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GU CONNECT
VIRTUAL EXPERTS KNOWLEDGE SHARE

INCORPORATING PARP INHIBITORS INTO PROSTATE CANCER CLINICAL PRACTICE

NOVEMBER 2022

PARPi, poly-ADP ribose polymerase inhibitors

TODAY YOU WILL LEARN HOW TO…

- Recognise the efficacy and safety profiles of PARP inhibitors for patients with prostate cancer, including an overview of the data in other tumour types
- Implement testing strategies to predict if a patient with prostate cancer is likely to respond to a PARP inhibitor or some other treatment
- Understand the data from combination studies with PARP inhibitors, their appropriate implementation in treatment strategies, and their impact on clinical practice

PARP, poly-ADP ribose polymerase

INTRODUCING THE SCIENTIFIC COMMITTEE

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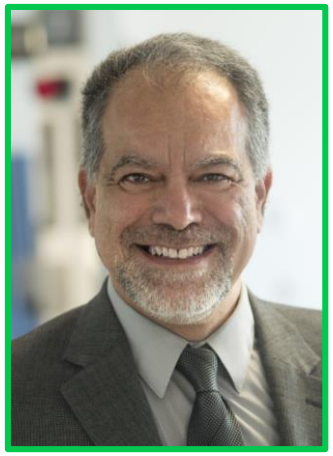

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CONTENT

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INCORPORATING PARP INHIBITORS INTO PROSTATE CANCER CLINICAL PRACTICE

Topic	Facilitator
Scene setting	Fred Saad
Use of PARP inhibitors beyond the first-line setting in mCRPC	Fred Saad/Gert Attard
Use of PARP inhibitors in the first-line setting in mCRPC	Tanya Dorff/ Neeraj Agarwal
Future perspectives and summary	Fred Saad

mCRPC, metastatic castration-resistant prostate cancer

INCORPORATING PARPi INTO PROSTATE CANCER CLINICAL PRACTICE

INTRODUCTION AND SCENE SETTING

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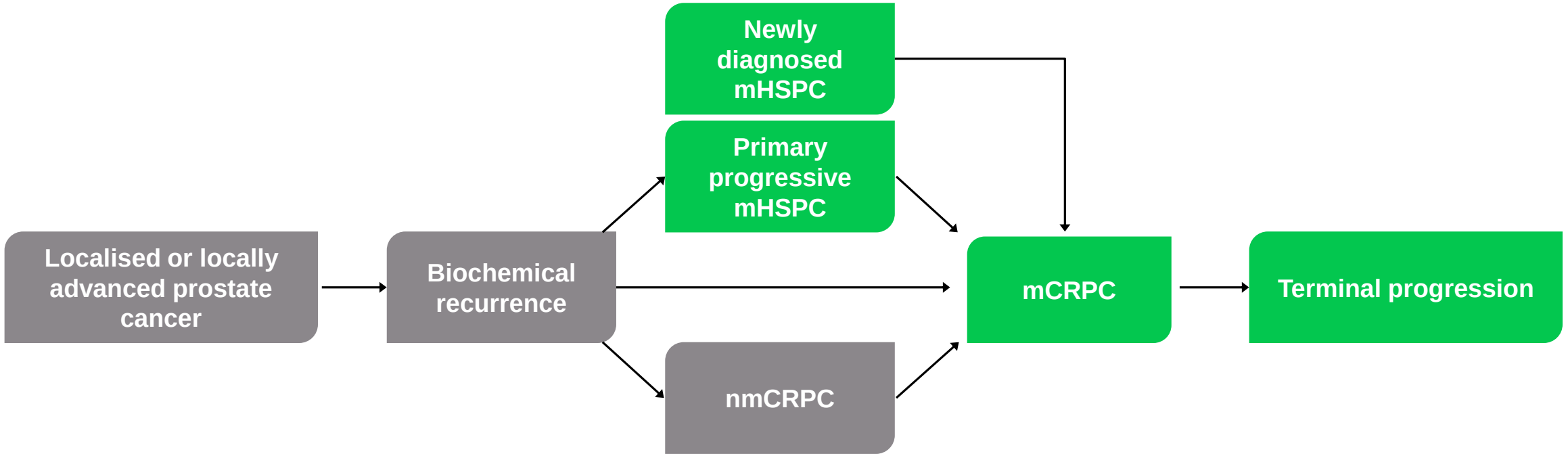
PARPi, poly-ADP ribose polymerase inhibitors

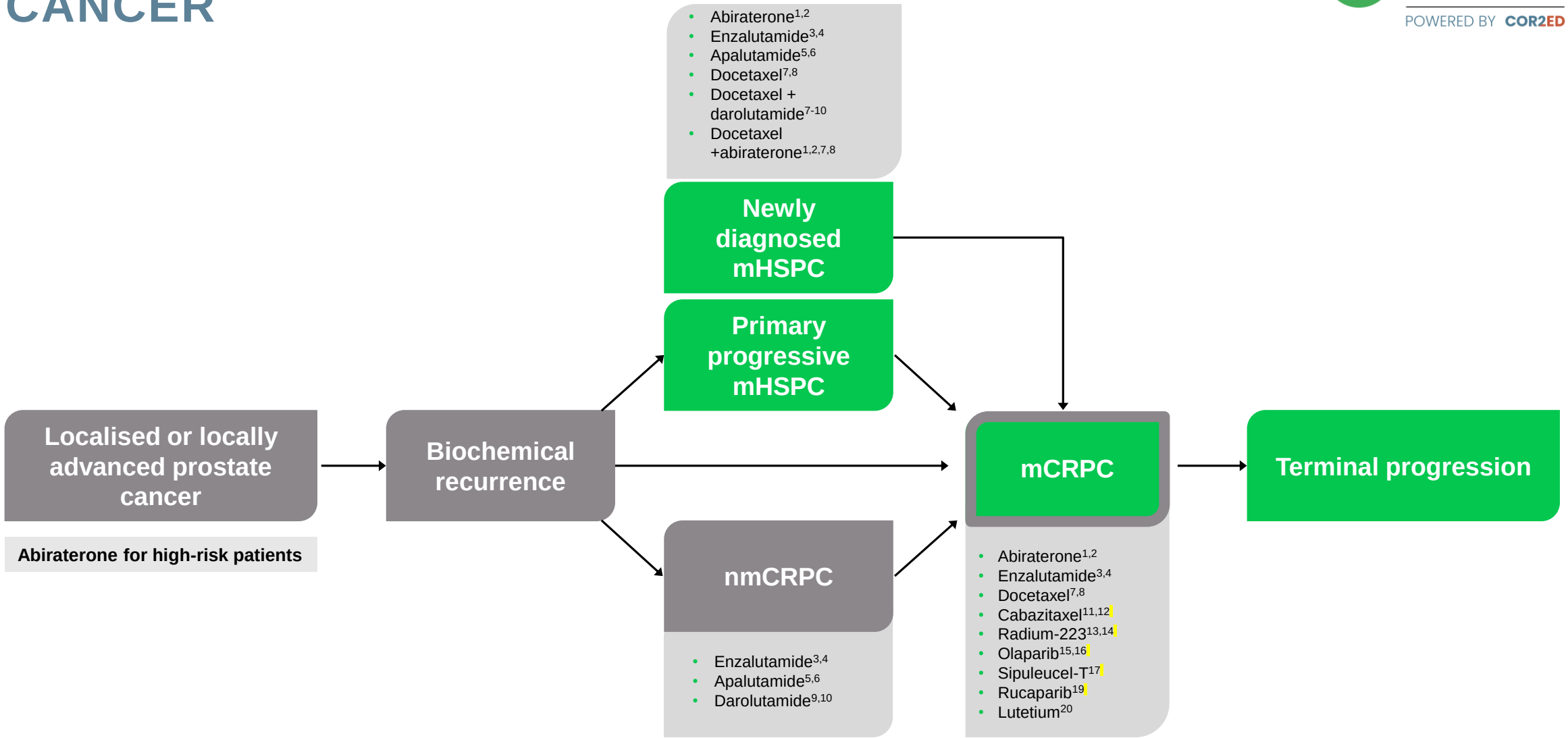
SPECTRUM OF PROSTATE CANCER



mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mCRPC, non-metastatic castration-resistant prostate cancer

Adapted from Scher HI, et al. PLoS One. 2015;10:e0139440; Scher HI, et al. J Clin Oncol. 2016;34:1402-18

SYSTEMIC TREATMENT OPTIONS FOR PROSTATE CANCER

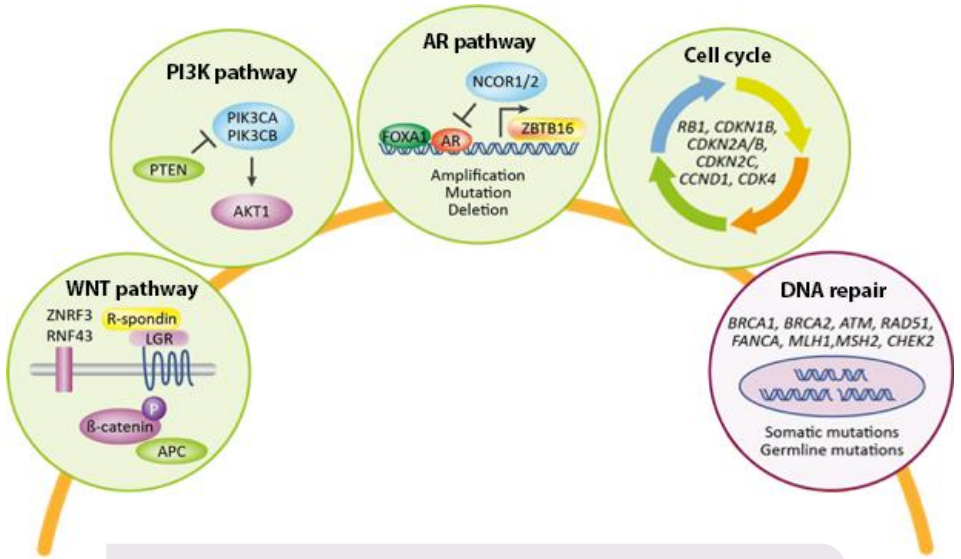


mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer

1. Abiraterone acetate PI; 2. Abiraterone acetate SmPC; 3. Enzalutamide PI; 4. Enzalutamide SmPC; 5. Apalutamide PI; 6. Apalutamide SmPC; 7. Docetaxel PI; 8. Docetaxel SmPC; 9. Darolutamide PI; 10. Darolutamide SmPC; 11. Cabazitaxel PI; 12. Cabazitaxel SmPC; 13. Radium Ra 223 dichloride PI; 14. Radium Ra 223 dichloride SmPC; 15. Olaparib PI; 16. Olaparib9 SmPC; 17. Sipuleucel-T PI; 18. Pembrolizumab PI; 19. Rucaparib PI; 20. Lutetium Lu 177 vipivotide tetraxetan PI. All accessed August 2022

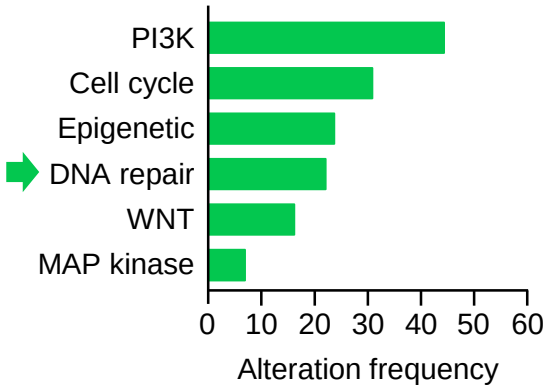
METASTATIC PROSTATE CANCER IS BIOLOGICALLY HETEROGENEOUS

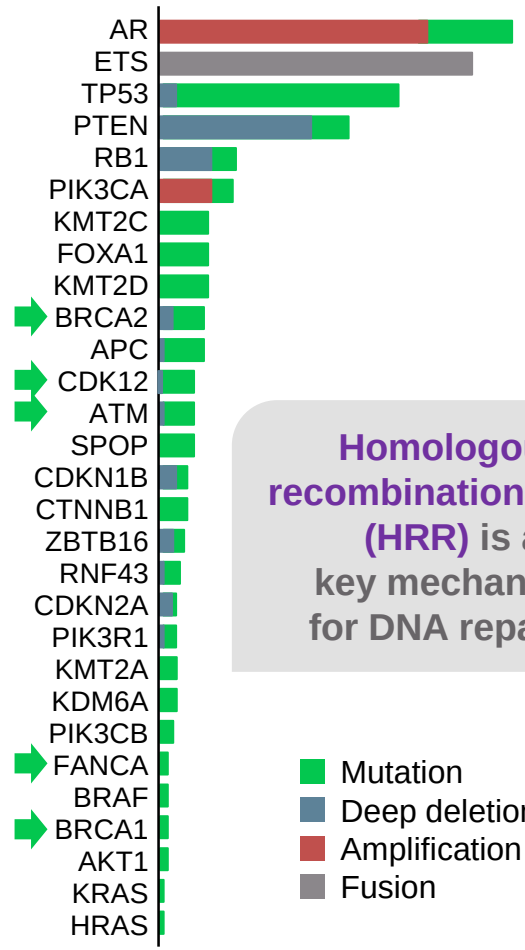
Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



~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

PATIENTS WITH HRR MUTATIONS (INCLUDING *BRCA2* MUTATIONS) ARE MORE LIKELY TO HAVE POOR OUTCOMES ON STANDARD-OF-CARE THERAPIES[1-3]

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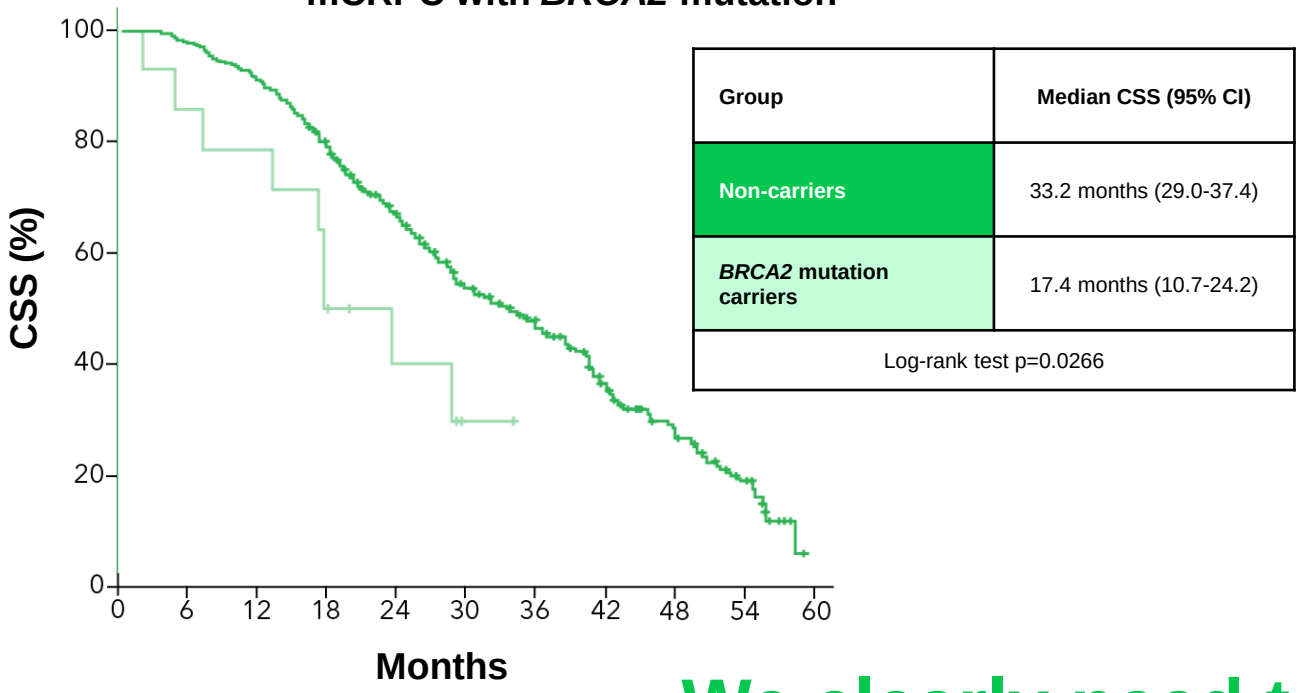
Patients with **germline HRR mutations** including *BRCA2* mutations are more likely to have **poor outcomes** on standard-of care-therapies[1,2]

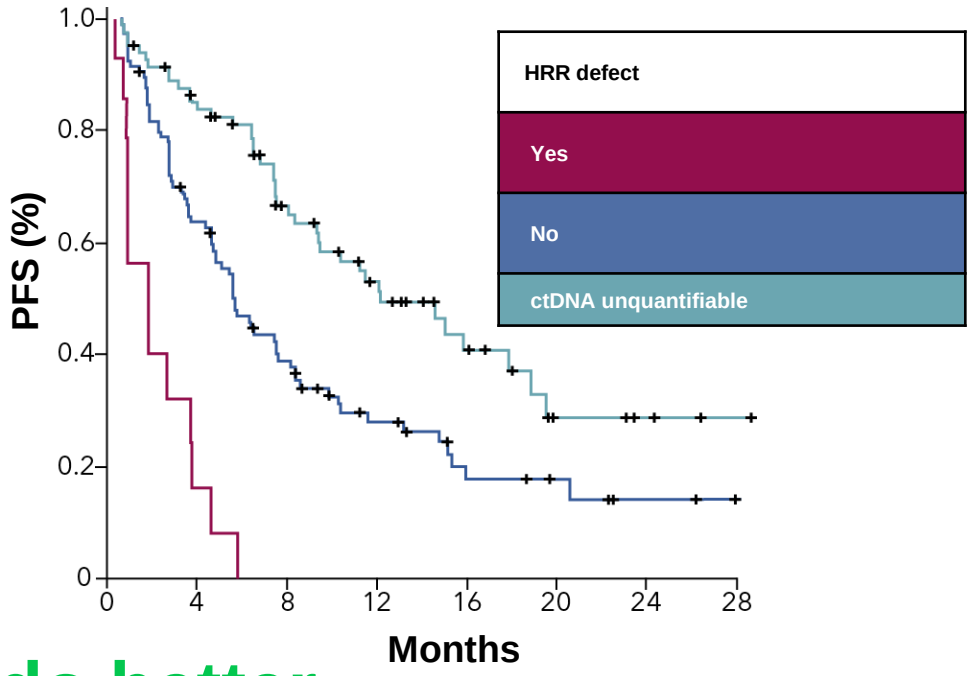
Poor responses to standard therapy also seen for **tumour HRR mutations**[3]

Cancer-specific survival in patients with mCRPC with *BRCA2* mutation[1]



Group	Median CSS (95% CI)
Non-carriers	33.2 months (29.0-37.4)
BRCA2 mutation carriers	17.4 months (10.7-24.2)
Log-rank test p=0.0266	

Time to progression in patients with mCRPC with HRR mutations[3]



We clearly need to do better

CI, confidence interval; CSS, cause-specific survival; ctDNA, circulating tumour DNA; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival

1. Adapted from: Castro E, et al. J Clin Oncol. 2019;6:490-503; 2. Annala M, et al. Eur Urol. 2017;72:34-42; 3. Annala M, et al. Cancer Discov. 2018;8:444-57

GOALS OF THIS MEETING

- Through short reviews of data and interactive clinical cases we hope to cover important aspects in the management of advanced prostate cancer
  - Importance of testing for HRR mutations
  - Appropriate timing and strategies for testing
  - Review appropriate use of PARP inhibitors in the continuum of care
  - Discuss and share insights in areas of controversy
  - Review ongoing work in the earlier use of PARP inhibitors in patients with HRR mutation and non-HRR mutation prostate cancer

HRR, homologous recombination repair; PARP, poly-ADP ribose polymerase

USE OF PARP INHIBITORS BEYOND THE FIRST-LINE SETTING IN mCRPC

Prof. Fred Saad, MD, FRCS

Prof. Gerhardt Attard, MD, FRCP, PhD

PARP, poly-ADP ribose polymerase

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[1,2,3,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]

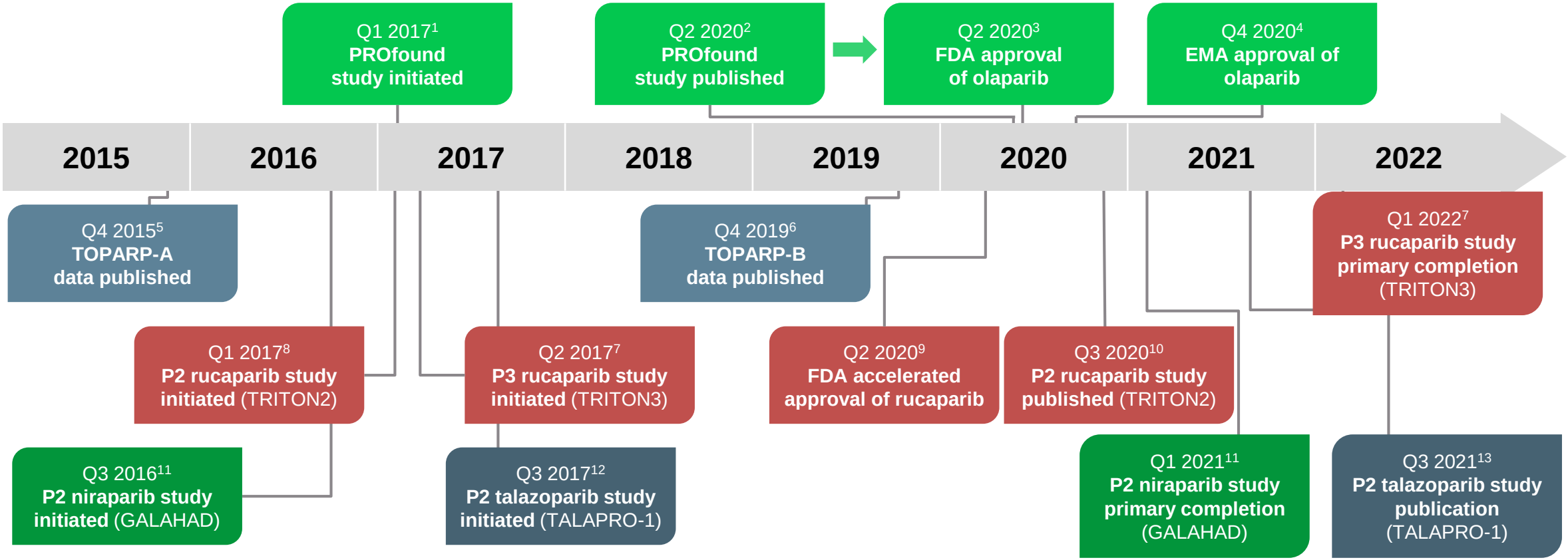
[c] Rucaparib is FDA-approved for the treatment of adult patients with a deleterious *BRCA* mutation-associated mCRPC who have been treated with AR-directed therapy and a taxane-based chemotherapy (no current approval in prostate cancer in Europe)[4]

[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.

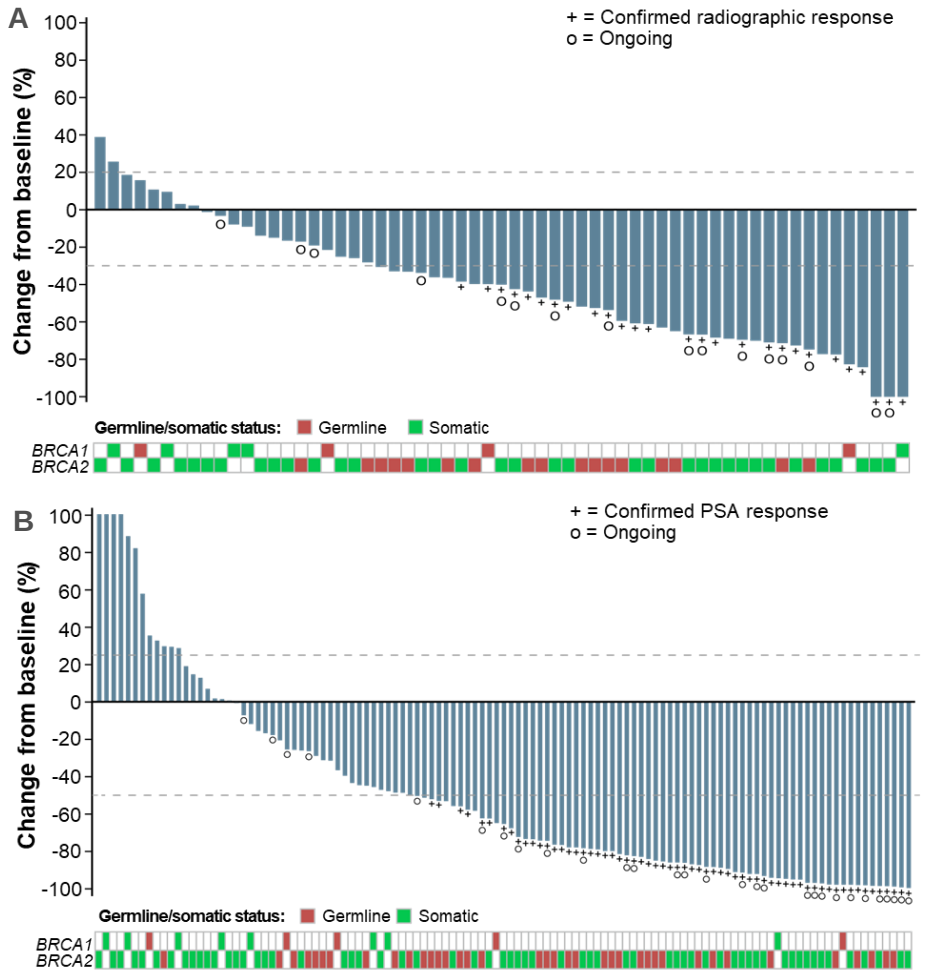
PHASE 2/3 PARP INHIBITOR MONOTHERAPY TRIALS IN mCRPC

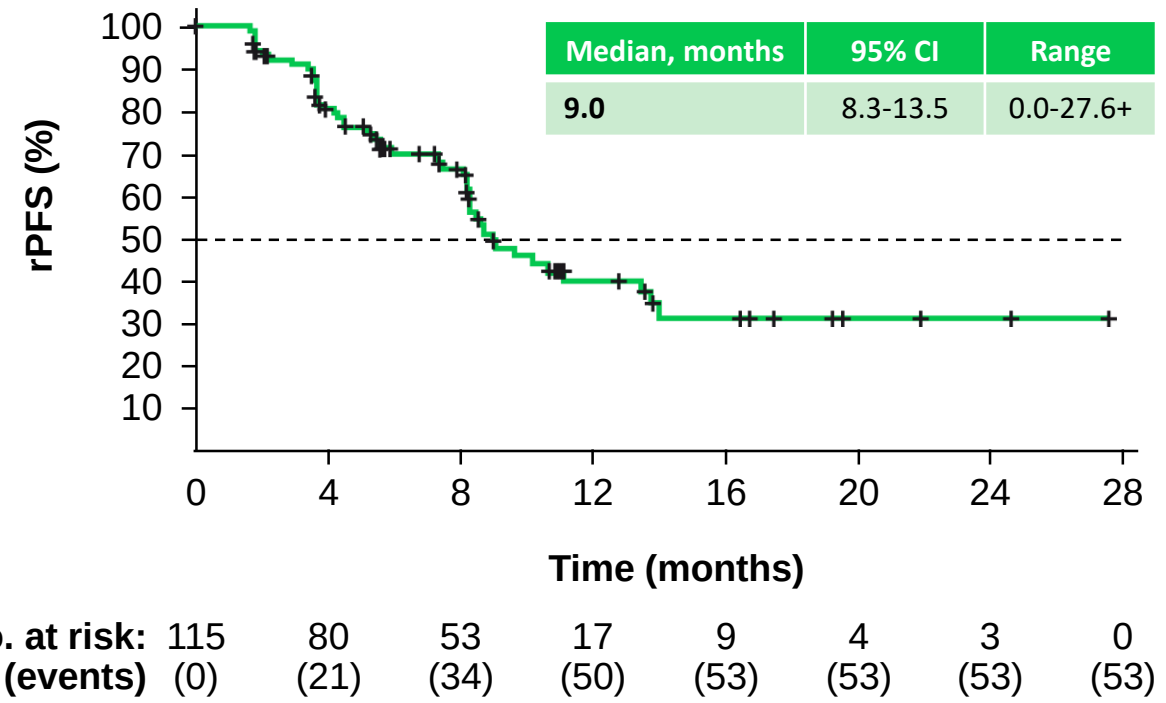


EMA, European Medicines Agency; FDA, United States Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; P, phase; PARP, poly-ADP ribose polymerase; Q, quarter

1. NCT02987543; 2. de Bono J, et al. N Engl J Med. 2020;382:2091-102; 3. FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer. www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer; 4. Lynparza SmPC; 5. Mateo J, et al. N Engl J Med. 2015;373:1697-708; 6. Mateo J, et al. Lancet Oncol. 2020;21:162-74; 7. NCT02975934; 8. NCT02952534; 9. FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer. www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate; 10. Abida W, et al. J Clin Oncol. 2020;38:3763-72; 11. NCT02854436; 12. NCT03148795; 13. de Bono JS, et al. Lancet Oncol. 2022;9:1250-64. All accessed August 2022.

TRITON2: POST NHA AND CHEMO RUCAPARIB MONOTHERAPY IN mCRPC WITH *BRCA1* OR *BRCA2* ALTERATIONS





Median, months	95% CI	Range
9.0	8.3-13.5	0.0-27.6+

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

Chemo, chemotherapy; CI, confidence interval; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; PSA, prostate-specific antigen, rPFS, radiographic progression-free survival

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

GALAHAD: NIRAPARIB MONOTHERAPY POST NHT AND CHEMO RESULTS FOR *BRCA*-ALTERED VS NON *BRCA*-ALTERED mCRPC

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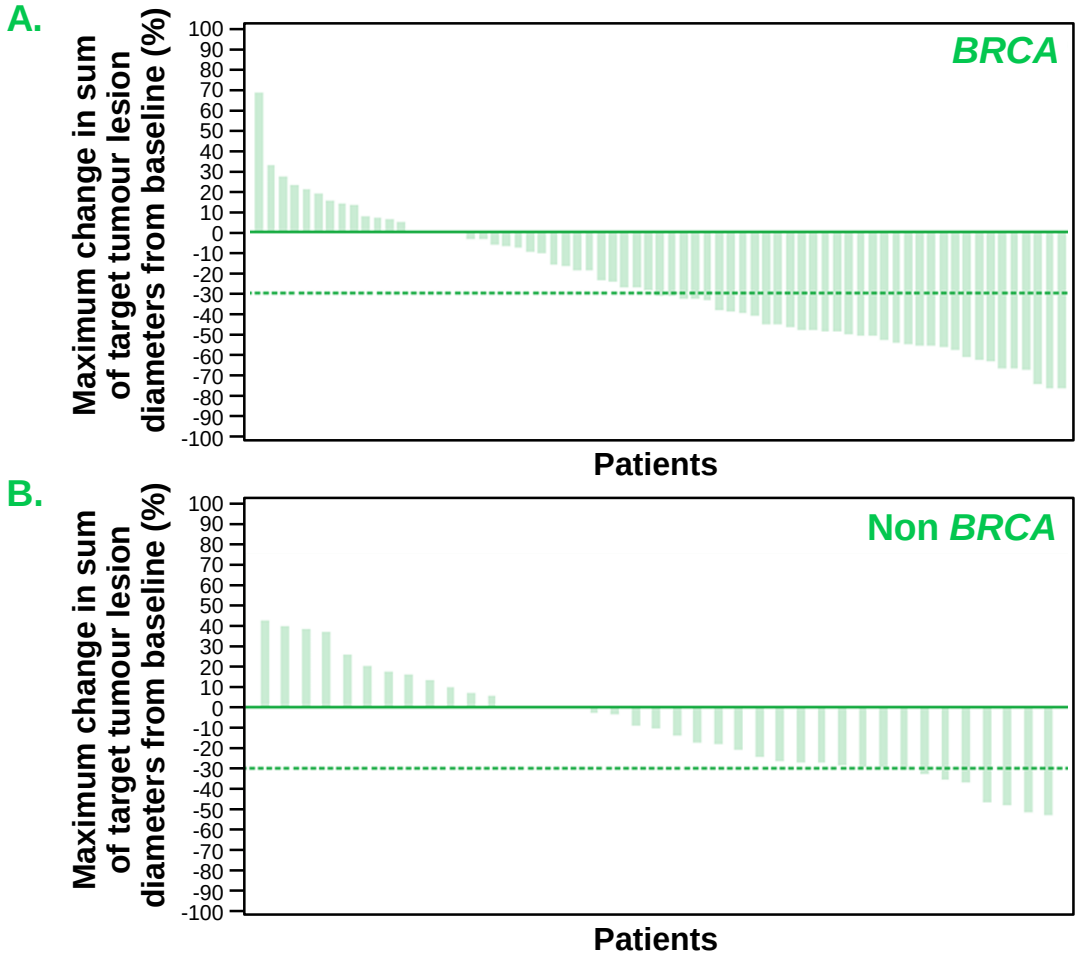
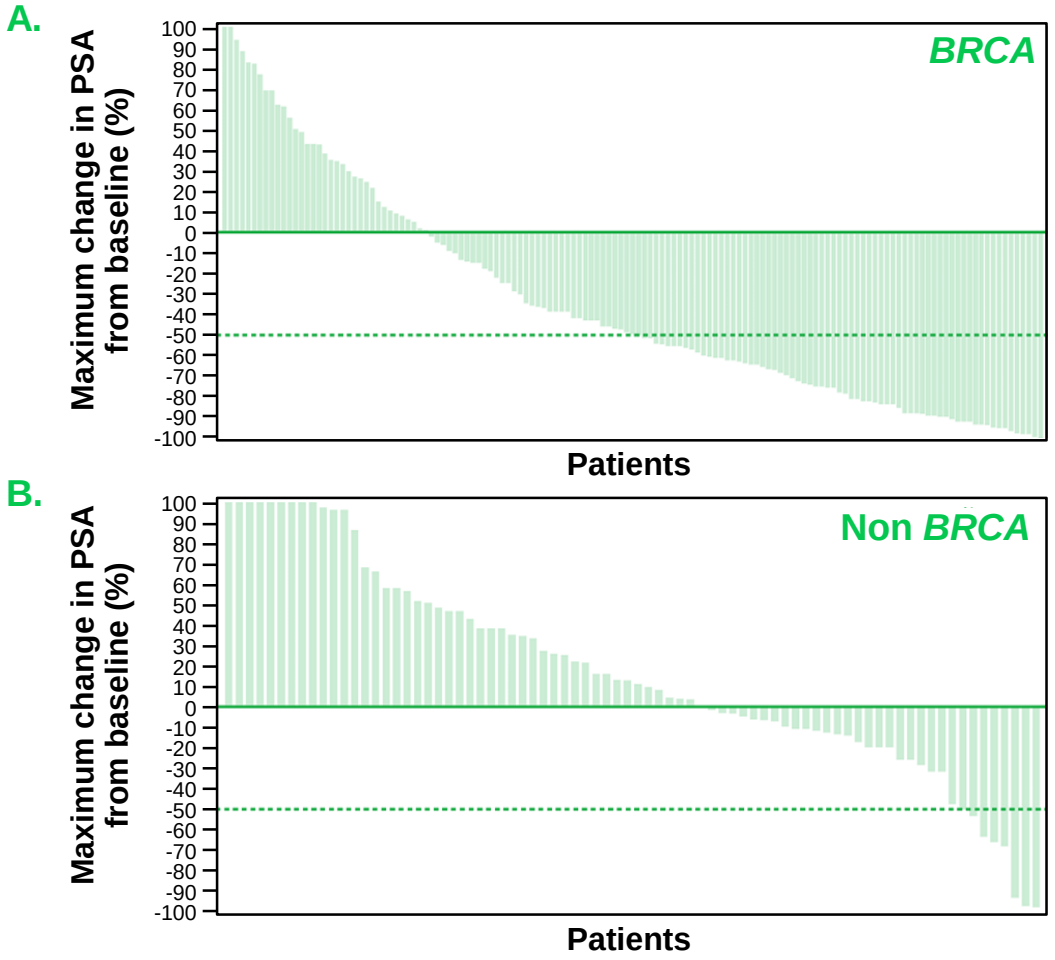
MEASURABLE RESPONSE



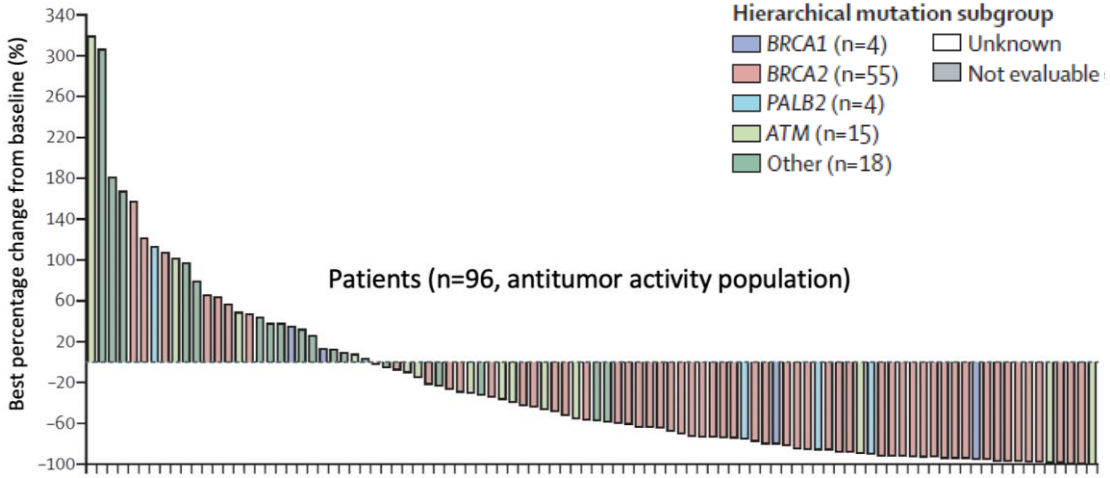
PSA RESPONSE

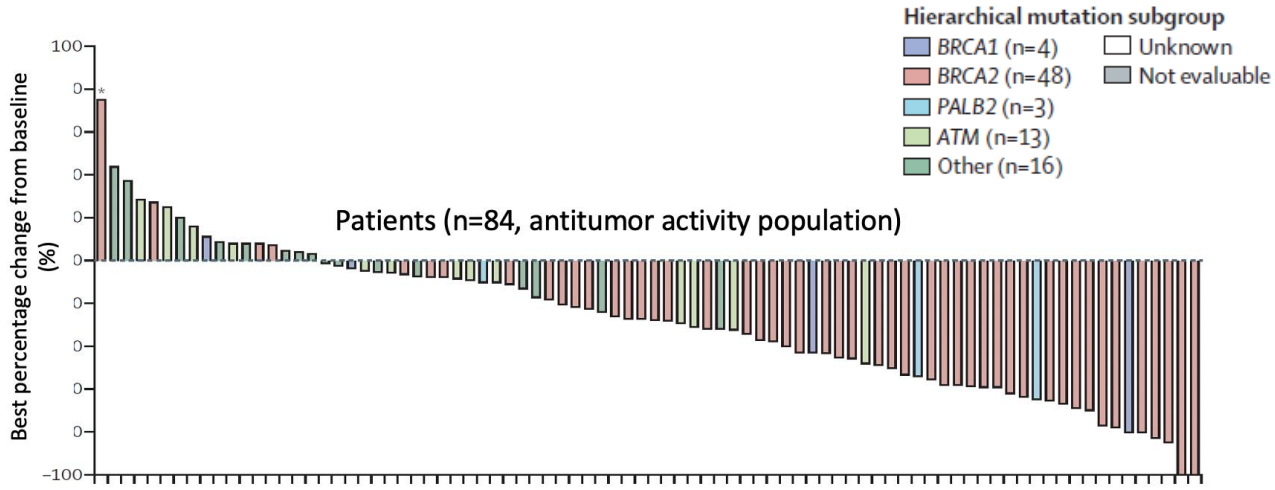


Patients were eligible to enter the study if a deleterious germline or somatic alteration was found in at least one of the following genes: *ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2*, and *PALB2*

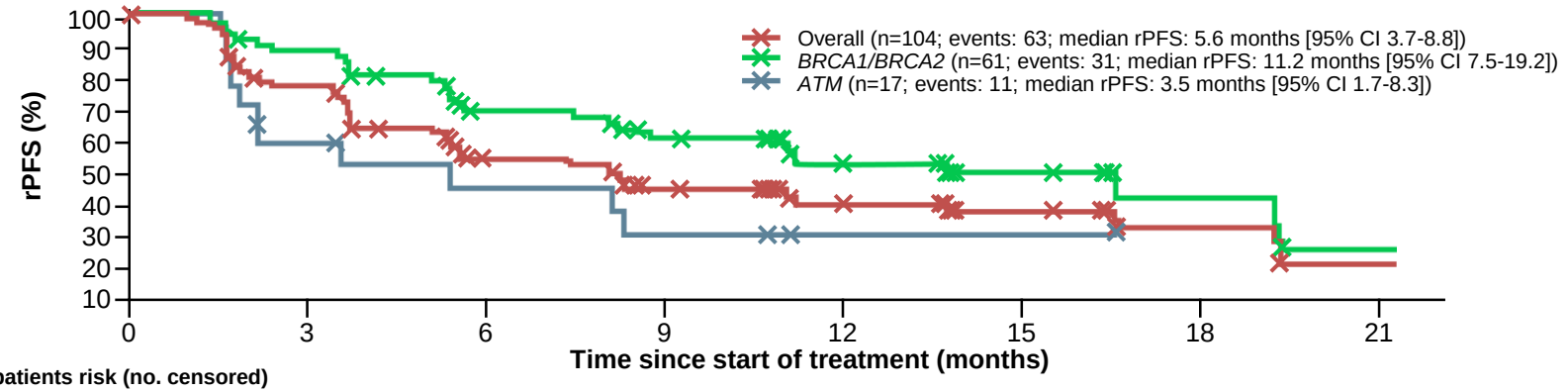
Chemo, chemotherapy; mCRPC, metastatic castration resistant prostate cancer; NHT, new hormonal therapy; PSA, prostate-specific antigen. Smith MR, et al. Lancet Oncol. 2022;23(3):362-73 (supplementary appendix)

TALAPRO-1: TALAZOPARIB MONOTHERAPY POST NHT AND CHEMO





rPFS by HRR gene altered[a]



No. of patients risk (no. censored)							
Overall	104 (0)	72 (7)	38 (18)	26 (22)	16 (29)	10 (34)	4 (39)
BRCA1/BRCA2	61 (0)	52 (1)	31 (10)	23 (14)	15 (19)	9 (24)	4 (28)
ATM	17 (0)	8 (2)	5 (3)	3 (3)	1 (5)	1 (5)	0 (6)

[a]BICR; antitumour activity population

BICR, blinded independent central review; chemo, chemotherapy; CI, confidence interval; NHT, new hormonal therapy; PSA, prostate specific antigen; rPFS, radiographic progression-free survival

Adapted from: de Bono J, et al. Lancet Oncol. 2021;22:1250-64

PROfound: FIRST PHASE 3 RCT OF A PARP INHIBITOR IN mCRPC (OLAPARIB VS ENZALUTAMIDE OR ABIRATERONE)

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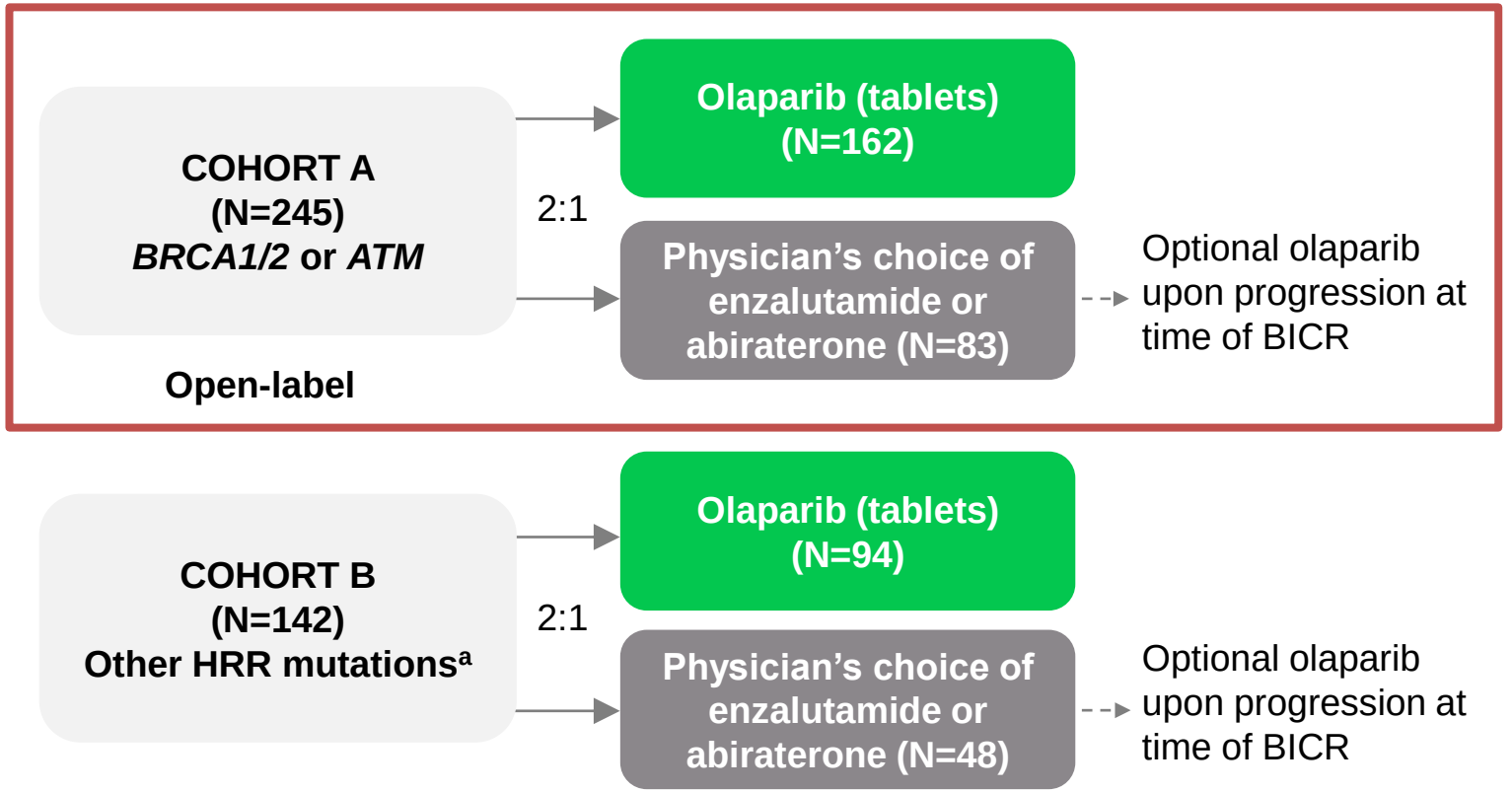
Randomised, open-label, phase 3 study

Key eligibility criteria

- mCRPC with disease progression on prior NHA e.g. abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR



Primary endpoint: rPFS by BICR using RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria (cohort A)

Key secondary endpoints:
- Cohort A: Confirmed ORR, time to pain progression, OS
- Cohort A + B: rPFS

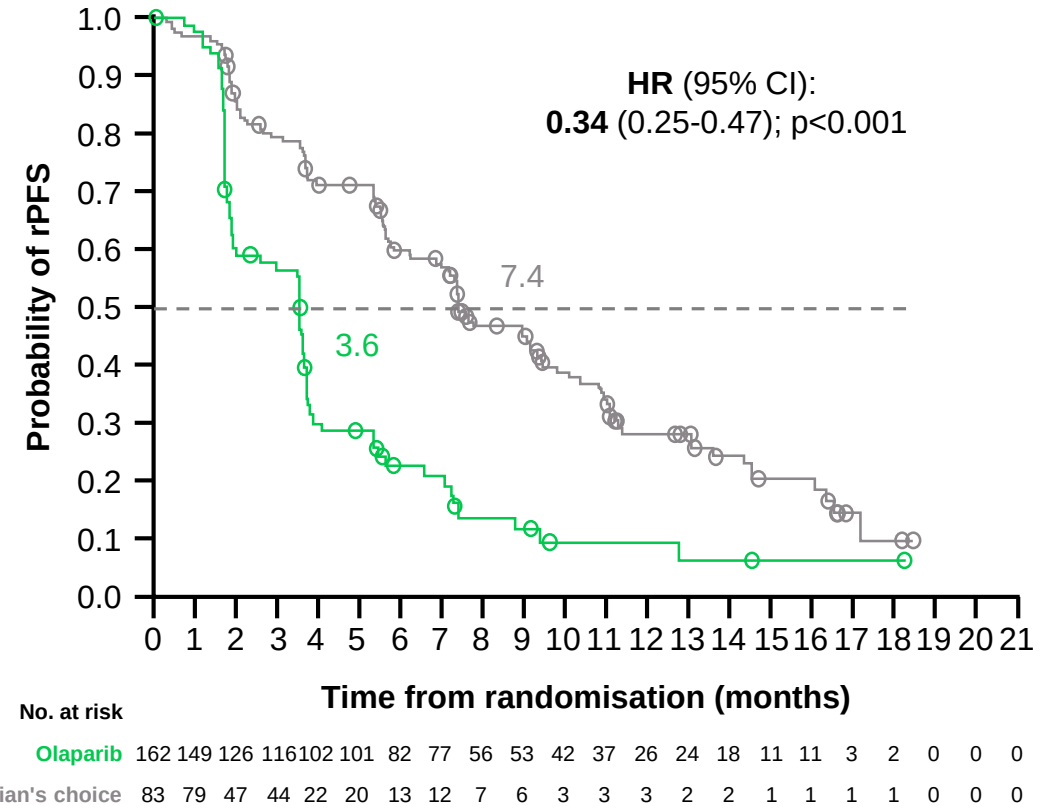
[a] Cohort B included patients with *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, or *RAD54L* mutations

ARAT, androgen receptor-axis-targeted therapies; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; ORR, objective response rate; OS, overall survival; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; PVWG3, Prostate Cancer Working Group 3; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumours

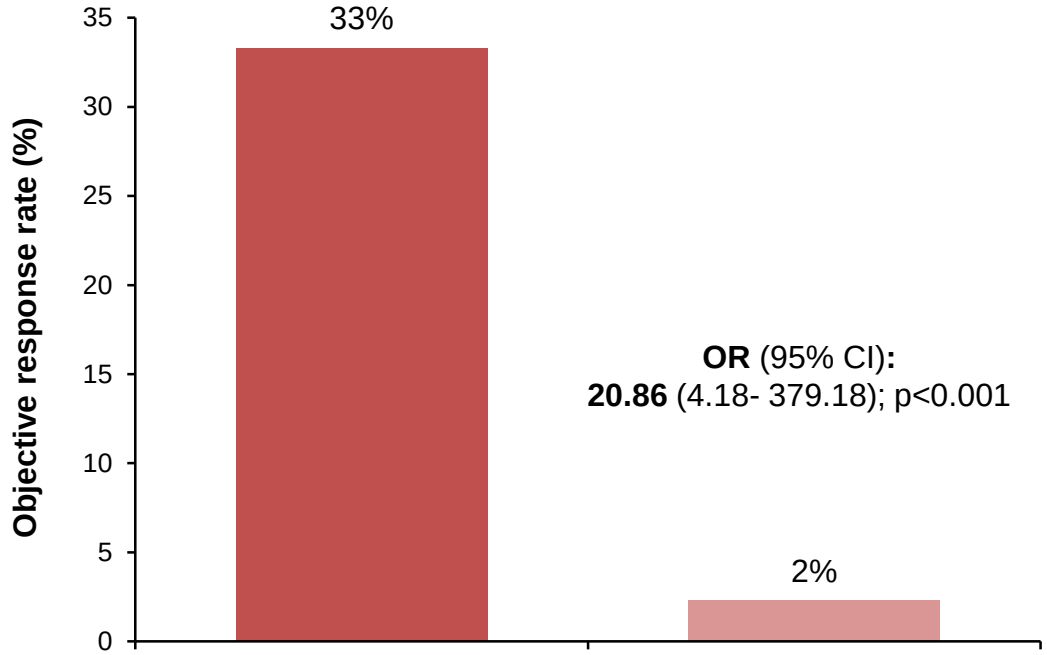
de Bono JS, et al. N Engl J Med. 2020;382:2091-102

PROfound PRIMARY ENDPOINT: SIGNIFICANT IMPROVEMENT IN rPFS IN mCRPC WITH *BRCA1/2* OR *ATM* MUTATIONS (COHORT A)

66% REDUCTION IN RISK OF PROGRESSION OR DEATH WITH OLAPARIB VS PHYSICIAN'S CHOICE



CONFIRMED ORR IN COHORT A



CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; OR, odds ratio; ORR, overall response rate; rPFS, radiographic progression-free survival

de Bono JS, et al. N Engl J Med. 2020;382:2091-102

PROfound SECONDARY ENDPOINT: SIGNIFICANT IMPROVEMENT IN OS IN mCRPC WITH *BRCA1/2* OR *ATM* MUTATIONS (COHORT A)

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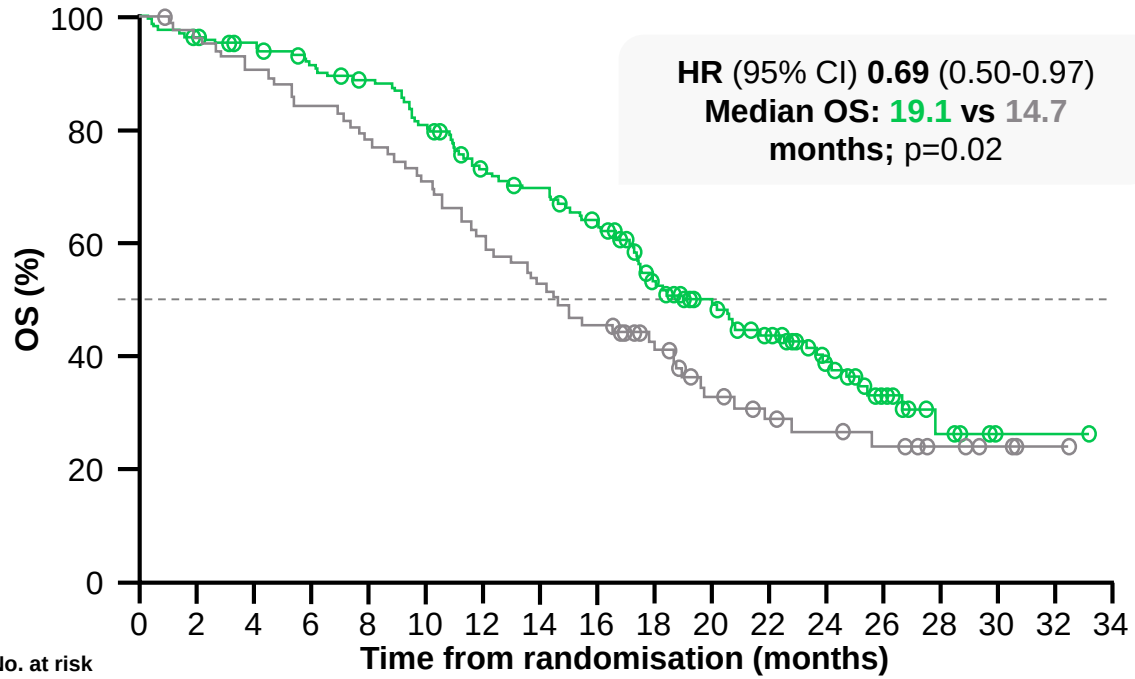
31% reduction in risk of death with olaparib vs physician's choice

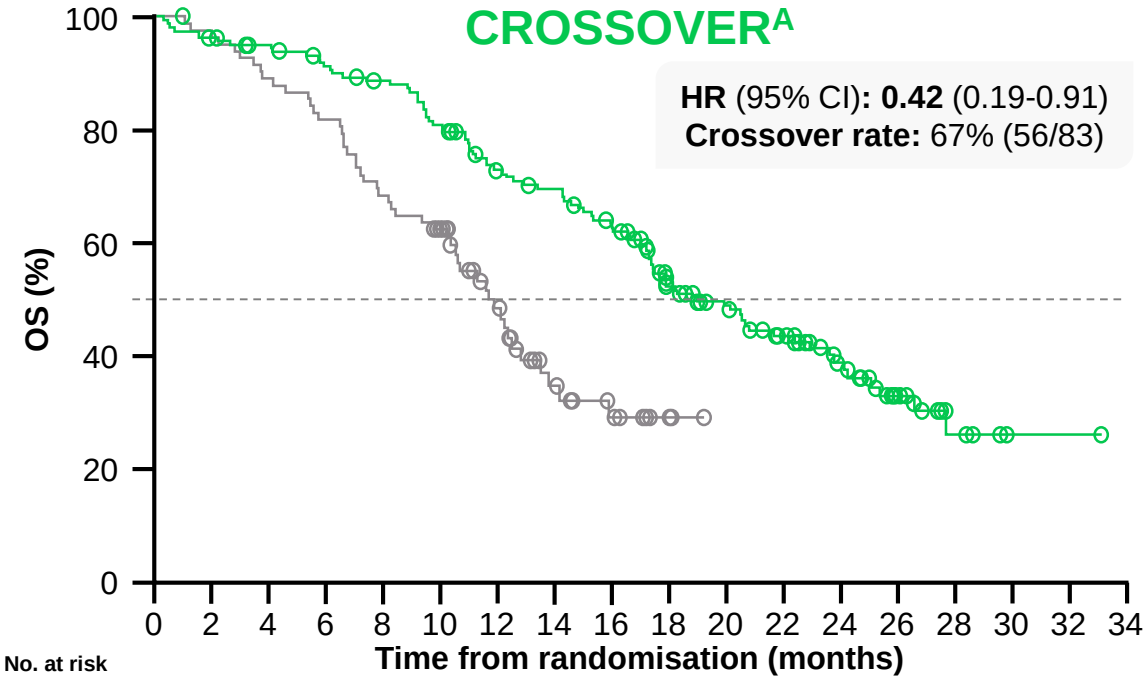
COHORT A



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

COHORT A WITH ADJUSTMENT FOR CROSSOVER[A]



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

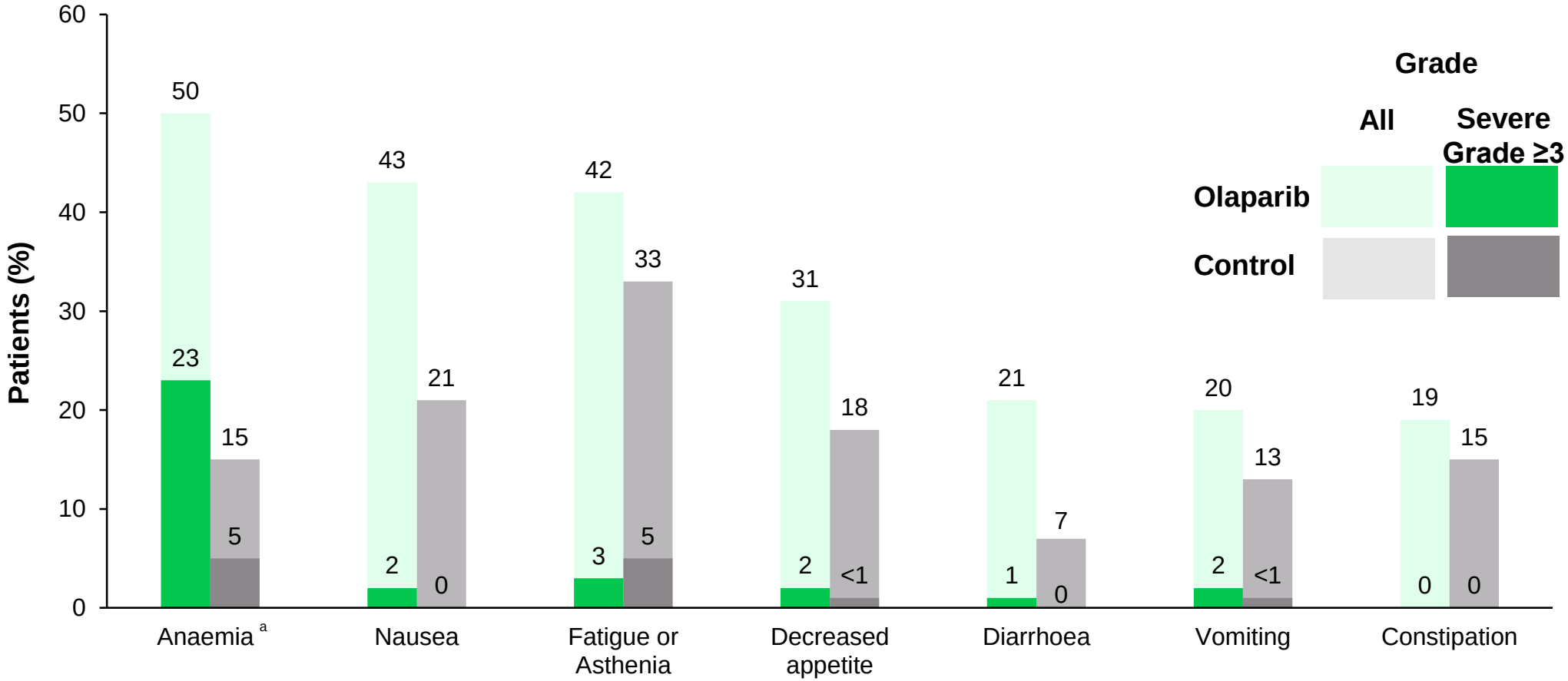
Median follow-up duration for censored patients: olaparib, 21.9 months; control, 21.0 months

[a] Re-censored; conducted using rank-preserving structural failure time model to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy

CI, confidence interval; HR, hazard ratio; OS, overall survival

Adapted from: Hussain M, et al. N Engl J Med. 2020;383:2345-57

TOLERABILITY PROFILE



Median duration of treatment was 7.6 months in the olaparib arm and 3.9 months in the control arm

[a] Grouped term.

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

AE PROFILES OF THE PARP INHIBITORS IN MONOTHERAPY PROSTATE CANCER TRIALS

Frequency of AEs in prostate cancer trials, all grade % (grade ≥3 %)	Olaparib (PROfound)[1]	Rucaparib (TRITON-2)[2]	Niraparib (GALAHAD)[3]	Talazoparib (TALAPRO-1)[4]
Hypertension	NR	NR	11.8 (4.2)	5.5 (3.1)
Increased ALT/AST	NR	33.0 (5.2)	12.8 (2.8)	11.8 (2.4)
Insomnia	NR	NR	8.3 (0.3)	NR
Alopecia	NR	NR	NR	NR

Frequency and grade of cytopenias in prostate cancer trials, %	Olaparib (PROfound)[1]	Rucaparib (TRITON-2)[2]	Niraparib (GALAHAD)[3]	Talazoparib (TALAPRO-1)[4]
Anaemia grade ≥3	23	25.2	33	31
Neutropenia grade ≥3	NR[a]	7	10	8
Thrombocytopenia grade ≥3	NR[a]	9.6	16	9

Please note that head-to-head studies were not conducted between these products. This data is presented for information purposes only

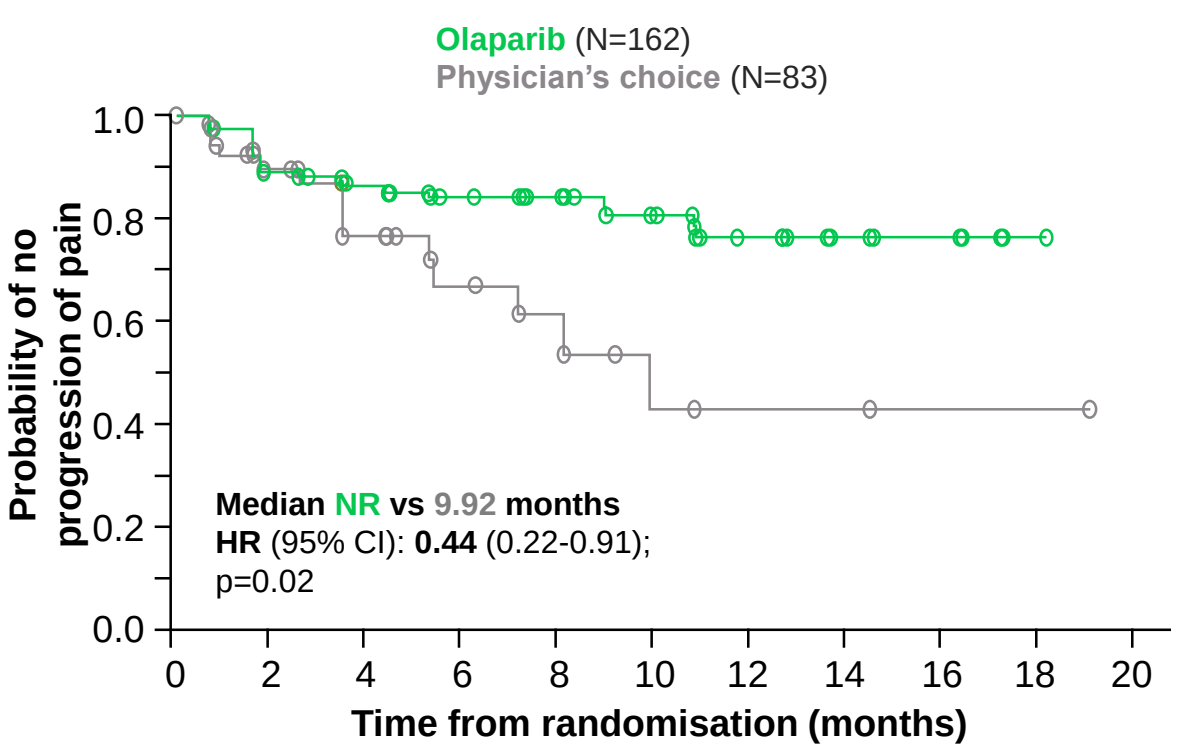
[a]Frequency of G3 AEs not reported but 1% of patients experienced TEAE leading to treatment discontinuation

AE, adverse event; PARP, Poly-ADP ribose polymerase

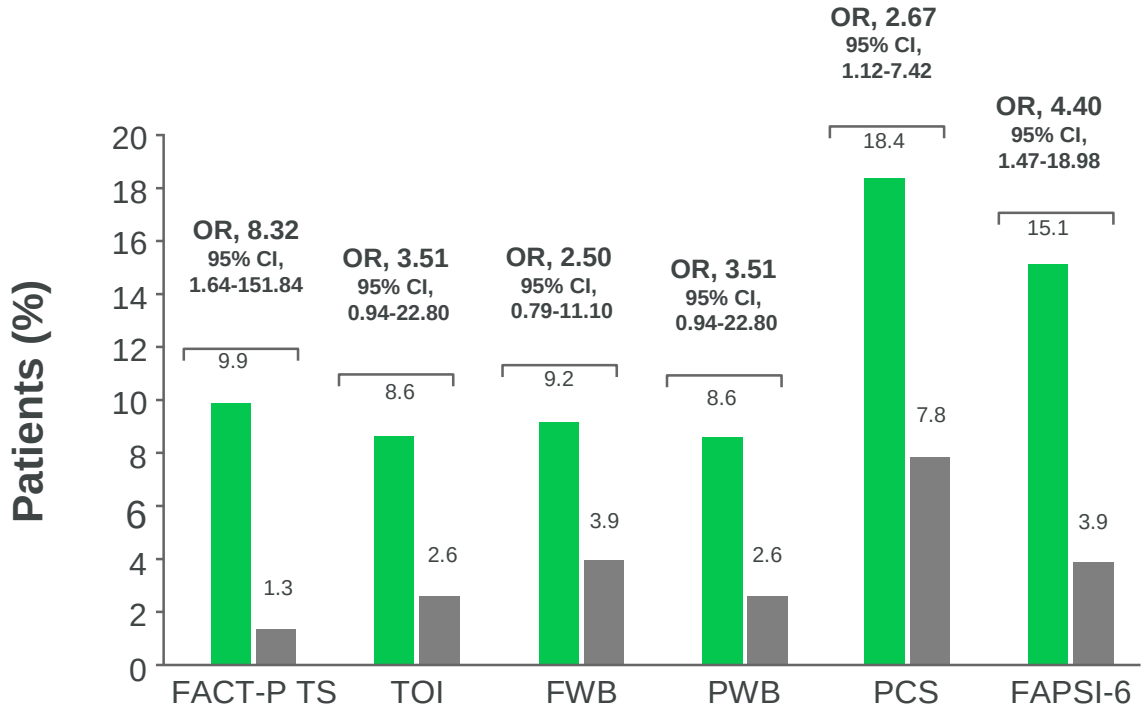
1. Hussain M, et al. New Engl J Med. 2020;383:2345-57; 2. Abida W, et al. J Clin Oncol. 2020;38:3763-72 (supplement); 3. Smith MR, et al. Lancet. 2022;22:362-73; 4. de Bono JS, et al. Lancet Oncol. 2021;22:1250-64

PROfound SECONDARY ENDPOINTS: IMPROVEMENTS IN MULTIPLE CLINICAL AND PATIENT-REPORTED ENDPOINTS IN mCRPC WITH *BRCA1/2* OR *ATM* MUTATIONS (COHORT A)

TIME TO PAIN PROGRESSION IN COHORT A[1,2]



IMPROVEMENT IN PATIENT-REPORTED HRQOL[3]



CI, confidence interval; FACT-P TS, Functional Assessment of Cancer Therapy–Prostate Total Score; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FWB, functional wellbeing; HR, hazard ratio; HRQoL, health-related QoL; NR, not reached; OR, odds ratio; pcNHA, physician's choice of new hormonal agent; PCS, prostate cancer subscale; PWB, physical wellbeing; QoL, quality of life; TOI, Trial Outcome Index

1. de Bono JS, et al. N Engl J Med. 2020;382:2091-102; 2. Hussain M, et al. Presented at ESMO 2019; September 27–October 1; Barcelona, Spain. Abstract LBA12_PR; 3. Thiery-Vuillemin A, et al. Lancet Oncol. 2022;23:393-405

TRITON3: RUCAPARIB MONOTHERAPY IN mCRPC WITH *BRCA1/2* OR *ATM* ALTERATIONS[a]

CONFIRMATORY PHASE 3 STUDY

	All patients (*BRCA1/2* and *ATM* mutations)		*BRCA* mutations	
	Rucaparib N= 270	Physician choice[b] N=135	Rucaparib N=201	Physician choice[b] N=101
Median rPFS	10.2 mo	6.4 mo	11.2 mo	6.4 mo
	HR (95%CI): 0.61 (0.47-0.80) P=0.0003		HR (95%CI): 0.50 (0.36-0.69) P<0.0001	

[a] patients enrolled in TRITON3 could have received prior taxane chemotherapy for CSPC and one prior novel hormonal agent in any disease setting
[b]docetaxel, abiraterone acetate, or enzalutamide

- Most common (≥5%) TEAEs ≥ G3 for rucaparib treated patients: anaemia (23.7%), neutropaenia (7.4%), asthenia/fatigue (7.0%), thrombocytopaenia (5.9%), increased ALT/AST (5.2%)
- Discontinuation due to TEAEs: 14.8% rucaparib vs 21.5% for control arm

ALT, alanine transaminase; AST, aspartate transferase; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; mo, months; NHT, novel hormonal therapy; rPFS, radiographic, progression-free survival; TEAE, treatment emergent adverse event
Presented by Boye A, et al. Twenty-Ninth Annual Prostate Cancer Foundation Scientific Retreat 2022; Clovis Oncology, Inc. - TRITON3 Phase 3 Trial of Rubraca® (rucaparib) Achieves Primary Endpoint in Men with Metastatic Castration-Resistant Prostate Cancer with BRCA or ATM Mutations. Accessed 10-Nov-2022

PATIENT CASE DISCUSSION

CASE DISCUSSION

Patient: Age 68 years

Presents with: Moderate urinary symptoms

Medical history:

- Well-controlled hypertension and angina; relieved by stent 4 years prior
- No known family history of cancer

PSA 132

Digital rectal exam: Nodule/induration suspected stage T3

TRUS biopsy: 9/12 cores; Adenocarcinoma Gleason 4+4

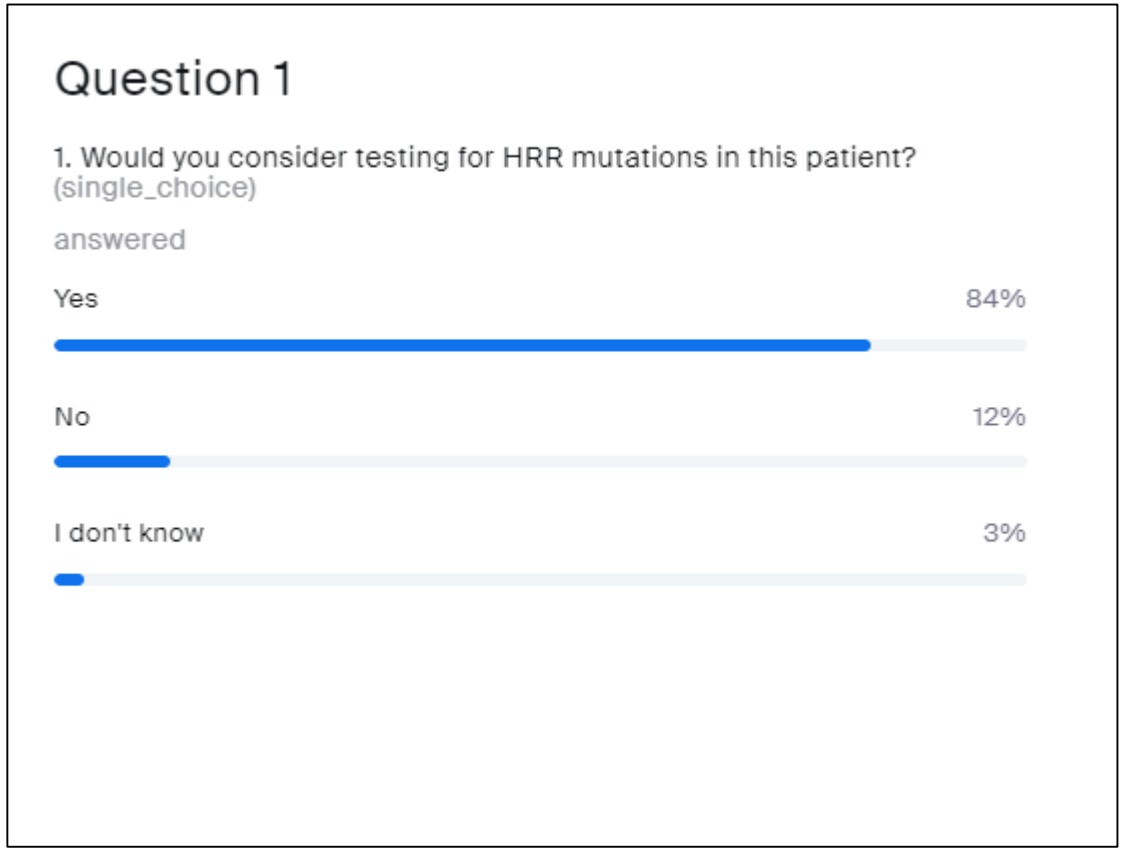
Imaging:

- Metastases in hip, lumbar spine, and ribs
- Multiple retroperitoneal lymph nodes between 1 and 3 cm and 2 pulmonary nodules suspicious of metastases

DRE, digital rectal exam; PSA, prostate-specific antigen; T, tumour stage; TRUS, transrectal ultrasound

WOULD YOU CONSIDER TESTING FOR HRR MUTATIONS IN THIS PATIENT?

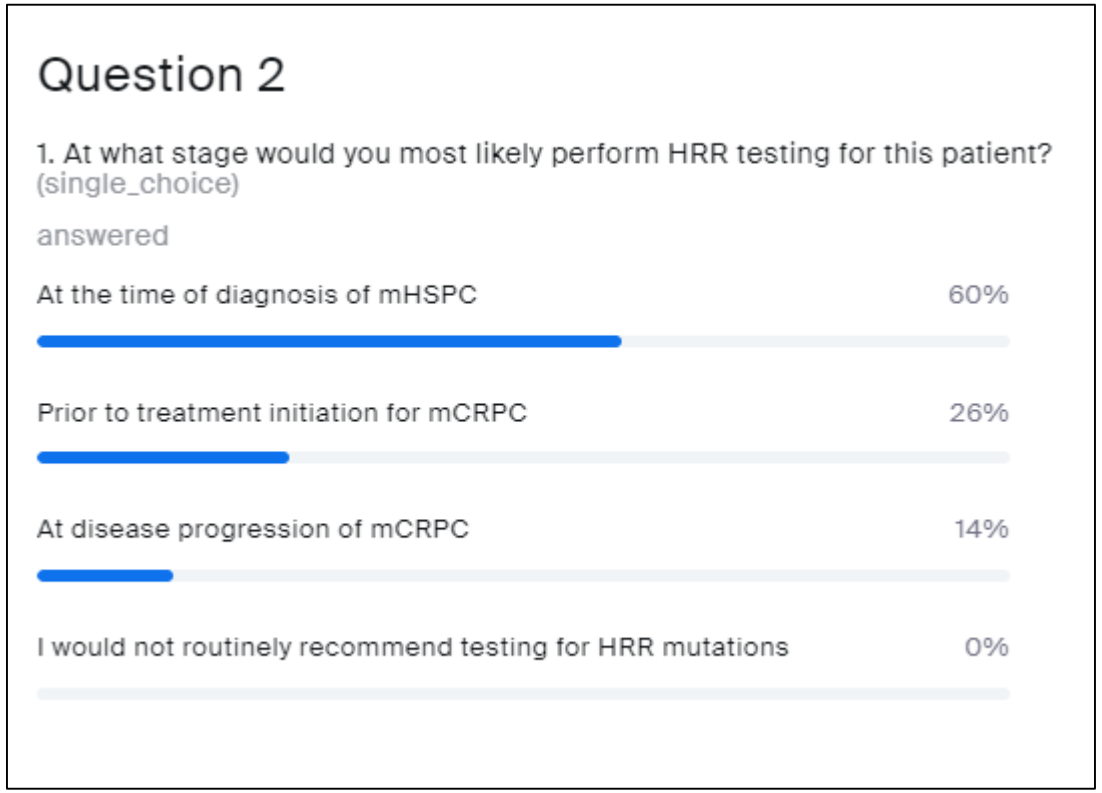
- Yes
- No
- Don’t know



HRR, homologous recombination repair

AT WHAT STAGE WOULD YOU MOST LIKELY PERFORM HRR TESTING FOR THIS PATIENT

- At the time of diagnosis of mHSPC
- Prior to treatment initiation for mCRPC
- At disease progression of mCRPC
- I would not routinely recommend testing for HRR mutations



HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer

CASE DISCUSSION

Patient: Age 68 years

Presents with: Moderate LUTS

Medical history:

- Well-controlled hypertension and angina; relieved by stent 4 years prior
- No known family history of cancer

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

Staging: T2b/T3 by DRE

Imaging:

- **Metastases in hip, lumbar spine and ribs**
- **Multiple retroperitoneal lymph nodes between 1 and 3 cm and 2 pulmonary nodules suspicious of metastases**

Slight discomfort in lumbar spine

Imaging:

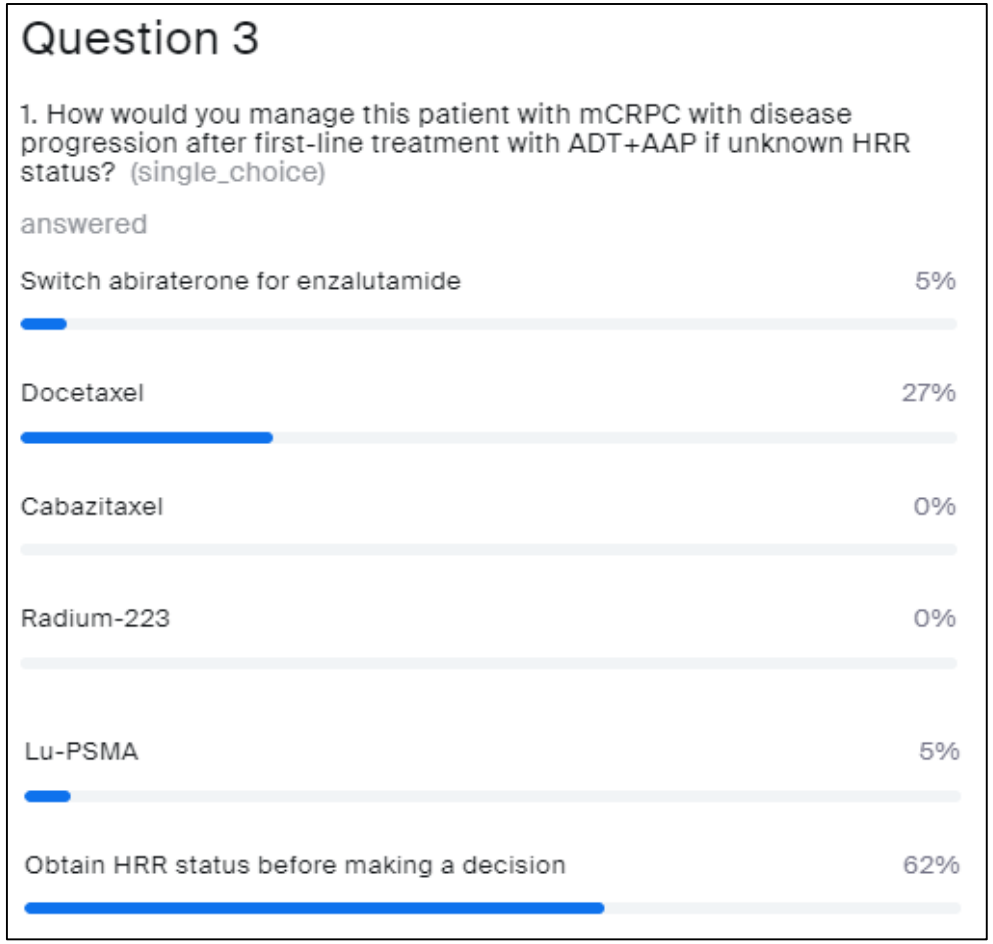
- **Progression of bone and soft-tissue metastases**
- **Haemoglobin: 10gm/dL**

ADT, androgen-deprivation therapy; DRE, digital rectal exam; LUTS, lower urinary-tract symptoms; PSA, prostate-specific antigen'; T, tumour stage

HOW WOULD YOU MANAGE THIS PATIENT WITH mCRPC WITH DISEASE PROGRESSION AFTER FIRST-LINE TREATMENT WITH ADT + AAP?

IF UNKNOWN HRR STATUS

- Switch abiraterone for enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223
- Lu-PSMA
- Obtain HRR status before making a decision



ADT, androgen-deprivation therapy; AAP, abiraterone acetate and prednisone/prednisolone; HRR, homologous recombination repair; Lu-PSMA, lutetium prostate-specific membrane antigen; mCRPC, metastatic castration-resistant prostate cancer

HOW WOULD YOU TREAT THIS PATIENT?

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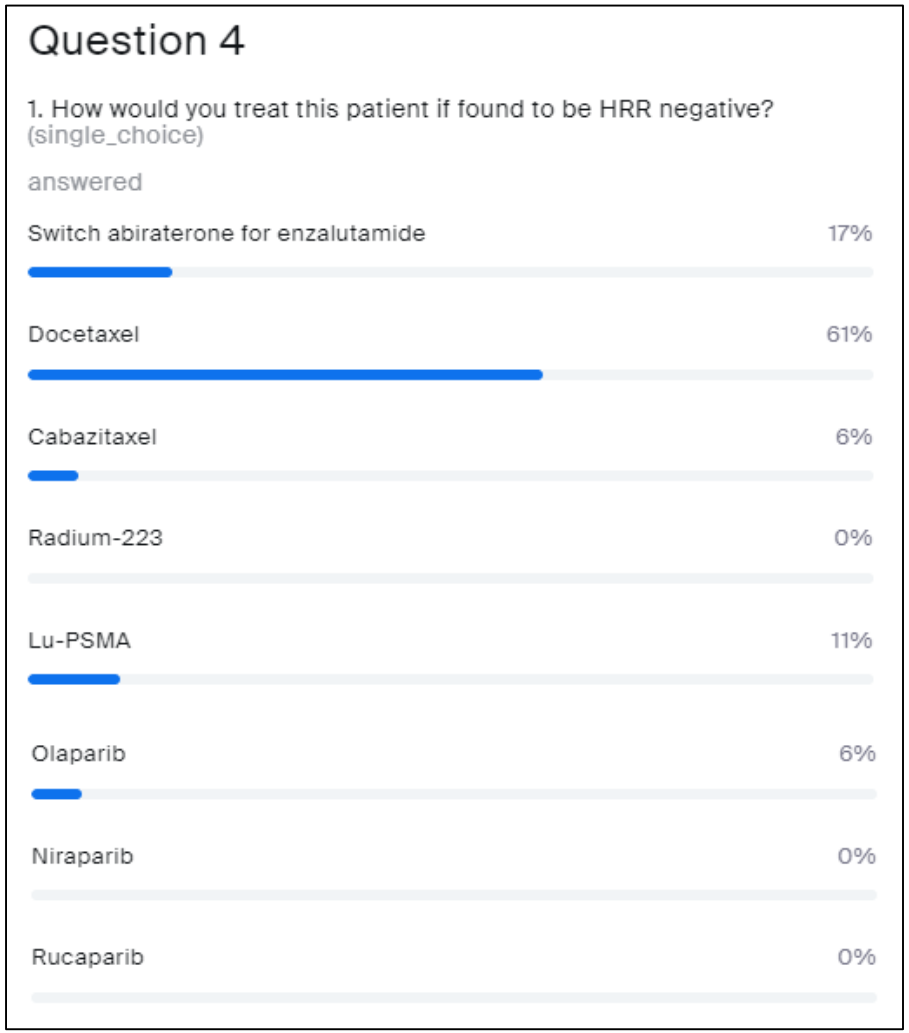
IF FOUND TO BE HRRd NEGATIVE

- Switch abiraterone for enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223
- Lu-PSMA
- Olaparib
- Niraparib
- Rucaparib



HRRd, homologous recombination repair deficient; Lu-PSMA, lutetium prostate-specific membrane antigen

HOW WOULD YOU TREAT THIS PATIENT?

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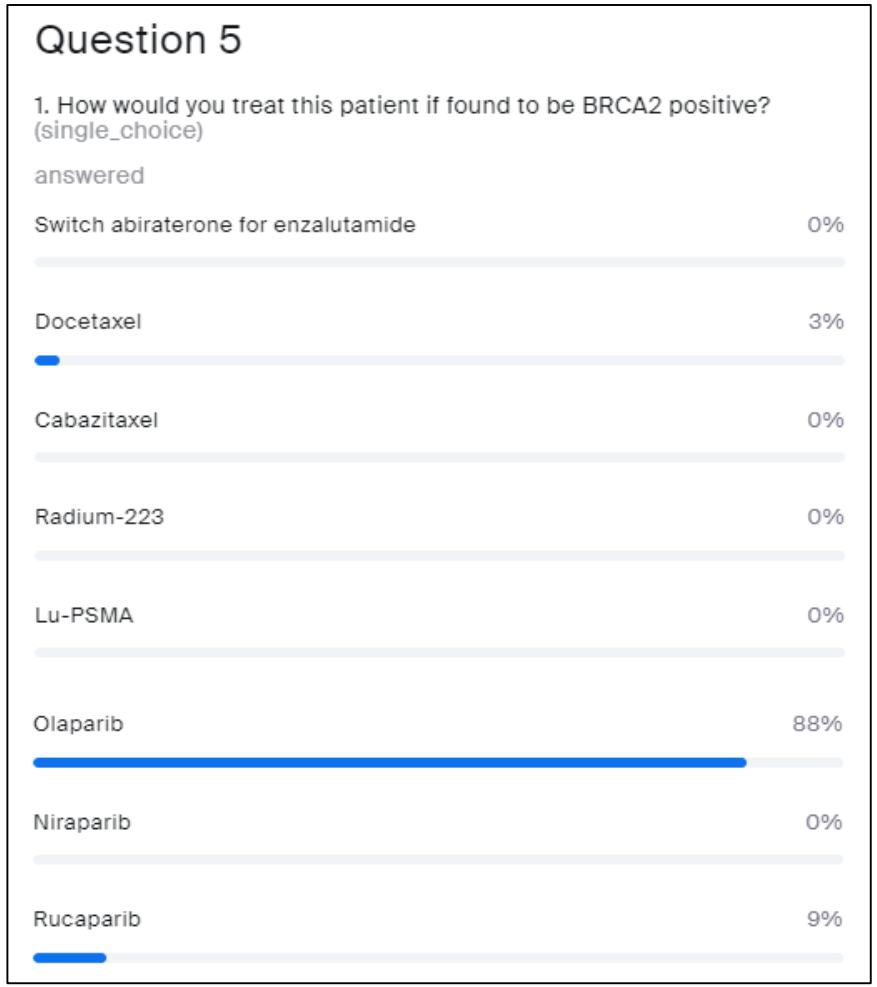
IF FOUND TO BE *BRCA2* POSITIVE

- Switch abiraterone for enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223
- Lu-PSMA
- Olaparib
- Niraparib
- Rucaparib



Lu-PSMA, lutetium prostate-specific membrane antigen

IS EARLIER BETTER WITH OLAPARIB?

PROfound SECONDARY ENDPOINT: SIGNIFICANT IMPROVEMENT IN OS IN mCRPC WITH *BRCA1/2* OR *ATM* MUTATIONS (COHORT A)

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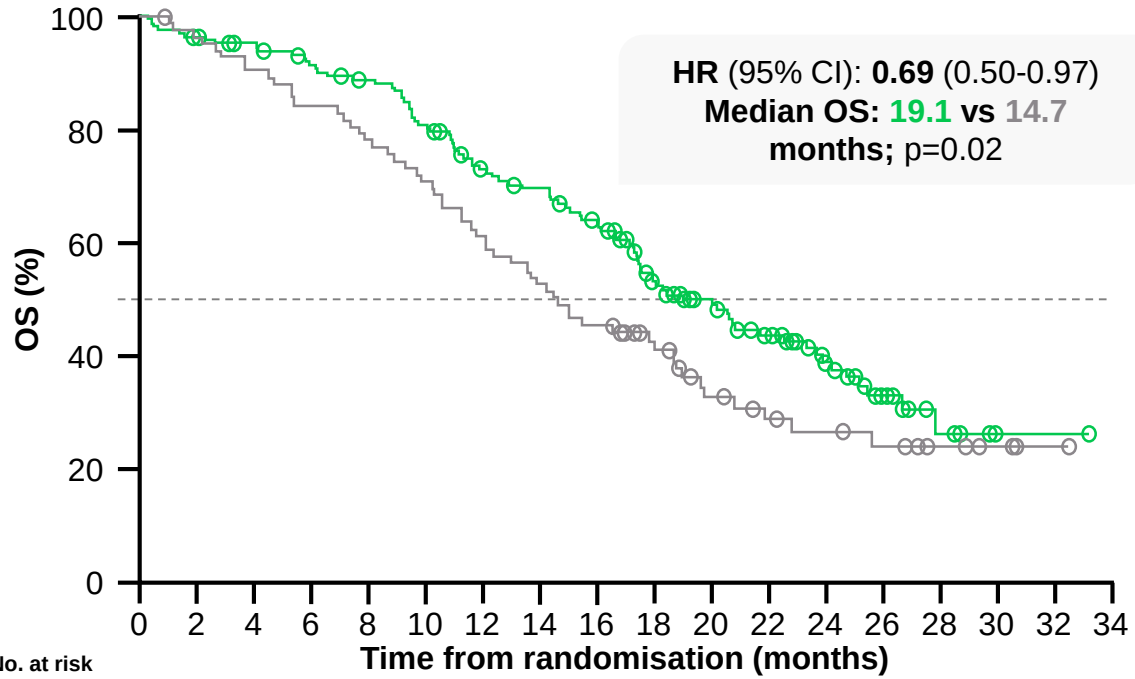
31% reduction in risk of death with olaparib vs physician's choice

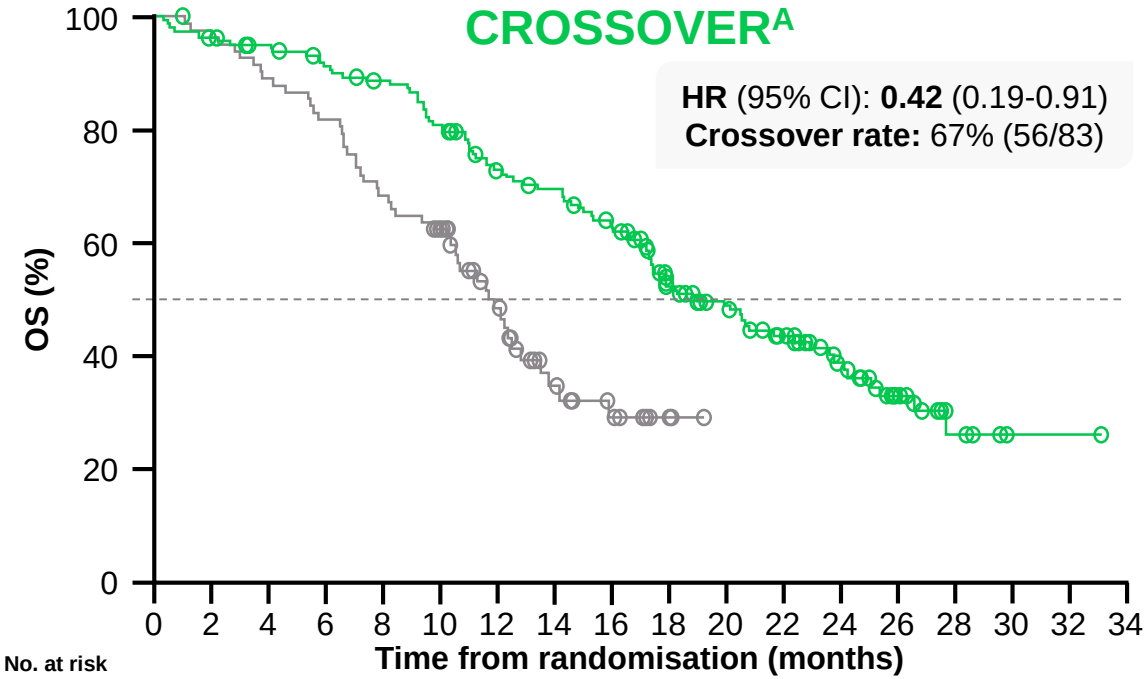
COHORT A



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

COHORT A WITH ADJUSTMENT FOR CROSSOVER[A]



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

Median follow-up duration for censored patients: Olaparib 21.9 months vs control 21.0 months

[a] Re-censored; conducted using rank-preserving structural failure time model to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy

CI, confidence interval; HR, hazard ratio; OS, overall survival

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

MEDIAN rPFS AND FINAL OS FOR THE *BRCA1* AND *BRCA2* SUBGROUP WAS LONGER WITH OLAPARIB VS PHYSICIAN'S CHOICE[1,2]

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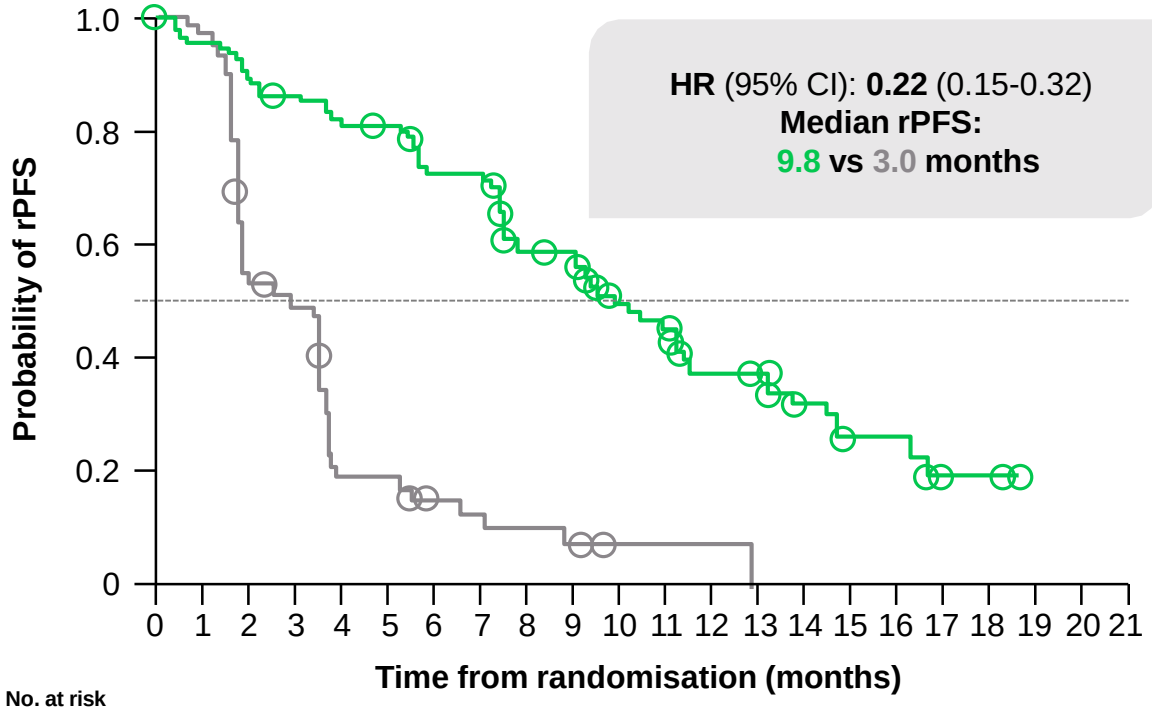
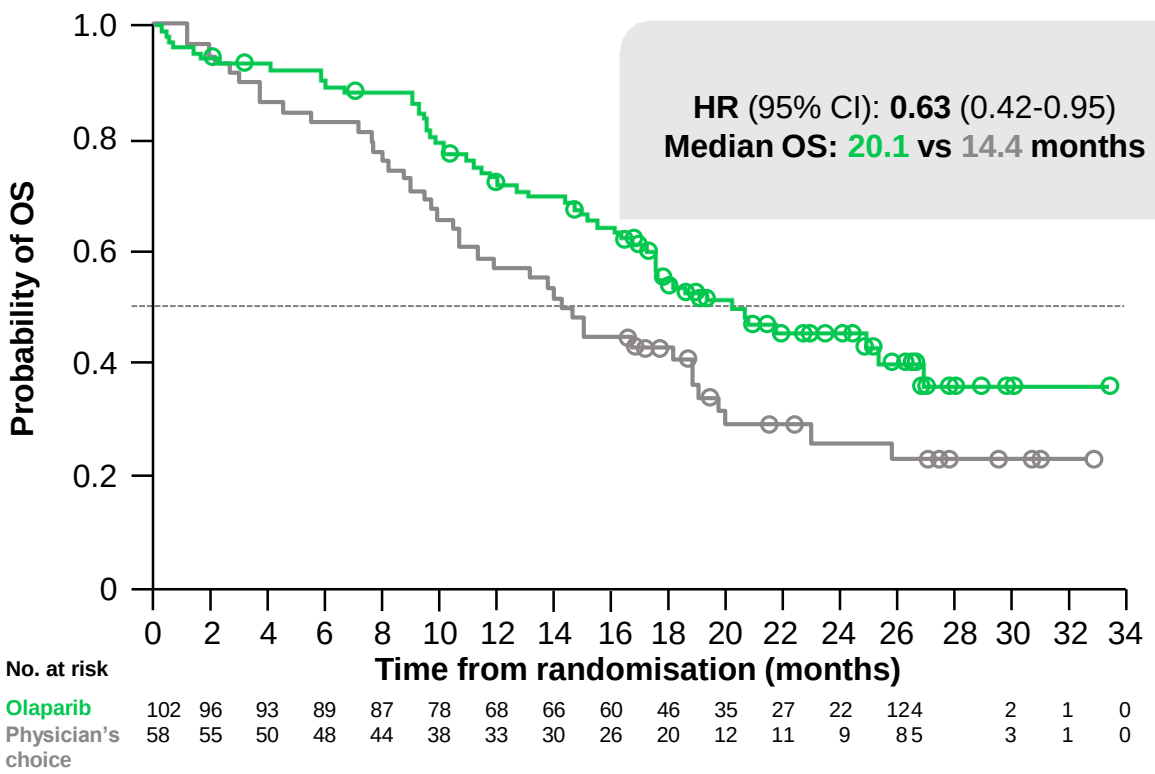
rPFS[1]



OS[2]



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102 (supplement); 2. de Bono J, et al. J Clin Oncol 2021; 39: suppl 6; abstr 126

IN WHAT SEQUENCE?

FOR FINAL OS, AN IMPROVED TREATMENT EFFECT WAS SEEN WITH OLAPARIB IN PATIENTS WITH *BRCA* MUTATION-POSITIVE mCRPC AND WHO HAD NOT RECEIVED A TAXANE[a]

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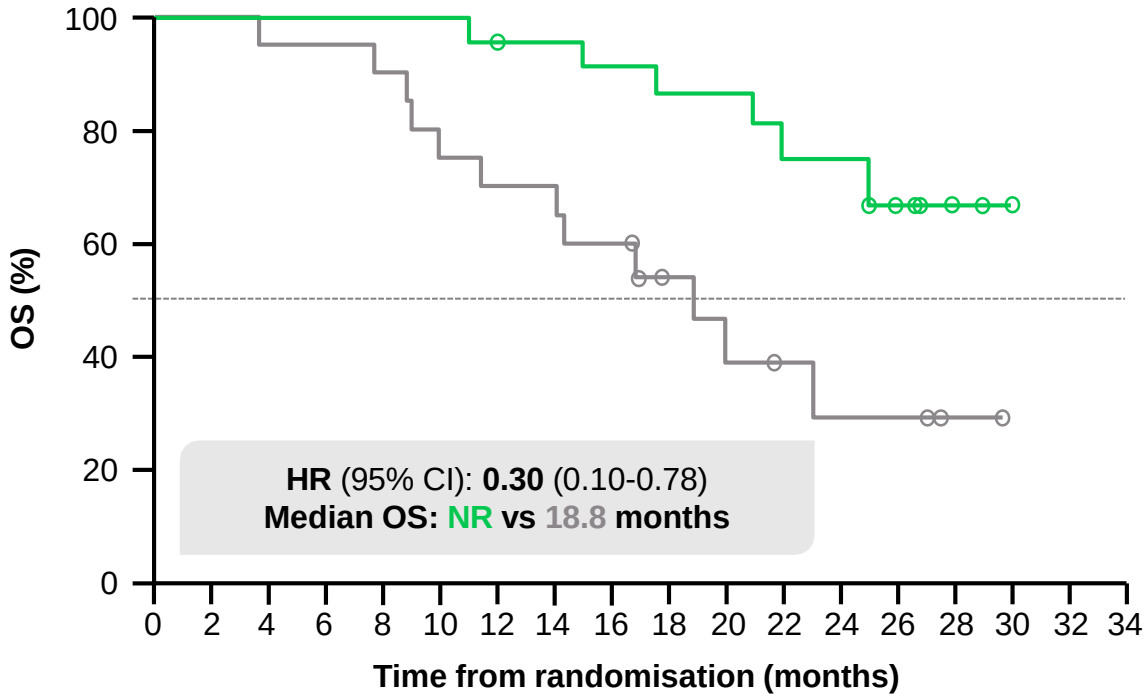
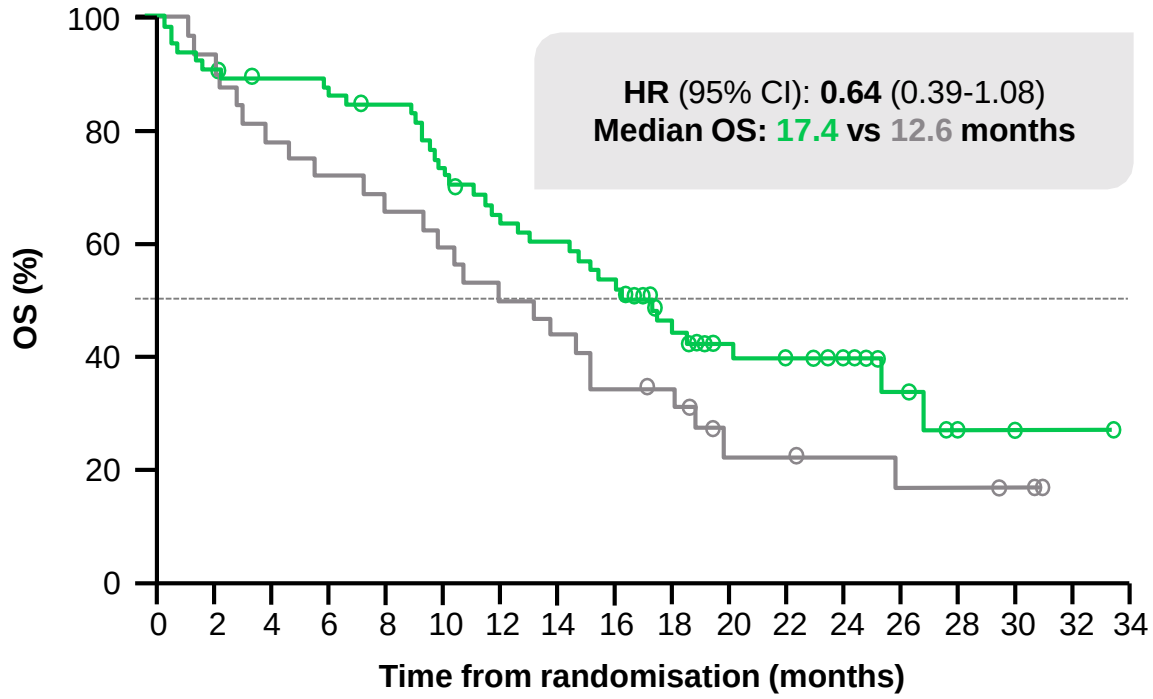
NO PRIOR TAXANE



No. at risk																		
Olaparib	23	23	23	23	23	23	21	21	20	18	16	10	10	5	2	0	0	0
Physician's choice	20	20	19	19	18	15	14	13	12	7	5	4	3	3	1	0	0	0

PRIOR TAXANE



No. at risk																		
Olaparib	66	60	57	55	53	46	38	36	32	23	16	15	11	6	2	2	1	0
Physician's choice	32	29	25	23	21	19	16	14	11	10	5	5	4	3	3	2	0	0

[a] Data are reported only for patients with alteration in a single gene

CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; OS, overall survival

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

WHAT ABOUT NHT TO NHT IN PATIENTS WITH mCRPC?

mCRPC, metastatic castration-resistant prostate cancer; NHT, new hormonal therapy

rPFS AND OS BENEFIT FOR OLAPARIB WAS SHOWN AGAINST BOTH ENZALUTAMIDE AND ABIRATERONE (COHORT A)

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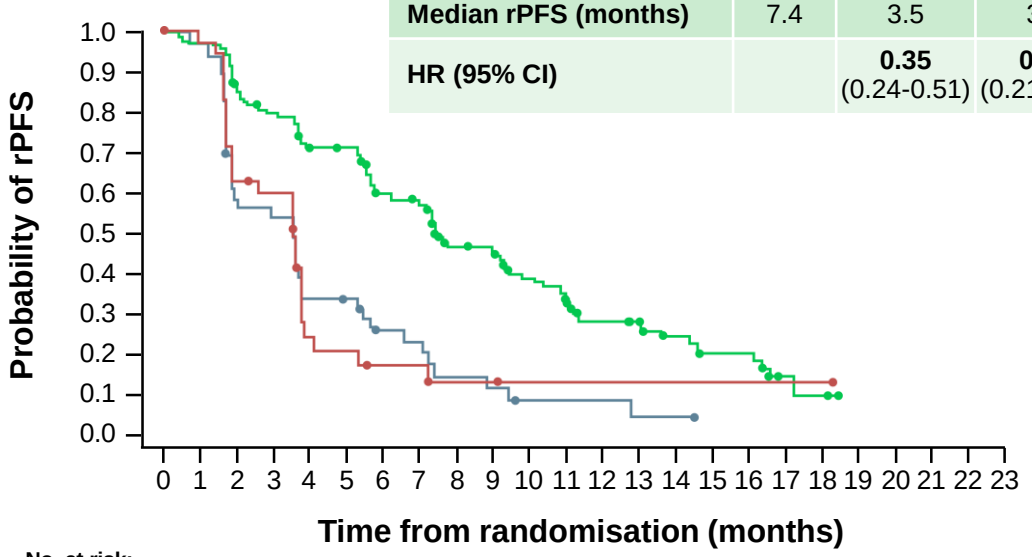
rPFS

	Ola	Abi	Enza
Median rPFS (months)	7.4	3.5	3.6
HR (95% CI)		**0.35** (0.24-0.51)	**0.33** (0.21-0.52)

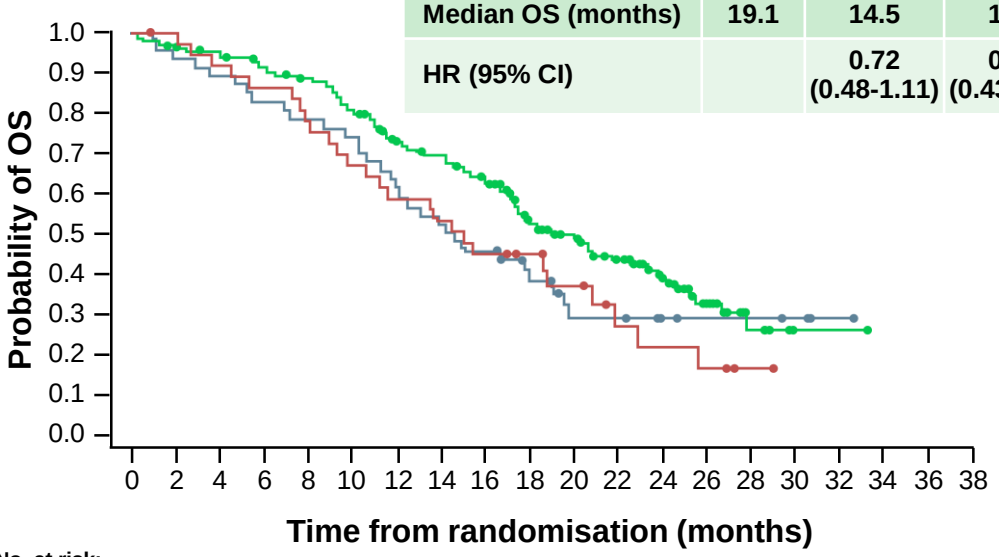


No. at risk:

Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0
Abiraterone	46	45	25	24	15	14	9	8	5	4	2	2	2	1	1	0	0	0	0	0	0
Enzalutamide	37	34	22	20	7	6	4	4	2	2	1	1	1	1	1	1	1	1	0	0	

OS

	Ola	Abi	Enza
Median OS (months)	19.1	14.5	14.9
HR (95% CI)		0.72 (0.48-1.11)	0.65 (0.43-1.03)



No. at risk:

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	16	6	2	1	0		
Abiraterone	46	43	41	38	36	34	29	24	21	15	9	9	7	6	5	3	1	0		
Enzalutamide	37	36	33	31	28	24	21	19	16	12	9	6	4	3	1	0	0	0		

Findings suggests that sequential use of an NHA may be of limited benefit

Abi, abiraterone; CI, confidence interval; Enza, enzalutamide; HR, hazard ratio; NHA, new hormonal agent; Ola, olaparib; OS, overall survival; rPFS, radiographic progression-free survival

Saad F, et al. AUA 2021: PD34-09 (oral presentation)

BEST PERCENTAGE CHANGE FROM BASELINE IN PSA (COHORT A)

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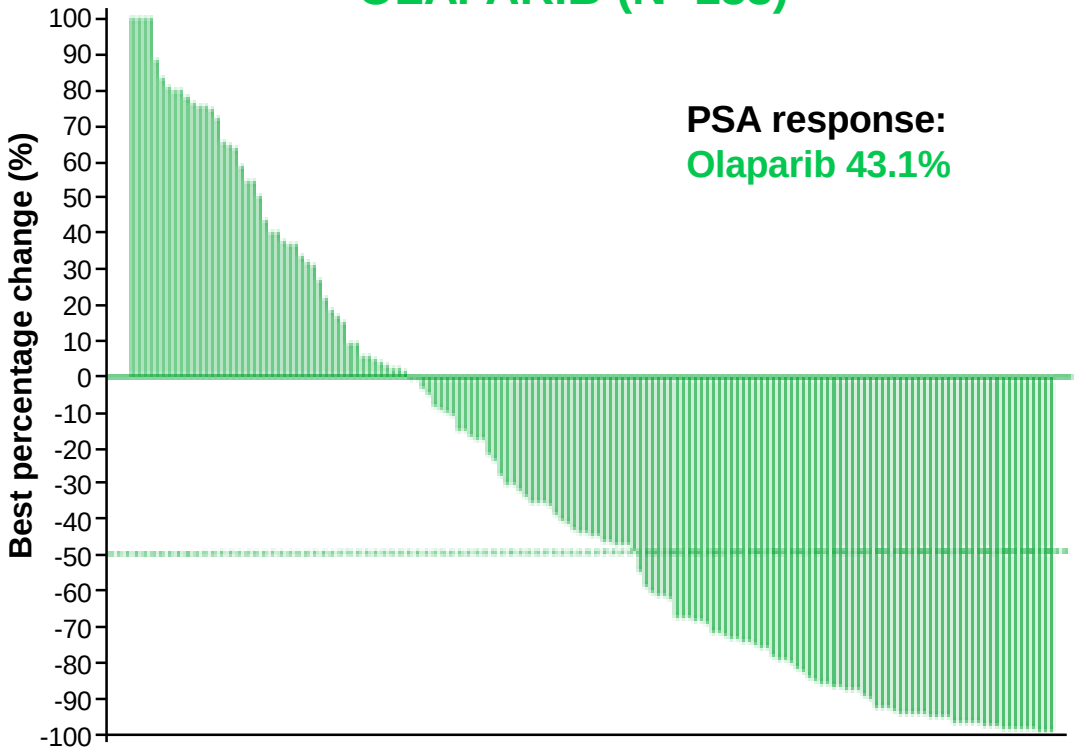
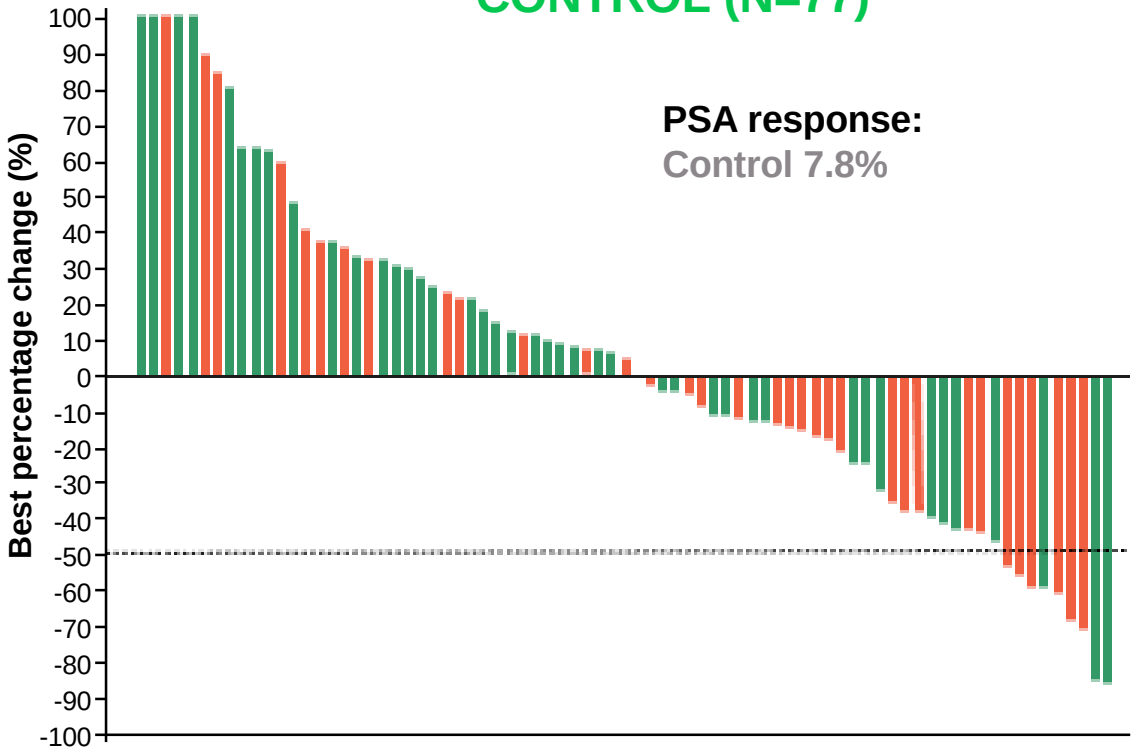
OLAPARIB (N=153)



CONTROL (N=77)



Best percentage change in PSA was not influenced by sequence of NHA

NHA, new hormonal agent; PSA, prostate-specific antigen

Saad F, et al. AUA 2021: PD34-09 (oral presentation)

HOW WOULD YOU TREAT THIS PATIENT?

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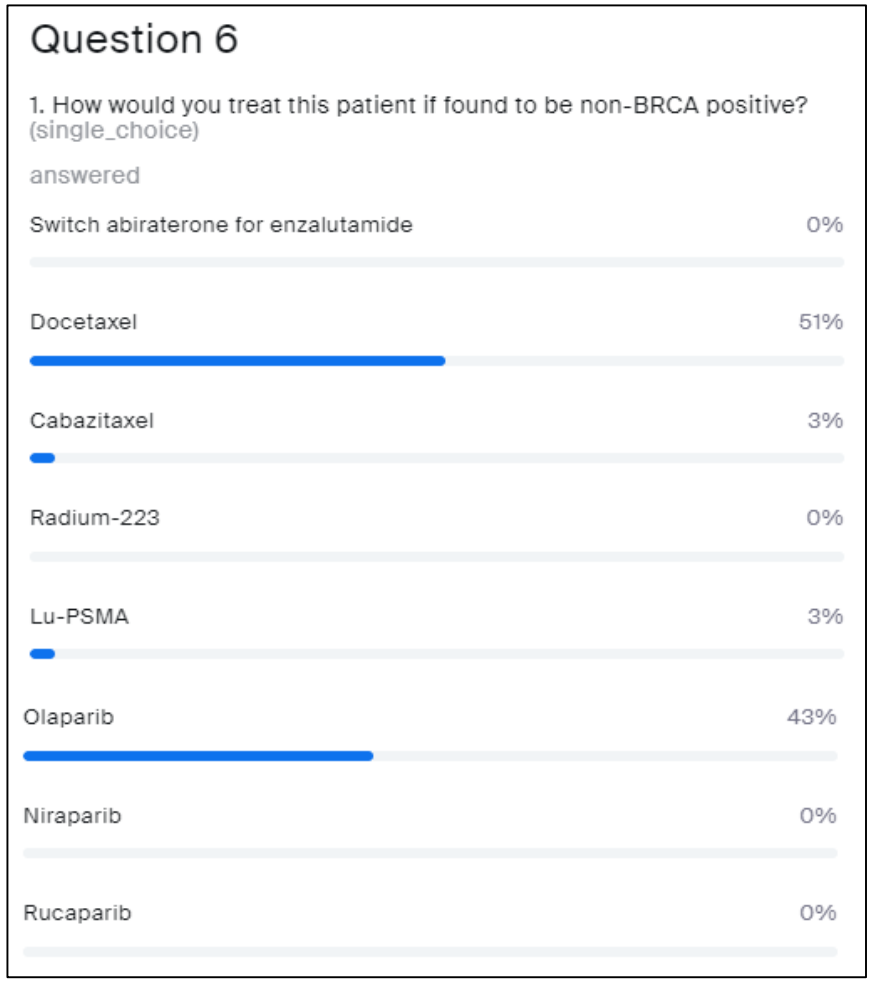
IF FOUND TO BE NON-*BRCA* POSITIVE

- Switch abiraterone for enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223
- Lu-PSMA
- Olaparib
- Niraparib
- Rucaparib



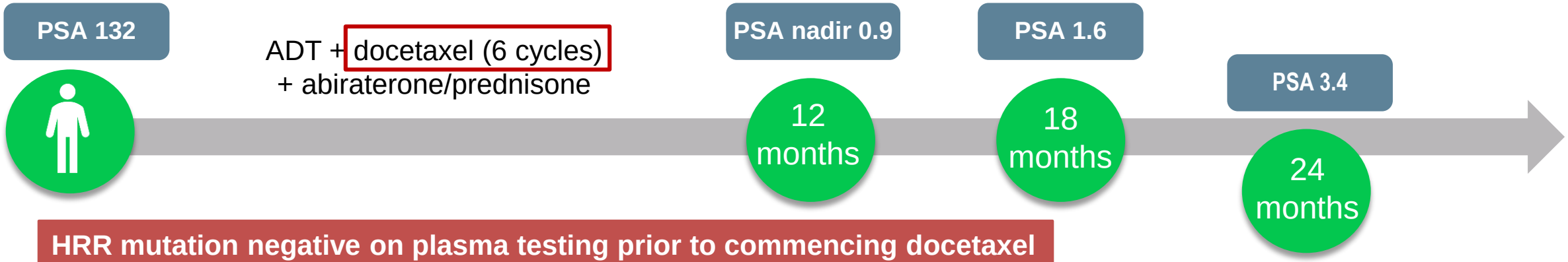
Lu-PSMA, lutetium prostate-specific membrane antigen

Patient: Age 68 years

Presents with: Moderate LUTS

Medical history:

- Well-controlled hypertension and angina; relieved by stent 4 years prior
- No known family history of cancer



HRR mutation negative on plasma testing prior to commencing docetaxel

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

Staging: T2b/T3 by DRE

Imaging:

- **Metastases in hip, lumbar spine and ribs**
- **Multiple retroperitoneal lymph nodes between 1 and 3 cm and 2 pulmonary nodules suspicious of metastases**

Slight discomfort in lumbar spine

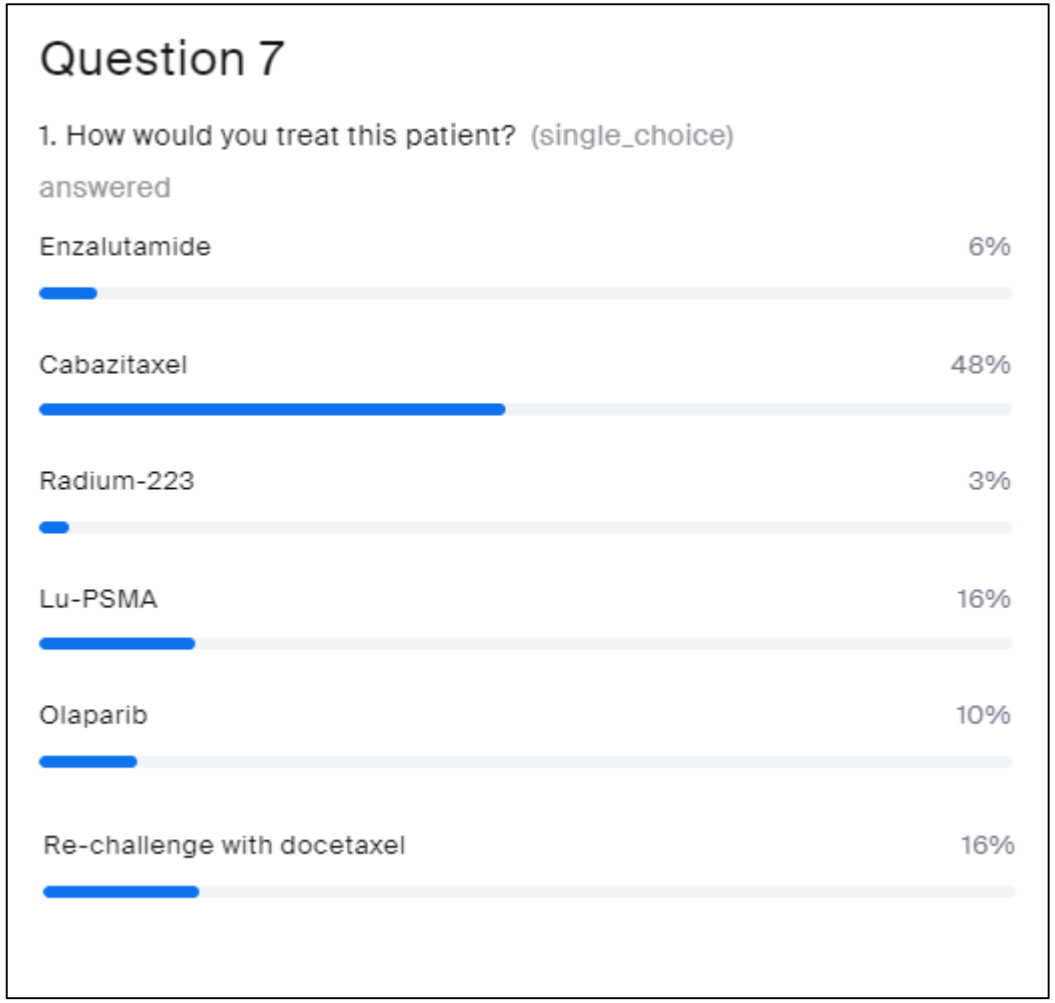
Imaging:

- **Progression of bone and soft-tissue metastases**
- **Haemoglobin: 10gm/dL**

ADT, androgen-deprivation therapy; DRE, digital rectal exam; HRR, homologous recombination repair; LUTS, lower urinary-tract symptoms; PSA, prostate-specific antigen

HOW WOULD YOU TREAT THIS PATIENT?

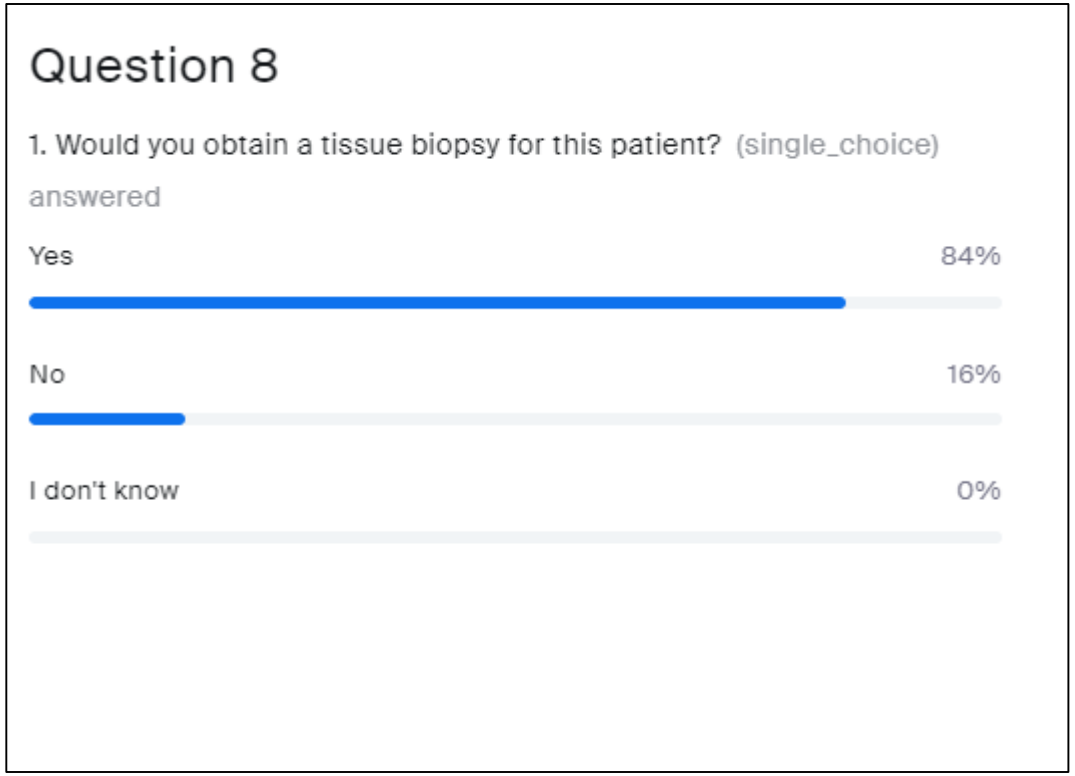
- Enzalutamide
- Cabazitaxel
- Radium-223
- Lu-PSMA
- Olaparib
- Re-challenge with docetaxel



Lu-PSMA, lutetium prostate-specific membrane antigen

WOULD YOU OBTAIN A TISSUE BIOPSY FOR THIS PATIENT?

- Yes
- No
- I don’t know



USE OF PARP INHIBITORS IN THE FIRST-LINE SETTING IN mCRPC

Assoc. Prof. Tanya Dorff, MD

Prof. Neeraj Agarwal, MD

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

CASE DISCUSSION

Patient: Age 68 years

Presents with: Moderate urinary symptoms

Medical history:

- Well-controlled hypertension and angina; relieved by stent 4 years prior
- No known family history of cancer

PSA: Nadir 0.1 rising to 5.0

Imaging: 2 new bone lesions (on bone scan)

PSA, prostate-specific antigen

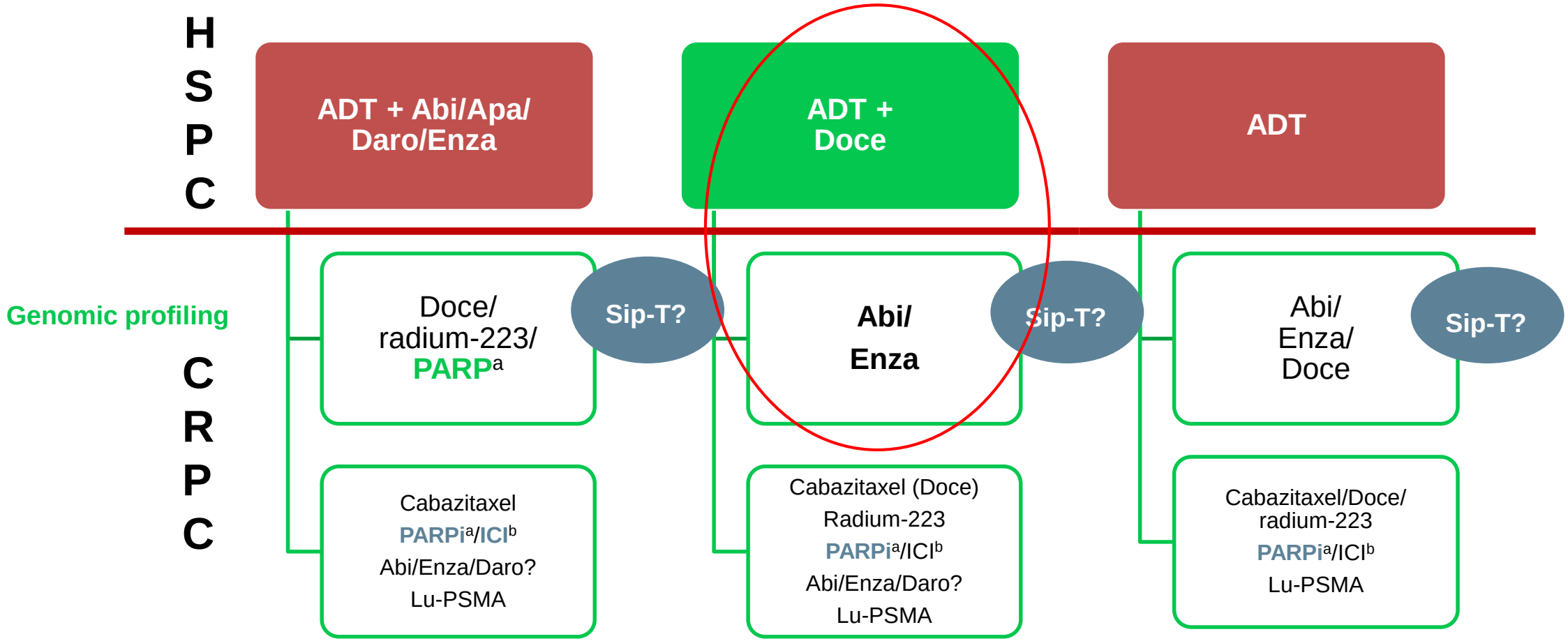
“LIFE EXTENDING THERAPIES” FOR mCRPC

- **Abiraterone**
  - COU301: Median OS 14.8 months vs 10.9 months for placebo (post taxane)[1]
  - COU 302: PFS 8.3 months → 16.5 months (pre taxane)[2]
- **Enzalutamide**
  - AFFIRM: Median OS 18.4 months vs 13.6 for placebo[3] (post taxane)
  - PREVAIL: Median OS 32.4 months vs 30.2[4] pre taxane (17-month delay in chemotherapy)
- **Sipuleucel-T**
  - IMPACT: Median OS 23.2 months[5] (vs 18.9 months for placebo)
- **Cabazitaxel**
  - Median OS 15.1 months vs 12.7 months mitoxantrone (post taxane)[6]
- **Radium-223**
  - ALSYMPCA: Median OS 14.9 months (vs 11.3 months for placebo)[7]

mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival

1. de Bono J, et al. N Engl J Med. 2011;364:1995-2005; 2. Rahtkopf D, et al. J Clin Oncol. 2012;31 Suppl: Abstract 5; 3. Scher HI, et al, N Engl J Med. 2012;367:1187-97;
4. Beer TM, et al. J Clin Oncol. 2014;32 Suppl: LBA1; 5. Higano CS, et al. Cancer. 2009;115:3670-9; 6. de Bono JS, et al. Lancet. 2010;376:1147-54;
7. Parker C, et al. N Engl J Med. 2013;369:213-2

CURRENT PARADIGMS FOR METASTATIC PROSTATE CANCER

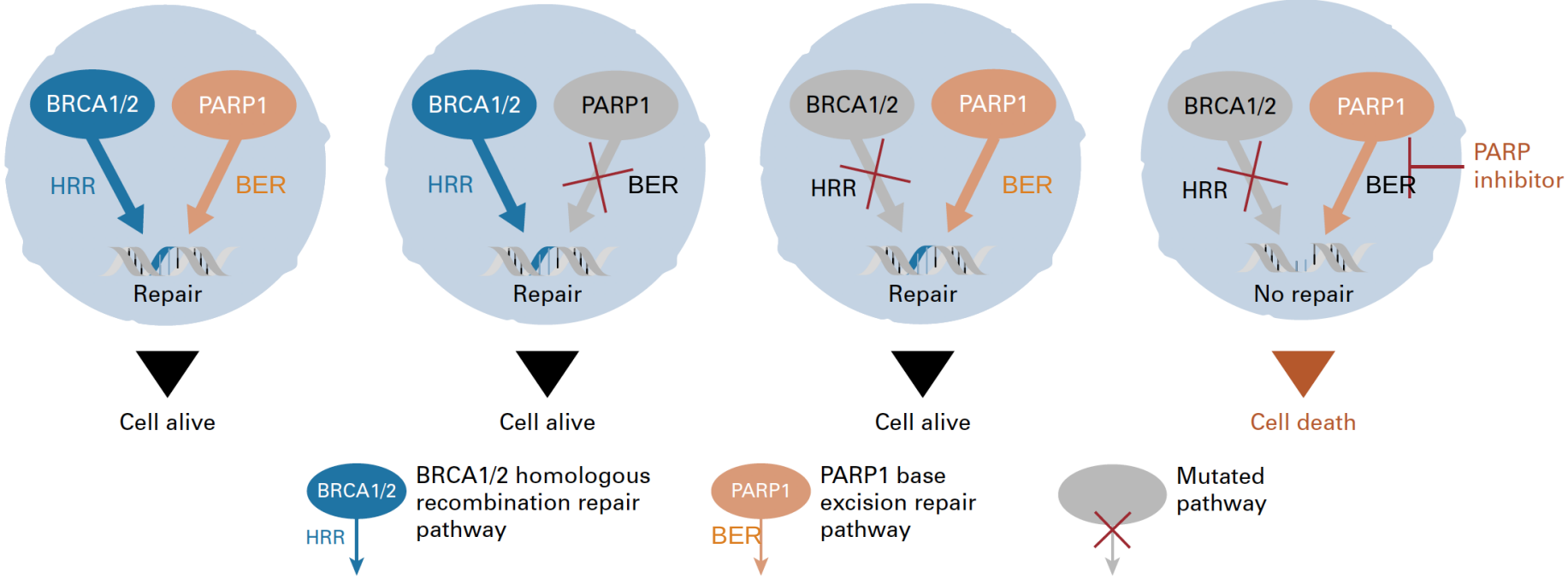


[a] If DNA repair mutation identified; [b] i.e. Pembrolizumab if microsatellite-instable high; Abi, abiraterone; ADT, androgen-deprivation therapy; Apa, apalutamide; CRPC, castration-resistant prostate cancer; Daro, darolutamide; Enza, enzalutamide; HSPC, hormone-sensitive prostate cancer; ICI, immune checkpoint inhibitor; Lu-PSMA, lutetium prostate-specific membrane antigen; Sip-T, sipuleucel-T; PARP, poly-ADP ribose polymerase

Dorff T, personal communication

PARP INHIBITORS: "SYNTHETIC LETHALITY" IN CANCER

- ***BRCA*: "copy editor"; HRR**
- **PARP: "spell check"; BER**

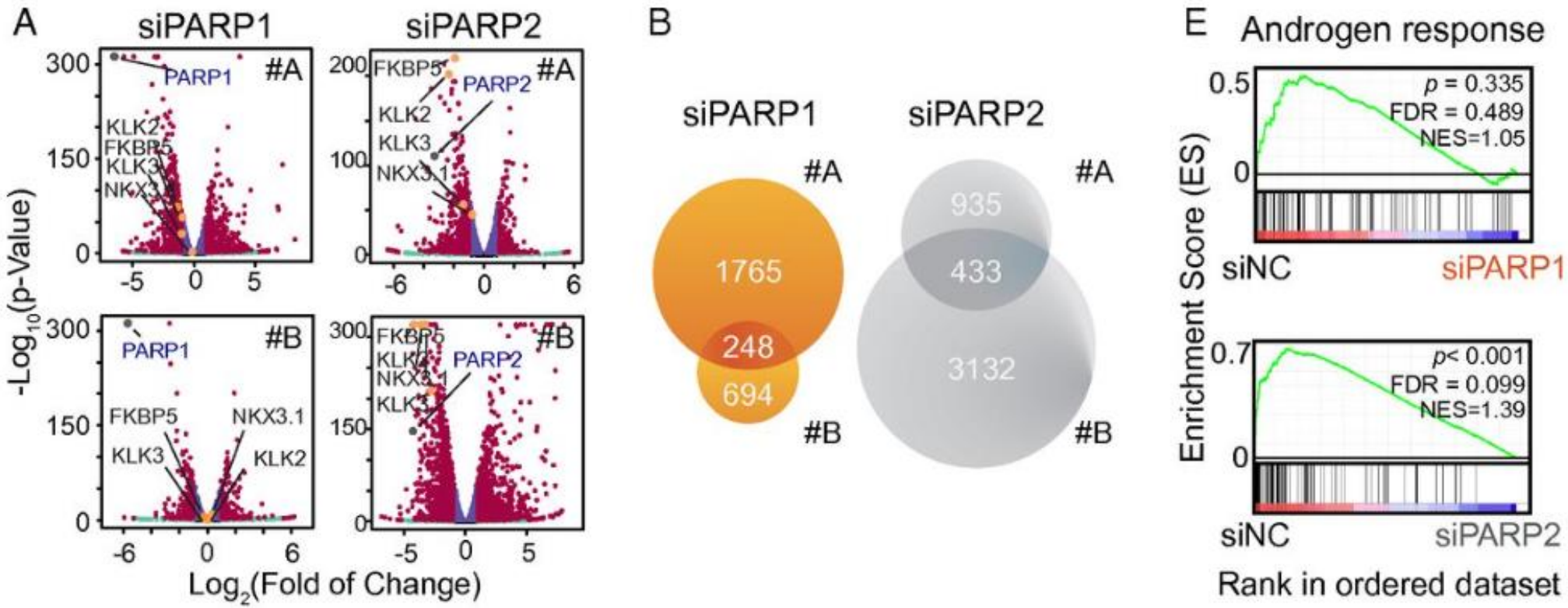


PARP is required for single-strand break repair (e.g. via BER)
MOA – inhibiting SSB/BER is synthetic lethal with HRD

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;37:2257-69; Banerjee S, et al. Nat Rev Clin Oncol. 2010;7:508-19

PARP ALSO IMPACTS TRANSCRIPTION OF AR-REGULATED GENES

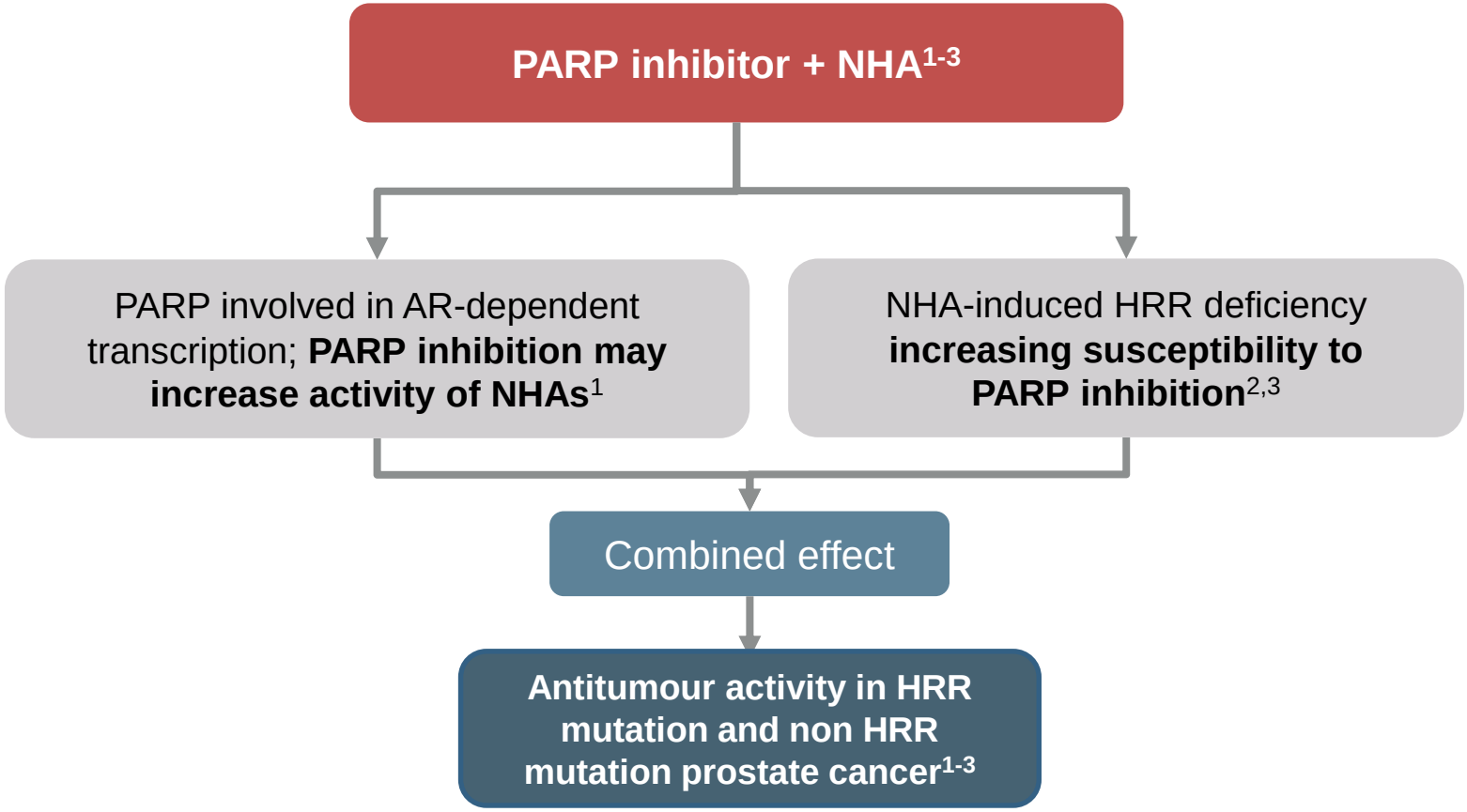


AR, androgen receptor; (si) PARP, (small interfere RNA)-poly-ADP ribose polymerase

Reproduced from: Gui B, et al. Proc Natl Acad Sci U S A. 2019;116:14573-82

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



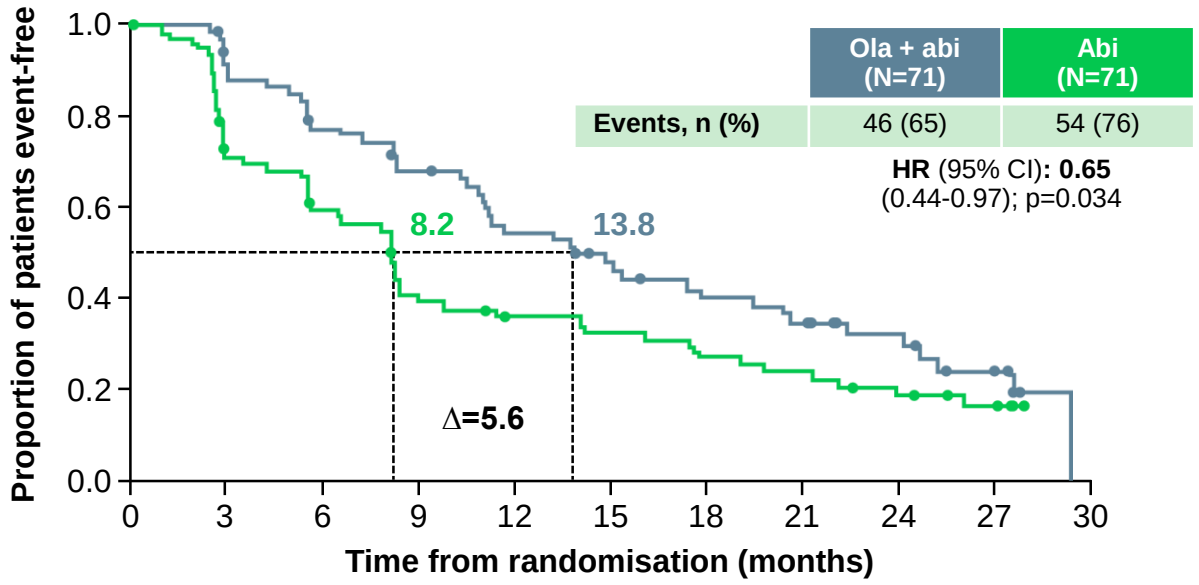
AR, androgen receptor; HRR, homologous recombination repair; NHA, novel hormonal agent; PARP, poly-ADP ribose polymerase

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)

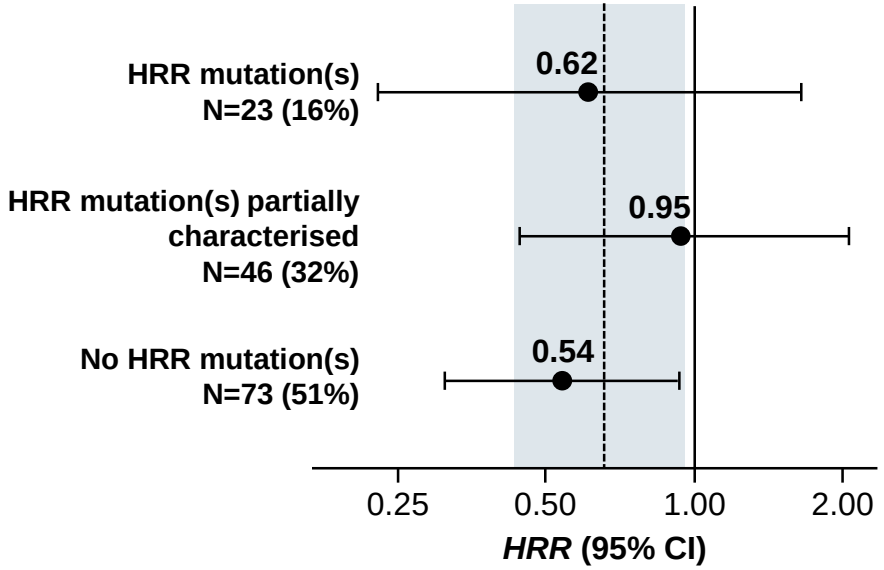
OLAPARIB AND ABIRATERONE: A RANDOMISED PHASE 2 STUDY

- Patients with mCRPC, unselected by HRR mutation status, with prior docetaxel treatment
- Randomised 1:1 to full dose of olaparib + abiraterone vs placebo + abiraterone[a]
- Statistically significant improvement in rPFS with olaparib + abiraterone, irrespective of *HRR* mutation status

INVESTIGATOR-ASSESSED rPFS



rPFS BY *HRR* MUTATION SUBGROUP[b]



[a] Olaparib 300 mg BID, abiraterone 1,000 mg QD and all patients also received prednisone/prednisolone 5 mg BID

[b] Dashed line and shaded area show HR and 95% CI, respectively, for the intent to treat population

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

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

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

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

Randomise 1:1

Olaparib 300 mg BID[a] + abiraterone 1,000 mg Qd[b] (n=399)
Full dose of abiraterone and olaparib used

Placebo + abiraterone 1,000 mg QD[b] (n=397)
Full dose of abiraterone used

Primary endpoint:
- rPFS by investigator assessment

Key secondary endpoint:
- OS (alpha control)

Additional endpoints:
- TFST, ORR, PFS2
- HRR gene mutation[c] status (by tissue and ctDNA 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

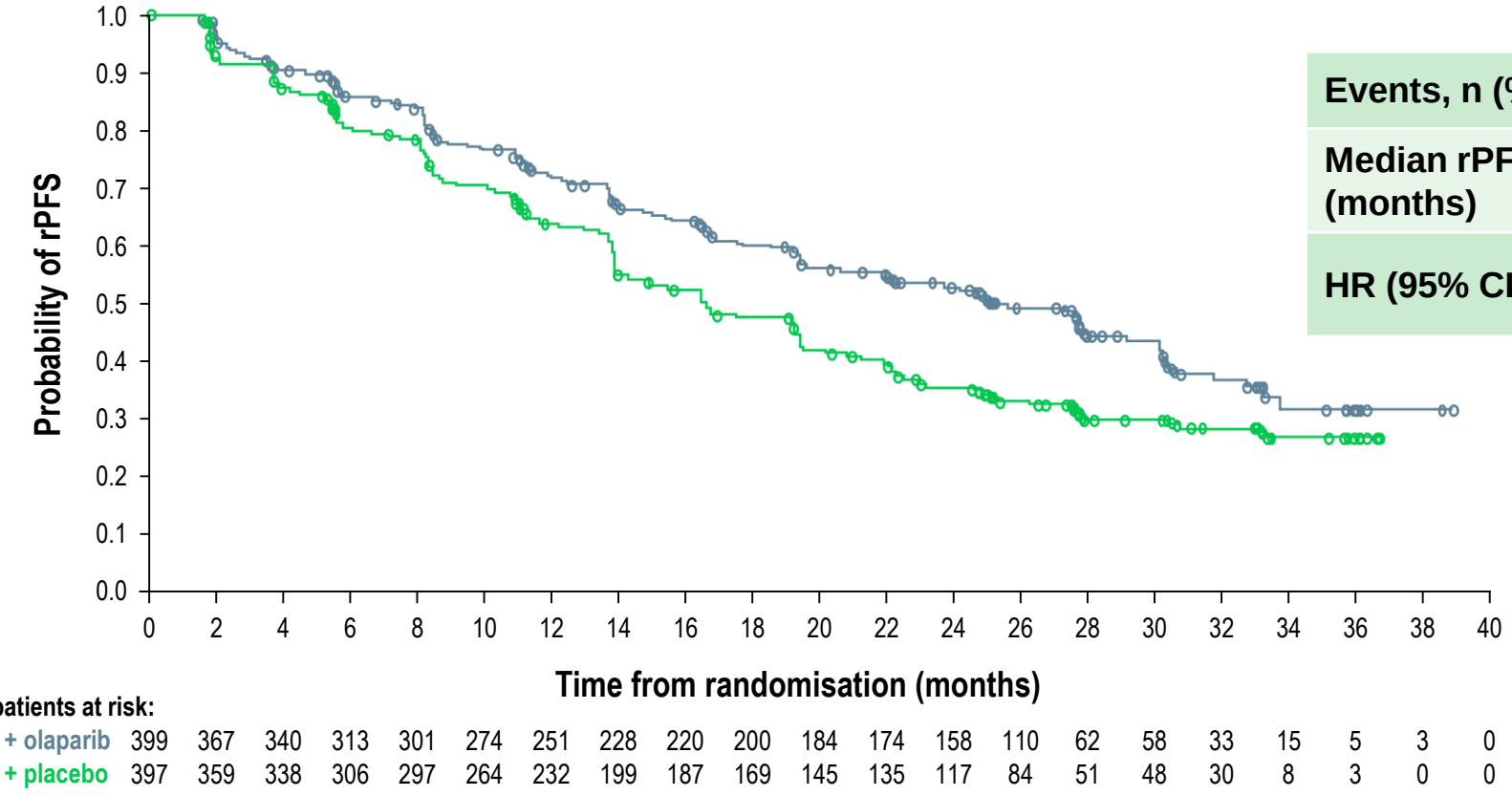
[a] Full dose of olaparib used; [b] abiraterone used in combination with prednisone or prednisolone 5 mg BID; [c] HRR mutation, including 14-gene panel, using the FoundationOne®CDx test and FoundationOne®Liquid CDx test

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



	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]	

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

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

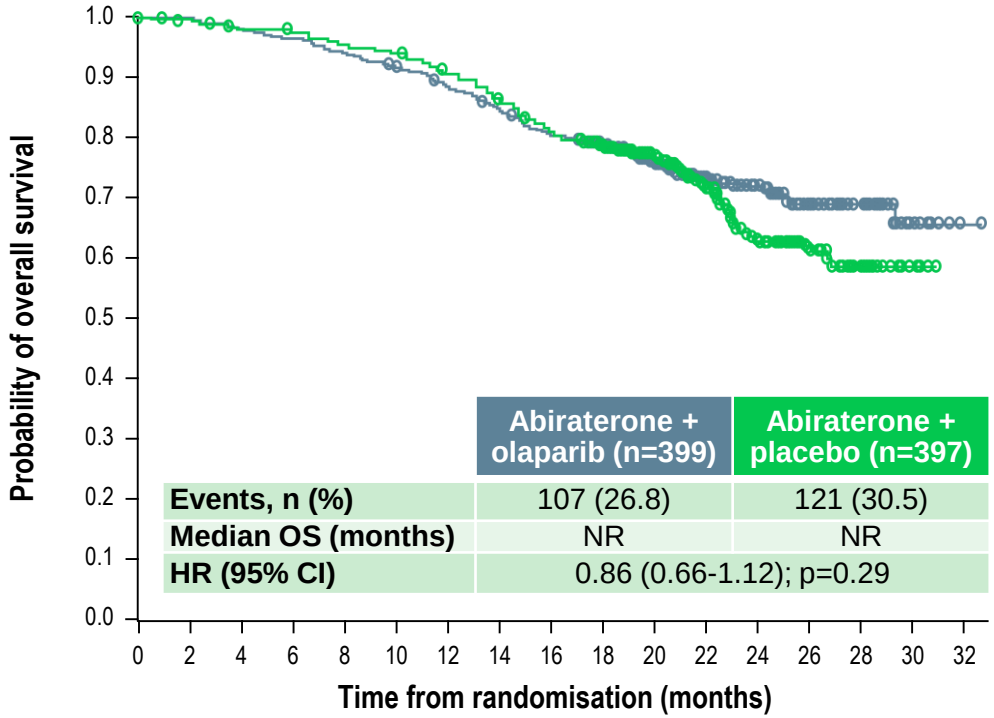
Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 oral presentation)

PROpel KEY SECONDARY ENDPOINT: OS IN THE ITT POPULATION

GU connect® POWERED BY COR2ED

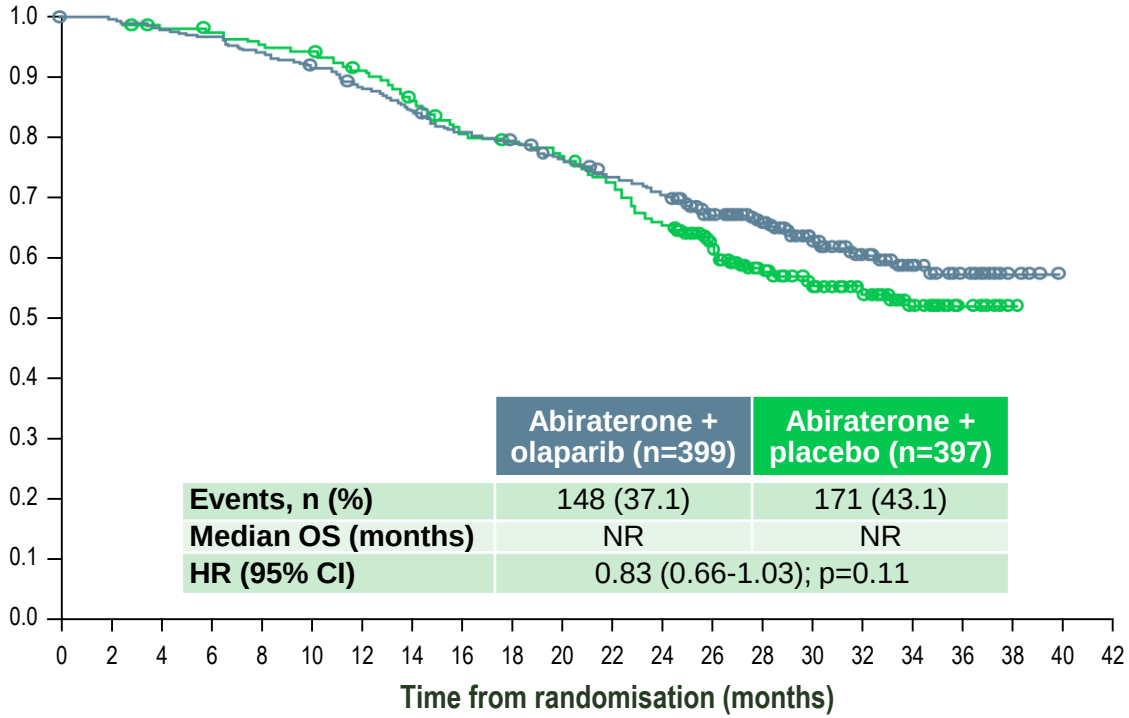
AT DCO2, THERE WAS A CONTINUED TREND TOWARDS IMPROVED OS WITH ABIRATERONE + OLAPARIB, WITH KM CURVES SHOWING CLEAR SEPARATION BETWEEN THE ARMS AFTER ~22 MONTHS BEFORE EXTENSIVE CENSORING WAS OBSERVED

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	

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	

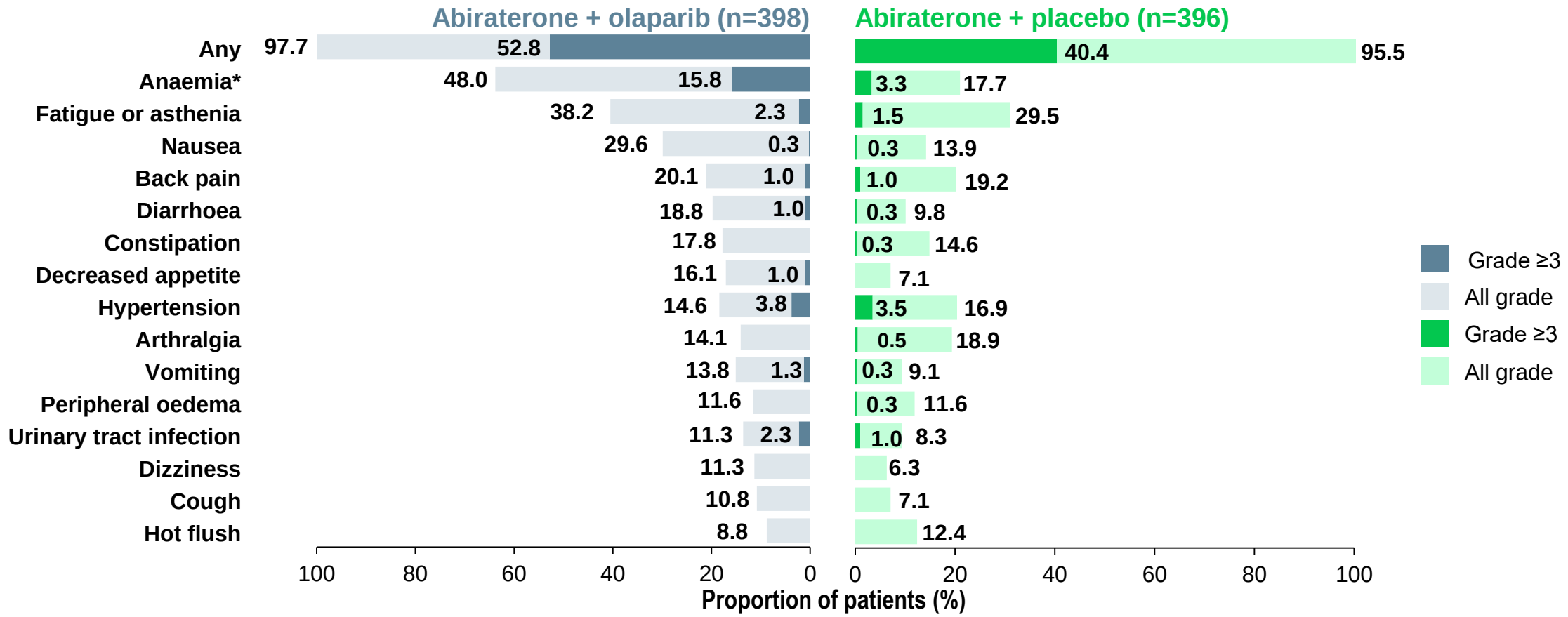
Number of patients at risk:

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

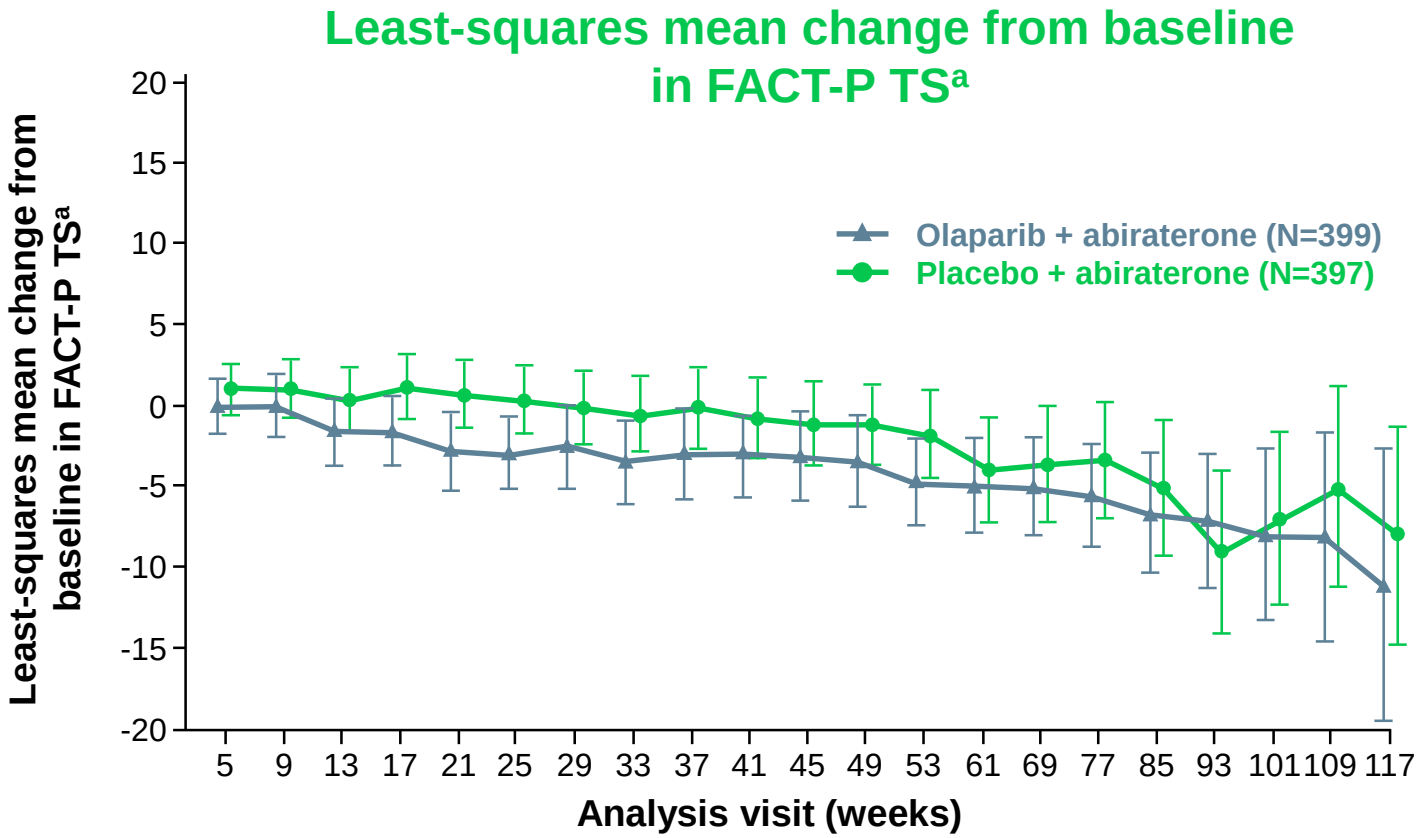
* Anaemia category includes anaemia, decreased haemoglobin level, decreased red-cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia

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

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 resulted in no detriment to quality of life, allowing most patients stay on therapy

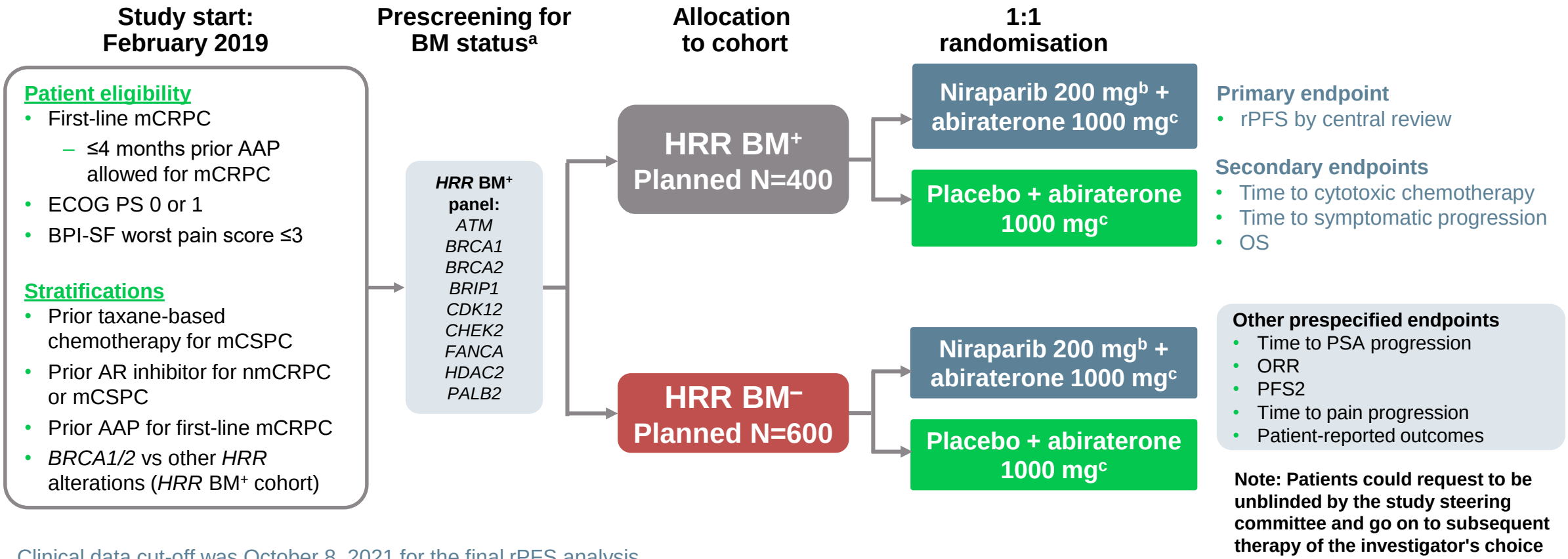
[a] Plot includes 95% confidence limits. FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156
A clinically meaningful change in FACT-P total score is 10

FACT-P TS, Functional Assessment of Cancer Therapy-Prostate Total Score

Saad F, et al. J Clin Oncol. 2022;40 Suppl: Abstract 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

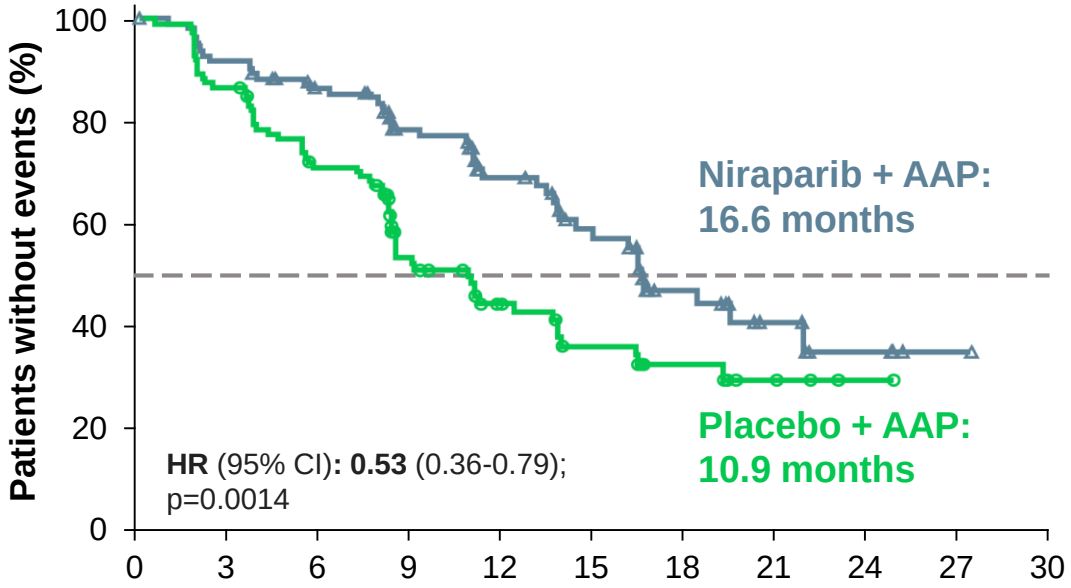
[c] Abiraterone given in combination with prednisone or prednisolone 5 mg BID

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: PRIMARY ENDPOINT

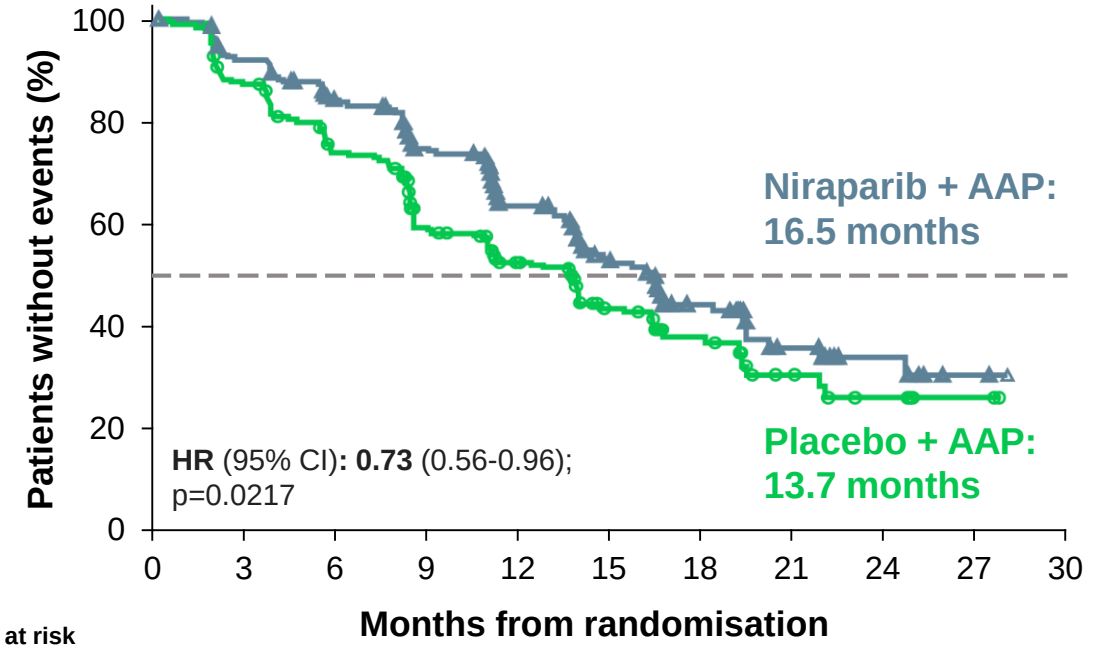
BRCA1/2 MUTATION-POSITIVE rPFS ASSESSED BY CENTRAL REVIEW



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

Median follow-up: 16.7 months

ALL HRR BM+ PATIENTS rPFS ASSESSED BY CENTRAL REVIEW



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

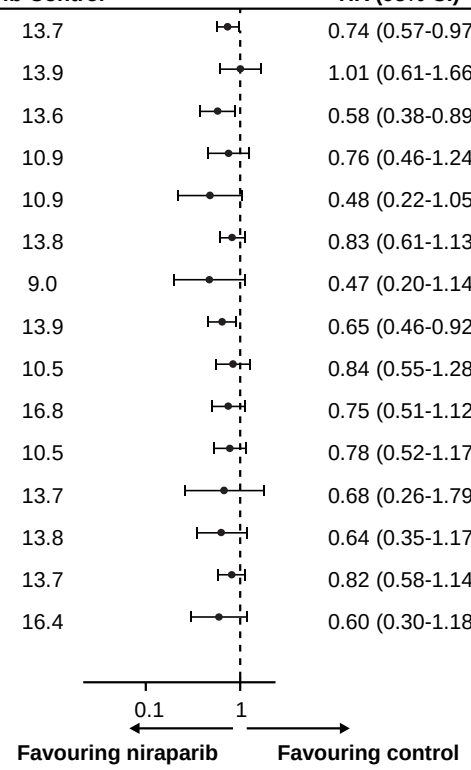
Median follow-up: 18.6 months

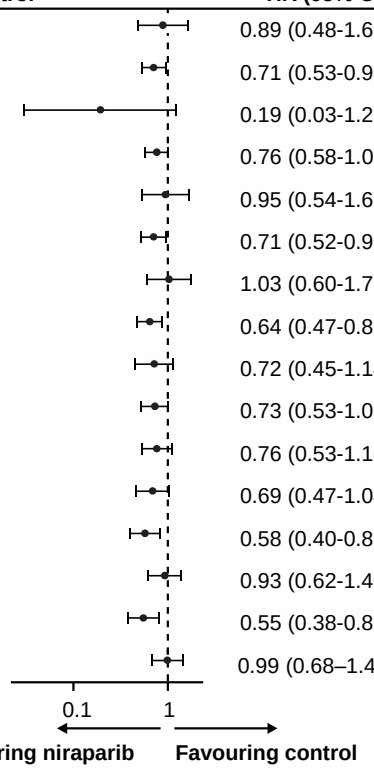
AAP, abiraterone acetate and prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; rPFS, radiographic progression-free survival

Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

MAGNITUDE ALL HRR BM+: PRESPECIFIED SUBGROUP ANALYSIS OF rPFS

Variable	Subgroup	Median (months) Niraparib	Median (months) Control	HR (95% CI)	Events/N Niraparib	Events/N Control
All HRR mutation-positive 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 metastases 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





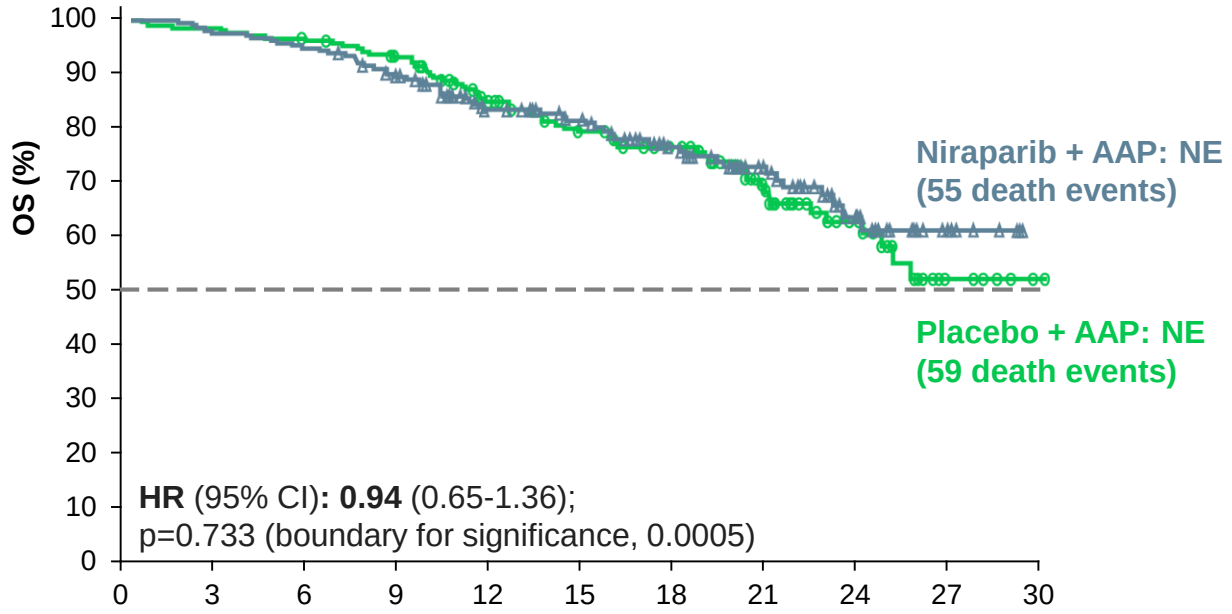
[a] Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide

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

AAP, abiraterone acetate and 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: Abstract 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											
Niraparib + AAP	212	207	200	180	146	110	84	52	20	4	0
Placebo + 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 OS data are immature

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

Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

MAGNITUDE HRR BM+: TEAEs CONSISTENT WITH THE KNOWN SAFETY PROFILE FOR EACH THERAPY

GU connect® POWERED BY COR2ED

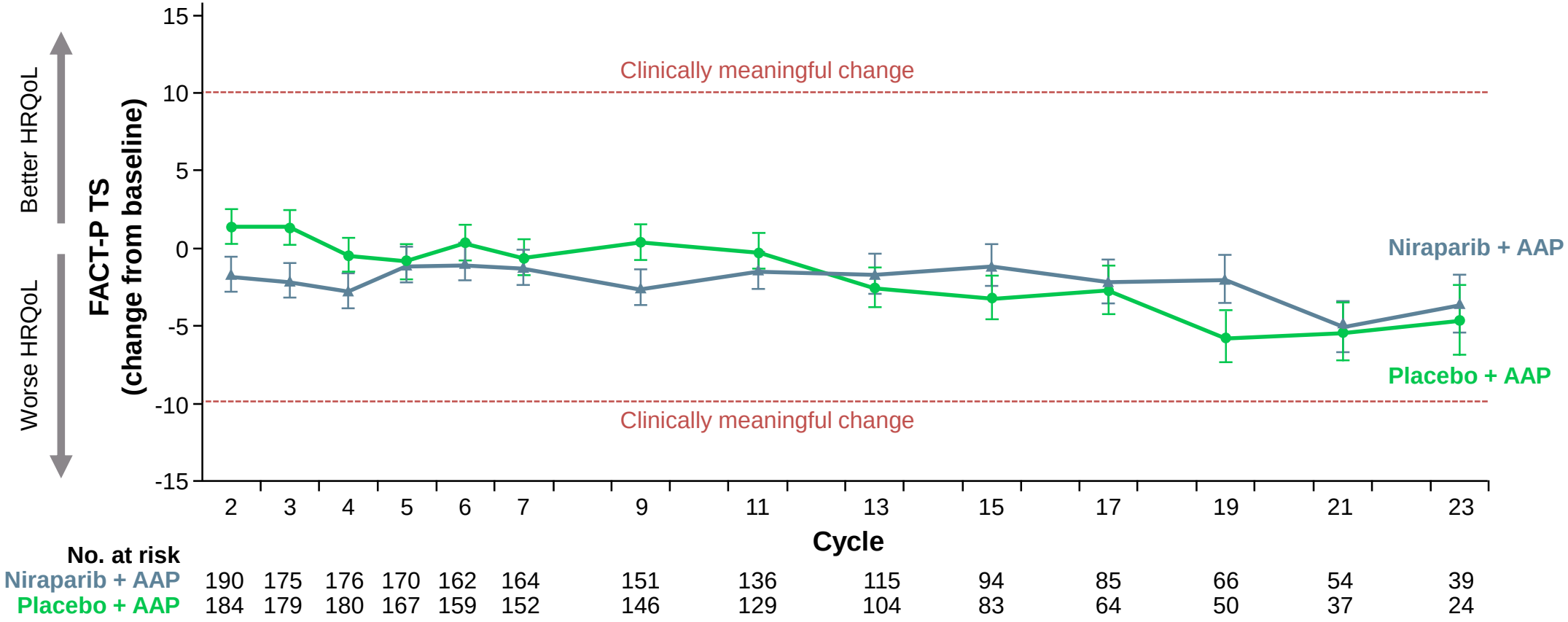
TEAEs occurring at >20% in the niraparib arm or otherwise of clinical interest, n (%)		Niraparib + AAP (n=212)		Placebo + AAP (n=211)	
		All grades	Grade ≥3	All grades	Grade ≥3
Haematologic	Anaemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopaenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropenia	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 and prednisone/prednisolone; BM, biomarker; HRR, homologous recombination repair; TEAE, treatment-emergent adverse event

Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

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



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

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

Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

DESIGN AND BASELINE COMPARISON OF PROpel AND MAGNITUDE TRIALS

	PROpel[1] (N=796)	MAGNITUDE[2] (N=423)
Primary endpoint	rPFS (investigator view)	rPFS (central view)
Prior NHA in mCSPC, n (%)	Allowed as long as stopped at least 12 months before enrollment (abiraterone not allowed) 1 (0.3)	13 (3.0)[a]
Prior docetaxel in mCSPC, n (%)	179 (22.5)	85 (20)[a]
HRR status required at randomisation	No	Yes
HRR analysis	Tissue or ctDNA	Tissue or ctDNA
HRR mutation status, n (%)		
HRR mutation positive	226 (28.4)	423 (100)
Non-HRR mutation	552 (69.3)	-
HRR mutation-status unknown	18 (2.3)	-
***BRCA* mutation prevalence, n (%)**		
BRCA1	12 (1.5)	16 (3.8)
BRCA2	73 (9.2)	174 (41)

[a] Includes prior therapy for nmCRPC/mCSPC

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

ctDNA, circulating tumour DNA; HRR, homologous recombination repair; mCSPC, metastatic castration sensitive prostate cancer; NHA, new hormonal agent; rPFS, radiographic progression free survival

1. Saad F, et al. Journal of Clinical Oncology2022; 40 Suppl: Abstract 11 (ASCO GU 2022 oral presentation); 2. Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

RESULTS COMPARISON OF PROpel AND MAGNITUDE TRIALS

	PROpel (N=796)	MAGNITUDE (N=423)
rPFS		
All comers	+ (HR 0.66)	Not reported
HRR mutation negative	+ (HR 0.76)	No benefit
HRR mutation positive	+ (HR 0.50)	+ (HR 0.73)
BRCA1/2	+ (HR 0.23)	+ (HR 0.53)
OS	Immature	Immature

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

HRR, homologous recombination repair; rPFS, radiographic progression free survival

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: Abstract 12 (ASCO GU 2022 oral presentation); 4. Saad F, et al. Annals of Oncology 2022; 33 (suppl_7): S616-S652

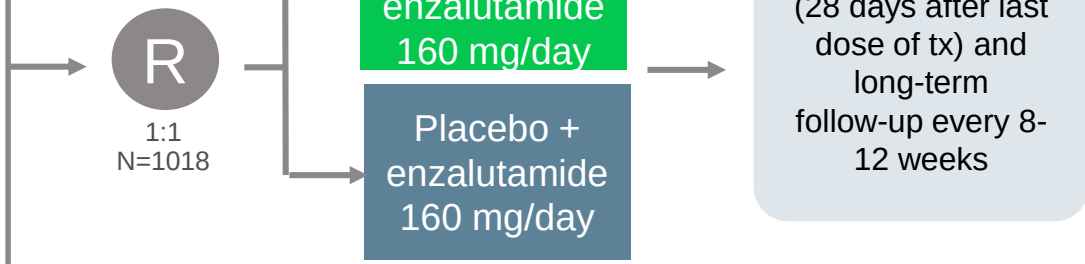
TALAPRO-2: FIRST-LINE TALAZOPARIB + ENZALUTAMIDE IN mCRPC

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

GU connect® POWERED BY COR2ED

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

PATIENT CASE DISCUSSION

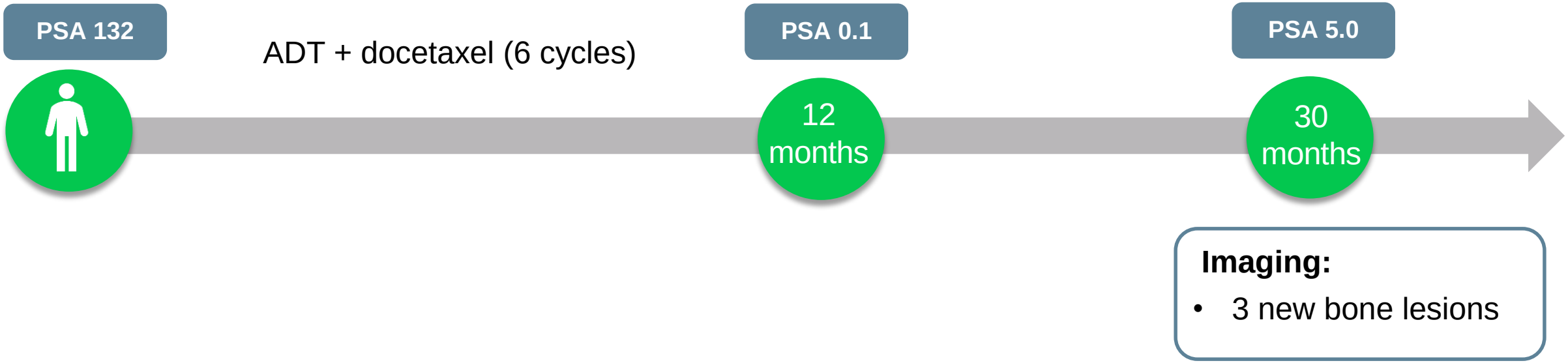
CASE DISCUSSION

Patient: Age 65 years

Presents with: mCRPC with rising PSA

Medical history:

- *de novo* (synchronous), high volume mCSPC (Gleason 5+4) treated with ADT + upfront docetaxel (six cycles) for 30 months



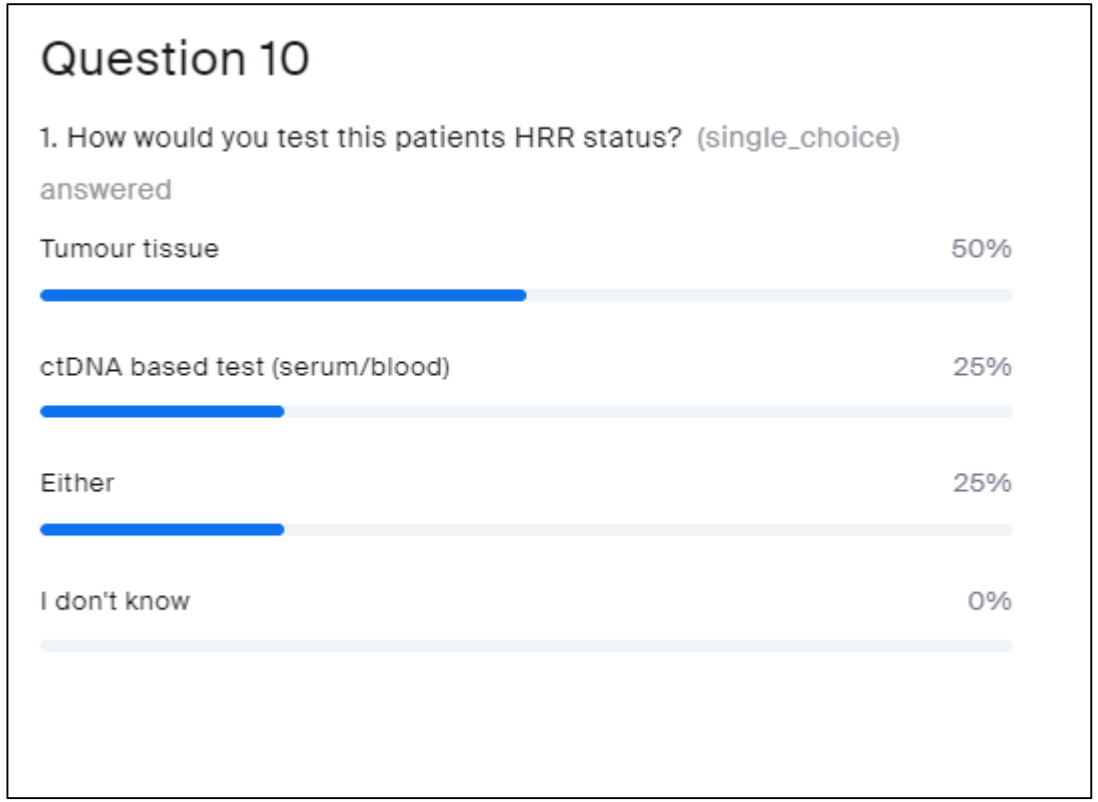
Imaging:

- 3 new bone lesions

ADT, androgen-deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen

HOW WOULD YOU TEST THIS PATIENTS HRR STATUS?

- Tumour tissue
- ctDNA based test (serum/blood)
- Either
- I don’t know



DATA ON HRRm TESTING IN PROPEL DEMONSTRATES GOOD CONCORDANCE BETWEEN ctDNA AND TUMOUR TISSUE TESTING

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	Tumour tissue test			
ctDNA-based test	**HRRm**	**Non-HRRm**	**HRRm unknown**	**Total**
HRRm	90	51	57	198
Non-HRRm	22	328	186	536
HRRm unknown	6	38	18	62
Total	118	417	261	796

Positive-percent agreement	80.4% (90/112; 95% CI, 72–87%)
Negative-percent agreement	86.5% (328/379; 95% CI, 83–90%)
Overall-percent agreement	85.1% (418/491; 95% CI, 82–88%)
Positive predictive value	63.8% (90/141; 95% CI, 55–72%)
Negative predictive value	93.7% (328/350; 95% CI, 90–96%)

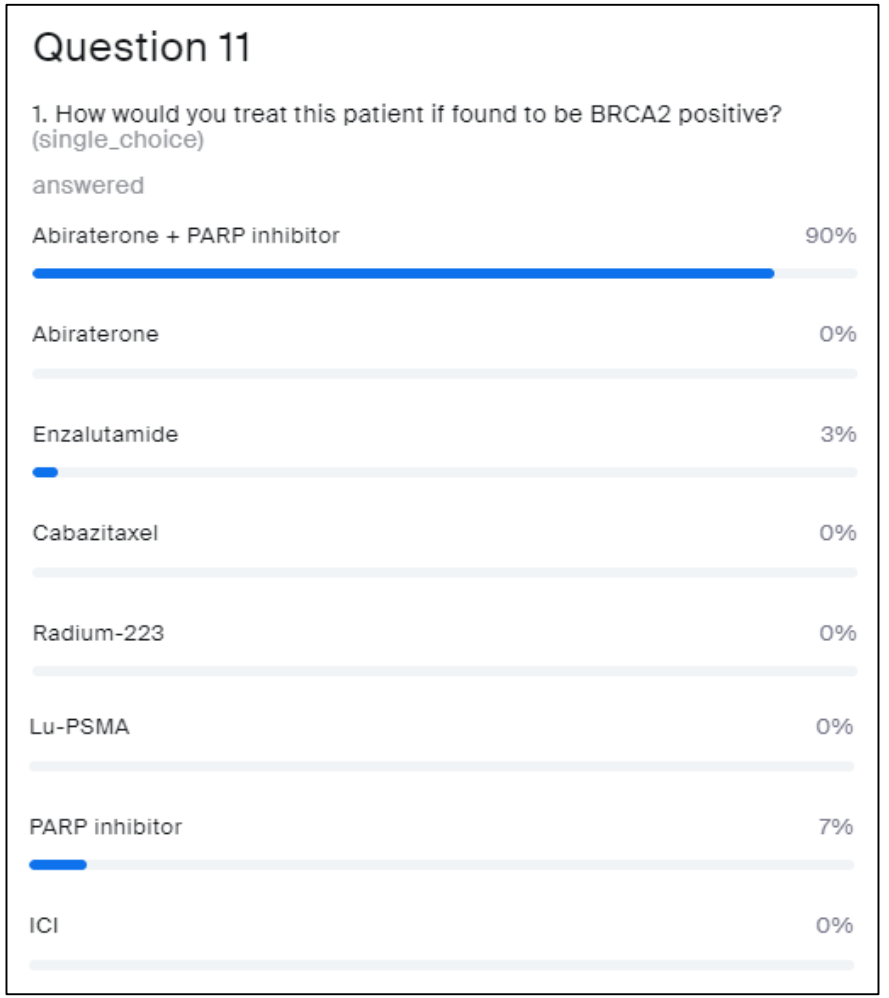
CI, confidence interval; ctDNA, circulating tumour DNA; HRRm, homologous recombination repair gene mutation

Armstrong AJ, et al. Presented at ESMO 9th–13th September 2022, Paris, France. Poster 1370P

PATIENT WAS FOUND TO BE *BRCA2* POSITIVE

HOW WOULD YOU TREAT HIM?

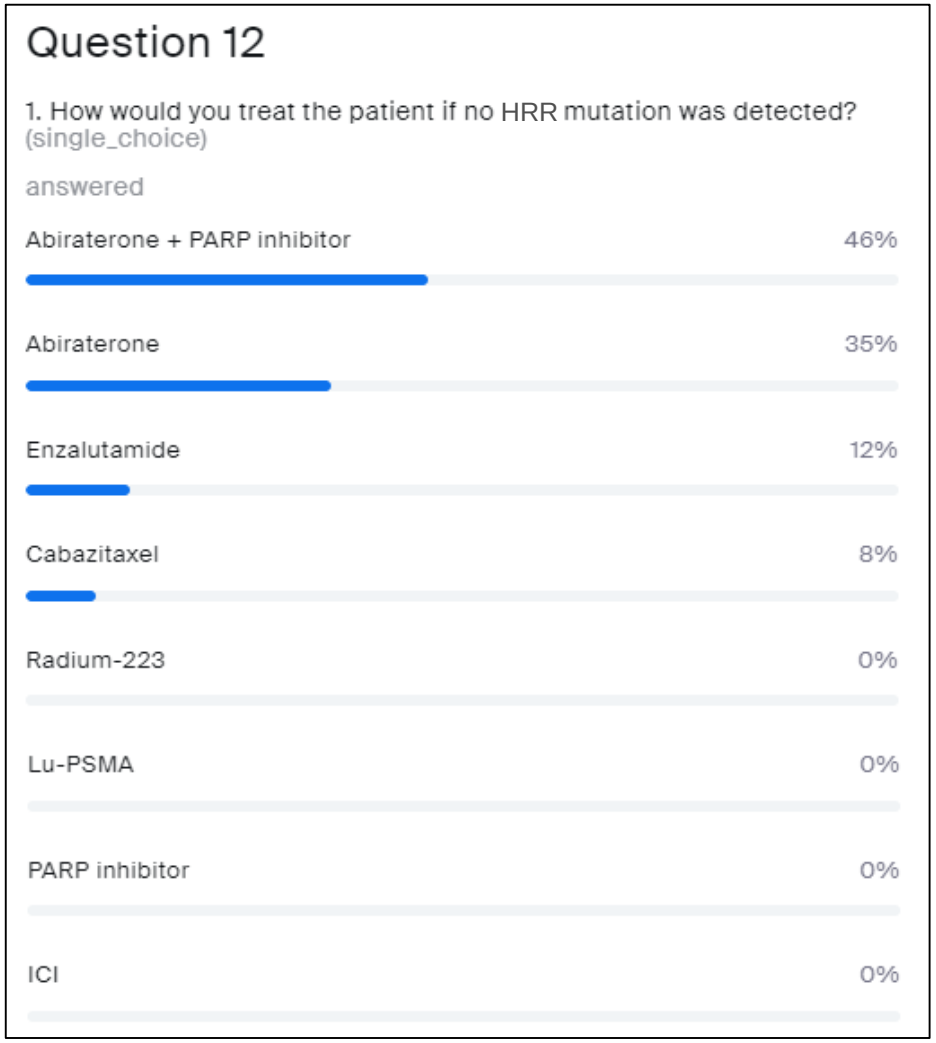
- Abiraterone + PARP inhibitor
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223
- Lu-PSMA
- PARP inhibitor
- ICI



ICI, immune checkpoint inhibitor; Lu-PSMA, lutetium prostate-specific membrane antigen; PARP, poly-ADP ribose polymerase

HOW WOULD YOU TREAT THE PATIENT IF NO HRR MUTATION WAS DETECTED?

- Abiraterone + PARP inhibitor
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223
- Lu-PSMA
- PARP inhibitor
- ICI

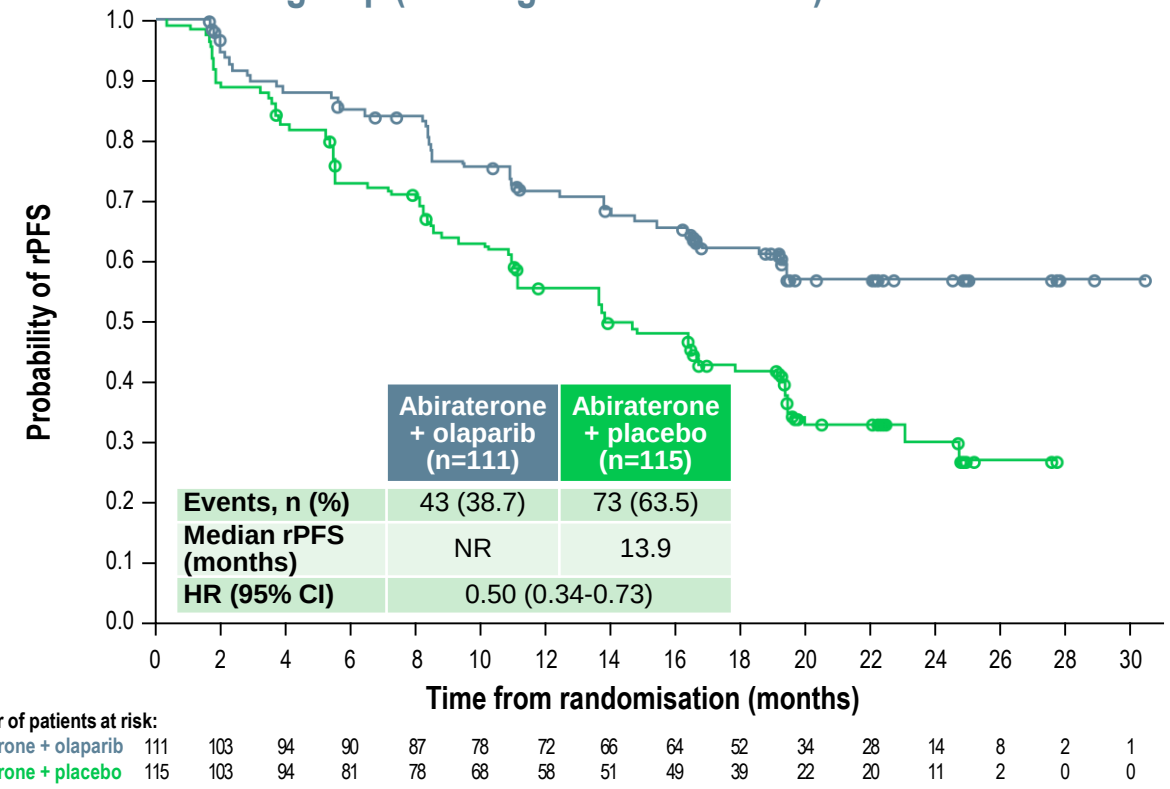


HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; Lu-PSMA, lutetium prostate-specific membrane antigen; PARP, poly-ADP ribose polymerase

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)



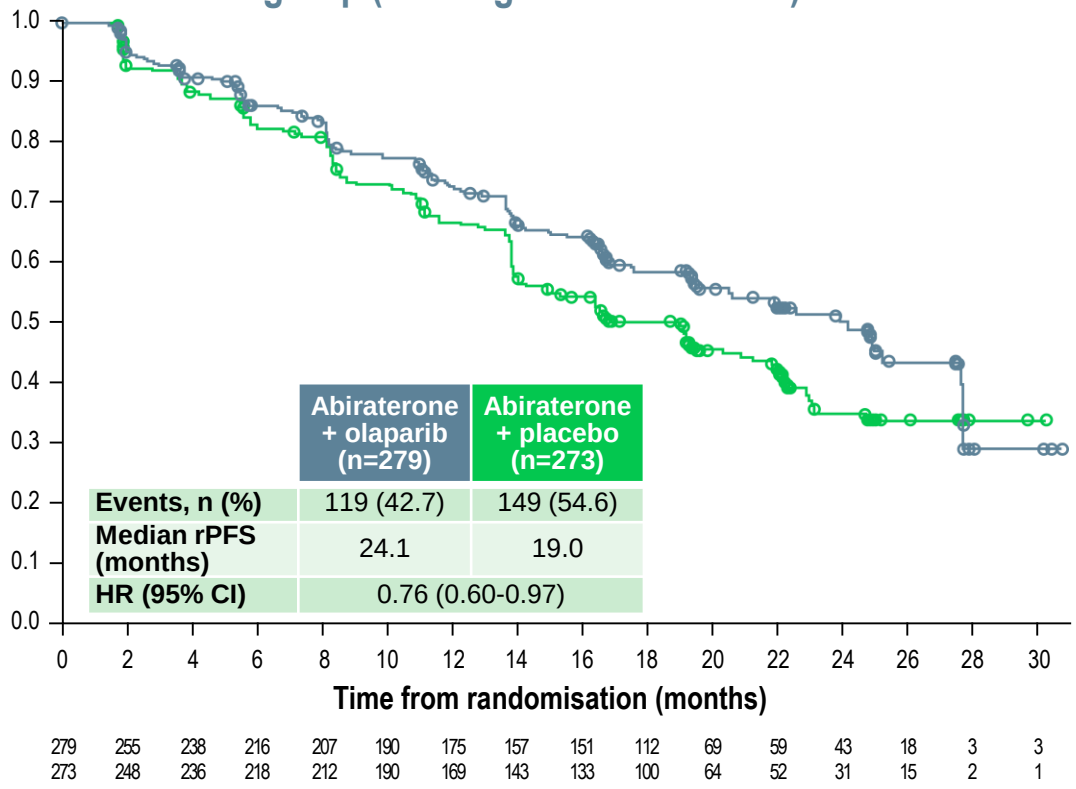
	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS (months)	NR	13.9
HR (95% CI)	0.50 (0.34-0.73)	

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

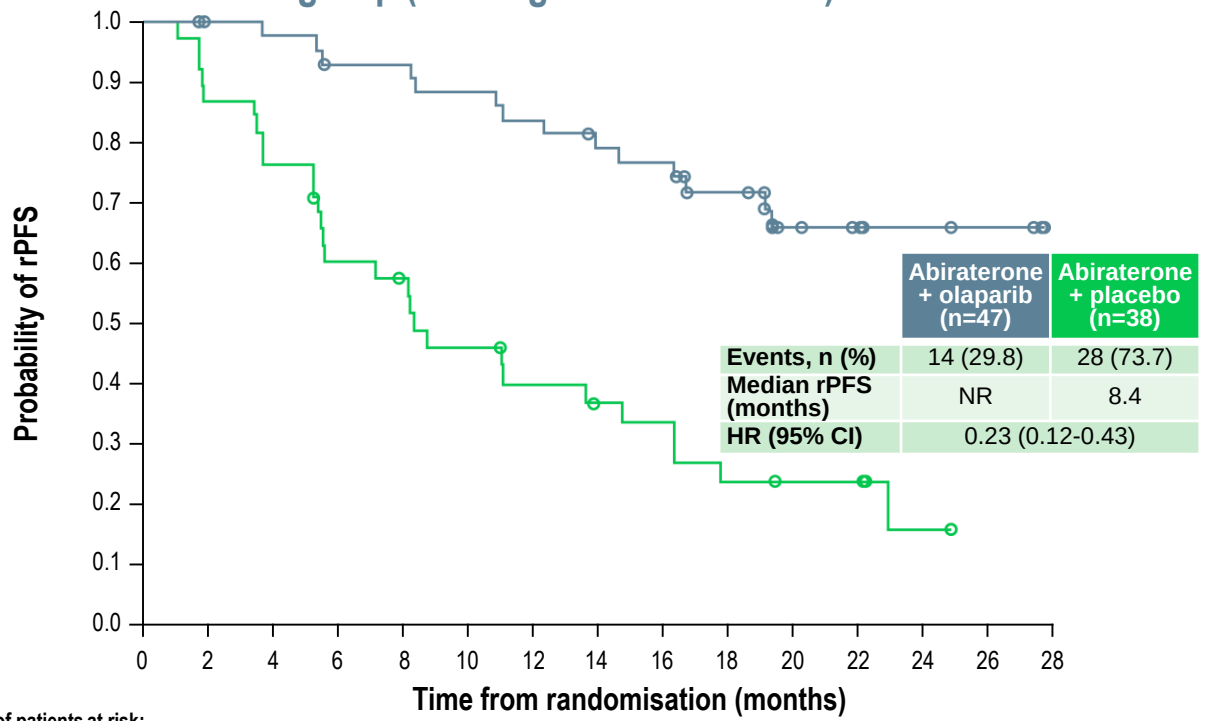
Patient enrolment was not based on HRRm status; however, HRRm testing was prespecified. HRR status was determined after randomisation and before primary analysis using results from tumour tissue and plasma ctDNA HRRm tests. A total of 18 patients did not have a valid HRR testing result from either a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



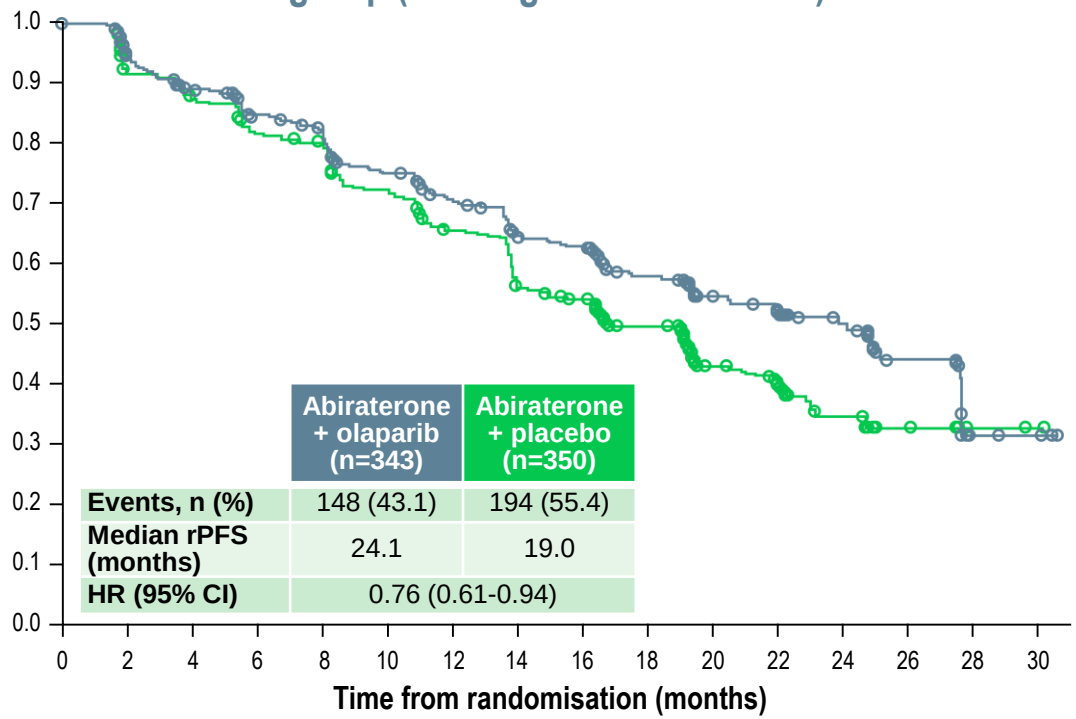
	Abiraterone + olaparib (n=47)	Abiraterone + placebo (n=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median rPFS (months)	NR	8.4
HR (95% CI)	0.23 (0.12-0.43)	

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

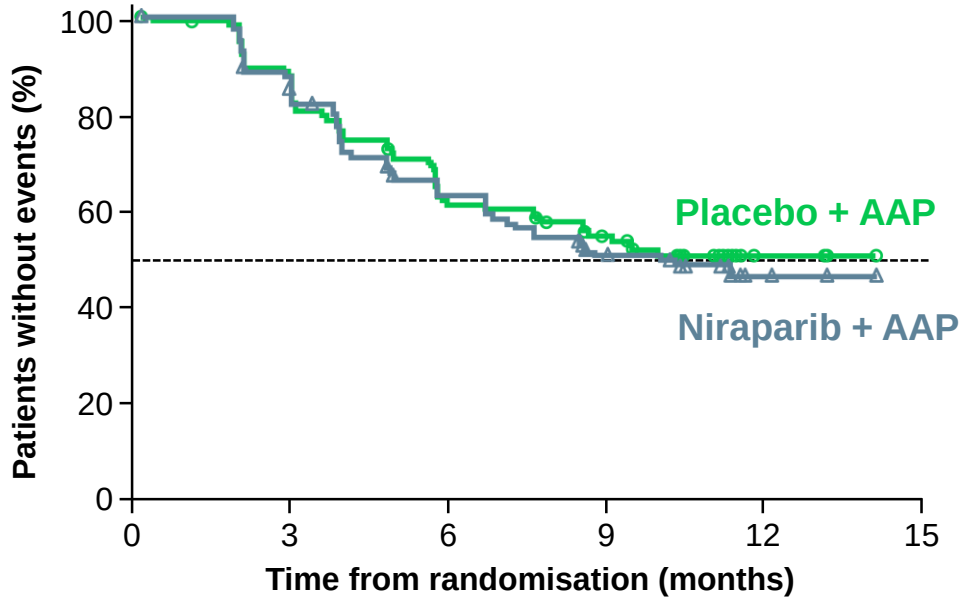
[a] *BRCA2*m: HR 0.25, 95% CI 0.12-0.48. Non-*BRCA2*m: HR 0.74, 95% CI 0.60-0.92. Patient enrolment was not based on HRRm status; however, the HRRm and *BRCA*m status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma 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

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

MAGNITUDE HRR BM⁻: PRESPECIFIED EARLY FUTILITY ANALYSIS – NO BENEFIT OF NIRA + AAP IN HRR BM⁻ PATIENTS

COMPOSITE PROGRESSION ENDPOINT (RADIOGRAPHIC OR PSA PROGRESSION)



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

- Composite endpoint[a] (N=233)
  HR (95% CI):1.09[b] (0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3 or 4 toxicity was observed using niraparib + APP vs placebo + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrolment in this cohort

[a] rPFS or PSA progression, whichever occurred first

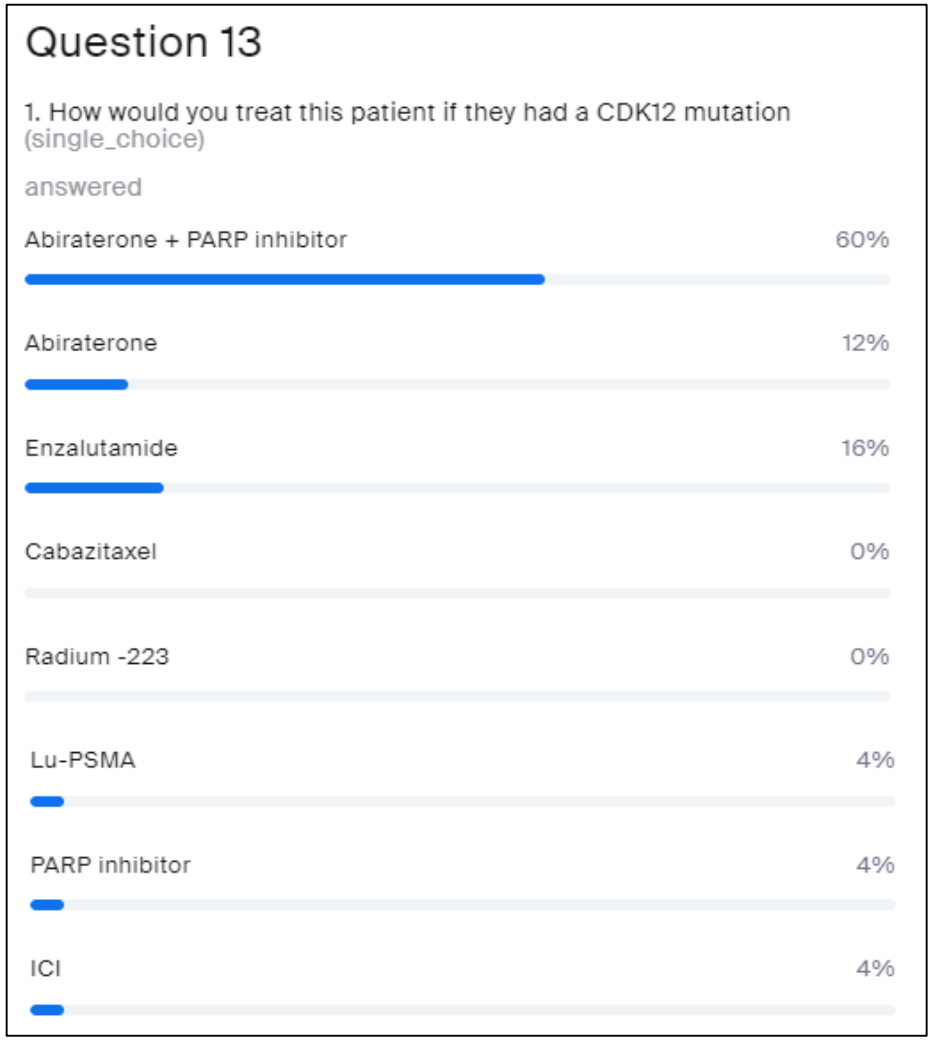
[b] Breakdown of composite endpoint events: 83 PSA events (HR [95% CI):1.03 [0.67-1.59]); 65 rPFS events (HR [95% CI]: 1.03 [0.63-1.67])

AAP, abiraterone acetate and 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; PSA, prostate-specific antigen, rPFS, radiographic progression-free survival

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

HOW WOULD YOU TREAT THIS PATIENT IF THEY HAD A *CDK12* MUTATION?

- Abiraterone + PARP inhibitor
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223
- Lu-PSMA
- PARP inhibitor
- ICI

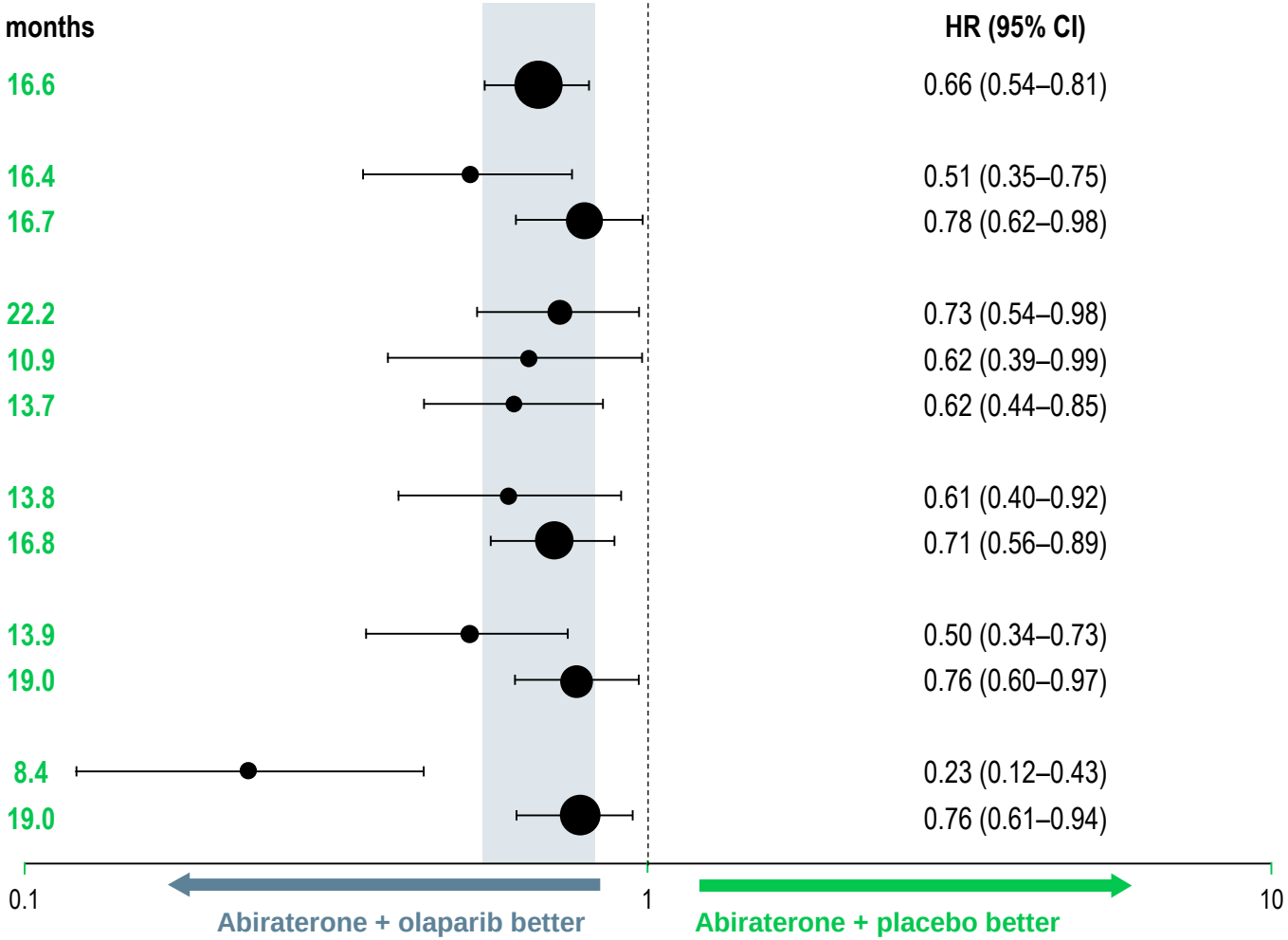


ICI, immune checkpoint inhibitor; Lu-PSMA, lutetium prostate-specific membrane antigen; PARP, poly-ADP ribose polymerase

PROpel: SUBGROUP ANALYSIS OF rPFS

AN rPFS BENEFIT WAS OBSERVED ACROSS ALL PATIENT SUBGROUPS, INCLUDING THE HRRm AND *BRCA*m BIOMARKER SUBGROUPS (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)

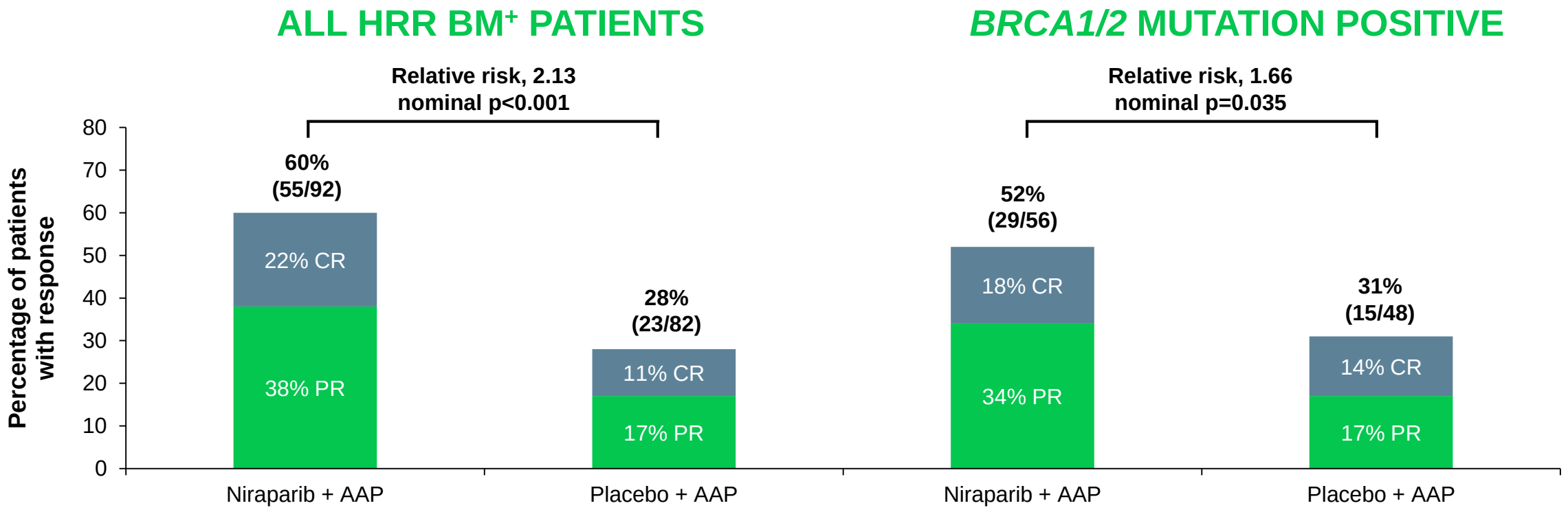


[a] The HRRm and *BRCA*m status of patients in PROpel was determined after randomisation and before primary analysis using aggregated results from tumour tissue and plasma ctDNA HRRm tests. Aggregate HRRm and *BRCA*m subgroup analyses are post-hoc exploratory analyses. Results shown are by investigator 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. Annals of Oncology 2022; 33 (suppl_7): S616-S652 (ESMO 2022 oral presentation)

MAGNITUDE: NIRAPARIB + AAP IMPROVES OVERALL RESPONSE RATE CONSISTENTLY ACROSS GENE ALTERATIONS



Niraparib + AAP nearly doubles ORR rate and provides deeper response in patients with measurable disease

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; ORR, overall response rate; PR, partial response

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

MAGNITUDE: NIRAPARIB + AAP PROLONGS TIME TO CYTOTOXIC CHEMOTHERAPY ACROSS GENE ALTERATIONS

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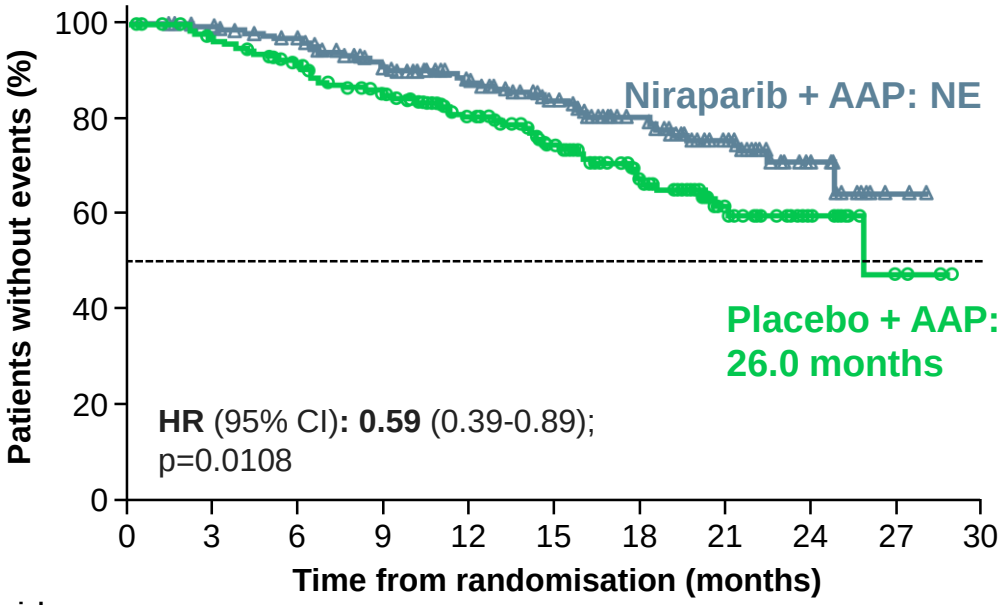
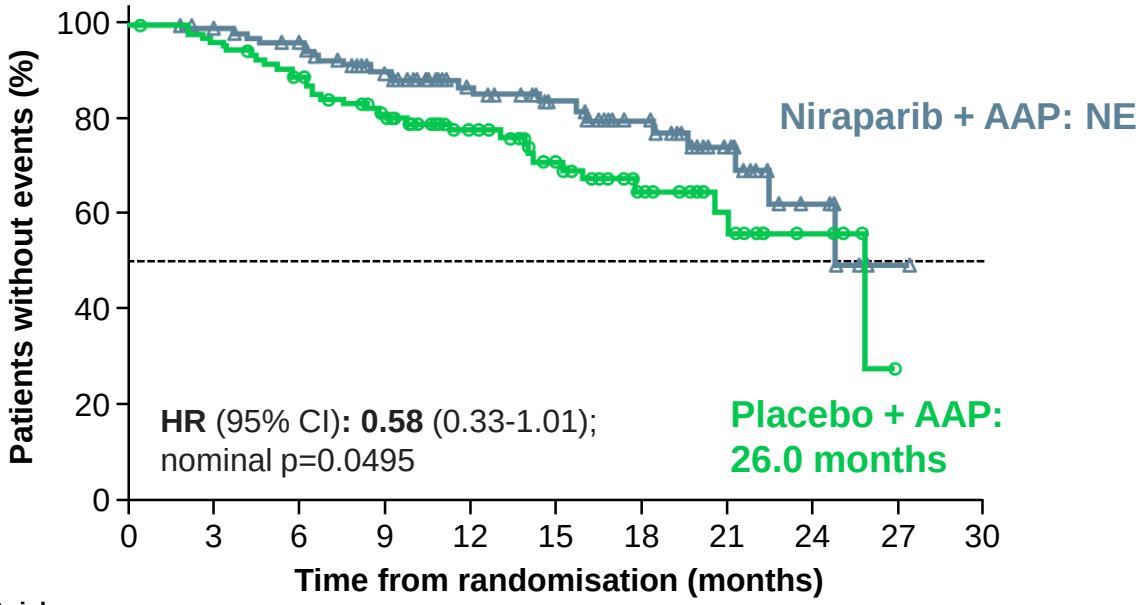
ALL HRR BM+ PATIENTS



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

BRCA1/2 MUTATION POSITIVE



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

Niraparib + AAP provided a consistent magnitude of improvement (>40%) across evaluated groups

AAP, abiraterone acetate and prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable

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

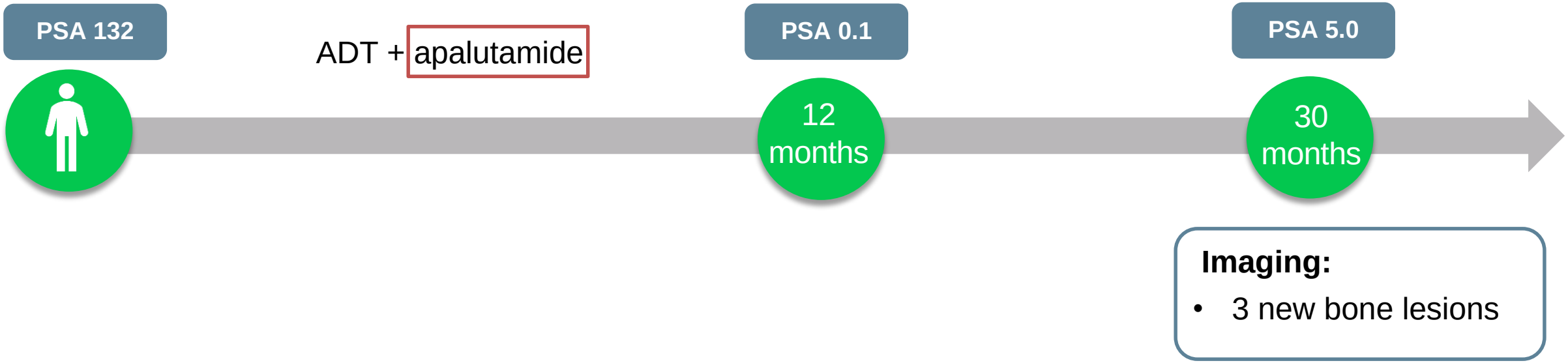
CASE DISCUSSION

Patient: Age 65 years

Presents with: mCRPC with rising PSA

Medical history:

- *de novo* (synchronous), high volume mCSPC (Gleason 5+4) treated with ADT + upfront docetaxel (six cycles) for 30 months



Imaging:

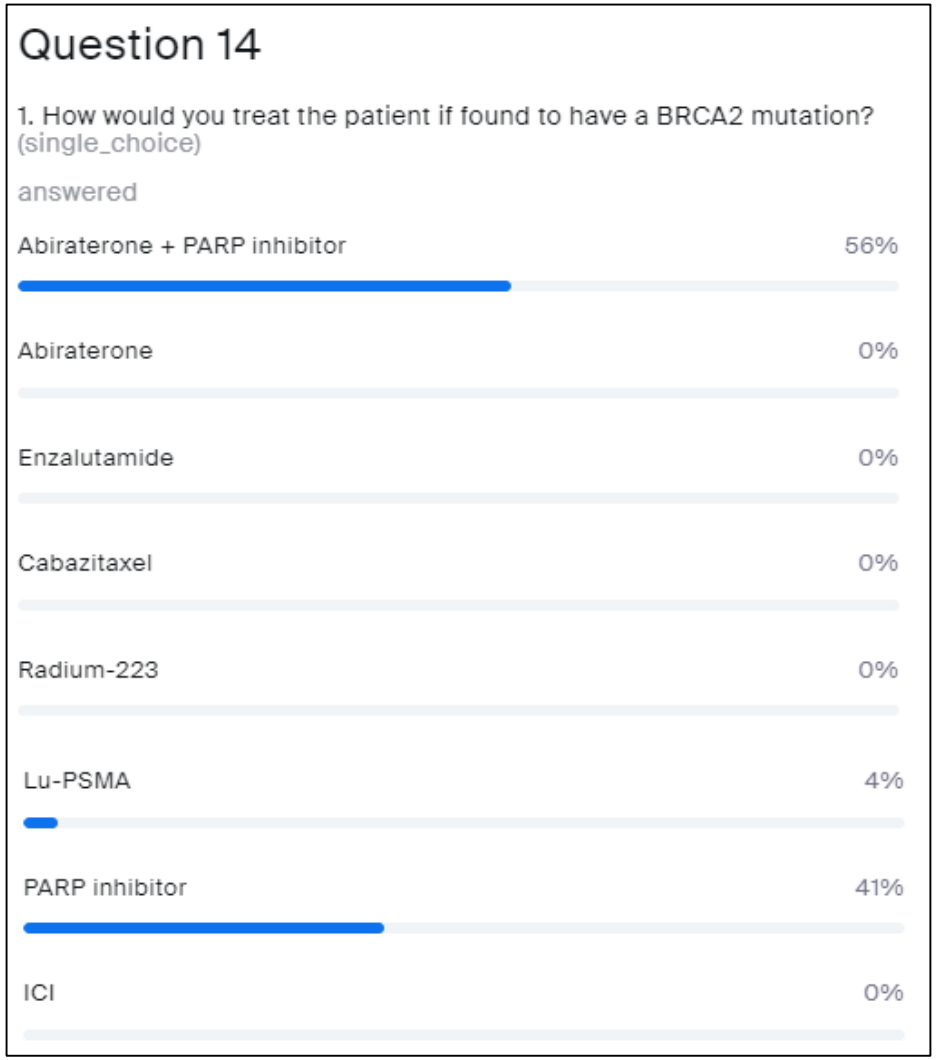
- 3 new bone lesions

ADT, androgen-deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen

THE PATIENT IS FOUND TO HAVE A *BRCA2* MUTATION

HOW WOULD YOU TREAT?

- Abiraterone + PARP inhibitor
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223
- Lu-PSMA
- PARP inhibitor
- ICI



ICI, immune checkpoint inhibitor; Lu-PSMA, lutetium prostate-specific membrane antigen; PARP, poly-ADP ribose polymerase

QUESTIONS
PANEL DISCUSSION

FUTURE PERSPECTIVES AND SUMMARY

Prof. Fred Saad, MD, FRCS

PARP INHIBITOR MONOTHERAPY OR PARP INHIBITOR + ARAT IN THE FUTURE LANDSCAPE?

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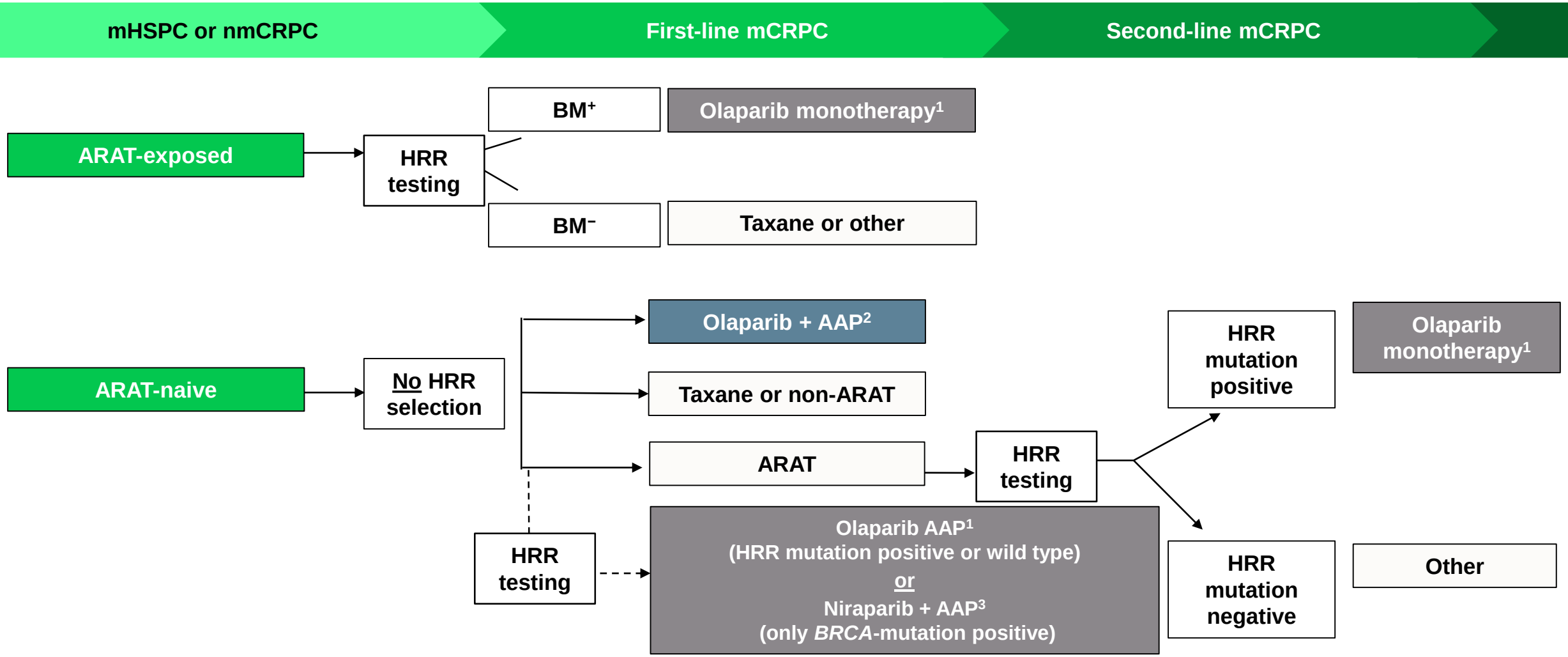

ARAT, androgen receptor axis-targeted therapies; AAP, abiraterone acetate and prednisone/prednisolone; BM, biomarker; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; (n)mCRPC, (non-)metastatic castration-resistant prostate cancer

1. de Bono JS, et al. N Engl J Med. 2020;382:2091-102; 2. Saad F, et al. J Clin Oncol. 2022;40 Suppl: Abstract 11 (ASCO GU 2022 oral presentation); 3. Chi K, et al. J Clin Oncol. 2022;40 Suppl: Abstract 12 (ASCO GU 2022 oral presentation)

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

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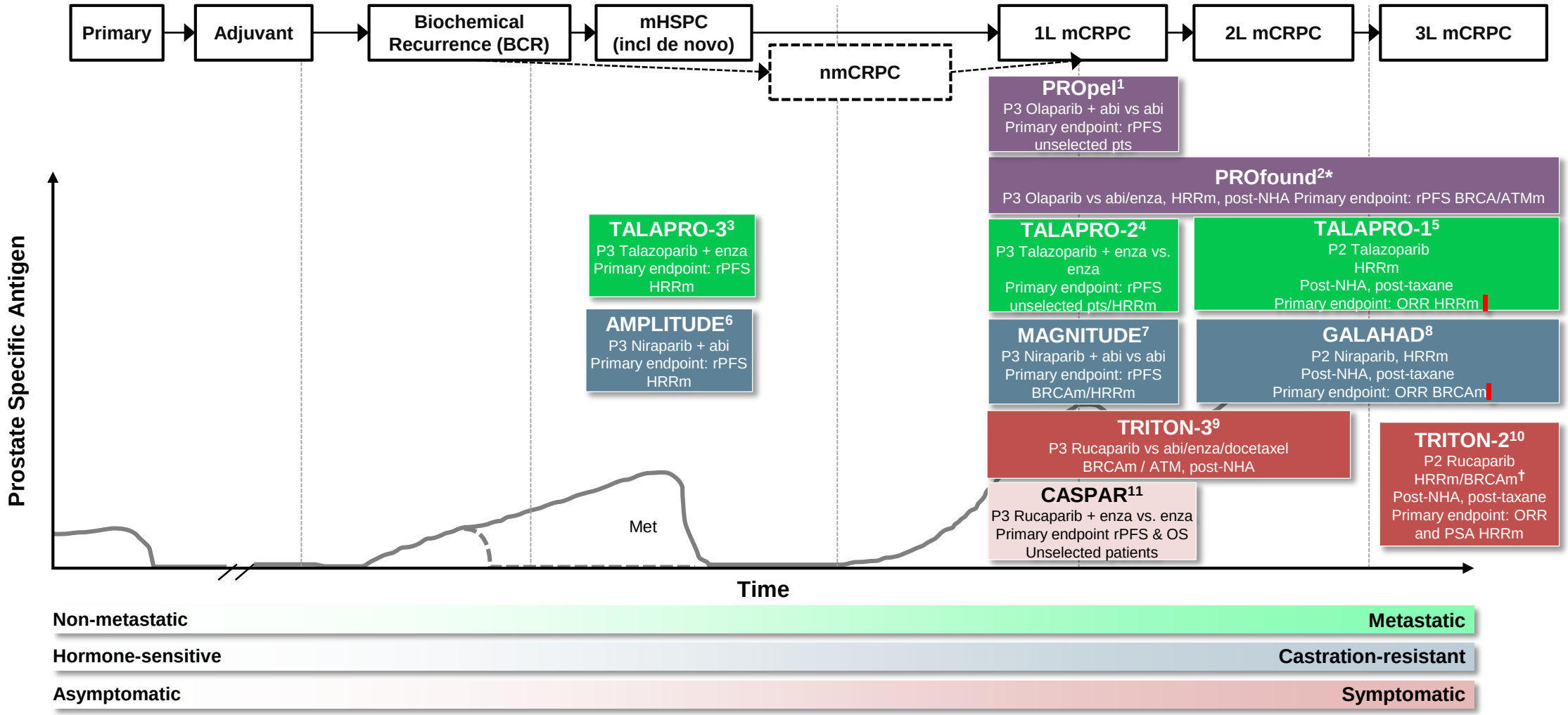

Please see slide notes for references. [a] As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA[12,13]; [b] As a result of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

CONCLUSION

- Patients in the mCRPC state live less than 3 years even with the best available treatments
- A significant proportion of men destined to die of prostate cancer harbour HRR mutations
  - Treatment improves PFS and OS
  - Strategies to identify patients is challenging but critically important
- Future will likely include earlier introduction of PARP inhibitor and possibly treatment beyond patients with HRR/DDR mutations

DDR, DNA damage repair; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PARP, poly-ADP ribose polymerase; PFS, progression-free survival

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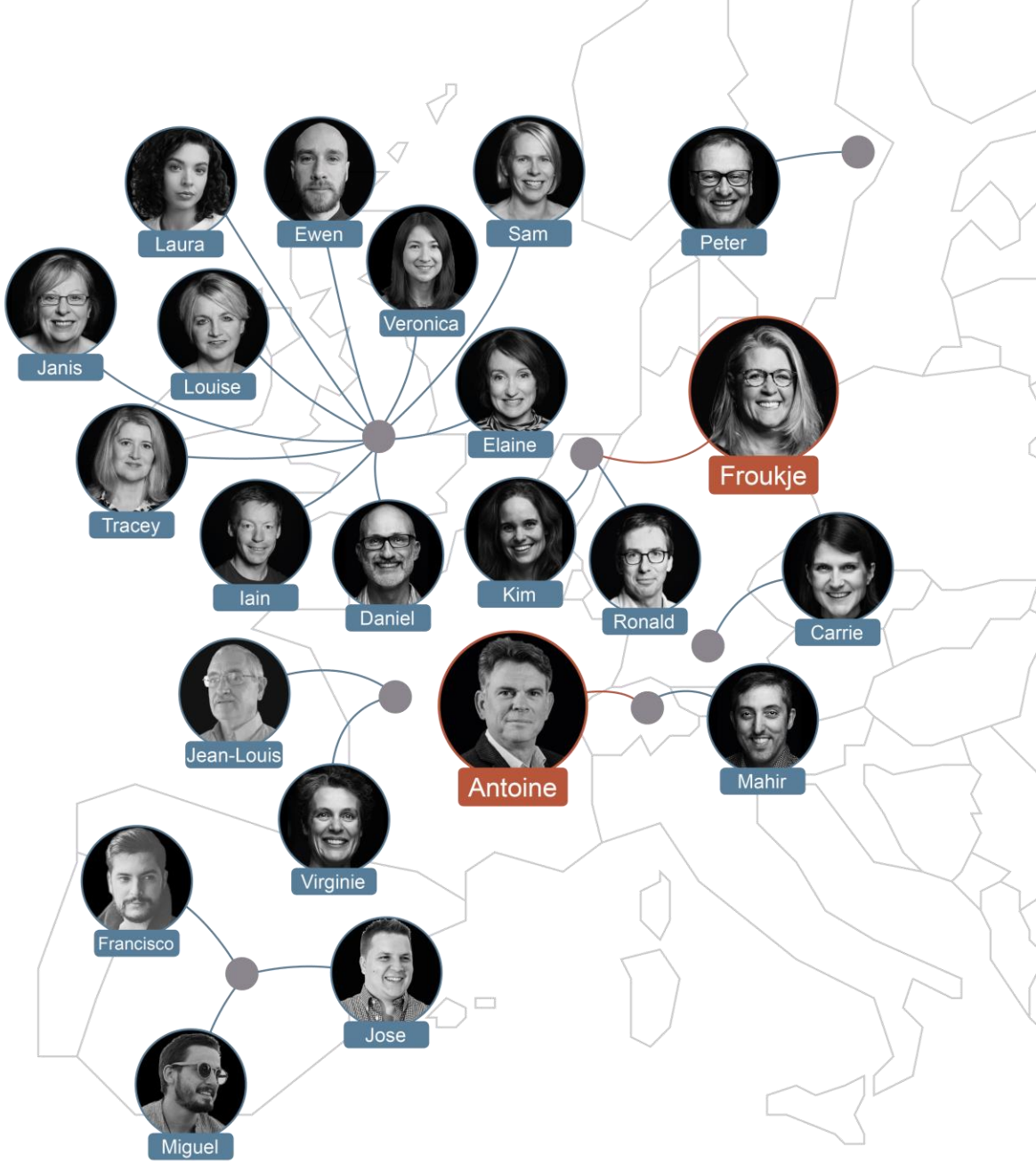

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