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EXPERTS KNOWLEDGE SHARE

TARGETING ADVANCED PROSTATE CANCER WITH PARP INHIBITORS: WHO, WHEN AND HOW?

Prof. Fred Saad, MD FRCS (Canada)
Assoc. Prof. Tanya Dorff, MD (USA)
Prof. Gerhardt Attard, MD FRCP PhD (UK)

7th March 2022

PARPi, poly-ADP ribose polymerase inhibitors

INTRODUCING THE SCIENTIFIC COMMITTEE

Fred Saad

**Professor and Chairman of Urology,
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center, Canada**

- President of the National Cancer Institute of Canada G-U Group, the Canadian Urologic Oncology Group and GU Global
- Member of ten editorial boards and serves as a reviewer for more than 30 urology and oncology journals. Published over 300 scientific articles and book chapters and has collaborated on over 800 scientific abstracts presented at scientific meetings around the world.
- Co-editor of several books, including the first two editions of Understanding Prostate Cancer, which sold over 150,000 copies.
- Main research interests include molecular prognostic markers in prostate cancer and new treatments for advanced prostate cancer. He is currently coordinating more than 40 clinical and basic research projects in urologic oncology.

Tanya Dorff

**Associate Professor of Medicine
Section Chief, Genitourinary Cancers,
City of Hope Comprehensive Cancer Centre, USA**

- Medical oncologist and GU CONNECT member
- Authored more than 45 peer reviewed articles as well as 35 review articles /commentaries.
- Associate editor for Clinical Genitourinary Cancer and Seminars in Urologic Oncology and has lectured on prostate and bladder cancer treatment nationally and internationally and has presented her research at national meetings.
- Principal investigator for more than a dozen clinical trials, involving targeted therapy and immunotherapy, for genitourinary cancers.
- Current research interests include the effects of fasting on chemotherapy side effects and cancer control and immunotherapy for prostate cancer.

Gerhardt Attard

**Clinician Scientist and Team Leader at University College London Cancer Institute
Honorary medical oncology consultant at Royal Marsden NHS Foundation Trust, UK**

- Medical oncologist and GU CONNECT member
- Experienced clinical trialist in CRPC and a co-author of more than 100 peer-reviewed manuscripts, including several important papers on advanced prostate cancer.
- Associate editor with ESMO official journal Annals of Oncology and sits on the scientific advisory boards of several companies.
- Main research interest is dissecting treatment resistance, currently with a focus on plasma DNA analysis, in order to inform on the development of novel therapeutics and biomarkers for castration-resistant prostate cancer (CRPC).
- Awards include the ASCO Foundation Annual Merit Award in 2007, the Medical Research Society/Academy of Medical Sciences Sue McCarthy Prize in 2010 and the Cancer Research UK Future Leaders Award in 2017.

EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

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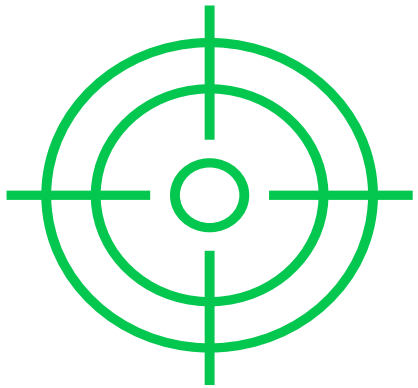

TARGETING ADVANCED PROSTATE CANCER WITH PARP INHIBITORS: WHO, WHEN AND HOW?

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

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TARGETING ADVANCED PROSTATE CANCER WITH PARP INHIBITORS: WHO, WHEN AND HOW?

Content	
Overview and scene setting	Prof. Fred Saad
Who should you treat?	Prof. Gerhardt Attard
Why you should treat	Assoc. Prof. Tanya Dorff
When to consider combinations	Prof. Fred Saad
Future perspectives and summary	Prof. Fred Saad

DISCLAIMER

This meeting is supported by an independent medical educational grant from AstraZeneca. The programme is therefore independent; the content is not influenced by AstraZeneca and is the sole responsibility of the experts

Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

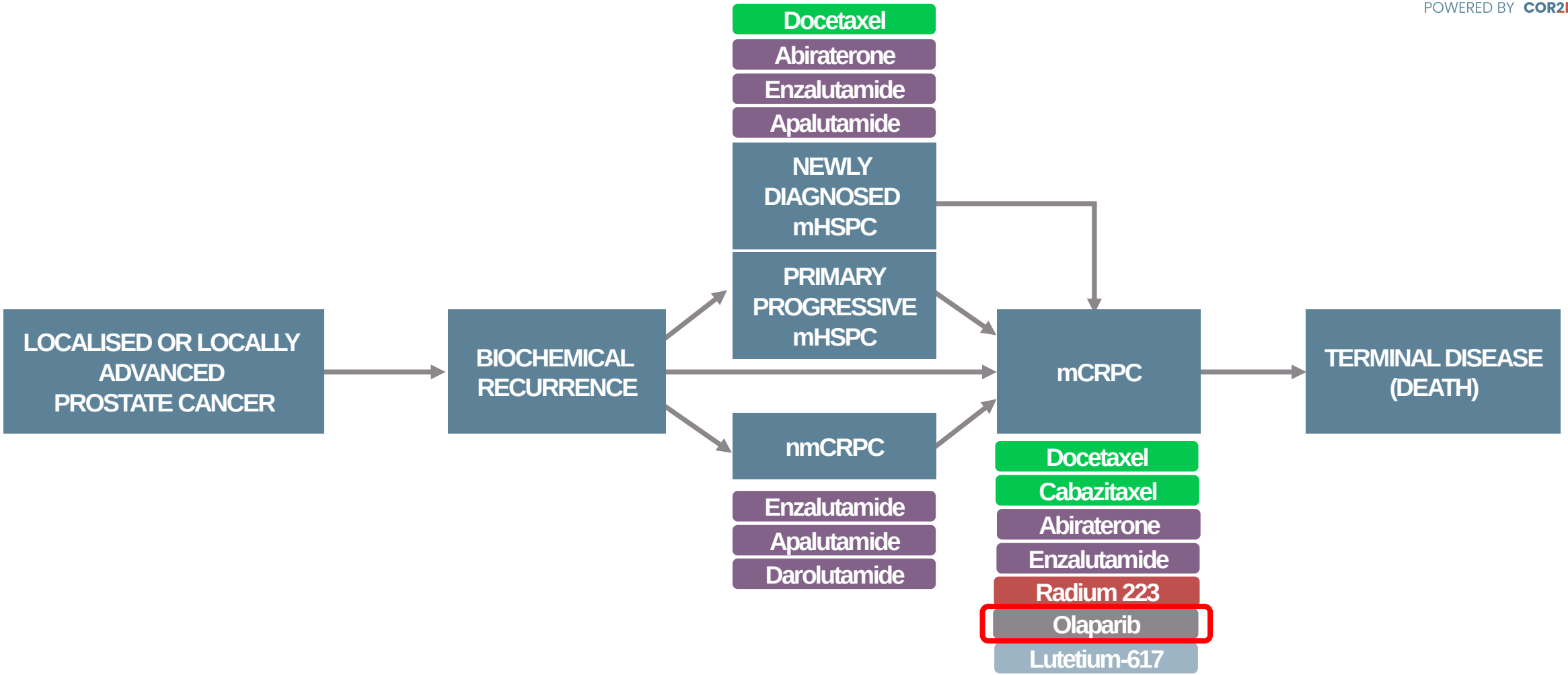
TARGETING ADVANCED PROSTATE CANCER WITH PARP INHIBITORS: WHO, WHEN AND HOW?

OVERVIEW AND SCENE SETTING

Prof. Fred Saad, MD FRCS
Professor and Chairman of Urology, Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center, Montreal, QC, Canada

PARPI, poly-ADP ribose polymerase inhibitors

THE PROSTATE CANCER LANDSCAPE



All monotherapeutic options added to ADT

ADT, androgen deprivation therapy; mHSPC, metastatic hormone sensitive prostate cancer; (n)mCRPC, (non-)metastatic castration resistant prostate cancer

WHO SHOULD YOU TREAT?

Prof. Gerhardt Attard, MD FRCP PhD
University College London Cancer Institute
London, United Kingdom
#Attardlab
www.Attardlab.com

DISCLOSURES

Prof. Gerhardt Attard has received received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:

- Abbott Laboratories, Astellas Pharma, AstraZeneca, Bayer Healthcare Pharmaceuticals, Essa Pharmaceuticals, Innocrin Pharma, Janssen-Cilag, Millennium Pharmaceuticals, Novartis, Pfizer, Roche/Ventana, Sanofi-Aventis, Takeda, Veridex

GENOMIC INSTABILITY IS A TARGETABLE HALLMARK OF CANCER

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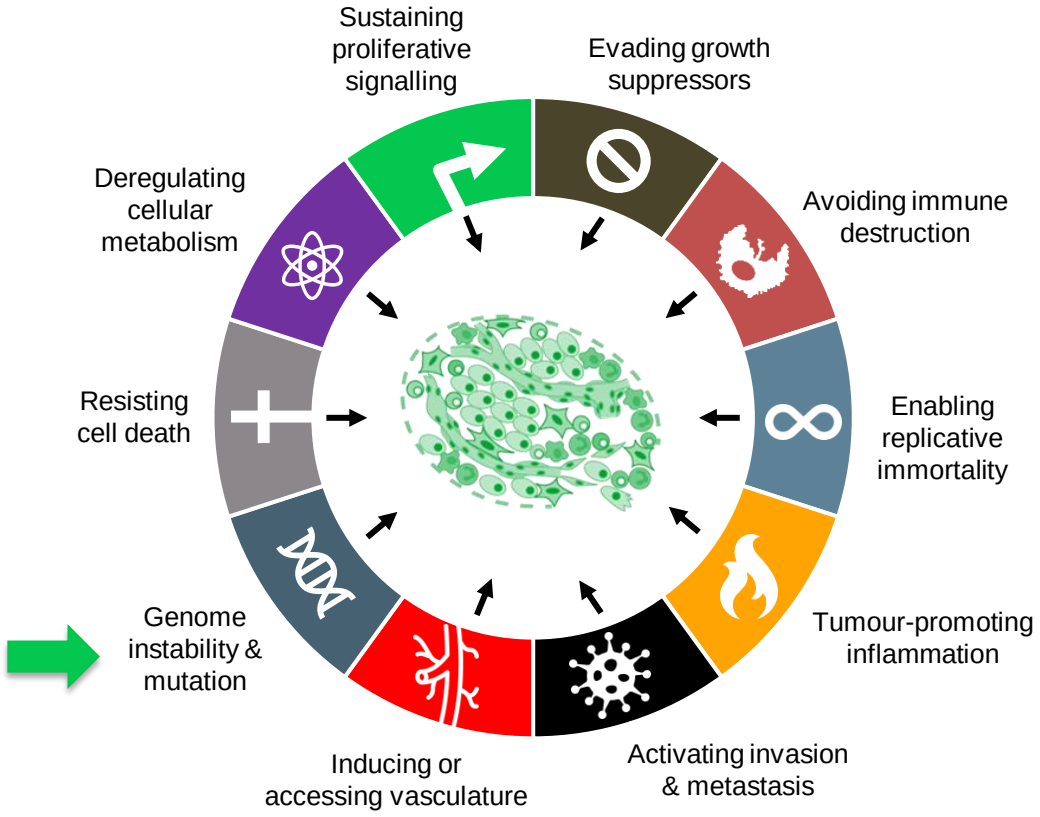
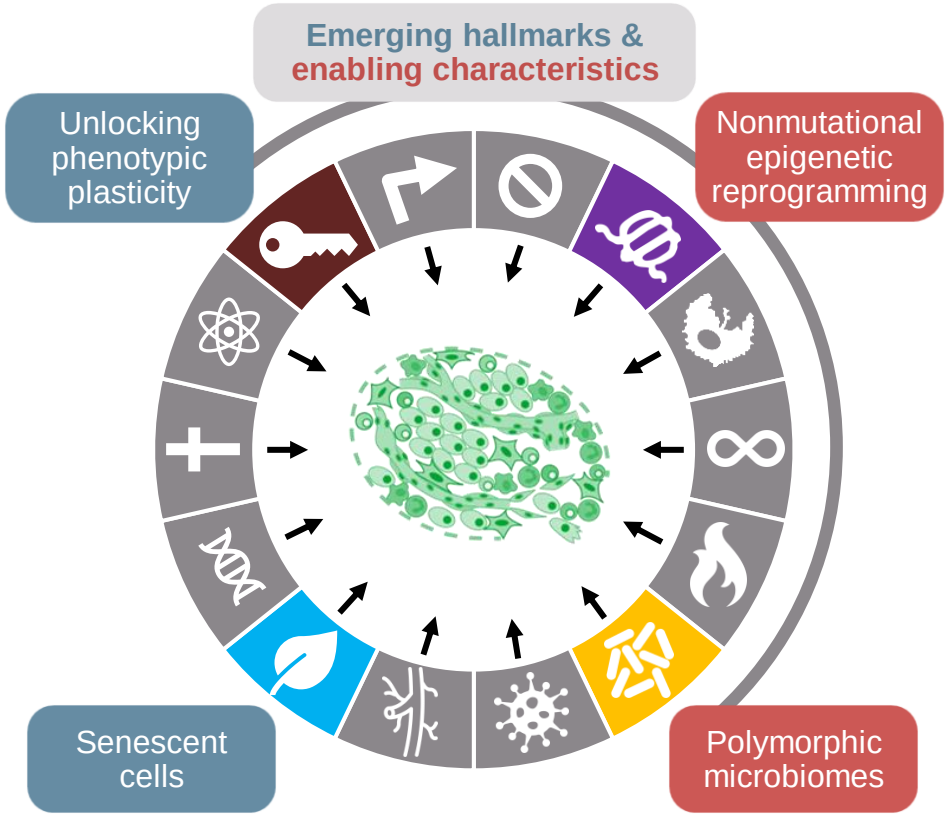
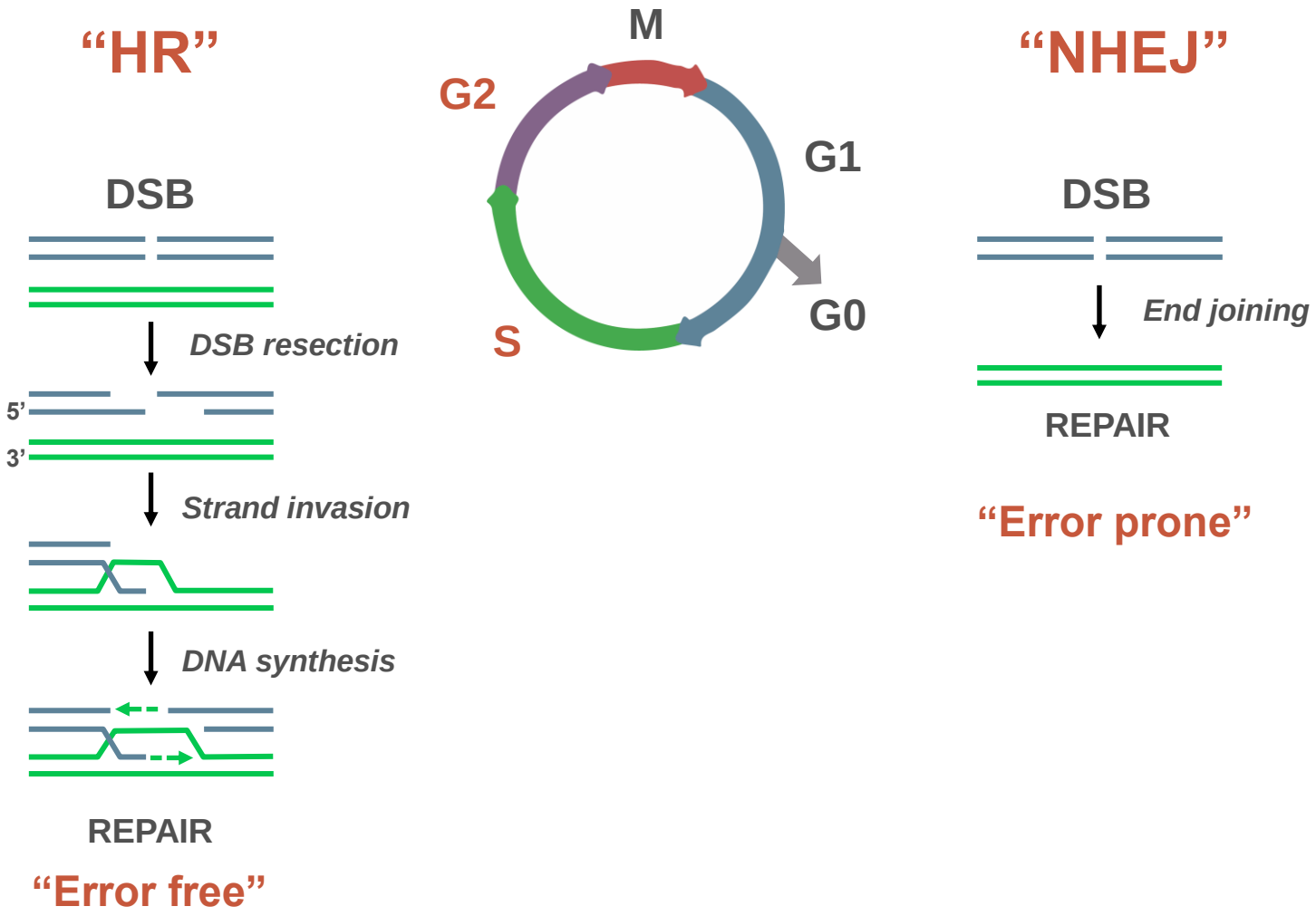
HALLMARKS OF CANCER





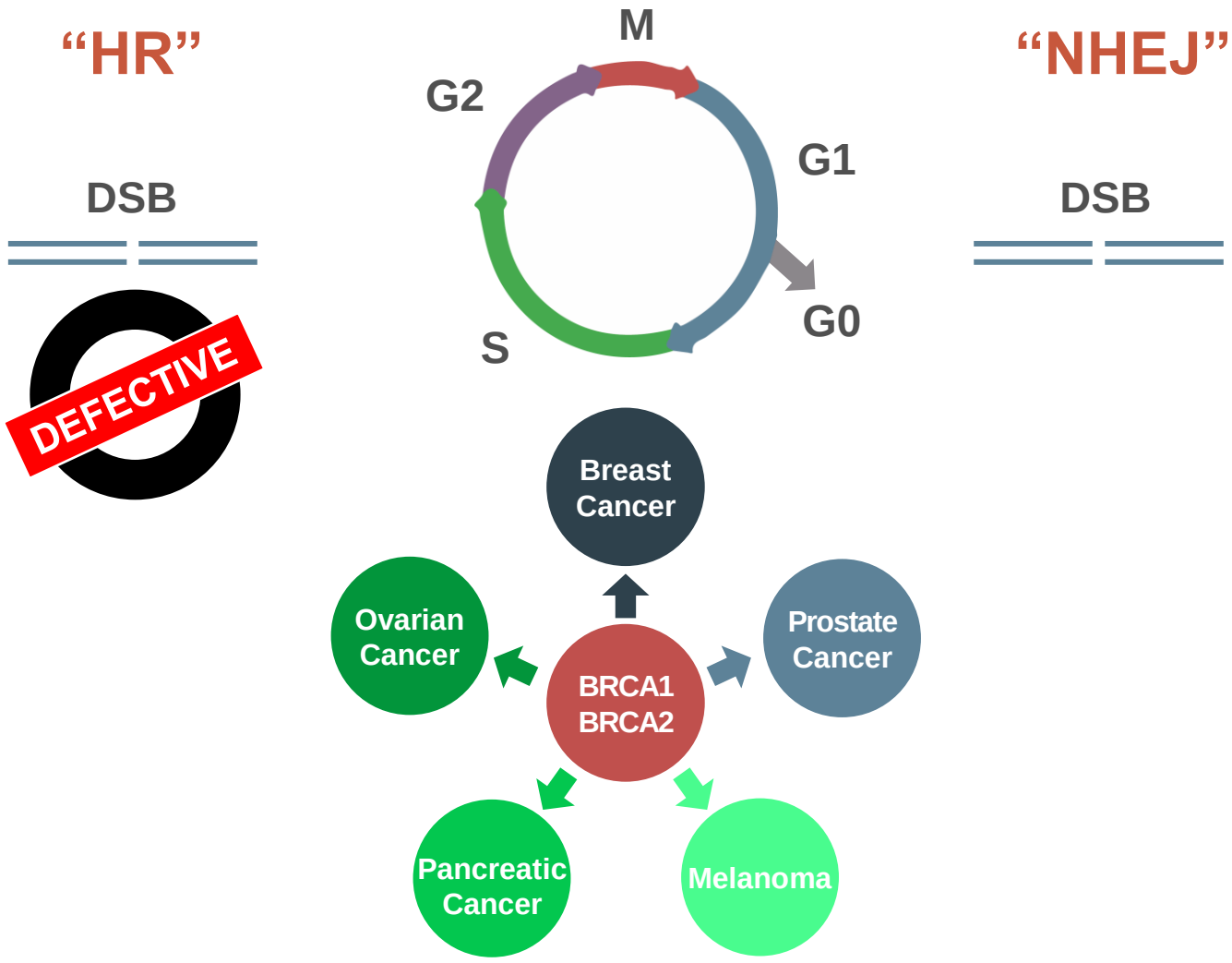
Adapted from Hanahan, D. Cancer Discov. 2022;12:31-46

DSB REPAIR: CELL CYCLE



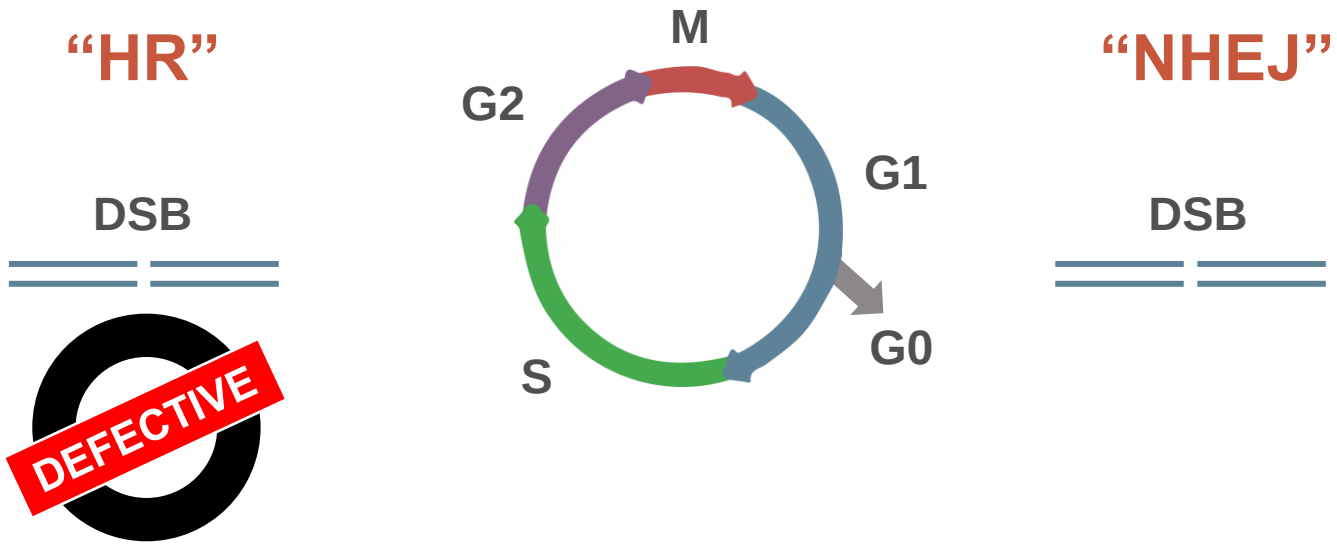
DSB, double-strand break; G, growth; HR, homologous recombination; M, mitosis; NHEJ, non-homologous end joining; S, synthesis

DSB REPAIR DEFECTS: CANCER PREDISPOSITION



BRCA1/2, breast cancer type 1/2 susceptibility protein; DSB, double-strand break; G, growth; HR, homologous recombination; M, mitosis; NHEJ, non-homologous end joining; S, synthesis

DSB REPAIR DEFECTS: THERAPEUTIC EXPLOITATION IN CANCER



Helleday, Jackson, Ashworth

Lynparza® olaparib

Zejula™ niraparib

Rubraca® (rucaparib) 300 mg tablets

TALZENNA™ talazoparib 1 mg capsules

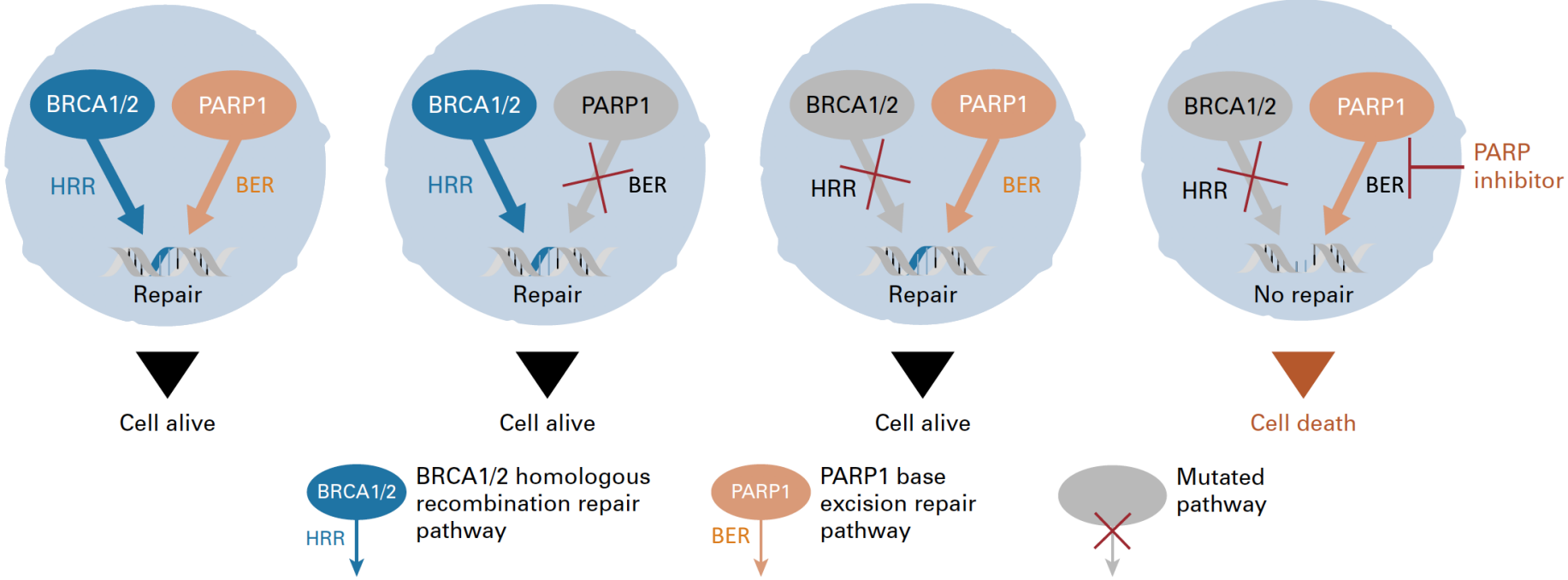
PARP inhibitors: therapeutic exploitation in cancer

BRCA2, breast cancer type 2 susceptibility protein; DSB, double-strand break; G, growth; HR, homologous recombination; M, mitosis; M, molarity; NHEJ, non-homologous end joining; PARP, poly-ADP ribose polymerase; S, synthesis

Bryant HE, et al. Nature. 2005;434:913-917; Farmer H, et al. Nature. 2005;434:917-921; Tutt ANJ, et al. Cold Spring Harb Symp Quant Biol. 2005;70:139-148

PARP INHIBITORS: ‘SYNTHETIC LETHALITY’ IN CANCER

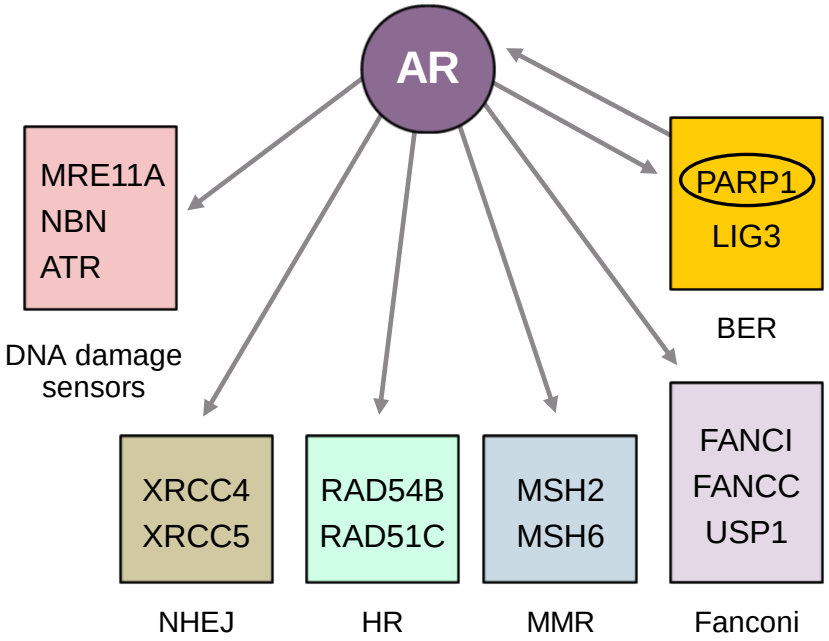
- ***BRCA*: “copy editor”;** homologous recombination repair (HRR)
- **PARP: “spell check”;** base excision repair (BER)

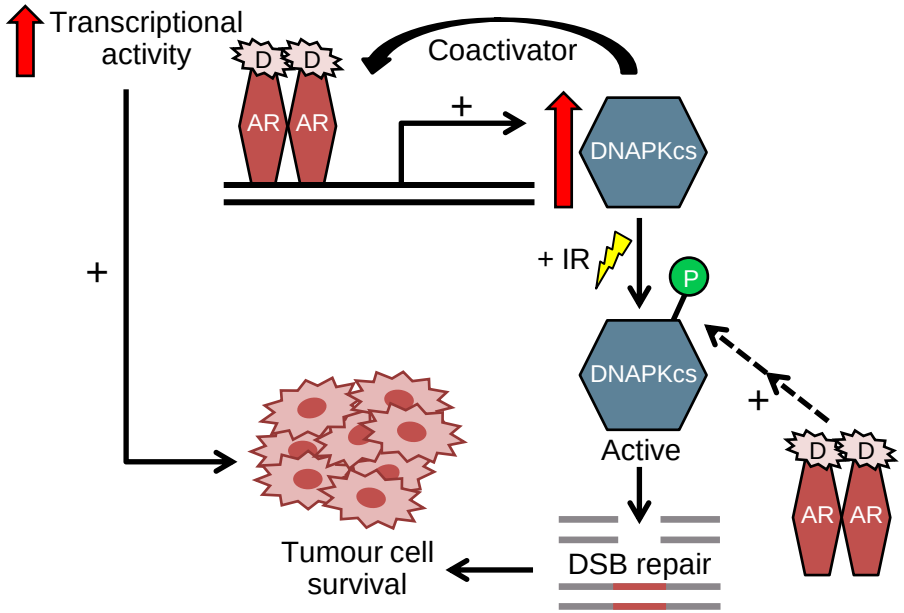


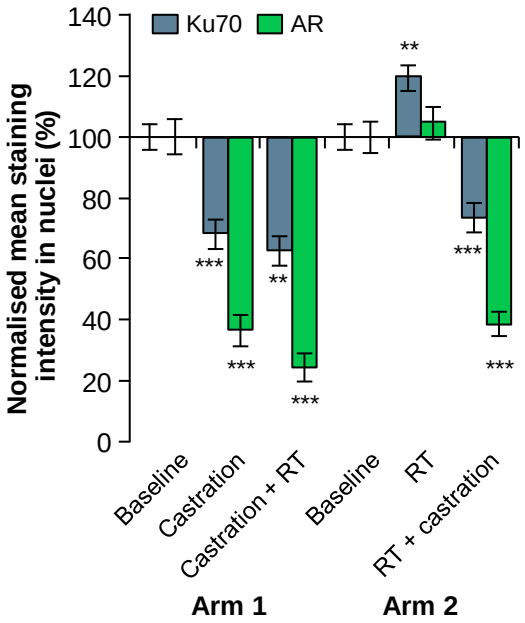
PARP is required for single-strand break repair (e.g. via BER)
MOA – inhibiting SSB/BER is synthetic lethal with HRD

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):2257-2269; Banerjee S, et al. Nat Rev Clin Oncol 2010; 7: 508-519

ANDROGEN RECEPTOR INHIBITION IMPAIRS DOUBLE STRAND DNA REPAIR







AR, androgen receptor; BER, base excision repair; DSB, double-strand break; HR, homologous recombination; MMR, mismatch repair; NEHJ, non-homologous end-joining; RT, radiotherapy

Polkinghorn W, et al. Cancer Discovery. 2013;3:1245-53; Goodwin J, et al. Cancer Discovery. 2013;3:1254-71; Tarish F, et al., Sci Transl Med. 2015;7:312re11

CO-OPERATION OF INHIBITION OF PARP AND AR: A RANDOMIZED PHASE 2 mCRPC TRIAL

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HRRm

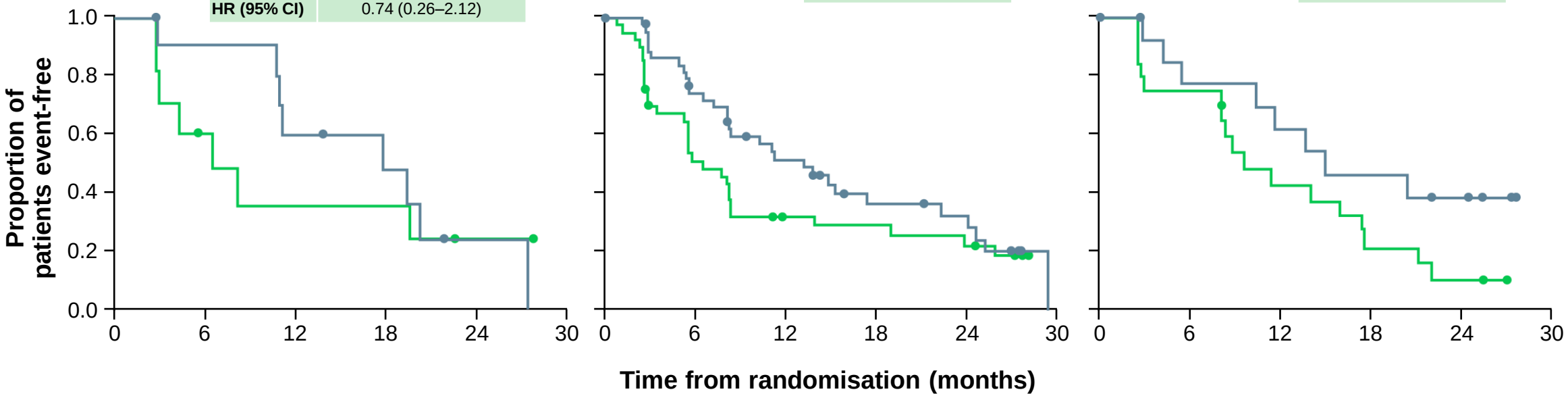
	Olap + Abi (n=11)	Abi (n=10)
Events, n (%)	8 (73)	7 (70)
KM median, months	17.8	6.5
HR (95% CI)	0.74 (0.26–2.12)	

HRRpc*

Olap + Abi (n=45)	Abi (n=41)
30 (67)	30 (73)
13.1	6.4
0.67 (0.40–1.13)	

HRRwt

Olap + Abi (n=15)	Abi (n=20)
8 (53)	17 (85)
15.0	9.7
0.52 (0.24–1.15)	



*80/86 patients HRRwt by plasma and/or germline testing

Abi, abiraterone; CI, confidence interval; HR, hazard ratio; HRR(m)(pc)(wt), homologous recombination repair (mutation)(partially characterised)(wild-type); KM, Kaplan-Meir; Olap, olaparib

Clarke N, et al. The Lancet Oncology. 2018;19:975-86

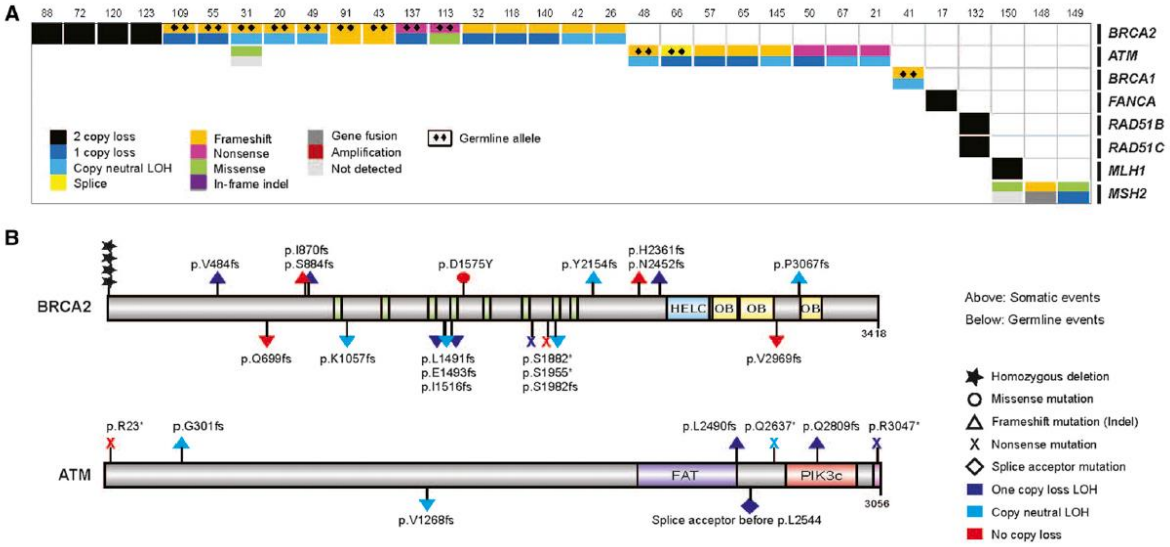
DDR MUTATIONS IN METASTATIC PROSTATE CANCER

Prevalence and Screening

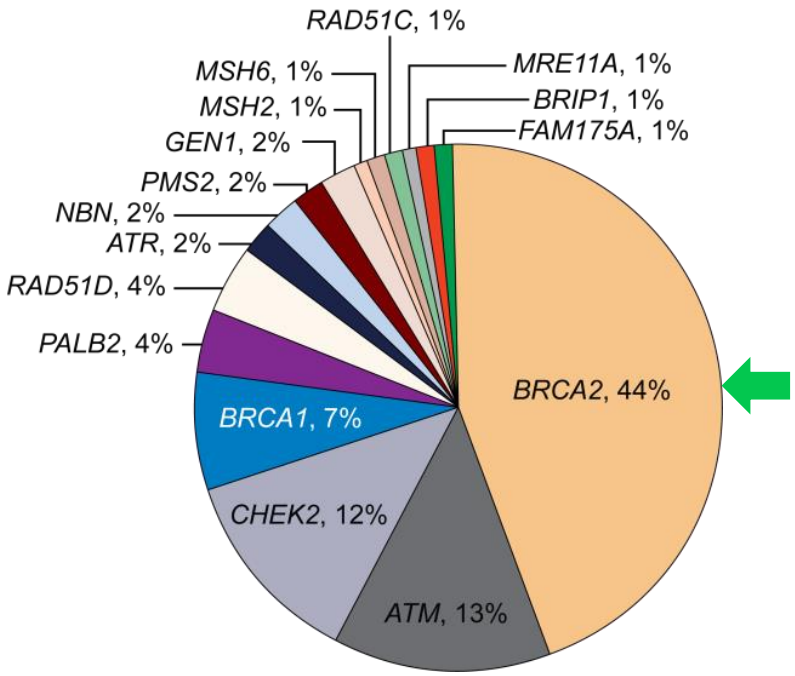
DNA REPAIR GENE ALTERATIONS (SOMATIC AND GERMLINE) ARE COMMON IN METASTATIC PROSTATE CANCER

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

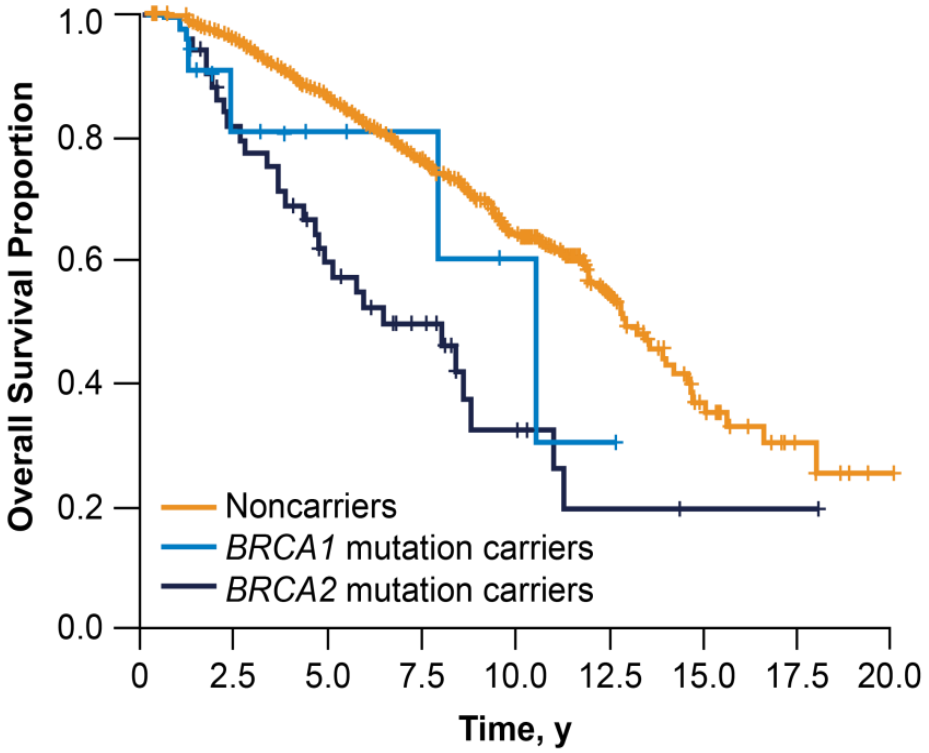


- **~12%** of men with metastatic prostate cancer have germline mutations in one or more of 16 DNA repair genes

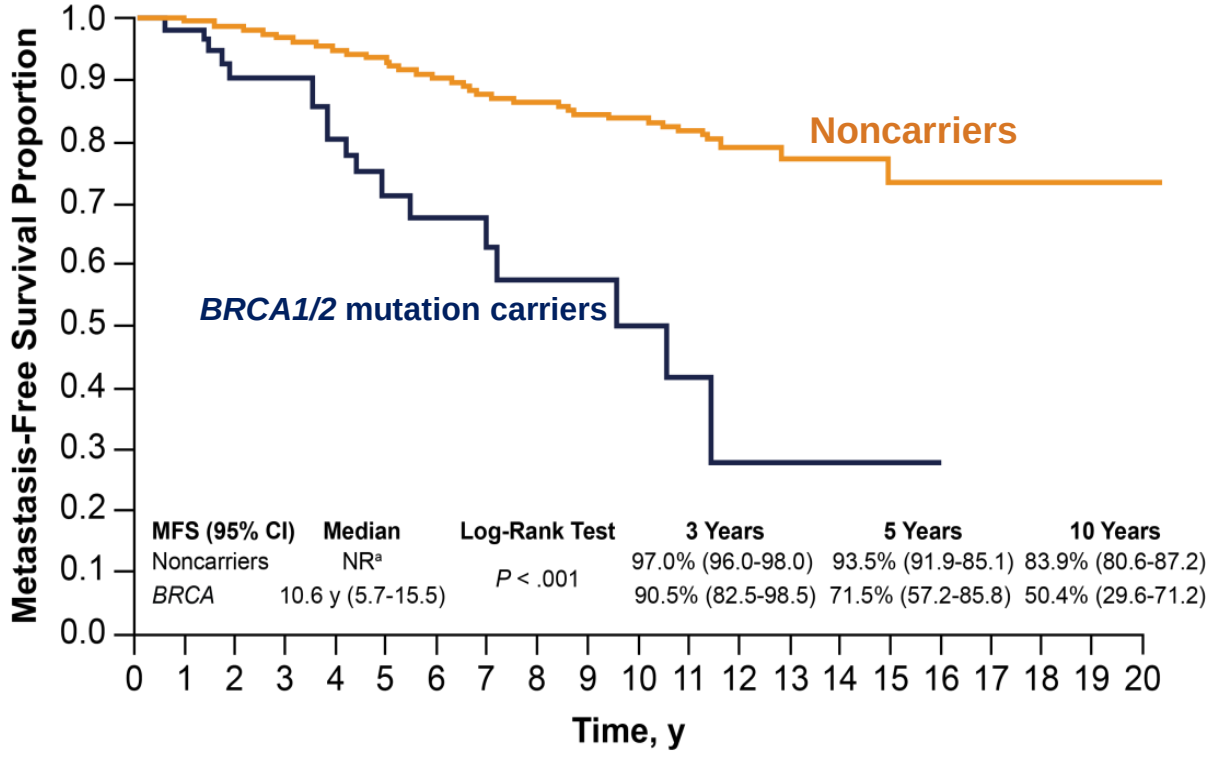
LOH, loss of heterozygosity; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer

1. Robinson D, et al. Cell. 2015;161:1215-1228; 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-453; 3. Antonarakis ES, et al. Eur Urol. 2018;74:218-225

BRCA2 CARRIERS WITH M0 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;31:1748-1757; 2. Castro E, et al. Eur Urol. 2015;68:186-193

FAMILY HISTORY IS THE STRONGEST KNOWN RISK FACTOR FOR PROSTATE CANCER

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- A father or brother with prostate cancer doubles a man's risk of prostate cancer
- A mother or sister with breast cancer diagnosed before age 50 significantly increases a woman's risk of breast cancer
- A mother or sister with breast cancer can affect a man's risk of prostate cancer

Chen YC, et al. Prostate. 2008;68(14):1582-1591; Colditz GA, et al. Breast Cancer Res Treat. 2012;133(3):1097-1104

NCCN GUIDELINES (V3.2022) FOR GENETIC TESTING

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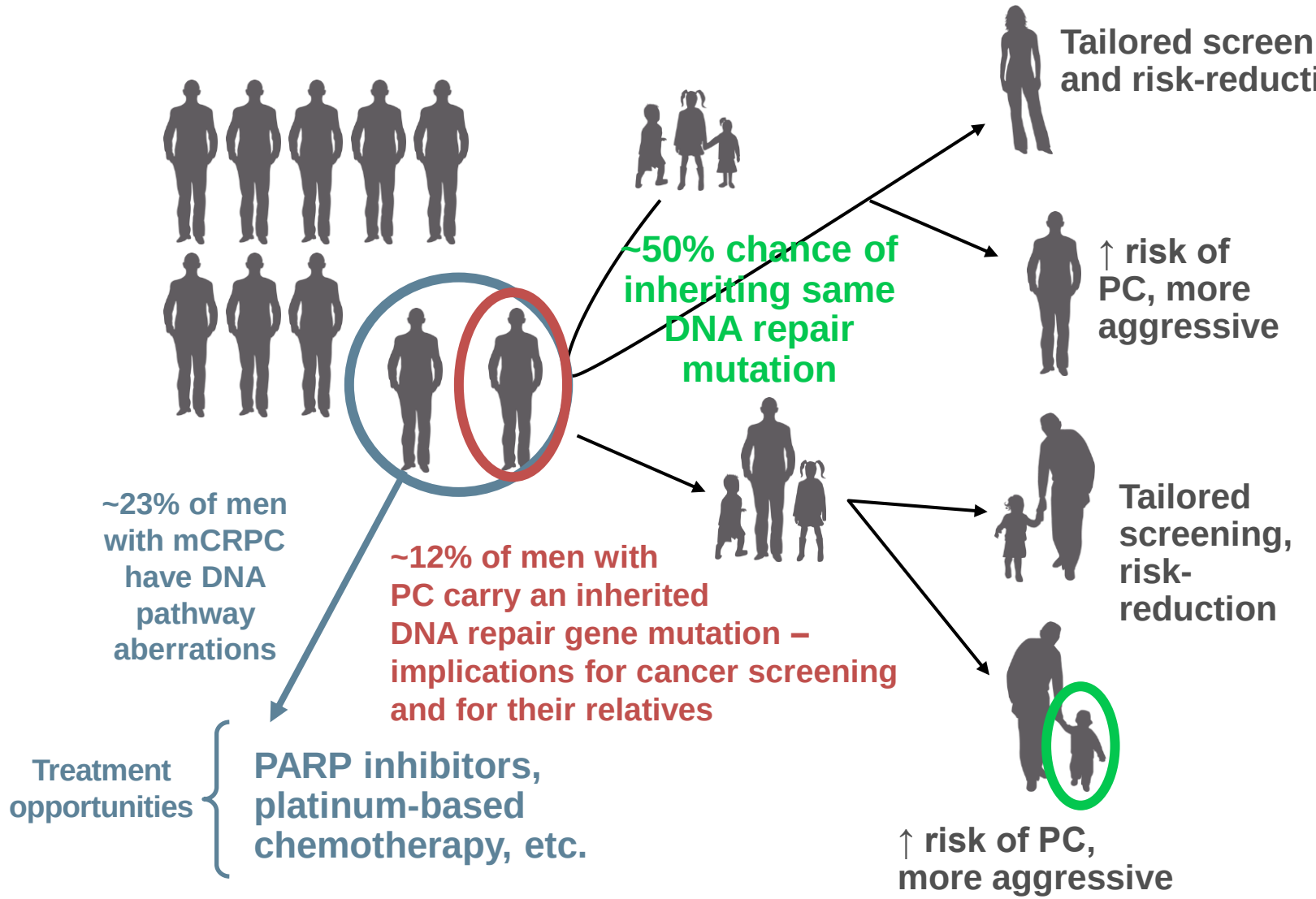
Germline testing	Somatic tumour testing
• Germline testing is recommended for patients with a personal history of PC in the following scenarios: – Metastatic, regional (node +), very high-risk localised, high-risk localised PC – By family history[a] and/or ancestry • ≥ 1 first-, second- or third-degree relative with: breast cancer at ≤50 y, male breast cancer, ovarian cancer, exocrine pancreatic cancer or metastatic, regional, very-high risk, high-risk PC at any age • ≥ 1 first-degree relative (brother/father) with PC[b] at ≤60 y • ≥ 2 first-, second- or third-degree relatives with: breast or PC[b] at any age • ≥ 3 first- or second- degree relatives with: Lynch syndrome-related cancers especially if diagnosed < 50y • A known family history of familial cancer risk mutation mutation (e.g. *BRCA1/2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM*) – Ashkenazi Jewish ancestry – Personal history of breast cancer	• Recommend evaluating tumour for alterations in homologous recombination DNA repair genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12* in patients with metastatic PC • Can be considered in men with regional PC • Testing for microsatellite instability-high or mismatch repair deficient status is recommended in patients with metastatic castration resistant prostate cancer (mCRPC), and may be considered in patients with regional or castration-naïve metastatic PC • TMB testing may be considered in patients with mCRPC

[a] Close blood relatives include 1st, 2nd and 3rd degree relatives on the same side of the family; [b]Family history of PC should not include relatives with clinically localised Grade Group 1 disease
ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer; TMB, tumour mutational burden

National Comprehensive Cancer Network. Prostate Cancer (Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed Feb 2022

CASCADING IMPACT



- Full family history should be collected:
  - 3 or 4 generation pedigree
  - Ancestry and consanguinity information
  - Any prior genetic testing
- Family history:
  - Guides choice of broad vs narrow gene panel
  - Determines a patient's criteria for testing
  - Identifies the most appropriate family members for testing
  - Informs screening if test is negative

HR, homologous recombination; mCRPC, metastatic castration resistant prostate cancer; PARP, poly-ADP ribose polymerase; PC, prostate cancer

Cheng HH, et al. J Natl Compr Canc Netw. 2019;17:515-521; Pritchard CC, et al. N Engl J Med. 2016;375:443-453; Szymaniak BM, et al. JCO Oncol Pract. 2020;16:811-819; Antonarakis ES, et al. Eur Urol. 2018;74:218-225

Figure adapted from Cheng H. https://www.ustoo.org/Pathways-Seattle-Webcast

HOW DO WE TEST?

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Germline

Somatic

MYRIAD myRisk® Hereditary Cancer

CARIS LIFE SCIENCES

GUARDANT

NEO GENOMICS

FOUNDATION MEDICINE

INVITAE

color

Ambry Genetics®

Academic/In house

TEMPUS

CONCLUSIONS

- **DDR mutations are a therapeutic target** in metastatic prostate cancer
- **PARPi** work by the concept of “synthetic lethality”
- **Somatic (in ~40% of cases = germline) mutations** related to DDR occur in 15-30% of metastatic prostate cancer
- Somatic and germline **testing should be considered for all patients with metastatic prostate cancer** and some patients with high-risk regional and locally-advanced prostate cancer
- AR inhibition induces HRR deficiency and **could increase susceptibility to PARP inhibition** in both DDR mutant and WT prostate cancer

DDR, DNA damage repair; PARPi, poly-ADP ribose polymerase inhibitors

WHY YOU SHOULD TREAT

PARP INHIBITORS: KEY EFFICACY AND SAFETY CONSIDERATIONS

Tanya Dorff, MD
Associate Professor of Medicine
Section Chief, Genitourinary Cancers,
City of Hope, Los Angeles, USA

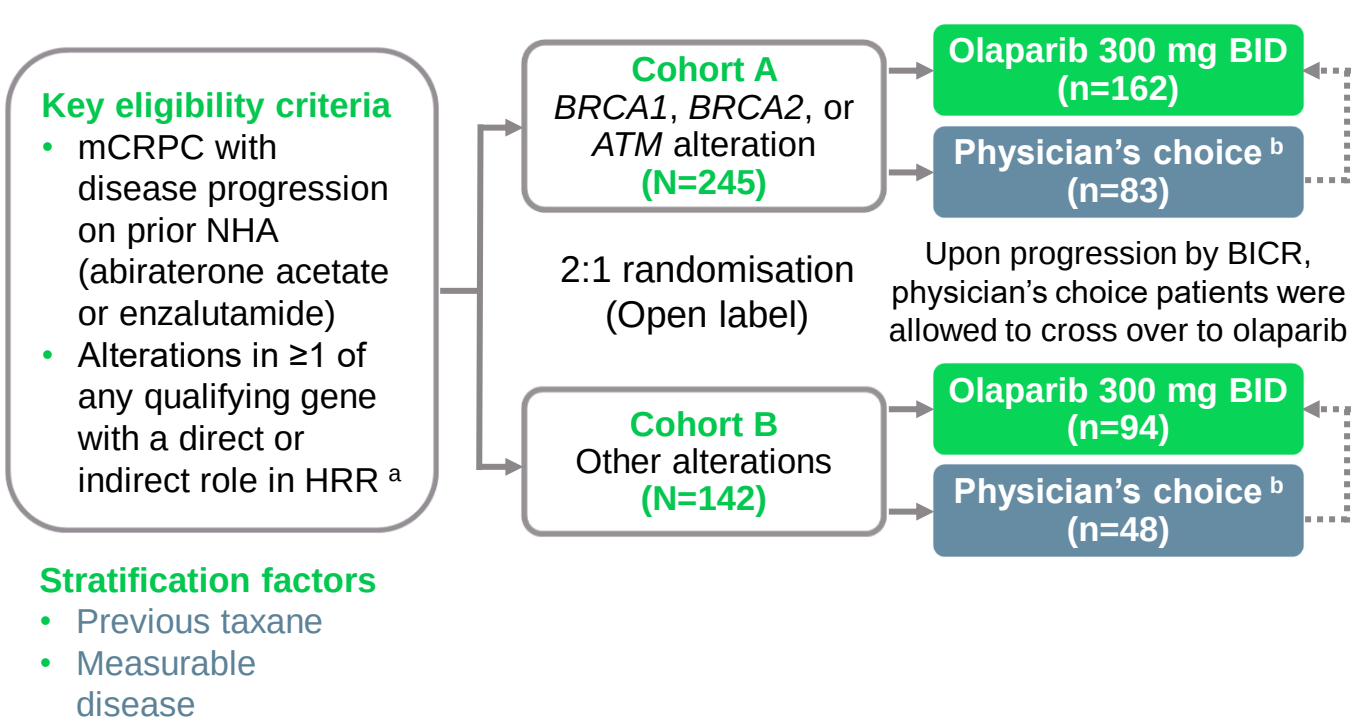
PARP, poly ADP ribose polymerase (PARP) inhibitors

DISCLOSURES

Assoc. Prof. Tanya Dorff has received financial support/sponsorship for research support, consultation or speaker fees from the following companies:

- Advanced Accelerator Applications, Bayer, BMS, Exelixis, Seattle Genetics

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

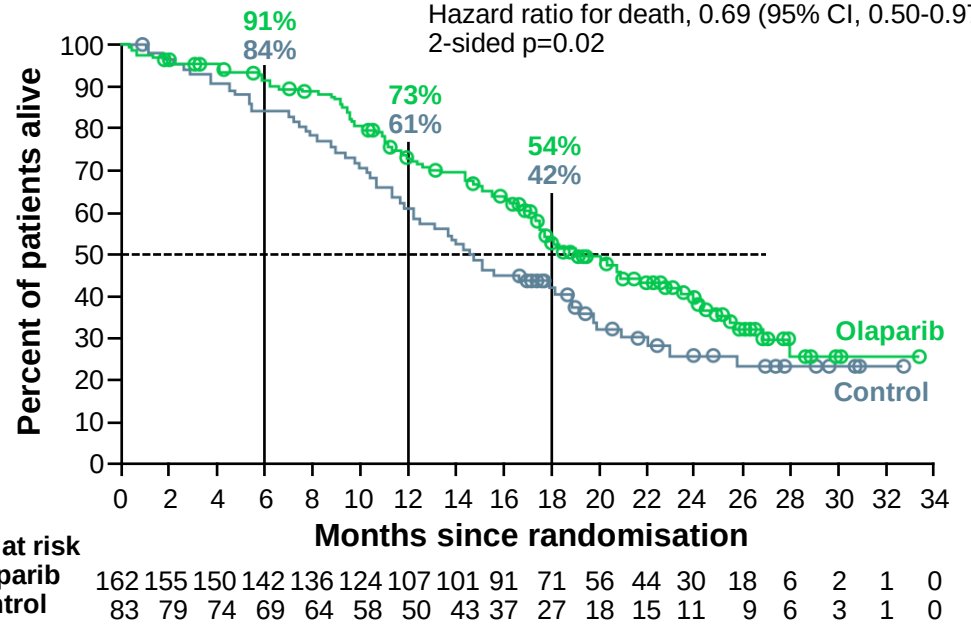
de Bono J, et al. N Engl J Med. 2020;382:2091-2102; Hussain M, et al. N Engl J Med. 2020;383(24):2345-2357

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)

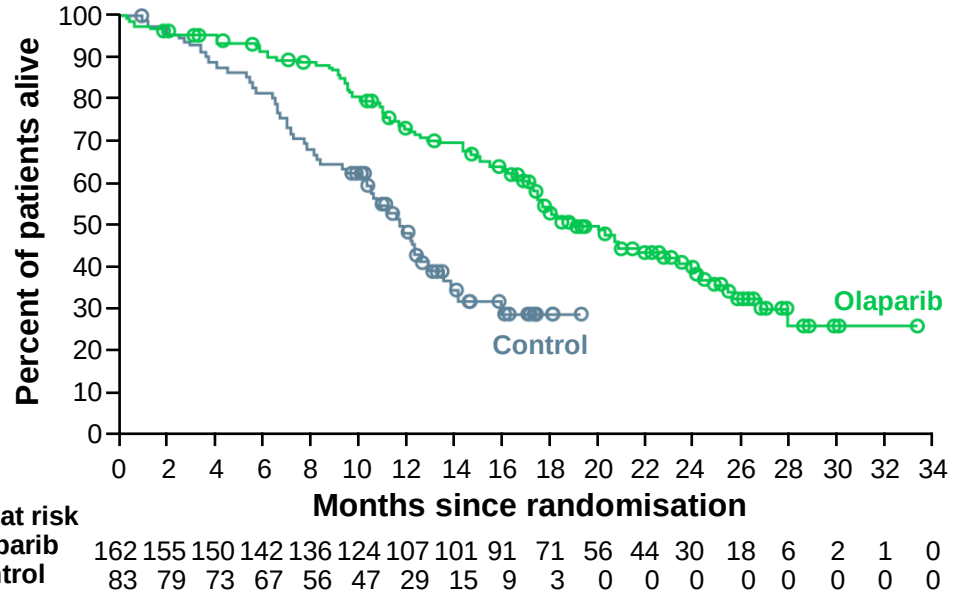
Hazard ratio for death, 0.69 (95% CI, 0.50-0.97)
2-sided p=0.02



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!

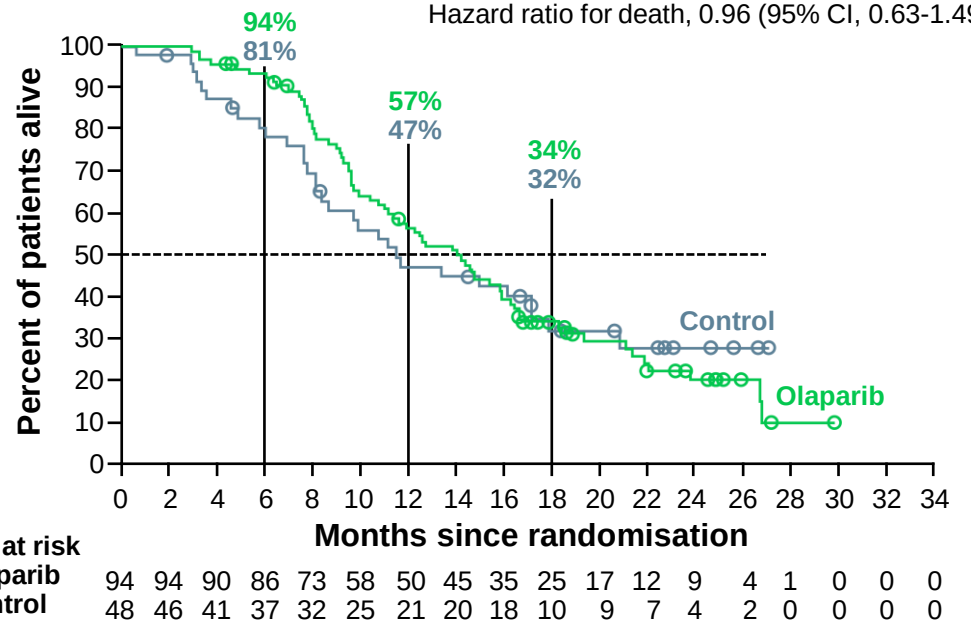
ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein; CI, confidence interval; HR, hazard ratio; OS, overall survival
Hussain M, et al. N Engl J Med. 2020;383(24):2345-2357

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)

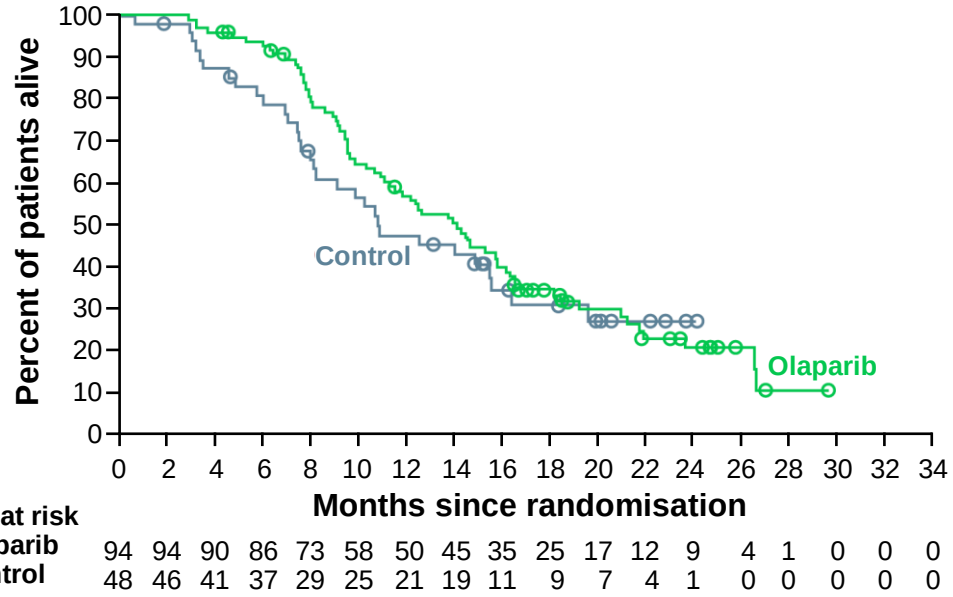
Hazard ratio for death, 0.96 (95% CI, 0.63-1.49)



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):2345-2357

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):2345-2357

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 bcal 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; 38:3763-3772

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

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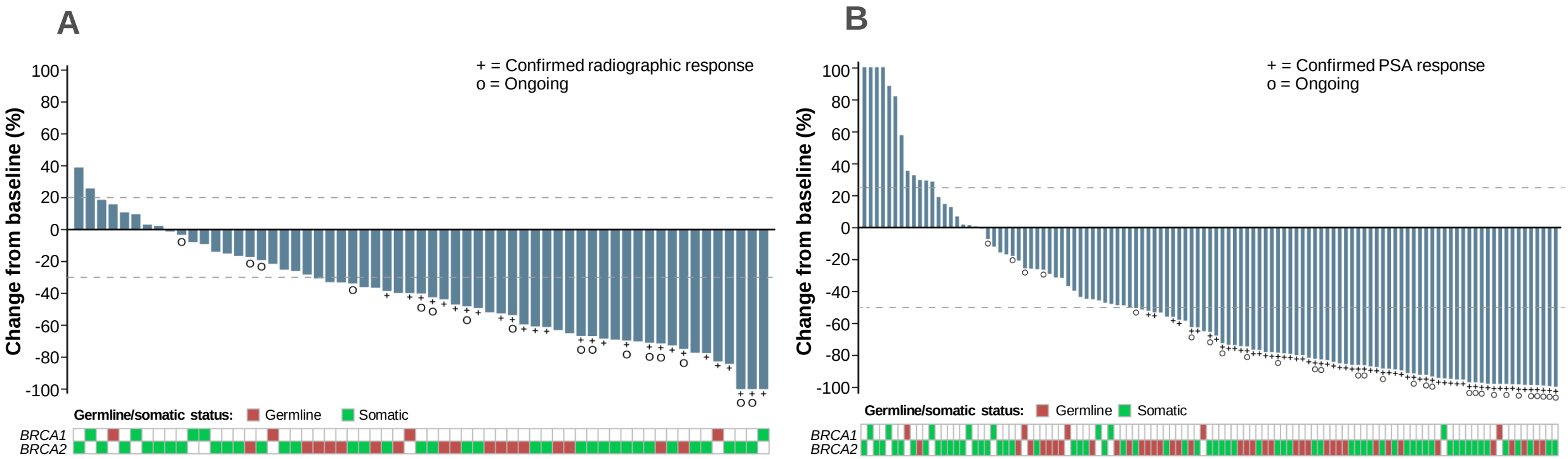
TUMOUR RESPONSE (EVALUABLE POPULATION)

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;38:3763-3772

TRITON2: RUCAPARIB IN mCRPC NON-BRCA DDR GENE ALTERATIONS

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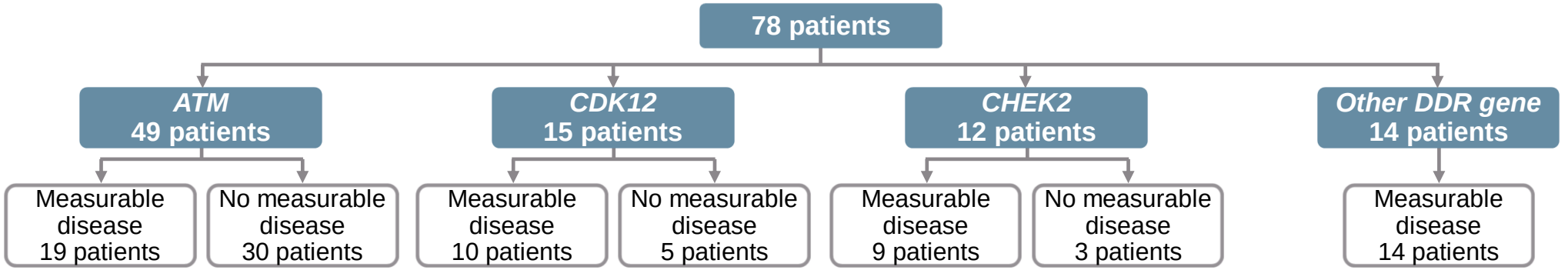

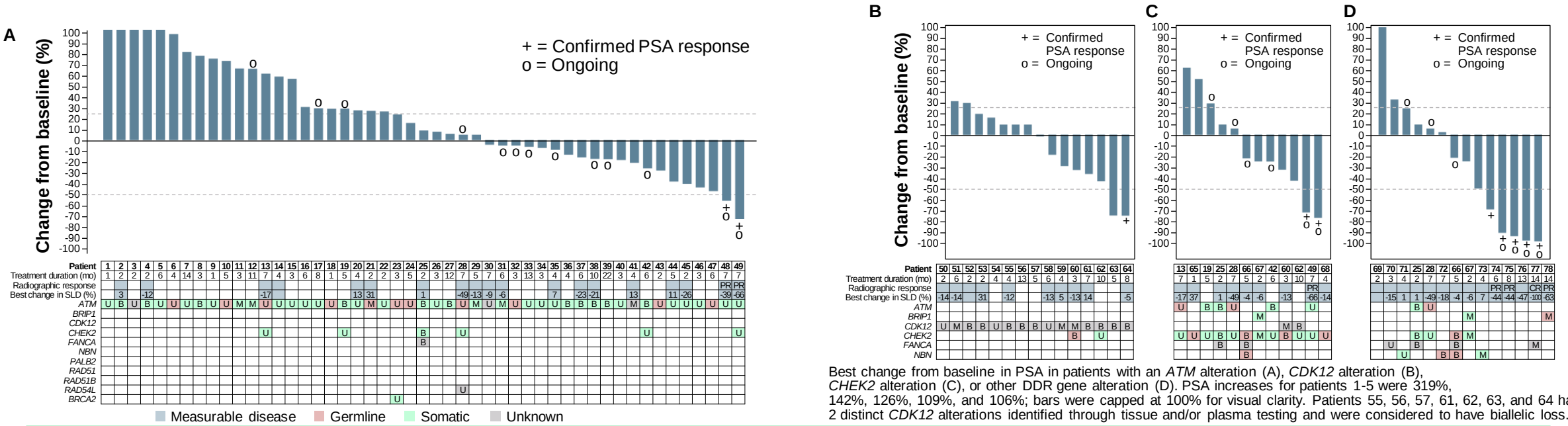

Best change from baseline in PSA in patients with an *ATM* alteration (A), *CDK12* alteration (B), *CHEK2* alteration (C), or other DDR gene alteration (D). PSA increases for patients 1-5 were 319%, 142%, 126%, 109%, and 106%; bars were capped at 100% for visual clarity. Patients 55, 56, 57, 61, 62, 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;26:2487-2496

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;38:3763-3772

OTHER PARPi IN DEVELOPMENT: RELATIVE STRENGTH

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PARP inhibitor	Enzyme FP IC_{50}[a]	Relative PARP trapping	Dose for pivotal trials
Olaparib	PARP1: 7 nM PARP2: 6 nM	1	300 mg bid
Niraparib	PARP1: 34 nM PARP2: 1,302 nM	2	300 mg qd
Rucaparib	PARP1: 7 nM PARP2: 123 nM	1	600 mg bid
Talazoparib	PARP1: 5 nM PARP2: 12 nM	100	1 mg qd

bid, twice daily; FP, fluorescence polarisation; IC50, 50% inhibitory concentration; PARP, poly-ADP ribose polymerase; qd, once daily

[a] The smaller the value, the lower the concentration of drug required to have an effect

Antonarakis E, et al. Eur Urol Oncol. 2020;3(5):594-611

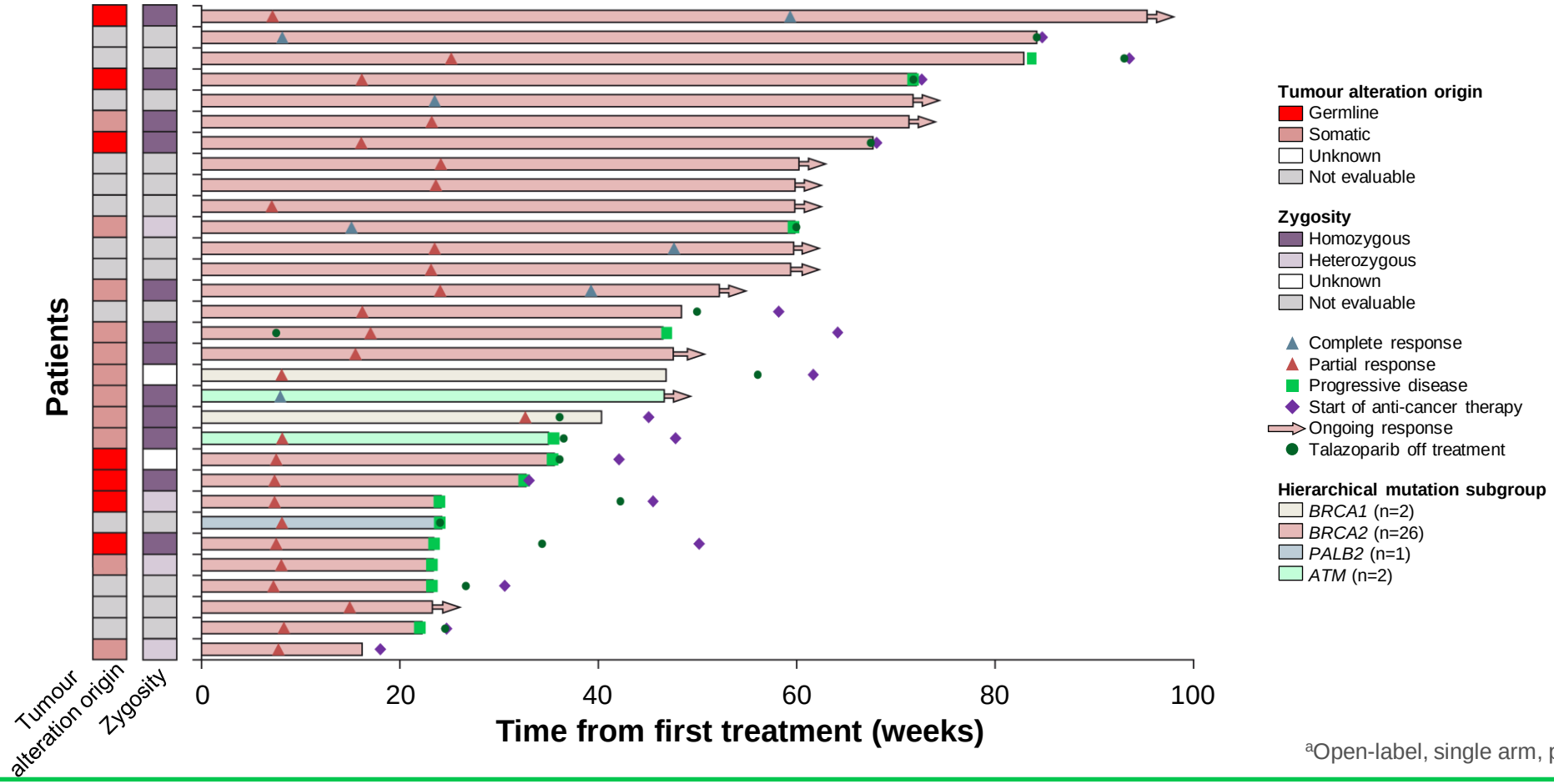
PARPi IN DEVELOPMENT FOR mCRPC

Clinical trial	Study Type	Treatment	Key efficacy results	Key safety results (PARP inhibitor arm)
GALAHAD[1] (NCT02854436)	Phase 2, single arm, open label	Niraparib	Final analysis median follow-up duration: 10 months **ORR:** *BRCA* cohort: 34.2% (n=26/76); non-*BRCA* cohort: 10.6% (n=5/47) **Median rPFS (mo):** *BRCA* cohort (n=142): 8.08 non-*BRCA* (N=81): 3.71	Most common grade 3+ AEs: Anaemia: 33% Thrombocytopenia: 16% Neutropenia: 10%
TALAPRO-1[2] (NCT03148795)	Phase 2, single arm, open label	Talazoparib	Median follow-up: 16.4 months **ORR (n=104):** *BRCA1/2*: 46% *ATM*: 12% *PALB2*: 25% Other: 0% **Median rPFS (mo):** *BRCA1/2* (n=61): 11.2 *PALB2* (n=4): 5.6 *ATM* (n=17): 3.5	Most common grade 3+ AEs: Anaemia: 31% Thrombocytopenia: 9% Neutropenia: 8%

AEs, adverse events; ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein; m, mutated; mCRPC, metastatic castration resistant prostate cancer; mo, months; OS, overall survival; ORR, objective response rate; PARP, poly-ADP ribose polymerase; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression free survival. Antonarakis E, et al. Eur Urol Oncol. 2020;3(5):594-611; 1. Smith M, et al. Lancet Oncology 2022. 23: 362-373; 2. de Bono J, et al. Lancet Oncol. 2021; 22: 1250-1264;

WHAT SHOULD YOU/YOUR PATIENT EXPECT: RESPONSE

TALAPRO-1[a]: RESPONSE TO TALAZOPARIB IN mCRPC PATIENTS



[a]Open-label, single arm, phase 2 trial

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein

DeBono JS, et al. Lancet Oncol. 2021;22:1250-1264

TALAZOPARIB SIDE EFFECTS

TALAPRO-1 STUDY: ALL-CAUSE TEAEs INCIDENCE ≥10% (N=127)

	Grade 1-2	Grade 3	Grade 4
Any treatment-emergent adverse event	50 (39%)	57 (45%)	4 (3%)
Non-haematological			
Nausea	39 (31%)	3 (2%)	0
Decreased appetite	32 (25%)	4 (3%)	0
Asthenia	25 (20%)	5 (4%)	0
Fatigue	23 (18%)	2 (2%)	0
Constipation	22 (17%)	1 (1%)	0
Diarrhoea	21 (17%)	0	0
Peripheral oedema	20 (16%)	1 (1%)	0
Back pain	16 (13%)	1 (1%)	0
Dyspnoea	15 (12%)	2 (2%)	0
Vomiting	15 (12%)	2 (2%)	0
Dizziness	15 (12%)	0	0

	Grade 1-2	Grade 3	Grade 4
Haematological			
Any	22 (17%)	41 (32%)	5 (4%)
Anaemia	23 (18%)	39 (31%)	0
Thrombocytopenia	13 (10%)	7 (6%)	4 (3%)
Neutropenia	11 (9%)	10 (8%)	0
Leukopenia	12 (9%)	1 (1%)	0
Lymphopenia	4 (3%)	4 (3%)	2 (2%)

Data are n (%). Data presented are for events reported in at least 10% of patients

DeBono JS, et al. Lancet Oncol. 2021;22:1250-1264

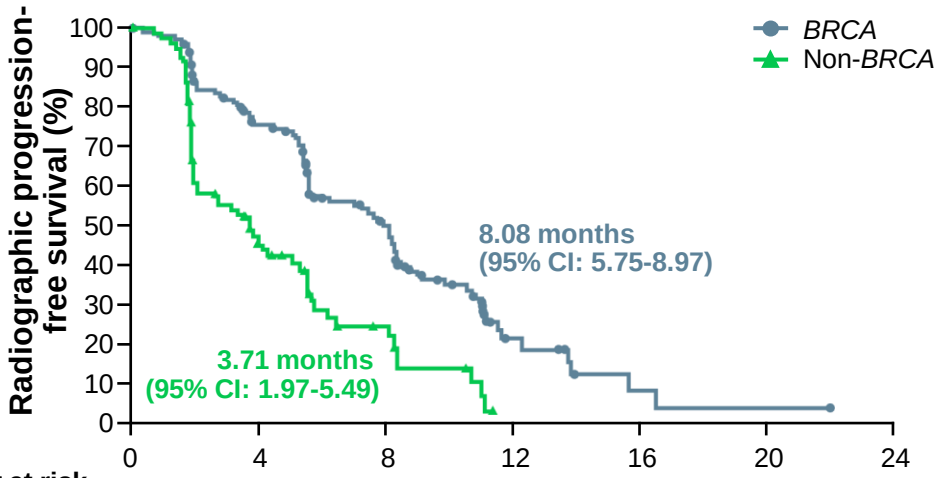
NIRAPARIB: GALAHAD, PHASE 2, SINGLE-ARM STUDY

OBJECTIVE RESPONSE RATE

	Measurable *BRCA* cohort[a] (N=76)	Measurable non-*BRCA* cohort[b] (N=47)
Objective response rate	26 (34.2%; 23.7-46.0)	5 (10.6%; 3.5-23.1)
Complete response	2 (3%)	0
Partial response	24 (32%)	5 (11%)

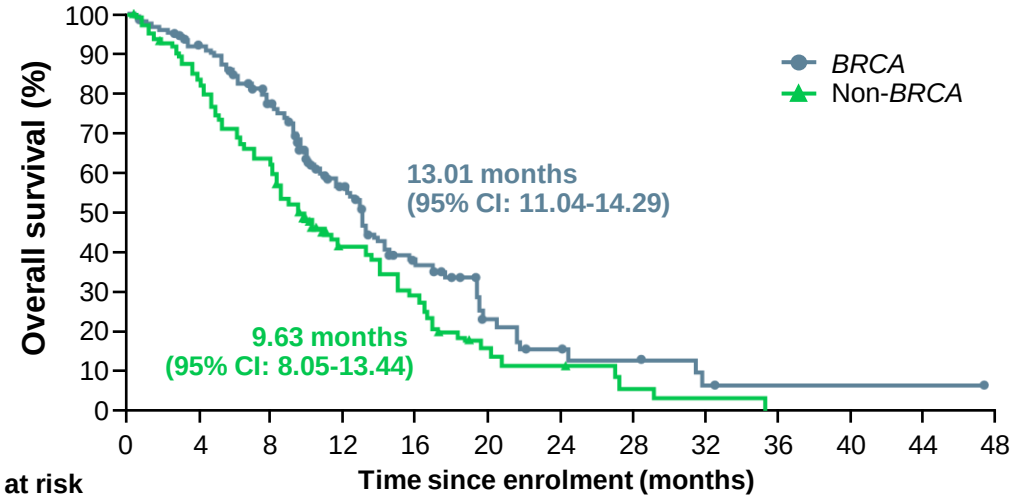
Data are n (%; 95% CI) or n (%). [a] Primary efficacy analysis cohort.
[b] Objective response rate in measurable non-BRCA patients with a secondary efficacy endpoint

RADIOGRAPHIC PROGRESSION-FREE SURVIVAL



Number at risk (number censored)							
BRCA	142 (0)	91 (19)	49 (33)	9 (51)	2 (54)	1 (54)	0 (55)
Non-*BRCA*	81 (0)	27 (15)	10 (21)	0 (24)	0 (24)	0 (24)	0 (24)

OVERALL SURVIVAL



Number at risk (number censored)													
BRCA	142 (0)	126 (5)	100 (11)	53 (33)	26 (43)	12 (49)	7 (50)	5 (51)	2 (52)	1 (53)	1 (53)	1 (53)	0 (54)
Non-*BRCA*	81 (0)	66 (2)	49 (2)	23 (13)	16 (13)	7 (15)	5 (15)	2 (16)	1 (16)	0 (16)	0 (16)	0 (16)	0 (16)

CI, confidence interval

Smith M, et al. Lancet Oncol. 2022;23:362-373

NIRAPARIB SIDE EFFECTS

GALAHAD STUDY: ALL-CAUSE TEAEs (N=288)

	Grade 1-2	Grade 3	Grade 4	Grade 5
Nausea	154 (53%)	15 (5%)	0	0
Vomiting	101 (35%)	10 (3%)	0	0
Constipation	95 (33%)	5 (2%)	1 (<1%)	0
Fatigue	87 (30%)	19 (7%)	0	0
Decreased appetite	85 (29%)	8 (3%)	0	0
Anaemia	61 (21%)	92 (32%)	2 (1%)	1 (<1%)
Thrombocytopenia	52 (18%)	24 (8%)	23 (8%)	0
Back pain	51 (18%)	13 (4%)	0	0
Arthralgia	38 (13%)	6 (2%)	0	0
Asthenia	37 (13%)	11 (4%)	0	0
Neutropenia	27 (9%)	17 (6%)	11 (4%)	0
Bone pain	23 (8%)	9 (3%)	0	0
Hypertension	22 (8%)	12 (4%)	0	0
Blood alkaline phosphatase increased	15 (5%)	11 (4%)	0	0
Stomatitis	15 (5%)	6 (2%)	0	0
Leukopenia	14 (5%)	11 (4%)	3 (1%)	0
γ-glutamyl transferase increased	13 (4%)	11 (4%)	1 (<1%)	0
Lymphopenia	11 (4%)	12 (4%)	1 (<1%)	0
Hypophosphataemia	7 (2%)	6 (2%)	1 (<1%)	0
Spinal cord compression	1 (<1%)	7 (2%)	0	0
General physical health deterioration	1 (<1%)	7 (2%)	1 (<1%)	4 (1%)

Data are n (%). Data are presented for grade 1–2 treatment-emergent adverse events with a combined incidence of ≥20% or any higher-grade (grade 3–5) treatment-emergent adverse events with an incidence of ≥2%.

Smith M, et al. Lancet Oncol. 2022;23:362-373

PARP INHIBITORS IN OTHER CANCER

APPROVED INDICATIONS

	Olaparib	Rucaparib	Niraparib	Talazoparib
Ovarian Cancer	√	√	√	
Breast Cancer	√			√
Pancreatic Cancer	√			
Prostate Cancer	√	√		

- Extensive safety data reported across all tumour types

Product Prescribing Information

SAFETY OF PARP INHIBITORS IN OTHER CANCERS/ LTFU

- **Maintenance Olaparib in Ovarian CA with BRCA mutation[1,2] (SOLO1/GOG3004)** n=260
  - 1% MDS/AML in primary report; no additional cases in the long-term follow up
- **Olaparib LTFU Breast/Ovarian/Fallopian tube cancer[3]** n=21:
  - Grade 2+ anaemia most common in cycles 1-6 (29%); dropped to 19% in cycles 7-12 and 18% in cycles 13-24 while grade 2+ lymphopaenia stable over time
- **Rucaparib maintenance Ovarian CA (ARIEL3)[4]**
  - 23% grade 3+ anaemia in those taking >12 months, 21% in 6-≤ 12 months
- **Niraparib LTFU Ovarian CA (ENGOT-OV16/NOVA)[5]**
  - Grade ≥ 3 thrombocytopenia decreased from 28% (month 1) to 9% and 5% (months 2 and 3, respectively) with protocol-directed dose interruptions and/or reductions
  - AML and MDS were reported in 2 and 6 niraparib-treated patients, respectively, and in 1 placebo patient each
- **Talazoparib final OS analysis Breast CA (EMBRACA trial)[6]**
  - Haematologic grade 3-4 AEs in 56.6% of patients treated with talazoparib and 38.9% of patients, respectively.
  - Grade 3 or 4 anaemia was reported in 40.2% of patients who received talazoparib and 4.8% of patients who received placebo
  - No confirmed cases of MDS. 1 case of AML in a patient who received capecitabine and 1 case of AML in a patient who received talazoparib

AML, acute myeloid leukaemia; CA, cancer; LTFU, long-term follow-up; MDS, myelodysplastic syndromes; OS, overall survival

1. Moore K, et al. N Engl J Med. 2018;379(26):2495-505; 2. Banerjee S, et al. Lancet Oncol. 2021;22:1721-31; 3. Van der Noll R, et al. Br J Cancer. 2015;113:396-402; 4. Clamp AR, et al. Int J Gyn Cancer. 2021;31:949-58; 5. Mirza M, et al. Gynecol Oncol 2020;159:442-8; 6. Litton J, et al. Annals of Oncology. 2020;31:1526-35

TOXICITY MANAGEMENT

Bone marrow toxicities are predominant cause of treatment discontinuation

- Anaemia
  - In TALAPRO-1: 35% received ≥1 blood transfusion
  - In PROfound: 21% grade 3+ anaemia
  - In TRITON2: 25.2% grade 3+ anaemia, 28% ≥1 transfusion
- Leukopenia/infection
  - 8% grade 3 ANC talazoparib, 4% grade 3+ olaparib
- Pulmonary emboli
  - PROfound: 4% with olaparib vs 1% with abi/enza control; 6% in TALAPRO-1
- No MDS or AML seen

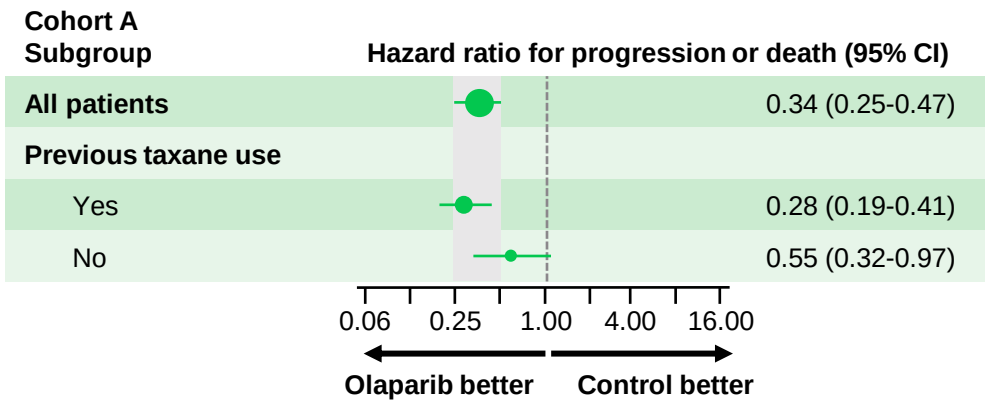
Abi, abiraterone; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; enza, enzalutamide; MDS, myelodysplastic syndromes

DeBono J, et al. N Engl J Med. 2020;382(22):2091-2102; Abida W, et al. J Clin Oncol. 2020;38:3763-3772; DeBono J, et al. Lancet Oncol. 2021;22:1250-1264

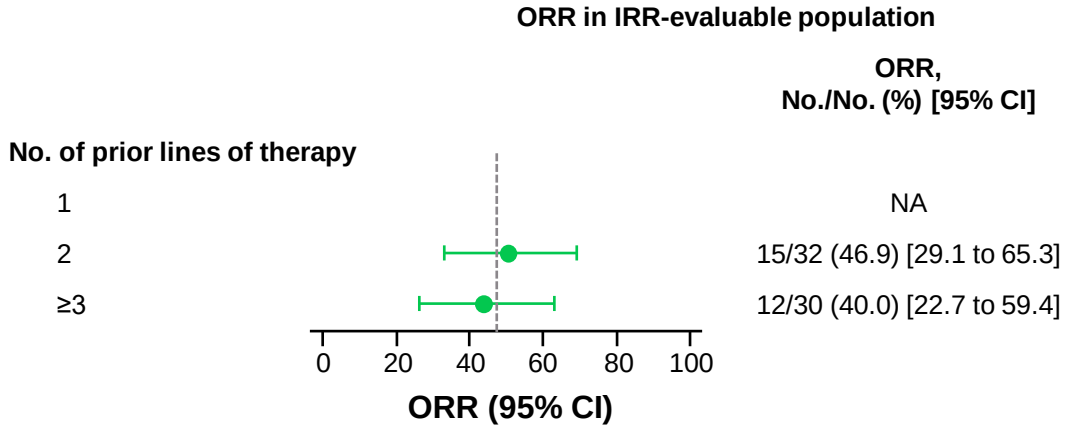
QUESTIONS OF SEQUENCING

- Most PARPi trials mCRPC include post-docetaxel majority
  - PROFOUND: 35% of patients without prior taxanes
  - TALAPRO-1: nearly 50% had two prior lines of taxane chemo
  - TRITON2: rucaparib lumped AR and chemo lines

PROfound



TRITON2



AR, androgen receptor; chemo, chemotherapy; CI, confidence interval; IRR, independent radiology review; mCRPC, metastatic castration resistant prostate cancer; ORR, objective response rate; PARPi, poly-ADP ribose polymerase inhibitors

DeBono J, et al. N Engl J Med. 2020;382(22):2091-2102; Abida W, et al. J Clin Oncol. 2020;38:3763-3772; DeBono J, et al. Lancet Oncol. 2021;22:1250-1264; DeBono J, et al. Journal of Clinical Oncology 2020; 38, no. 6_suppl: 119-119.

CONCLUSIONS

- Level 1 evidence for overall survival prolongation with olaparib in *HRR*-mutated *(particularly BRCA)* mCRPC
  - Mostly post-taxane chemo
- Lower-level evidence for *ATM* and other HRD (non-*BRCA* mutations)
  - Need more patients with these alterations
- Level 2 evidence for rucaparib, talazoparib
  - Strong efficacy signal
- Toxicity: primarily myelosuppression (ANAEMIA)
- Optimal sequence of PARPi is unknown
- Combination strategies and patient selection are still being defined

ATM, ataxia telangiectasia mutated; BRCA, breast cancer type susceptibility protein; chemo, chemotherapy; HRD, homologous repair defects; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; PARPi, poly-ADP ribose polymerase inhibitors

WHEN TO CONSIDER COMBINATIONS

COMBINATION THERAPY WITH PARPi STRATEGY FOR IMPROVING FIRST-LINE THERAPY IN mCRPC

Prof. Fred Saad, MD FRCS
Professor and Chairman of Urology, Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center, Montreal, QC, Canada

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

DISCLOSURES

Prof. Fred Saad has received honorarium as a consultant and funding for research (institution) from the following companies:

- Amgen, Astellas, AstraZeneca, Bayer, BMS, Janssen, Myovant, Pfizer, Sanofi

PHASE 3 TRIALS IN mCRPC

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All studies monotherapeutic and had an inactive/non-life prolonging control arm

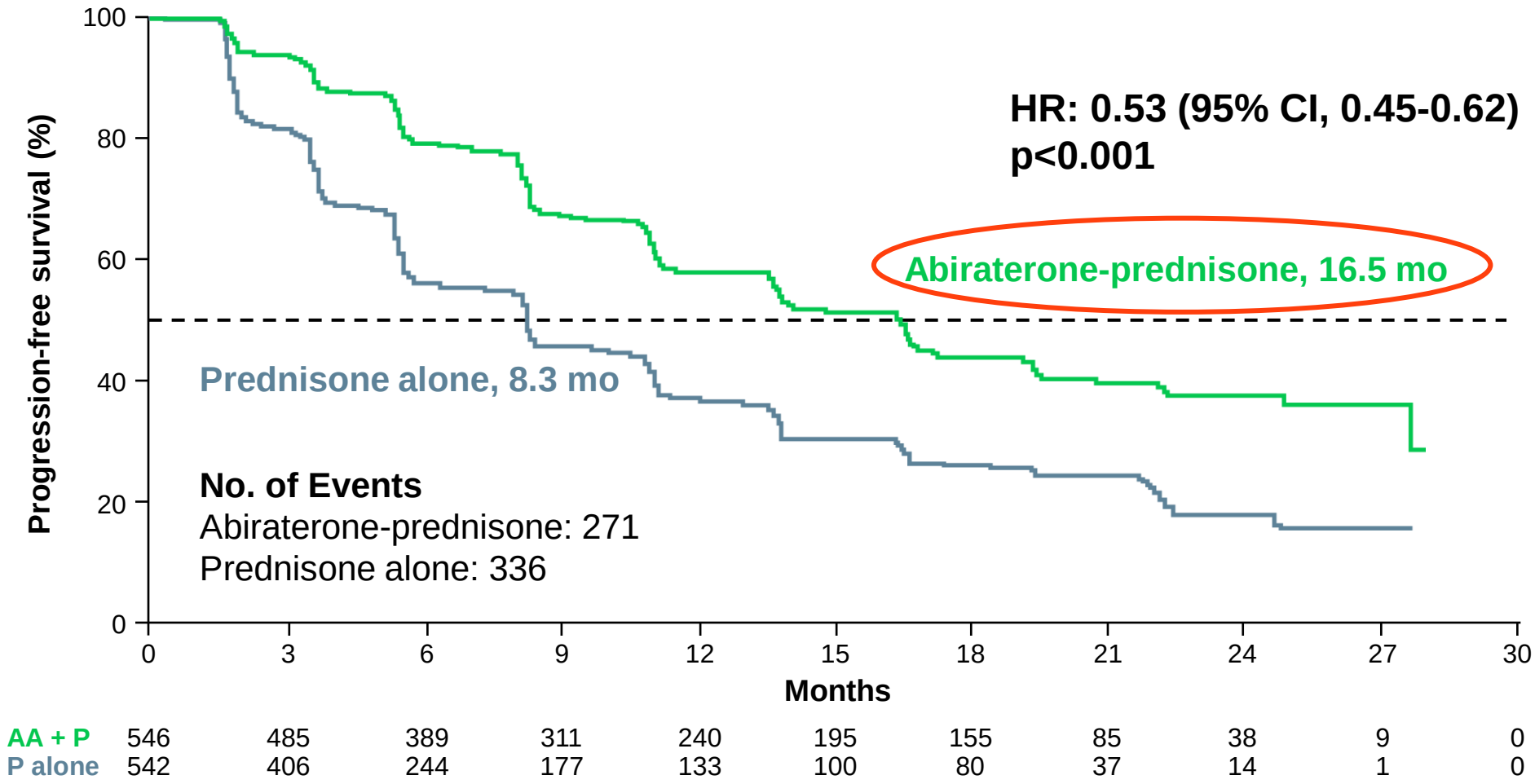
Study	Agents	N	Indication	HR	ΔOS (mo)
TAX-327[1]	DOC / P vs mito / P	1006	mCRPC, symptomatic or not	0.76	+2.4
COU-AA-302[2]	ABI / P vs P	1088	mCRPC (pre-DOC), mild / no symptoms No visceral metastases	0.81	+4.4
COU-AA-301[3]	ABI / P vs P	1195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL[4]	ENZ vs PBO	1717	mCRPC (pre-DOC), mild / no symptoms	0.77	+4.0
AFFIRM[5]	ENZ vs PBO	1199	mCRPC (post-DOC)	0.63	+4.8
TROPIC[6]	CABA / P vs mito / P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[7]	Radium-223 vs PBO	921	mCRPC (post-DOC or ineligible/declined DOC)	0.70	+3.6
PROfound[8]	Olaparib vs NHT	245[a]	mCRPC post-NHT (with HRRm)	0.69[a]	+4.4

[a]Results for cohort A of study: patients with alterations in *BRCA1, BRCA2, ATM*

ABI, abiraterone; CABA, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; mCRPC, metastatic castration resistant prostate cancer; mito, mitoxantrone; mo, months; NHT, neoadjuvant hormonal therapy; OS, overall survival; P, prednisone; PBO, placebo

1. Tannock IF, et al. N Engl J Med. 2004;351:1502-1512; 2. Ryan CJ, et al. Lancet Oncol. 2015;16:152-160; 3. Fizazi K, et al. Lancet Oncol. 2012;13(10):983-992; 4. Beer TM, et al. Eur Urol. 2017;71:151-154; 5. Scher HI, et al. N Engl J Med. 2012;367:1187-1197; 6. de Bono JS, et al. Lancet. 2010;376:1147-1154; 7. Parker C, et al. N Engl J Med. 2013;369: 213-23; 8. Hussain M, et al. N Engl J Med. 2020;383:2345-2357

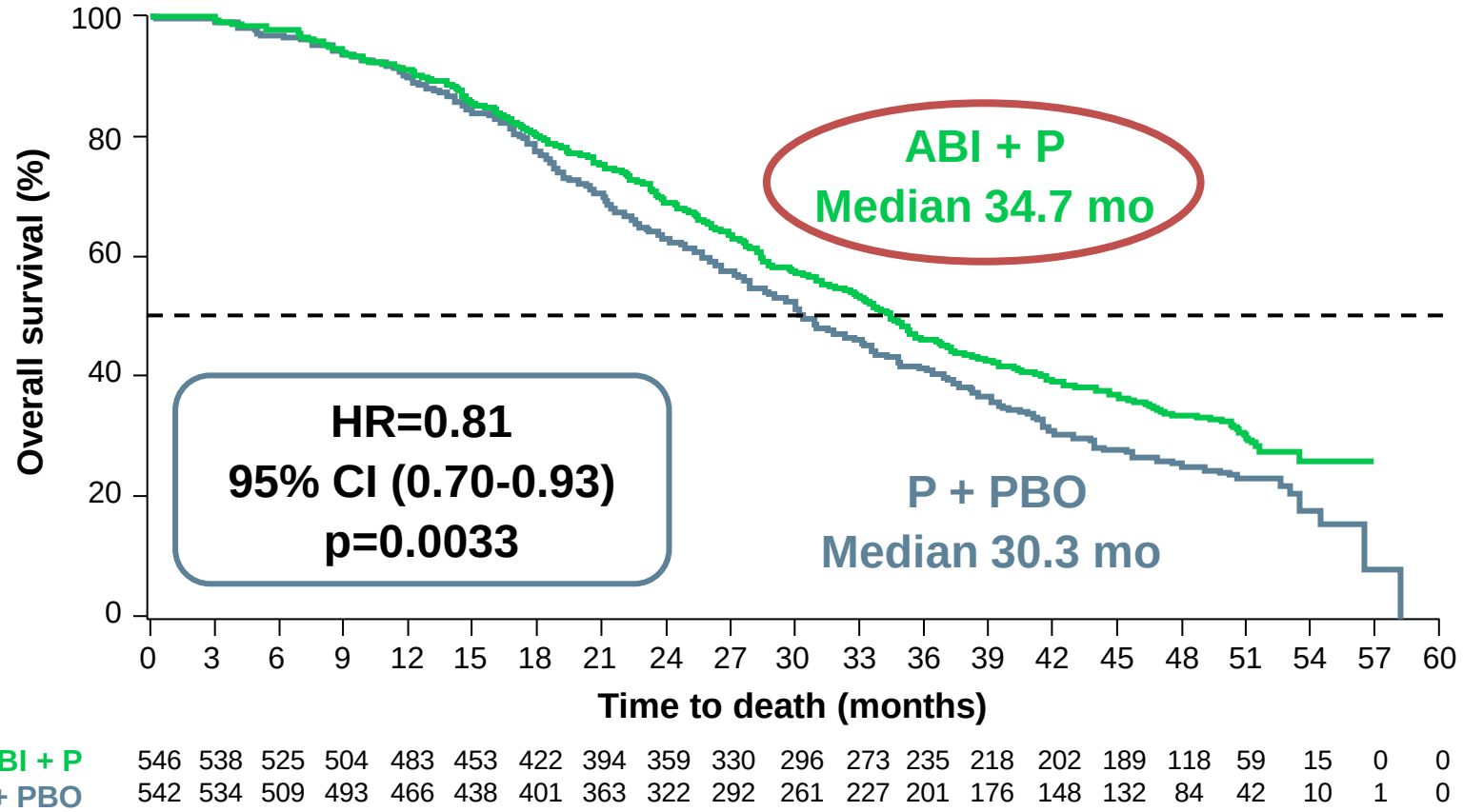
ABIRATERONE: RADIOGRAPHIC PROGRESSION-FREE SURVIVAL



AA, abiraterone acetate; CI, confidence interval; HR, hazard ratio; P, prednisone

Ryan C, et al. N Engl J Med 2013; 368:138-148

ABIRATERONE FIRST-LINE: OVERALL SURVIVAL



ABI, abiraterone; CI, confidence interval; HR, hazard ratio; mo, months; P, prednisone; PBO, placebo

Ryan CJ, et al. Lancet Oncol. 2015;16:152-160

WHY DID PATIENTS LIVE SO LONG?
PATIENTS BETTER TREATED THAN IN THE REAL WORLD

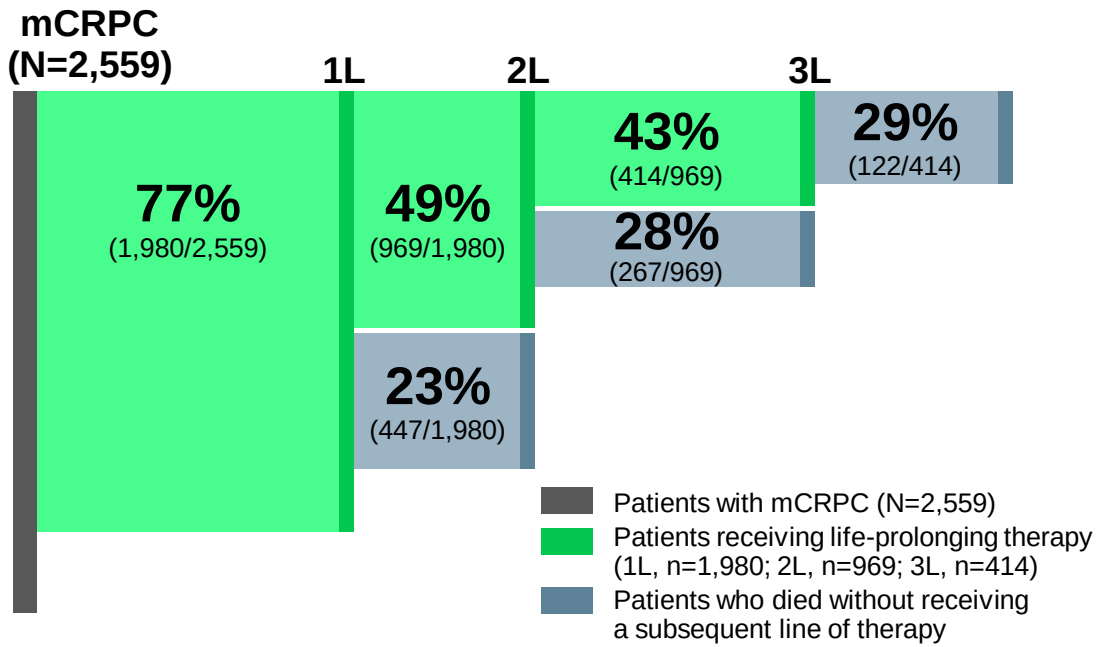
Subsequent therapy[1]	ABI + P (N=546)	P + PBO (N=542)
N (%) with selected subsequent therapy	365 (67%)	435 (80%)
Subsequent therapies		
Abiraterone	69 (13%)	238 (44%)
Cabazitaxel	100 (18%)	105 (19%)
Docetaxel	311 (57%)	331 (61%)
Enzalutamide	87 (16%)	54 (10%)
Ketoconazole	42 (8%)	68 (13%)
Radium-223	20 (4%)	7 (1%)
Sipuleucel-T	45 (8%)	32 (6%)

ABI, abiraterone; P, prednisone; PBO, placebo

1. Ryan CJ, et al. Lancet Oncol. 2015;16:152-160

REAL-WORLD TREATMENT PATTERNS IN mCRPC

PATIENTS WITH mCRPC RECEIVING LIFE-PROLONGING ANTI-CANCER TREATMENT BY LINE OF THERAPY



38%

of all mCRPC patients received 2L therapy (969/2,559)

16%

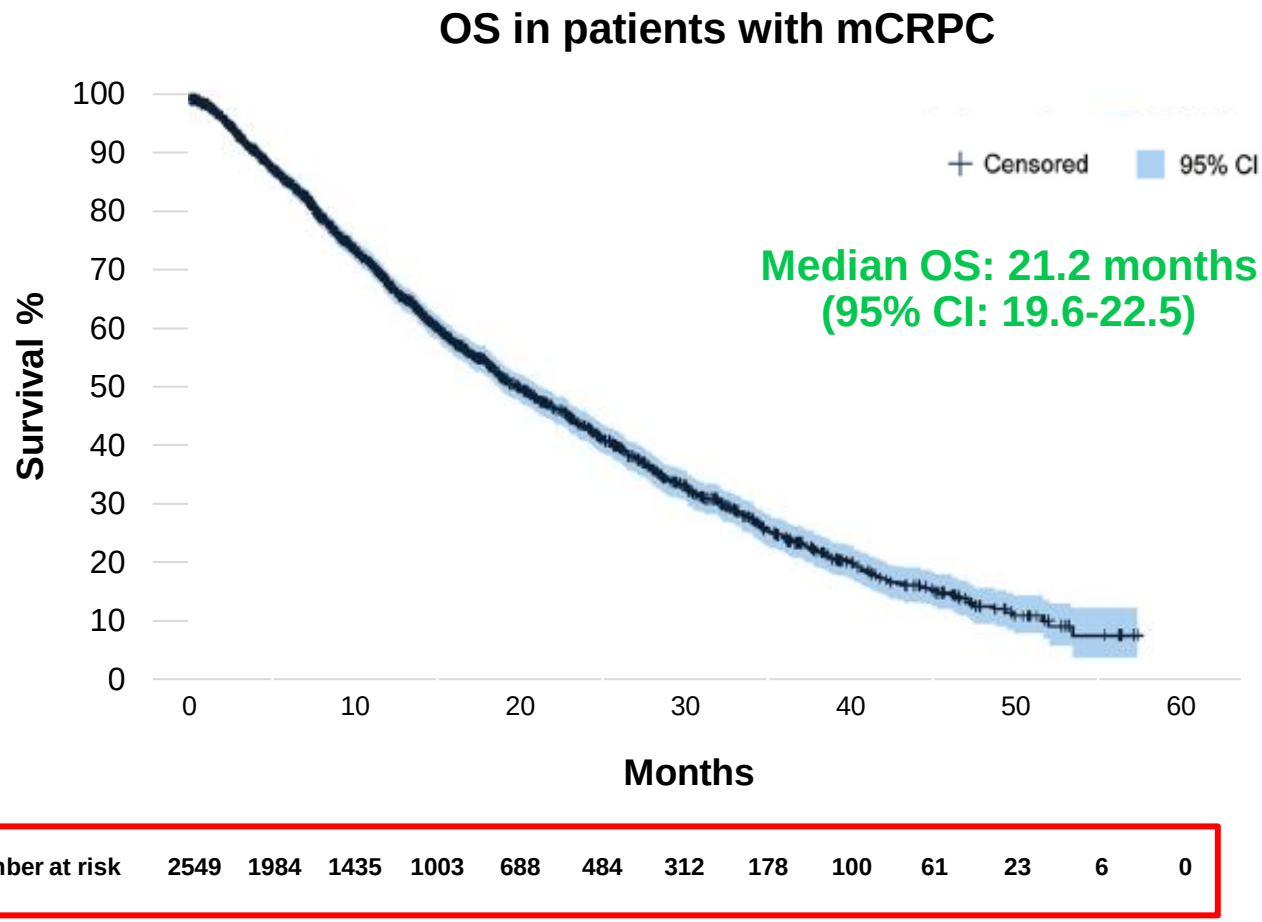
of all mCRPC patients received 3L therapy (414/2,559)

A total of 23%, 28% and 29% of patients did not receive a subsequent line of therapy after 1L, 2L and 3L therapy, respectively. In this Sankey diagram, a node to the right illustrates patients with mCRPC (grey) transitioning to a subsequent line of therapy (green) or death without receiving a subsequent line (blue).

1L, first line; 2L, second line; 3L, third line; mCRPC, metastatic castration resistant prostate cancer

George DJ, et al. Clin Genitourin Cancer. 2020;18(4):284-294

REAL-WORLD TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH mCRPC: RESULTS

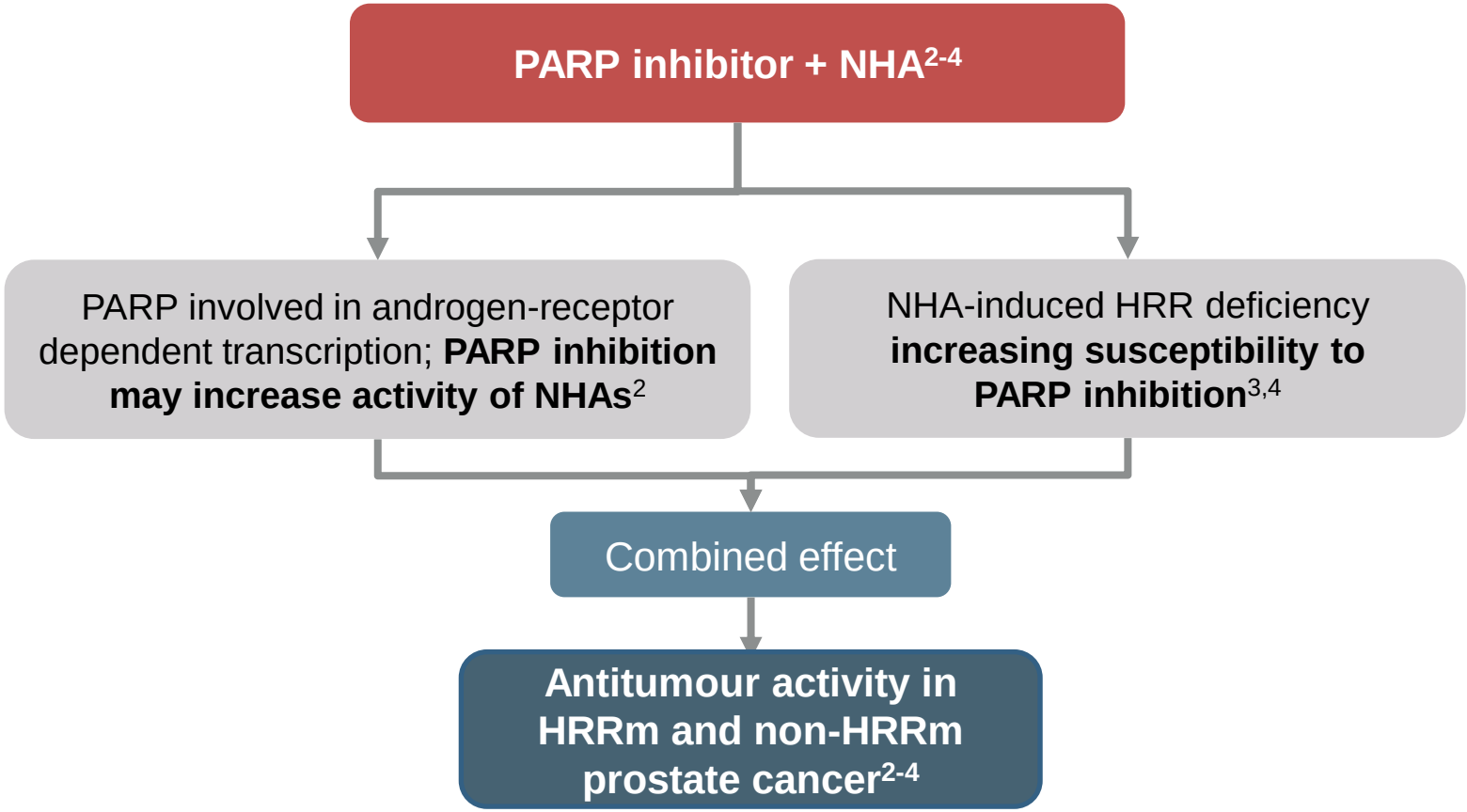


CI, confidence interval; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival

George DJ, et al. Clin Genitourin Cancer. 2020;18(4):284-294

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

Adapted from 2. Schiewer MJ, et al Cancer Discov. 2012;2:1134-1149; 3. Polkinghorn WR, et al. Cancer Discov. 2013;3:1245-1253; 4. Asim M, et al. Nat Commun. 2017;8:374; Saad F, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11)

PHASE 3 PARPi + NHA COMBINATION STUDIES IN 1L mCRPC

	PROpel	TALAPRO-2	MAGNITUDE	CASPAR
Treatments	Olaparib 300 mg BID + Abiraterone 1000 mg QD	Talazoparib 0.5 mg QD + Enzalutamide 160 mg QD	Niraparib 200 mg QD + Abiraterone 1000 mg QD	Rucaparib + Enzalutamide QD
Primary endpoint	rPFS (INV) all-comers	rPFS (BICR) in ITT and DDR	rPFS (BICR) in DDR and in patients on co-formulation	rPFS, OS in ITT
Setting and therapy-related exclusion criteria	• PCa: may have received taxane in mCSPC • mCRPC: no prior therapy	• PCa: may have received taxane or abiraterone in mCSPC • mCRPC: no prior therapy	• mCRPC: no prior therapy (<4 months of abiraterone allowed) • mHSPC: taxane and NHA allowed in mCSPC (no prior abiraterone)	• mCRPC: no prior treatment • Non-mCRPC: prior abiraterone, apalutamide and darolutamide allowed • mCSPC, nmCSPC and nmCRPC: prior docetaxel and/or NHA allowed
Stratification factors	• Metastases: bone only vs visceral vs other • Docetaxel treatment in mCSPC: yes vs no	• Prior treatment NHA/taxanes: yes or no • DDR mutations status: deficient vs non-deficient/unknown	• Prior chemo mCSPC • Prior ARi nmCRPC/ mCSPC • Prior AAP for L1 mCRPC • *BRCA1/2* vs other HRR gene alterations (HRR BM+ cohort)	Not available
Study design and diagnostic testing	• Randomised, double-blind, Phase 3 • Retrospective biomarker analysis (tissue)	• Randomised, double-blind, Phase 3 • DDR prospective testing (blood/tissue, liquid biopsy)	• Randomised, double-blind, Phase 3 • Prospective biomarker analysis (blood/tissue)	• Randomised, double-blind, Phase 3 • DDR prospective testing (tissue)

1L, first-line; BICR, blinded independent central review; BID, twice daily; DDR, DNA damage repair; INV, investigator-assessed; ITT, intention to treat; (n)mCRPC, (non)metastatic castration resistant prostate cancer; (n)mCSPC, (non)metastatic castration-sensitive prostate cancer; NHA, novel hormonal agents; OS, overall survival; PARPI, poly-ADP ribose polymerase inhibitors; PCa, prostate cancer; QD, once daily; rPFS, radiographic progression-free survival; Internally created summary document based on data contained in these respective ClinicalTrials.gov reference sources

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)

PROpel: BASELINE PATIENT CHARACTERISTICS

Well-balanced between treatment arms

	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Median (range) age, years	69.0 (43–91)	70.0 (46–88)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Symptomatic (pain),[a] n (%)	**103 (25.8)**	**80 (20.2)**
Site of metastases, n (%)		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	133 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Lung	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
Docetaxel treatment at mHSPC stage, n (%)	**90 (22.6)**	**89 (22.4)**
Median PSA, ug/L (IQR)	17.90 (6.09–67.00)	16.81 (6.26–53.30)
HRRm status[b]		
HRRm	**111 (27.8)**	**115 (29.0)**
Non-HRRm	**279 (69.9)**	**273 (68.8)**
HRRm unknown	**9 (2.3)**	**9 (2.3)**

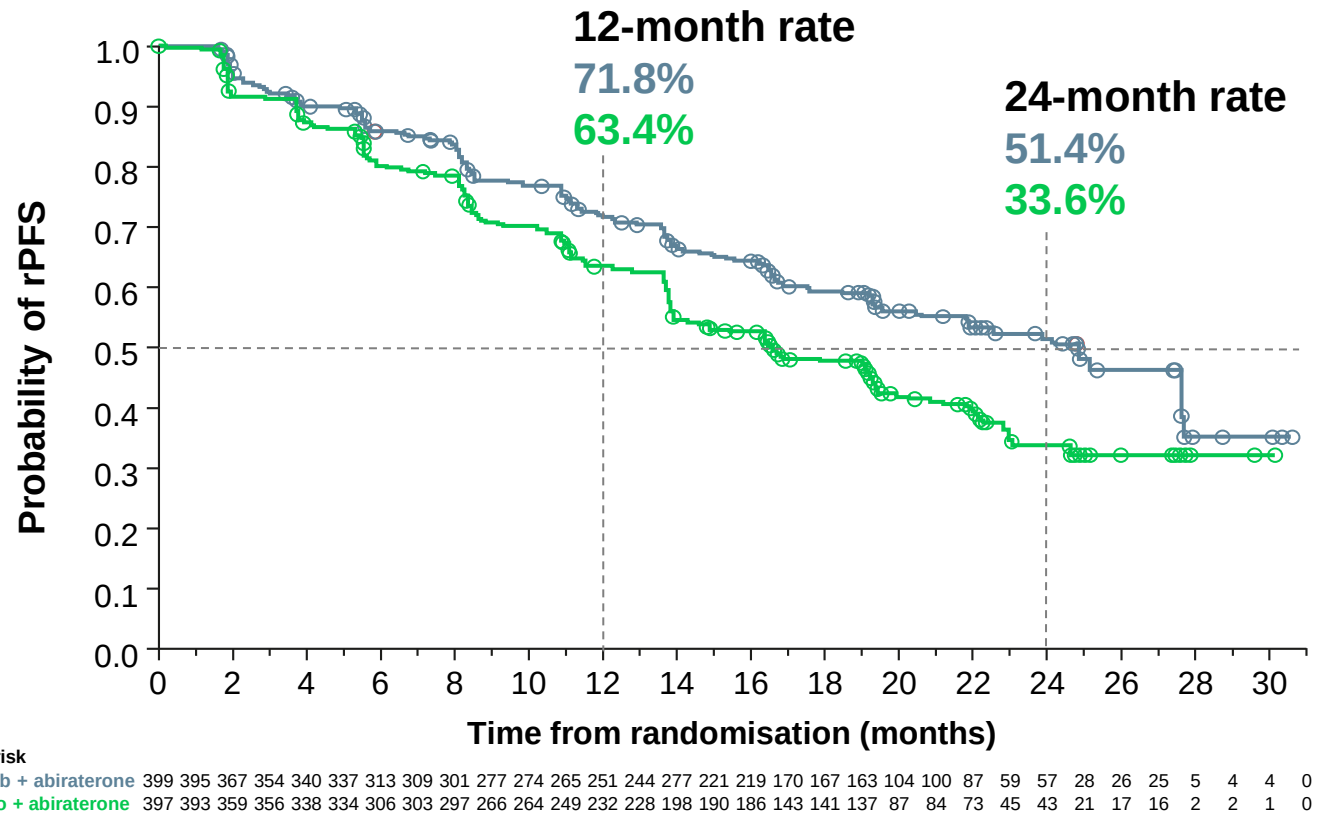
[a]Patients with symptomatic pain at baseline: BPI-SF item #3 score ≥4 and/or opiate use at baseline.
[b]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm 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.

BPI-SF, Brief Pain Inventory – Short Form; ctDNA, circulating tumour DNA; HRRm, homologous recombination mutation; IQR, interquartile range; PSA, prostate-specific antigen.

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

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]

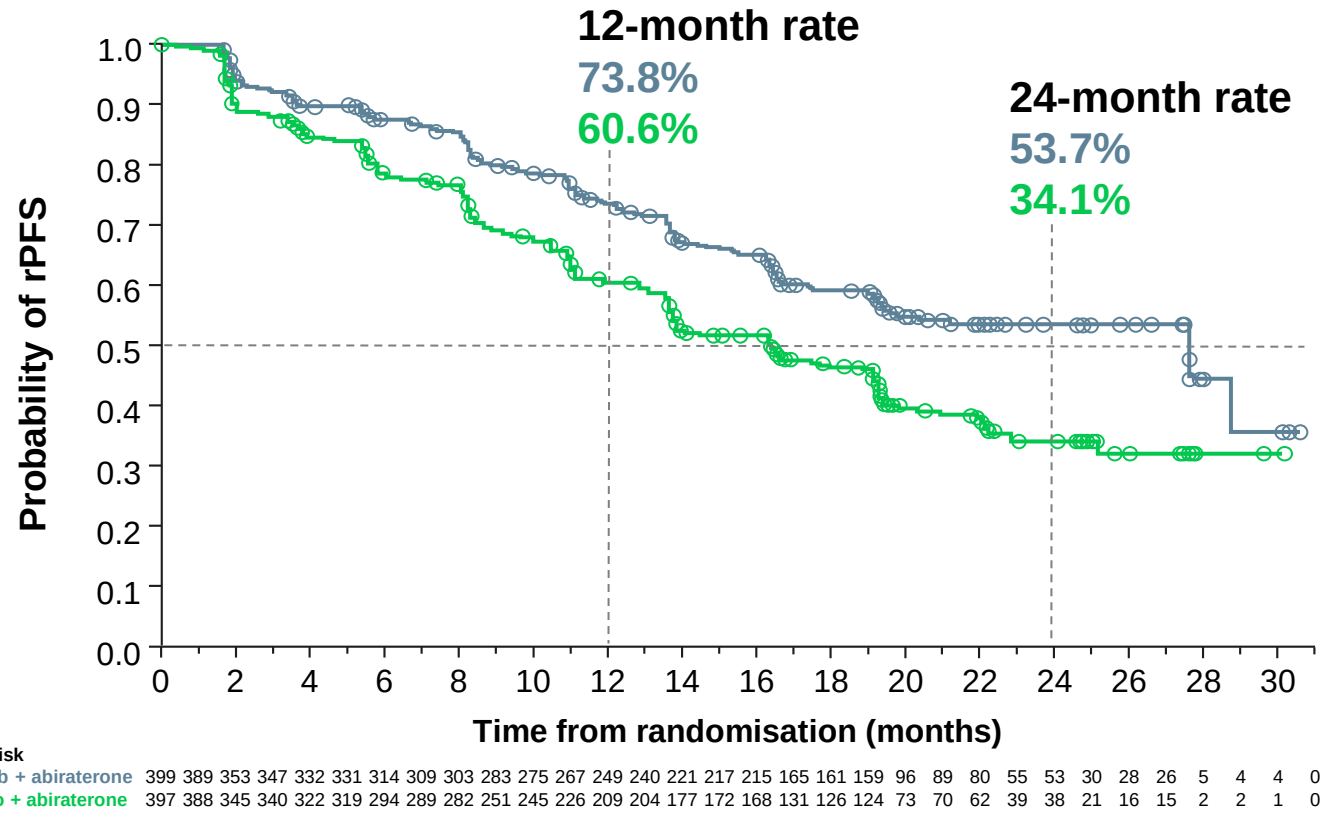
Events: 394; Maturity 49.5%
[a]In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

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

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

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

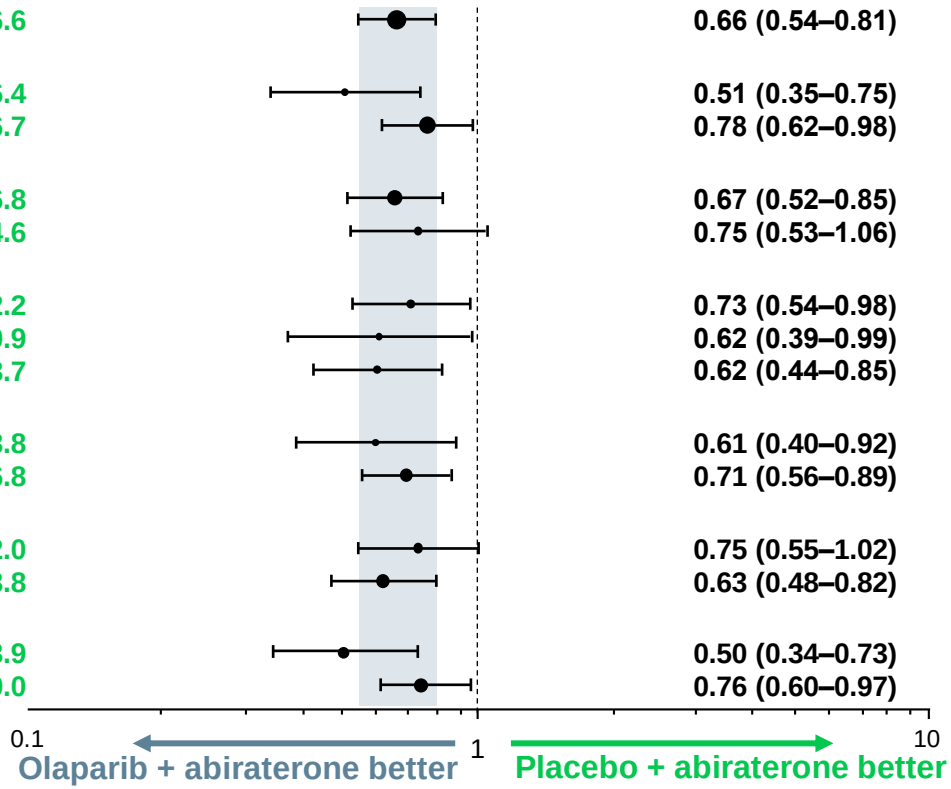
CI, confidence interval; HR, hazard ratio; rPFS, radiographic progression-free survival

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

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

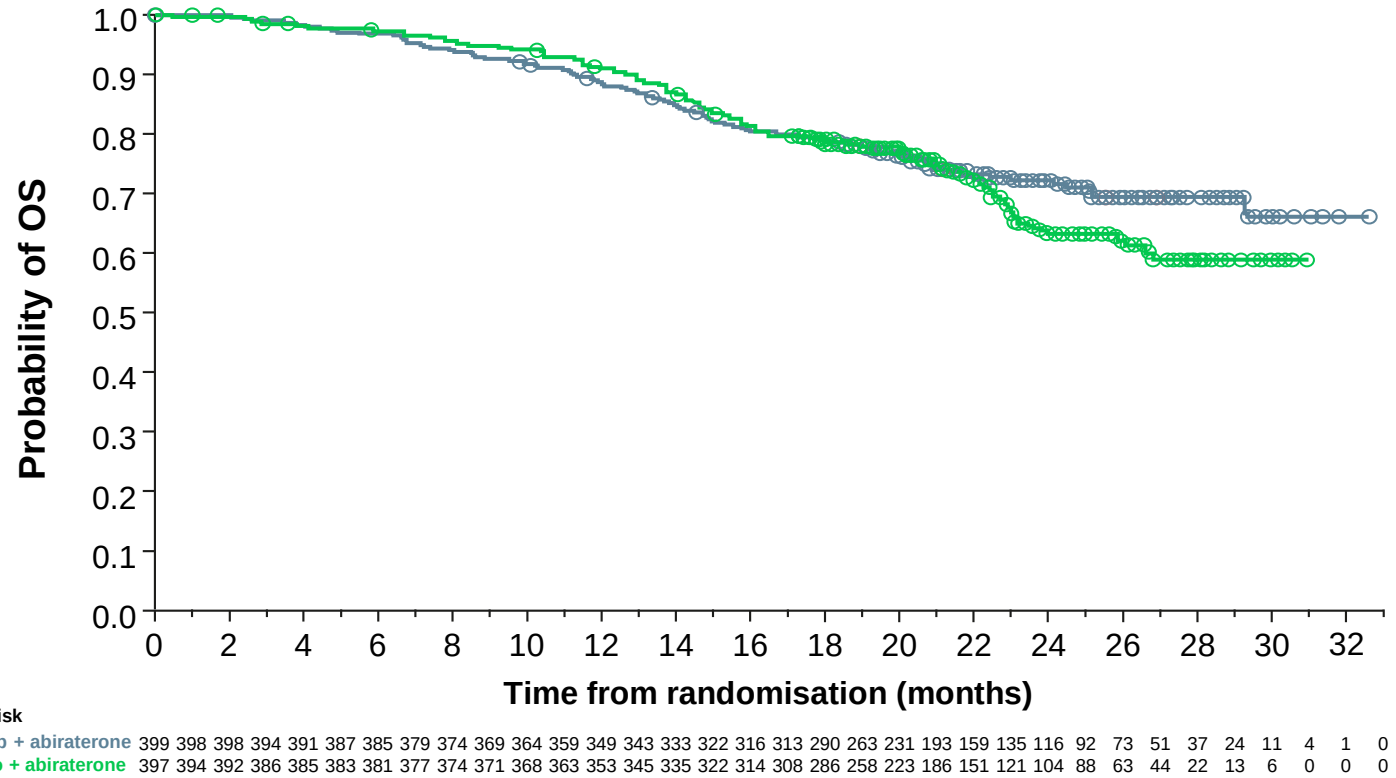
Global interaction test not significant at 10% level. [a]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified 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

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

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

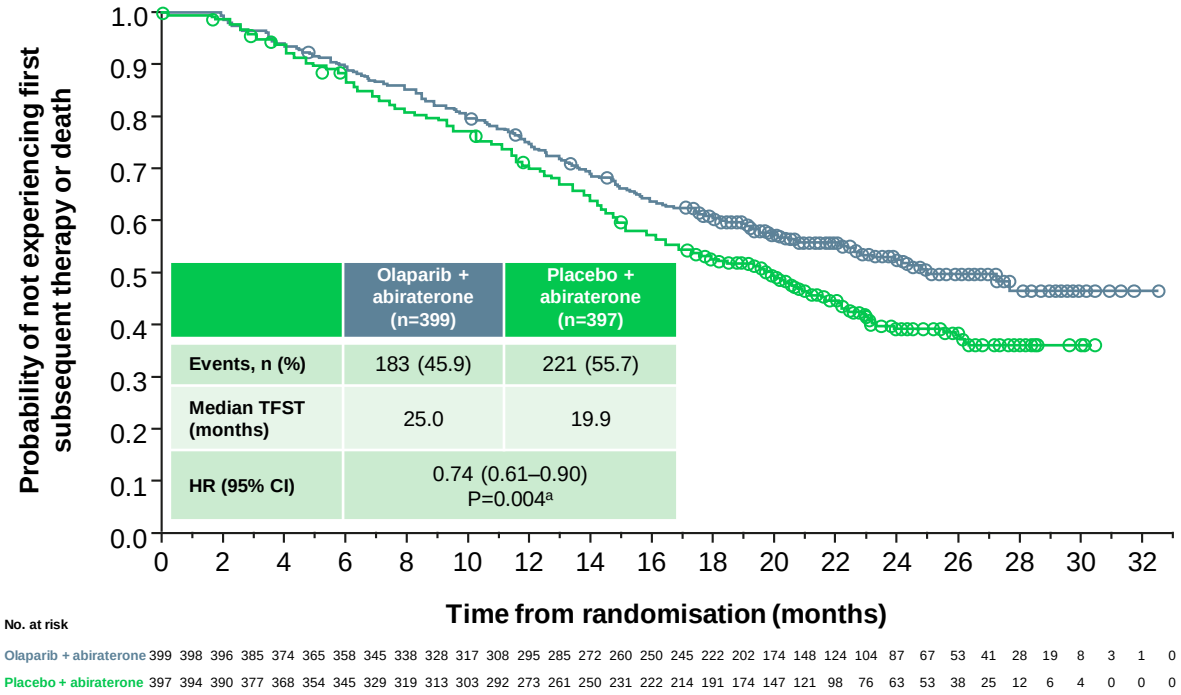
CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival

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

PROpel: TFST AND PFS2

TFST AND PFS2 RESULTS SUPPORT LONGER-TERM BENEFIT WITH OLAPARIB + ABIRATERONE

Time to first subsequent therapy or death (TFST)

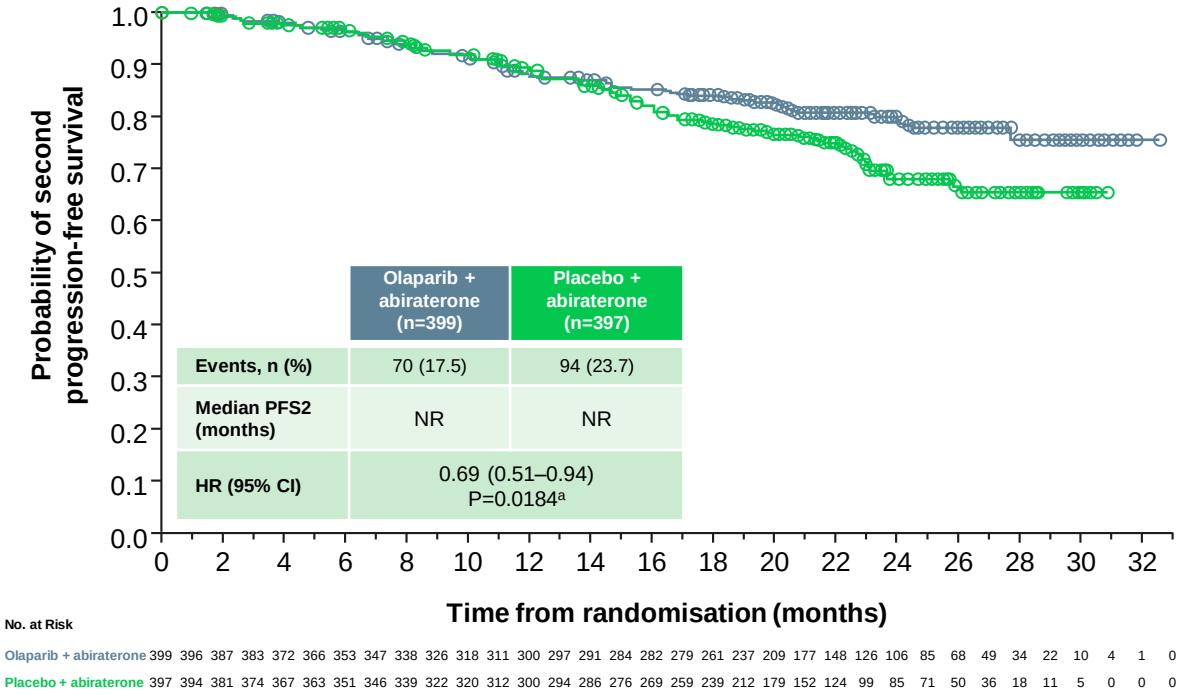


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	183 (45.9)	221 (55.7)
Median TFST (months)	25.0	19.9
HR (95% CI)	0.74 (0.61–0.90) P=0.004[a]	

No. at risk

Olaparib + abiraterone	399	398	396	385	374	365	358	345	338	328	317	308	295	285	272	260	250	245	222	202	174	148	124	104	87	67	53	41	28	19	8	3	1	0
Placebo + abiraterone	397	394	390	377	368	354	345	329	319	313	303	292	273	261	250	231	222	214	191	174	147	121	98	76	63	53	38	25	12	6	4	0	0	0

Time to second progression or death (PFS2)



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	70 (17.5)	94 (23.7)
Median PFS2 (months)	NR	NR
HR (95% CI)	0.69 (0.51–0.94) P=0.0184[a]	

No. at Risk

Olaparib + abiraterone	399	396	387	383	372	366	353	347	338	326	318	311	300	297	291	284	282	279	261	237	209	177	148	126	106	85	68	49	34	22	10	4	1	0
Placebo + abiraterone	397	394	381	374	367	363	351	346	339	322	320	312	300	294	286	276	269	259	239	212	179	152	124	99	85	71	50	36	18	11	5	0	0	0

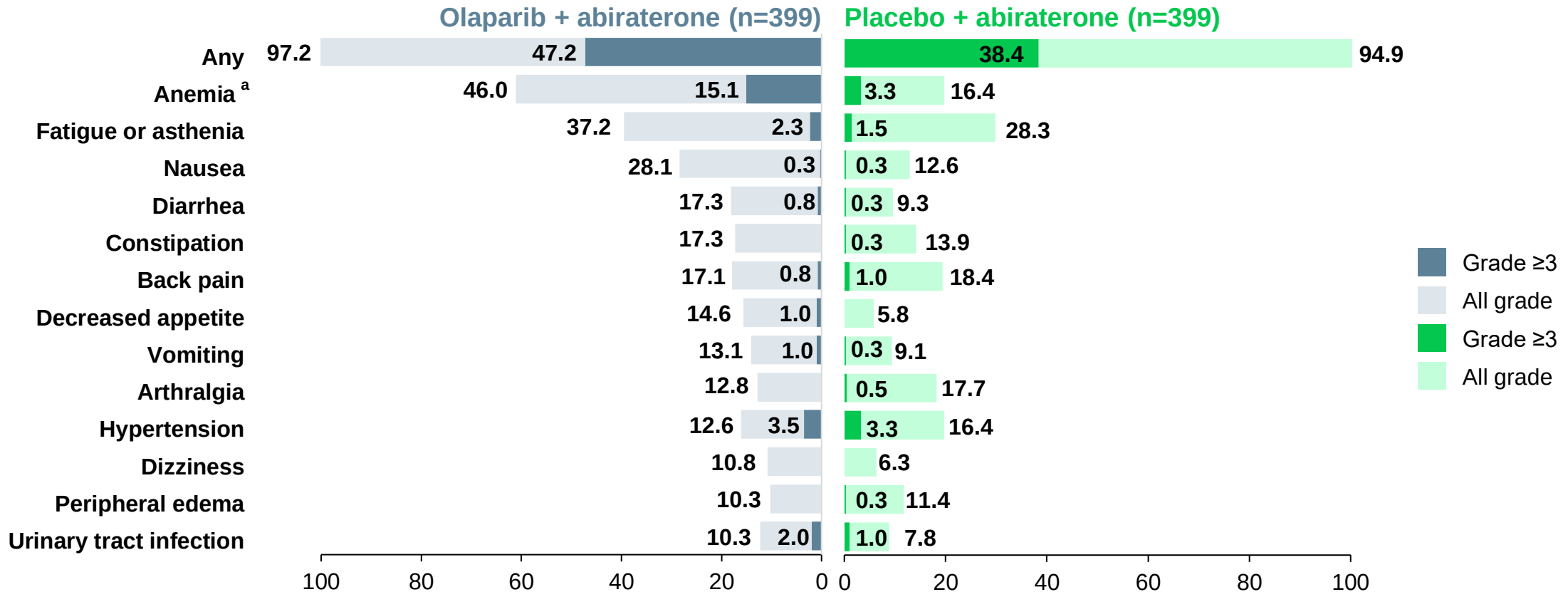
[a]Nominal

CI, confidence interval; HR, hazard ratio; NR, not reached;

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

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

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

MAGNITUDE: RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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

Study start: February 2019

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)

Prescreening for BM status[a]

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

Allocation to cohort

1:1 randomisation

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.

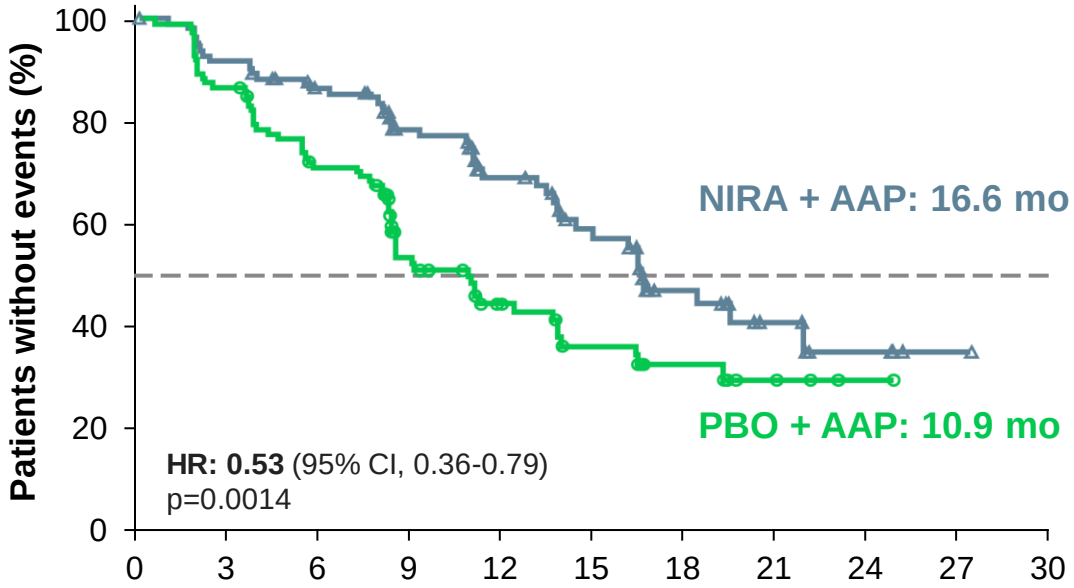
AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination 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)

MAGNITUDE *BRCA1/2*-MUTATED: PRIMARY ENDPOINT

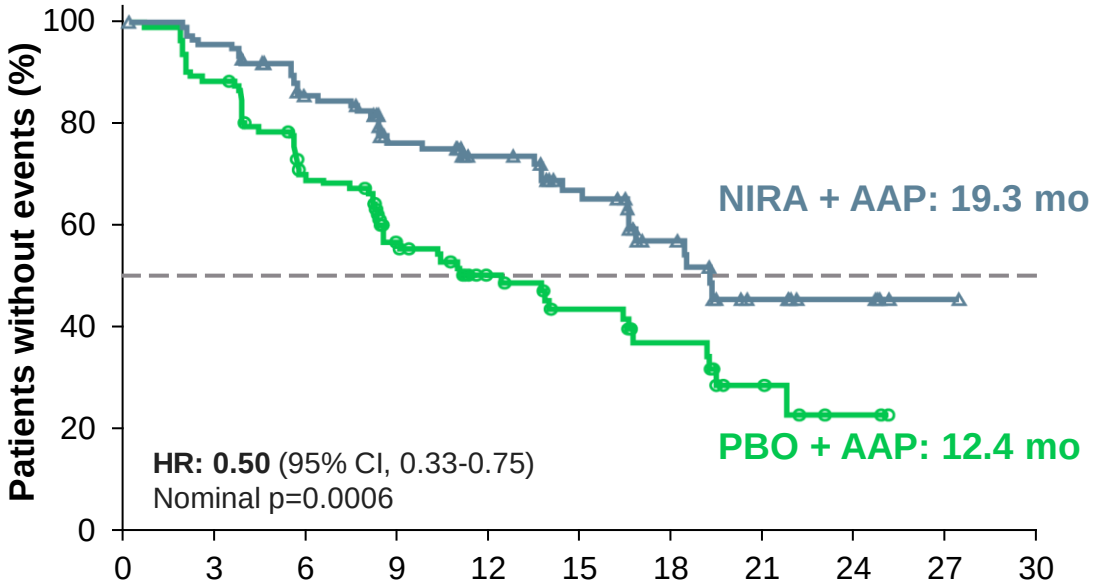
NIRA + AAP REDUCED THE RISK OF rPFS OR DEATH BY 47%

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.

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MAGNITUDE ALL HRR BM+: PRIMARY ENDPOINT

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

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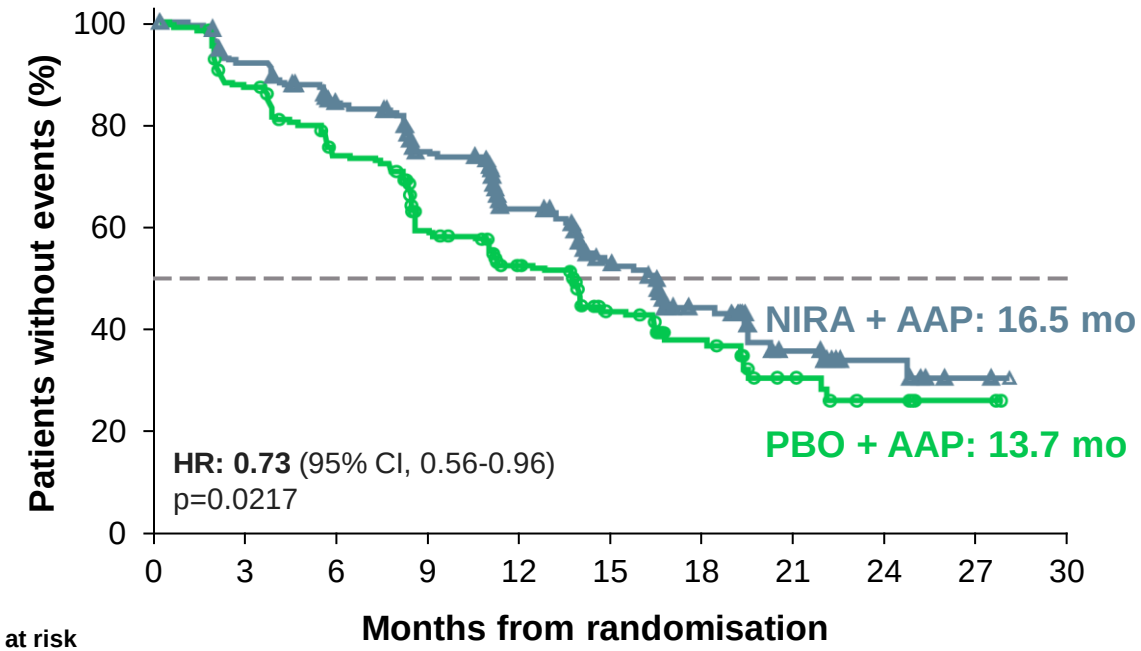
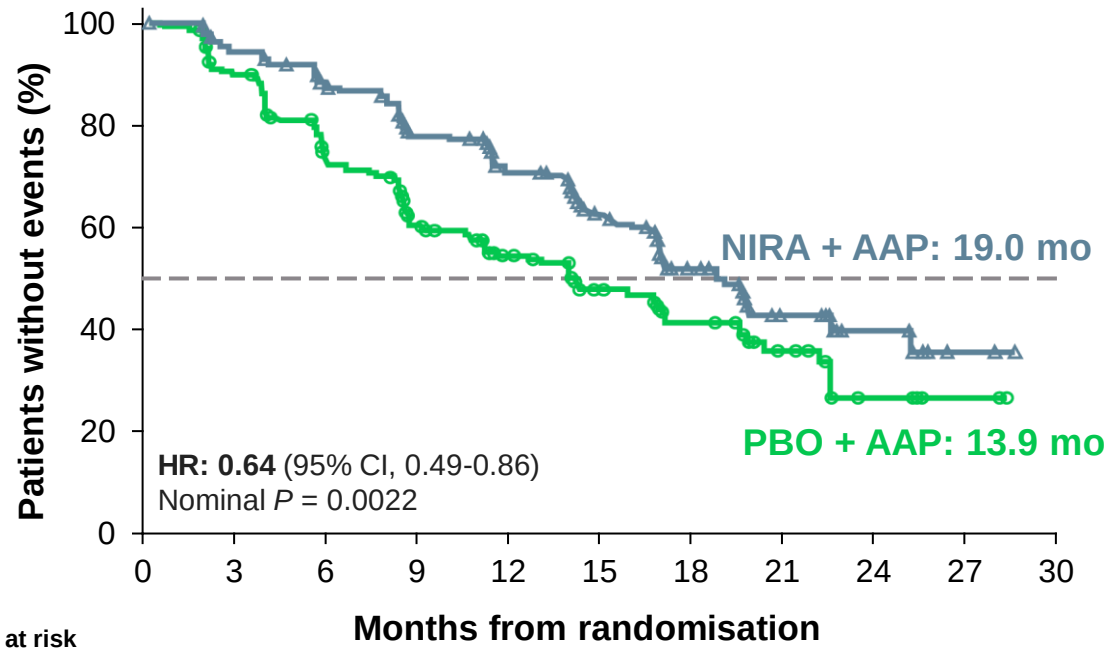
rPFS assessed by central review



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.

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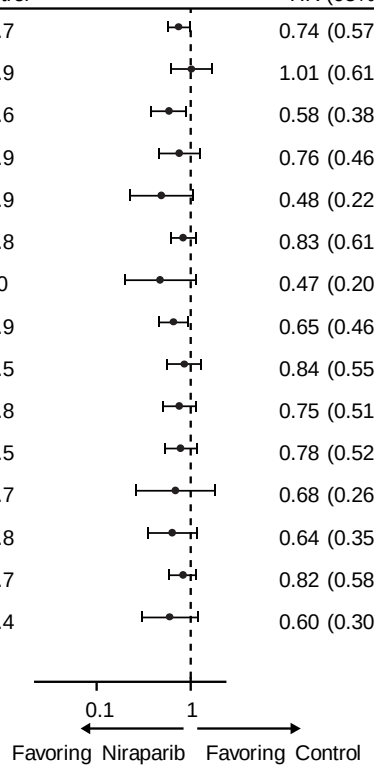
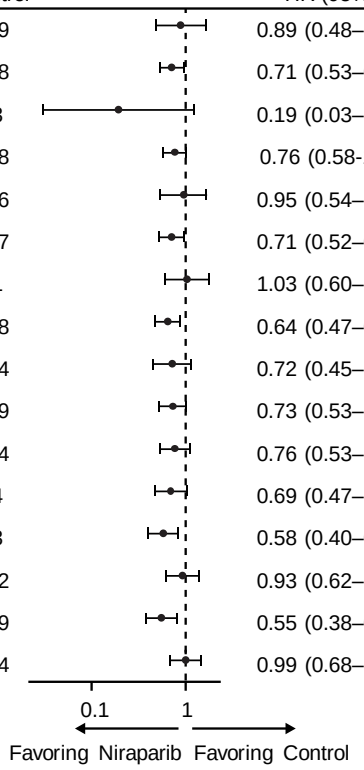
MAGNITUDE ALL HRR BM+: PRESPECIFIED SUBGROUP ANALYSIS OF rPFS

Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
All HRR+ 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.

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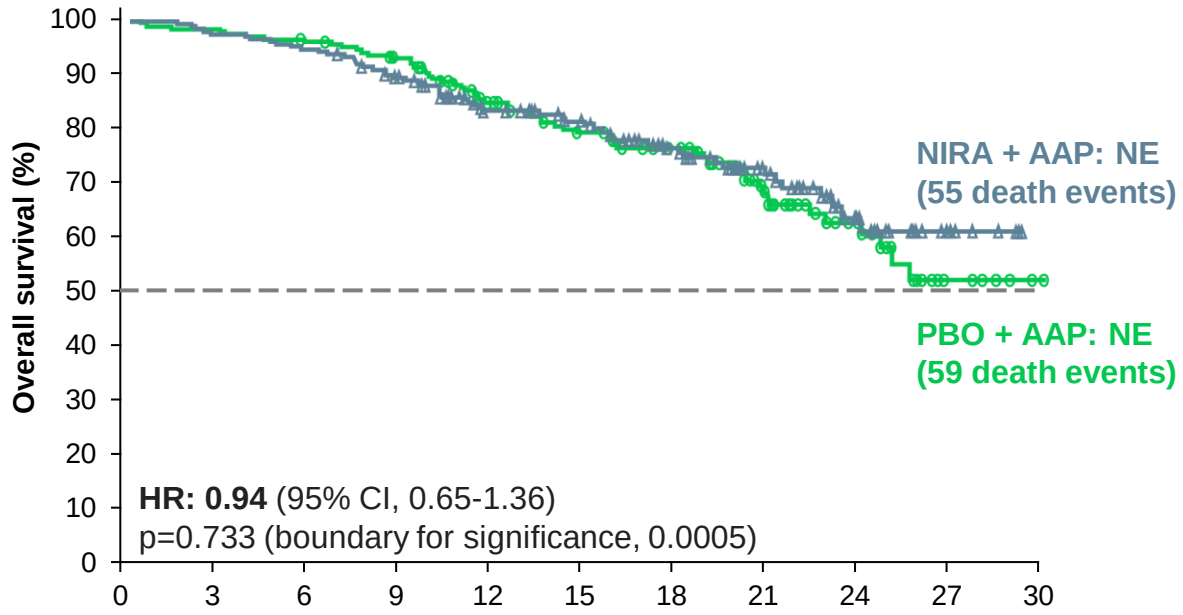
MAGNITUDE ALL HRR BM+: OVERALL SURVIVAL FIRST INTERIM ANALYSIS



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

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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.

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PERSONAL VIEW AND CHALLENGES IN mCRPC

- Survival of men with mCRPC in the real world remains a problem
- Good first-line options but early resistance/progression is a challenge
- Second-line options are available, **but** many patients do not get more than 1 line of effective therapy in the real world
- Less than half the men with prostate cancer will receive chemotherapy before dying from prostate cancer
- Building on effective first-line options for mCRPC is critically needed
- PARP/NHT combination fulfills an unmet need of effective and tolerable first-line combinations

mCRPC, metastatic castration resistant prostate cancer; NHT, novel hormonal therapy; PARP, poly-ADP ribose polymerase

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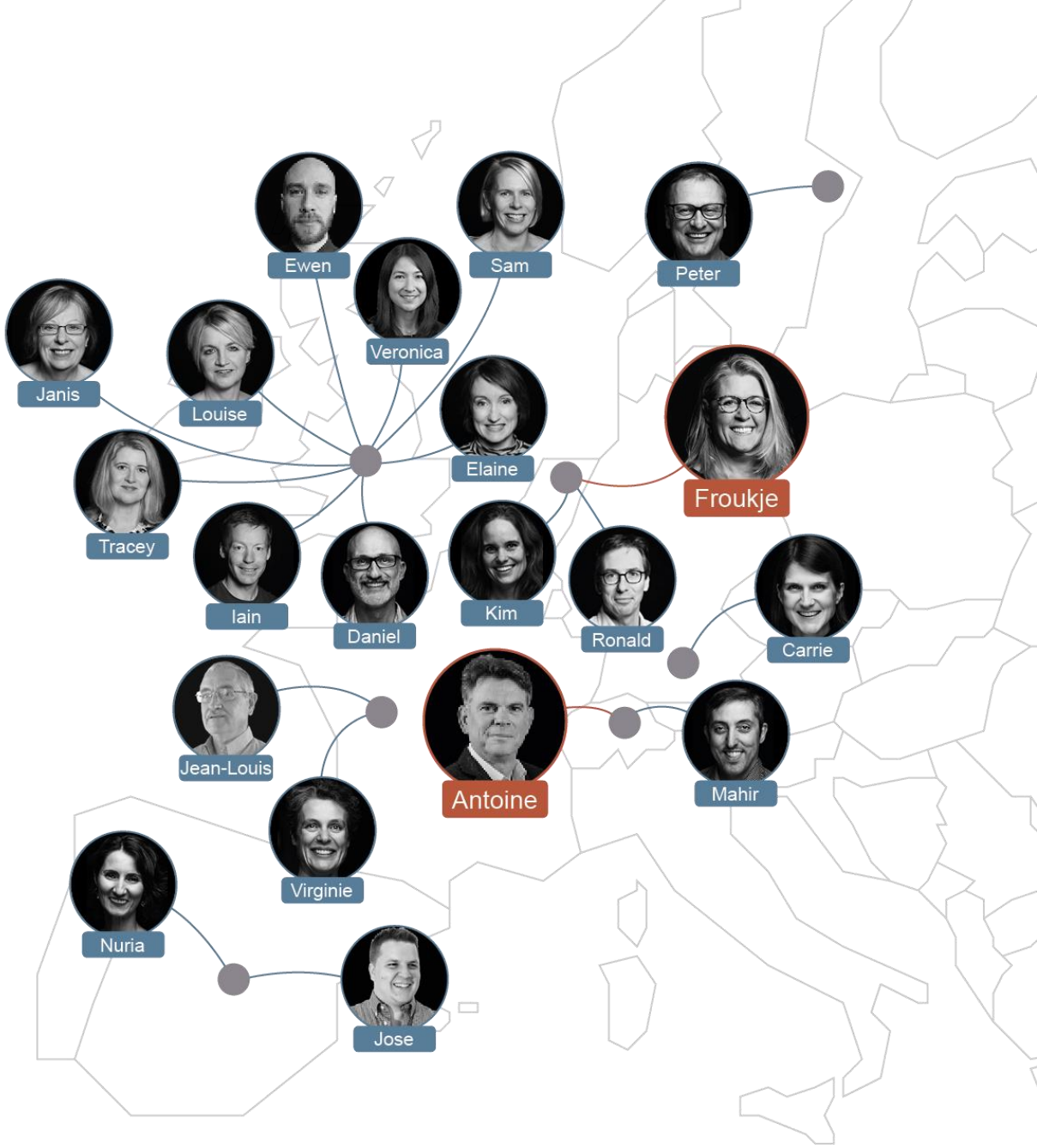

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