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ANIMATED VIDEO

CLINICAL IMPLEMENTATION OF TESTING AND PARPi MONOTHERAPY, AND THE PATIENT JOURNEY FOR PROSTATE CANCER PATIENTS

Dr Neal Shore, MD, FACS

Carolina Urologic Research Center and Chief Medical Officer for Genesis Care, USA

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PARPi, poly-ADP ribose polymerase inhibitors

EDUCATIONAL OBJECTIVES

1. Recognise the **efficacy and safety** profiles of PARP inhibitors, know their differences and understand the place of PARP inhibitor monotherapy in the treatment landscape for patients with mCRPC
2. Understand the **role of testing** for assessment of HRRm status and subsequent decision making for treatment with PARP inhibitors as monotherapy

HRRm, homologous recombinant repair gene mutations; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly-ADP ribose polymerase

CLINICAL TAKEAWAYS

- PARP inhibitors are effective drugs as monotherapy in mCRPC patients with HRR alterations
- Genetic testing is important to inform on prognosis, help with treatment decision making and for understanding inherited risk
- *BRCA* mutations are associated with poor outcomes in mCRPC patients
- Patients with tumours harbouring *BRCA1/BRCA2* alteration appear to derive the greatest clinical benefit from PARP inhibitor monotherapy, but patients with other HRR alterations might also derive benefit

BRCA1/2, breast cancer gene 1/2; HRR, homologous recombinant repair gene; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly-ADP ribose polymerase

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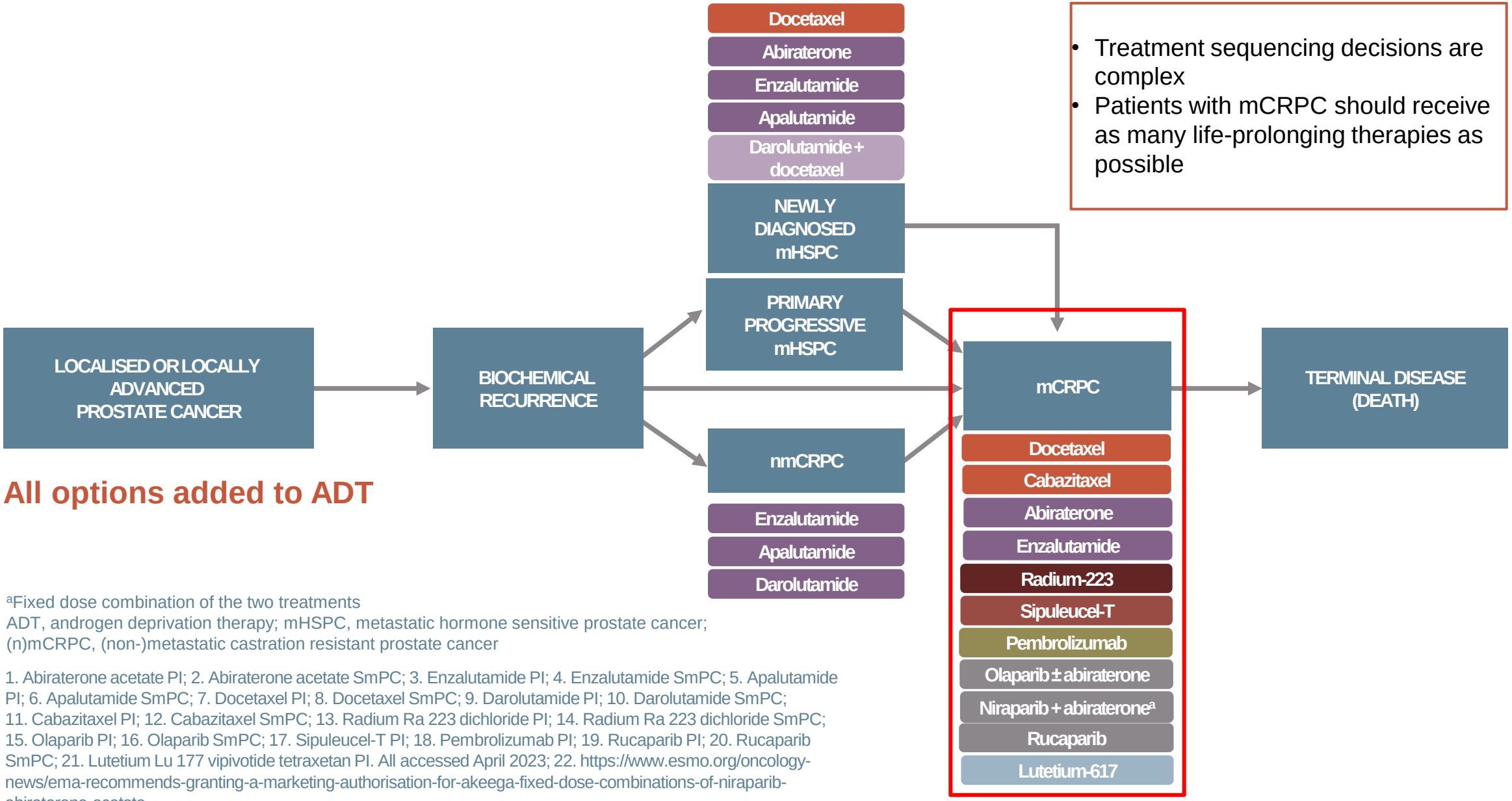
PROSTATE CANCER LANDSCAPE: TREATMENT OPTIONS

THE PROSTATE CANCER LANDSCAPE IS COMPLICATED!

- Treatment sequencing decisions are complex
- Patients with mCRPC should receive as many life-prolonging therapies as possible



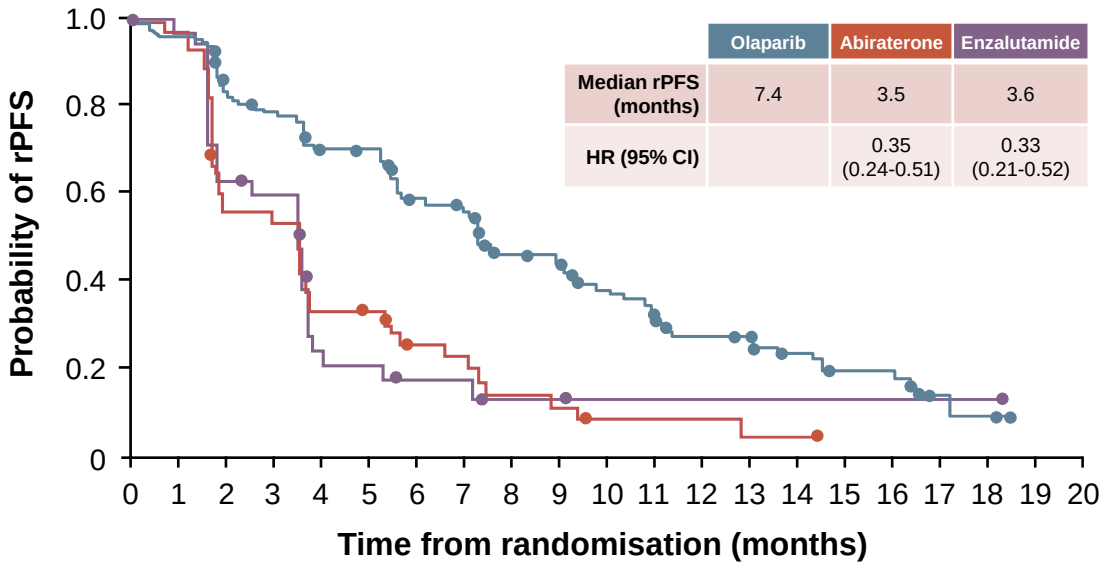
All options added to ADT

[a]Fixed dose combination of the two treatments
ADT, androgen deprivation therapy; mHSPC, metastatic hormone sensitive prostate cancer; (n)mCRPC, (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. Olaparib SmPC; 17. Sipuleucel-T PI; 18. Pembrolizumab PI; 19. Rucaparib PI; 20. Rucaparib SmPC; 21. Lutetium Lu 177 vipivotide tetraxetan PI. All accessed April 2023; 22. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate

TREATMENTS WITH DIFFERENT MOAs OFFER GREATER BENEFIT THAN SEQUENTIAL USE OF NHAS[1,2]

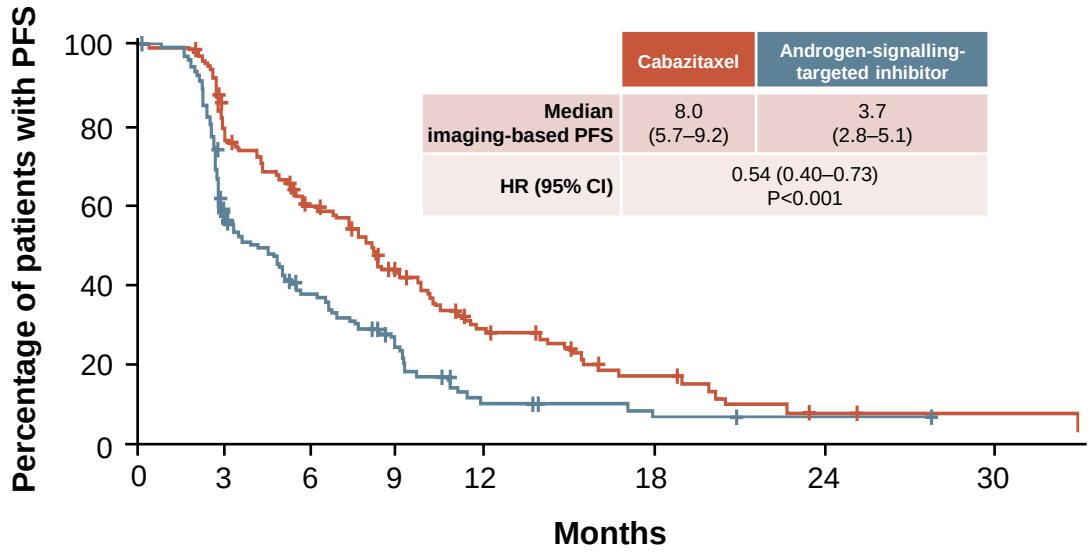
PROfound: rPFS in Cohort A[1]



	Olaparib	Abiraterone	Enzalutamide
Median rPFS (months)	7.4	3.5	3.6
HR (95% CI)		0.35 (0.24-0.51)	0.33 (0.21-0.52)

- **PROfound compared olaparib with either abiraterone or enzalutamide in patients previously treated with NHA[1]**
- **Olaparib was more beneficial in improving rPFS and OS irrespective of the choice of NHA[1]**

CARD: imaging-based PFS[2]



	Cabazitaxel	Androgen-signalling-targeted inhibitor
Median imaging-based PFS	8.0 (5.7–9.2)	3.7 (2.8–5.1)
HR (95% CI)	0.54 (0.40–0.73) P<0.001	

- **CARD compared cabazitaxel with abiraterone or enzalutamide in patients with mCRPC previously treated with DOC and the alternative NHA[2]**
- **In the control arm, the response rate and the duration of response to a second NHA were poor[2]**

CI, confidence interval; DOC, docetaxel; HR, hazard ratio; mCRPC, metastatic castration resistance prostate cancer; NHA, new hormonal agent; OS, overall survival; PFS, progression-free survival; rPFS, radiographic PFS

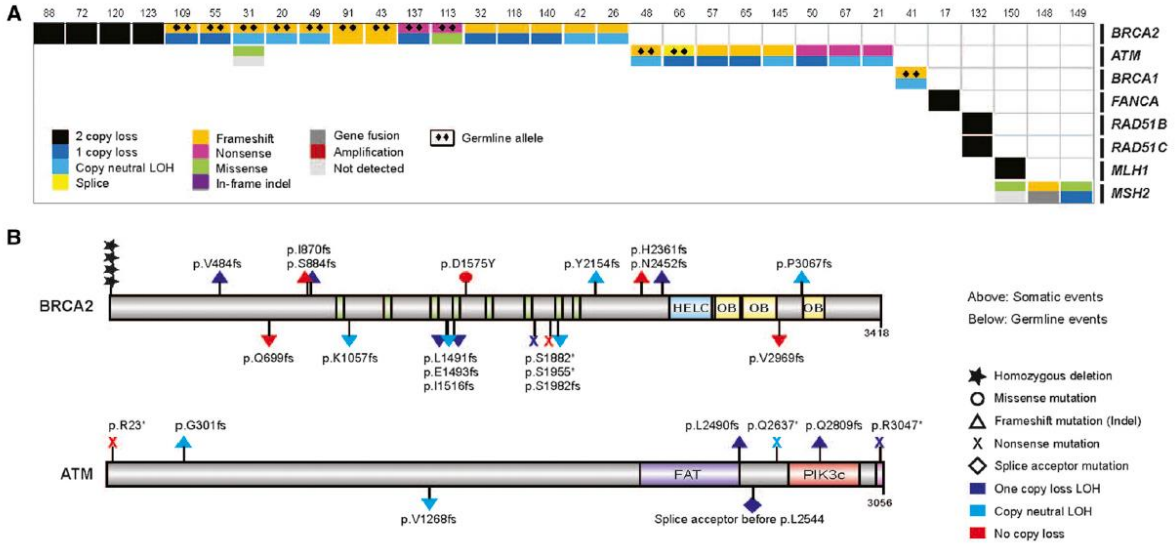
1. Saad F, et al. Presented at AUA 2021. 10–13 September. Abstract 21-5996. 2. De Wit R, et al. N Engl J Med. 2019;26:381:2506-18.

DNA DAMAGE REPAIR MUTATIONS AND GENETIC TESTING

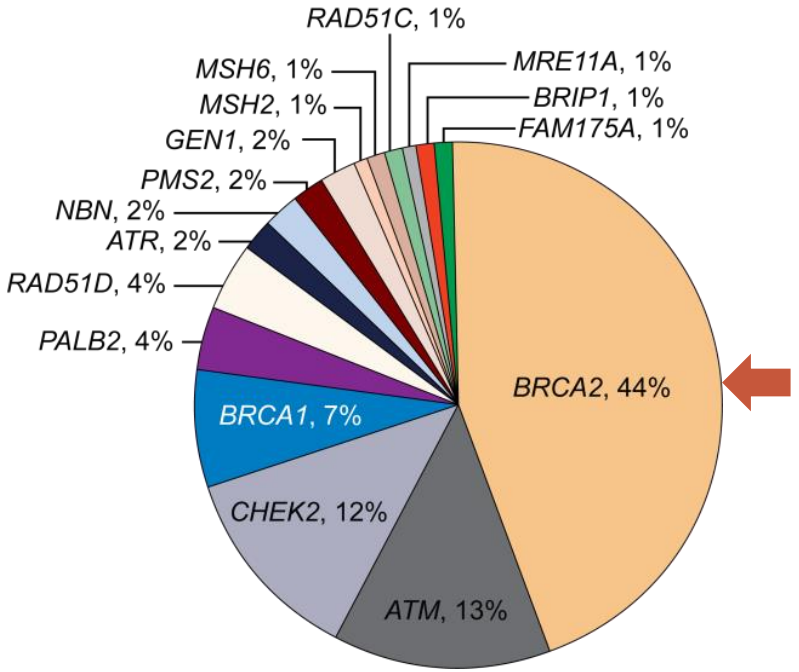
DNA DAMAGE-REPAIR MUTATIONS OCCUR IN APPROXIMATELY A QUARTER OF mCRPC PATIENTS

SOMATIC

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



GERMLINE

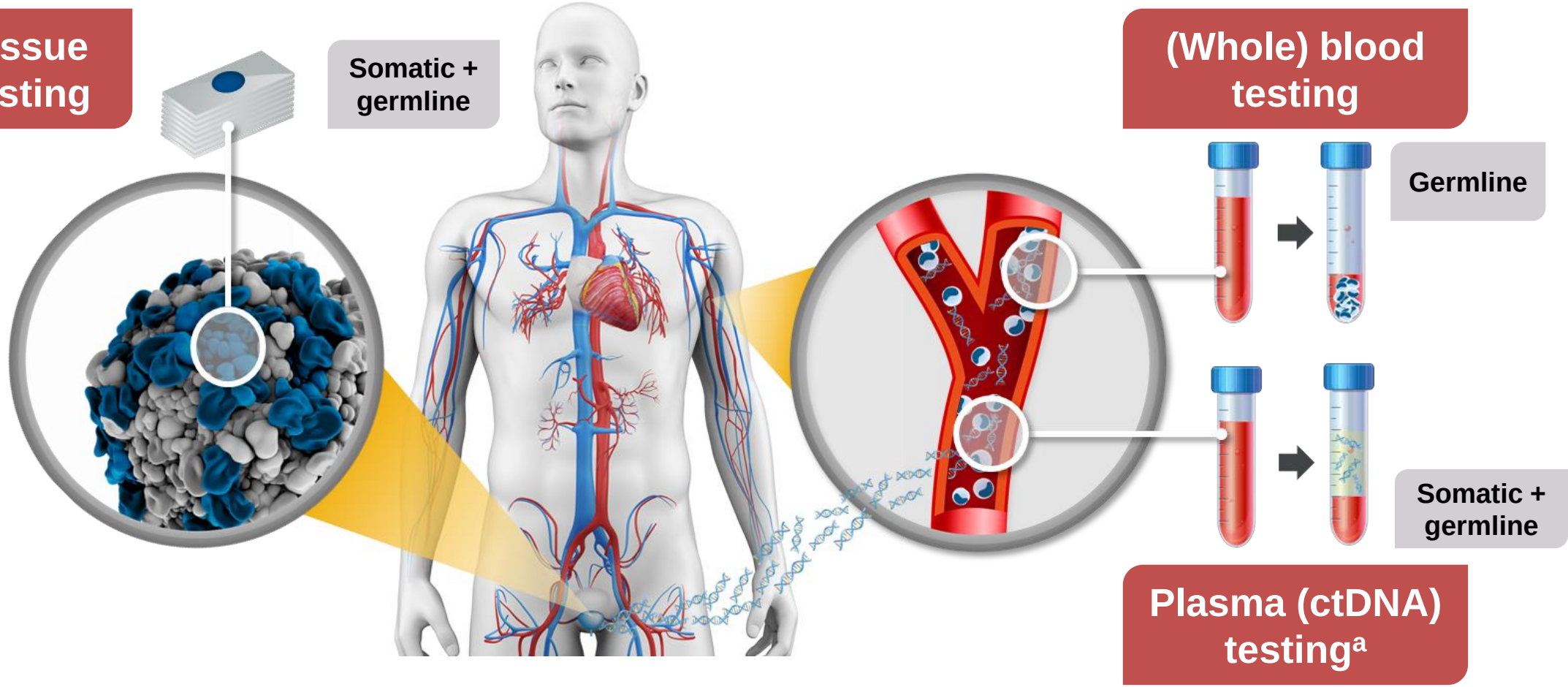


- **~12%** of men with metastatic prostate cancer have germline mutations in one or more of the 16 DNA repair genes

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

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

THERE ARE SEVERAL WAYS TO IDENTIFY *BRCA* / HRR MUTATIONS IN PROSTATE CANCER

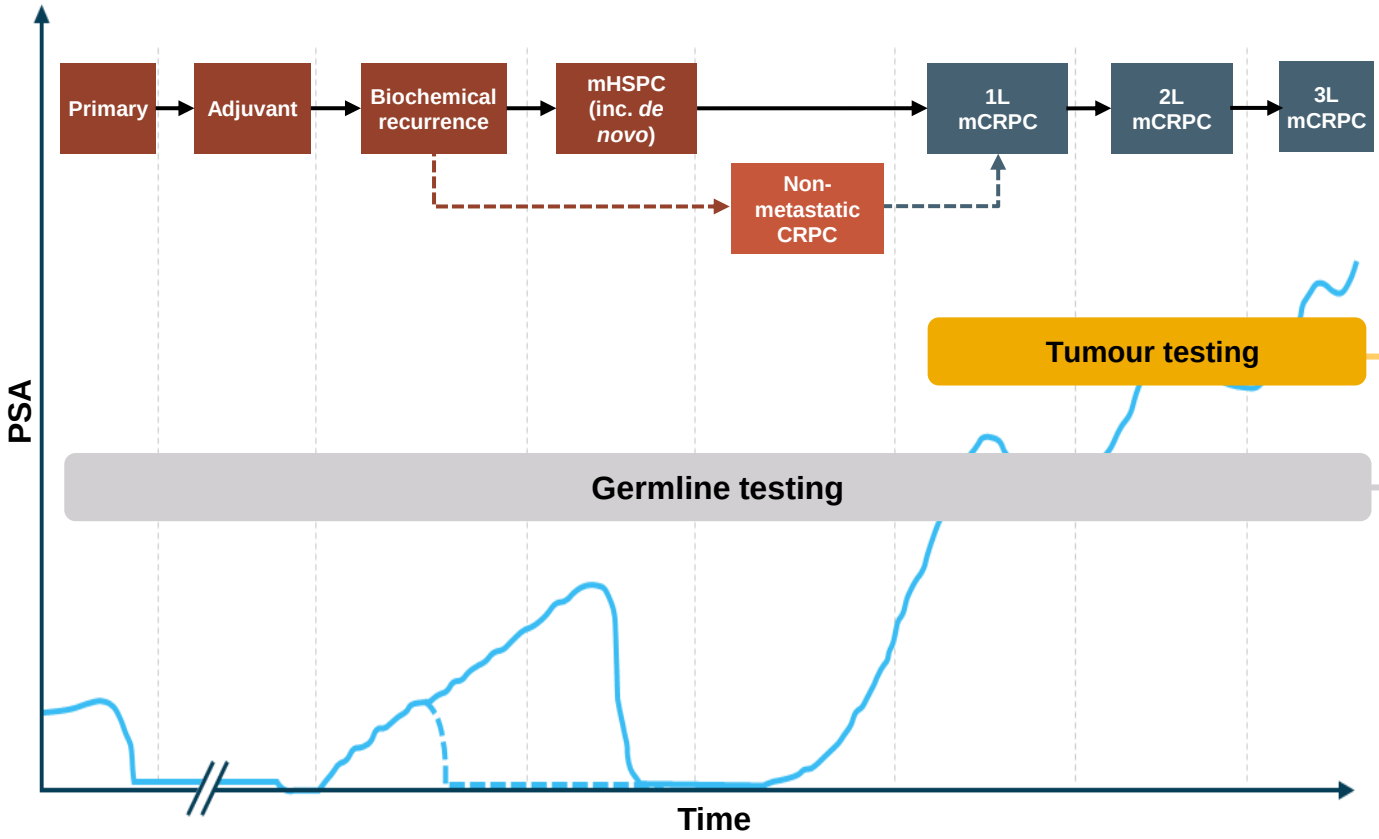


[a]Tumour cells shed DNA into the circulation through necrosis or apoptosis. ctDNA can be isolated from a plasma sample

BRCA, breast cancer gene; ctDNA, circulating tumour DNA; HRR, homologous recombination repair

1. Cheng HH, et al. J Natl Compr Canc Netw. 2019;17:515-21; 2. Haber DA, Velculescu VE. Cancer Discov. 2014;4:650-61

CONSIDERATIONS FOR WHEN TO TEST FOR *HRR*m ARE INCLUDED IN INTERNATIONAL GUIDELINES



Based on Scher et al, 2016

ESMO[1,2]

- Recommended for ***BRCA2*** and other **DDR genes** associated with cancer predisposition in patients with family history of cancer
- Should be considered in all patients with metastatic prostate cancer

- **Consider HRRm** and **MSI dMRR** testing in patients with **mCRPC**

EAU/EANM/ESTRO/ESUR/ISUP/SIOG[3]

- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age <60 years;
- Men with multiple family members diagnosed with csPCa at age <60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

- **Consider HRRm** and **dMRR** testing in all patients with **mPC**

NCCN[4]

- Metastatic, regional (node positive), very-high-risk localised, or high-risk localised PCa
- Family history of certain cancers
- Known family history of familial cancer risk mutation
- Personal history of breast cancer

- **Consider HRRm** testing in patients with **mPC**

AUA/SUO[5]

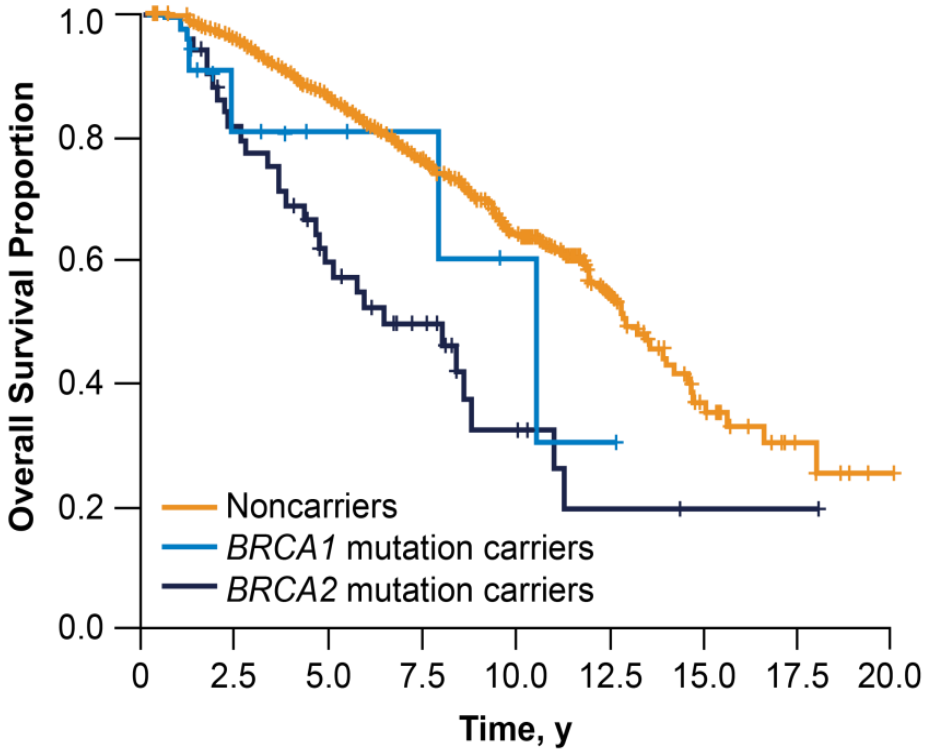
- Testing for **DDR, MSI dMMR, TMB and other potential mutations in mCRPC** patients
- Consider for **mHSPC patients**

- Testing for **DDR, MSI dMMR, TMB and other potential mutations in mCRPC** patients
- Consider for **mHSPC patients**

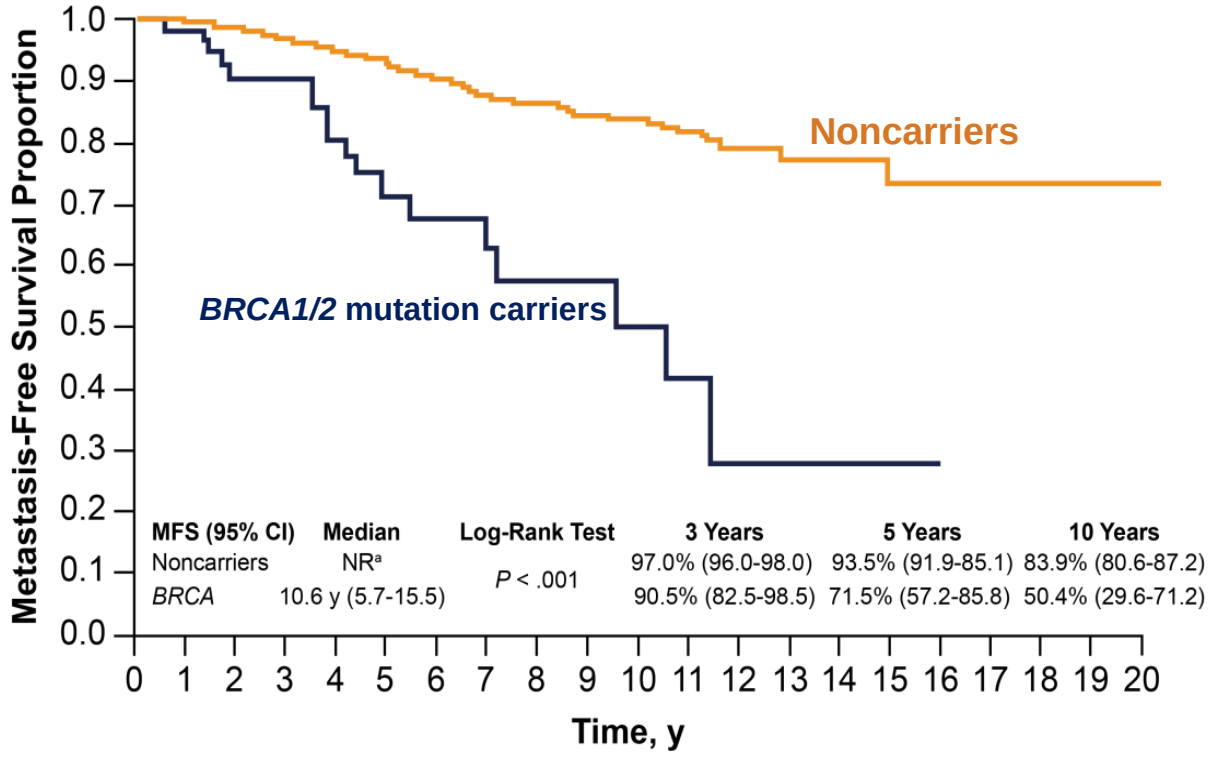
1L/2L/3L, first/second/third line; BRCA2, breast cancer gene 2; CRPC, castration-resistant prostate cancer; csPCa, clinically significant PCa; DDR, DNA damage repair; dMMR, mismatch repair damage; HRRm, homologous recombination repair mutation; mCRPC, metastatic CRPC; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; MSI, microsatellite; PCa, prostate cancer; PSA, prostate-specific antigen; TMB, tumour mutational burden

1. Parker C, et al. Annals of Oncology 2020; 31(9): 1119-34; 2. Fizazi K, et al. Annals of Oncology 2023 https://doi.org/10.1016/j.annonc.2023.02.015 ; 3. Mottet N, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf (d56bochluxqnz.cloudfront.net) Accessed May 2023); 4. National Comprehensive Cancer Network. Prostate Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed May 2023; 5. Lowrance W, et al. J Urol. 2023; 209(6):10.1097/JU.0000000000003452; 6. Scher HI, et al. J Clin Oncol 2016; 34 (12): 1402-1418

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



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



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

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

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

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

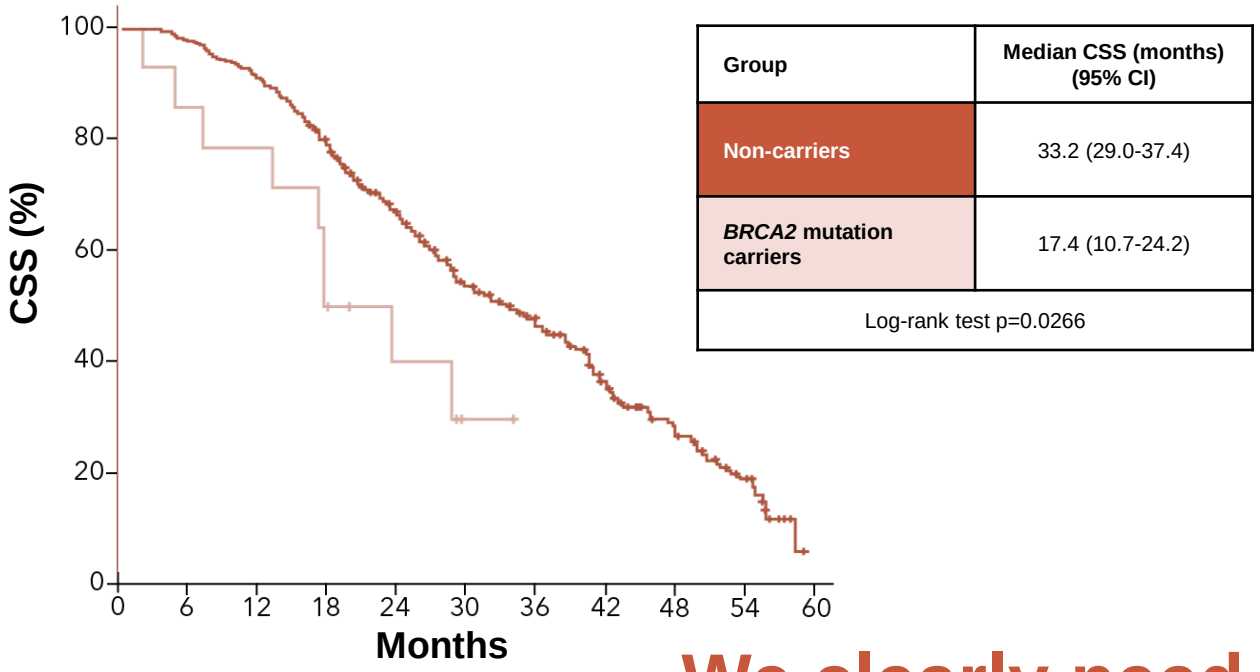
1. Castro E, et al. J Clin Oncol. 2013;31:1748-57; 2. Castro E, et al. Eur Urol. 2015;68:186-93

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

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

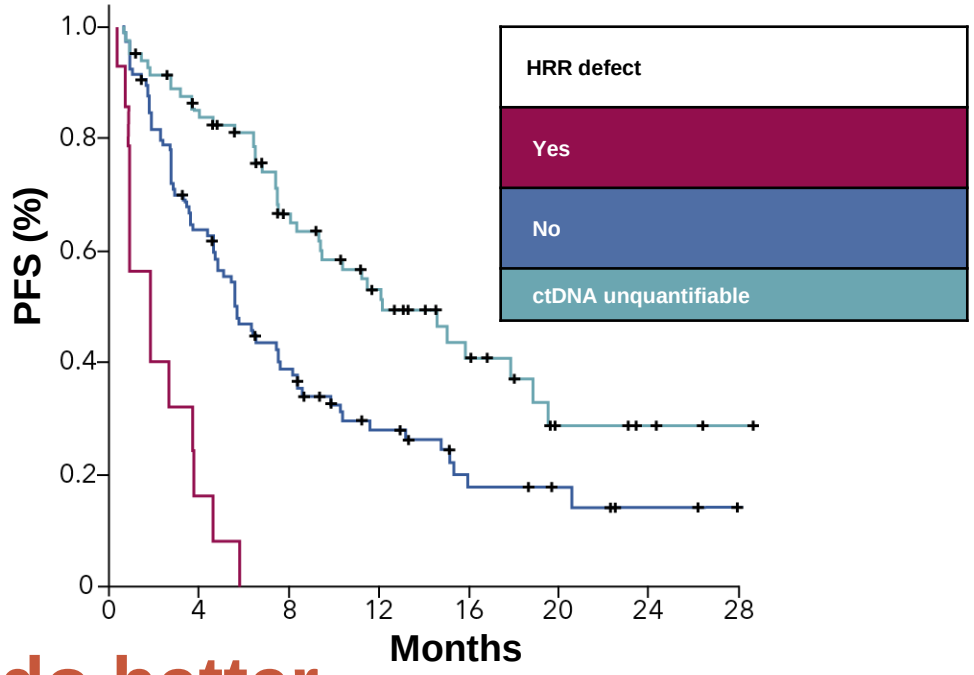
Poor responses to standard therapy also seen for **tumour HRR mutations**[2]

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



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

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



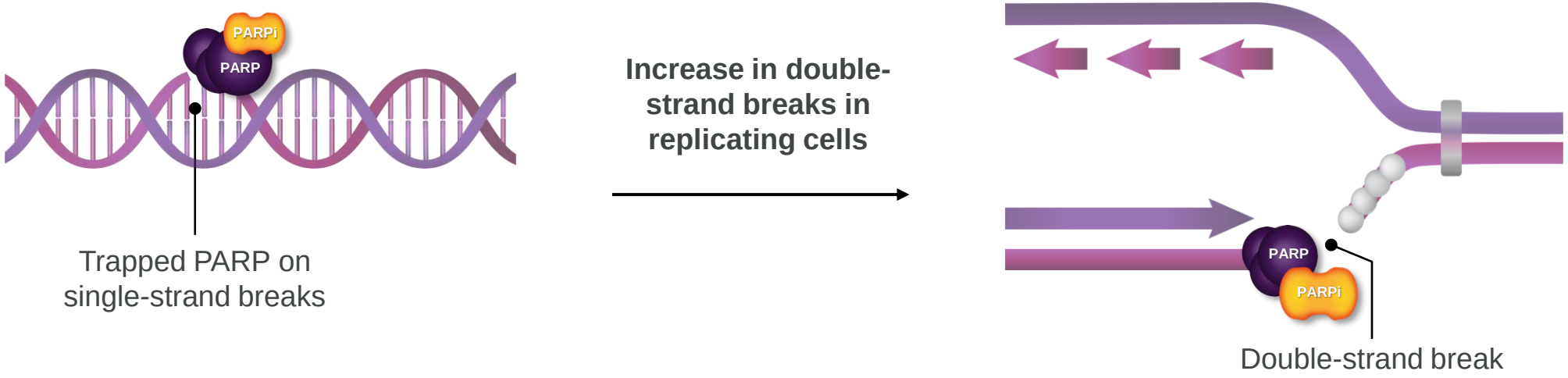
We clearly need to do better

BRCA2, breast cancer gene 2; 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

FOR PATIENTS WITH HRRm, PARPis ARE A TREATMENT OPTION AS THEY TRIGGER CELL DEATH IN CANCER CELLS WITH AN HRR DEFICIENCY[1]

PARPi MECHANISM OF ACTION



HRR(m), homologous recombination repair (mutation); PARP(i), poly-ADP ribose polymerase (inhibitor)

Adapted from: 1. O'Connor MJ. Mol Cell. 2015;60:547-60

INTRODUCING THE PATIENT CASE

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

Germline *BRCA2* mutation detection which is pathogenic.
Consider patient for treatment with a PARPi

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 two pulmonary nodules suspicious of metastases**

Slight discomfort in lumbar spine

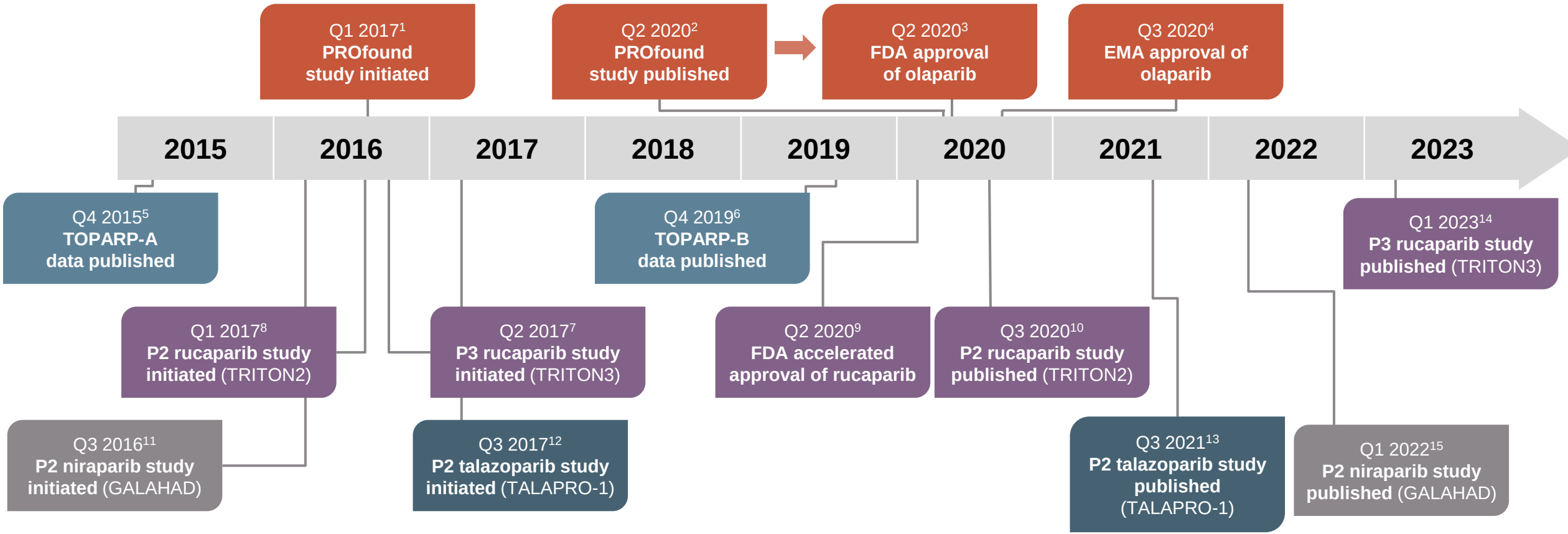
Imaging:

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

ADT, androgen-deprivation therapy; BRCA2, breast cancer gene 2; DRE, digital rectal exam; LUTS, lower urinary-tract symptoms; PSA, prostate-specific antigen; T, tumour stage

PARPi KEY TRIAL DATA

PHASE 2/3 PARP INHIBITOR MONOTHERAPY TRIALS IN mCRPC



EMA, European Medicines Agency; FDA, United States Food and Drug Administration; 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. www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer; 4. https://www.esmo.org/oncology-news/ema-recommends-extension-of-indications-for-olaparib2; 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.https://clinicaltrials.gov/ct2/show/NCT02975934; 8. https://clinicaltrials.gov/ct2/show/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. https://clinicaltrials.gov/ct2/show/NCT02854436; 12.https://clinicaltrials.gov/ct2/show/NCT03148795; 13. de Bono JS, et al. Lancet Oncol. 2022;9:1250-64. All accessed April 2023; 14. Fizazi K, et al. N Engl J Med 2023; 388: 719-32; 15. Smith MR, et al. Lancet Oncol. 2022;23: 362-73

PHASE 2 AND 3 CLINICAL TRIALS IN mCRPC USING PARPis AS MONOTHERAPY

	Olaparib		Niraparib	Talazoparib	Rucaparib	
Trial name	**TOPARP-B[1-2a]**	**PROfound[3-5]**	**GALAHAD[6]**	**TALAPRO-1[7]**	**TRITON2[8-9]**	**TRITON3[10-11]**
Phase	2	3	2	2	2	3
Required prior therapy	1–2 taxane-based regimens, but ~90% were post-abiraterone / enzalutamide	Progression on NHA for mPC and/or CRPC	≥1 taxane-based regimen for mPC AND ≥1 NHA for mCRPC or nmCRPC and subsequent mets	≥1 taxane-based regimen AND ≥1 NHA for mCRPC	1 taxane-based regimen AND ≥1 NHA for CRPC	Evidence of disease progression after treatment with 1 prior NHA; no prior chemotherapy for mCRPC
Primary endpoint	Composite response[b]	rPFS by BICR in Cohort A (*BRCA1*, *BRCA2*, or *ATM* mutations)	ORR (germline *BRCA* or biallelic *BRCA*)	ORR	ORR	rPFS
HRRm panel	Any HRR gene (GeneRead DNAseq Mix-n-Match Panel V2 from Qiagen covering 113 genes)	15 genes (*BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*)	8 genes (biallelic *BRCA1, BRCA2, ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2* OR germline *BRCA* alteration)	11 genes (monoallelic or biallelic *BRCA1, BRCA2, CHEK2, ATM, ATR, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*)	15 genes (germline or somatic) (monoallelic or biallelic *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*)	3 genes (somatic or germline mutation in *BRCA1, BRCA2, or ATM*)

[a]NOTE: TOPARP-B included 300 mg BID and 400 mg BID treatment arms for olaparib. 400 mg BID is not the recommended tablet dose for olaparib.

[b]Defined as a composite of any of the following outcomes: radiological objective response (RECIST v1.1), a decrease in PSA of 50% or more from baseline, or conversion of circulating tumour cell count (from ≥5 cells per 7.5 mL of blood at baseline to <5 cells per 7.5 mL of blood).

ATM, ataxia telangiectasia mutated; BICR, Blinded Independent Central Review; BID, twice a day; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK1/2, checkpoint kinase 1/2; CRPC, castration-resistant prostate cancer; HDAC2, histone deacetylase 2; HRR, homologous recombination repair; HRRm, HRR mutation; mets, metastases; mPC, metastatic prostate cancer; NBN, nibrin; NHA, novel hormonal agent; (n)mCRPC, (non)-metastatic castration-resistant prostate cancer; ORR, objective response rate; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PPP2R2A, protein phosphatase 2 regulatory subunit B alpha; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival

1. Mateo J, et al. N Engl J Med. 2015;373:1697-708; 2. Mateo J, et al. Lancet Oncol. 2020;21:162–74; 3. de Bono J, et al. N Engl J Med. 2020;382:2091-102; 4. Hussain M, et al. N Engl J Med. 2020;383:2345-57; 5. https://www.clinicaltrials.gov/ct2/show/NCT02987543; 6. Smith MR, et al. Lancet Oncol. 2022;23: 362-73; 7. de Bono JS, et al. Lancet Oncol. 2021;22(9):1250-64; 8. Abida W, et al. J Clin Oncol. 2020;32:3763-72; 9. Abida W, et al. Clin Cancer Res. 2020;26:2487-96; 10. https://clinicaltrials.gov/ct2/show/NCT02975934; 11. Bryce AL, et al. Prostate Cancer Foundation Retreat 2022 (oral presentation: https://clovisoncology.com/files/PCF2022_Bryce_Oral.pdf)

OUTCOMES FROM PHASE 2 NON-REGISTRATIONAL STUDIES

	Olaparib	Niraparib	Talazoparib
Trial name	**TOPARP-B[1–2]**	**GALAHAD[3]**	**TALAPRO-1[4]**
Phase	2	2	2
Dose	300/400mg bid[a]	300mg QD	1mg QD[c]
Required prior therapy	1–2 taxane-based regimens, but >90% were post-abiraterone / enzalutamide	≥1 taxane-based regimen for mPC AND ≥1 NHA for mCRPC or nmCRPC and subsequent mets	1-2 taxane-based regimen for mPC AND ≥1 NHA for mCRPC
Primary endpoint	Composite response[b]	ORR (germline *BRCA* or biallelic *BRCA*)	ORR
ORR in *BRCA*m population	TOPARP-B: 52.4%	34.2%	46% *BRCA2* 50% *BRCA1*

These are not head-to-head trial comparisons. Because clinical trials are conducted under widely varying conditions, endpoints observed in the clinical trials of one drug cannot be directly compared with those in clinical trials of another drug.

[a]Note: TOPARP-B included 300 mg BID and 400 mg BID treatment arms for olaparib. 400 mg BID is not the recommended tablet dose for olaparib.

[b] Defined as a composite of any of the following outcomes: radiological objective response (RECIST v1.1), a decrease in PSA of 50% or more from baseline, or conversion of circulating tumour cell count (from ≥5 cells per 7.5 mL of blood at baseline to <5 cells per 7.5 mL of blood).

[c]0·75 mg per day for patients with moderate renal impairment, defined as an estimated glomerular filtration rate of 30–59 mL/min per 1·73 m²

BID, twice a day; BRCA, breast cancer gene; BRCAm, BRCA mutation; CRPC, castration-resistant prostate cancer; HRR, homologous recombination repair; mets, metastases; mPC, metastatic prostate cancer; NHA, novel hormonal agent; (n)mCRPC, (non)-metastatic castration-resistant prostate cancer; ORR, objective response rate; PSA, prostate specific antigen; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours

1. Mateo J, et al. N Engl J Med. 2015;373:1697-708; 2. Mateo J, et al. Lancet Oncol. 2020;21:162-74; 3. Smith MR, et al. Lancet Oncol. 2022;23: 362-73; 4. de Bono JS, et al. Lancet Oncol. 2021;22(9):1250-64

AE PROFILES OF PARPi FROM MONOTHERAPY TRIALS

Frequency of AEs in prostate cancer trials – All Grade (Grade ≥3)	Olaparib (PROfound)[1]	Rucaparib (TRITON2)[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

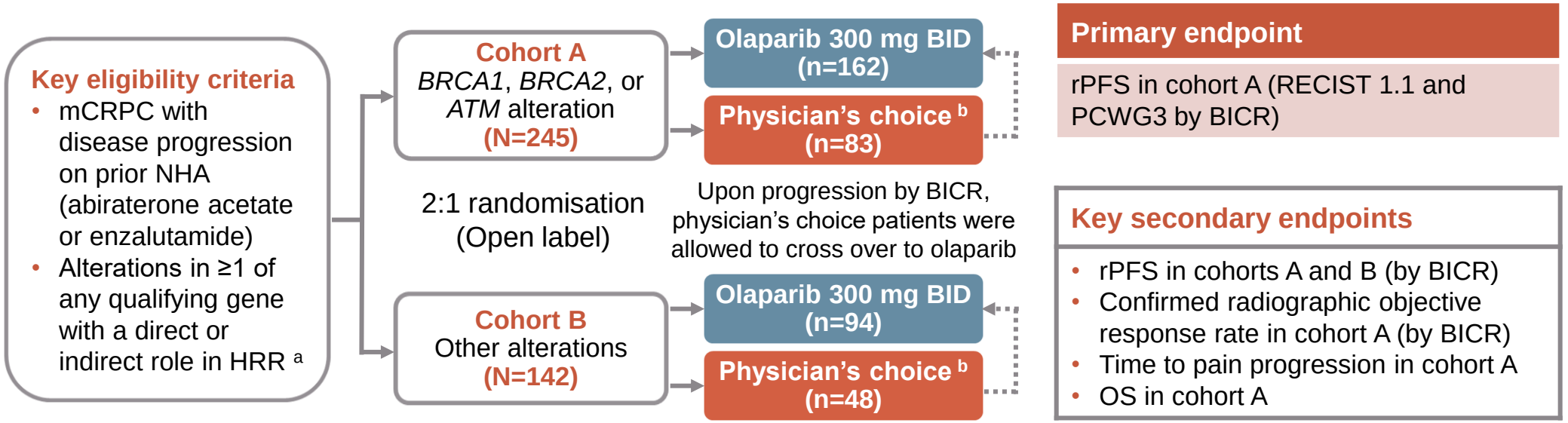
Frequency and grade of cytopenias in prostate cancer trials	Olaparib (PROfound)[1]	Rucaparib (TRITON2)[2]	Niraparib (GALAHAD)[3]	Talazoparib (TALAPRO-1)[4]
Anaemia Grade ≥3 (%)	23	25	33	31
Neutropenia Grade ≥3 (%)	NR[a]	7	10	8
Thrombocytopenia Grade ≥3 (%)	NR[a]	10	16	9

Please note that head-to-head studies were not conducted between these products. This data is for information purposes only, and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. AEs highlighted in blue if value ≥10%

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported; PARPi, poly-ADP ribose polymerase inhibitor

1. Hussain M, et al. New Engl J Med. 2020;383:2345-57; 2. Abida W, et al. J Clin Oncol. 2020;38(32):3763-72 (supplementary appendix);
3. Smith MR, et al. Lancet Oncol. 2022;23(3):362-73; 4. de Bono JS, et al. Lancet Oncol. 2021;22(9):1250-64

PROfound: PHASE 3 DATA WITH OLAPARIB IN mCRPC (REGISTRATIONAL STUDY)



[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

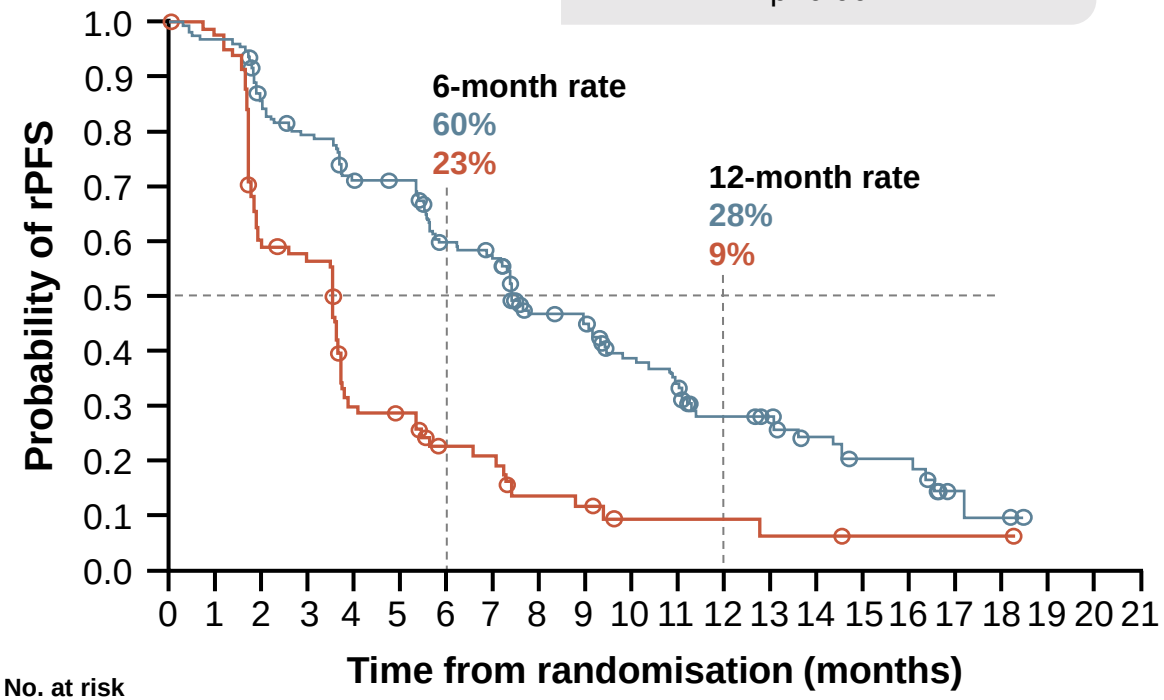
ATM, ataxia telangiectasia mutated; BICR, blinded independent central review; BID, twice daily; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK1/2, checkpoint kinase 1/2; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PALB2, partner and localiser of BRCA2; PCWG3, Prostate Cancer Working Group 3; PPP2R2A, protein phosphatase 2 regulatory subunit B alpha; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival

de Bono J, et al. N Engl J Med. 2020;382:2091-102; Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

PROfound: OLAPARIB MONOTHERAPY IMPROVES rPFS COMPARED TO NHA RECHALLENGE

COHORT A: *BRCA1/2* or *ATM*

HR (95% CI) **0.34** (0.25-0.47)
Median PFS: 7.4 vs 3.6 months;
p<0.001

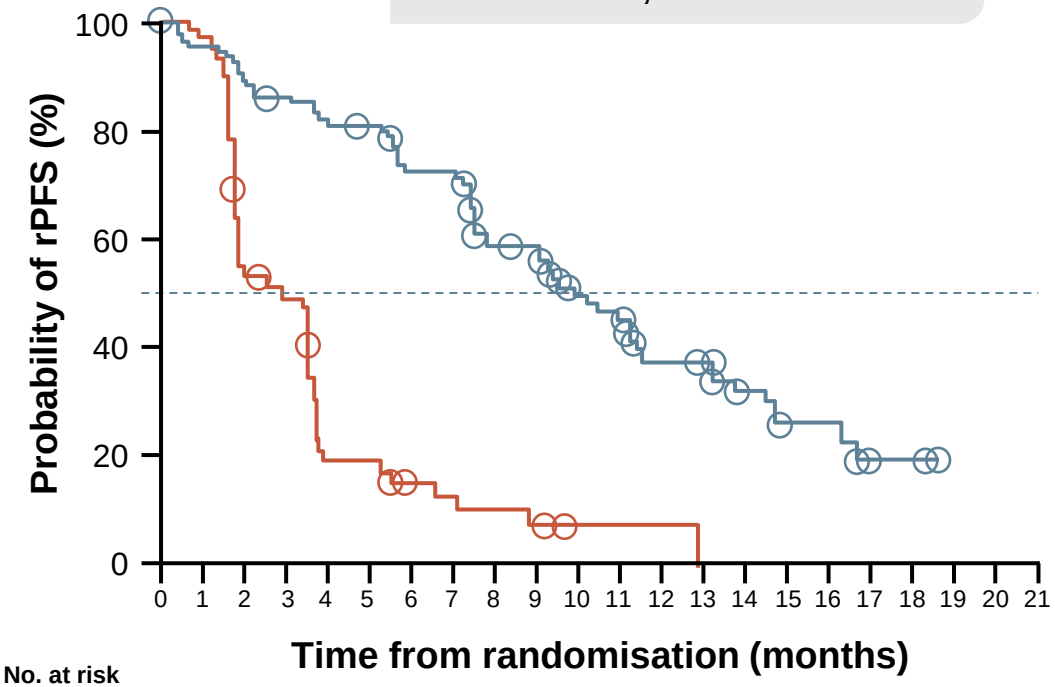


No. at risk																					
Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

COHORT A. PFS by BICR assessment, data maturity=71%. Data cut-off date: 4 June 2019

BRCA1 and/or *BRCA2*

rPFS[a]
HR, 0.22 (95% CI, 0.15-0.32)
Median rPFS, 9.8 vs 3.0 months



No. at risk																					
Olaparib	102	93	87	83	78	77	67	66	48	45	36	33	23	22	16	8	8	2	2	0	0	0
Physician's choice	58	56	30	27	10	10	6	5	4	3	1	1	1	0	0	0	0	0	0	0	0	0

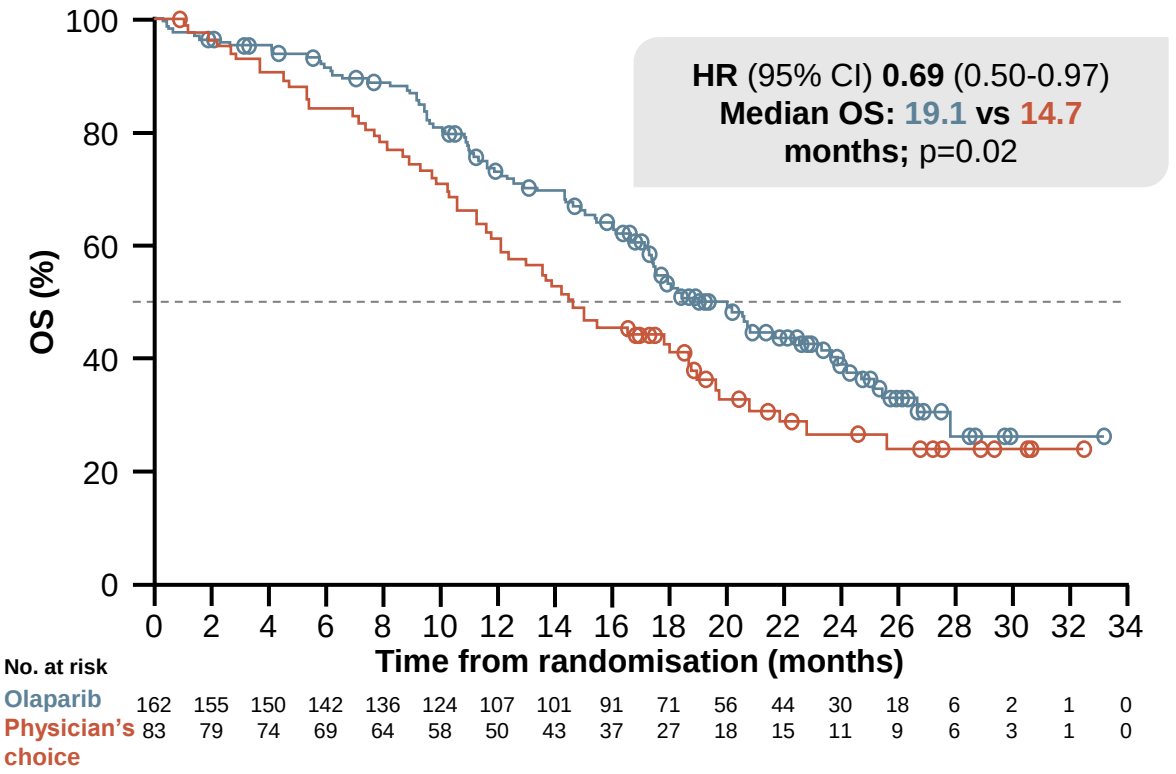
[a] The study was not powered for gene-by-gene analysis.

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NHA, new hormonal agent; (r)PFS, (radiographic) progression-free survival

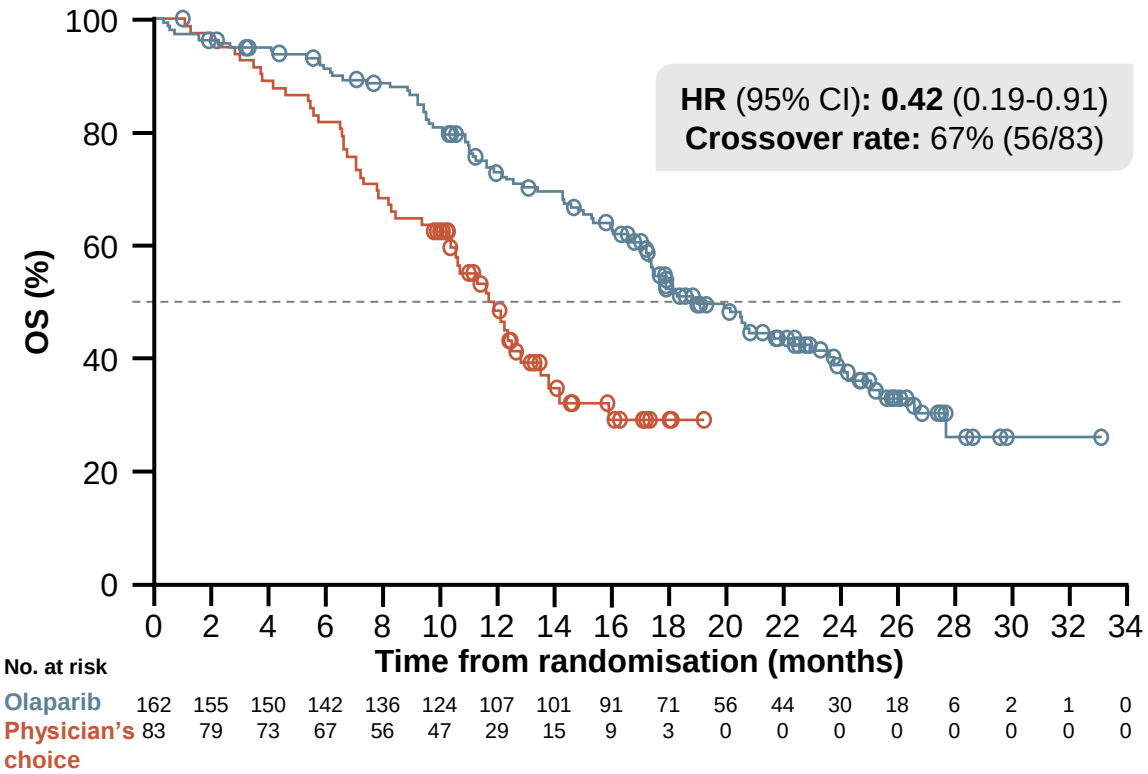
de Bono J, et al. N Engl J Med. 2020;382:2091-102 (Supplementary appendix)

PROfound: 31% REDUCTION IN DEATH WITH OLAPARIB MONOTHERAPY COMPARED TO NHA RECHALLENGE

COHORT A: *BRCA1/2* OR *ATM* MUTATIONS



COHORT A WITH ADJUSTMENT FOR CROSSOVER[a]



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

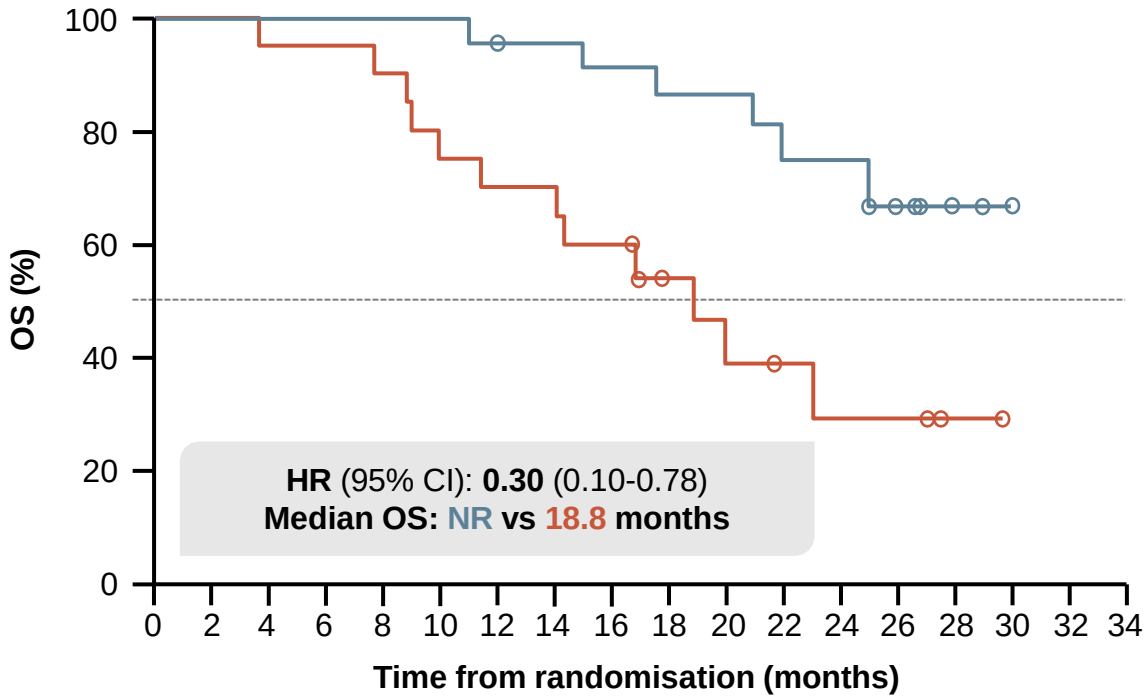
[a] Re-censored; conducted using rank-preserving structural failure time model to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy

BRCA1/2, breast cancer gene 1/2; CI, confidence interval; HR, hazard ratio; NHA, new hormonal agents; OS, overall survival

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

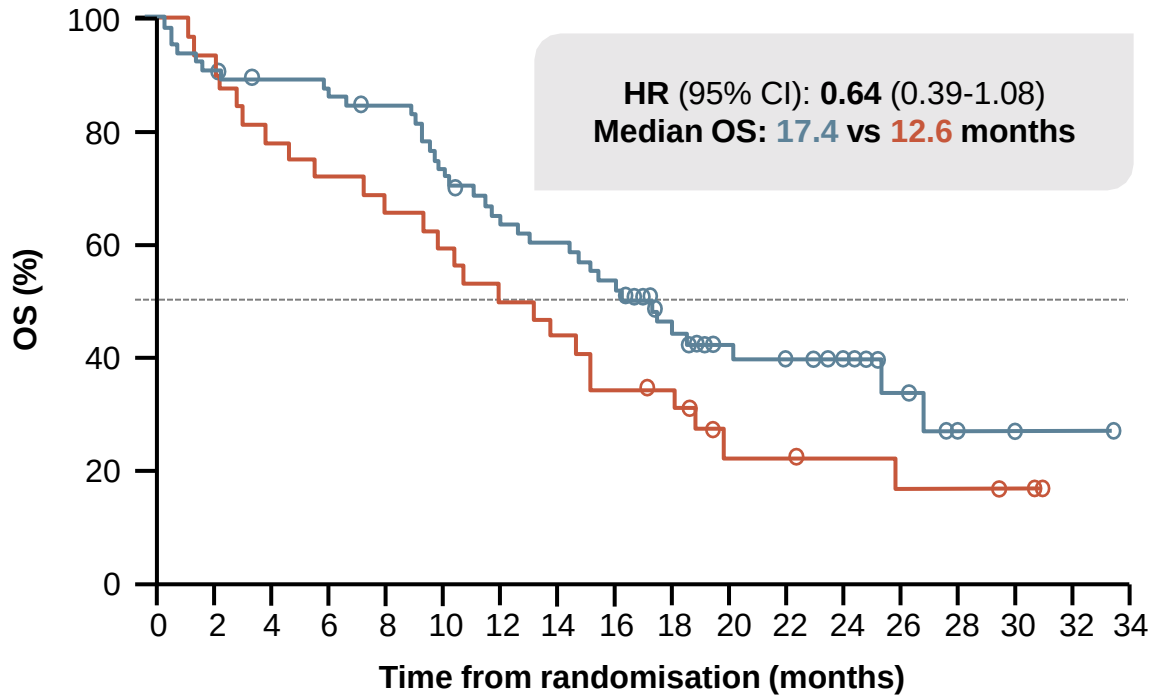
FOR FINAL OS, AN IMPROVED TREATMENT EFFECT WAS SEEN WITH OLAPARIB IN PATIENTS WITH *BRCA* MUTATION-POSITIVE mCRPC AND WHO HAD NOT RECEIVED A TAXANE[a]

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



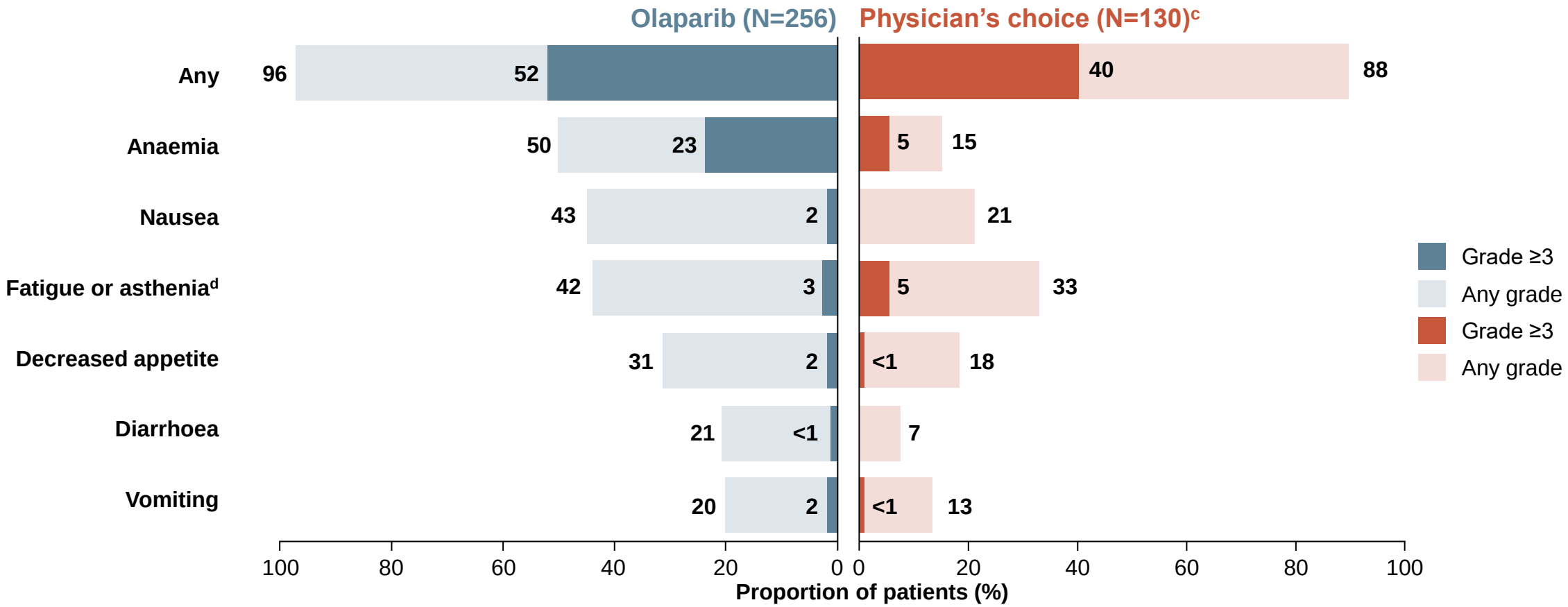
No. at risk																		
Olaparib	66	60	57	55	53	46	38	36	32	23	16	15	11	6	2	2	1	0
Physician's choice	32	29	25	23	21	19	16	14	11	10	5	5	4	3	3	2	0	0

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

BRCA, breast cancer 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)

PROfound: MOST COMMON AEs (≥20% ANY GRADE[a]) IN THE OVERALL POPULATION[b]

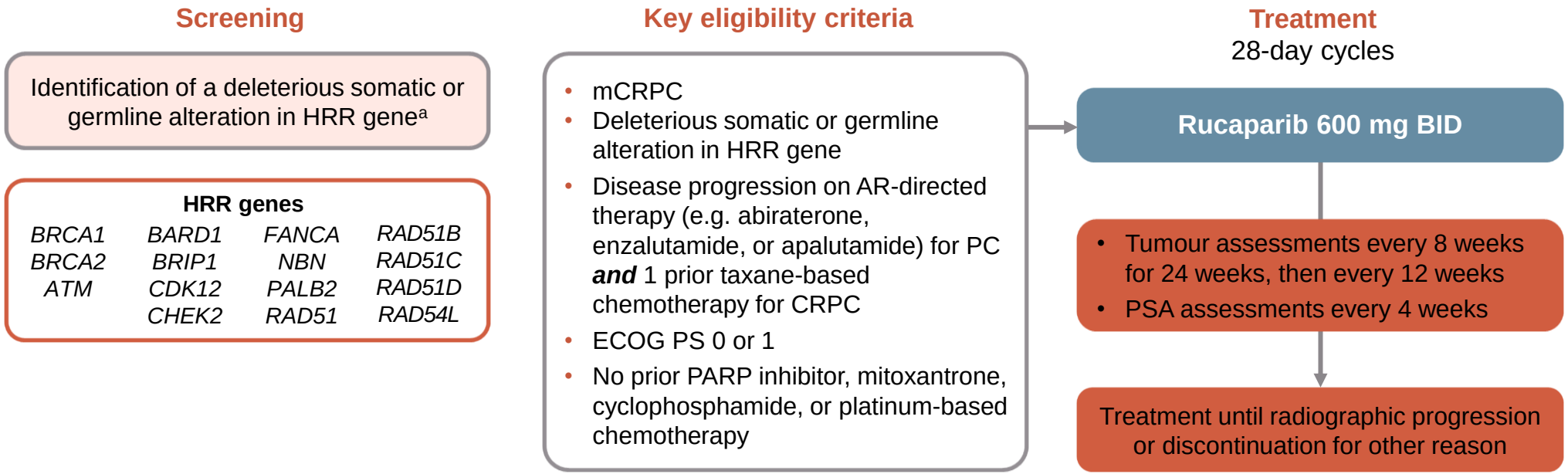


[b] ≥20% any grade AEs in either treatment arm; [b] Patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D,* and / or *RAD54L*. Note, there were no cases of myelodysplastic syndromes or AML during the 30-day safety follow-up. There has since been one fatal case of AML 54 days after discontinuation of olaparib. [c] One patient in the control group did not receive treatment. [d] Grouped term.

AE, adverse event; AML, acute myeloid leukaemia; ATM, ataxia telangiectasia mutated; BRCA, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase 2; DCO, data cut-off; OS, overall survival; PALB2, partner and localiser of BRCA2; PARP, poly-ADP ribose polymerase; PPP2R2A, protein phosphatase 2 regulatory subunit B alpha

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

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



Primary endpoints[b]

- Patients with measurable disease at baseline: confirmed ORR per modified RECIST[c]/PCWG3 by central assessment
- Patients with non-measurable disease at baseline: confirmed PSA response (≥50% decrease) rate[d]

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

AR, androgen receptor; ATM, ataxia telangiectasia mutated; BID, twice daily; BID, twice a day; BRCA, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase 2; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mCRPC, metastatic CRPC; MRI, magnetic resonance imaging; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; PALB2, partner and localiser of BRCA2; 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. ESMO 2019, abstract 2754 (poster discussion); Abida W, et al. J Clin Oncol. 2020;38:3763-72 (Supplementary appendix)

TRITON2: RUCAPARIB HAS ANTI-TUMOUR ACTIVITY IN mCRPC PATIENTS WITH *BRCA1/2* ALTERATIONS[1]

Response	Investigator-evaluable population (N=65)	IRR-evaluable population (N=62)
Confirmed ORR, n (% [95% CI])[a]	33 (50.8 [38.1-63.4])	27 (43.5 [31.0-56.7])
Complete response, n (%)	4 (6.2)	7 (11.3)
Partial response, n (%)	29 (44.6)	20 (32.3)
Stable disease, n (%)	25 (38.5)	28 (45.2)
Progressive disease, n (%)	6 (9.2)	6 (9.7)
Not evaluable, n (%)	1 (1.5)	1 (1.6)
	Overall efficacy population (N=115)	
Confirmed PSA, n (% [95% CI])	63 (54.8 [45.2-64.1])	

Visit cut-off date: December 23, 2019

[a] Per modified RECIST/Prostate Cancer Clinical Trials Working Group 3 criteria

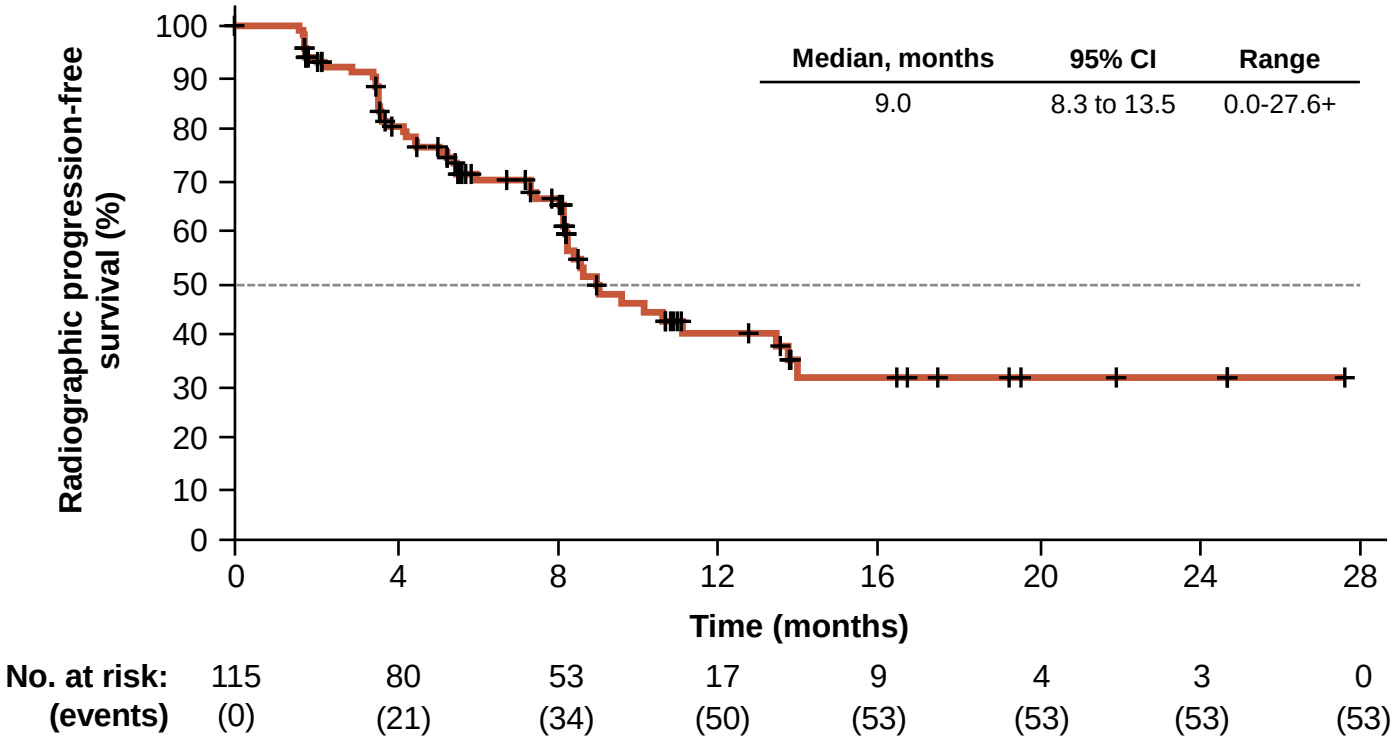
- Patients harbouring an ATM or CDK12 alteration did not receive significant benefit[2]

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CI, confidence interval; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours version 1.1

1. Abida W, et al. J Clin Oncol 2020;38:3763-72; 2. Abida W, et al. Clin Cancer Res. 2020;26:2487-96

TRITON2: RUCAPARIB ACHIEVED A MEDIAN rPFS OF 9 MONTHS IN mCRPC PATIENTS WITH *BRCA* ALTERATIONS

- FDA granted accelerated approval based on data from TRITON2



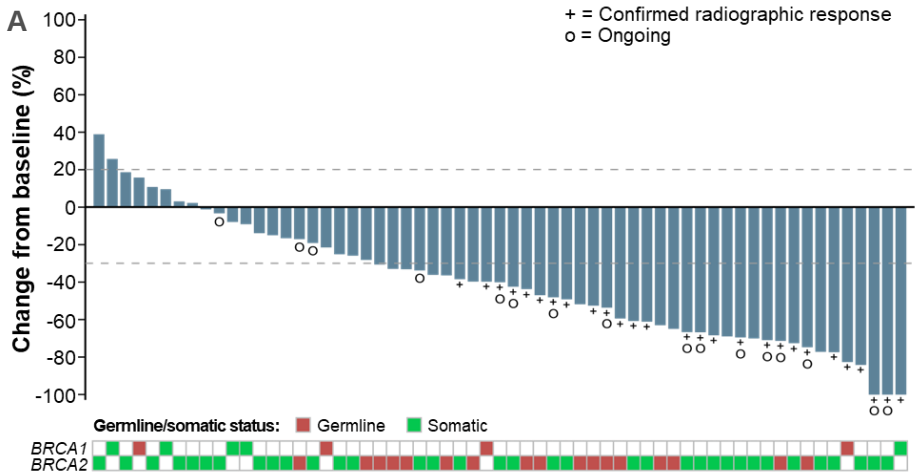
rPFS by blinded independent radiology review assessment. Visit cut-off date: December 23, 2019.
Progression was assessed per modified RECIST/PWCG3 criteria.

BRCA, breast cancer gene; CI, confidence interval; FDA, Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1; rPFS, radiographic progression-free survival

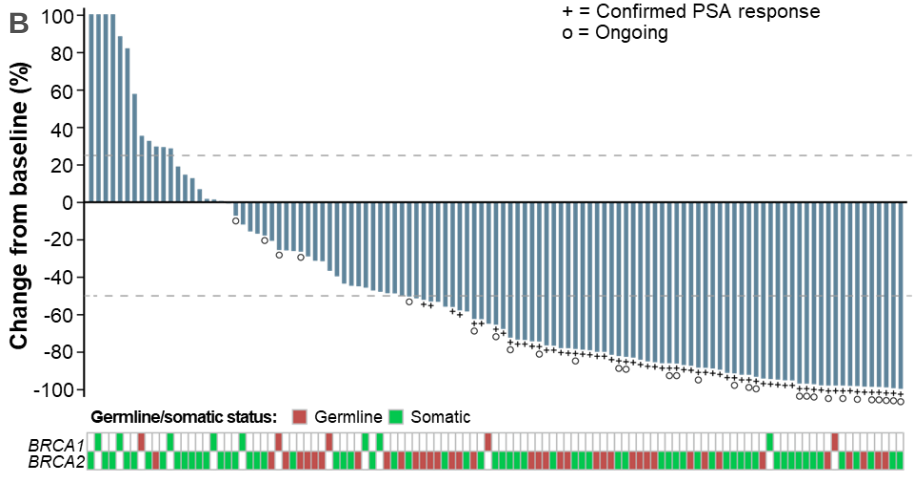
Abida W, et al. J Clin Oncol. 2020;38:3763-72; FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer | FDA

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

Best change from baseline in sum of target lesion(s) in the IRR-evaluable population



Best change from baseline in PSA in the overall efficacy population



BRCA1/2, breast cancer gene 1/2; chemo, chemotherapy; CI, confidence interval; IRR, independent radiology review; 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

TRITON2: RUCAPARIB SIDE EFFECTS

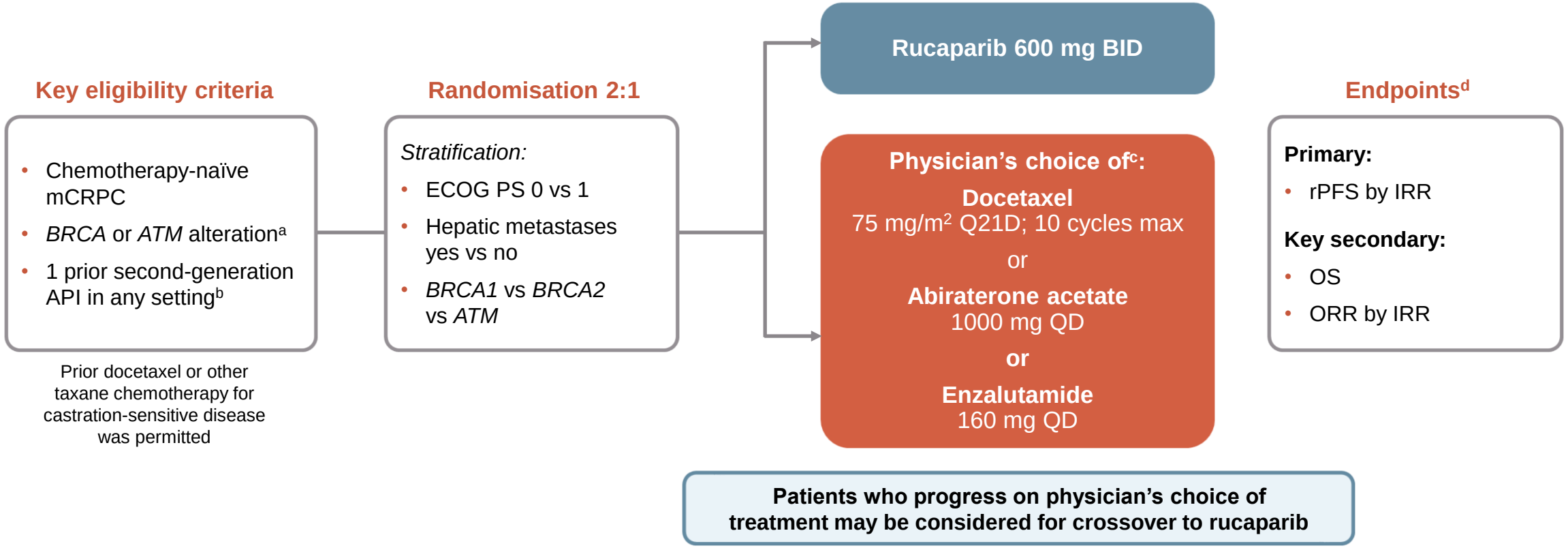
Individual TEAE (preferred terms) occurring in ≥15% of patients N=115; n (%)	Any grade	Grade ≥3
Asthenia/fatigue	71 (61.7)	10 (8.7)
Nausea	60 (52.2)	3 (2.6)
Anaemia/decreased hemoglobin	50 (43.5)	29 (25.2)
ALT/AST increased	38 (33.0)	6 (5.2)
Decreased appetite	32 (27.8)	2 (1.7)
Constipation	31 (27.0)	1 (0.9)
Thrombocytopenia/decreased platelets	29 (25.2)	11 (9.6)
Vomiting	25 (21.7)	1 (0.9)
Diarrhoea	23 (20.0)	0
Dizziness	21 (18.3)	0
Blood creatinine increased	18 (15.7)	1 (0.9)

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

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

TRITON3 STUDY DESIGN

CONFIRMATORY STUDY FOR ACCELERATED APPROVAL OF RUCAPARIB

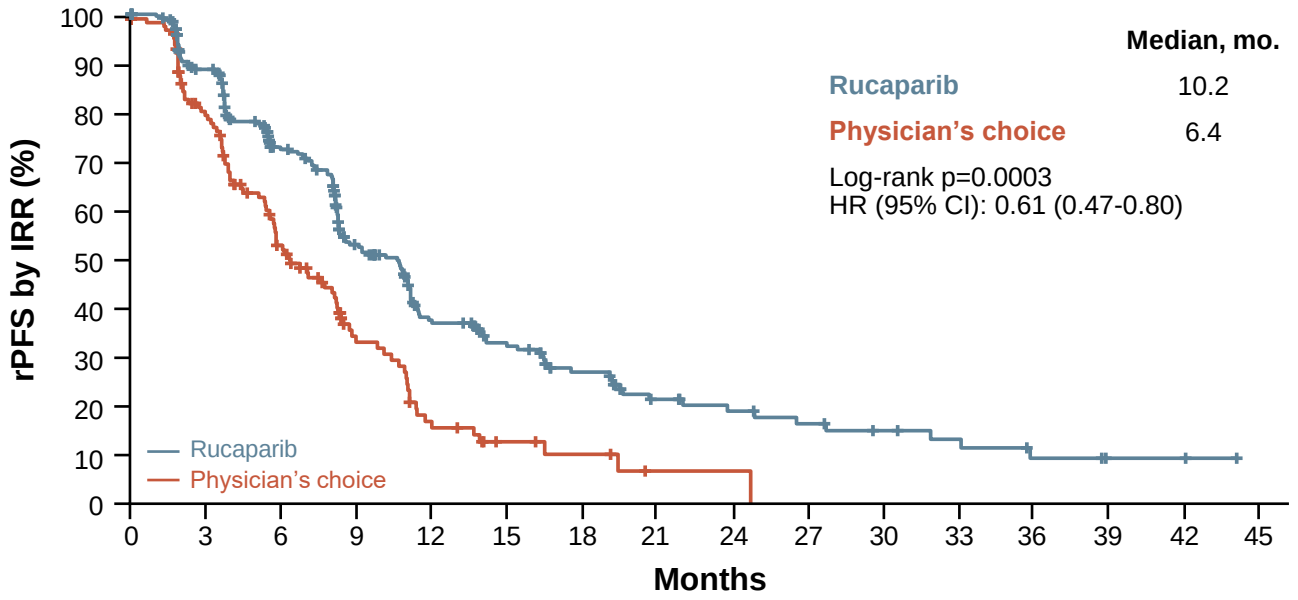


Visit cut-off date: 25 August 2022. [a] Determined by Foundation Medicine testing of tissue or plasma. [b] Protocol amendment June 19, 2018: patients' qualifying second-generation API could be in any setting. [c] If chosen, patients received whichever second-generation API had not yet been received. [d] Tumour assessments were conducted at baseline and every 8 weeks for 24 weeks, then every 12 weeks, via CT/MRI and technetium-bone scans.

API, androgen pathway inhibitor; ATM, ataxia telangiectasia mutated; BID, twice daily; BRCA1/2, breast cancer gene 1/2; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; Q21D, every 21 days; QD, once daily; rPFS, radiographic progression-free survival

Bryce AL, et al. Prostate Cancer Foundation Retreat 2022; Fizazi K, et al. N Engl J Med 2023; 388: 719-32

TRITON3: RUCAPARIB IMPROVES rPFS VS PHYSICIAN'S CHOICE IN ITT POPULATION



	Median, mo.	95% CI
Rucaparib	10.2	8.3-11.2
Physician's choice	6.4	5.6-8.2

Log-rank p=0.0003
HR (95% CI): 0.61 (0.47-0.80)

Patients at risk (events)

Rucaparib	270 (0)	220 (29)	155 (68)	99 (108)	61 (135)	46 (142)	31 (150)	19 (156)	15 (158)	12 (160)	9 (161)	7 (162)	4 (164)	2 (164)	2 (164)	0 (164)
Physician's choice	135 (0)	97 (25)	58 (56)	28 (74)	13 (88)	6 (91)	4 (92)	1 (93)	1 (93)	0 (94)						

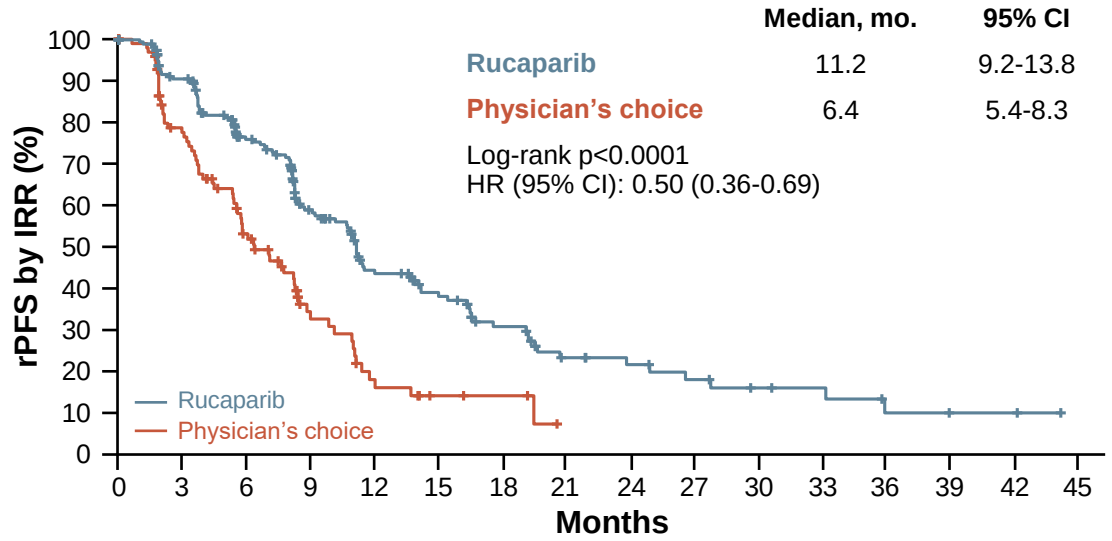
Data maturity: 64% (258/405). The *ATM* subgroup completed enrolment in December 2019

ATM, ataxia telangiectasia mutated; CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; ITT, intention-to-treat; mo., months; rPFS, radiographic progression-free survival

Bryce AL, et al. Prostate Cancer Foundation Retreat 2022; Fizazi K, et al. N Engl J Med 2023; 388: 719-32

TRITON3: RUCAPARIB IMPROVES rPFS VS PHYSICIAN'S CHOICE IN *BRCA* SUBGROUP

rPFS by IRR in the *BRCA* subgroup



	Median, mo.	95% CI
Rucaparib	11.2	9.2-13.8
Physician's choice	6.4	5.4-8.3

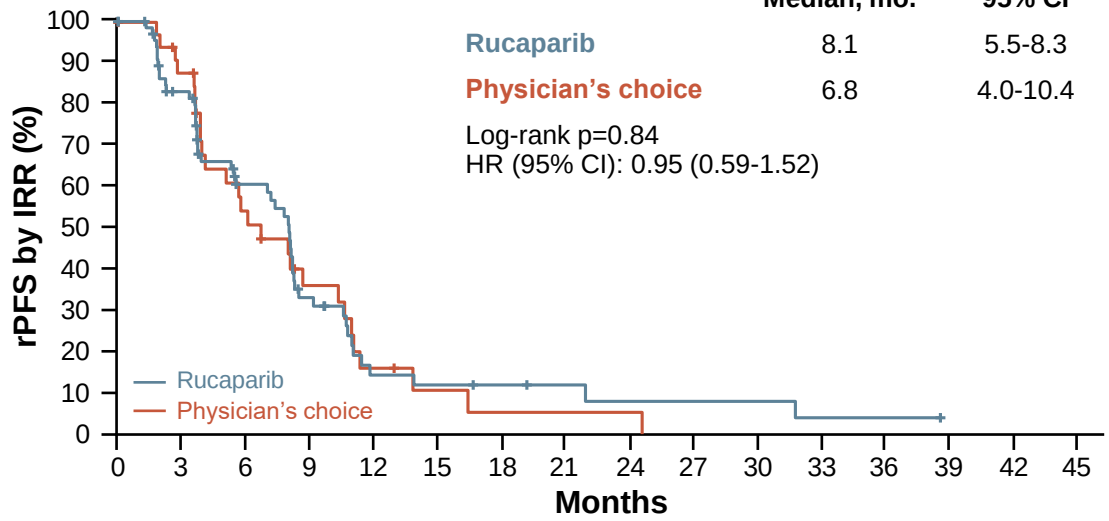
Log-rank p<0.0001
HR (95% CI): 0.50 (0.36-0.69)

Patients at risk (events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Physician's choice	101 (0)	69 (21)	42 (42)	19 (55)	9 (64)	4 (66)	3 (66)	0 (67)								

Data maturity: 60% (182/302).

rPFS by IRR in the *ATM* subgroup



	Median, mo.	95% CI
Rucaparib	8.1	5.5-8.3
Physician's choice	6.8	4.0-10.4

Log-rank p=0.84
HR (95% CI): 0.95 (0.59-1.52)

Patients at risk (events)

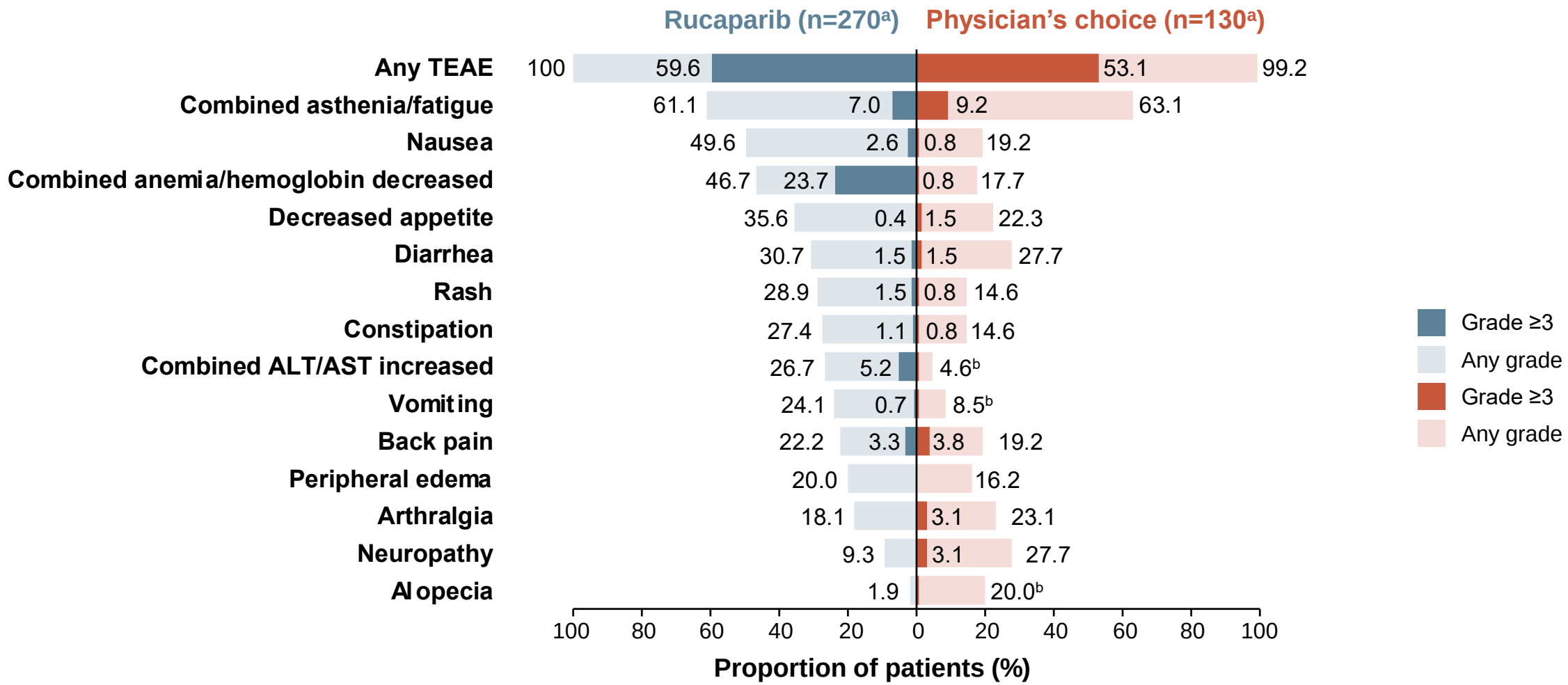
Rucaparib	69 (0)	51 (11)	31 (24)	16 (38)	6 (46)	5 (47)	4 (47)	3 (47)	2 (48)	2 (48)	2 (48)	1 (49)	1 (49)	0 (49)		
Physician's choice	34 (0)	28 (4)	16 (14)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)						

Data maturity: 74% (76/103). The *ATM* subgroup completed enrolment in December 2019

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; mo., months; rPFS, radiographic progression-free survival

Bryce AL, et al. Prostate Cancer Foundation Retreat 2022; Fizazi K, et al. N Engl J Med 2023; 388: 719-32

TRITON3: MOST COMMON TEAEs (≥20% ANY GRADE)



[a] Safety population (all patients who received ≥1 dose of protocol-specified treatment). [b] Grade ≥3, 0.8%

Neuropathy includes neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, and polyneuropathy.

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

Bryce AL, et al. Prostate Cancer Foundation Retreat 2022; Fizazi K, et al. N Engl J Med 2023; 388: 719-32

TREATMENT OPTIONS FOR PATIENT CASE

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 two pulmonary nodules suspicious of metastases**

Slight discomfort in lumbar spine

Imaging:

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

ADT, androgen-deprivation therapy; BRCA2, breast cancer gene 2; DRE, digital rectal exam; LUTS, lower urinary-tract symptoms; PSA, prostate-specific antigen; T, tumour stage

PARP INHIBITORS ARE APPROVED IN PROSTATE CANCER

Olaparib FDA-approved indication[1]

Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and **HRRm**, who have **progressed** on enzalutamide or abiraterone acetate, selected using an **FDA-approved** Lynparza **companion diagnostic**

Olaparib EMA-approved indication[2]

- Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and a ***BRCAm***, who have **progressed** on prior therapy, including an **NHA**. Determine *BRCAm* status with a **validated test method**
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with **mCRPC in whom chemotherapy is not clinically indicated**

Rucaparib FDA-approved indication[3]

Indicated as **monotherapy** for the treatment of adult patients with ***BRCAm* mCRPC** who have **progressed on** AR-directed therapy and a **taxane[a]**

[a]Rucaparib has no current approval in prostate cancer in Europe[4]

- Treatment should continue **until progression** or **unacceptable toxicity**. An LHRH analogue should be continued in patients who are not surgically castrated[1,2]
- Talazoparib is not currently approved in prostate cancer

Niraparib EMA-approved indication[5]

Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone or prednisolone for the treatment of adult patients with **mCRPC and *BRCA1/2* gene mutations** (germline and/or somatic) **in whom chemotherapy is not clinically indicated**

AR, androgen receptor; BRCAm, breast cancer gene mutation; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PARP, poly-ADP ribose polymerase

1. Lynparza (olaparib) US prescribing information (Aug-2022); 2. Lynparza (olaparib) summary of product characteristics (Mar 2023); 3. Rubraca (rucaparib) US prescribing information (Jun 2022); 4. Rubraca (rucaparib) summary of product characteristics (Dec 2022); 5. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate

TREATMENT CHOICE

- **PARP inhibitors are effective** drugs as monotherapy **in mCRPC patients with HRR alterations**
- **Genetic testing is important** to inform on prognosis, help with treatment decision making and for understanding inherited risk
- *BRCA* mutations are associated with poor outcomes in mCRPC patients
- Patients with tumours harbouring ***BRCA1/BRCA2* alterations** appear to derive the **greatest clinical benefit from PARP inhibitors**, but patients with other HRR alterations might also derive benefit

BRCA1/2, breast cancer gene 1/2; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase

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