GU CONNECT MICRO LEARNING

THE USE OF PARP INHIBITORS IN PROSTATE CANCER TREATMENT AND THE RATIONALE BEHIND COMBINATION TREATMENT

MODULE TWO

UPDATED DECEMBER 2023

mCRPC, metastatic castration-resistant prostate cancer; PARP, poly-ADP ribose polymerase

MODULE TWO

EVOLVING LANDSCAPE OF PARPi IN mCRPC: COMBINATION WITH ANTI-ANDROGENS

THIS MODULE HAS BEEN DEVELOPED BY TWO INTERNATIONAL EXPERTS

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DISCLAIMER AND DISCLOSURES

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- **Dr. Pasquale Rescigno:** AZ, Janssen, MSD Italy, BMS and Gilead

EDUCATIONAL OBJECTIVES

- Understand the data of combination studies with PARP inhibitors
- Recognise the rationale and mechanism of action of the combination of PARPi and anti-androgen therapies
- Consider implementation of combination treatment in clinical practice

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 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 PARPi, but patients with other HRR alterations also derive benefit
- PARP inhibitors combined with novel hormonal agents are 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

RATIONALE FOR COMBINATION OF PARPi WITH NHT

NHT, novel hormonal therapy; PARPi, poly (ADP-ribose) polymerase inhibitor

METASTATIC PROSTATE CANCER IS BIOLOGICALLY HETEROGENEOUS

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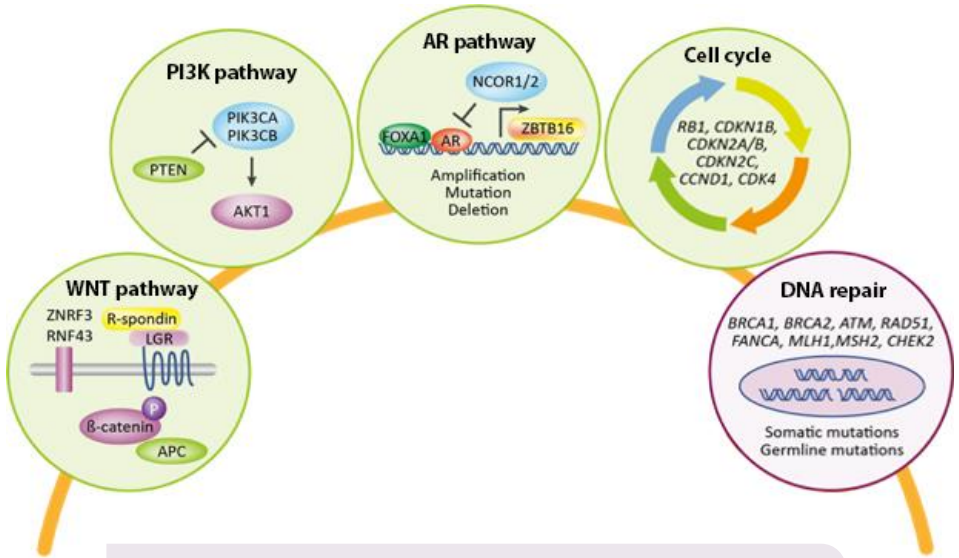
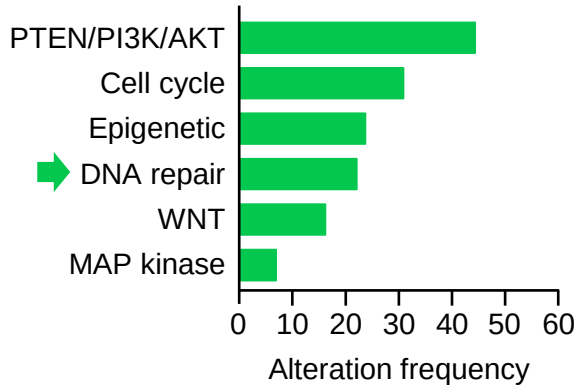
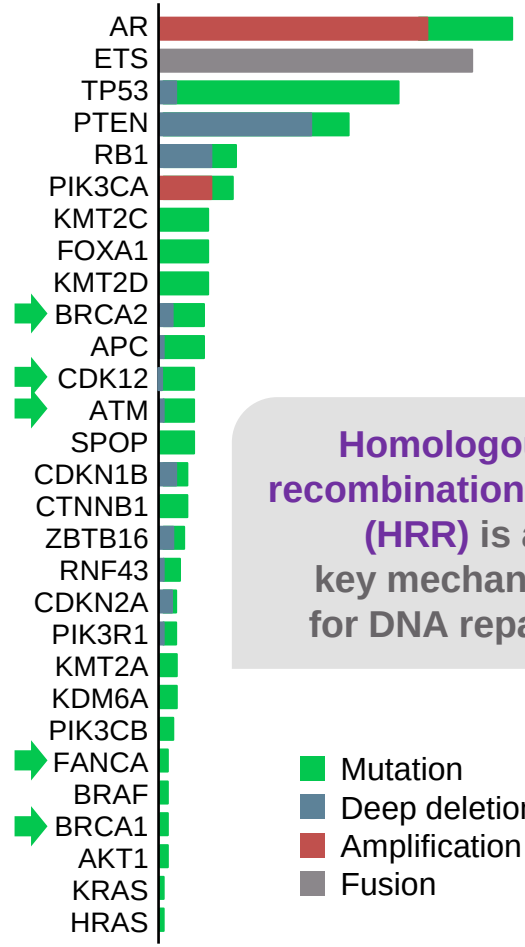
Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



~23% of of mCRPC harbour **DNA repair aberrations[1]**

Approximately 25% of patients with mCRPC have alterations associated with DNA repair pathways[a,2]





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

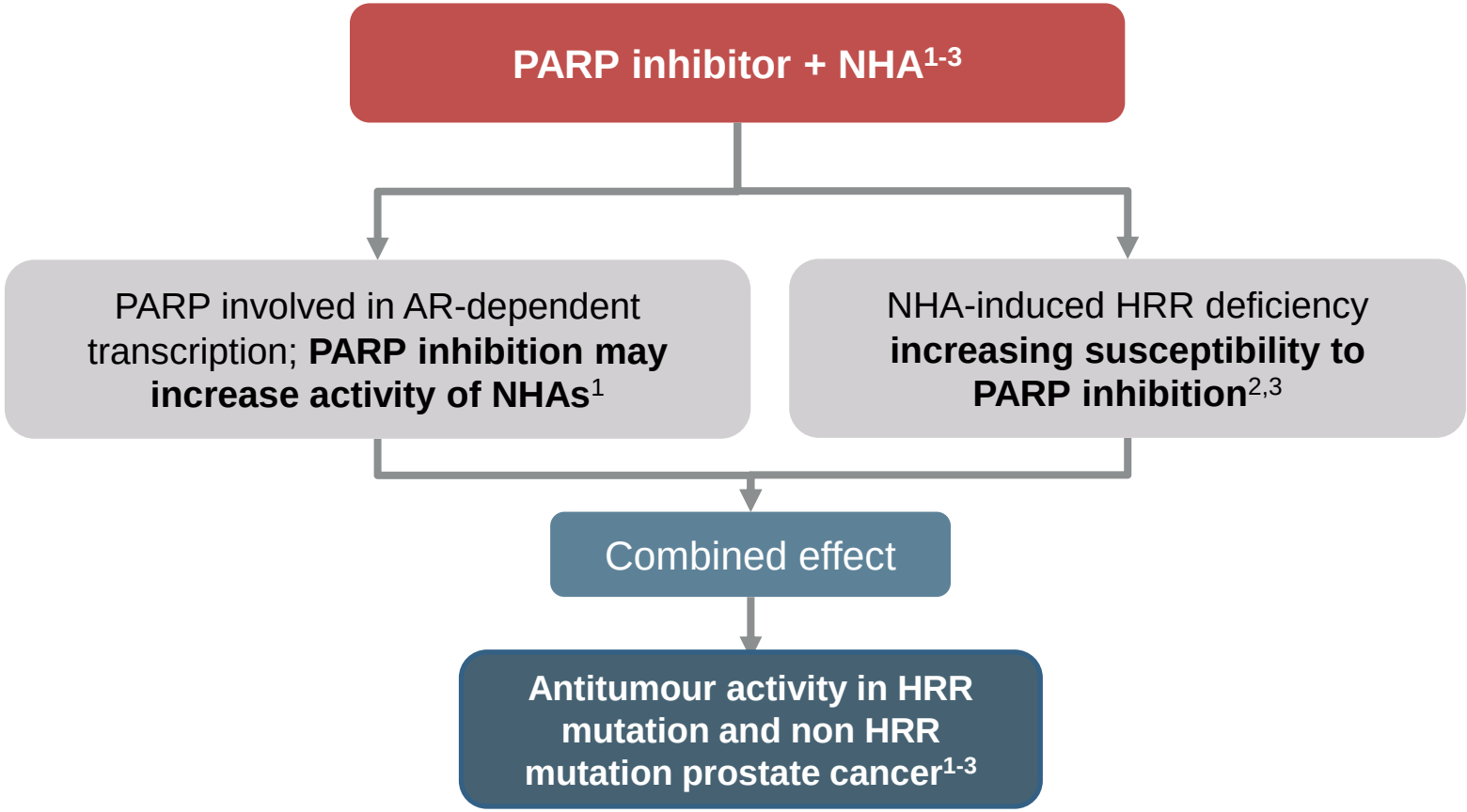
[a] A multi-institutional study profiling 444 tumours from 429 mCRPC patients

AR, androgen receptor; ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; mCRPC, metastatic castration-resistant prostate cancer; PI3K, phosphoinositide 3-kinase; WNT, wingless integration

1. Robinson D, et al. Cell. 2015;161:1215-28; 2. Abida W, et al. Proc Natl Acad Sci U S A. 2019;116:11428-36; 3. Lord CJ and Ashworth A. Nature. 2012;481:287-93; 4. O'Connor MJ. Mol Cell. 2015;60:547-60

RATIONALE FOR COMBINING PARP INHIBITORS AND NHAs

Interaction between PARP signalling and AR signalling pathways may explain the combined effect of agents observed in preclinical models



AR, androgen receptor; HRR, homologous recombination repair; NHA, novel hormonal agent; PARP, poly-ADP ribose polymerase

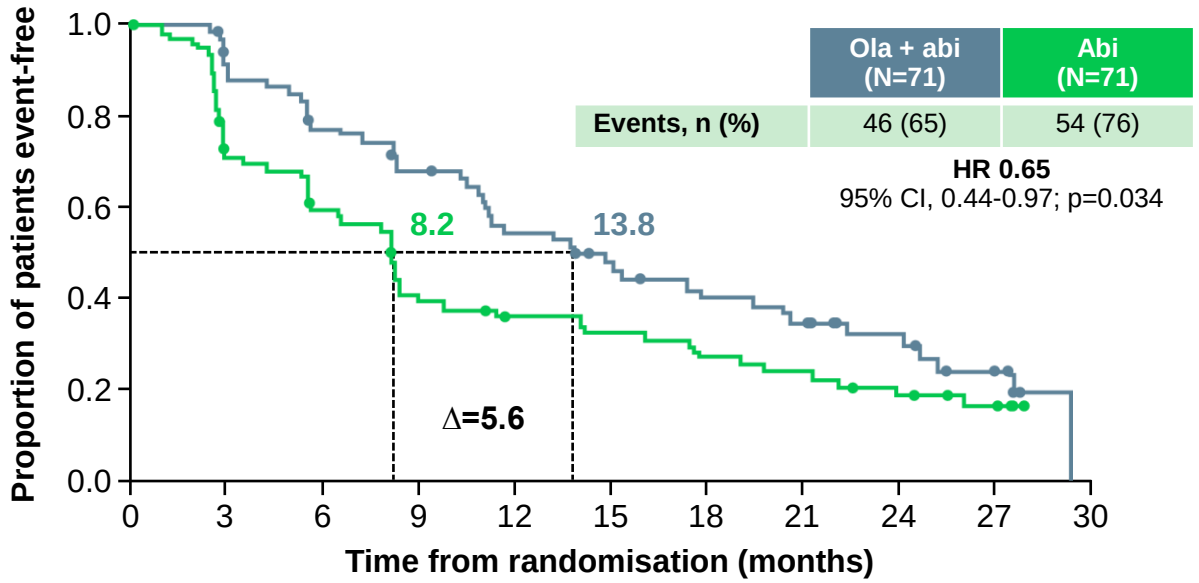
1. Schiewer MJ, et al. Cancer Discov. 2012;2:1134-49; 2. Polkinghorn WR, et al. Cancer Discov. 2013;3:1245-53; 3. Asim M, et al. Nat Commun. 2017;8:374;

Adapted from Saad F, et al. J Clin Oncol. 2022;40 Suppl: Abstract 11 (ASCO GU 2022 oral presentation)

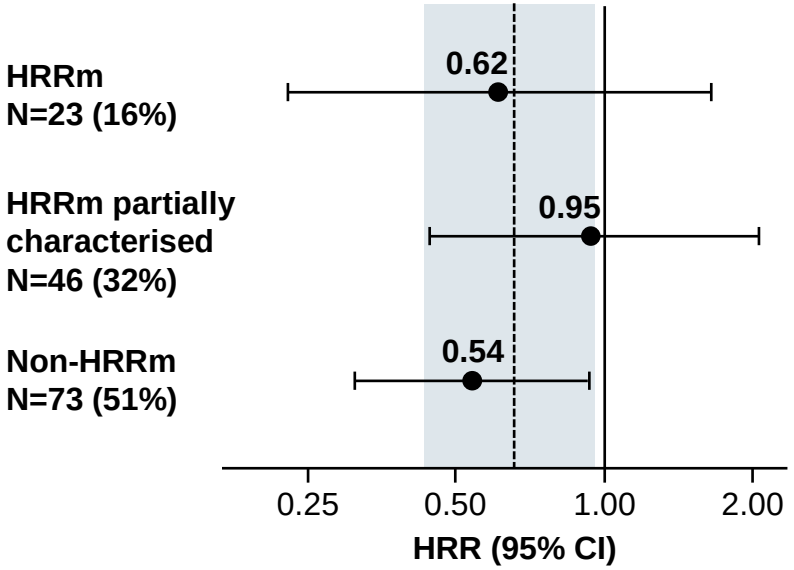
STUDY 8: A PHASE II STUDY OF OLAPARIB AND ABIRATERONE

- Patients: mCRPC with progression on docetaxel, **unselected by HRRm status**
- Randomised 1:1 to full dose of olaparib + abiraterone vs placebo + abiraterone†
- Statistically significant improvement in rPFS with olaparib + abiraterone, **irrespective of HRRm status**

INVESTIGATOR-ASSESSED rPFS



rPFS BY HRRm SUBGROUP*



* Dashed line and shaded area show HR and 95% CI, respectively, for the intent to treat population; † Olaparib 300 mg bd, abiraterone 1000 mg od and all patients also received prednisone/prednisolone 5 mg bd

Abi, abiraterone; bd, twice daily; CI, confidence interval; HR, hazard ratio; HRRm, homologous recombination repair mutation; mCRPC, metastatic castration-resistant prostate cancer; od, once daily; Ola, Olaparib; rPFS, radiographic progression-free survival

Clarke N, et al. Lancet Oncol. 2018;19:975-86; Carr T, et al. Cancers. 2021;13:5830. Adapted from: Saad F, et al. J Clin Oncol. 40, 2022 (suppl 6; abstr 11) (ASCO GU 2022 oral presentation)

KEY PARPi COMBINATION TRIALS IN 1L mCRPC

Which patient subgroups benefit?

PROpel: STUDY DESIGN

A GLOBAL, RANDOMISED, DOUBLE-BLIND PHASE 3 TRIAL

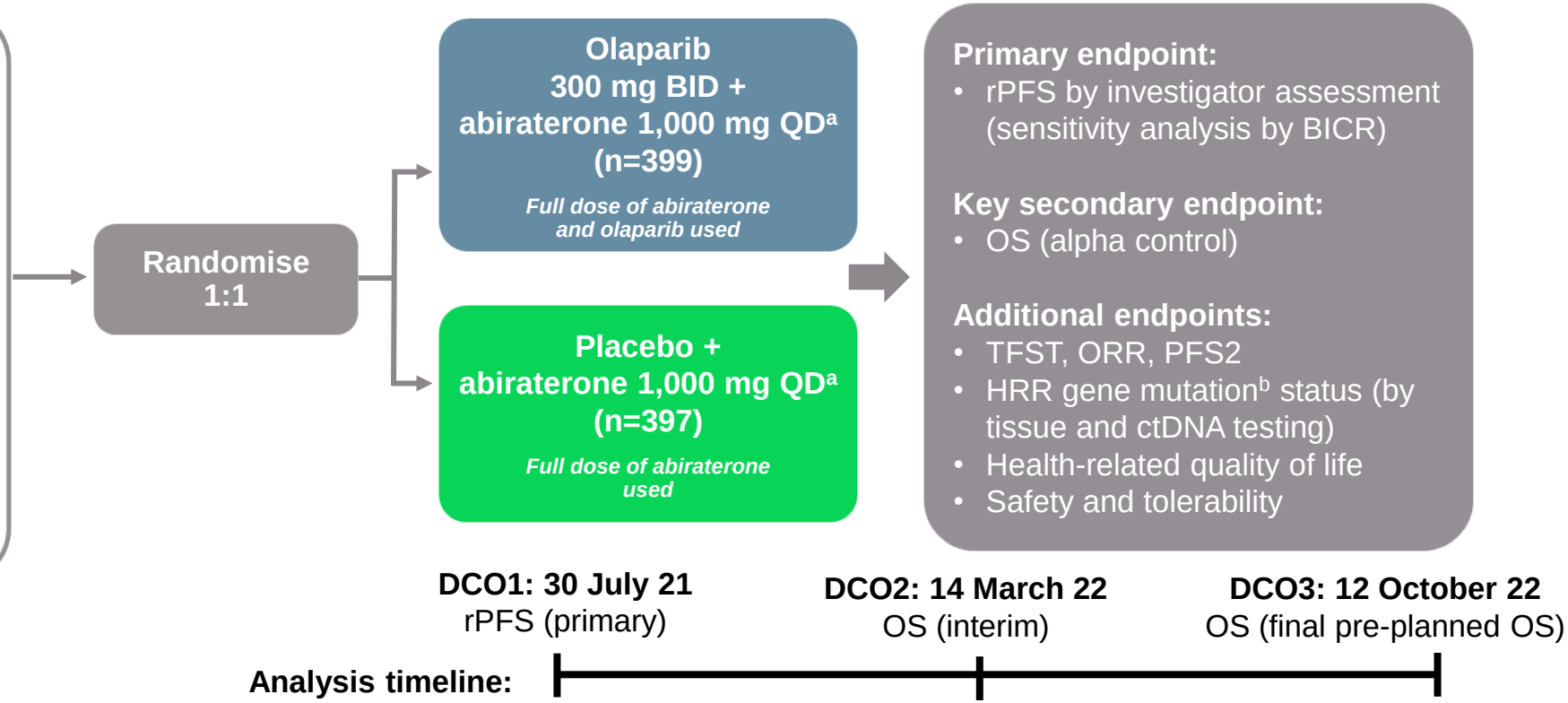
Key eligibility criteria

- 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



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

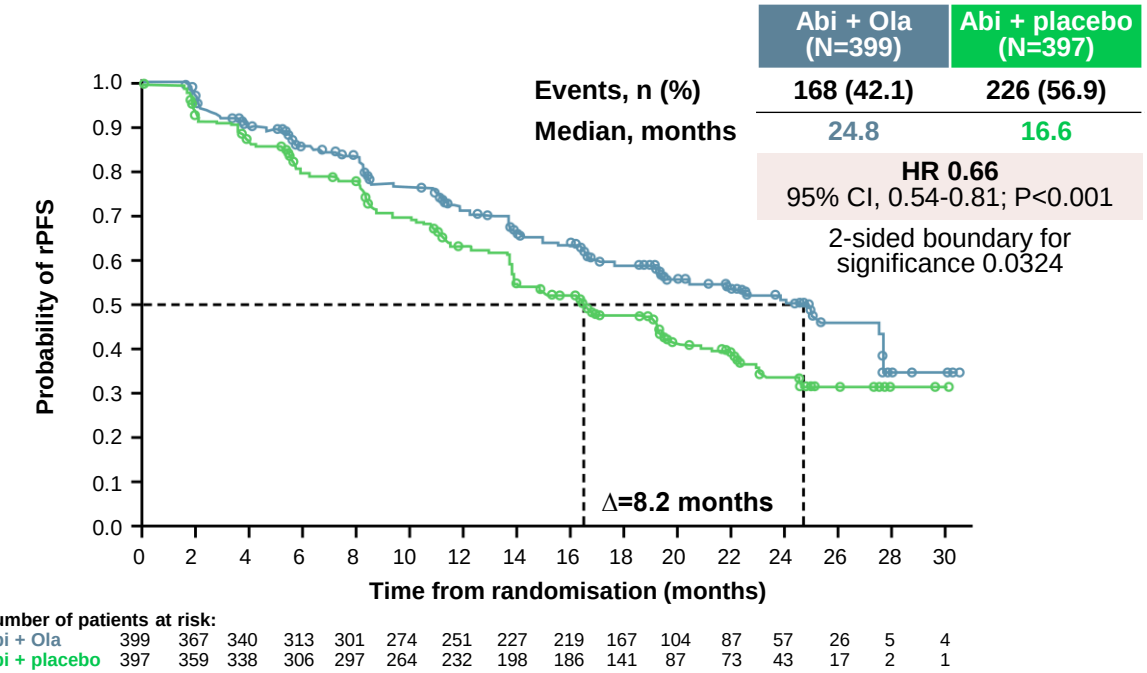
ADT, androgen-deprivation therapy; BID, twice daily; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate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

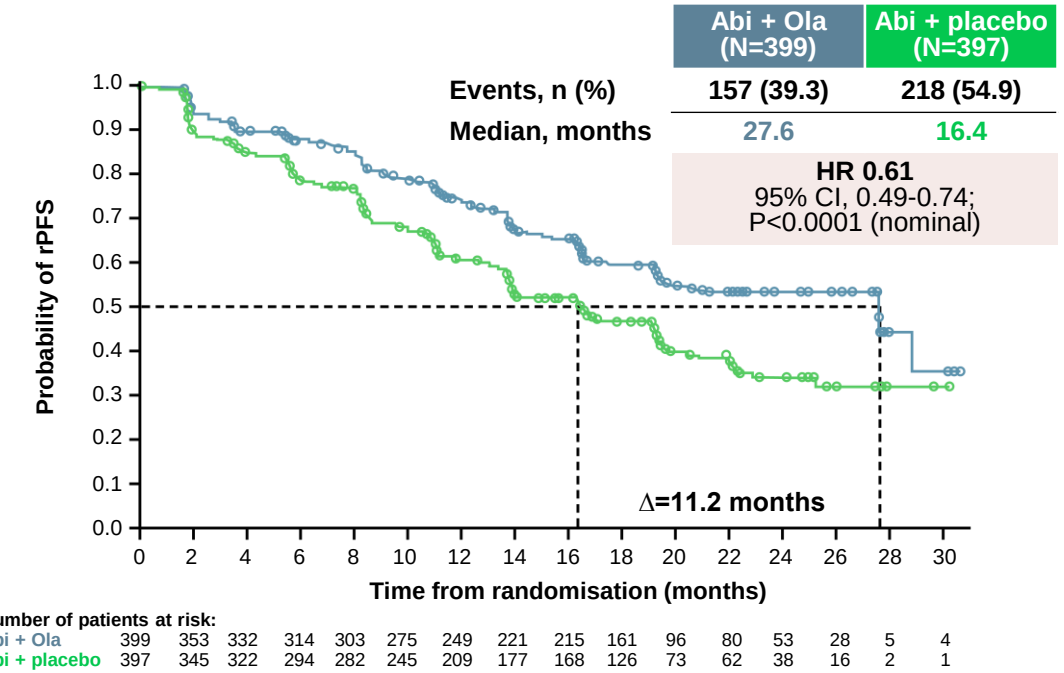
PROpel: PRIMARY rPFS RESULTS (DCO1)[1]

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)

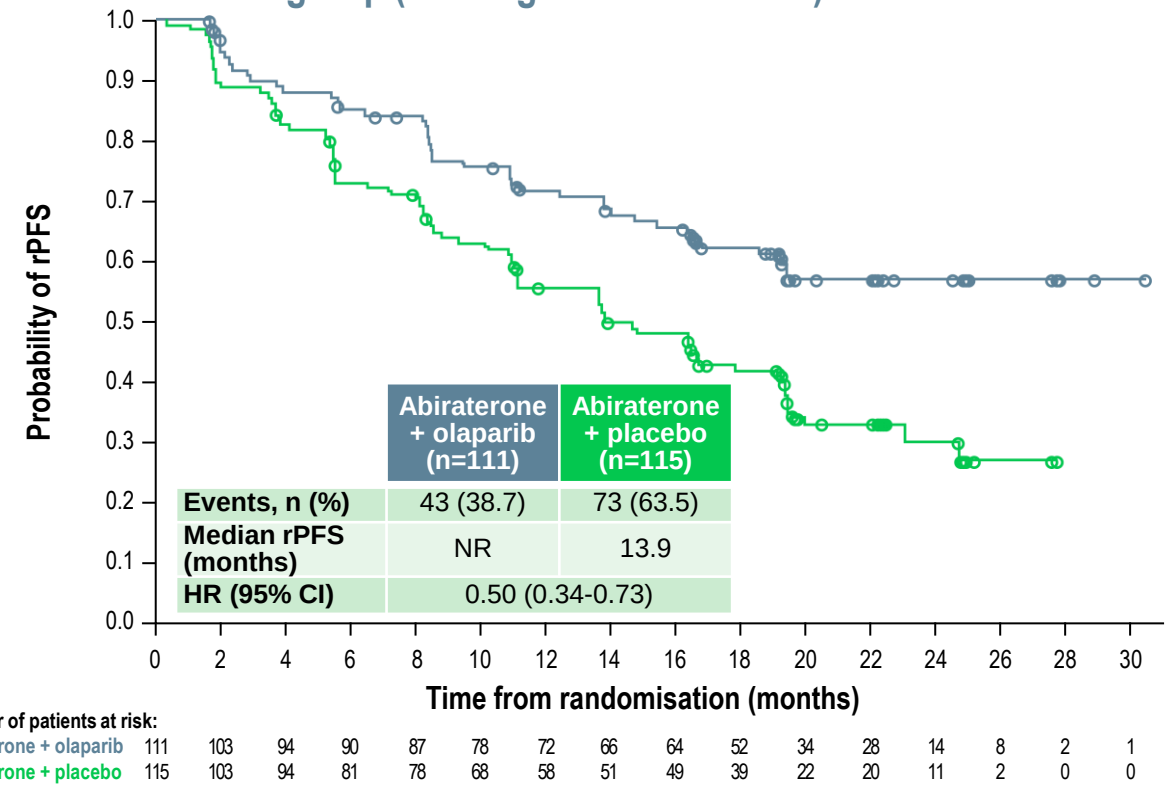
Abi, abiraterone; CI, confidence interval; DCO1, first data cut-off; HR, hazard ratio; ITT, intention-to-treat; Ola, olaparib; rPFS, radiographic progression-free survival

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: rPFS FOR HRRm AND NON-HRRm SUBGROUPS

A BENEFIT WAS OBSERVED WITH ABIRATERONE + OLAPARIB ACROSS HRRm AND NON-HRRm SUBGROUPS (DCO1)

HRRm subgroup (investigator assessment)



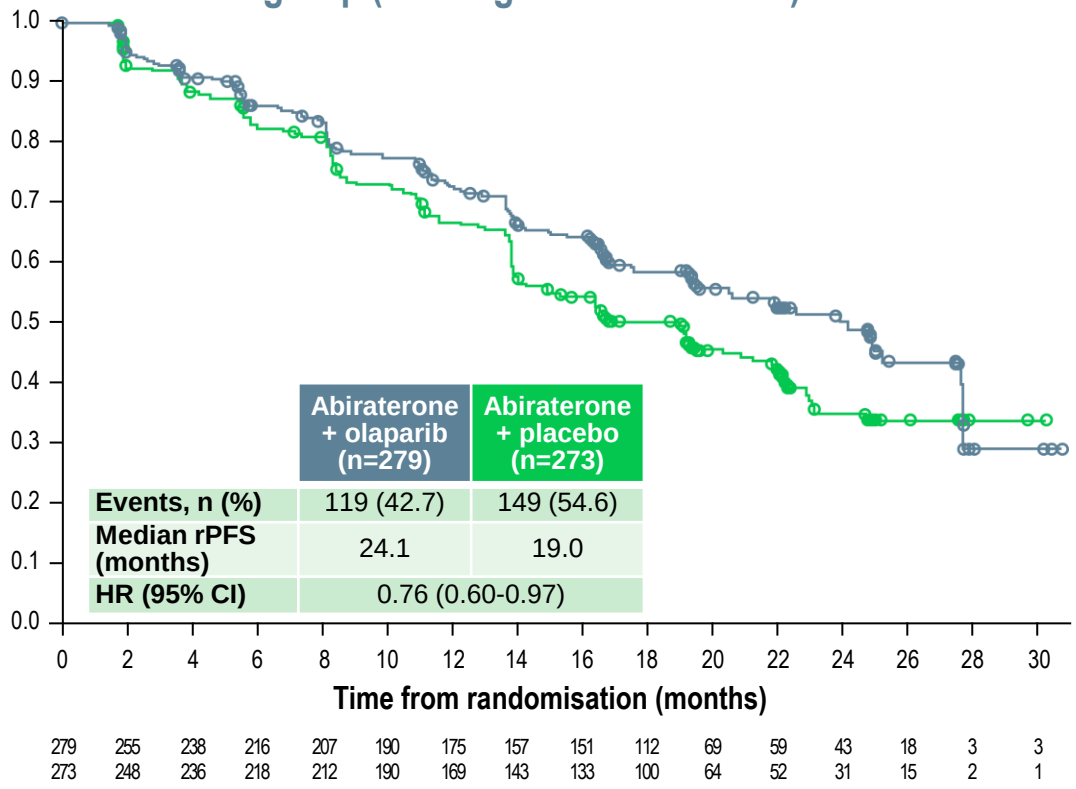
	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS (months)	NR	13.9
HR (95% CI)	0.50 (0.34-0.73)	

Number of patients at risk:

Abiraterone + olaparib	111	103	94	90	87	78	72	66	64	52	34	28	14	8	2	1
Abiraterone + placebo	115	103	94	81	78	68	58	51	49	39	22	20	11	2	0	0

Sensitivity analysis by blinded independent central review: Median 28.8 vs 13.8 months; HR 0.45, 95% CI 0.31-0.65

Non-HRRm subgroup (investigator assessment)



	Abiraterone + olaparib (n=279)	Abiraterone + placebo (n=273)
Events, n (%)	119 (42.7)	149 (54.6)
Median rPFS (months)	24.1	19.0
HR (95% CI)	0.76 (0.60-0.97)	

Abiraterone + olaparib	279	255	238	216	207	190	175	157	151	112	69	59	43	18	3	3
Abiraterone + placebo	273	248	236	218	212	190	169	143	133	100	64	52	31	15	2	1

Sensitivity analysis by blinded independent central review: Median 27.6 vs 19.1 months; HR 0.72, 95% CI 0.56-0.93

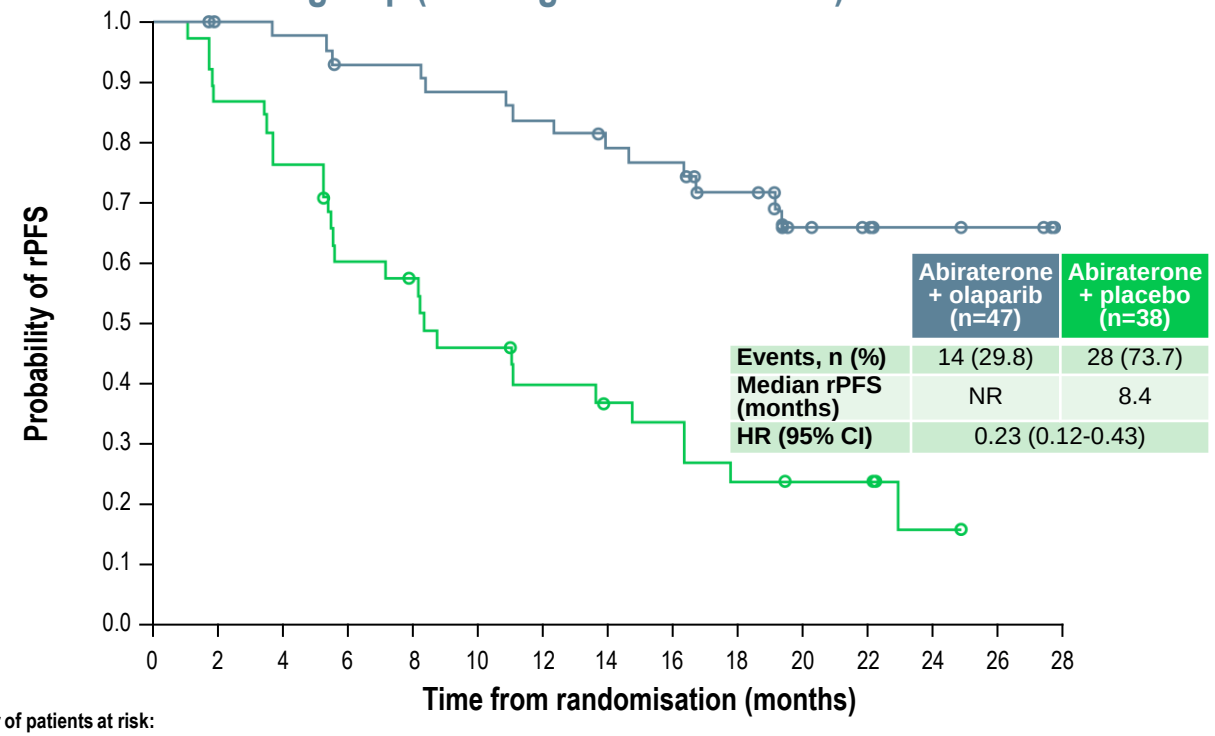
Patient enrolment was not based on HRRm status; however, HRRm testing was prespecified. HRR status was determined after randomisation and before primary analysis using results from tumour tissue and plasma ctDNA HRRm tests. A total of 18 patients did not have a valid HRR testing result from either a tumour tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post-hoc exploratory analysis. A circle indicates a censored observation CI, confidence interval; ctDNA, circulating tumour DNA; DCO1, first data cut-off; HR, hazard ratio; HRRm, homologous recombination repair mutation; NR, not reached; rPFS, radiographic progression-free survival

Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 oral presentation)

PROpel: rPFS FOR *BRCA*m AND NON-*BRCA*m SUBGROUPS

A BENEFIT WAS OBSERVED WITH ABIRATERONE + OLAPARIB ACROSS *BRCA*m, NON-*BRCA*m, *BRCA2* AND NON-*BRCA2* SUBGROUPS (DCO1)[a]

*BRCA*m subgroup (investigator assessment)



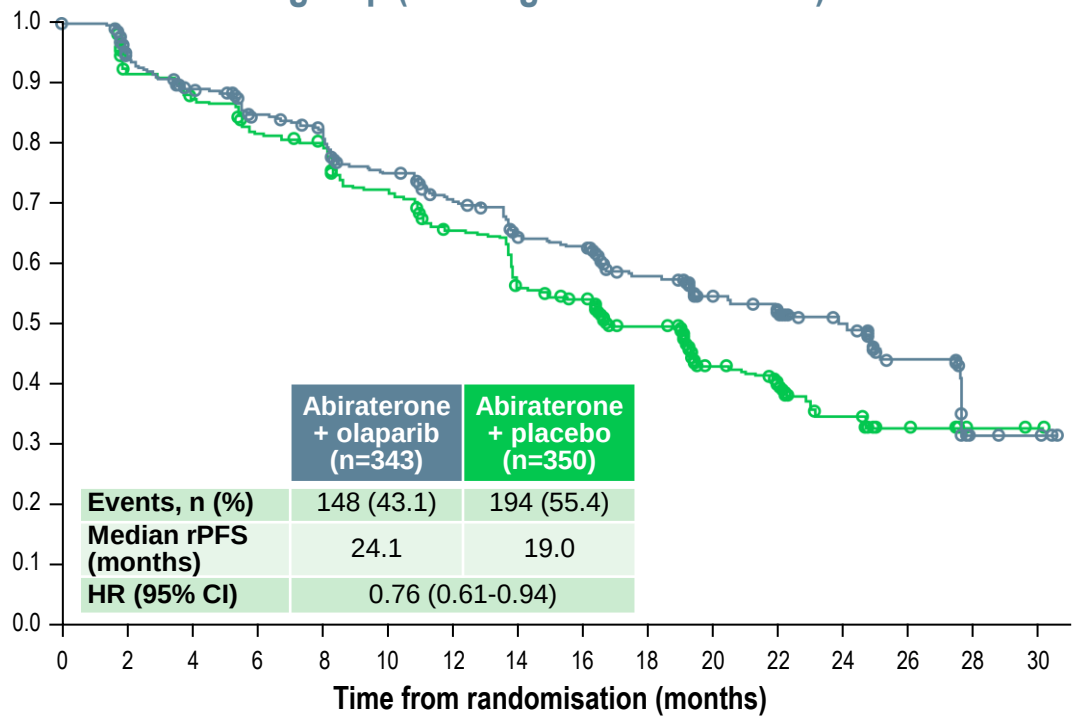
	Abiraterone + olaparib (n=47)	Abiraterone + placebo (n=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median rPFS (months)	NR	8.4
HR (95% CI)	0.23 (0.12-0.43)	

Number of patients at risk:

Abiraterone + olaparib	47	44	43	40	40	38	36	33	32	27	16	14	7	5	0
Abiraterone + placebo	38	33	29	22	20	16	13	11	10	7	6	6	2	0	0

Sensitivity analysis by blinded independent central review: Median NR vs 8.4 months; HR 0.18, 95% CI 0.09-0.34

Non-*BRCA*m subgroup (investigator assessment)



	Abiraterone + olaparib (n=343)	Abiraterone + placebo (n=350)
Events, n (%)	148 (43.1)	194 (55.4)
Median rPFS (months)	24.1	19.0
HR (95% CI)	0.76 (0.61-0.94)	

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Abiraterone + olaparib	343	314	289	266	254	230	211	190	183	137	87	73	50	21	5	4
Abiraterone + placebo	350	318	301	277	270	242	214	183	172	132	80	66	40	17	2	1

Sensitivity analysis by blinded independent central review: Median 27.6 vs 16.6 months; HR 0.72, 95% CI 0.58-0.90

[a] *BRCA2*m: HR 0.25, 95% CI 0.12-0.48. Non-*BRCA2*m: HR 0.74, 95% CI 0.60-0.92. Patient enrolment was not based on HRRm status; however, the HRRm and *BRCA*m status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA HRRm tests. This subgroup analysis is post-hoc exploratory analysis. A circle indicates a censored observation

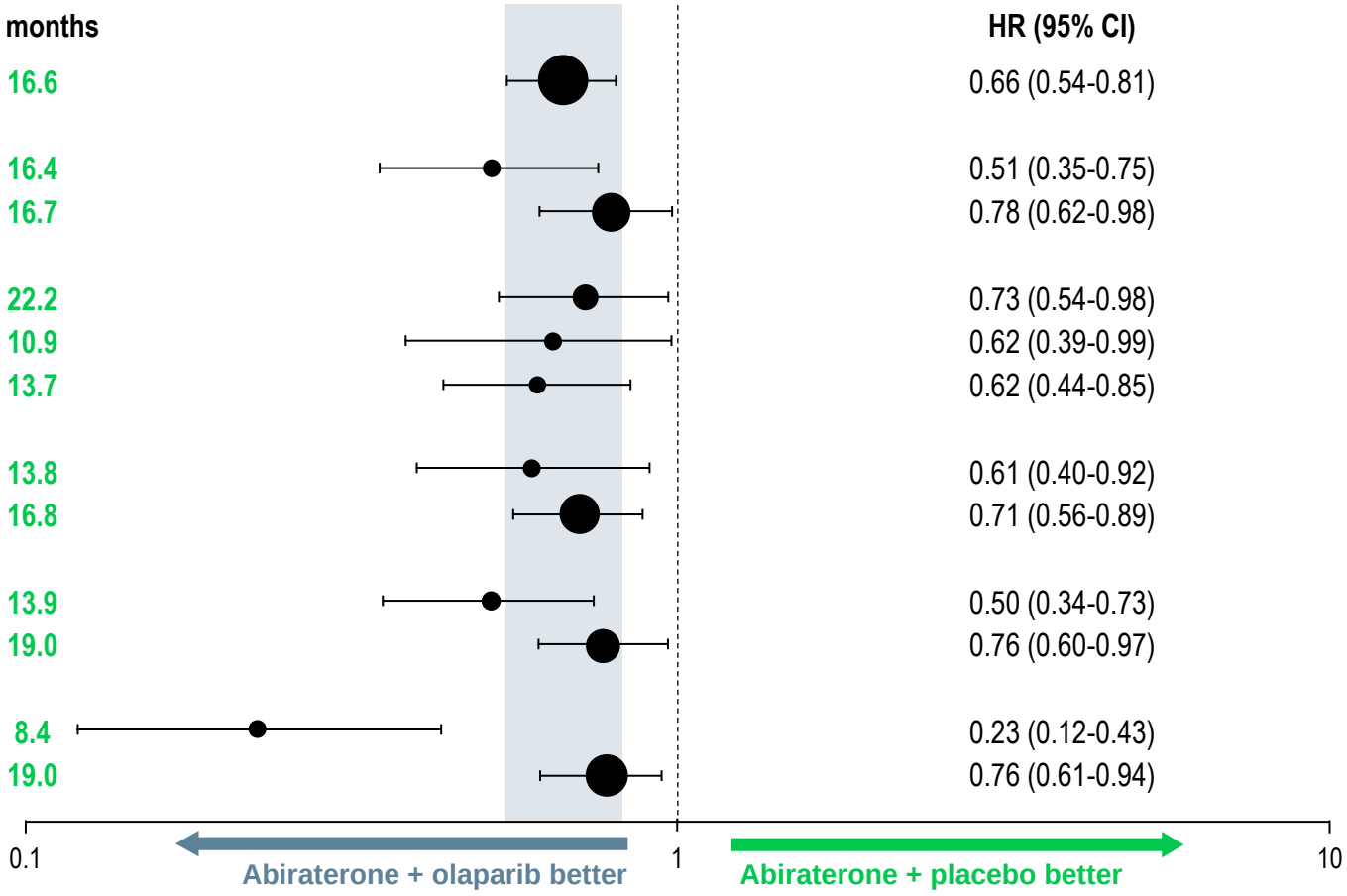
BRCA2, breast cancer gene 2; *BRCA*m, breast cancer gene mutation; CI, confidence interval; ctDNA, circulating tumour DNA; DCO1, first data cut-off; HR, hazard ratio; HRRm, homologous recombination repair mutation; NR, not reached; rPFS, radiographic progression-free survival

Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 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)



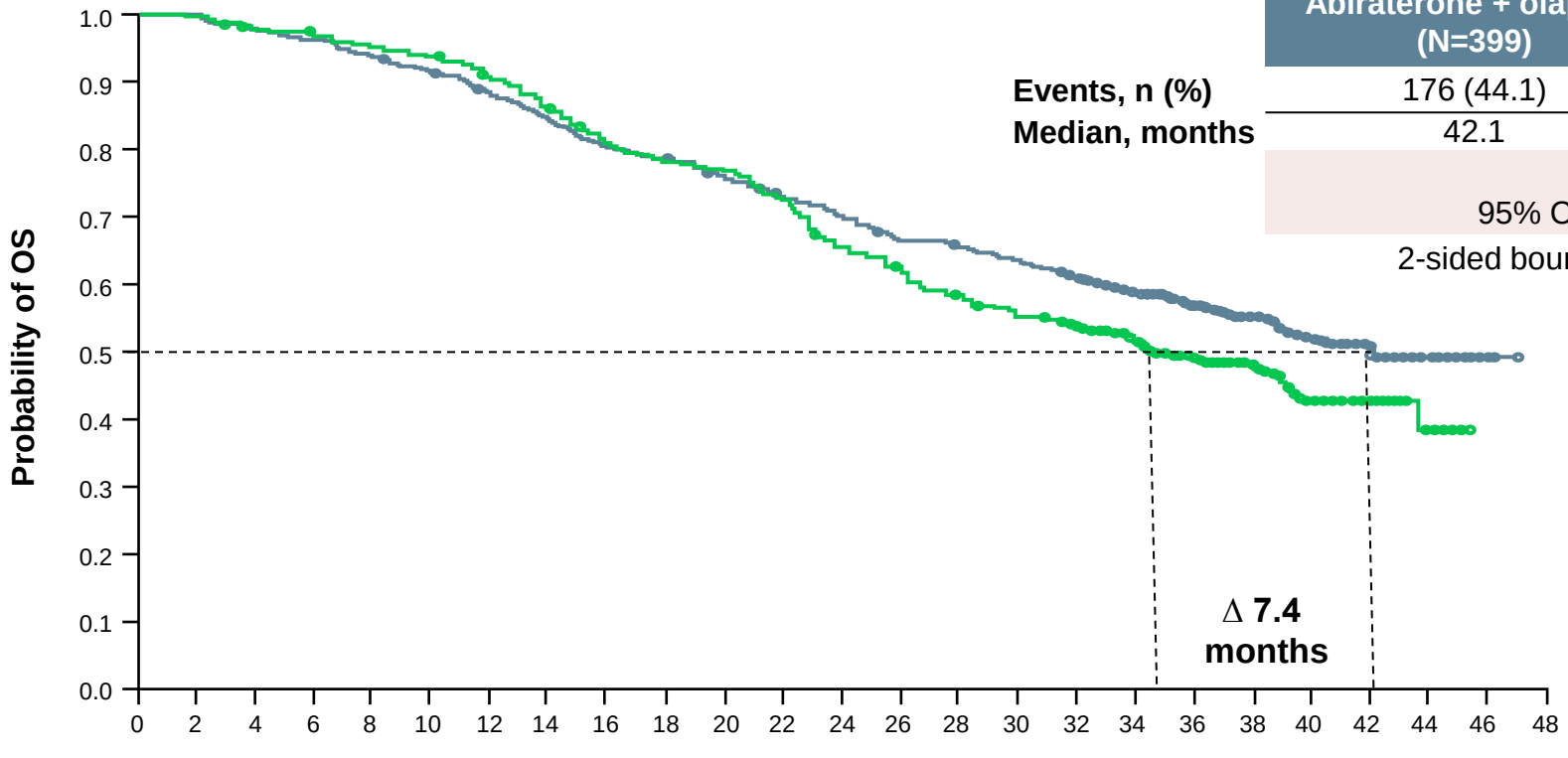
[a] The HRRm and BRCAm status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and/or plasma ctDNA HRRm tests. Aggregate HRRm and *BRCA*m subgroup analyses are post-hoc exploratory analyses. Results shown are by investigator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

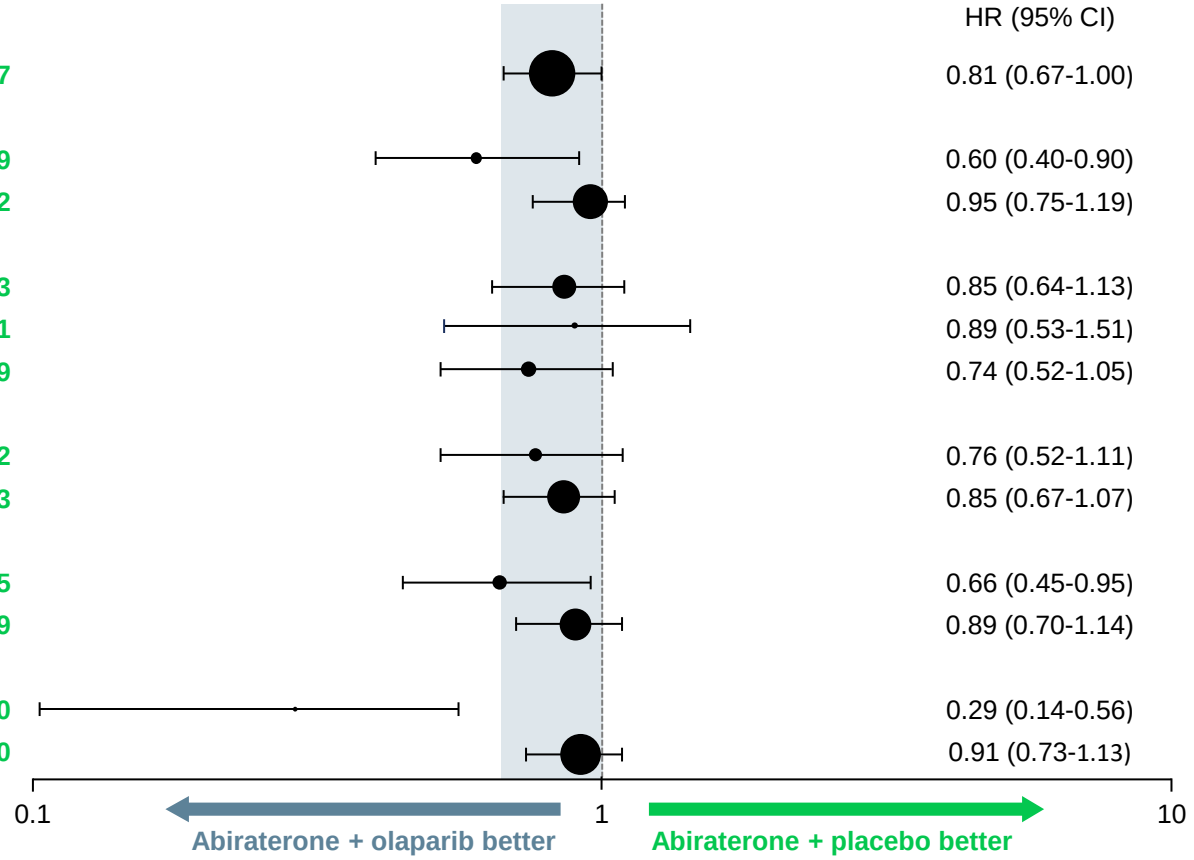
CI, confidence interval; DCO3, third data cut-off; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

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)



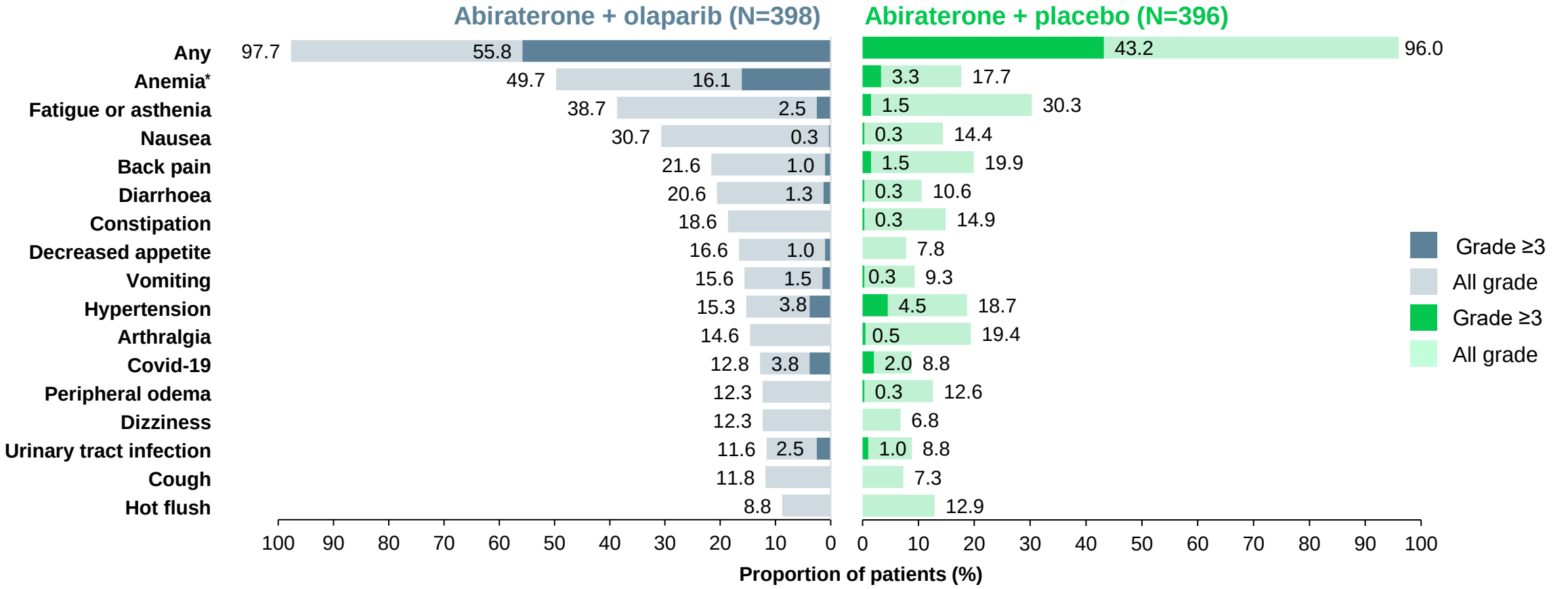
DCO3: 12 October 2022.
a HRRm and *BRCA*m status was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA tests. Aggregate subgroup analyses are post hoc and exploratory.

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

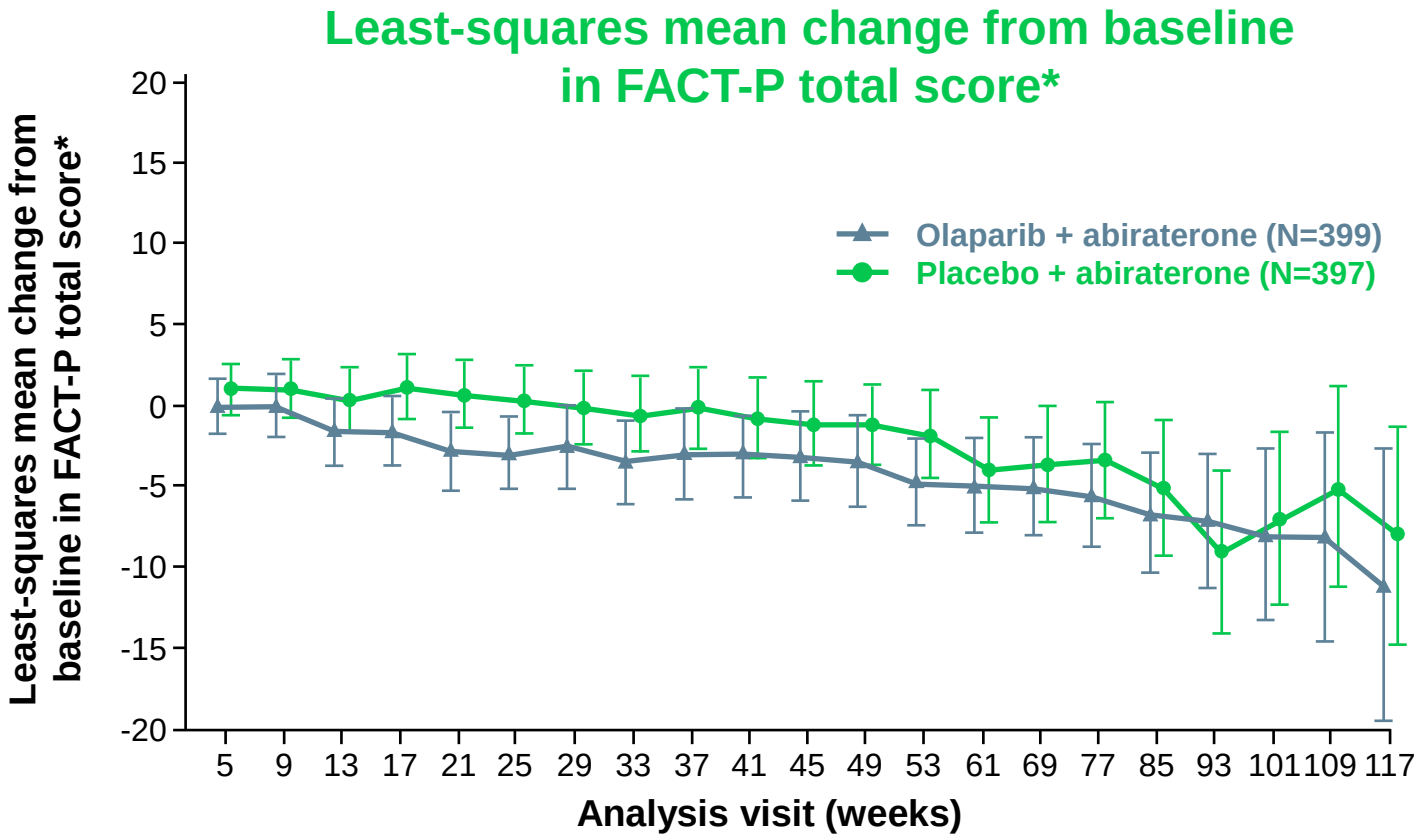
DCO3: 12 October 2022. Safety was assessed through the reporting of AEs according to NCI CTCAE v4.03 and laboratory assessments. *Grouped term anaemia category includes anaemia, decreased haemoglobin level, decreased red-cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic 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

PROpel: FACT-P QUALITY OF LIFE OVER TIME

QUALITY OF LIFE COMPARABLE BETWEEN TREATMENT ARMS



- Combination of olaparib and abiraterone was associated with similar in quality of life to single agent abiraterone and a majority of patients continued therapy

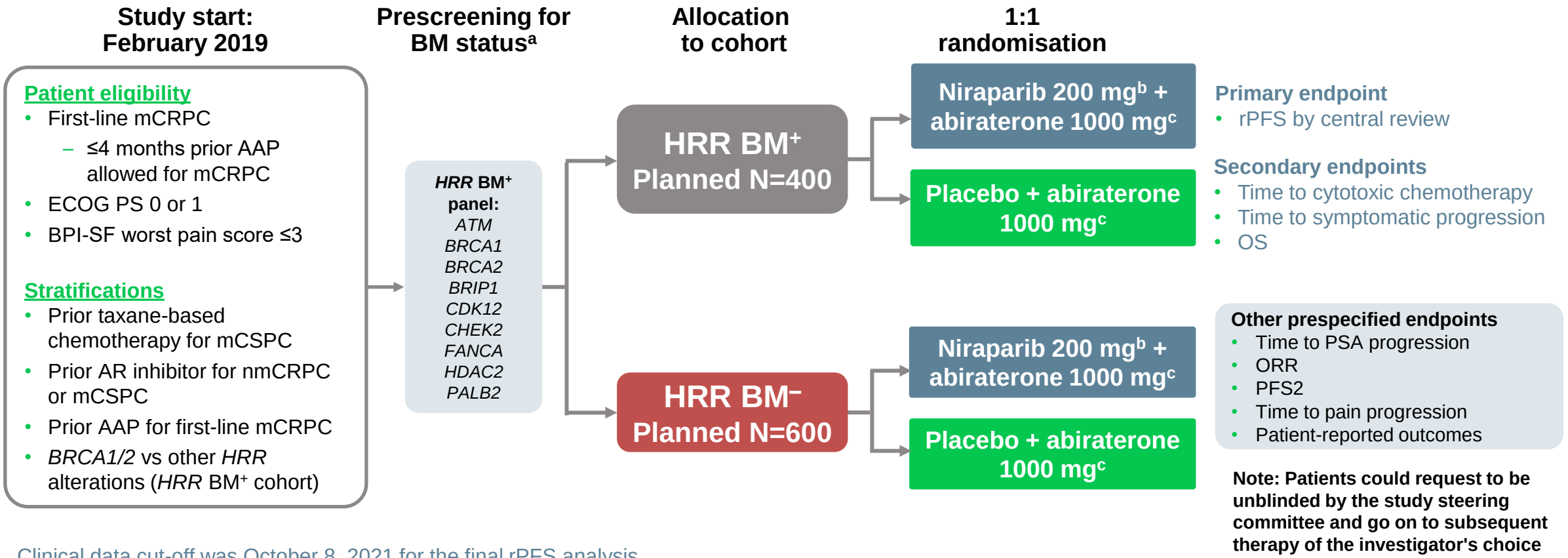
* Plot includes 95% confidence limits. FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change in FACT-P total score is 10.

FACT-P, Functional Assessment of Cancer Therapy-Prostate

Saad F, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 11) (ASCO GU 2022 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

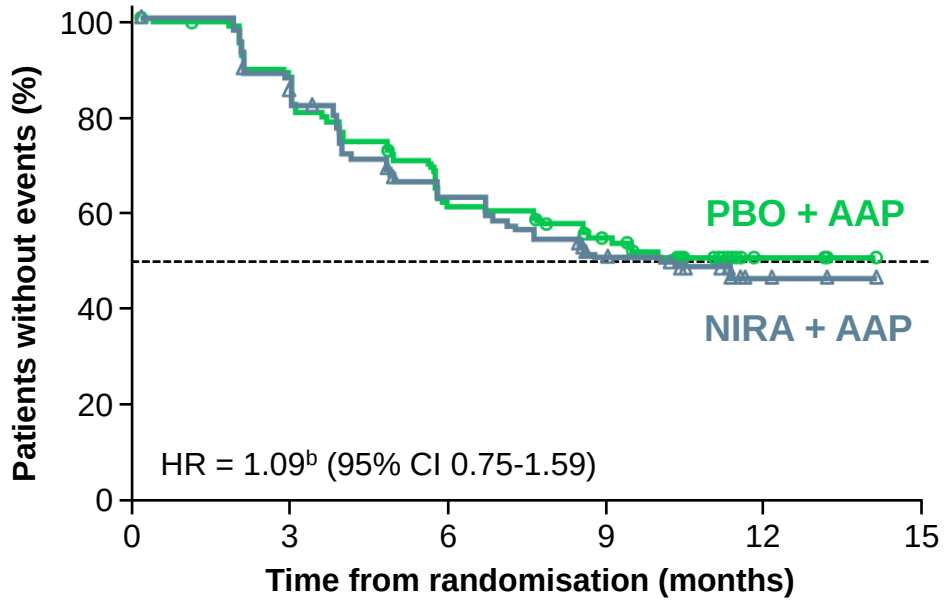
AAP, abiraterone acetate and prednisone/prednisolone; AR, androgen receptor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; 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)

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 enrollment 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)

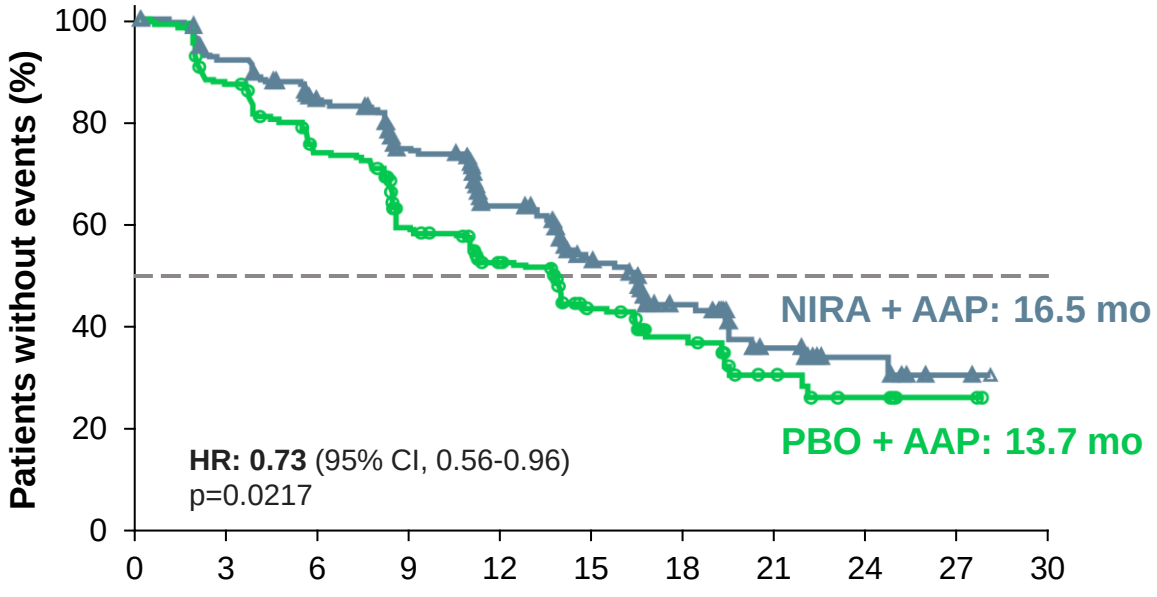
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA,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

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

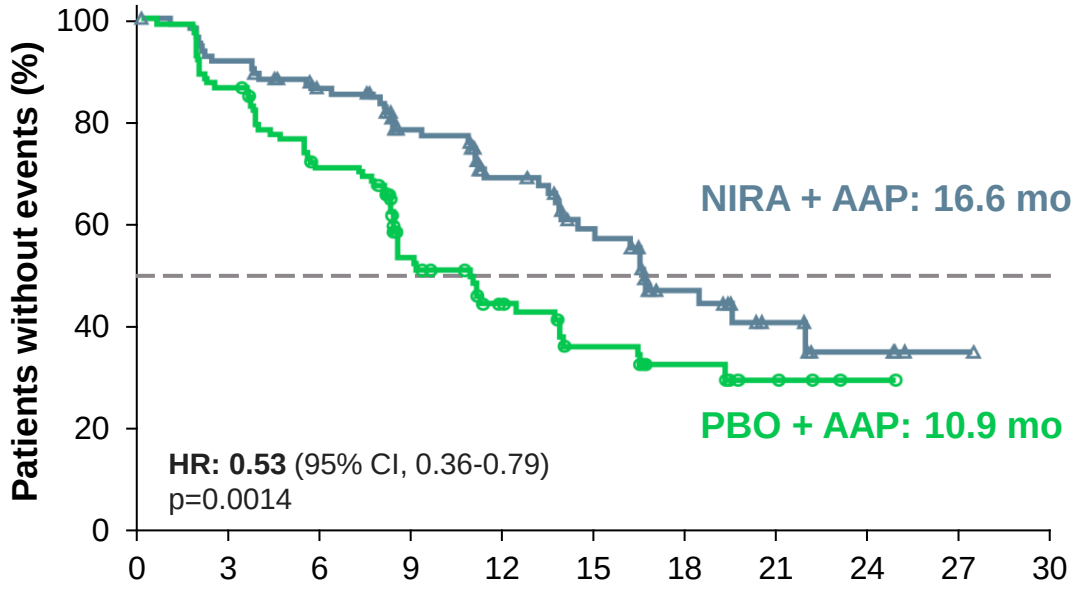
All HRR BM+ patients



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

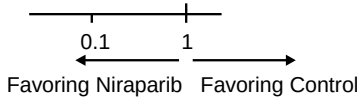
AAP, abiraterone acetate + prednisone/prednisolone; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

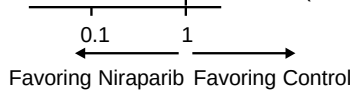
Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

MAGNITUDE 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





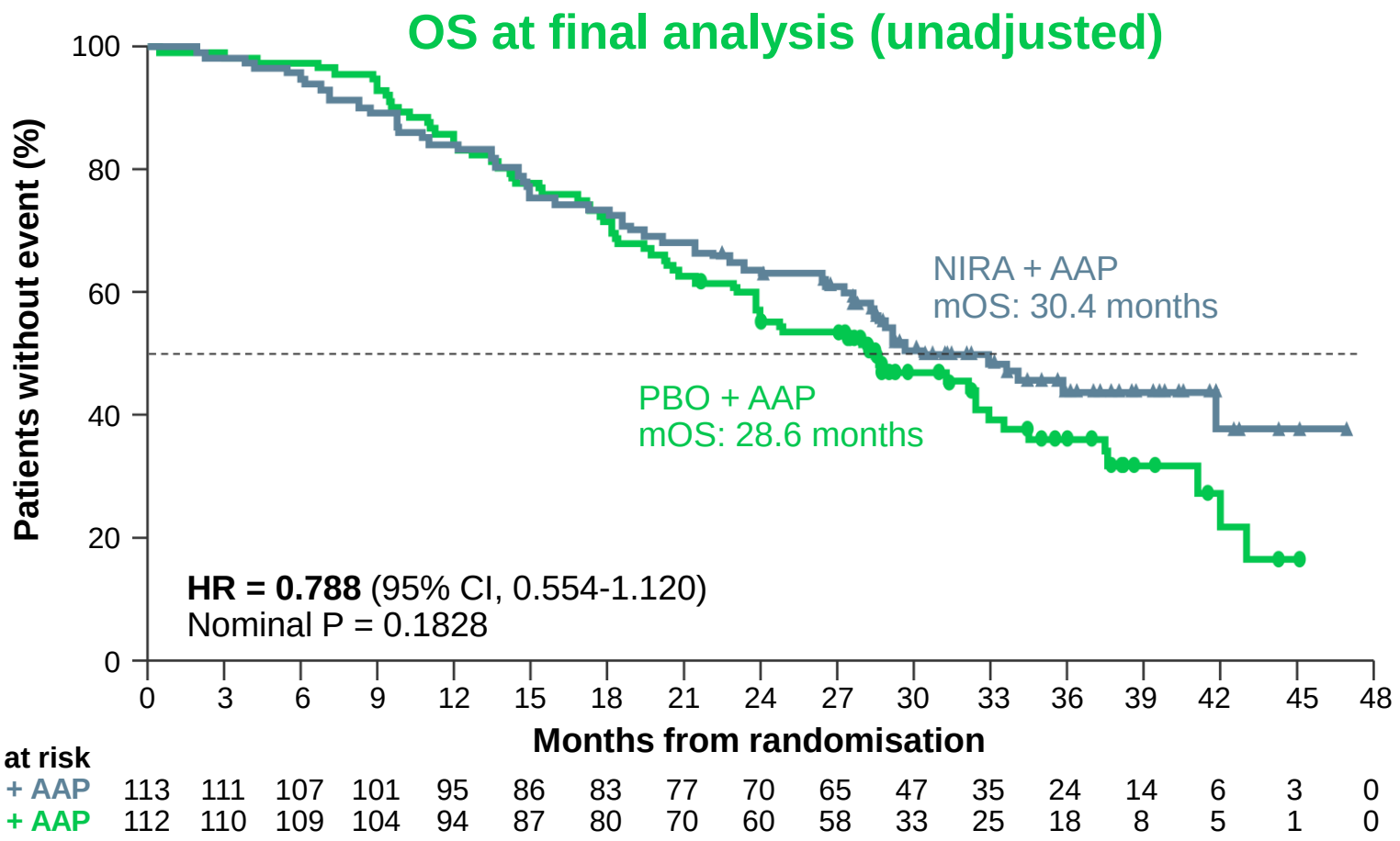
[a]Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide.
[b]Prior AAP use was up to 4 months prior to study start.

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; 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: FINAL OS ANALYSIS (*BRCA*+ PTS)

OS FAVOURED NIRA + AAP OVER PBO + AAP IN *BRCA*+ PATIENTS



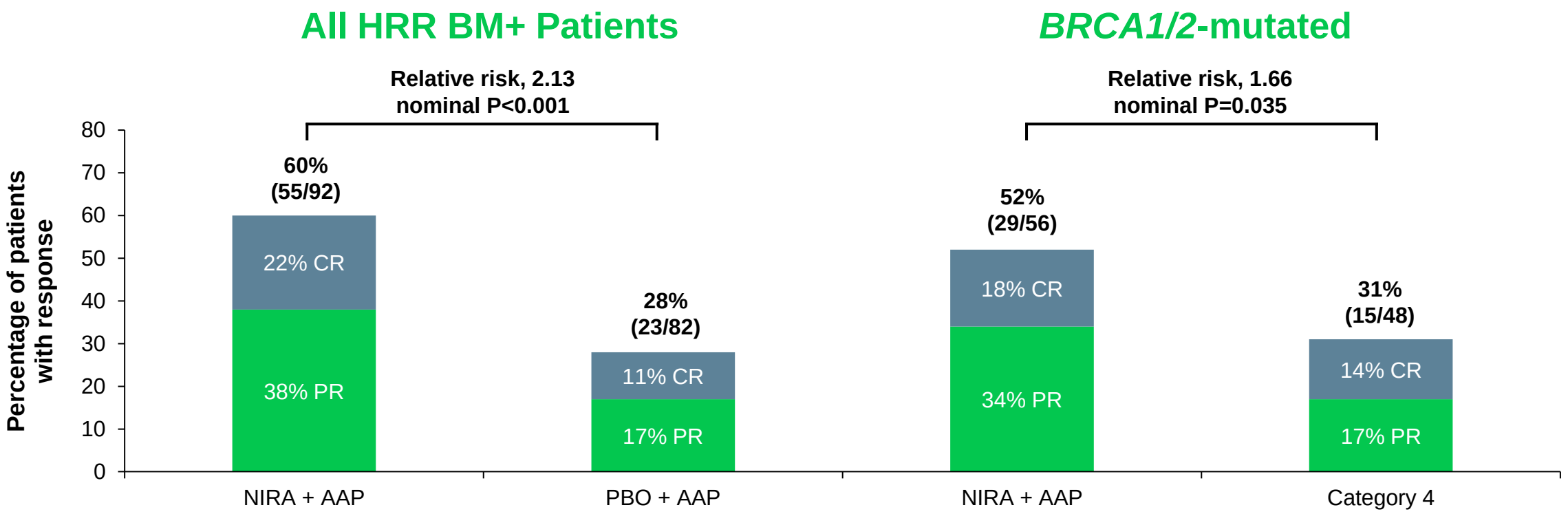
Does not account for baseline imbalances

AAP, abiraterone acetate + prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; (m)OS, (median) overall survival; NIRA, niraparib; PBO, placebo; PTS, patients

Chi K, et al. Annals of Oncology 2023; 34 (suppl_2): S1254-S1335. DOI: 10.1016/annonc/annonc1358; (ESMO 2023, oral presentation)

MAGNITUDE: OVERALL RESPONSE RATE

ABIRATERONE + NIRAPARIB IMPROVES ORR CONSISTENTLY ACROSS GENE ALTERATIONS



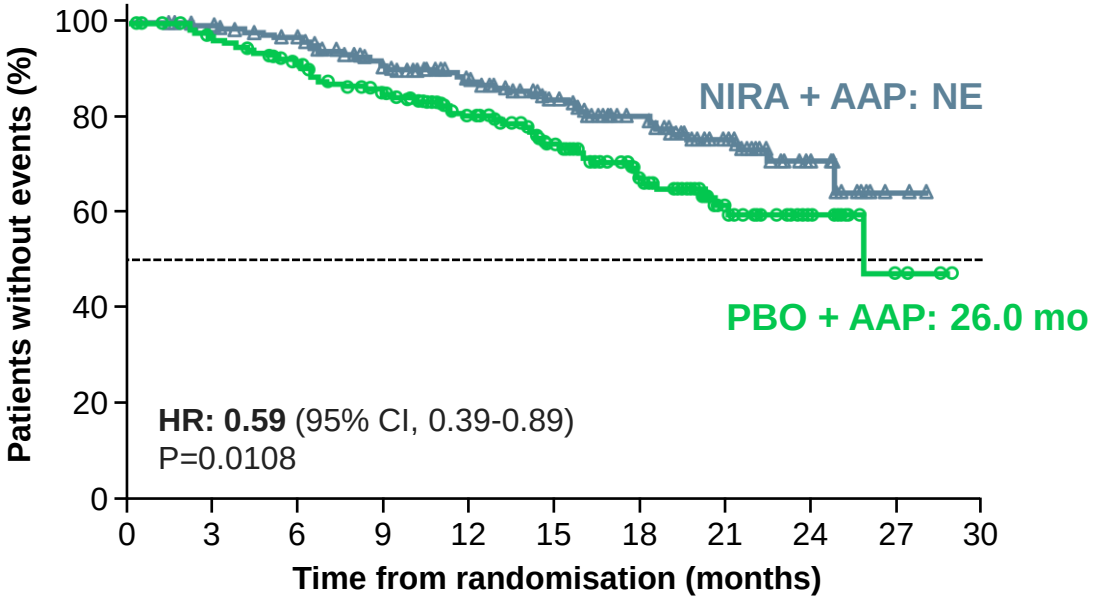
Note: Relative risk >1 favours niraparib and AAP treatment. Percent of responder is based on the number of subjects with measurable disease at baseline
AAP, abiraterone acetate plus prednisone; CR, complete response; HRR, homologous recombination repair, NIRA, niraparib; ORR, overall response rate PBO, placebo; PR, partial response

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: TIME TO CYTOTOXIC CHEMOTHERAPY

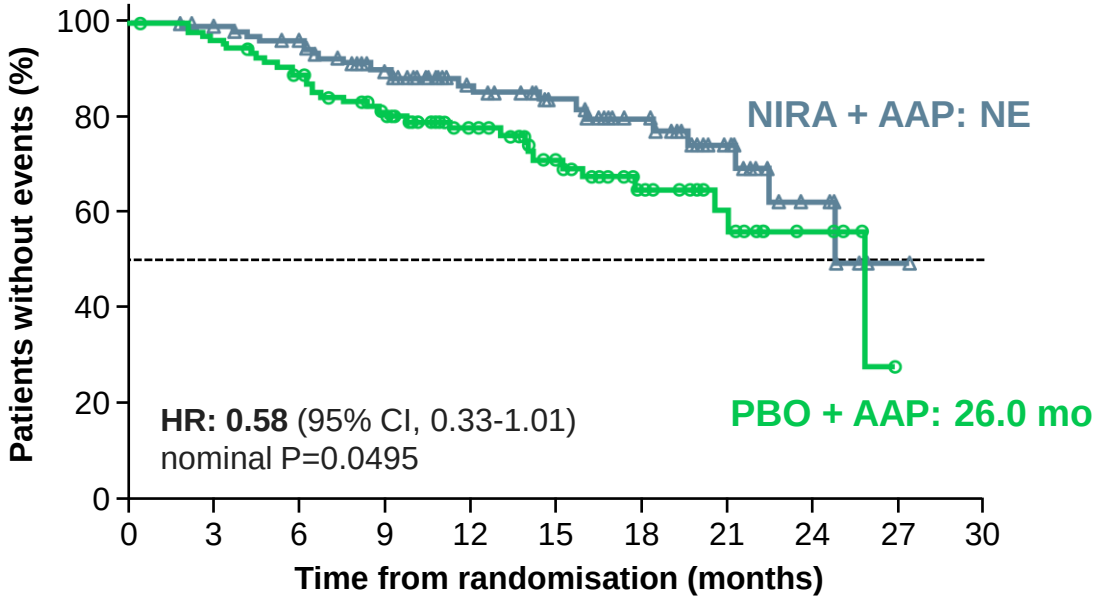
ABIRATERONE + NIRAPARIB PROLONGS TIME TO CHEMOTHERAPY ACROSS GENE ALTERATIONS

All HRR BM+



No. at risk											
NIRA + AAP	212	205	196	169	127	98	74	44	18	3	0
PBO + AAP	211	200	184	161	118	90	61	32	16	4	0

BRCA1/2-mutated



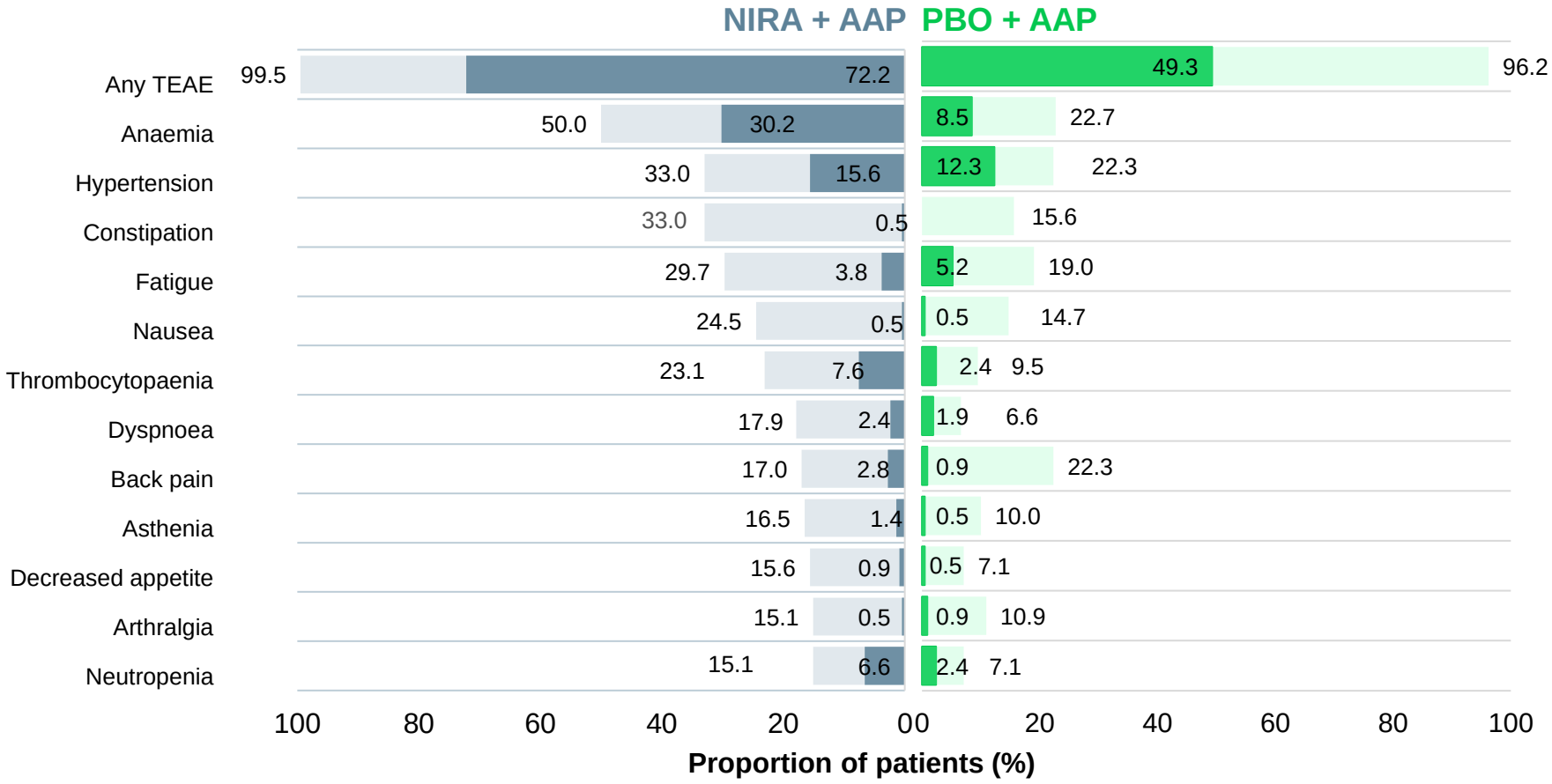
No. at risk											
NIRA + AAP	113	109	104	86	61	44	33	18	7	1	0
PBO + AAP	112	107	97	81	53	41	26	14	6	1	0

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair, NE, not estimable; NIRA, niraparib; 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 >15% IN NIRA ARM OR OF CLINICAL INTEREST (IA2)

TEAEs CONSISTENT WITH THE KNOWN SAFETY PROFILE FOR EACH THERAPY



- Pulmonary embolism occurred in four (1.9%) patients treated with niraparib plus AAP compared with two (0.9%) patients treated with placebo plus AAP
- No cases of myelodysplastic syndrome or acute myeloid leukemia occurred in the niraparib plus AAP group versus one (0.5%) in the placebo plus AAP group
- No cases of posterior reversible encephalopathy syndrome were observed in either group

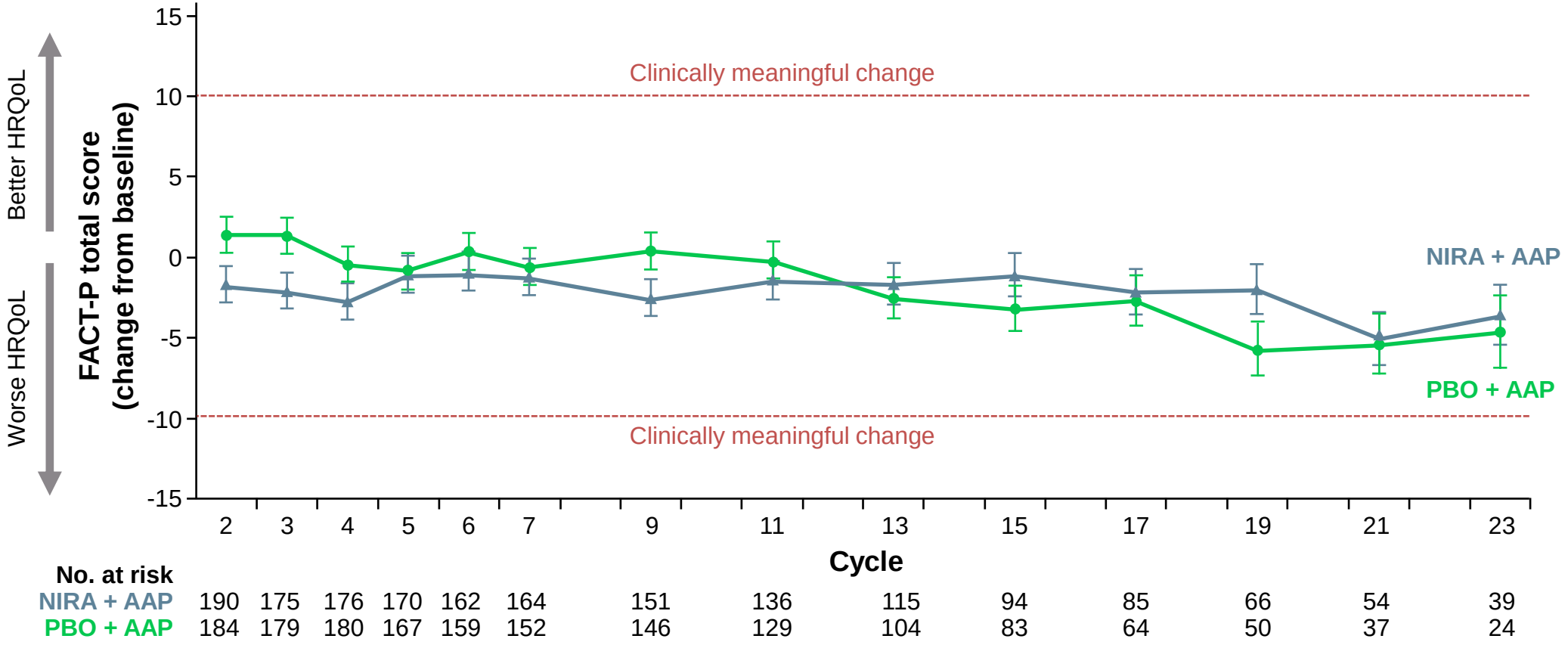
[a]Includes 1 Grade 5 event; [b]Includes 3 Grade 5 events

AAP, abiraterone acetate + prednisone / prednisolone; AML, acute myeloid leukaemia; BM, biomarker; HRR, homologous recombination repair; IA2, interim analysis 2; MDS, myelodysplastic syndrome; NIRA, niraparib; PBO, placebo; TEAE, treatment-emergent adverse event

Chi K, et al. Annals of Oncology 2023; 34 (9): 772-782

MAGNITUDE ALL HRR BM+: FACT-P QUALITY OF LIFE OVER TIME

QUALITY OF LIFE COMPARABLE BETWEEN TREATMENT ARMS



No. at risk														
NIRA + AAP	190	175	176	170	162	164	151	136	115	94	85	66	54	39
PBO + AAP	184	179	180	167	159	152	146	129	104	83	64	50	37	24

Note: The threshold for definition of FACT-P total score deterioration is ≤10.

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRR, homologous recombination repair; HRQoL, health-related quality of life; NIRA, niraparib; 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

DESIGN AND BASELINE COMPARISON OF PROPEL AND MAGNITUDE TRIALS

	PROpel[1,2] N=796	MAGNITUDE[3,4] N=423
Dose of PARPi	olaparib 300 mg bid	niraparib 200 mg QD
Primary endpoint	rPFS in unselected patients (investigator view)	rPFS in selected and unselected patients (central view)
Prior NHA in mCSPC	Allowed as long as stopped at least 12 mos before enrollment (abiraterone not allowed) 1 (0.3%)	13 (3.0%)[a]
Prior Docetaxel in mCSPC	179 (22.5%)	85 (20%)[a]
HRR status required at randomisation	No	Yes
HRR analysis	Tissue and/or ctDNA	Tissue or ctDNA or germline
HRRm status		
HRRm	226 (28.4%)	423 (100%)
Non-HRRm	552 (69.3%)	-
HRRm unknown	18 (2.3%)	-
BRCAm prevalence		
BRCA1	12 (1.5%)	16 (3.8%)
BRCA2	73 (9.2%)	174 (41%)

[a]includes prior therapy for nmCRPC/mCSPC; ctDNA, circulating tumour DNA; HRRm, homologous recombination repair mutation; mCSPC, metastatic castration sensitive prostate cancer; NHA, new hormonal agent; rPFS, radiographic progression free survival. **Please note that these studies cannot be directly compared. This data is presented for information purposes only**

1. Clarke N, et al. NEJM Evidence 2022: DOI: 10.1056/EVIDoa2200043; 2. Clarke N, et al. Lancet Oncol. 2018;19:975-86;
3. Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation); 4. Chi K, et al. Journal of Clinical Oncology 2023; 41: 3339-3351

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)

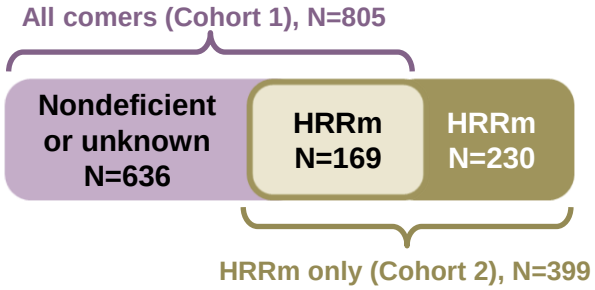
Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily

(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 reported 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

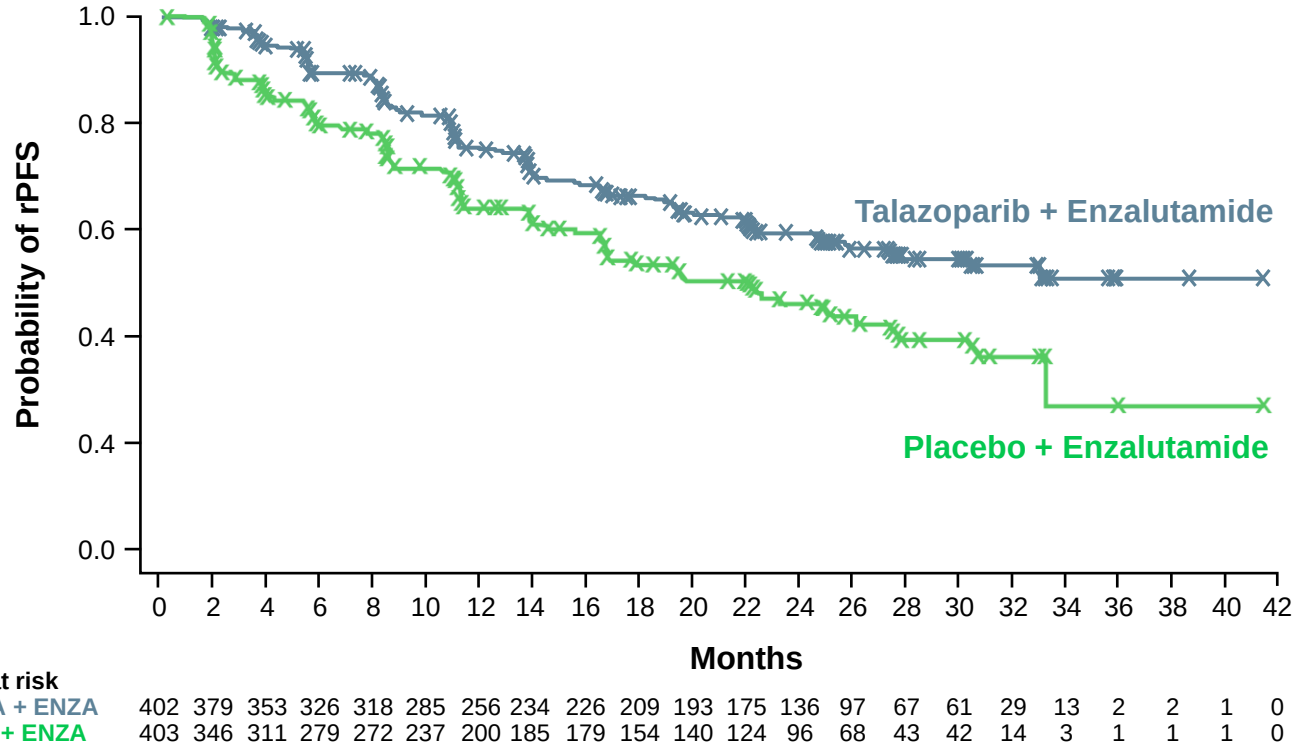
[b] Time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first

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); Agarwal A, et al. Lancet 2023;402: 291-303

TALAPRO-2 PRIMARY ENDPOINT: rPFS BY BICR

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



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

	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

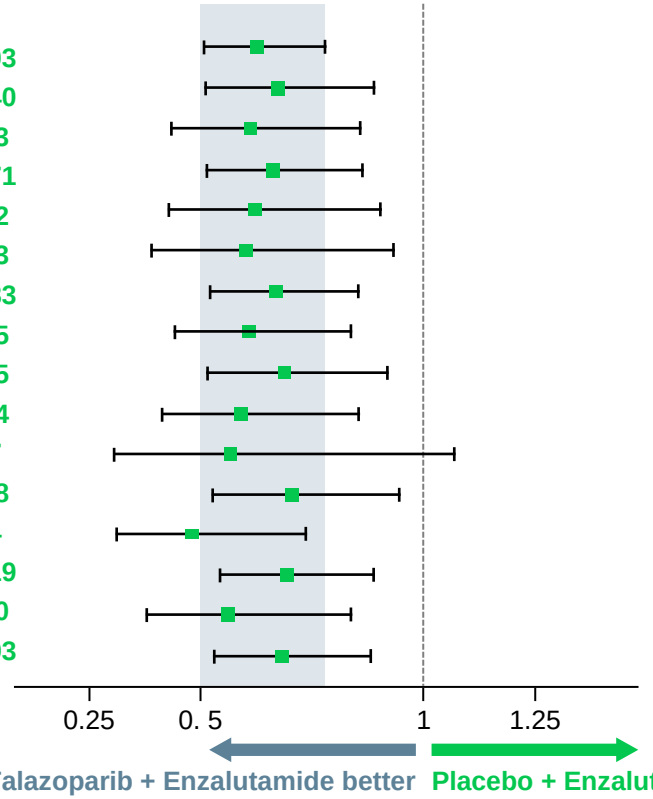
BICR, blinded independent central review; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; rPFS, radiographic progression-free survival; TALA, talazoparib

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

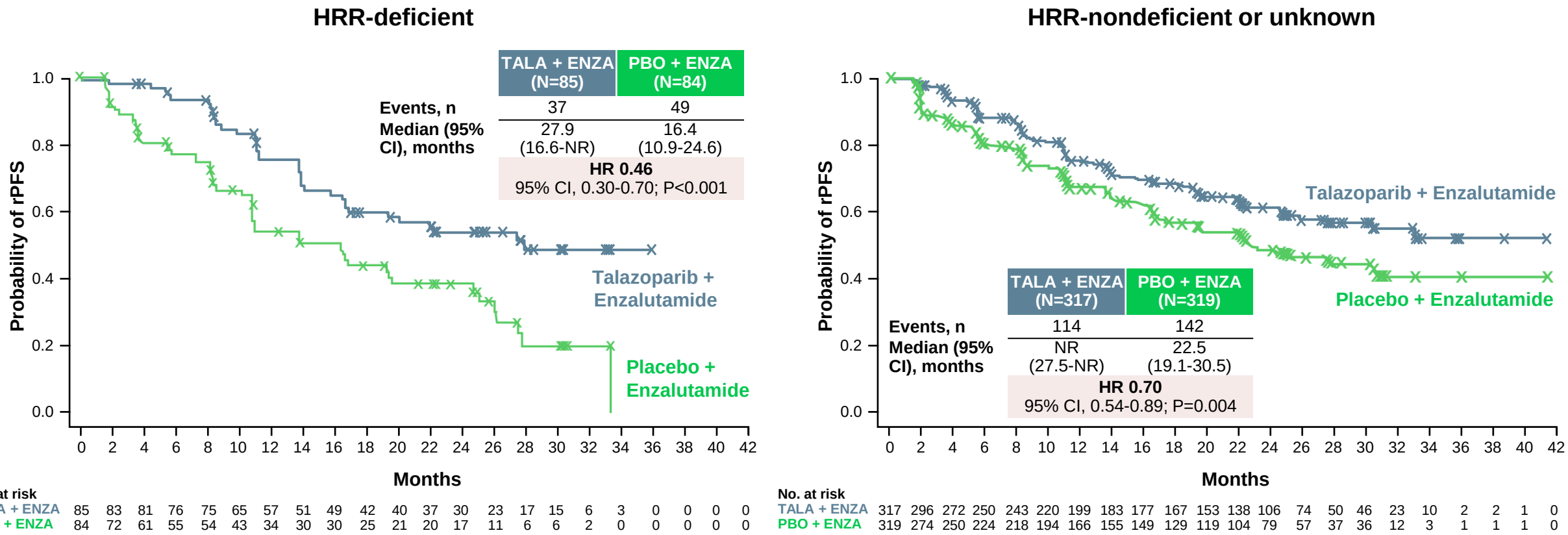
[a] Includes two patients in each treatment arm who received prior orteronel

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



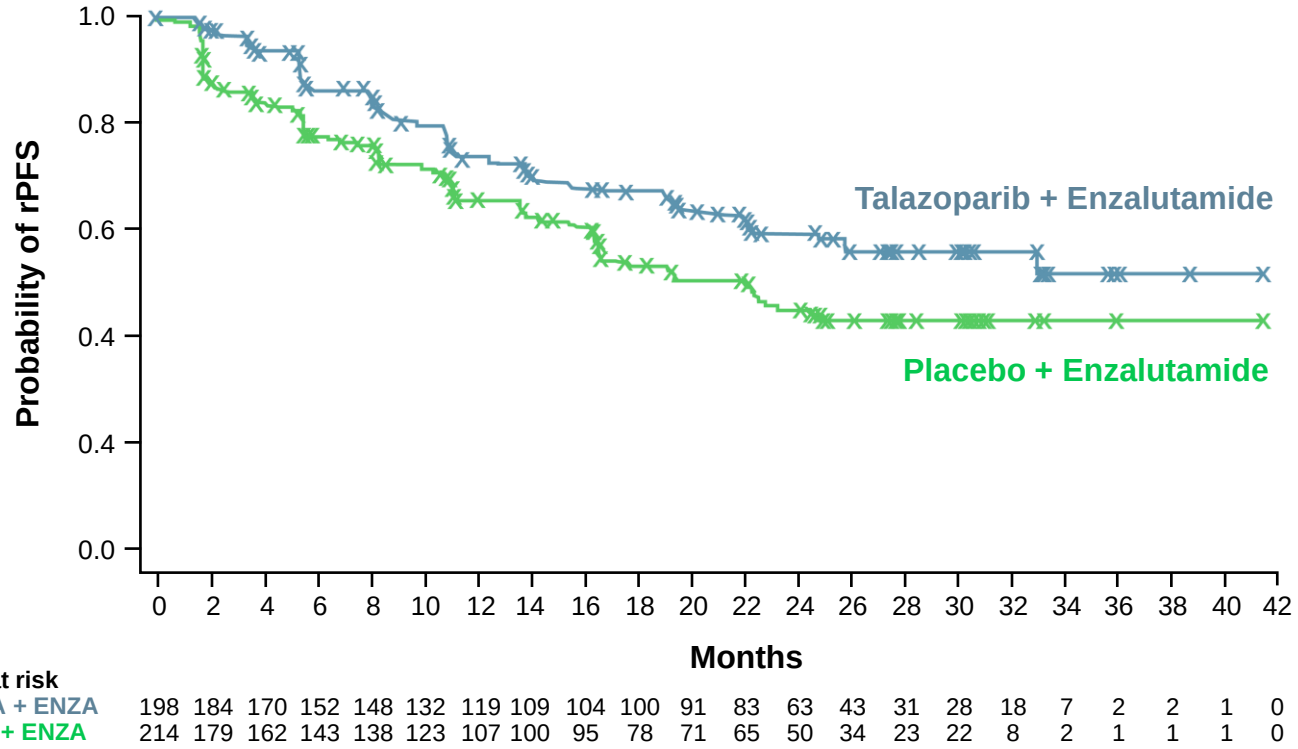
HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor

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		

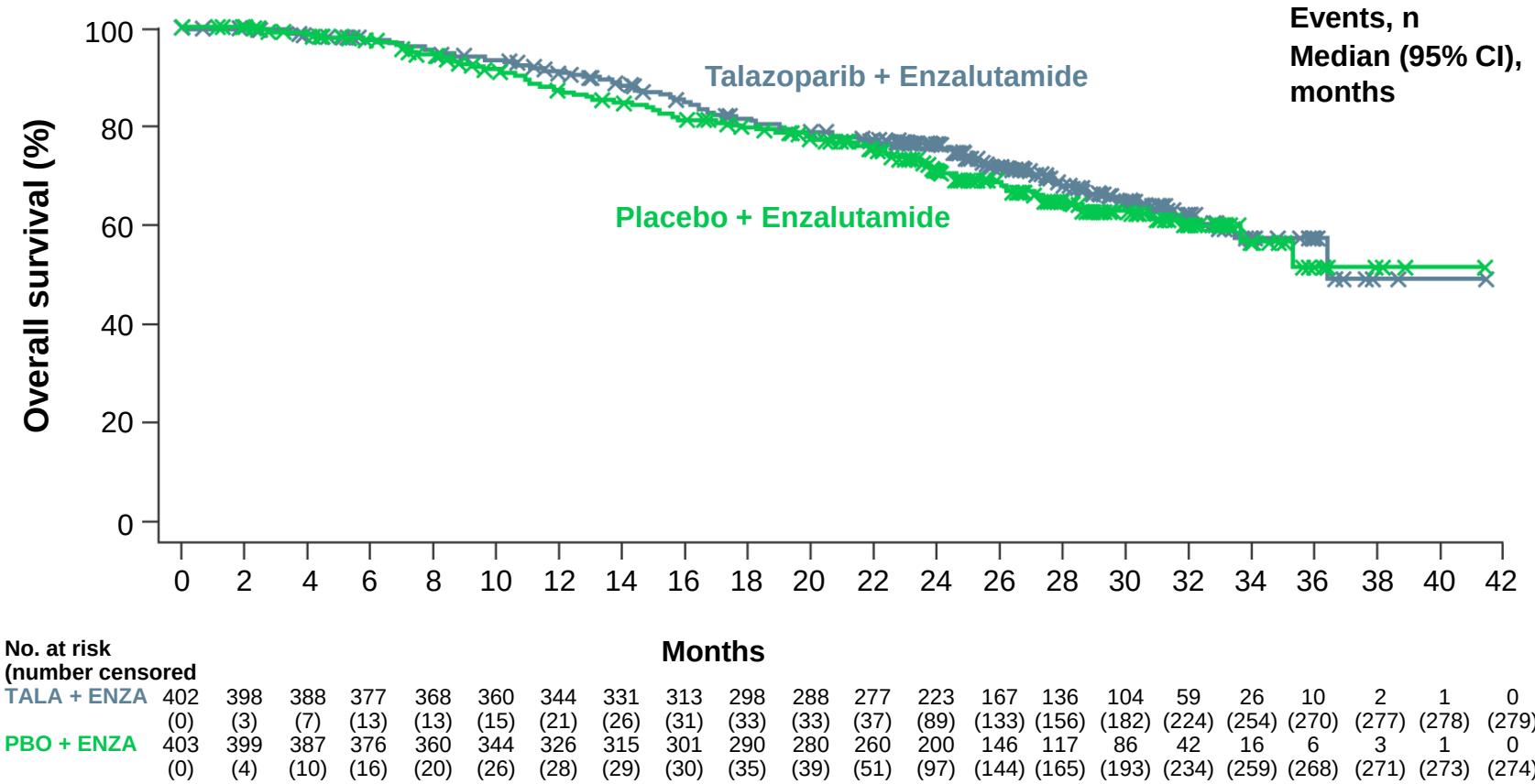
Exploratory endpoint analysis based on HRR gene alteration status derived from the clinical database (unstratified analysis)

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: INTERIM OVERALL SURVIVAL

OS IN THE ALL-COMER ITT POPULATION

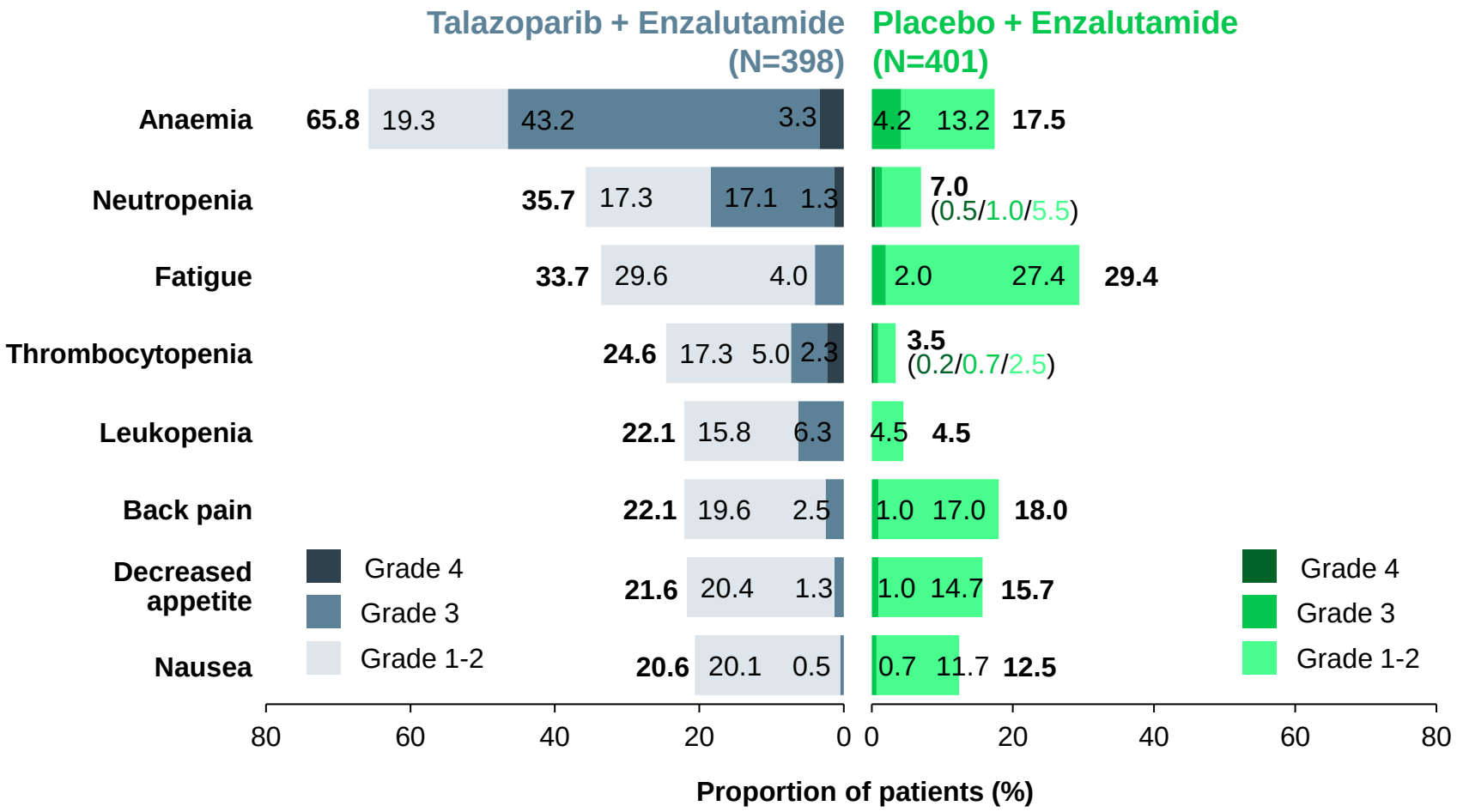


	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	123	129
Median (95% CI), months	36.4 (33.5-NR)	NR (33.7-NR)
HR 0.89 95% CI, 0.69-1.14; P=0.35		

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

Agarwal A, et al. Lancet 2023;402: 291-303 (supplementary appendix)

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

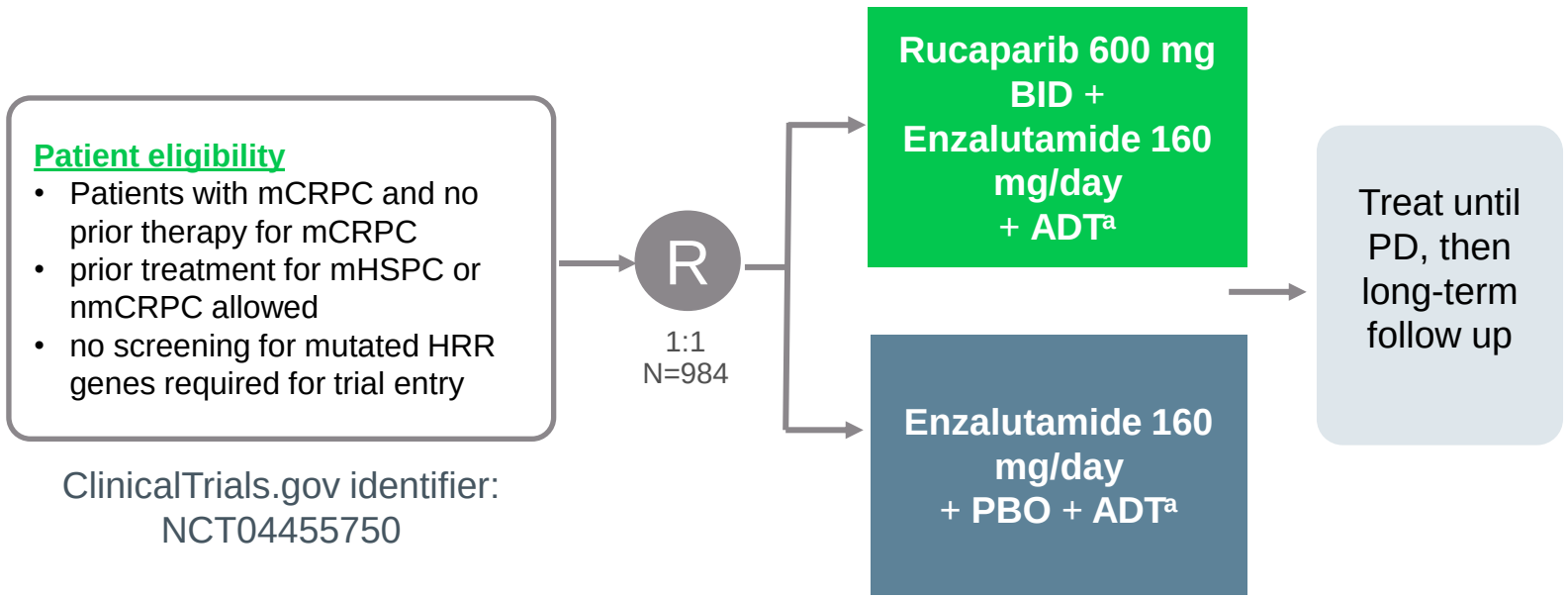
Agarwal A, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA17) (ASCO GU 2023 oral presentation); Agarwal A, et al. Lancet 2023;402: 291-303

OTHER PARPi AND ANTI-ANDROGEN COMBINATION TRIALS

PARPi, poly (ADP-ribose) polymerase inhibitor

CASPAR: FIRST-LINE RUCAPARIB + ENZALUTAMIDE IN mCRPC

ONGOING, RANDOMISED, OPEN-LABEL, PHASE 3 TRIAL



ClinicalTrials.gov identifier: NCT04455750

Primary endpoint:
- rPFS, OS

Key Secondary endpoints:
- rPFS and OS by HRR mutation status, ORR, safety, QoL

Correlative endpoints:
- Prevalence of germline and somatic HRR mutations; prevalence of AR aberrations pre- and posttherapy; prevalence of HRR reversion mutations posttherapy in PARPi arm; prevalence of "BRCAness" or NEPC transcriptional signature, or SLFN11 expression in tumour-derived exosomes and archival tissue

[a]Only patients who did not undergo bilateral orchiectomy will receive ADT

ADT, androgen-deprivation therapy; AR, androgen receptor; BID, twice daily; BRCA, breast cancer gene; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NEPC, neuroendocrine prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PBO, placebo; PD, progressive disease; QoL, quality of life; rPFS, radiographic progression-free survival.

CASPAR. ClinicalTrials.gov identifier: NCT04455750. Accessed October 11, 2022. https://clinicaltrials.gov/ct2/show/NCT04455750; Rao A, et al. J Clin Onc 2022; 40: no.6_suppl. TPS194

SELECT PARPi COMBINATION TRIALS IN mCRPC AND mCSPC

Study	Phase	Treatment arms	Patient population
mCRPC			
QUEST (NCT03431350)	1b/2	Niraparib + cetrelimab (anti-PD1) or AAP	• mCRPC (N=140)
BRCAAway (NCT03012321)	2	AAP vs olaparib vs olaparib + AAP	• mCRPC with DDR (N=70)
mCSPC			
NCT04734730	2	Talazoparib + abiraterone acetate+ ADT	• mCSPC (N=70)
ZZ First (NCT04332744)	2	Talazoparib + enzalutamide +ADT vs enzalutamide +ADT only	• Locally advanced or metastatic hormone-naive PC, no prior systemic tx (N=54)
AMPLITUDE (NCT04497844)	3	Niraparib plus abiraterone acetate vs Placebo plus abiraterone acetate	• mCSPC (N=788) • Deleterious germline or somatic HRR gene-mutated
TALAPRO-3 (NCT04821622)	3	Talazoparib plus enzalutamide vs Enzalutamide plus placebo	• mCSPC (N=550) • DDR gene-mutated

AAP, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; DDR, DNA damage repair; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; PARPi, PARP inhibitor; PC, prostate cancer; tx, treatment

www.clinicaltrials.gov

IMPLEMENTING PARPi COMBINATION TREATMENT IN CLINICAL PRACTICE

PARPi, poly (ADP-ribose) polymerase inhibitor

PARP INHIBITORS ARE APPROVED IN PROSTATE CANCER

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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**

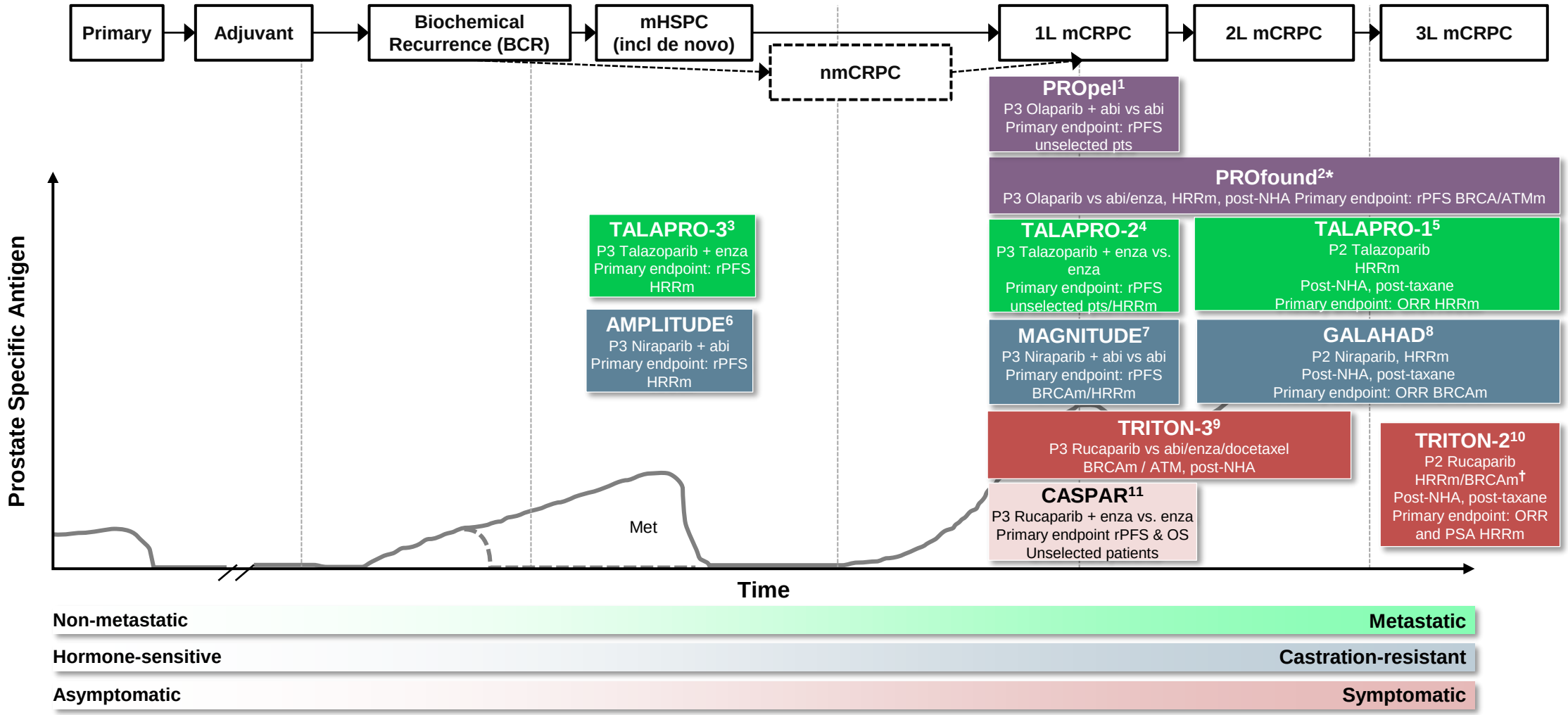
[a]Rucaparib has no current approval in prostate cancer in Europe

[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)

THERE ARE MULTIPLE TRIALS INVESTIGATING THE USE OF PARP INHIBITORS IN PROSTATE CANCER[1-11]



Please see slide notes for references. [a] As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA [b] As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane

Abi, abiraterone; BCR, biochemical recurrence; Enza, enzalutamide; FDA, US Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, new hormonal agent; nmCRPC, non-metastatic castration-resistant prostate cancer; Ola, olaparib; P, phase; PSA, prostate-specific antigen

AVAILABLE PARP INHIBITORS AND THEIR CURRENT TUMOUR INDICATIONS

	Olaparib	Rucaparib	Niraparib	Talazoparib
Single-agent dose (approved for olaparib, rucaparib, niraparib, and talazoparib)	300 mg BID	600 mg BID	200/300[d] mg QD	1 mg QD
Tumour indications	Ovarian cancer, breast cancer, pancreatic cancer, prostate cancer[1,2,a,b]	Ovarian cancer,[3,4] prostate cancer[4,c]	Ovarian cancer,[5,6] prostate cancer[7,8,e]	Breast cancer, prostate cancer[9,10,f]

[b] Olaparib is EMA-approved as monotherapy for the treatment of adult patients with mCRPC and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA and is approved by the EMA in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[2]

[c] Rucaparib is FDA-approved for the treatment of adult patients with a deleterious *BRCA* mutation-associated mCRPC who have been treated with AR-directed therapy and a taxane-based chemotherapy (no current approval in prostate cancer in Europe)[4]

[d] Niraparib FDA-approved dose is 300 mg QD and EMA approved dose is either 200 or 300 mg QD depending on weight and other factors.

[e] Approved as a fixed dose combination of niraparib/abiraterone acetate with prednisone by the FDA for: the treatment of adult patients with deleterious or suspected deleterious BRCAmutated (BRCAm) metastatic castration-resistant prostate cancer; and by the EMA for the treatment of adult patients with mCRPC and BRCA1/2 gene mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated

[f] Talazoparib is approved by the FDA in combination with enzalutamide for the treatment of adult patients with HRRm mCRPC (no current approval in prostate cancer in Europe)

AR, androgen receptor; BID, twice daily; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; QD, once daily; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PARP, poly-ADP ribose polymerase

1. Olaparib PI; 2. Olaparib SmPC; 3. Rucaparib SmPC; 4. Rucaparib PI; 5. Niraparib PI; 6. Niraparib SmPC; 7. Akeega PI; 8. Akeega SmPC; 9. Talazoparib SmPC; 10. Talazoparib PI. All accessed November 2023.

CONCLUSIONS

- Combination treatments of **NHAs and PARPi may provide combination benefit in mCRPC patients**
  - Combinations appear effective in HRR selected patients and may be effective in all-comer populations
- In first line mCRPC, treatment with:
  - **olaparib and abiraterone is associated with longer rPFS** than abiraterone alone. This occurred **in patients with and without HRR mutations**
  - **talazoparib and enzaluamide is associated with longer rPFS** than enzalutamide alone. This occurred **in patients with and without HRR mutations**
  - **niraparib and abiraterone is also associated with longer rPFS** than abiraterone alone. This occurred **in patients with HRR mutations only**
- Ongoing trials will demonstrate whether other PARPi/NHA combinations will benefit patients with advanced prostate cancer
- **Genetic testing is important** to help with treatment decision making and for understanding inherited risk

HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; NHA, novel hormonal agents; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitors; rPFS, radiographic progression-free survival

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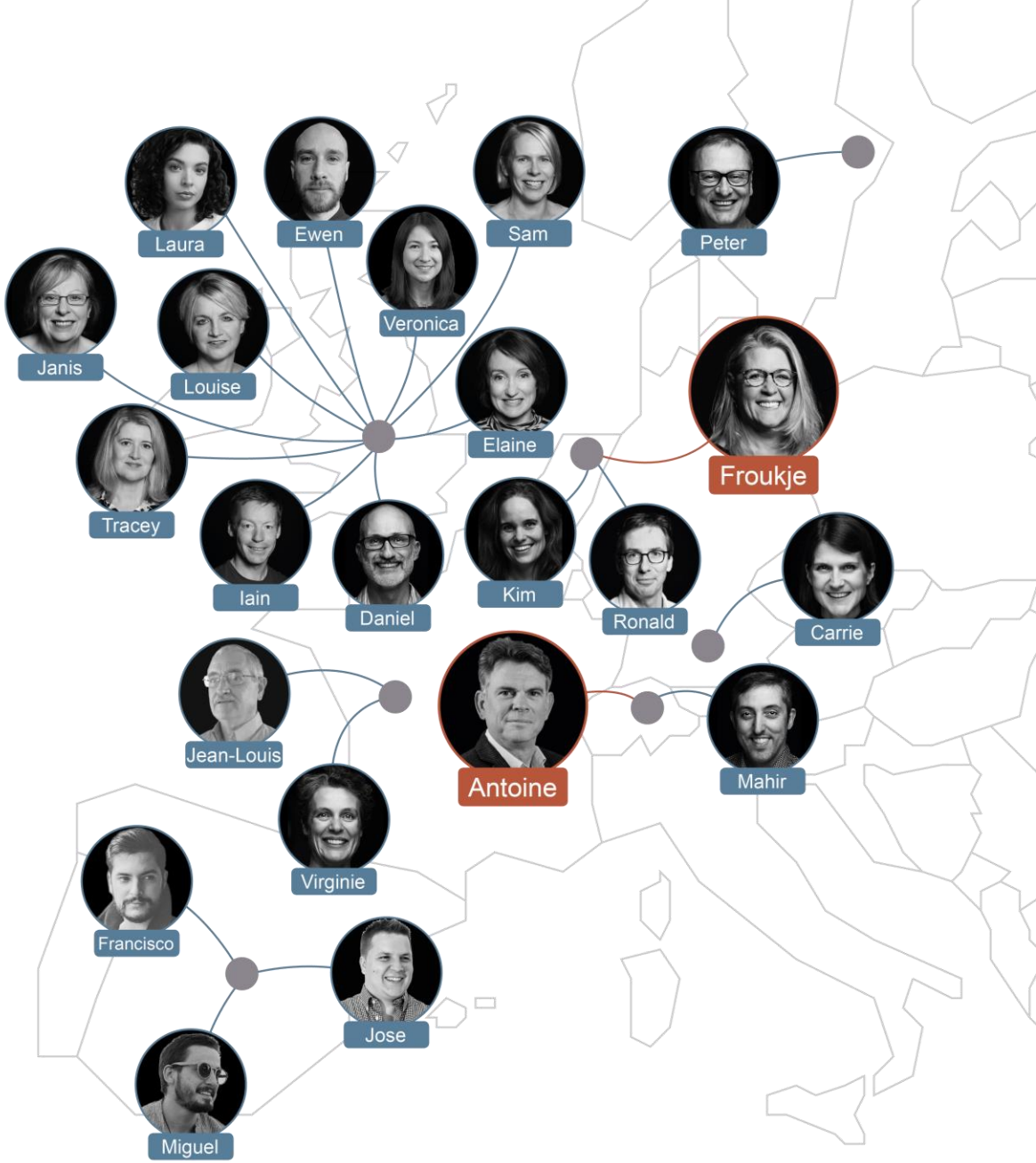

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