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PARP INHIBITORS IN PROSTATE CANCER LATEST DEVELOPMENTS

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PARPi, poly-ADP ribose polymerase inhibitors

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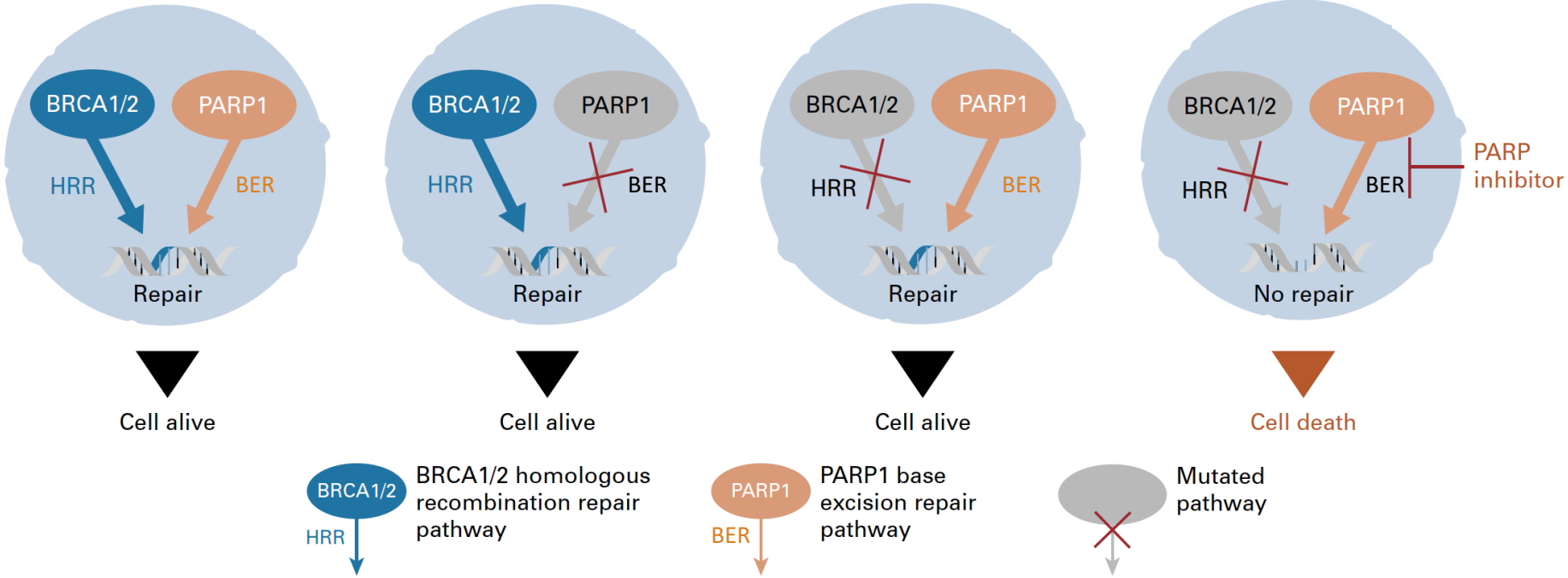
PARP INHIBITORS: ‘SYNTHETIC LETHALITY’ IN CANCER

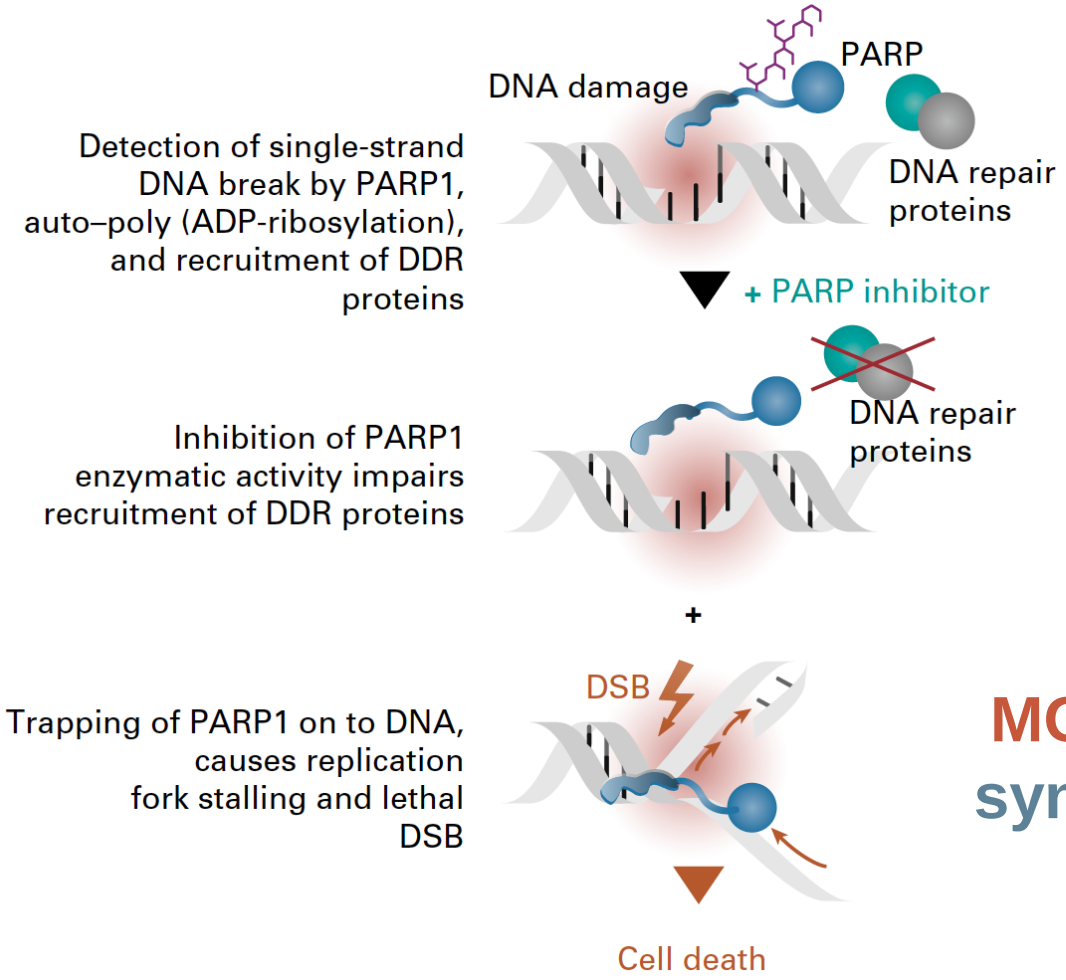
- ***BRCA*: “copy editor”;** homologous recombination repair (HRR)
- **PARP: “spell check”;** base excision repair (BER)



PARP is required for single-strand break repair (e.g. via BER)
MOA – inhibiting SSB/BER is synthetic lethal with HRD

BER, base excision repair; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRD, homologous recombination deficiency; HRR, homologous recombination repair; MOA, mode of action; PARP, poly-ADP ribose polymerase; SSB, single-strand break
Adapted from Gourley C, et al., J Clin Oncol. 2019;37(25):2257-69; Banerjee S, et al. Nat Rev Clin Oncol 2010; 7: 508-19

PARP INHIBITORS: ENZYMATIC INHIBITION & PARP TRAPPING



MOA – trapping PARP is synthetic lethal with HRD

ADP, adenosine diphosphate; DDR, DNA damage response; DSB, double-strand break; HRD, homologous recombination deficiency; MOA, mode of action; PARP, poly-ADP ribose polymerase

Adapted from Gourley C, et al. J Clin Oncol 2019; 37: 2257-69

DNA REPAIR GENE ALTERATIONS (SOMATIC AND GERMLINE) ARE COMMON IN METASTATIC PROSTATE CANCER

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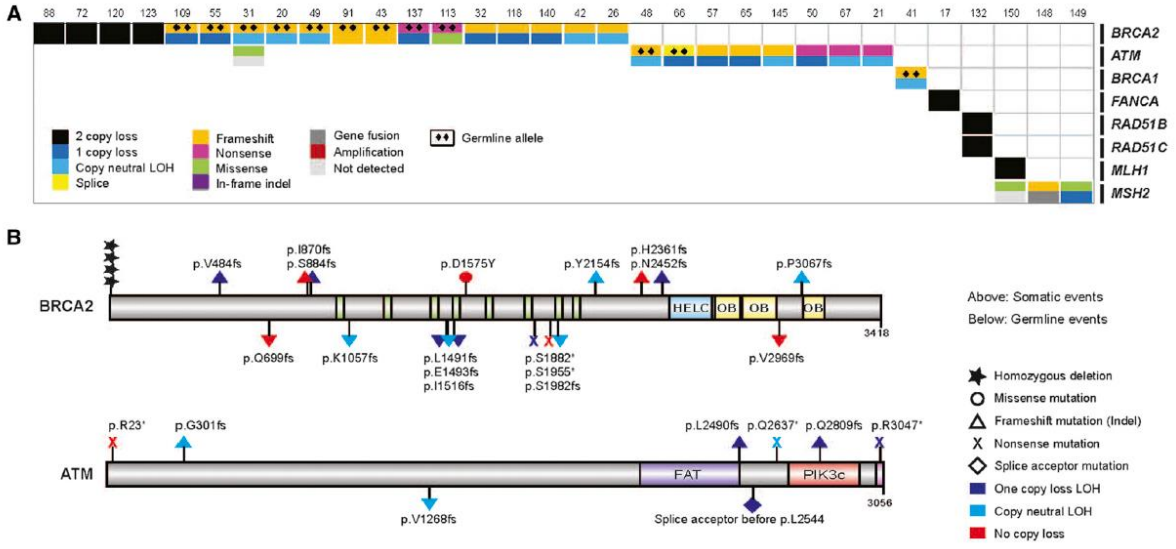
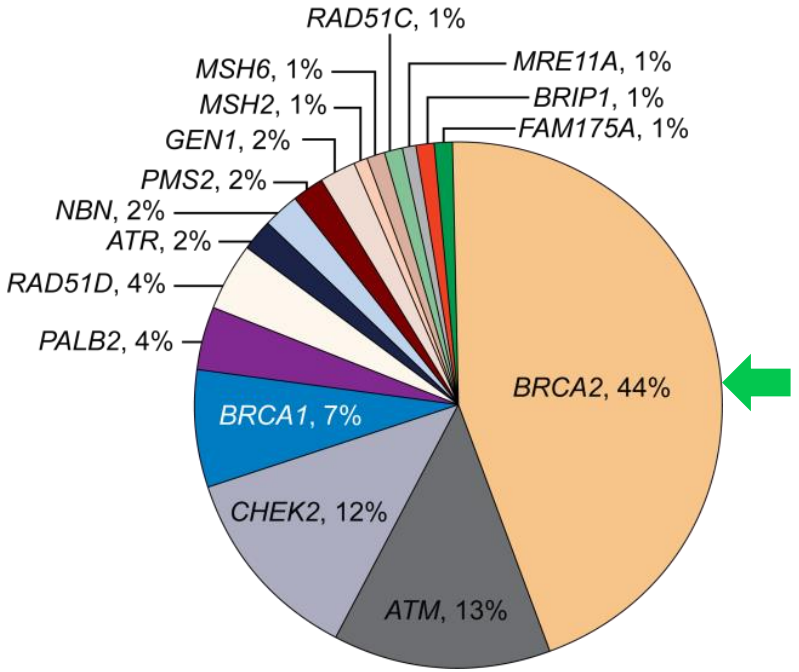
SOMATIC

- **~23%** of men with mCRPC have DNA repair pathway aberrations
- The incidence of DNA repair alterations is higher in men with **metastatic prostate cancer** than those with **localised disease**



GERMLINE

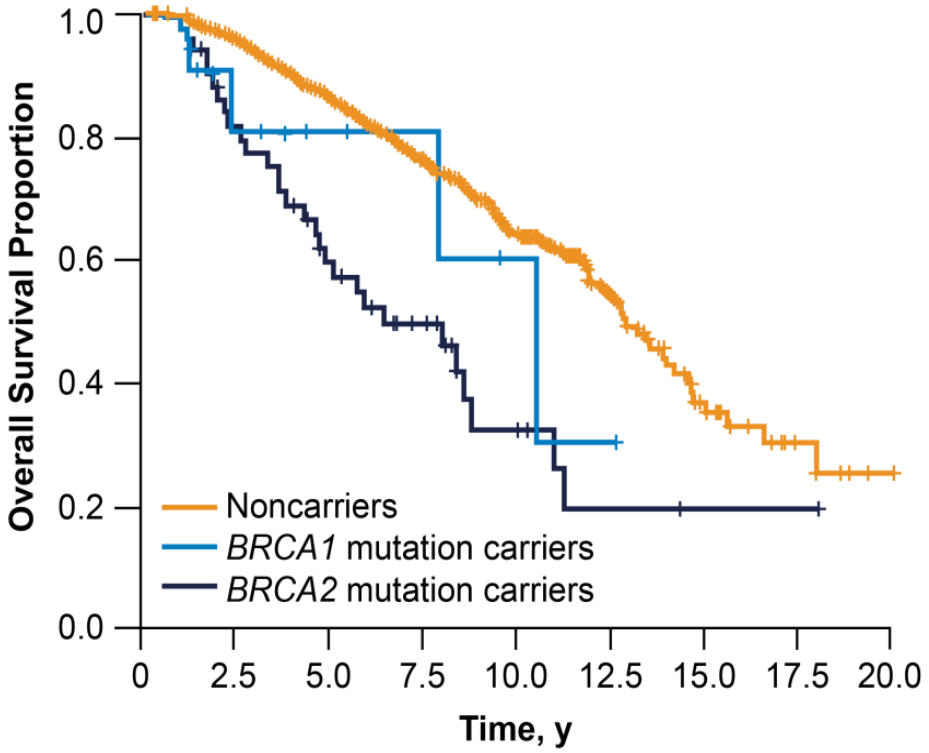


- **~12%** of men with metastatic prostate cancer have germline mutations in one or more of the 16 DNA repair genes

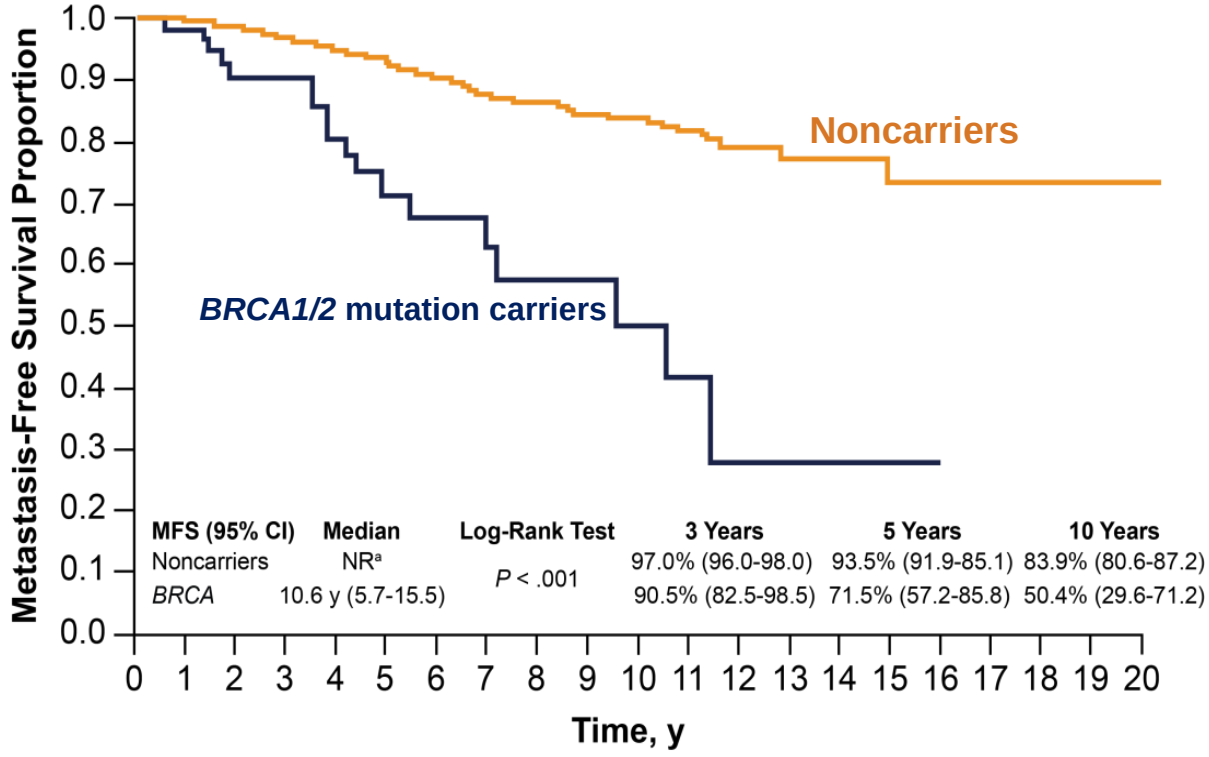
LOH, loss of heterozygosity; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer

1. Robinson D, et al. Cell. 2015;161:1215-28; 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-53; 3. Antonarakis ES, et al. Eur Urol. 2018;74:218-25

BRCA2 CARRIERS WITH PROSTATE CANCER HAVE WORSE PROGNOSIS[1,2]



No. at Risk									
Noncarriers	1,940	1,394	896	467	186	68	22	6	1
BRCA1 mutation carriers	18	12	5	4	2	1	0	0	0
BRCA2 mutation carriers	61	40	28	16	6	3	1	1	0



MFS (95% CI)	Median	Log-Rank Test	3 Years	5 Years	10 Years
Noncarriers	NR[a]	*P* < .001	97.0% (96.0-98.0)	93.5% (91.9-85.1)	83.9% (80.6-87.2)
BRCA	10.6 y (5.7-15.5)		90.5% (82.5-98.5)	71.5% (57.2-85.8)	50.4% (29.6-71.2)

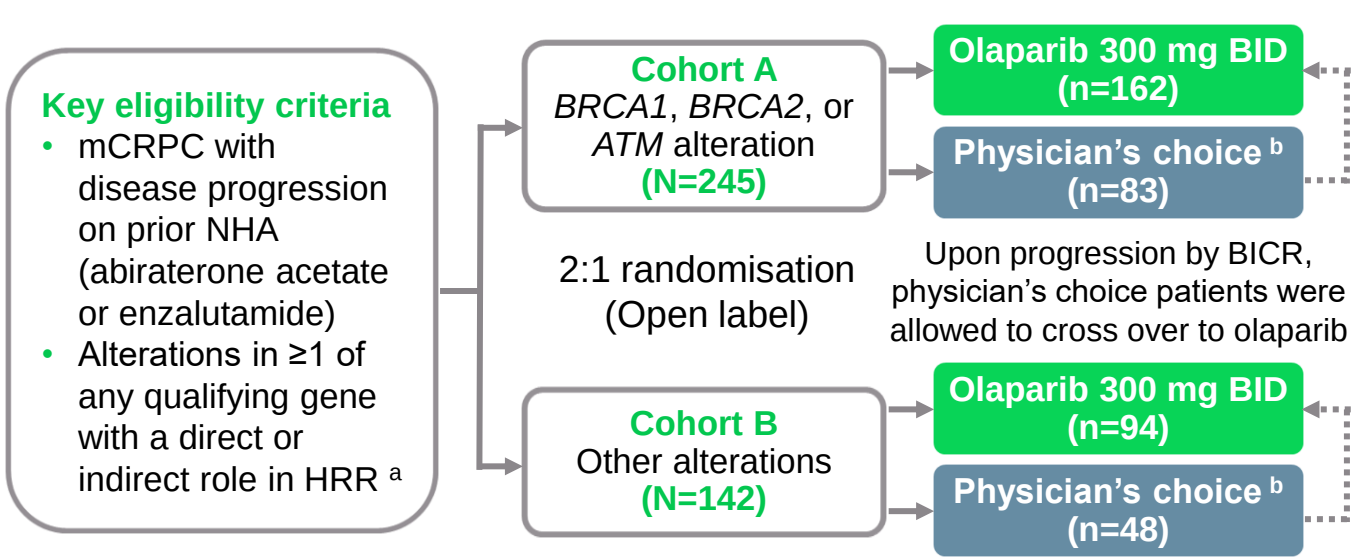
No. at Risk	Baseline	3 years	5 years	8 years	10 years	12 years	15 years	20 years
Noncarriers	1,235	865	646	285	140	57	18	1
BRCA	67	39	20	12	7	2	1	0

[a] Median survival not reached after a median of 64 months of follow-up

BRCA1/2, breast cancer type 1/2 susceptibility protein; CI, confidence interval; MFS, metastasis-free survival; NR, not reached; y, years

1. Castro E, et al. J Clin Oncol. 2013;31:1748-57; 2. Castro E, et al. Eur Urol. 2015;68:186-93

PROfound: PHASE 3 DATA WITH OLAPARIB IN mCRPC



Primary endpoint

rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)

Key secondary endpoints

- rPFS in cohorts A and B (by BICR)
- Confirmed radiographic objective response rate in cohort A (by BICR)
- Time to pain progression in cohort A
- OS in cohort A

[a] An investigational clinical trial assay, based on the FoundationOne® CDx next-generation sequencing test, used to prospectively select patients with alteration of *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* in their tumour tissue

[b] Physician's choice: enzalutamide 160 mg/day, or abiraterone 1,000 mg/day + prednisone 5 mg BID

ATM, ataxia telangiectasia mutated; BICR, blinded independent central review; BID, twice daily; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; QD, once daily

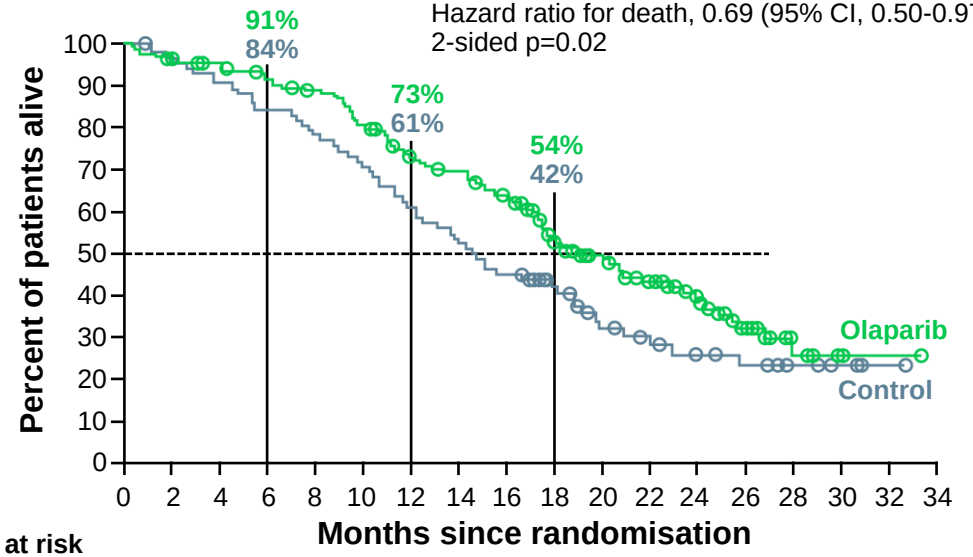
de Bono J, et al. N Engl J Med. 2020;382:2091-2102; Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

PROfound: FINAL OVERALL SURVIVAL

OS IN COHORT A (*BRCA1&2*, *ATM*)

	No. of Deaths/ No. of Patients	Median OS (95% CI), months
Olaparib	91/162	19.1 (17.4-23.4)
Control	57/83	14.7 (11.9-18.8)

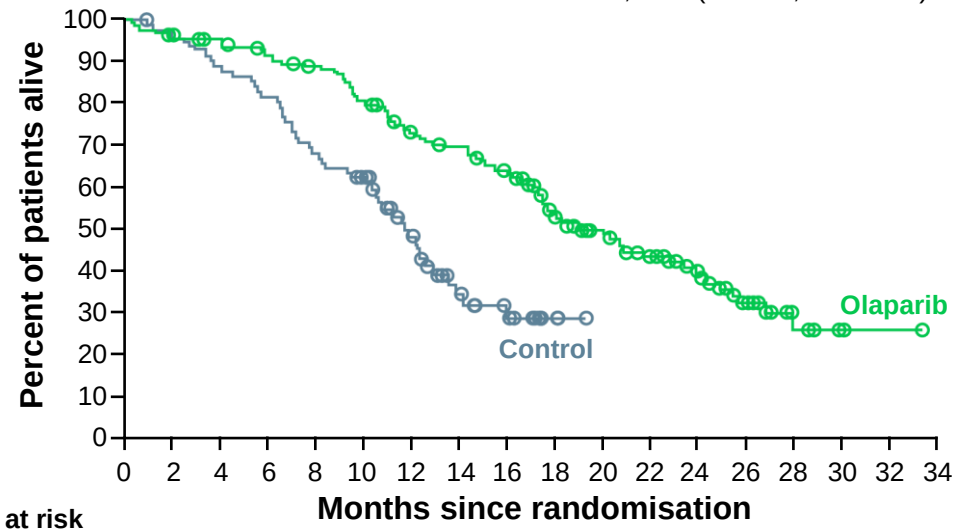
Hazard ratio for death, 0.69 (95% CI, 0.50-0.97)
2-sided p=0.02



No. at risk																	
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

CROSSOVER-ADJUSTED OS IN COHORT A

Patients who crossed over, 67% (56/83)
Hazard ratio for death, 0.42 (95% CI, 0.19-0.91)



No. at risk																	
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

- >80% crossover!

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein; CI, confidence interval; HR, hazard ratio; OS, overall survival

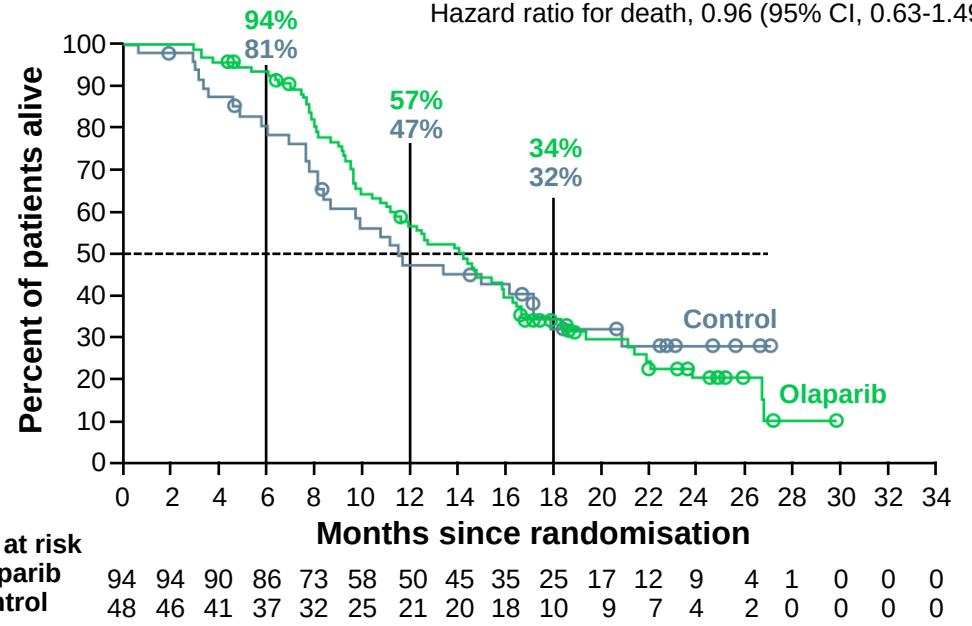
Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

PROfound: FINAL OVERALL SURVIVAL

OS IN COHORT B

	No. of Deaths/ No. of Patients	Median OS (95% CI), months
Olaparib	69/94	14.1 (11.1-15.9)
Control	31/48	11.5 (8.2-17.1)

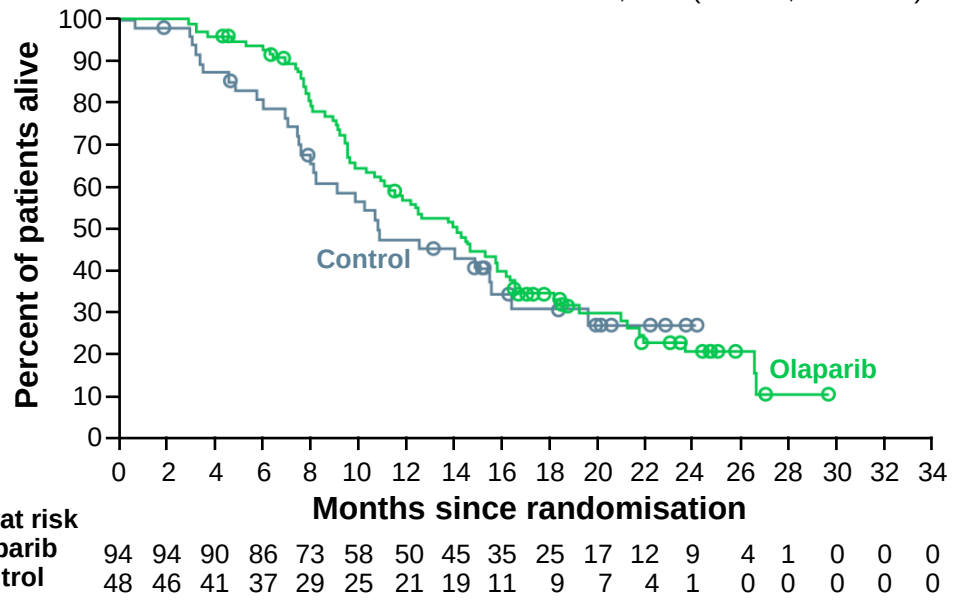
Hazard ratio for death, 0.96 (95% CI, 0.63-1.49)



No. at risk																	
Olaparib	94	94	90	86	73	58	50	45	35	25	17	12	9	4	1	0	0	0
Control	48	46	41	37	32	25	21	20	18	10	9	7	4	2	0	0	0	0

CROSSOVER-ADJUSTED OS IN COHORT B

Patients who crossed over, 63% (30/48)
Hazard ratio for death, 0.83 (95% CI, 0.11-5.98)



No. at risk																	
Olaparib	94	94	90	86	73	58	50	45	35	25	17	12	9	4	1	0	0	0
Control	48	46	41	37	29	25	21	19	11	9	7	4	1	0	0	0	0	0

CI, confidence interval; HR, hazard ratio; OS, overall survival
Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

OLAPARIB: SIDE EFFECT PROFILE

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Event	Olaparib (N=256)		Control (N=130)		Crossover (N=83)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event, n (%)	246 (96)	133 (52)	115 (88)	52 (40)	77 (93)	49 (59)
Anaemia	127 (50)	58 (23)	20 (15)	7 (5)	43 (52)	24 (29)
Nausea	110 (43)	4 (2)	27 (21)	0	24 (29)	2 (2)
Fatigue or asthenia	107 (42)	8 (3)	43 (33)	7 (5)	21 (25)	8 (10)
Decreased appetite	80 (31)	4 (2)	24 (18)	1 (<1)	15 (18)	2 (2)
Diarrhoea	55 (21)	2 (<1)	9 (7)	0	12 (14)	0
Vomiting	51 (20)	6 (2)	17 (13)	1 (<1)	16 (19)	1 (1)
Constipation	49 (19)	0	19 (15)	0	12 (14)	0
Back pain	36 (14)	2 (<1)	18 (14)	2 (2)	8 (10)	0
Peripheral oedema	34 (13)	0	10 (8)	0	3 (4)	0
Cough	29 (11)	0	3 (2)	0	4 (5)	0
Dyspnoea	27 (11)	6 (2)	5 (4)	0	4 (5)	1 (1)
Arthralgia	26 (10)	1 (<1)	14 (11)	0	4 (5)	0
Urinary tract infection	21 (8)	5 (2)	15 (12)	5 (4)	12 (14)	3 (4)
Any serious adverse event, n (%)	94 (37)	NA	39 (30)	NA	27 (33)	NA
Interruption of treatment because of adverse event, n (%)	119 (46)	NA	25 (19)	NA	44 (53)	NA

Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

TRITON2: OPEN LABEL, SINGLE-ARM, PHASE 2 STUDY OF RUCAPARIB IN mCRPC PATIENTS

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Screening

Identification of a deleterious somatic or germline alteration in HRR gene*

HRR genes

BRCA1	*BARD1*	*FANCA*	*RAD51B*
BRCA2	*BRIP1*	*NBN*	*RAD51C*
ATM	*CDK12*	*PALB2*	*RAD51D*
	CHEK2	*RAD51*	*RAD54L*

Key eligibility criteria

- mCRPC
- Deleterious somatic or germline alteration in HRR gene
- Disease progression on AR-directed therapy (eg, abiraterone, enzalutamide, or apalutamide) for PC ***and*** 1 prior taxane-based chemotherapy for CRPC
- ECOG PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

Treatment

28-day cycles

Rucaparib 600 mg BID

- Tumour assessments every 8 weeks for 24 weeks, then every 12 weeks
- PSA assessments every 4 weeks

Treatment until radiographic progression or discontinuation for other reason

Primary endpoints†

- Patients with measurable disease at baseline: confirmed ORR per modified RECIST/PCWG3 by central assessment
- Patients with no measurable disease at baseline: confirmed PSA response (≥50% decrease) rate §

*Alterations detected by local testing or central testing of blood or tumour samples. † Efficacy analyses in TRITON2 will be conducted separately based on HRR gene with alteration and presence/absence of measurable disease. ‡ RECIST modified to include up to 10 target lesions, maximum 5 per site, not including prostatic bed or bone lesions; MRI allowed. § The proportion of patients with a ≥50% decrease from baseline confirmed by a second consecutive measurement; PSA measurements performed by local laboratory.

AR, androgen receptor; BID, twice daily; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRR, homologous recombination repair, mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; PC, prostate cancer; PCWG3, prostate cancer working group 3; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours version 1.1

Abida W, et al. J Clin Oncol 2020; 38:3763-72

TRITON2: RUCAPARIB EFFICACY IN mCRPC PATIENTS WITH *BRCA1 & 2* ALTERATIONS

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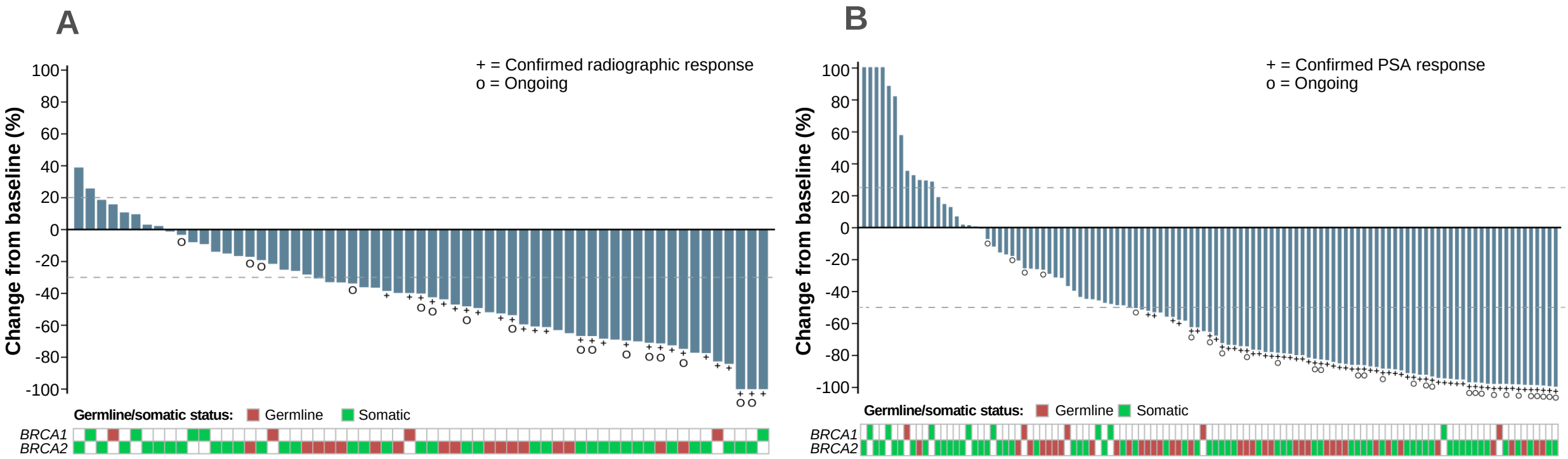
TUMOUR RESPONSE (EVALUABLE POPULATION)

PSA RESPONSE (EFFICACY POPULATION)



Best change from baseline in (A) sum of target lesion(s) in the independent radiology review-evaluable population and in (B) prostate-specific antigen (PSA) in the overall efficacy population

BRCA1/2, breast cancer type 1/2 susceptibility protein; PSA, prostate specific antigen

Abida W, et al. J Clin Oncol. 2020;38:3763-72

TRITON2: RUCAPARIB IN mCRPC NON-BRCA DDR GENE ALTERATIONS

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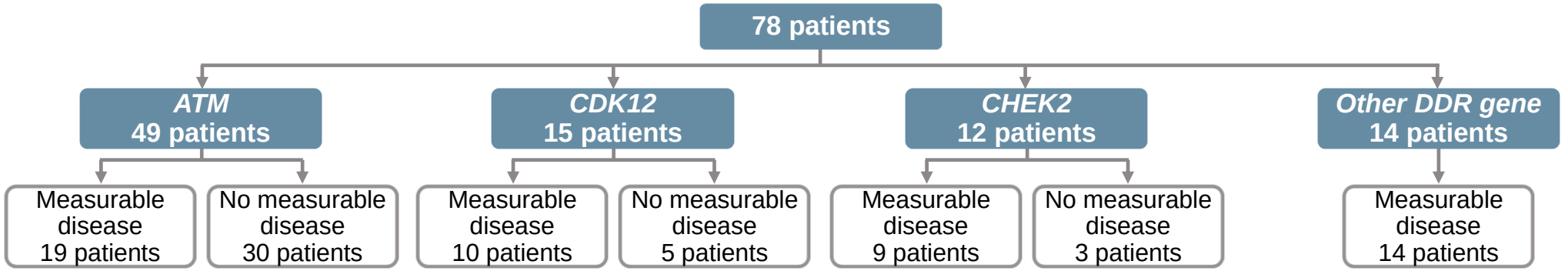

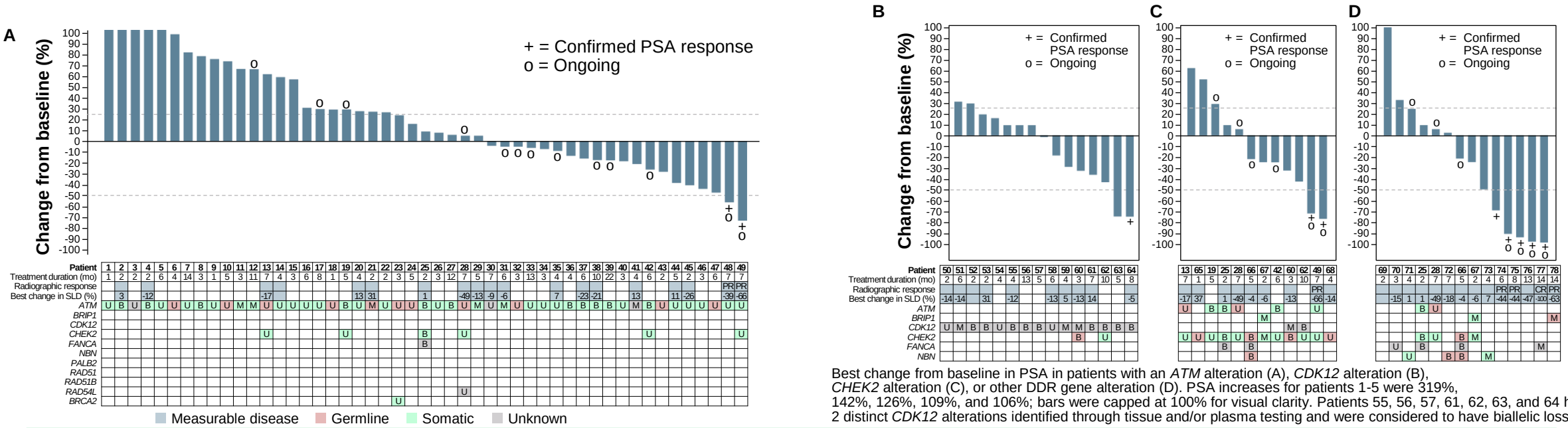

Best change from baseline in PSA in patients with an *ATM* alteration (A), *CDK12* alteration (B), *CHEK2* alteration (C), or other DDR gene alteration (D). PSA increases for patients 1-5 were 319%, 142%, 126%, 109%, and 106%; bars were capped at 100% for visual clarity. Patients 55, 56, 57, 61, 62, 63, and 64 had 2 distinct *CDK12* alterations identified through tissue and/or plasma testing and were considered to have biallelic loss.

ATM, ataxia telangiectasia mutated; BRCA (2), breast cancer type (2) susceptibility protein CR, complete response; DDR, DNA damage repair; mCRPC, metastatic castration resistant prostate cancer; mo, month; PR, partial response; PSA, prostate specific antigen; SLD, sum of the longest diameter

Abida W, et al. Clin Cancer Res. 2020;26:2487-96

RUCAPARIB SIDE EFFECTS

Individual TEAE (preferred terms) occurring in ≥15% of patients	Any grade	Grade ≥3
Asthenia/fatigue	71 (61.7)	10 (8.7)
Nausea	60 (52.2)	3 (2.6)
Anaemia/decreased hemoglobin	50 (43.5)	29 (25.2)
ALT/AST increased	38 (33.0)	6 (5.2)
Decreased appetite	32 (27.8)	2 (1.7)
Constipation	31 (27.0)	1 (0.9)
Thrombocytopenia/decreased platelets	29 (25.2)	11 (9.6)
Vomiting	25 (21.7)	1 (0.9)
Diarrhoea	23 (20.0)	0
Dizziness	21 (18.3)	0
Blood creatinine increased	18 (15.7)	1 (0.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event

Abida W, et al. J Clin Oncol. 2020;38:3763-72

RATIONALE FOR COMBINING PARP INHIBITORS AND NHAs

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Androgen receptor (AR) signalling regulates DNA repair in prostate cancer, providing a rationale for combined AR targeting with PARP inhibition[2]

- PARP involved in androgen-receptor dependent transcription[1]
  - PARP inhibition may increase activity of NHAs[1]
- NHA-induced HRR deficiency increasing susceptibility to PARP inhibition[2,3]
- Combined effects may lead to antitumour activity in HRRm and non-HRRm prostate cancer[1]

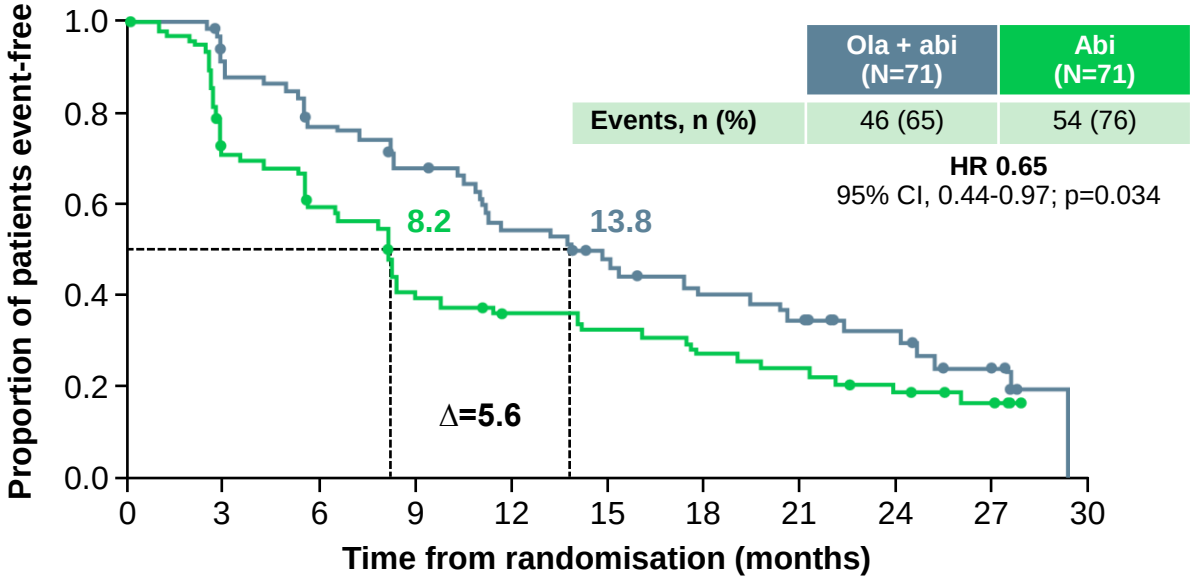
AR, androgen receptor; HRR, homologous recombination repair; HRRm, homologous recombination repair gene mutation; NHA, novel hormonal agent; PARP, poly-ADP ribose polymerase

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
Saad F, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11); Chi K, et al. J Clin Oncol. 2022; 40 (suppl 6; abstr 12)

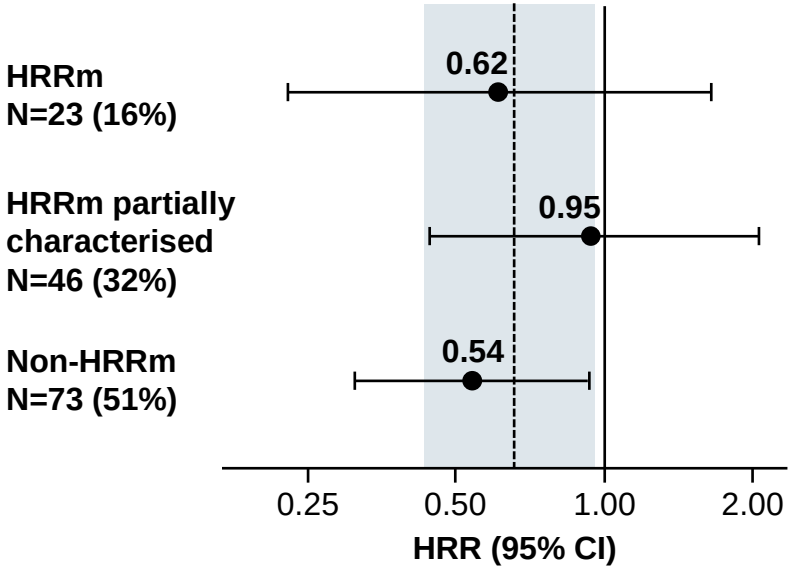
OLAPARIB AND ABIRATERONE: A RANDOMISED PHASE II STUDY

- Patients with mCRPC, unselected by HRRm status, with prior docetaxel treatment
- 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)

PROpel STUDY DESIGN

A GLOBAL, RANDOMISED, DOUBLE-BLIND PHASE 3 TRIAL

Key eligibility criteria
- 1L mCRPC
  - Docetaxel allowed at mCSPC stage
  - No prior abiraterone
  - Other NHAs allowed if stopped ≥12 months prior to enrolment
  - Ongoing ADT
  - ECOG performance status 0-1

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

Randomise 1:1

- **Olaparib 300 mg BID + abiraterone 1000 mg QD[a] (n=399)**
- **Placebo + abiraterone 1000 mg QD[a] (n=397)**

Primary endpoint:
- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoint:
- OS (alpha control)

Additional endpoints:
- TFST, ORR, PFS2
- HRRm[b] prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

NCT03732820

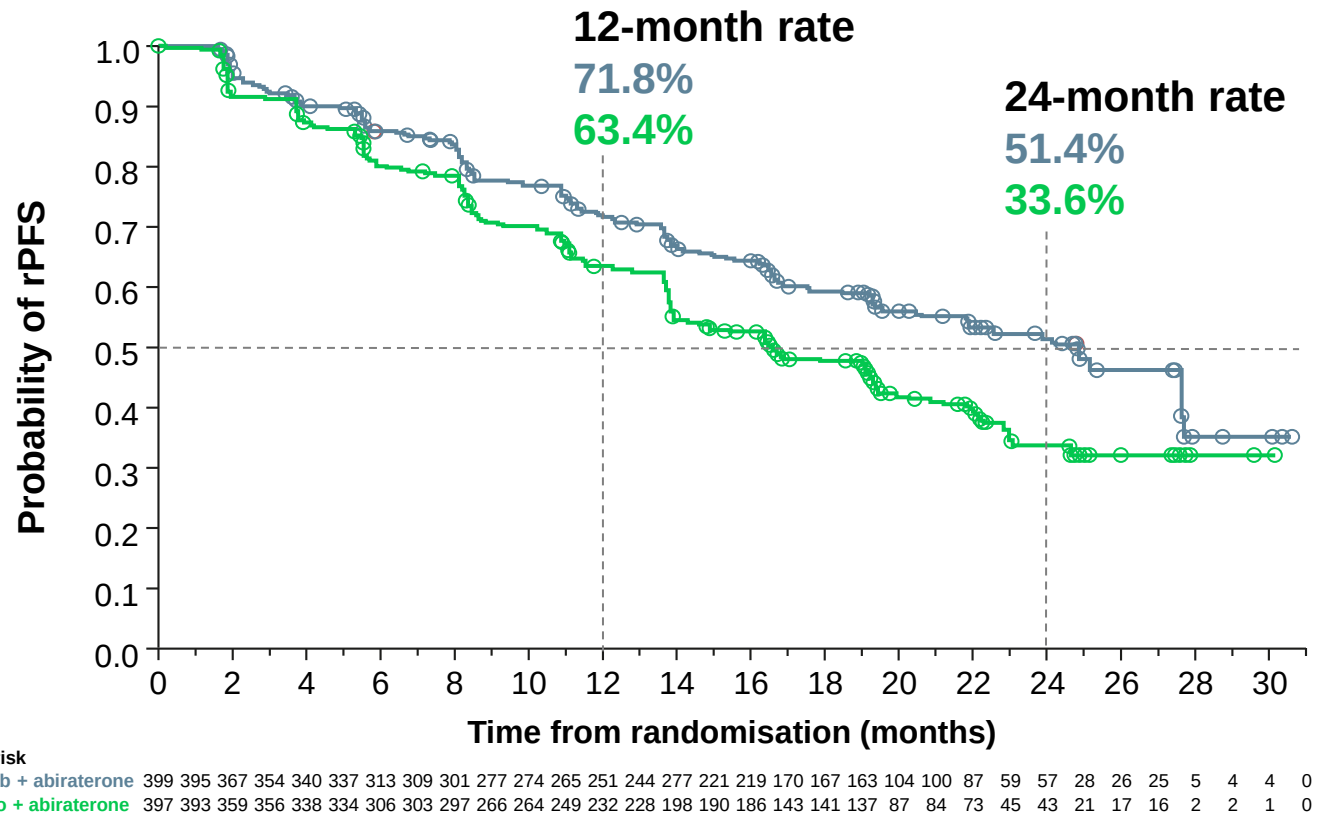
First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
[a]Full dose of Olaparib and/or abiraterone used, in combination with prednisone or prednisolone 5 mg bid. [b]HRRm, homologous recombination repair mutation, including 14 genes panel.

1L, first-line; ADT, androgen deprivation therapy; BICR, blinded independent central review; BID, twice daily; ECOG, Eastern Cooperative Oncology Group ; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; NHA, novel hormonal agents; ORR, objective response rate; OS, overall survival; PFS2, time to second progression; PO, orally; 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, no. 7_suppl:TPS340; ClinicalTrials.gov identifier: NCT03732820. Accessed Feb 2022. https://clinicaltrials.gov/ct2/show/NCT03732820;
Saad F, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11) (ASCO GU 2022 oral presentation)

PROpel PRIMARY ENDPOINT: rPFS BY INVESTIGATOR-ASSESSMENT

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); p<0.0001	

Pre-specified 2-sided alpha: 0.0324

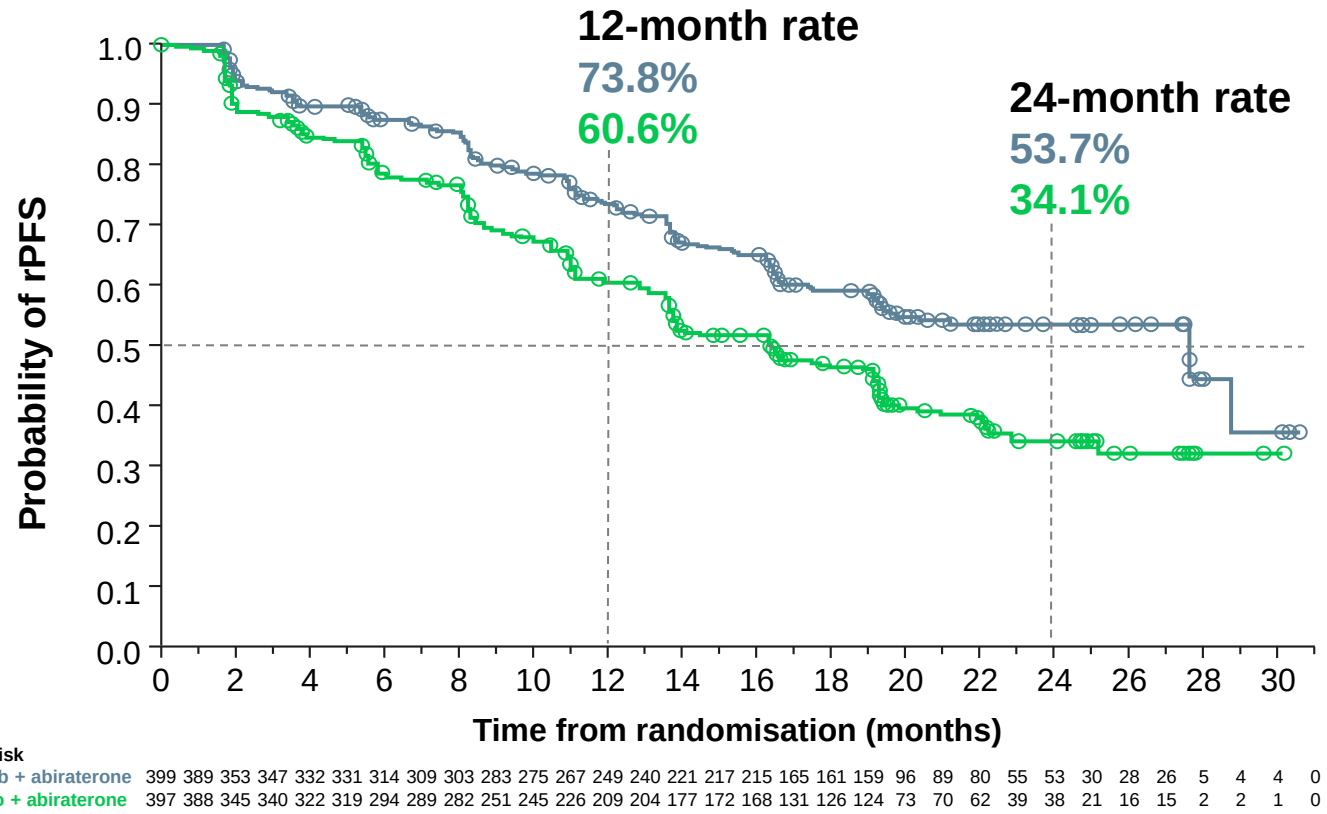
Median rPFS improvement of 8.2 months favors olaparib + abiraterone[a]

Events: 394; Maturity 49.5%
[a]In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

CI, confidence interval; HR, hazard ratio; rPFS, radiographic progression-free survival
Saad F, et al. J Clin Oncol. 2022; 40 (suppl 6; abstr 11) (ASCO GU 2022 oral presentation)

PROpel: rPFS BY BLINDED INDEPENDENT CENTRAL REVIEW[a]

39% RISK REDUCTION OF PROGRESSION OR DEATH WITH OLAPARIB + ABIRATERONE. HIGHLY CONSISTENT WITH THE PRIMARY ANALYSIS



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) p<0.0001[b]	

Median rPFS improvement of 11.2 months favours olaparib + abiraterone[c]

[a]Predefined sensitivity analysis. [b]Nominal. [c]In combination with prednisone or prednisolone

CI, confidence interval; HR, hazard ratio; rPFS, radiographic progression-free survival

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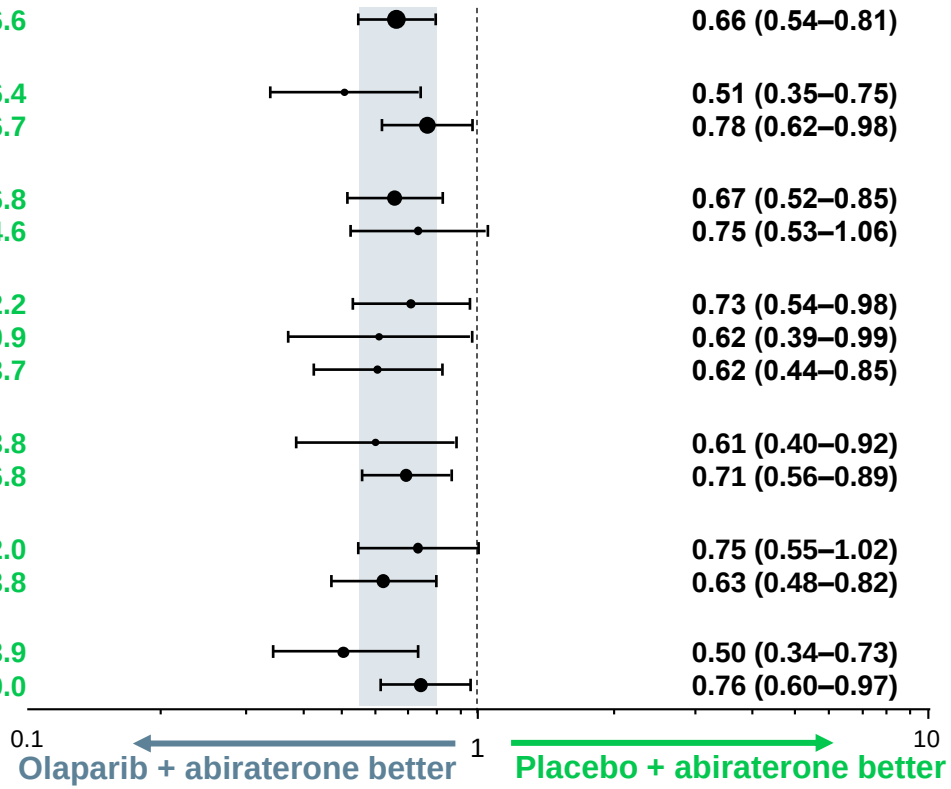
PROpel: SUBGROUP ANALYSIS OF rPFS

rPFS BENEFIT OBSERVED ACROSS ALL PRE-SPECIFIED SUBGROUPS

	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				
<65	227	NR	16.4	**0.51 (0.35–0.75)**
≥65	569	22.0	16.7	**0.78 (0.62–0.98)**
ECOG performance status at baseline				
0	558	24.9	16.8	**0.67 (0.52–0.85)**
1	236	17.5	14.6	**0.75 (0.53–1.06)**
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)**
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	**0.75 (0.55–1.02)**
Above or equal to median baseline PSA	397	18.5	13.8	**0.63 (0.48–0.82)**
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)**



Global interaction test not significant at 10% level

Global interaction test not significant at 10% level. [a]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumour tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post hoc exploratory analysis.

CI, confidence interval; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRR(m), homologous recombination (mutation); mHSPC, metastatic hormone sensitive prostate cancer; NR, not reached; PSA, prostate specific antigen; rPFS, radiographic progression-free survival

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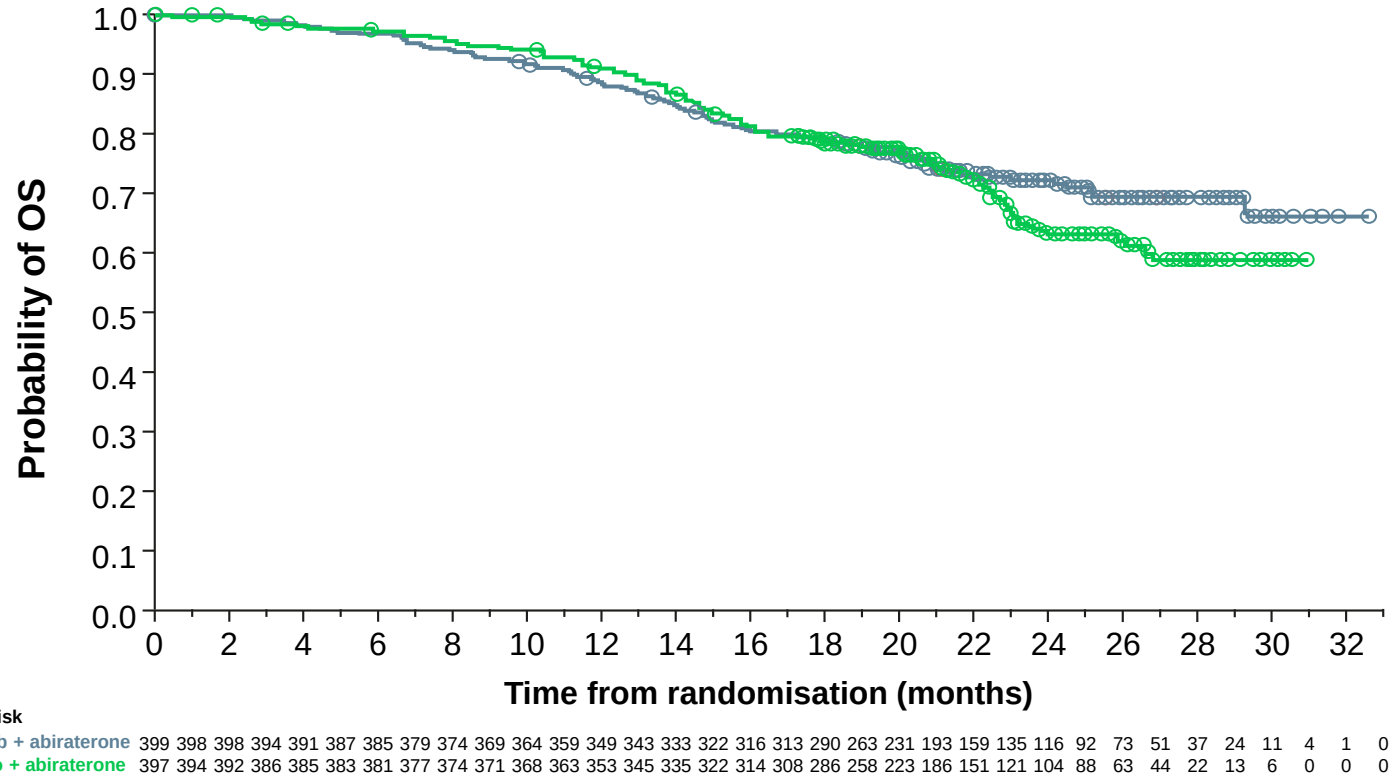
PROpel: OVERALL SURVIVAL

28.6% MATURITY; TREND TOWARDS IMPROVED OS WITH OLAPARIB + ABIRATERONE



Events: 228

	Olaparib + abiraterone (n=399)	Placebo + abiraterone (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	

Pre-specified 2-sided alpha: 0.001

CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival

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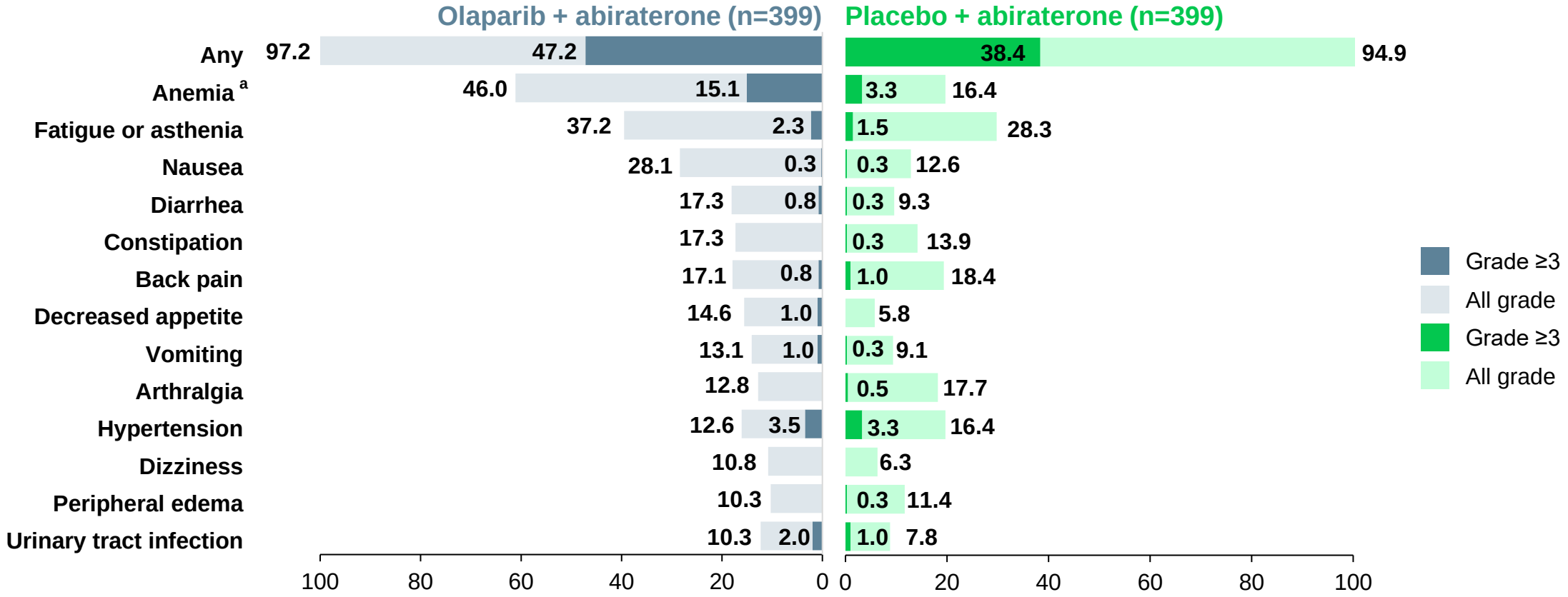
PROpel: MOST COMMON ADVERSE EVENTS

AE PROFILE WAS CONSISTENT WITH THE KNOWN TOXICITY PROFILES FOR 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.
[a]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

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PROpel: CARDIAC AND THROMBOEMBOLIC ADVERSE EVENTS

- Cardiac failure and arterial thromboembolic events were balanced between the two arms
- Numerically higher venous thromboembolic events were reported for olaparib + abiraterone
  - Pulmonary embolism was the most commonly reported venous thromboembolic event
  - Pulmonary embolism events were mostly incidental finding by CT scans and did not lead to discontinuation of olaparib or abiraterone

	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Cardiac failure SMQ, n (%)	6 (1.5)	5 (1.3)
Embolic and thrombotic events, arterial SMQ, n (%)	8 (2.0)	10 (2.5)
Embolic and thrombotic events, venous SMQ, n (%) Pulmonary embolism	29 (7.3) 26 (6.5)	13 (3.3) 7 (1.8)

CT, computed tomography; MedRA, medical dictionary for regulatory activities; SMQ, standardised MedDRA query

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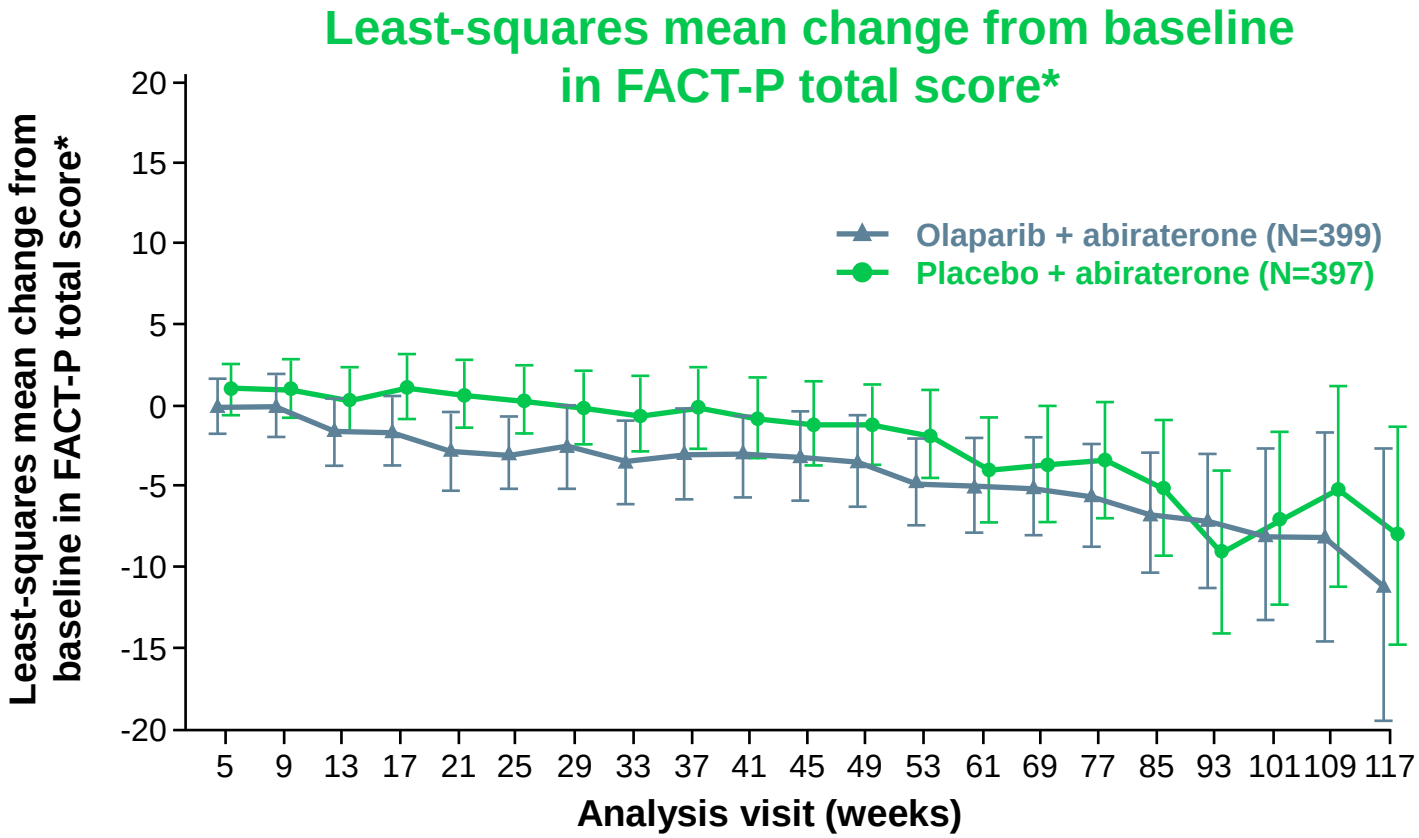
PROpel: FACT-P QUALITY OF LIFE OVER TIME

QUALITY OF LIFE COMPARABLE BETWEEN TREATMENT ARMS



- Combination of olaparib and abiraterone resulted in no detriment to quality of life allowing most patients stay on 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

PROSPECTIVELY SELECTED BIOMARKER COHORTS DESIGNED TO TEST HRR BM+ AND HRR BM–

Study start: February 2019

Prescreening for BM status[a]

Allocation to cohort

1:1 randomisation

Patient eligibility
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR BM+ cohort)

HRR BM+ panel:
ATM
BRCA1
BRCA2
BRIP1
CDK12
CHEK2
FANCA
HDAC2
PALB2

HRR BM+ Planned N=400
- Niraparib + AAP
- Placebo + AAP

HRR BM– Planned N=600
- Niraparib + AAP
- Placebo + AAP

Primary endpoint
- rPFS by central review

Secondary endpoints
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

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.

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; 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 6; abstr 12) (ASCO GU 2022 oral presentation)

MAGNITUDE *BRCA1/2*-MUTATED: PRIMARY ENDPOINT

NIRA + AAP SIGNIFICANTLY REDUCED THE RISK OF PROGRESSION OR DEATH BY 47%

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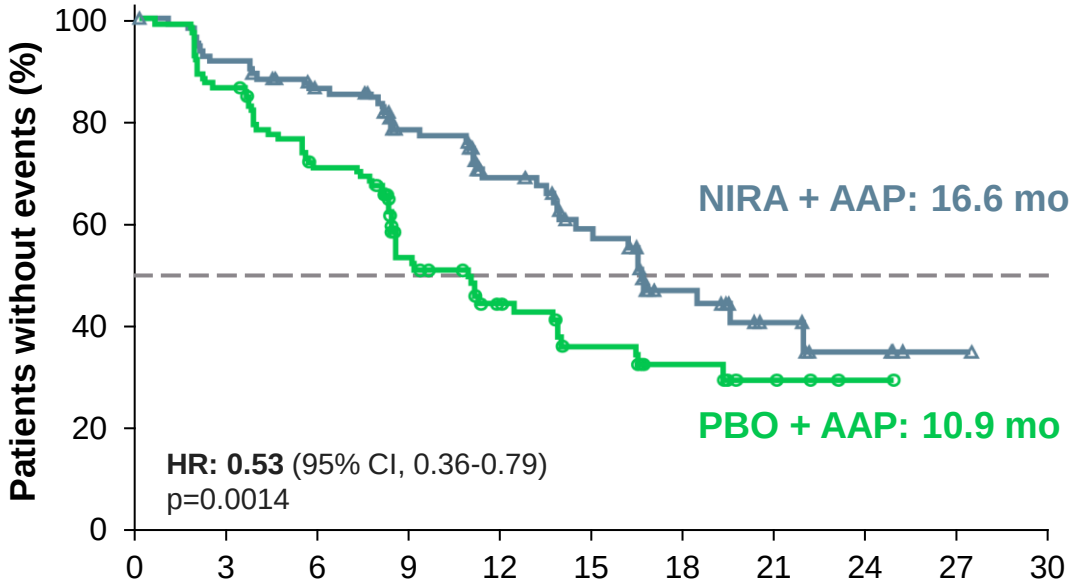
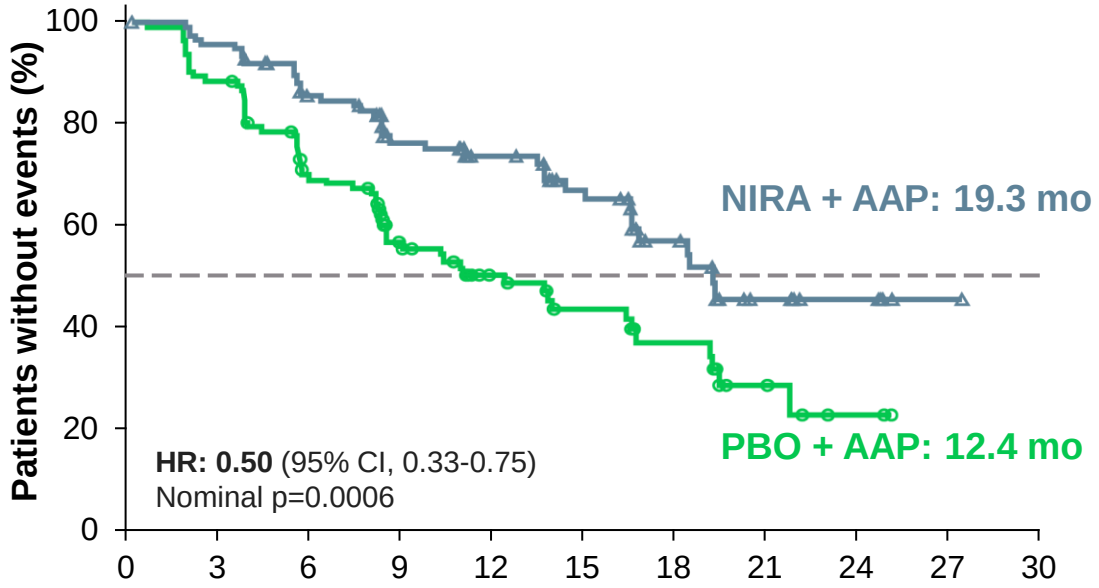
rPFS assessed by central review



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

rPFS assessed by investigator



No. at risk											
NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

Median follow-up 16.7 months

AAP, abiraterone acetate + prednisone/prednisolone; 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+: PRIMARY ENDPOINT

NIRA + AAP SIGNIFICANTLY REDUCED THE RISK OF PROGRESSION OR DEATH BY 27%

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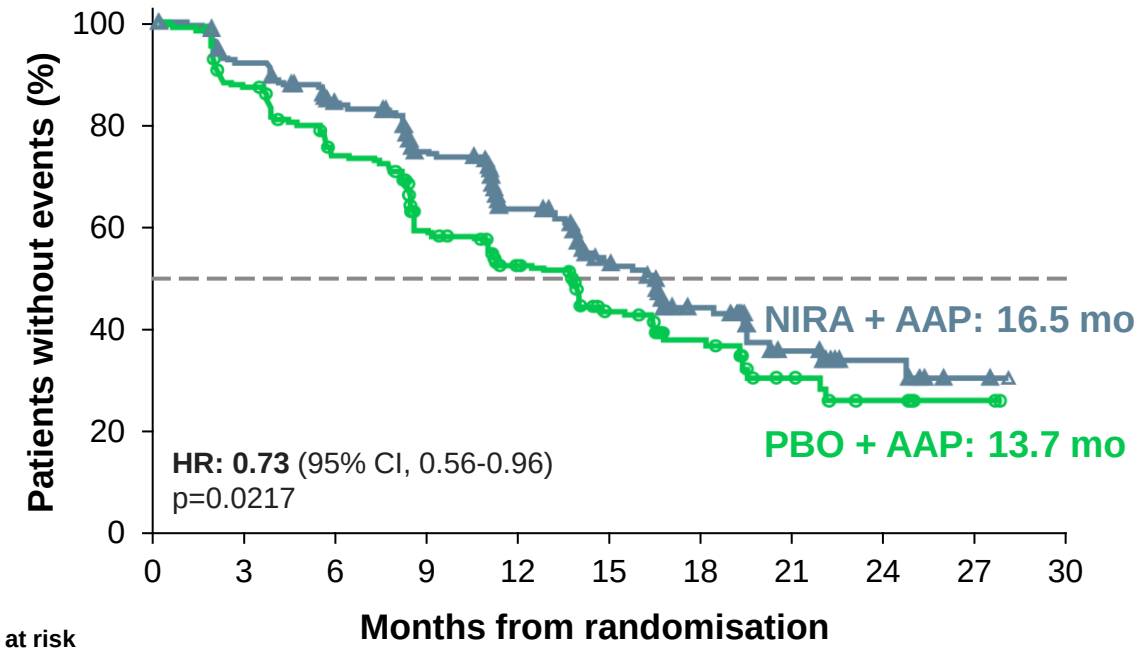
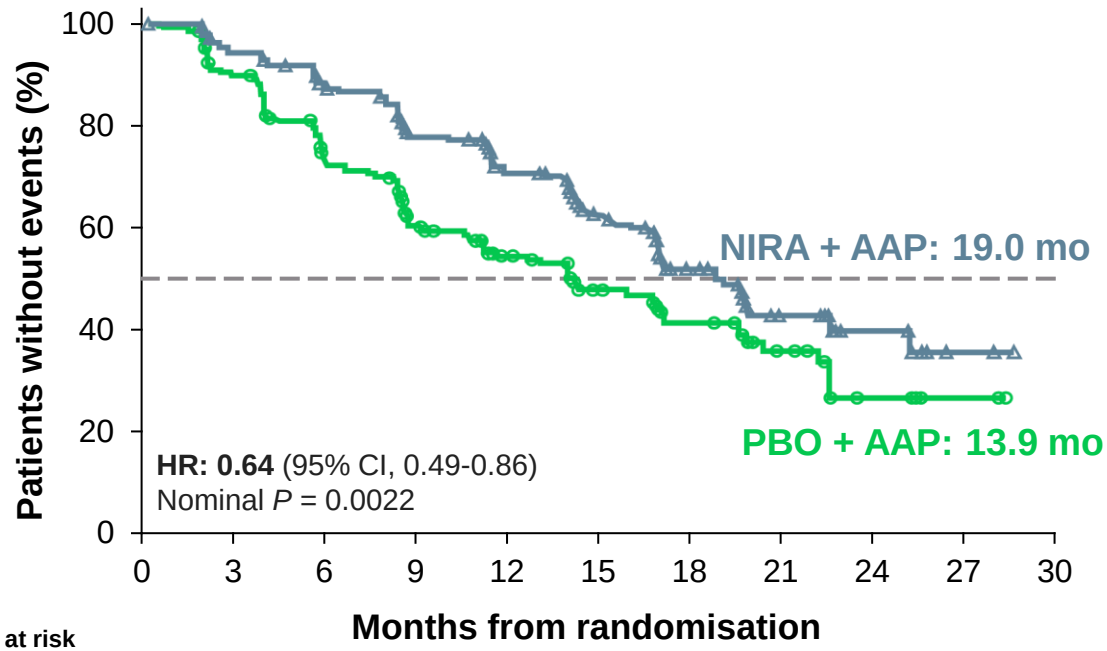
rPFS assessed by central review



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

rPFS assessed by investigator



No. at risk											
NIRA + AAP	212	197	174	136	108	75	50	23	11	2	0
PBO + AAP	211	187	145	103	81	58	41	20	9	2	0

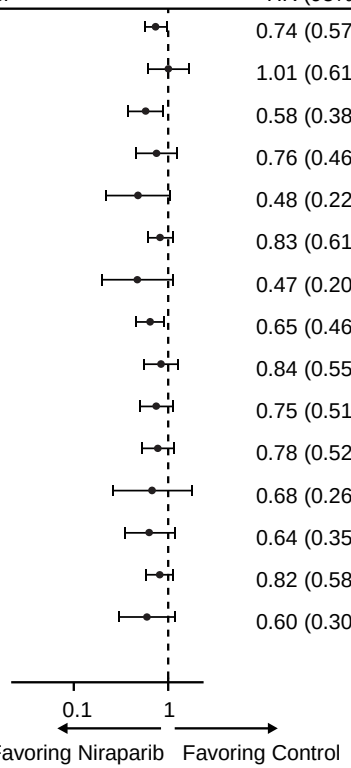
Median follow-up 18.6 months

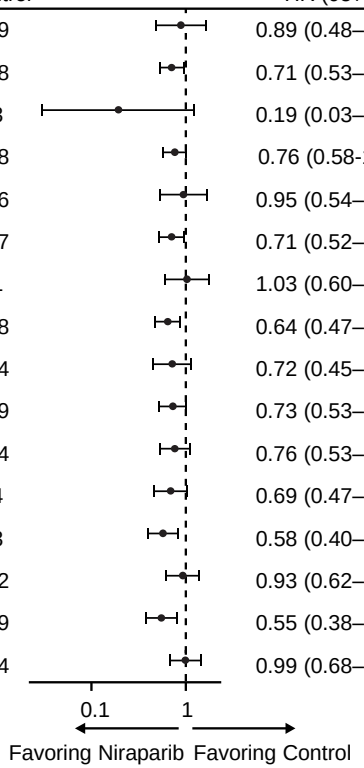
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

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

MAGNITUDE ALL HRR BM+: PRESPECIFIED SUBGROUP ANALYSIS OF rPFS SHOWED CONSISTENCY OF EFFECT

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



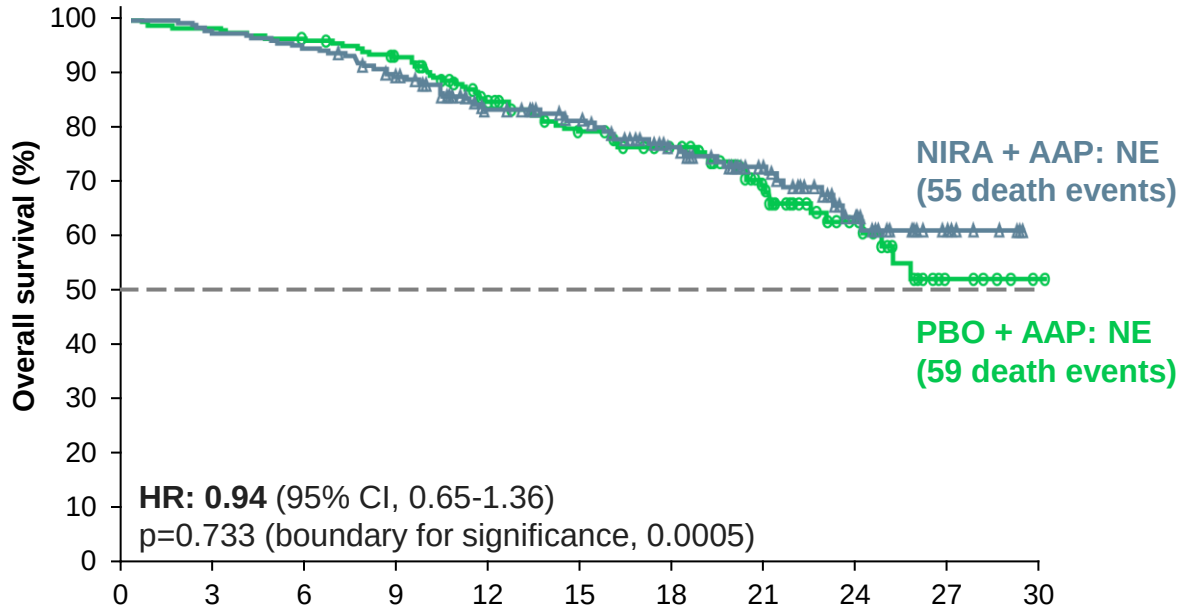


[a]Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide.
[b]Prior AAP use was up to 4 months prior to study start.

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 FIRST INTERIM ANALYSIS WITH MEDIAN FOLLOW-UP OF 18.6 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 HRR BM+: TEAEs CONSISTENT WITH THE KNOWN SAFETY PROFILE FOR EACH THERAPY

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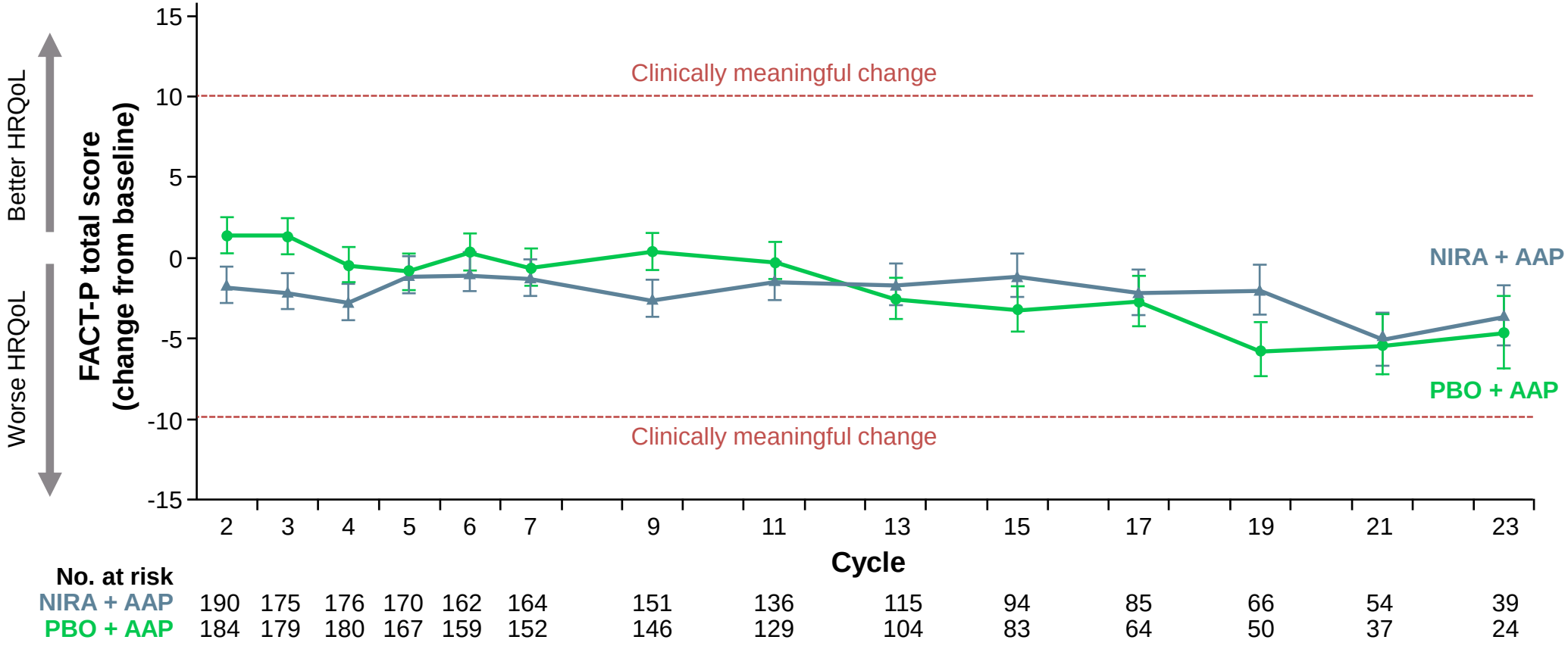
Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n=212		PBO + AAP, n=211	
		All grades	Grade ≥3	All grades	Grade ≥3
Haematologic	Anaemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopaenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropaenia	29 (13.7)	14 (6.6)	12 (5.7)	3 (1.4)
	Acute myeloid leukaemia/ Myelodysplastic syndrome	0	0	1 (0.5)	1 (0.5)
Cardiovascular	Hypertension	67 (31.6)	33 (15.6)	47 (22.3)	30 (14.2)
	Arrhythmia	27 (12.7)	6 (2.8)[a]	12 (5.7)	3 (1.4)
	Cardiac failure	4 (1.9)	3 (1.4)[a]	4 (1.9)	1 (0.5)
	Ischaemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)[b]
General disorders	Fatigue	56 (26.4)	7 (3.3)	35 (16.6)	9 (4.3)
Gastrointestinal	Constipation	65 (30.7)	–	29 (13.7)	–
	Nausea	50 (23.6)	1 (0.5)	29 (13.7)	0
Hepatotoxicity		25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders		6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)[a]

[a] Includes 1 grade 5 event.
[b] Includes 3 grade 5 events.

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo.

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

MAGNITUDE ALL HRR BM+: HRQoL WAS MAINTAINED WITH THE COMBINATION OF NIRA + AAP



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)

PARPi COMBINATIONS IN EARLIER STAGES OF PROSTATE CANCER

Study	Phase	Treatment line	Treatment arms	Patient population	Estimated completion date/status
AMPLITUDE (NCT04497844)	3	2L	Niraparib plus abiraterone acetate vs Placebo plus abiraterone acetate	• mCSPC • Deleterious germline or somatic HRR gene-mutated	November 15, 2024
TALAPRO-3 (NCT04821622)	3	2L	Talazoparib plus enzalutamide vs Enzalutamide plus placebo	• mCSPC • DDR gene-mutated	Recruiting

1L, first-line; 2L, second-line; ARSi, androgen receptor-signalling inhibitor; CRPC, castration-resistant prostate cancer; DDR, DNA damage repair; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer.

www.clinicaltrials.gov

SUMMARY

- Both trials, PROpel and MAGNITUDE, establish that combination of a PARPi + abiraterone in the first-line setting for HRR mutation positive mCRPC patients improves radiographic progression-free survival
- Even though overall survival data are immature for both trials, we expect the combination of a PARPi + abiraterone in the first-line setting for HRR mutation positive mCRPC patients will be approved by the FDA in the near future and can be offered to our patients
- In particular, once approved the combination of olaparib + abiraterone may be applicable to HRR mutation negative mCRPC patients if OS benefit results are noted
- Further studies are investigating AR signaling inhibitors in combination with PARPi in earlier stages of advanced prostate cancer, ie. mCSPC

FDA, Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PARP, poly-ADP ribose polymerase

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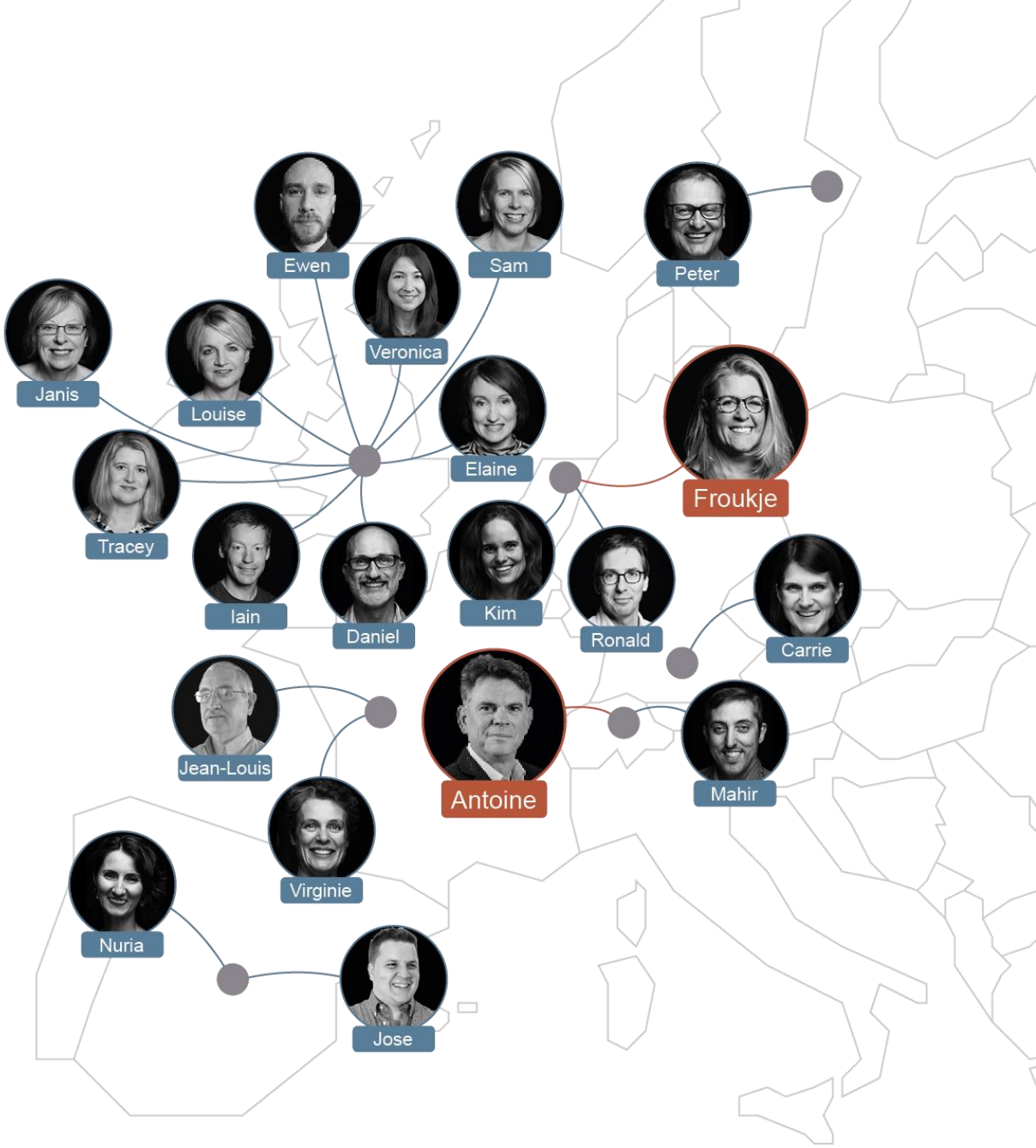

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