GU CONNECT MICRO E-LEARNING

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

MODULE TWO

DECEMBER 2022

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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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

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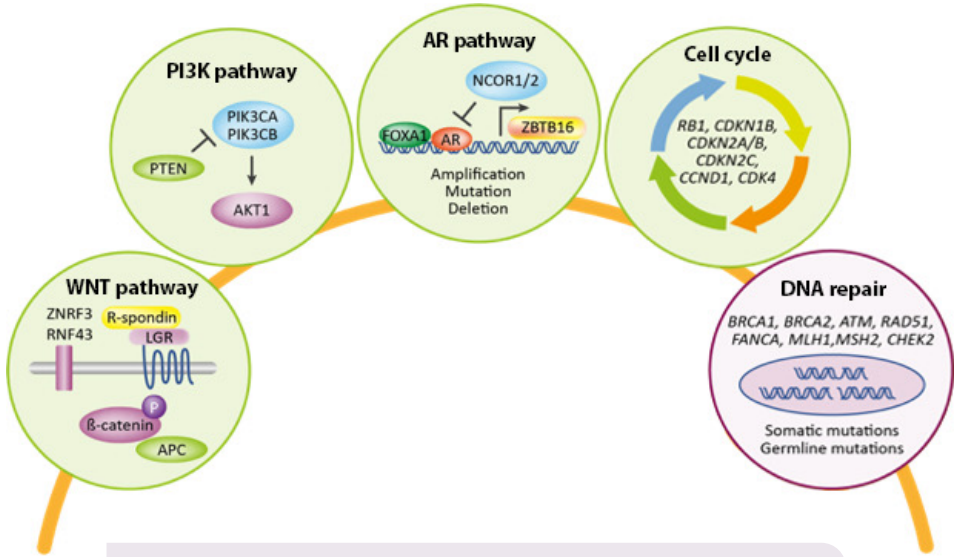
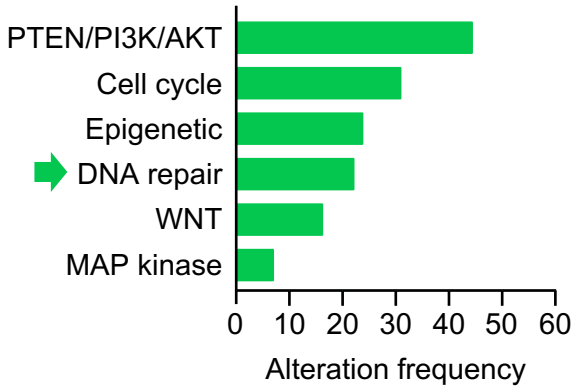
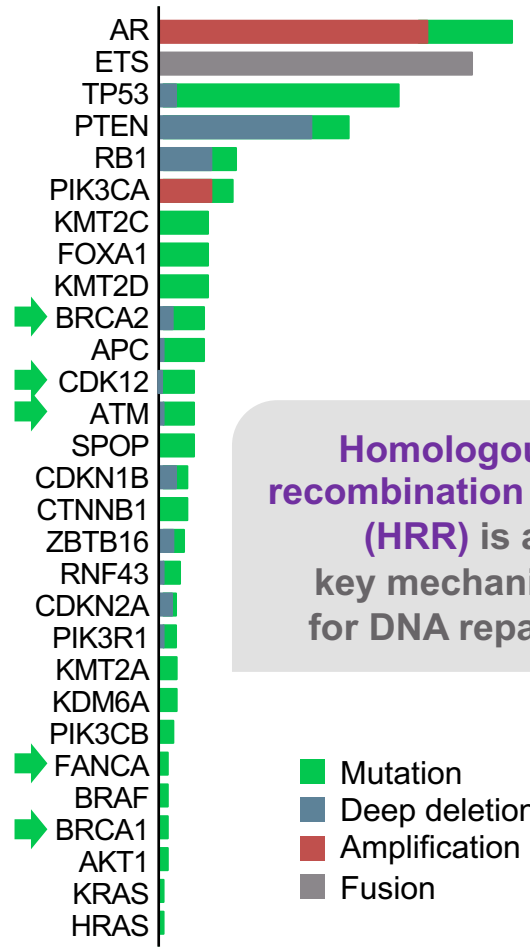
Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



~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

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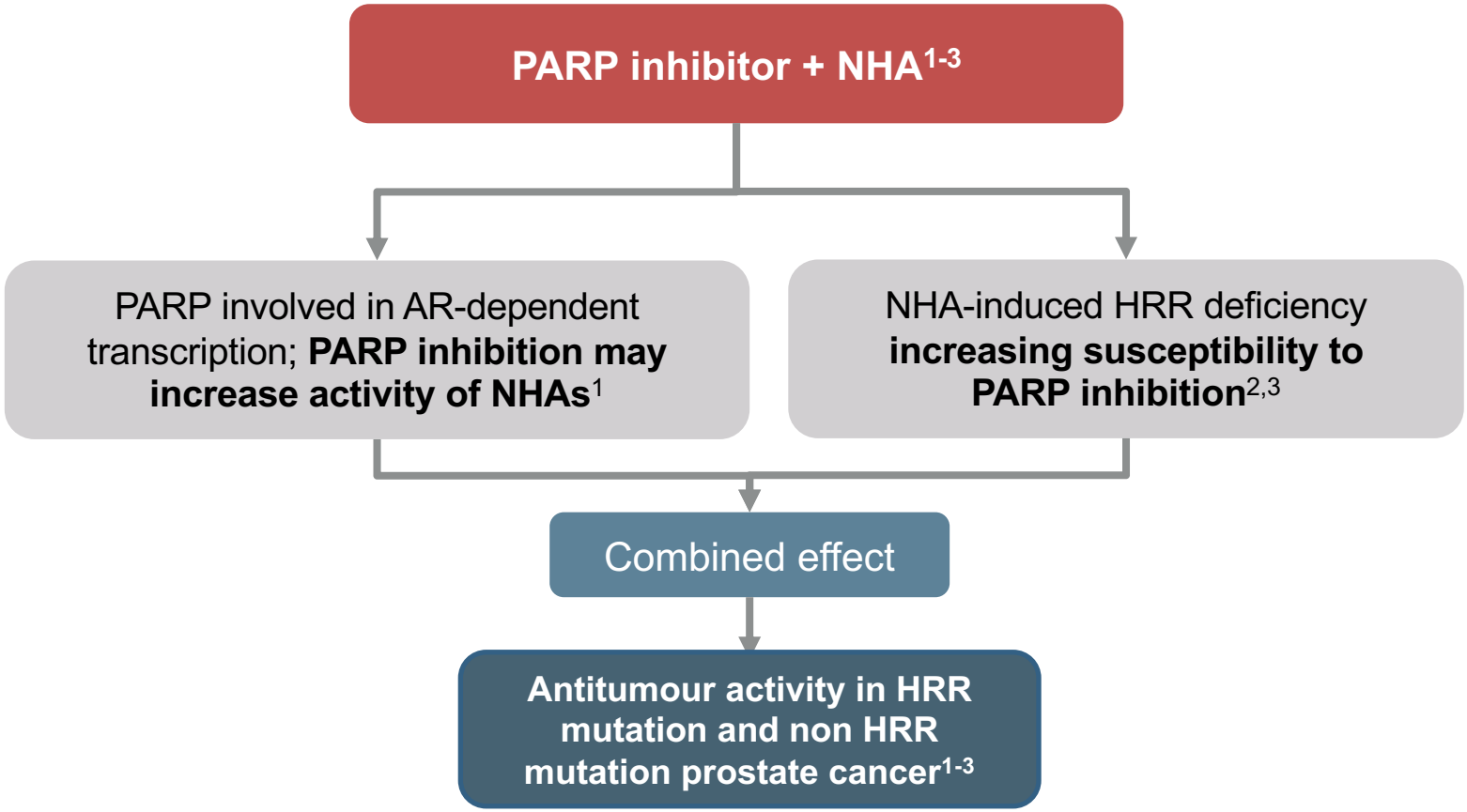
Interaction between PARP signalling and AR signalling pathways may explain the combined effect of agents observed in preclinical models



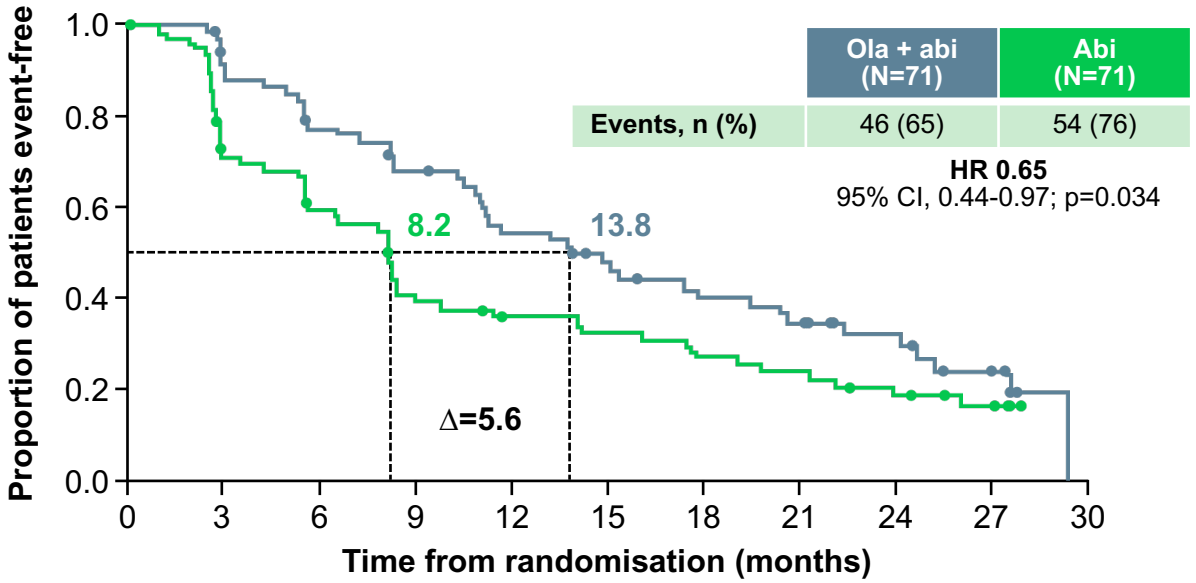
AR, androgen receptor; HRR, homologous recombination repair; NHA, novel hormonal agent; PARP, poly-ADP ribose polymerase

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)

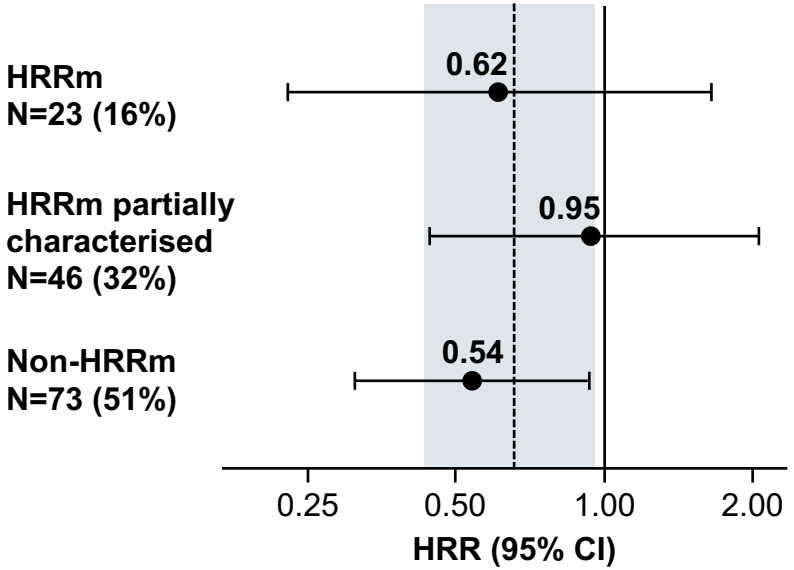
STUDY 8: A PHASE II STUDY OF OLAPARIB AND ABIRATERONE

- 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

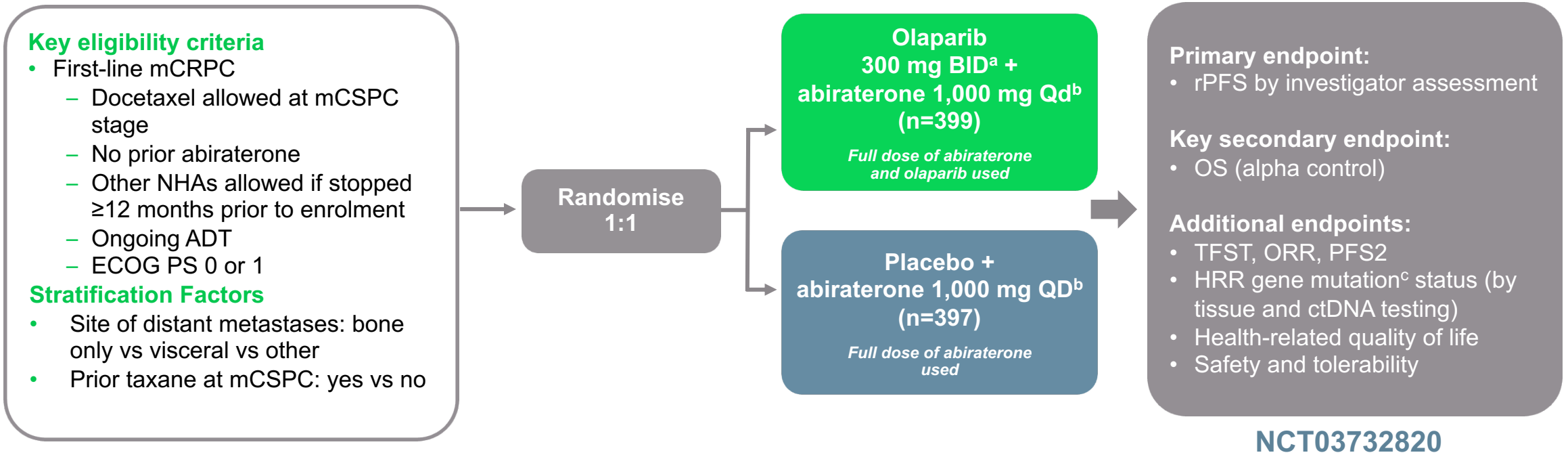
Clarke N, et al. Lancet Oncol. 2018;19:975-86; Carr T, et al. Cancers. 2021;13:5830. Adapted from: Saad F, et al. J Clin Oncol. 40, 2022 (suppl 6; abstr 11) (ASCO GU 2022 oral presentation)

KEY PARPi COMBINATION TRIALS IN 1L mCRPC

Which patient subgroups benefit?

PROpel STUDY DESIGN

A GLOBAL, RANDOMISED, DOUBLE-BLIND PHASE 3 TRIAL



NCT03732820

First patient randomized: Nov 2018; last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS

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

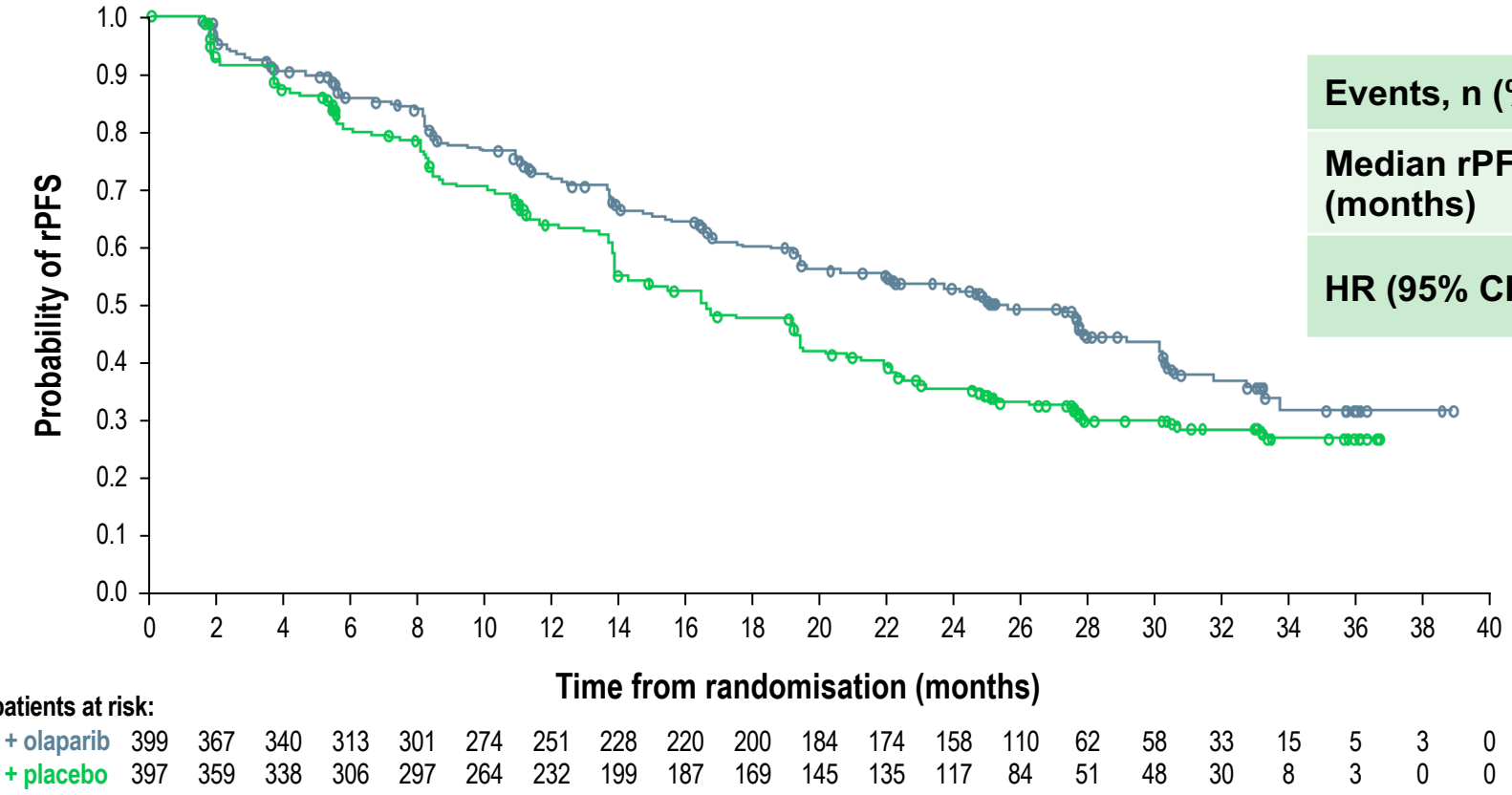
[a] Full dose of olaparib used; [b] abiraterone used in combination with prednisone or prednisolone 5 mg BID; [c] HRR mutation, including 14-gene panel, using the FoundationOne®CDx test and FoundationOne®Liquid CDx test

ADT, androgen-deprivation therapy; BICR, blinded independent central review; BID, twice daily; 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 agents; 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; TTPP, time to pain progression

Clarke NW, et al. J Clin Oncol. 2019;37 Suppl: TPS340; NCT03732820; Saad F, et al. J Clin Oncol. 2022;40 Suppl: Abstract 11 (ASCO GU 2022 oral presentation)

PROpel: UPDATED rPFS BY INVESTIGATOR ASSESSMENT IN THE ITT POPULATION

AT DCO2, rPFS WAS 8.6 MONTHS GREATER FOR ABIRATERONE + OLAPARIB VERSUS ABIRATERONE + PLACEBO



Number of patients at risk:

Abiraterone + olaparib	399	367	340	313	301	274	251	228	220	200	184	174	158	110	62	58	33	15	5	3	0
Abiraterone + placebo	397	359	338	306	297	264	232	199	187	169	145	135	117	84	51	48	30	8	3	0	0

	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	199 (49.9)	258 (65.0)
Median rPFS (months)	25.0	16.4
HR (95% CI)	0.67 (0.56-0.81); p<0.0001[a]	

Median duration of follow-up for censored patients was 24.9 months (range 0.03-38.80) in the abiraterone + olaparib arm and 27.4 months (range 0.03-36.76) in the abiraterone + placebo arm

[a] Nominal

CI, confidence interval; DCO2, second data cut-off; HR, hazard ratio; ITT, intention-to-treat; rPFS, radiographic progression-free survival

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

PROpel KEY SECONDARY ENDPOINT: OS IN THE ITT POPULATION

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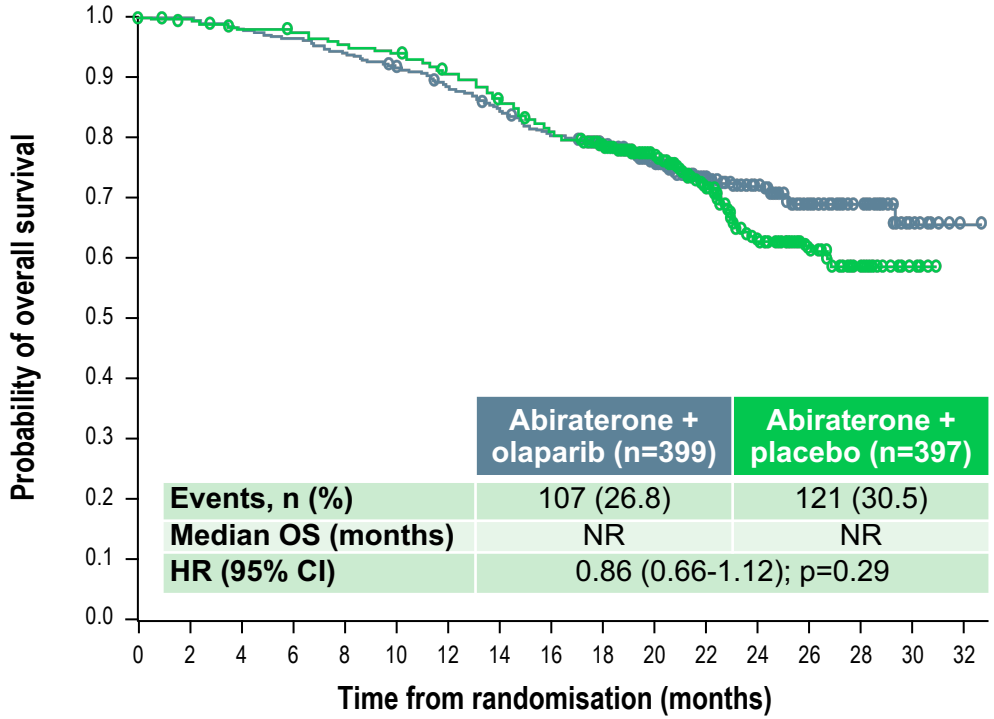
AT DCO2, THERE WAS A CONTINUED TREND TOWARDS IMPROVED OS WITH ABIRATERONE + OLAPARIB, WITH KM CURVES SHOWING SEPARATION BETWEEN THE ARMS AFTER ~22 MONTHS BEFORE EXTENSIVE CENSORING WAS OBSERVED

Primary analysis (DCO1, 28.6% maturity)

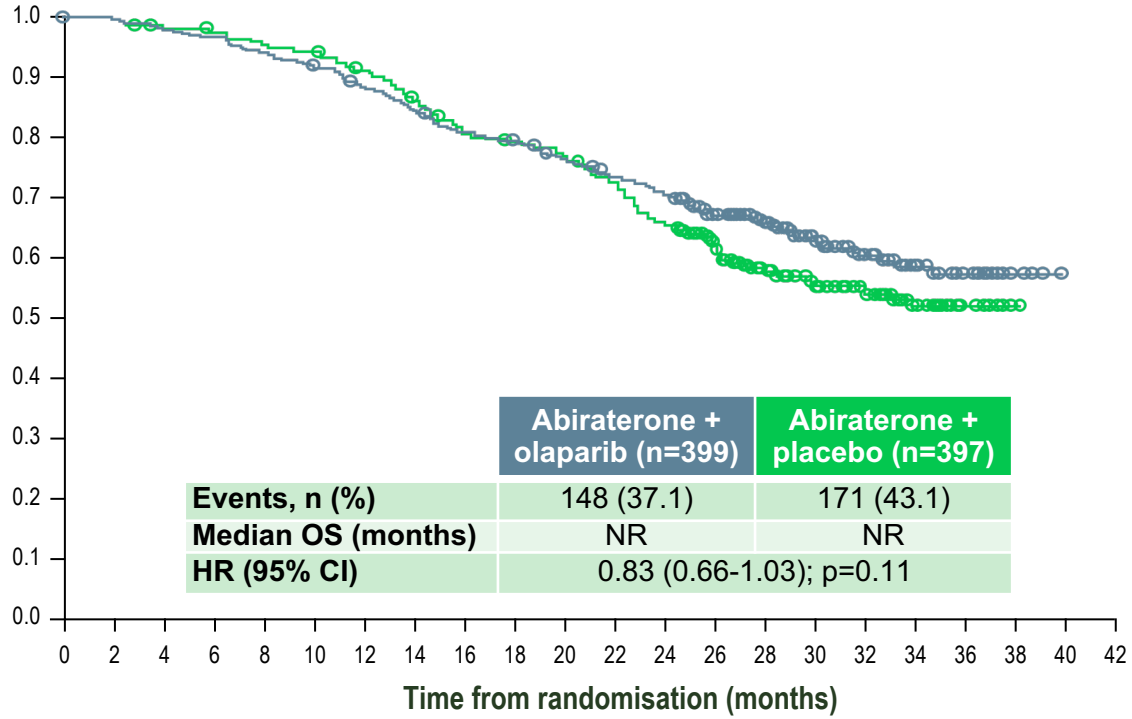


	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	107 (26.8)	121 (30.5)
Median OS (months)	NR	NR
HR (95% CI)	0.86 (0.66-1.12); p=0.29	

Number of patients at risk:

Abiraterone + olaparib	399	398	391	385	374	364	349	333	316	290	231	159	116	73	37	11	1	
Abiraterone + placebo	397	392	385	381	374	368	353	335	314	286	223	151	104	63	22	6	0	

Updated results (DCO2, 40.1% maturity)



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	148 (37.1)	171 (43.1)
Median OS (months)	NR	NR
HR (95% CI)	0.83 (0.66-1.03); p=0.11	

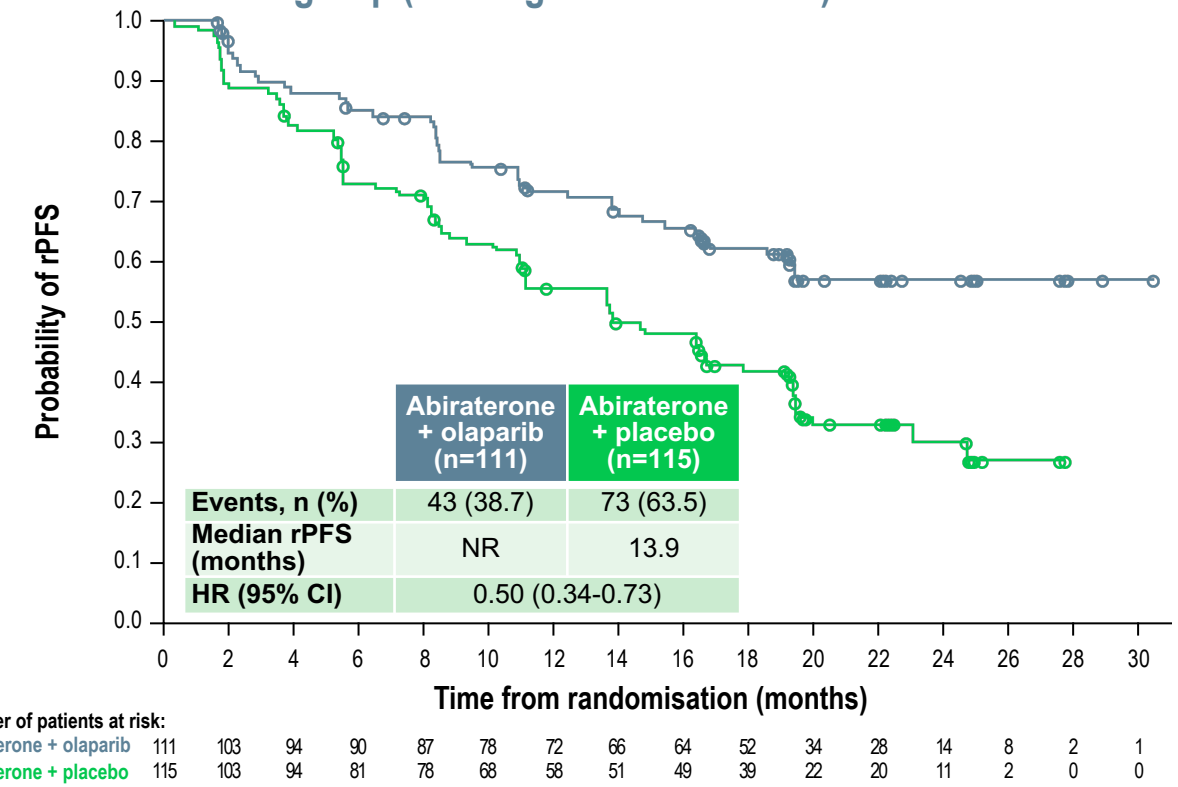
Abiraterone + olaparib	399	398	391	385	374	365	350	335	318	313	298	284	274	232	188	135	93	53	23	5	1	0
Abiraterone + placebo	397	395	388	383	376	370	355	337	316	304	300	280	253	211	154	106	81	46	13	1	0	0

Median duration of follow-up for censored patients at DCO1 was 22.2 months (range 0.03-32.56) in the abiraterone + olaparib arm and 21.8 months (range 0.10-30.88) in the abiraterone + placebo arm
Median duration of follow-up for censored patients at DCO2 was 30.0 months (range 0.03-40.02) in the abiraterone + olaparib arm and 29.4 months (range 2.89-38.34) in the abiraterone + placebo arm
CI, confidence interval; DCO1, first data cut-off; DCO2, second data cut-off; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan-Meier; NR, not reached; OS, overall survival
Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 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)



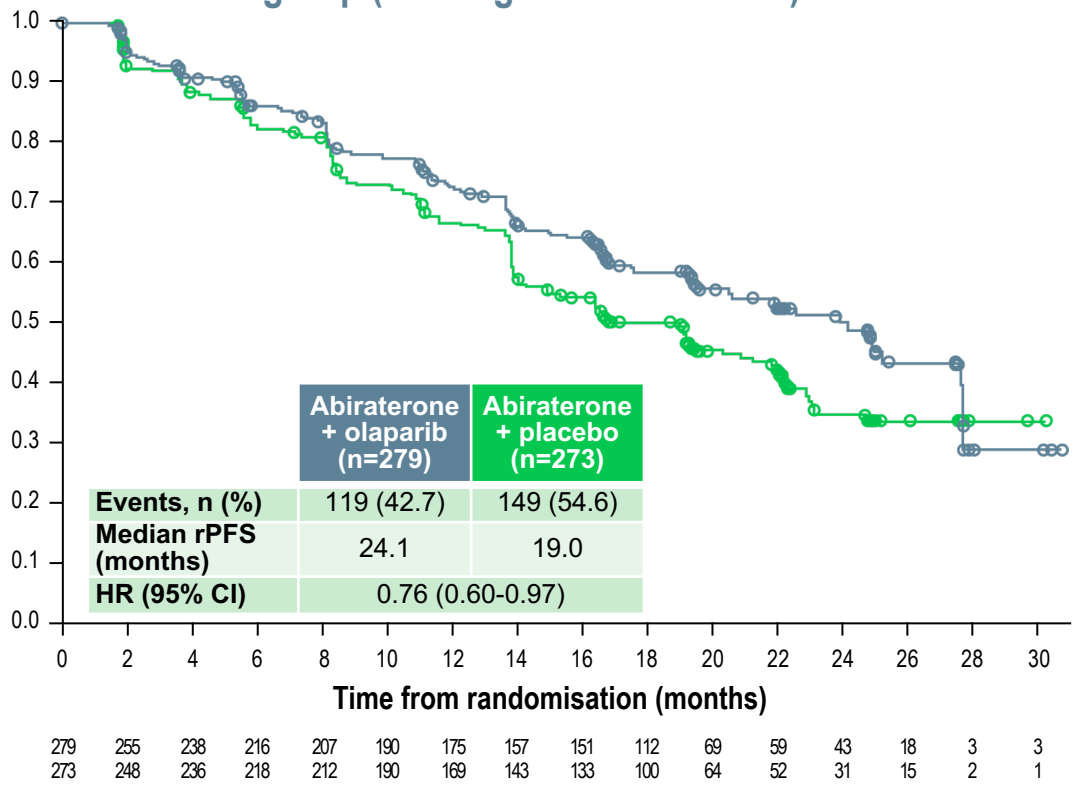
	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS (months)	NR	13.9
HR (95% CI)	0.50 (0.34-0.73)	

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

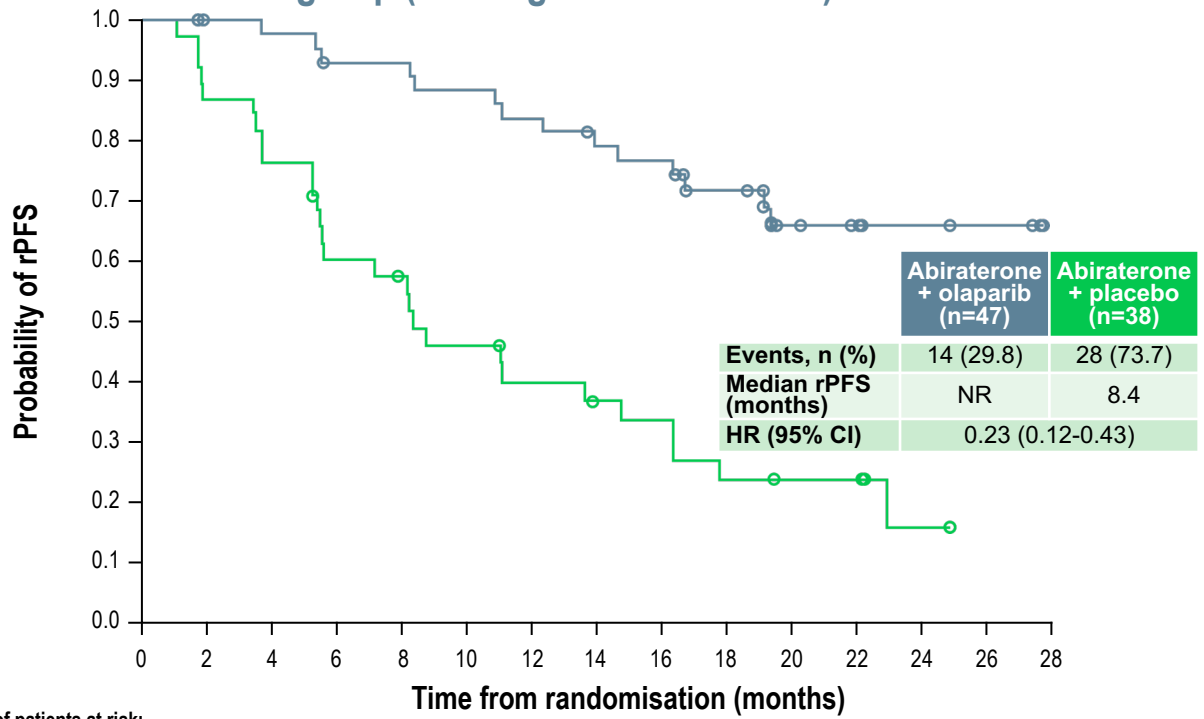
Patient enrolment was not based on HRRm status; however, HRRm testing was prespecified. HRR status was determined after randomisation and before primary analysis using results from tumour tissue and plasma ctDNA HRRm tests. A total of 18 patients did not have a valid HRR testing result from either a 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)



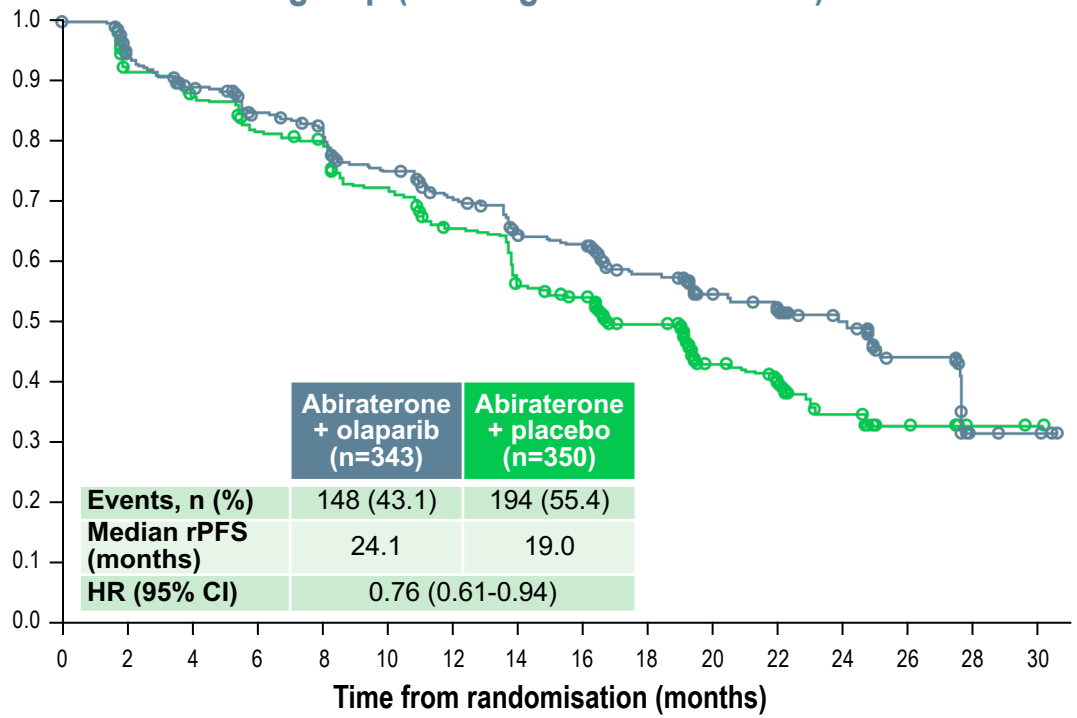
	Abiraterone + olaparib (n=47)	Abiraterone + placebo (n=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median rPFS (months)	NR	8.4
HR (95% CI)	0.23 (0.12-0.43)	

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)	

	343	314	289	266	254	230	211	190	183	137	87	73	50	21	5	4
	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

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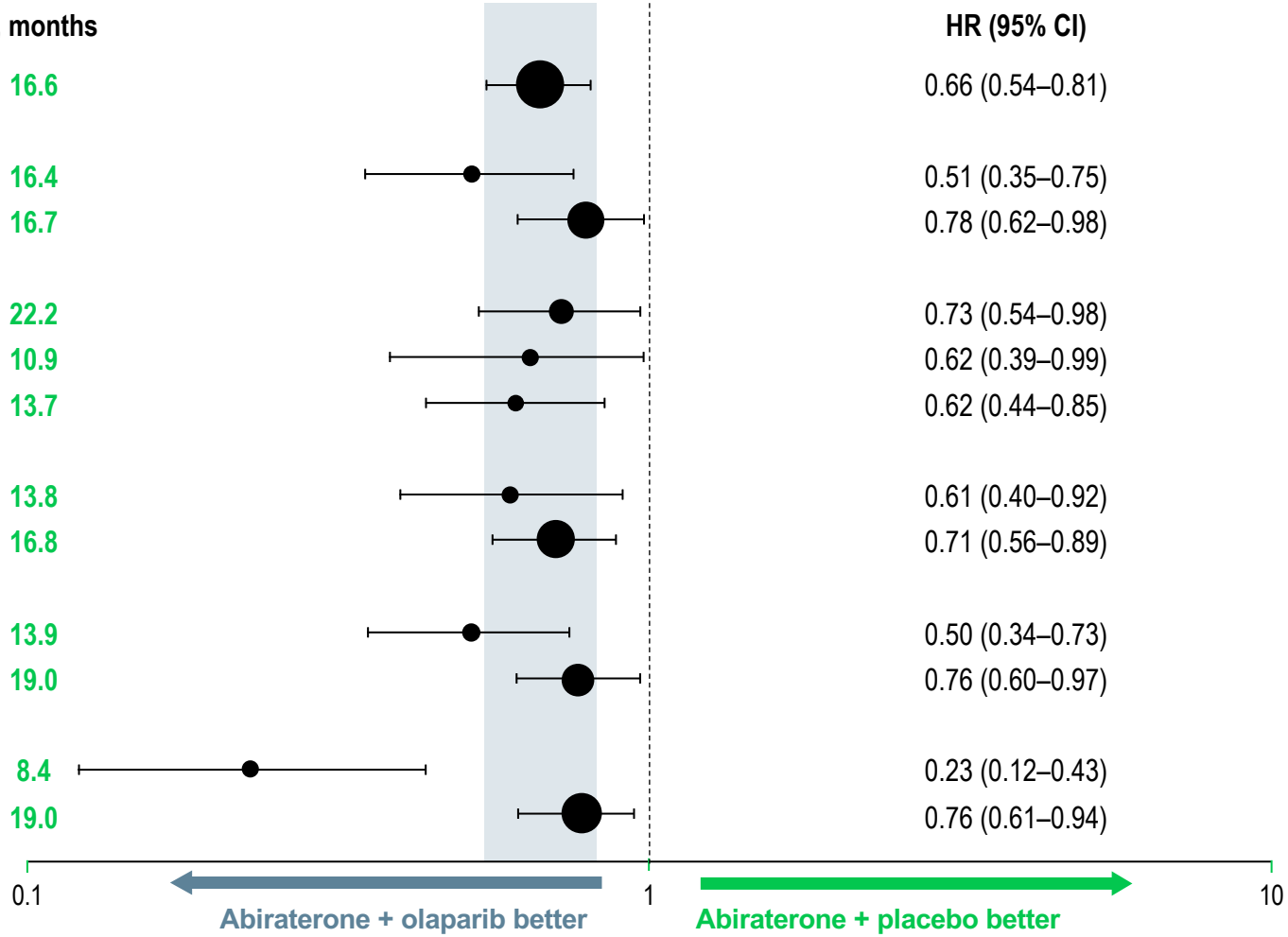
PROpel: SUBGROUP ANALYSIS OF rPFS

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)
BRCAm status[a]				
BRCAm	85	NR	8.4	0.23 (0.12–0.43)
Non-BRCAm	693	24.1	19.0	0.76 (0.61–0.94)



[a] 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/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

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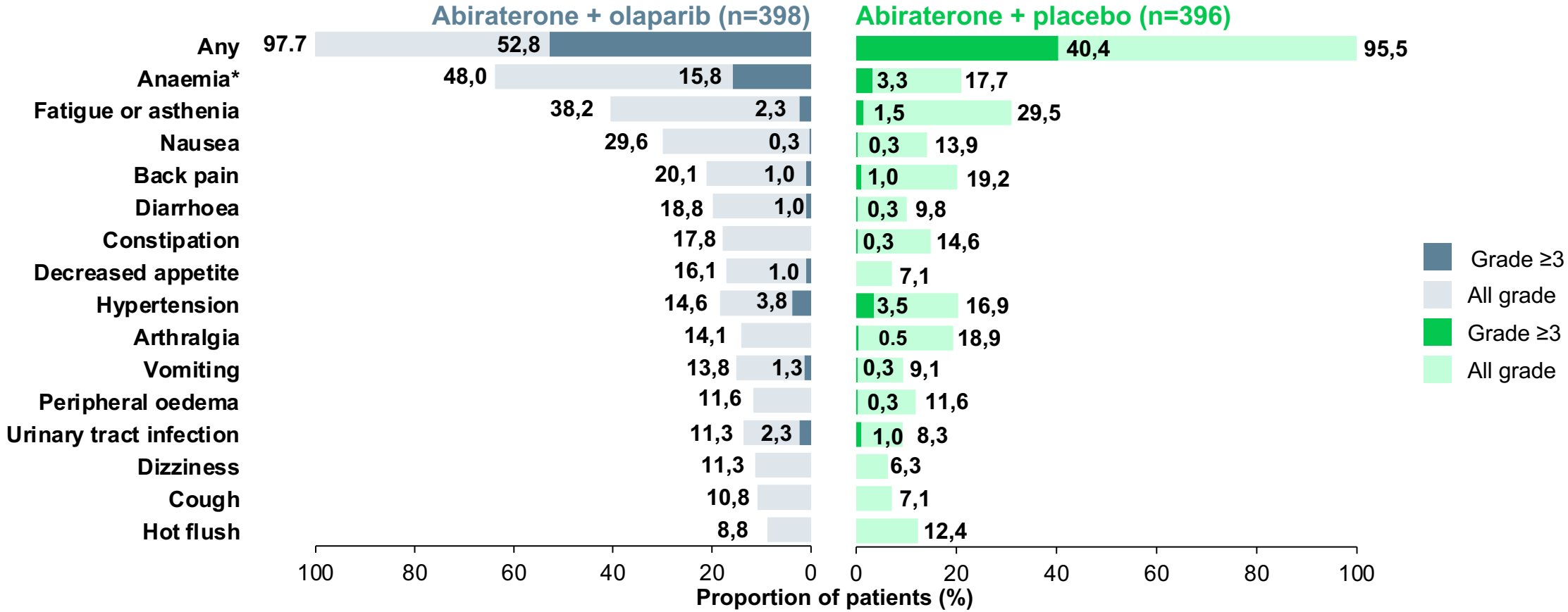
PROpel: MOST COMMON AEs (IN ≥10% PATIENTS)

THE AE PROFILE AT DCO2 REMAINED GENERALLY CONSISTENT WITH THE PROFILE AT DCO1 AND THE KNOWN PROFILES OF THE INDIVIDUAL DRUGS



Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments

* Anaemia category includes anaemia, decreased haemoglobin level, decreased red-cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia

AE, adverse event; DCO1, first data cut-off; DCO2, second data cut-off

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PROpel: OVERALL SAFETY PROFILE

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UPDATED OVERALL SAFETY RESULTS (DCO2) WERE CONSISTENT WITH THE PRIMARY ANALYSIS (DCO1)

	Abiraterone + olaparib (n=398)		Abiraterone + placebo (n=396)	
n (%)	**DCO1**	**DCO2**	**DCO1**	**DCO2**
Any AE	387 (97.2)	389 (97.7)	376 (94.9)	378 (95.5)
Any AE CTCAE Grade ≥3	188 (47.2)	210 (52.8)	152 (38.4)	160 (40.4)
Death due to an AE	**16 (4.0)**	**23 (5.8)**	**17 (4.3)**	**18 (4.5)**
Any AE leading to:				
Dose interruption of olaparib/placebo	178 (44.7)	190 (47.7)	100 (25.3)	108 (27.3)
Dose reduction of olaparib/placebo	80 (20.1)	85 (21.4)	22 (5.6)	22 (5.6)
Discontinuation of olaparib/placebo	**55 (13.8)**	**63 (15.8)**	**31 (7.8)**	**32 (8.1)**
Discontinuation of abiraterone	**34 (8.5)**	**41 (10.3)**	**35 (8.8)**	**35 (8.8)**

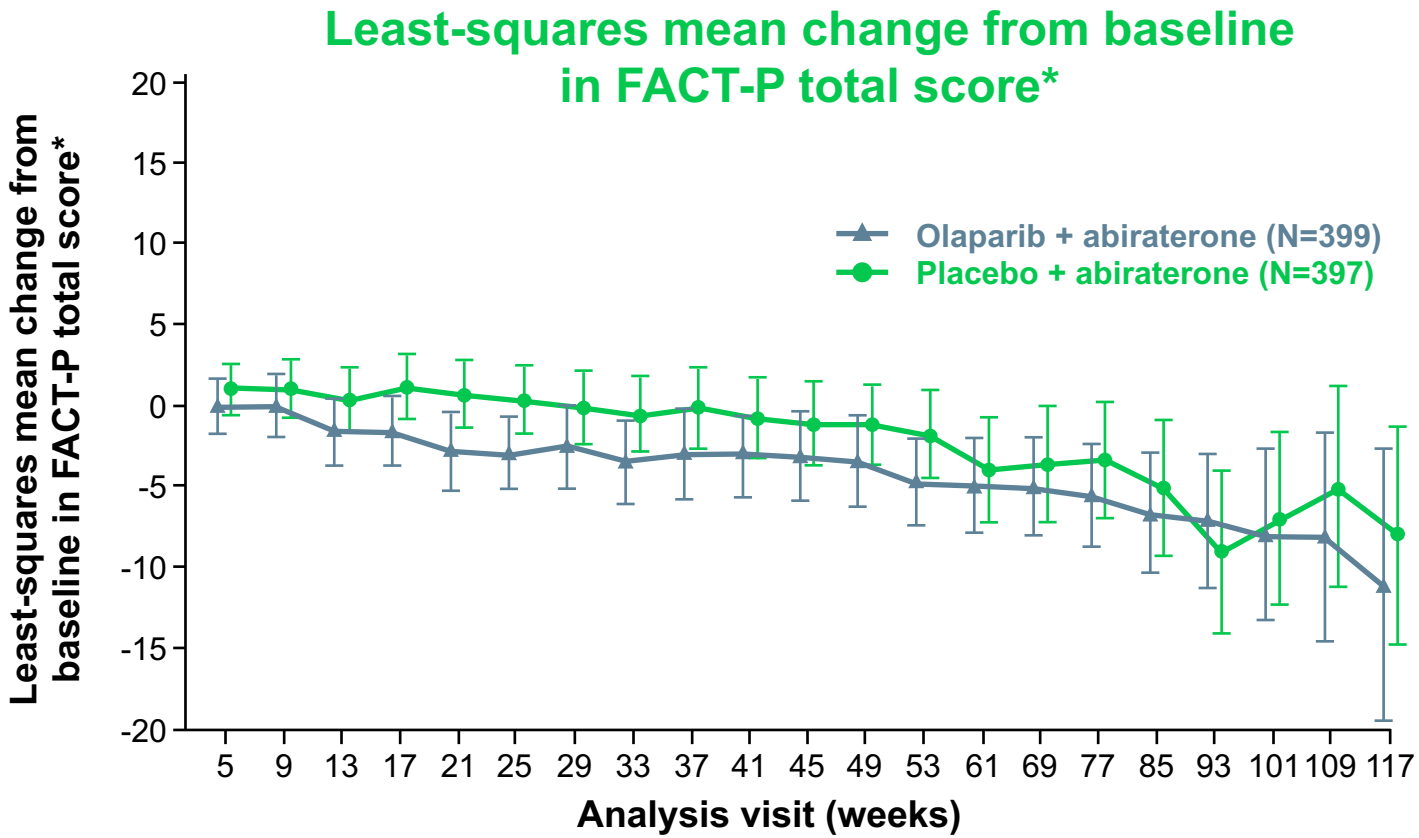
- One case of MDS/AML identified during hospital admission for fatal COVID-19 pneumonia
- Incidence of new primary malignancies and pneumonitis were balanced between treatment arms
- The incidence of pulmonary embolism and cardiovascular events was similar between DCO1 and DCO2

Primary analysis, DCO1: 30 July 2021; second data cut-off, DCO2: 14 March 2022

Patients ongoing treatment at DCO1: 180 for abiraterone + olaparib, 137 for abiraterone + placebo; patients ongoing treatment at DCO2: 138 for abiraterone + olaparib, 104 for abiraterone + placebo
At DCO1, median treatment duration of olaparib was 17.5 months, placebo was 15.7 months, abiraterone in the abiraterone + olaparib arm was 18.2 months and in the abiraterone + placebo arm was 15.7 months
At DCO2, median treatment duration of olaparib was 18.5 months, placebo was 15.7 months, abiraterone in the abiraterone + olaparib arm was 20.1 months and in the abiraterone + placebo arm was 15.7 months
AE, adverse event; AML, acute myeloid leukaemia; CTCAE, Common Terminology Criteria for Adverse Events version 4.03; DCO1, first data cut-off; DCO2, second data cut-off; MDS, myelodysplastic syndromes
Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 oral presentation)

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

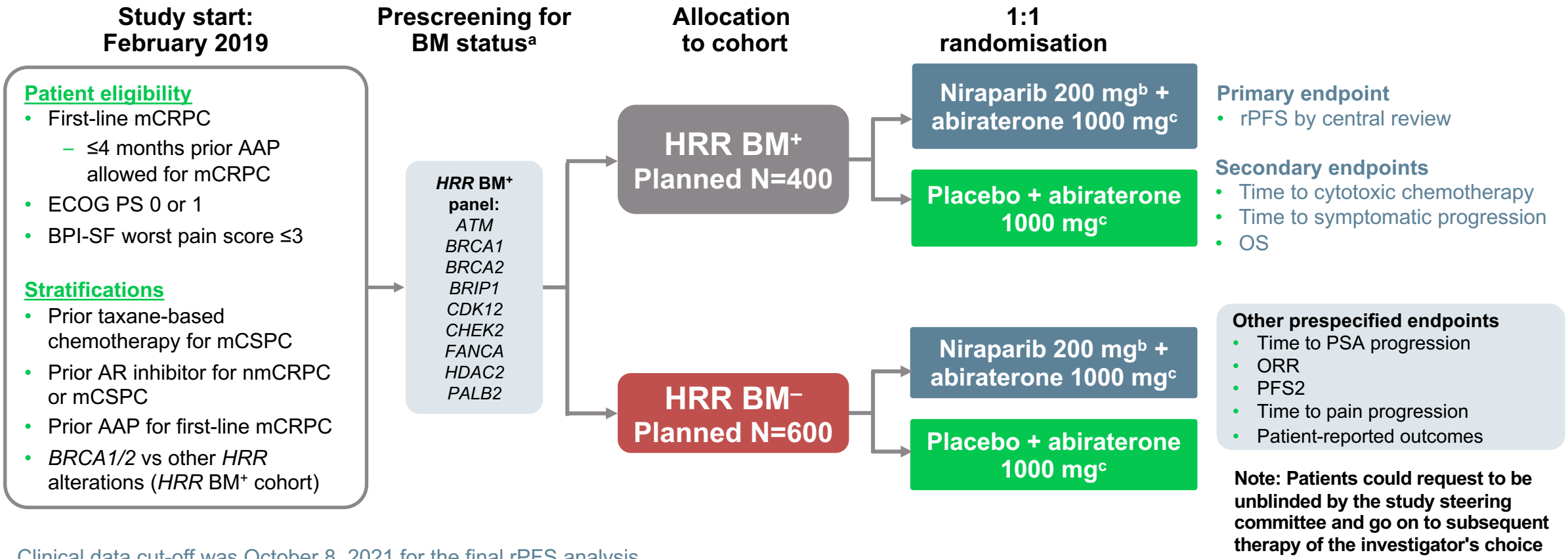
* Plot includes 95% confidence limits. FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156.
A clinically meaningful change in FACT-P total score is 10.

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

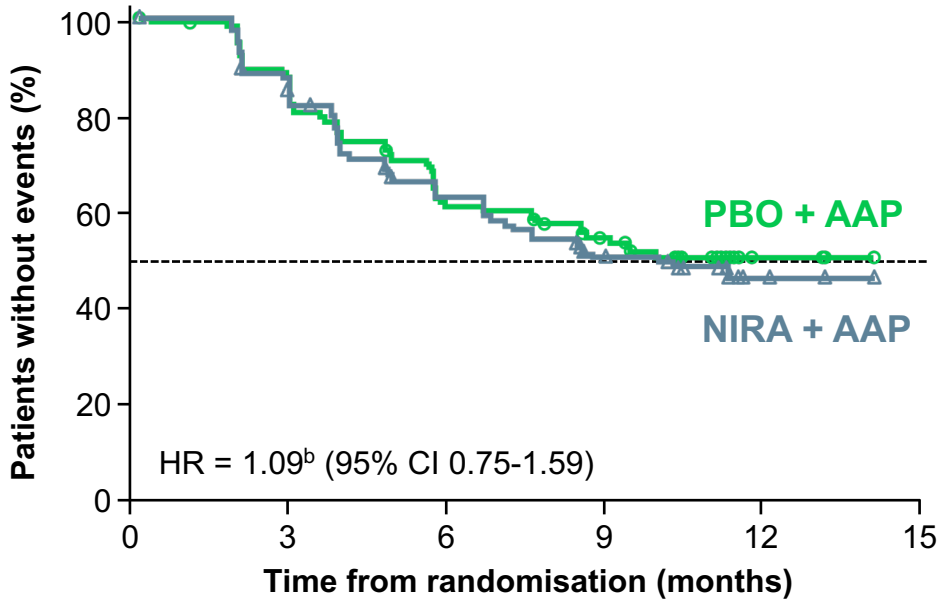
AAP, abiraterone acetate and prednisone/prednisolone; AR, androgen receptor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant 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)

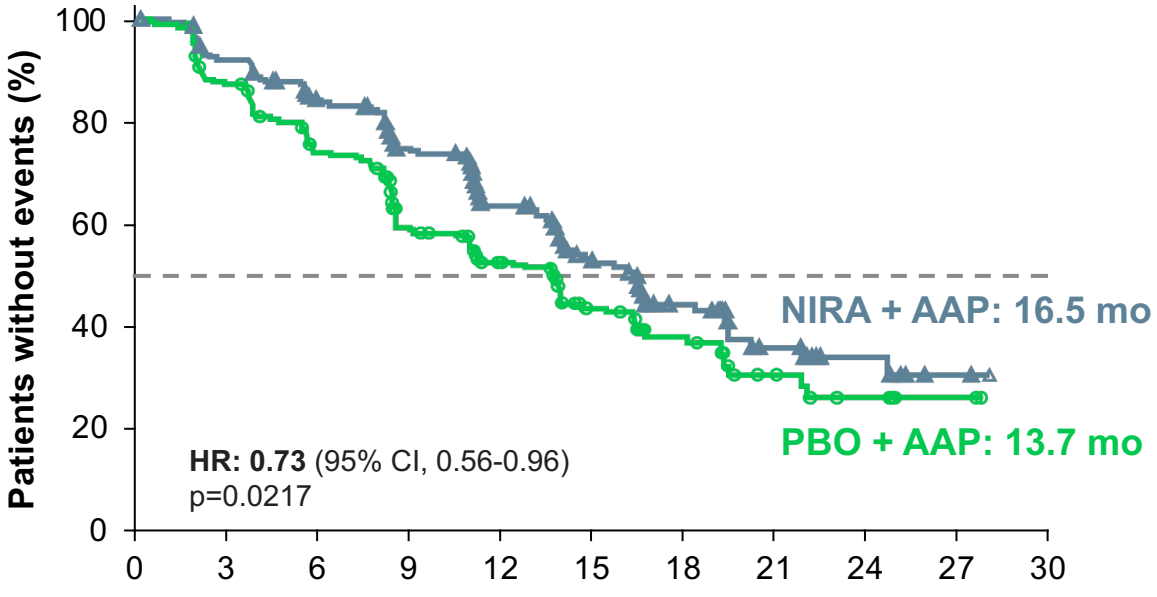
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA,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

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

MAGNITUDE: PRIMARY ENDPOINT rPFS (BICR)

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

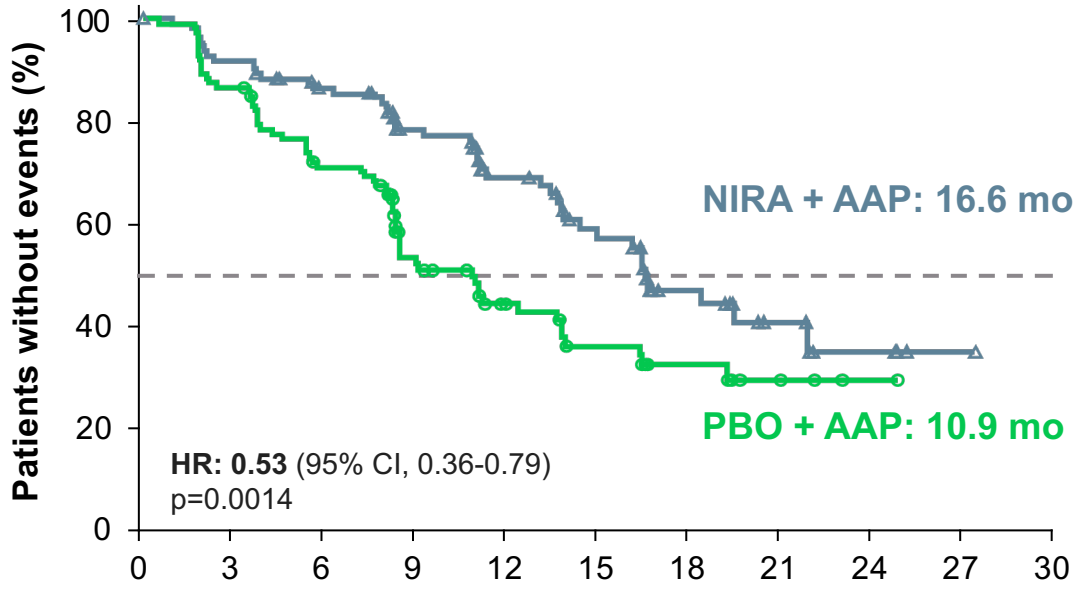
All HRR BM+ patients



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

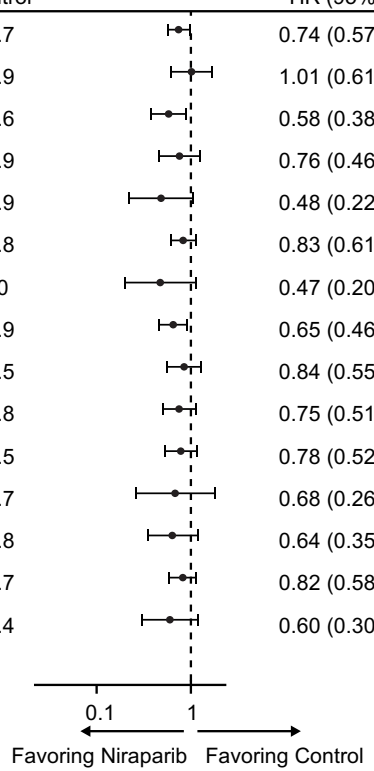
AAP, abiraterone acetate + prednisone/prednisolone; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival

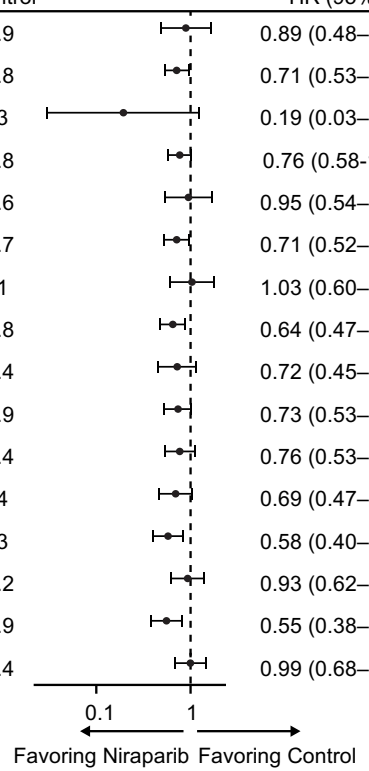
Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation)

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





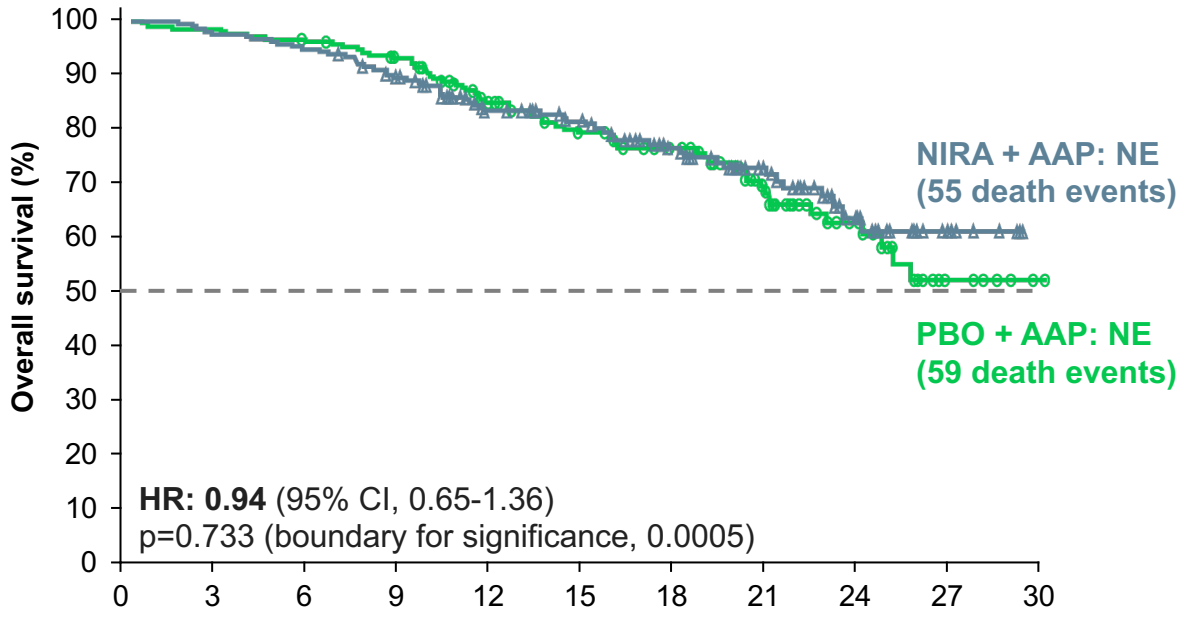
[a]Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide.
[b]Prior AAP use was up to 4 months prior to study start.

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)

MAGNITUDE ALL HRR BM+: OVERALL SURVIVAL

OS CURVES APPEAR TO SEPARATE AFTER 25 MONTHS



No. at risk											
NIRA + AAP	212	207	200	180	146	110	84	52	20	4	0
PBO + AAP	211	206	202	187	141	113	82	47	22	5	0

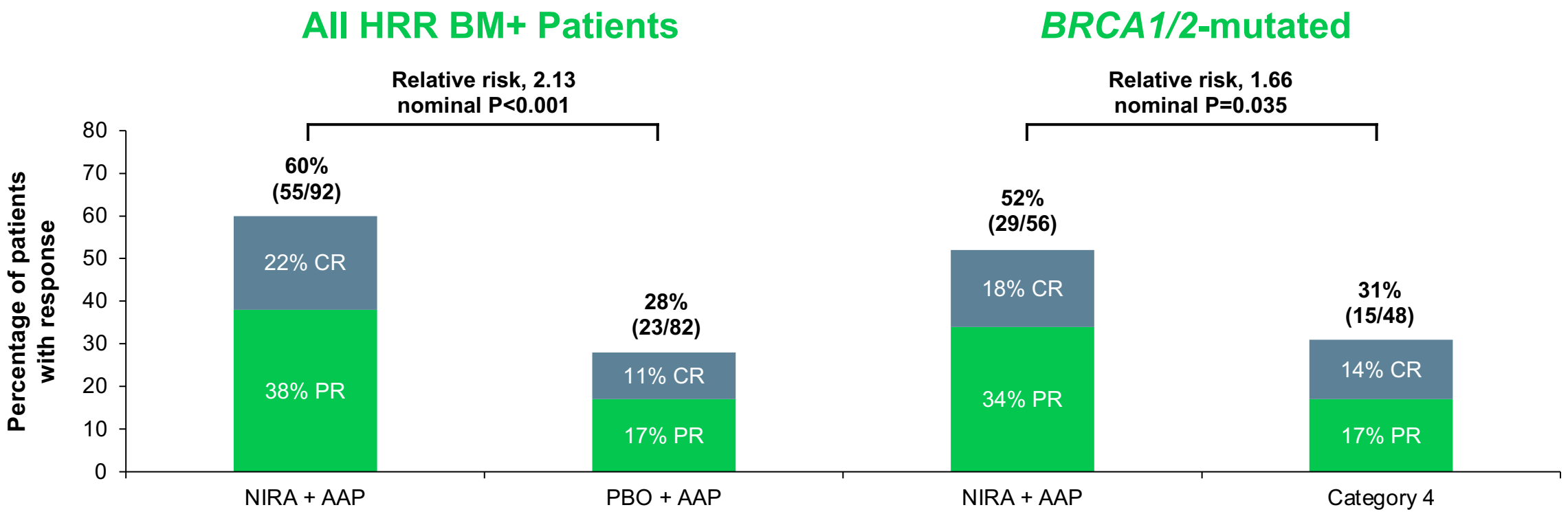
46.3% of the required death events for the final analysis observed and thus overall survival data are immature

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

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

MAGNITUDE: OVERALL RESPONSE RATE

ABIRATERONE + NIRAPARIB IMPROVES ORR CONSISTENTLY ACROSS GENE ALTERATIONS



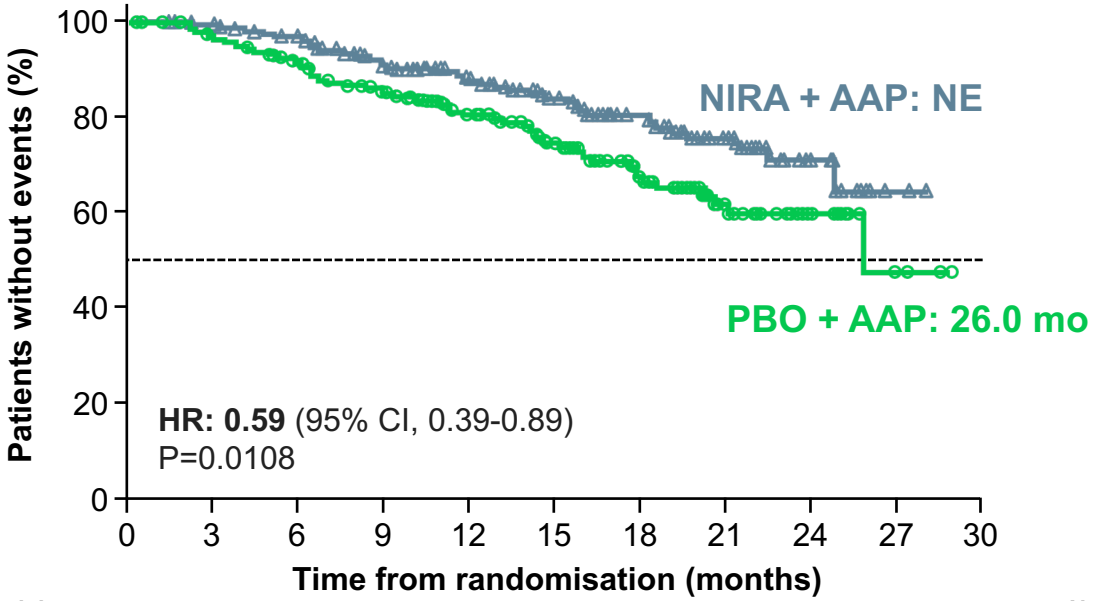
Note: Relative risk >1 favours niraparib and AAP treatment. Percent of responder is based on the number of subjects with measurable disease at baseline
AAP, abiraterone acetate plus prednisone; CR, complete response; HRR, homologous recombination repair, NIRA, niraparib; ORR, overall response rate PBO,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

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

MAGNITUDE: TIME TO CYTOTOXIC CHEMOTHERAPY

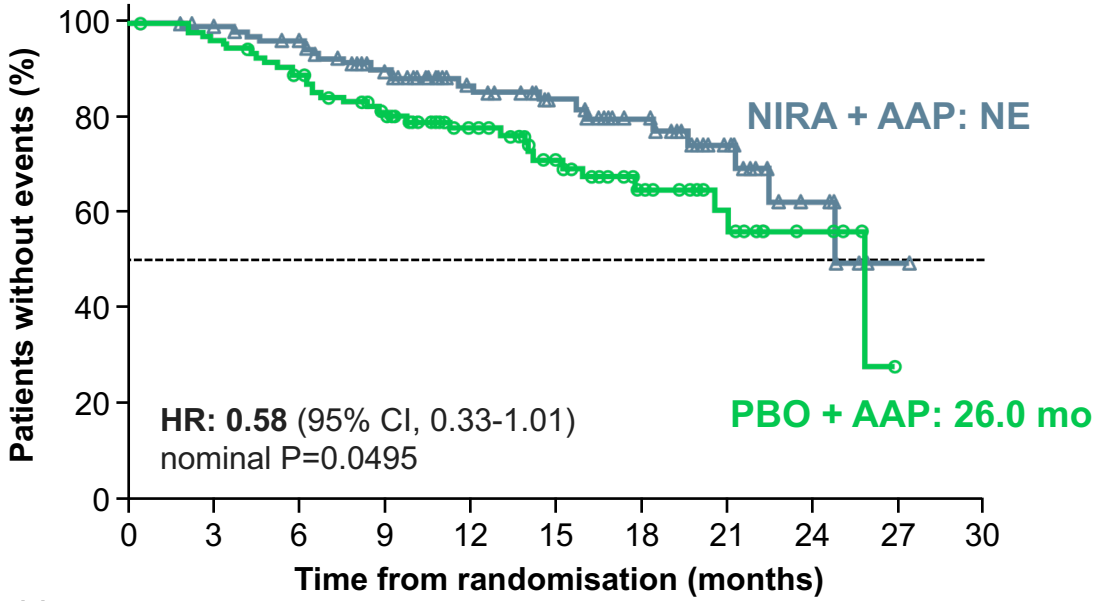
ABIRATERONE + NIRAPARIB PROLONGS TIME TO CHEMOTHERAPY ACROSS GENE ALTERATIONS

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



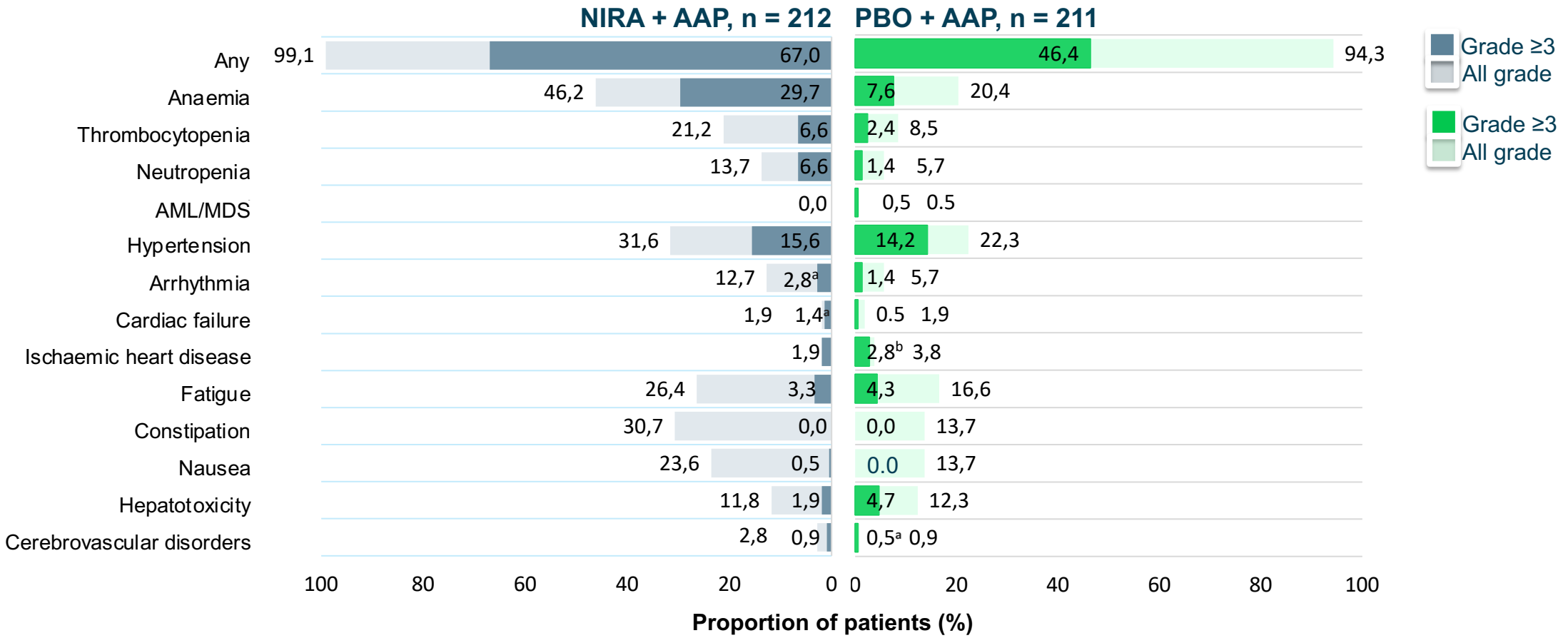
No. at risk											
NIRA + AAP	113	109	104	86	61	44	33	18	7	1	0
PBO + AAP	112	107	97	81	53	41	26	14	6	1	0

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)

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 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; 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)

MAGNITUDE: SUMMARY OF TEAEs IN HRR BM+

Overall summary, n (%)	Niraparib + AAP (n=212)	Placebo + AAP (n=211)
All TEAEs	210 (99.1)	199 (94.3)
Drug related	162 (76.4)	116 (55.0)
Grade 3 / 4 TEAEs	142 (67.0)	98 (46.4)
SAEs	76 (35.8)	52 (24.6)
Drug related[a]	24 (11.3)	6 (2.8)
Dose reduction due to an AR	42 (19.8)	7 (3.3)
Discontinuation of niraparib or placebo due to an AE	23 (10.8)	10 (4.7)
All deaths within 30 days of last dose	19 (9.0)	19 (9.0)
Death due to prostate cancer	8 (3.8)	12 (5.7)
AE	11 (5.2)	7 (3.3)

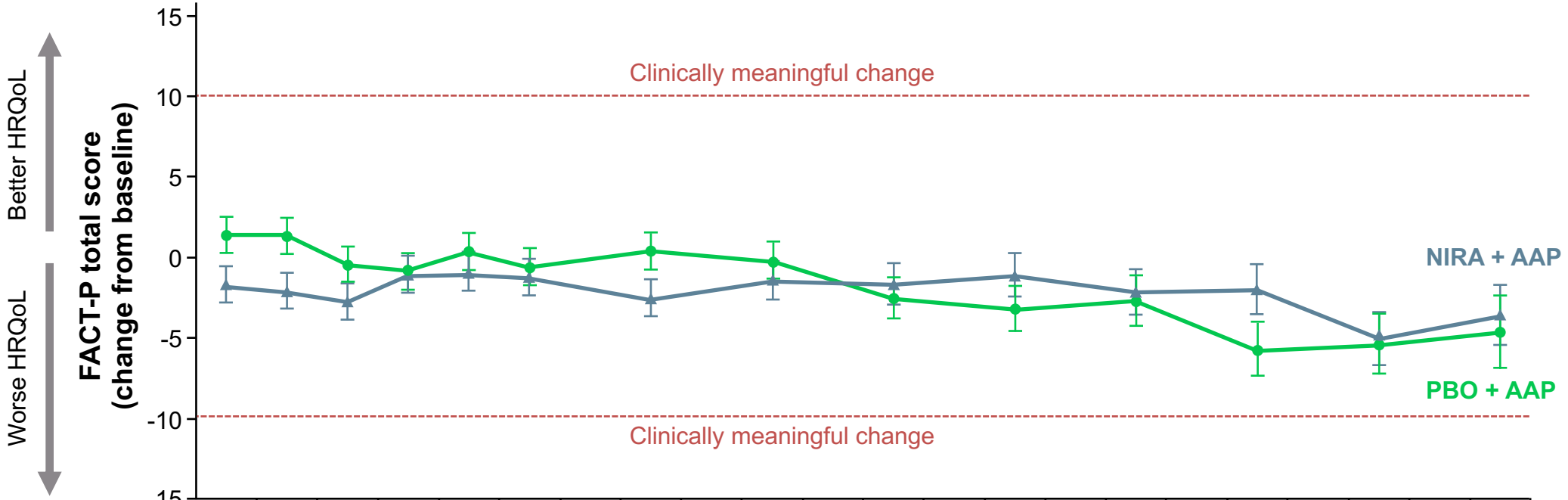
[a]AE categorised as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone; The most common AEs leading to dose reduction in the NIRA + AAP group were anaemia (13.2%) and thrombocytopenia (2.8%). Median relative dose intensity was 99% in the NIRA+ AAP group.

AAP, abiraterone acetate + prednisone / prednisolone; AR, androgen receptor; AE, adverse event; BM, biomarker; HRR, homologous recombination repair; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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

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)

DESIGN AND BASELINE COMPARISON OF PROPEL AND MAGNITUDE TRIALS

	PROpel[1,2] N=796	MAGNITUDE[3] 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)

OTHER PARPi AND ANTI-ANDROGEN COMBINATION TRIALS

PARPi, poly (ADP-ribose) polymerase inhibitor

TALAPRO-2: FIRST-LINE TALAZOPARIB + ENZALUTAMIDE IN mCRPC

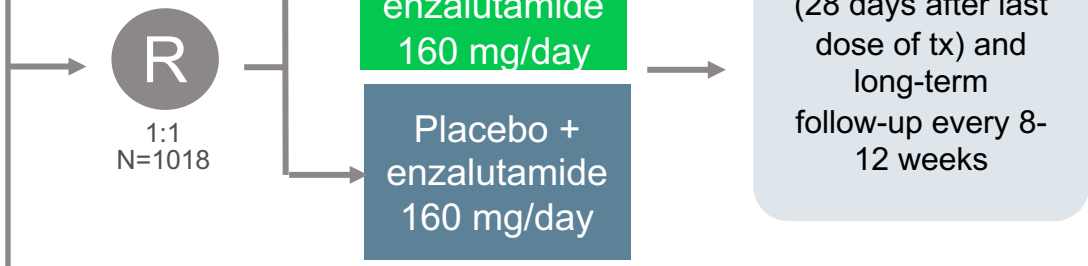
GU connect® POWERED BY COR2ED

GLOBAL, 2-PART, PHASE 3 TRIAL

- Part 1: non-randomised, open-label study confirming talazoparib starting dose in combination with enzalutamide (planned n=19)
- Part 2: randomised, double-blind, placebo-controlled study (planned n=1,018)

Patient eligibility
- Adult men with mCRPC
- adenocarcinoma of the prostate
- no small cell/signet cell features
- mild or no symptoms
- PD at study entry
- life expectancy ≥12 mos
- ECOG PS 0/1

Stratifications
- prior novel hormonal tx or taxane based CT for CSPC (yes vs no)
- DDR alteration status (deficient vs non-deficient/unknown)



Primary endpoint:
- rPFS per RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease) in DDR-unselected and DDR-mutant populations

Key secondary endpoint:
- OS, objective response, PSA response, PFS2, TTNT, PK, HRQoL
- Safety and tolerability

ClinicalTrials.gov identifier: NCT03395197

CSPC, castration-sensitive prostate cancer; CT, chemotherapy; DDR, DNA damage repair; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; PFS2, progression-free survival on next line of therapy; PK, pharmacokinetics; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival; TTNT, time to next therapy; tx, treatment

1. Agarwal N, et al. J Clin Oncol. 2020;38 15_suppl:TPS5598 (poster); 2. TALAPRO-2. ClinicalTrials.gov identifier: NCT03395197. Accessed October 11, 2022. https://clinicaltrials.gov/ct2/show/NCT03395197

TALAPRO-2:COMBINATION OF TALAZOPARIB PLUS ENZALUTAMIDE PROLONGS rPFS IN mCRPC

INITIAL DATA BASED ON PRESS RELEASE – AWAITING DATA PRESENTATION

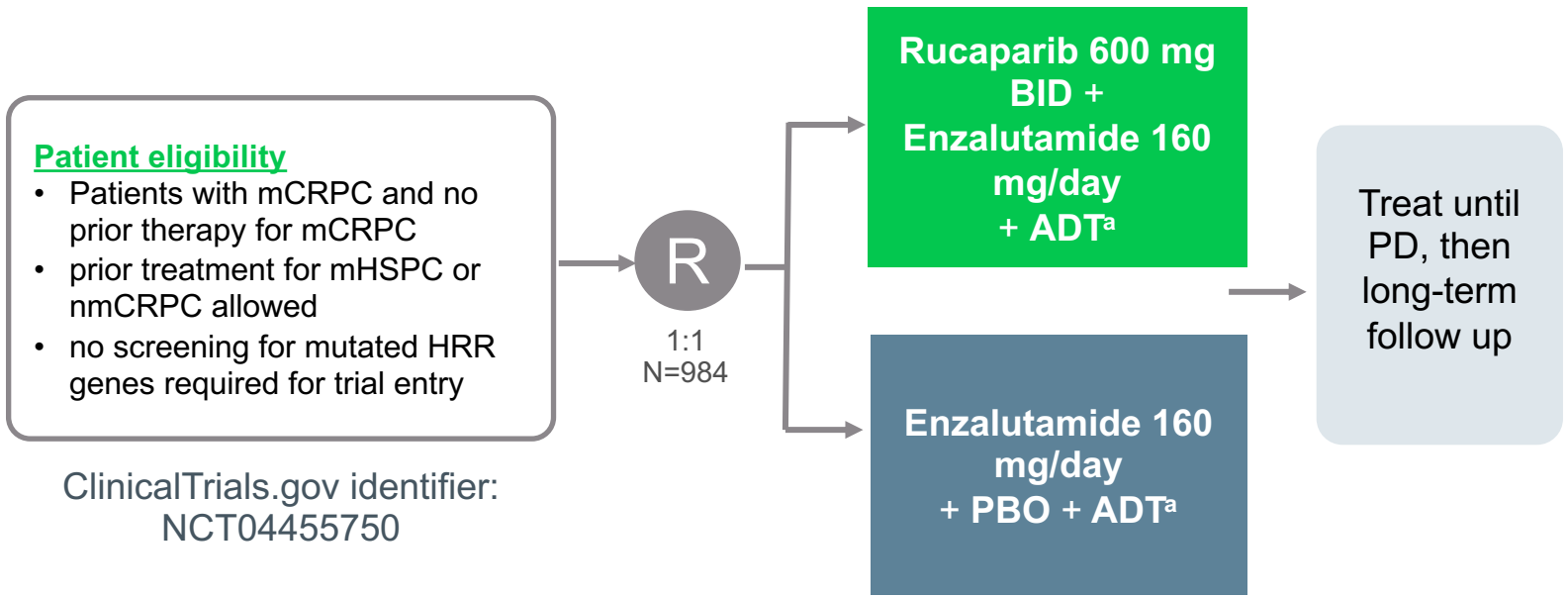
- The combination of talazoparib plus enzalutamide resulted in a **statistically significant and clinically meaningful improvement in rPFS** compared with placebo plus enzalutamide in 1L mCRPC pts
  - Robust, highly consistent **efficacy** observed **in patients with and without HRR gene mutations**
- A **trend toward improved overall survival** was observed but data immature
- **Benefits also observed in other secondary endpoints**:
  - investigator assessed rPFS,
  - PSA response,
  - time to PSA progression
  - ORR
- **Safety** of the combination treatment was generally **consistent with the known safety profile of the individual treatments**

1L, first-line; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; ORR, overall response rate; PSA, prostate specific antigen; rPFS, radiographic progression-free survival

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-topline-results-phase-3-talapro-2 Accessed 13th October 2022

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

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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

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

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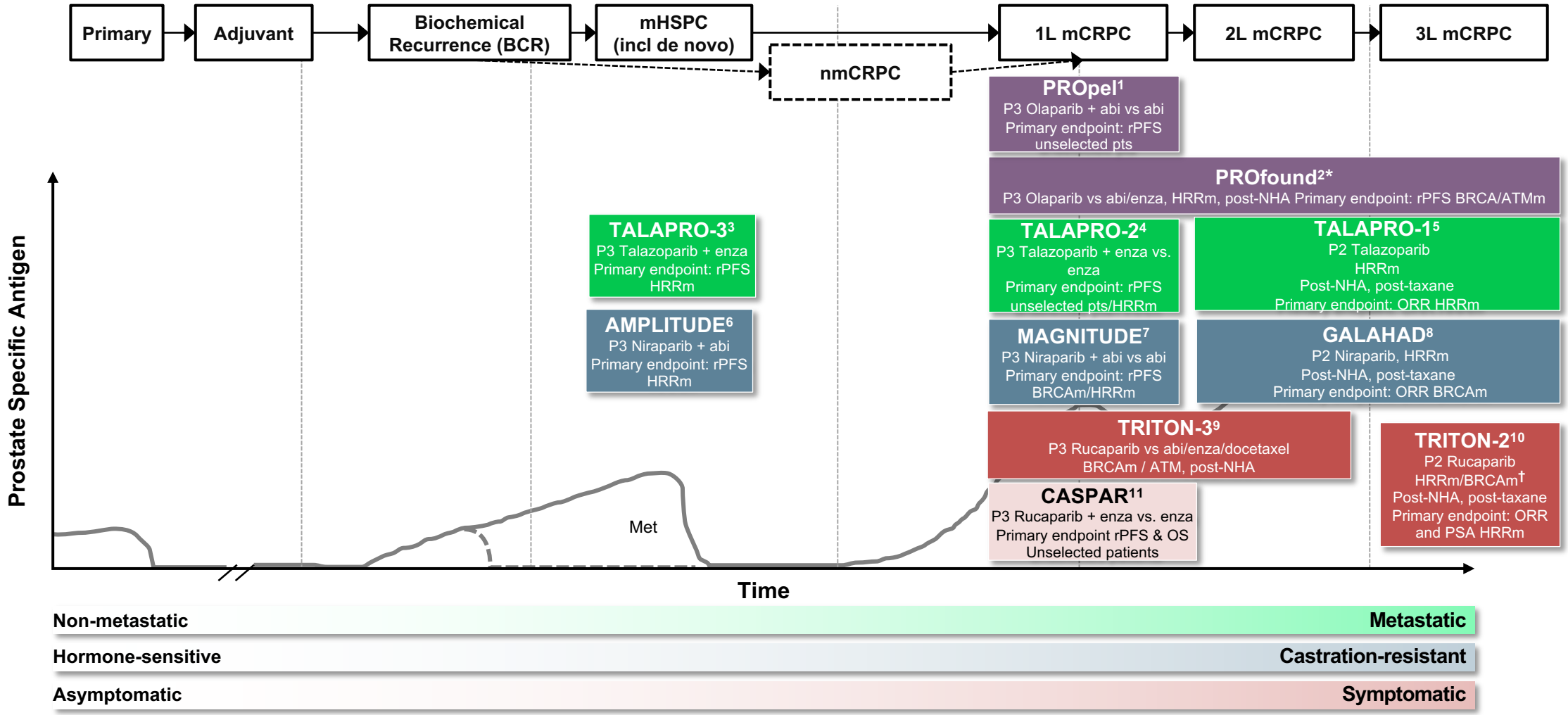

Please see slide notes for references. [a] As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA[12,13; b] As a result of 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[14]

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

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	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[1,2,3,a,b]	Ovarian cancer,[4,5] prostate cancer[5,c]	Ovarian cancer[6,7]	Breast cancer[8,9]

[a] Olaparib is FDA-approved for the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR mutation-positive mCRPC who have progressed following prior treatment with enzalutamide or abiraterone[1]

[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[2] and has received a positive recommendation from the EMA CHMP to be used in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[3]

[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

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. Lynparza: Pending EC decision | European Medicines Agency (europa.eu); 4. Rucaparib SmPC; 5. Rucaparib PI; 6. Niraparib PI; 7. Niraparib SmPC; 8. Talazoparib SmPC; Talazoparib PI. All accessed November 2022.

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. OS data remains immature
  - This occurred **in patients with and without HRR mutations**
- In first line mCRPC, treatment with **niraparib and abiraterone is associated with longer rPFS** than abiraterone alone. OS data remains immature
  - 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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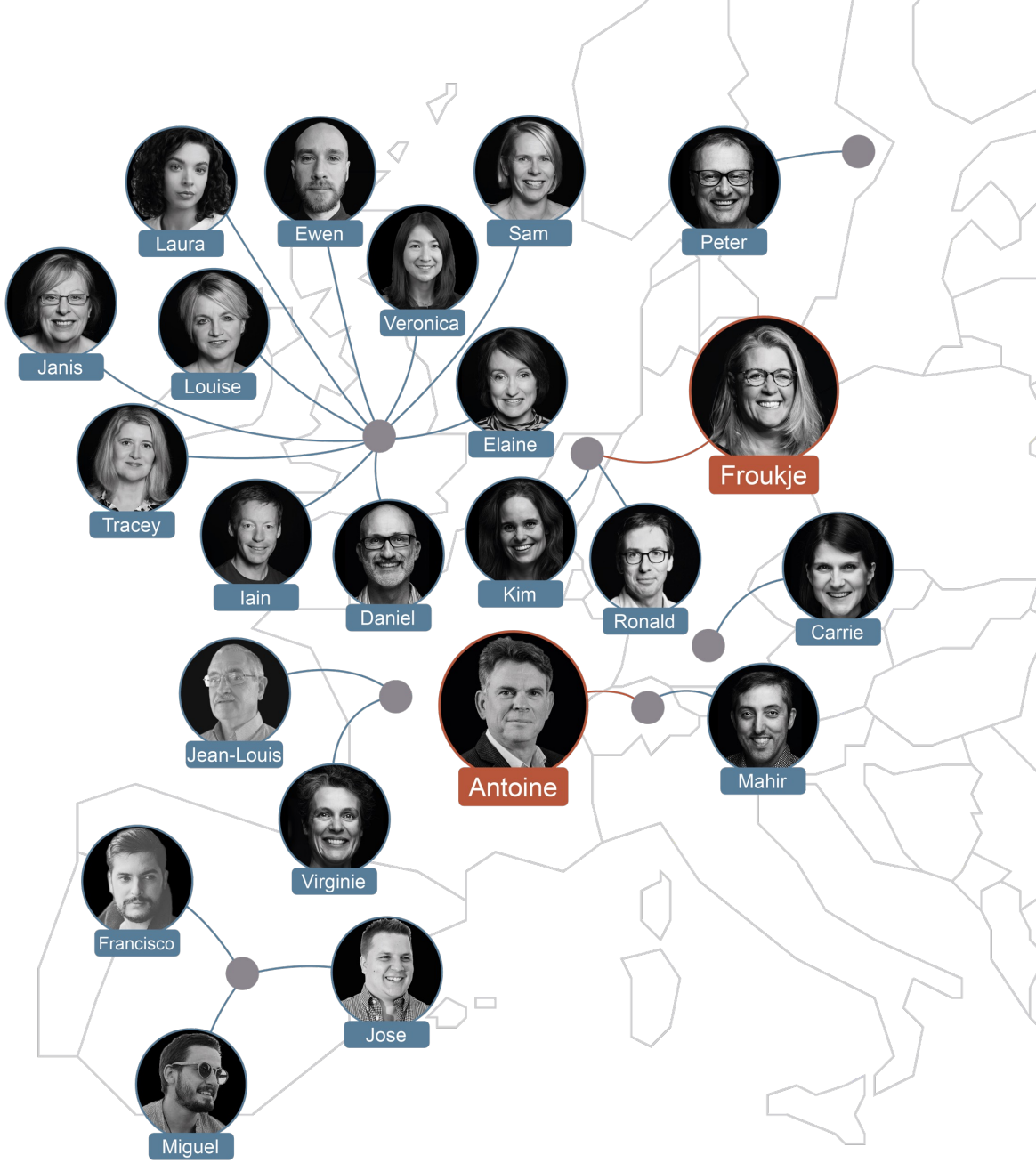

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