseline
- Grade 3-4 anaemia
  - Median time to onset was 3.3 months
  - Reported in 46.5% of men
- 8.3% discontinued talazoparib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

# 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

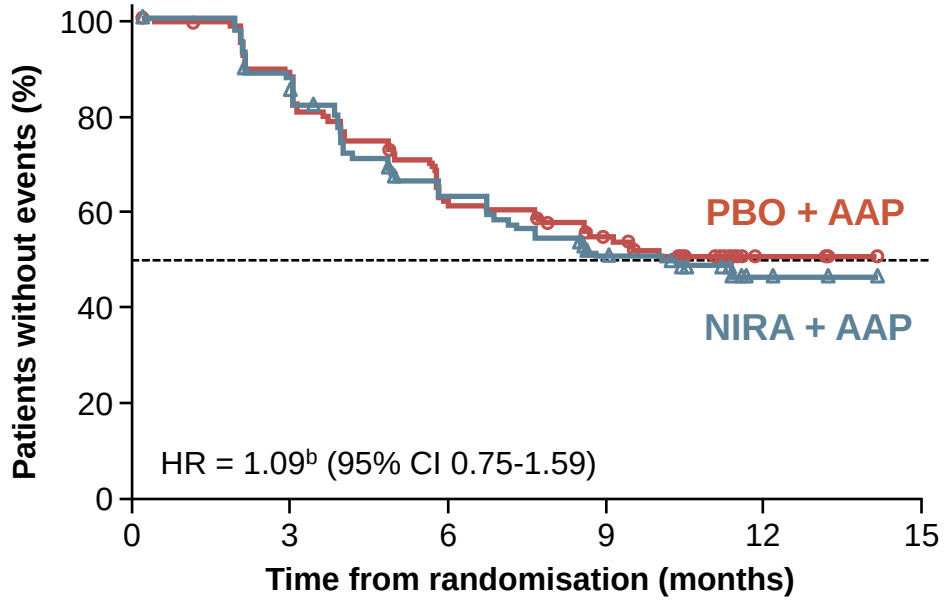
AAP, abiraterone acetate and prednisone/prednisolone; AR, androgen receptor; ATM, ataxia-telangiectasia gene; BID, twice daily; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase 2; CRPC, castration-resistant 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)

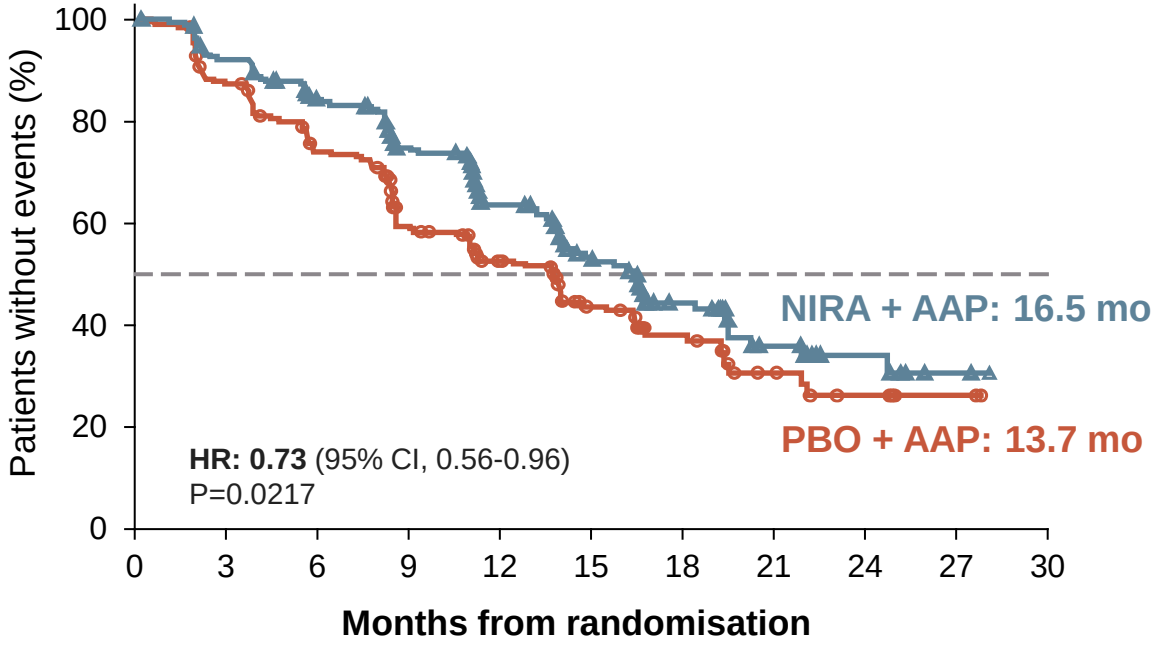
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate antigen;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

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

# MAGNITUDE: PRIMARY ENDPOINT rPFS (BICR)

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

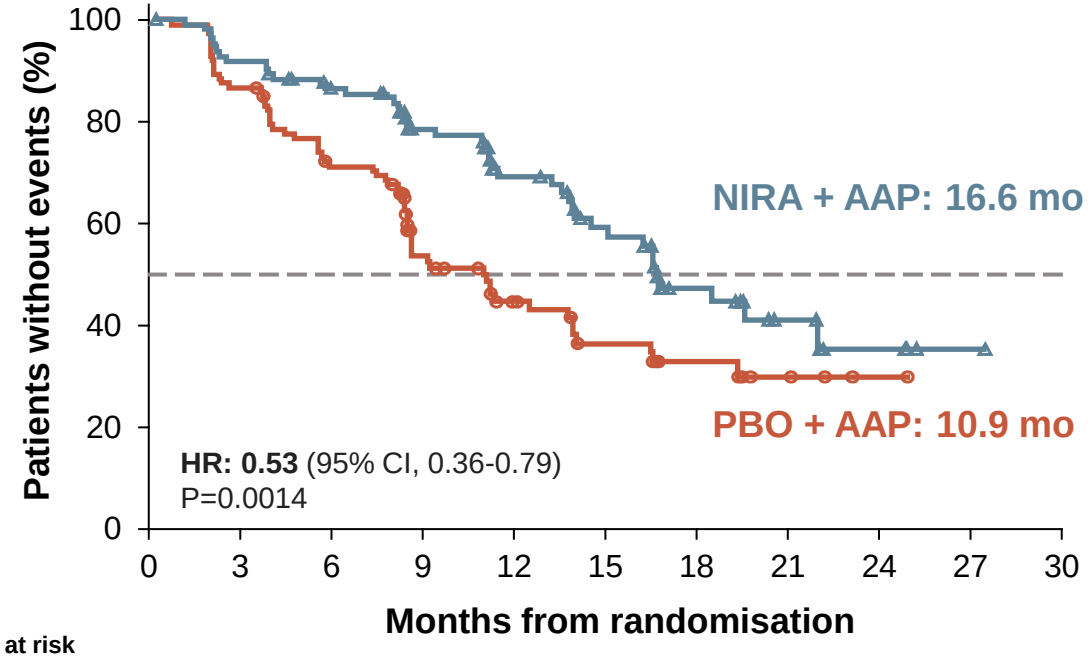
### All HRR BM+ patients




| 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

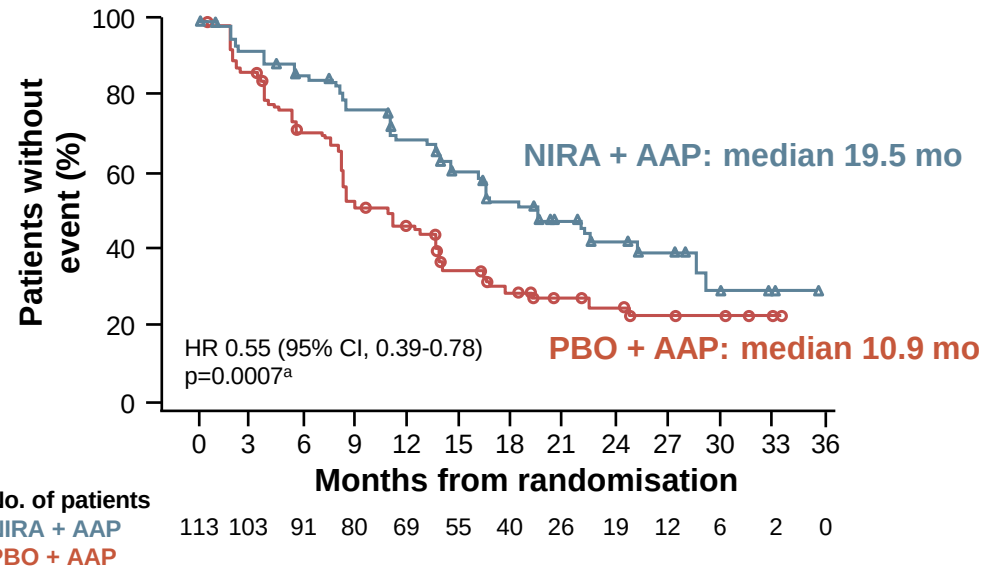
AAP, abiraterone acetate + prednisone/prednisolone; BICR, blinded independent central review; BM, biomarker; BRCA1/2, breast cancer gene 1/2; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

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

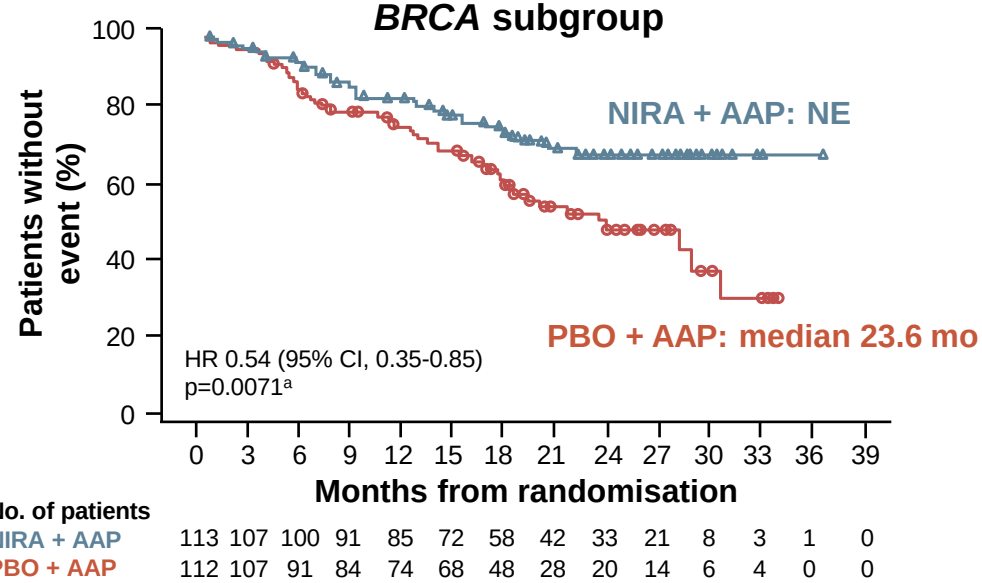
# MAGNITUDE *BRCA* PATIENTS: NIRA + AAP IMPROVED rPFS AND TIME TO SYMPTOMATIC PROGRESSION IN THE *BRCA* SUBGROUP

**With additional 8 months follow-up**

**rPFS by central review in the *BRCA* subgroup**




**Time to symptomatic progression 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)**

- 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

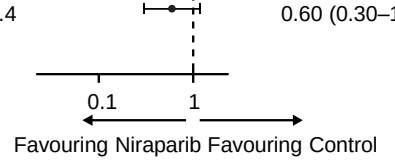
AAP, abiraterone acetate with prednisone; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRR+, homologous recombination repair positive; IA2, second interim analysis; mo, months; NE, not estimable; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

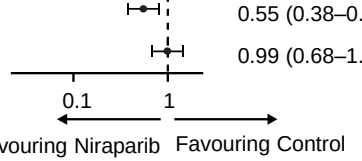
Efstathiou E, et al. J Clin Oncol 41, 2023 (suppl 6; abstr 170) (ASCO GU 2023 oral presentation)

# 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

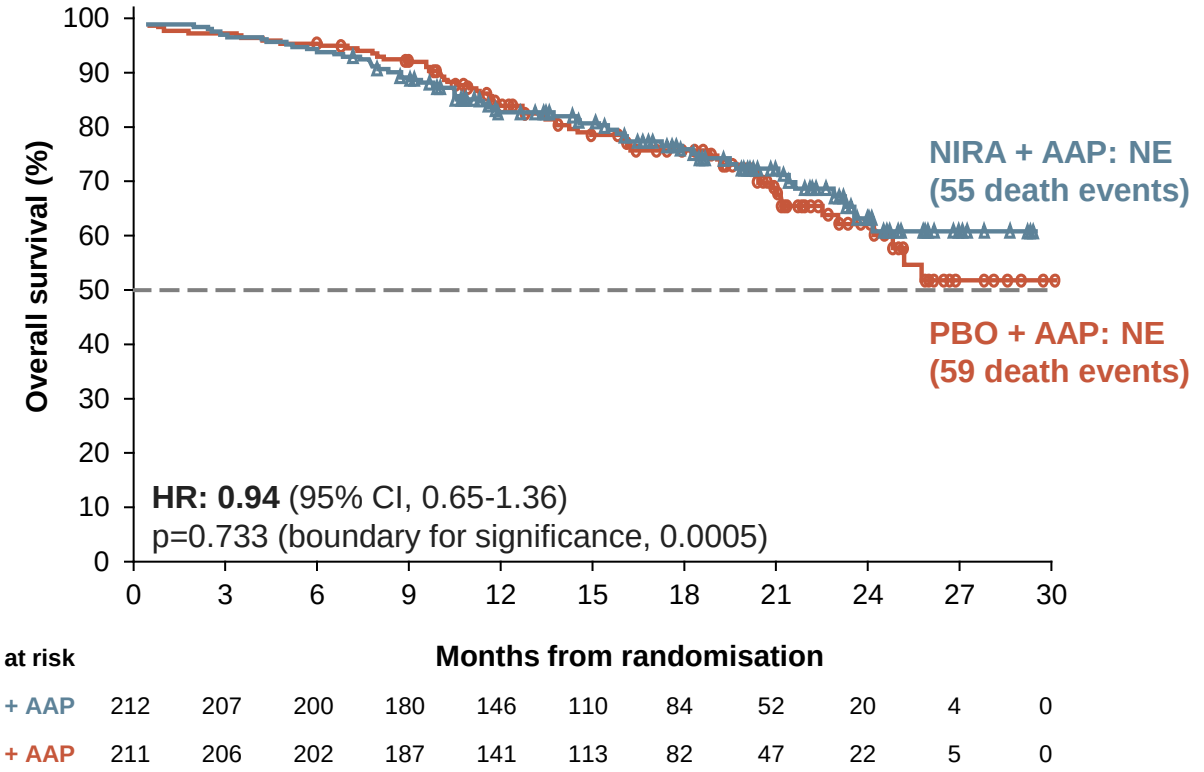
[b] Prior AAP use was up to 4 months prior to study start

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)

# MAGNITUDE ALL HRR BM+: OVERALL SURVIVAL

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



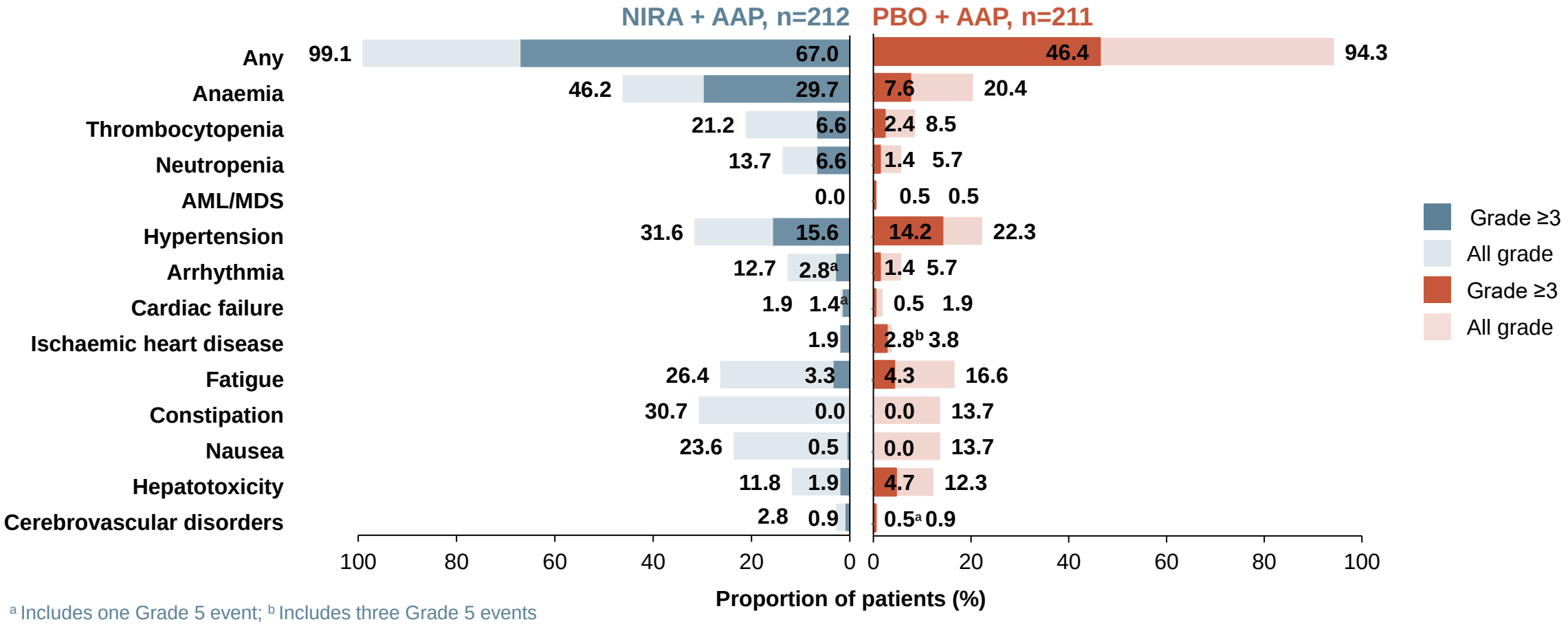

46.3% of the required death events for the final analysis observed and thus overall survival data are immature

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. J Clin Oncol. 2023; DOI: 10.1200/JCO.22.01649

# 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. J Clin Oncol. 2023; DOI: 10.1200/JCO.22.01649

# 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**

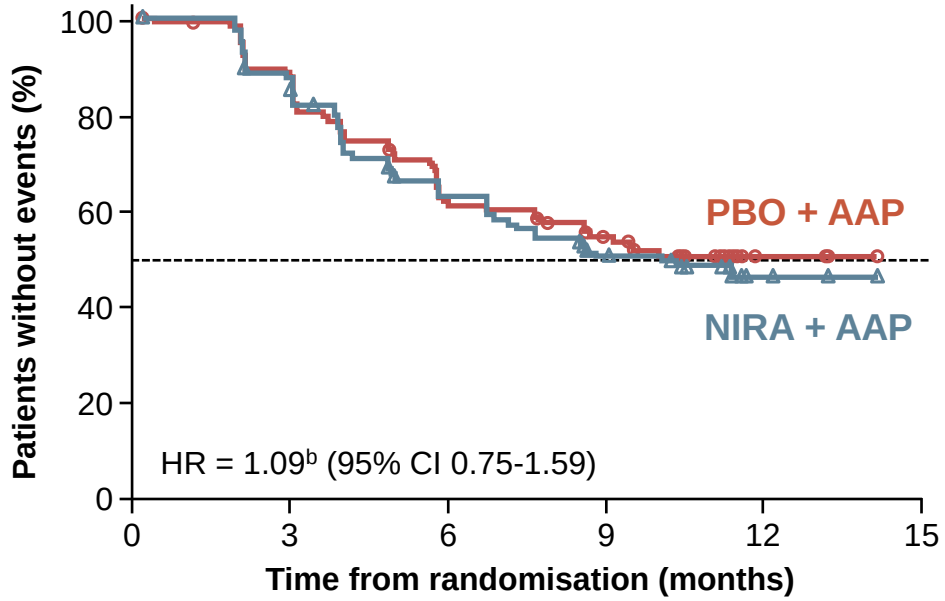
ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free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

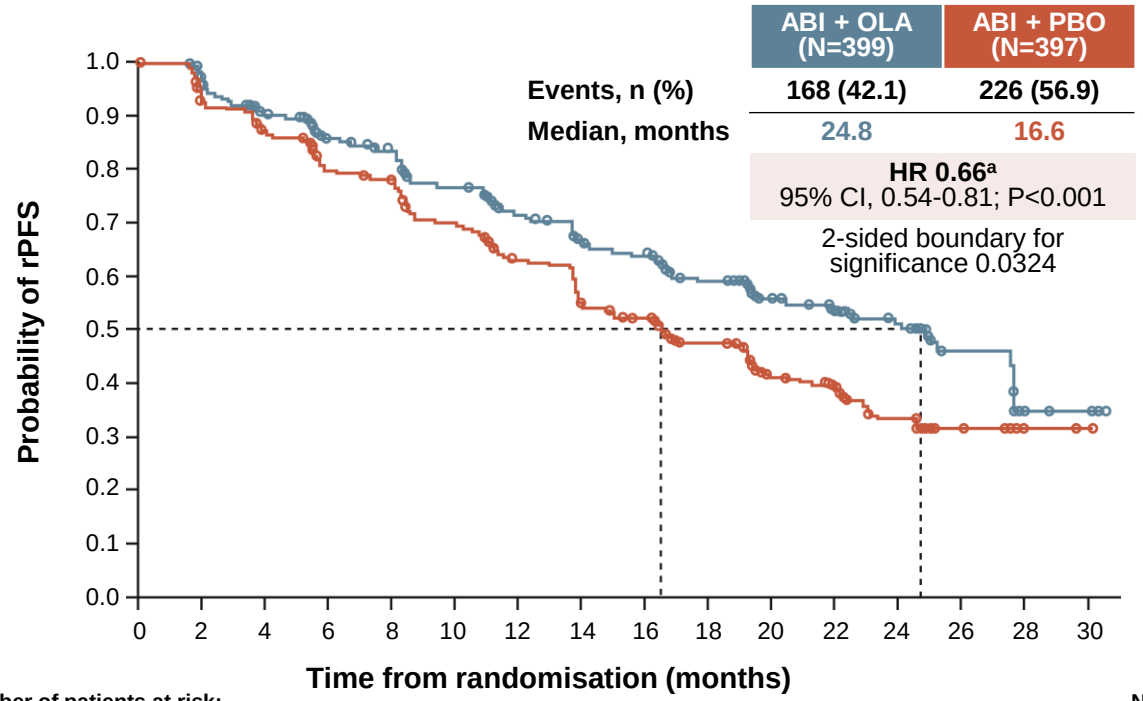
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate antigen;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

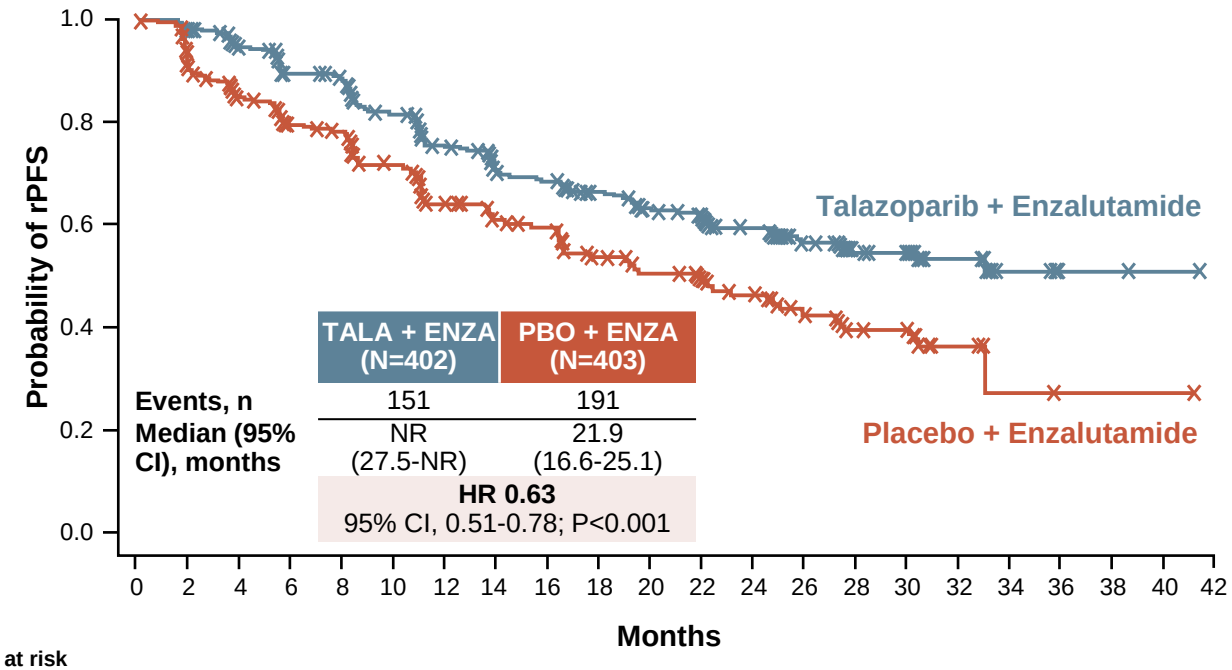



Number of patients at risk:

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

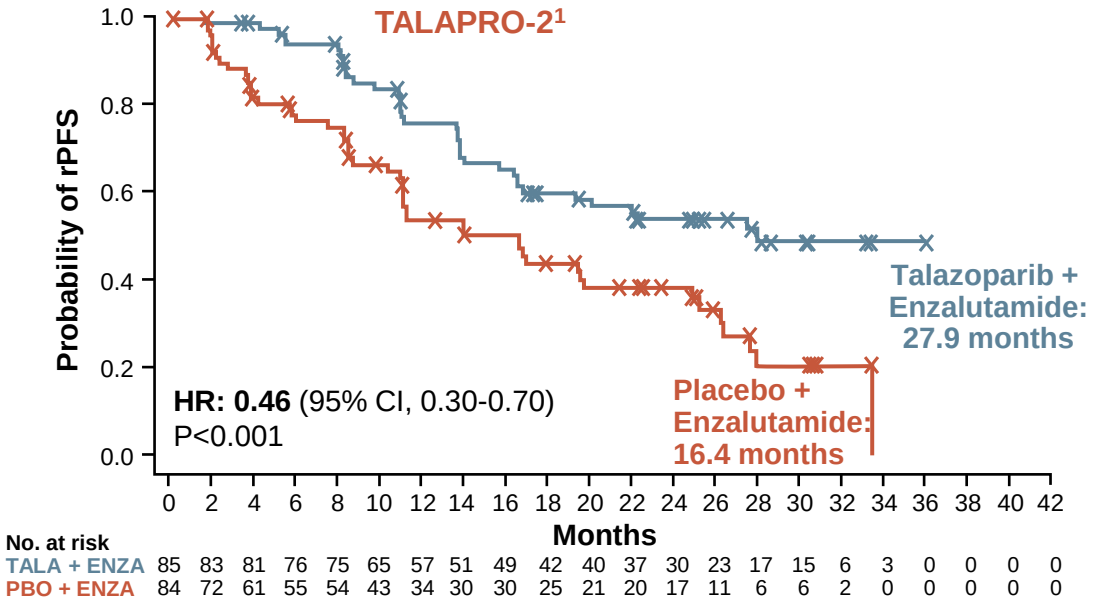
[a]HR for rPFS by BICR in pre-defined sensitivity analysis is 0.61

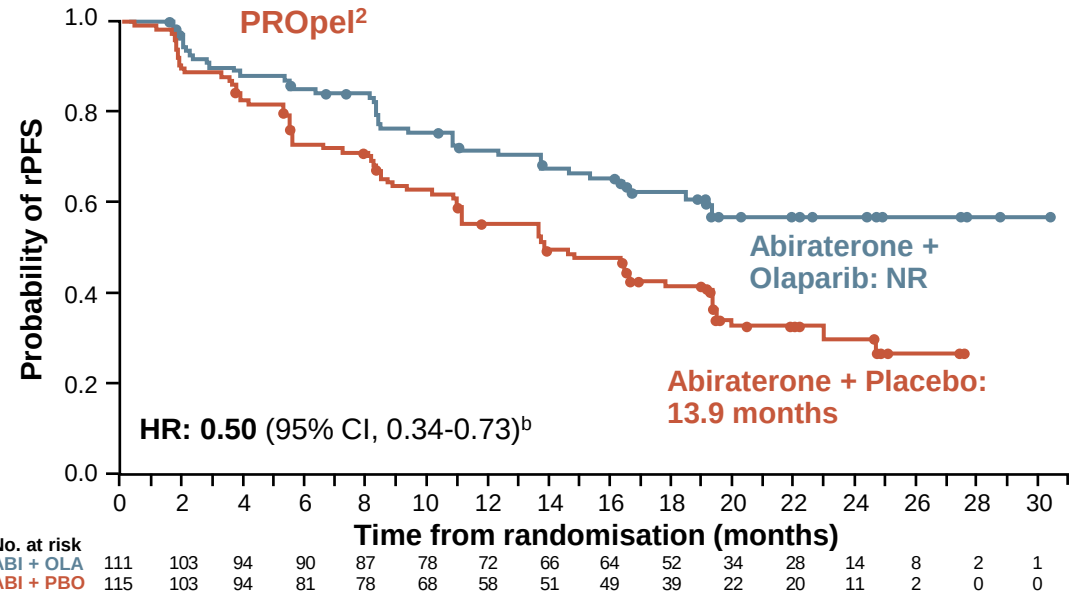
**Please note that these studies cannot be directly compared. The data are presented for information purposes only**

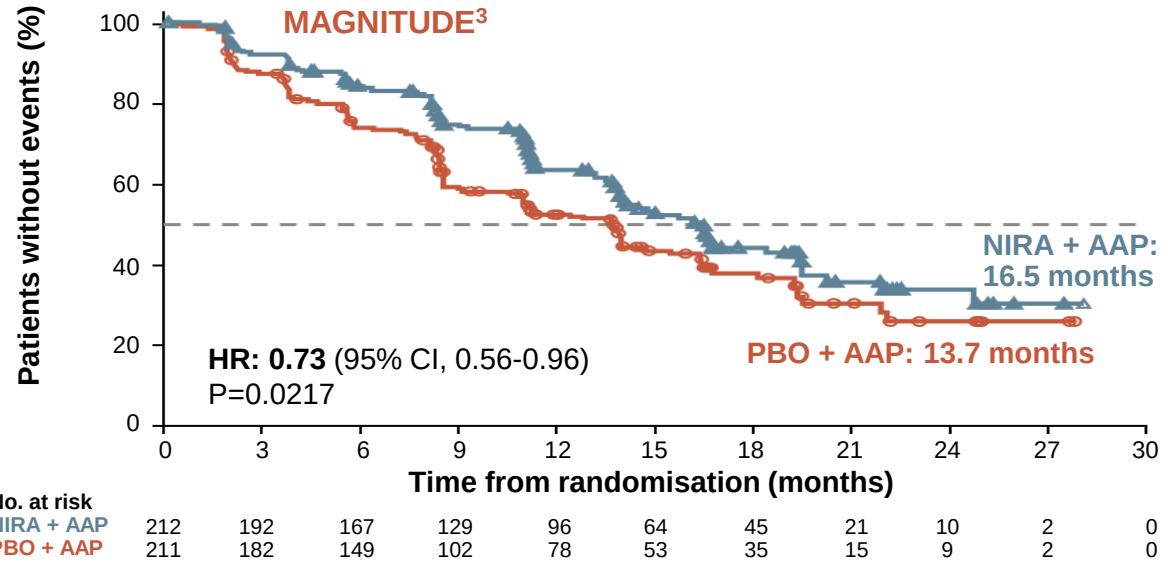
Abi, abiraterone acetate; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; Ola, Olaparib; rPFS, radiographic progression-free survival; TALA, talazoparib

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 |

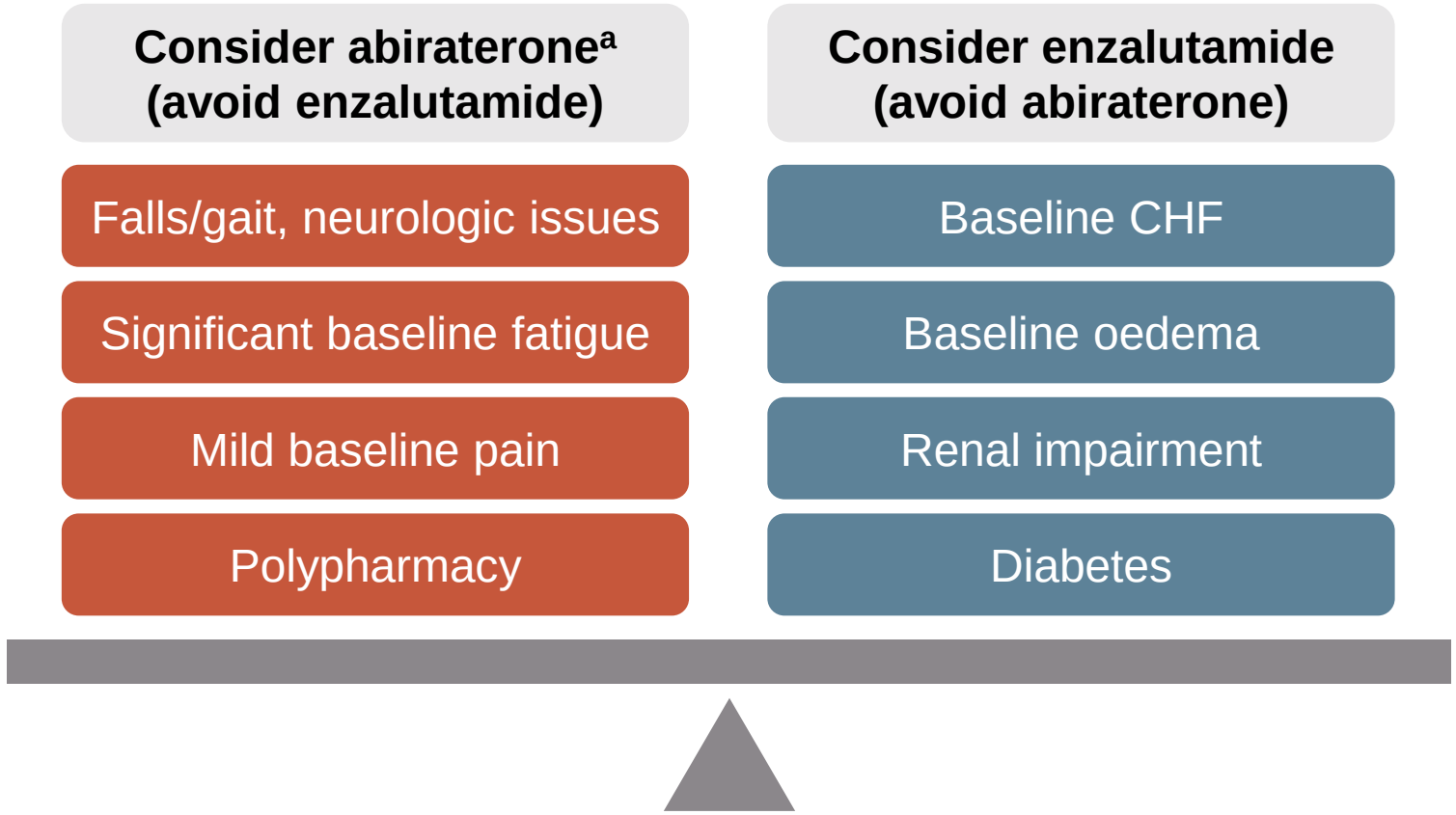
**Please note that these studies cannot be directly compared. The data are presented for information purposes only.**

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 and olaparib** 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, selected using an **FDA-approved** Lynparza **companion diagnostic**

## *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**. Determine *BRCAm* status with a **validated test method**
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with **mCRPC in whom chemotherapy is not clinically indicated**

## *Rucaparib FDA-approved indication[3]*

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

- Treatment should continue **until progression** or **unacceptable toxicity**. An LHRH analogue should be continued in patients who are not surgically castrated[1,2]
- Talazoparib is not currently approved in prostate cancer

**[a]Rucaparib has no current approval in prostate cancer in Europe[4]**

## *Niraparib EMA-approved indication[5]*

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**

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 (Aug-2022); 2. Lynparza (olaparib) summary of product characteristics (Mar 2023); 3. Rubraca (rucaparib) US prescribing information (Jun 2022); 4. Rubraca (rucaparib) summary of product characteristics (Dec 2022); 5. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate

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