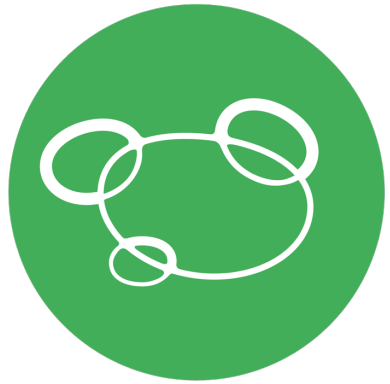

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GU CONNECT MICRO E-LEARNING

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

MODULE ONE

DECEMBER 2022

PARPi, poly-ADP ribose polymerase inhibitor

MODULE ONE

PARPi IN ADVANCED PROSTATE CANCER

THIS MODULE HAS BEEN DEVELOPED BY TWO INTERNATIONAL EXPERTS

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Assoc. Prof. Alicia Morgans

GU Medical Oncologist, Dana-Farber Cancer Institute, Boston, USA

Dr Pasquale Rescigno

Clinical Senior Lecturer, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, UK

DISCLAIMER AND DISCLOSURES

Please note: The views expressed within this presentation are the personal opinions of the authors. They do not necessarily represent the views of the authors' academic institutions, or the rest of the GU CONNECT group.

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EDUCATIONAL OBJECTIVES

- Understand the mechanism of action of PARPi's
- Understand the role of genetic testing
- Recognise the efficacy and safety profiles of PARP inhibitors
- Understand their differences across tumour types
- Understand the place of PARP inhibitors in the treatment landscape for patients with prostate cancer

PARP(i), poly-ADP ribose polymerase (inhibitors)

CLINICAL TAKEAWAYS

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

PARPi MECHANISM OF ACTION

PARPi, poly-ADP ribose polymerase inhibitor

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

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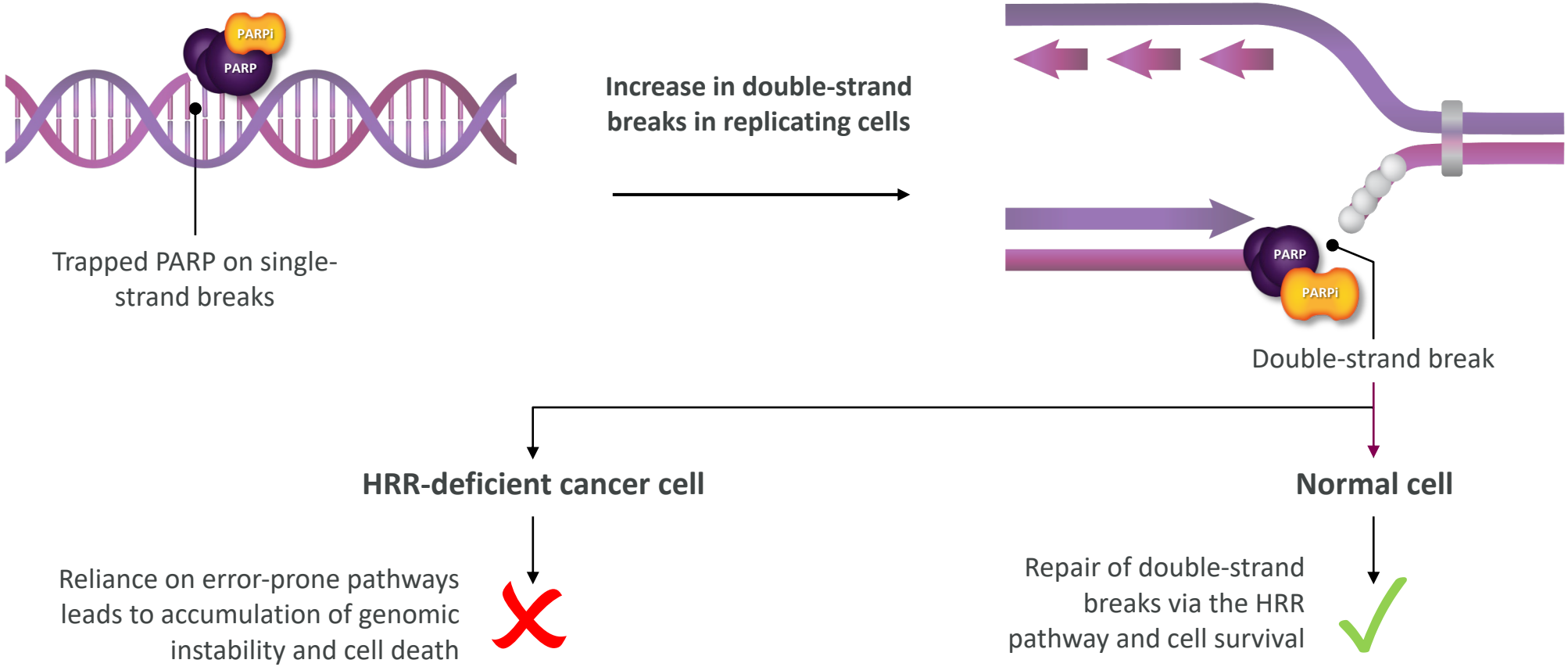
PARPi MECHANISM OF ACTION



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

DNA REPAIR PATHWAY ABERRATIONS: HOMOLOGOUS RECOMBINATION REPAIR (HRR) DEFECTS

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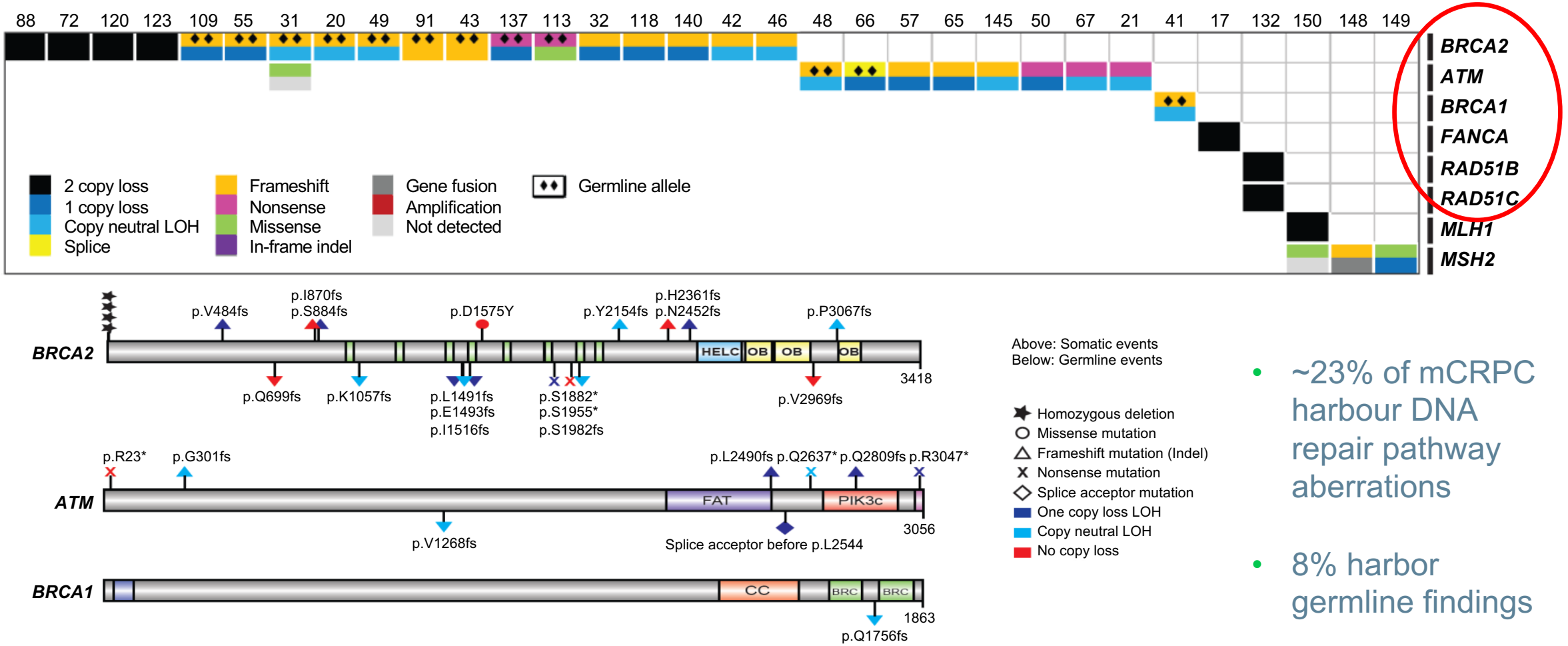

- ~23% of mCRPC harbour DNA repair pathway aberrations
- 8% harbor germline findings

ATM, ataxia telangiectasia mutated; BRC, Brca repeat; BRCA1/2, breast cancer gene 1/2; CC, coiled coil; FAT, FRAP-ATM-TRRAP domain; HELC, helical domain; HRR, homologous recombination repair; LOH, loss of heterozygosity; mCRPC, metastatic castration-resistant prostate cancer; OB, oligonucleotide binding fold; PIK3c, phosphoinositide 3-kinase domain

Robinson D, et al. Cell. 2015;161:1215-28

DNA DAMAGE REPAIR MUTATIONS AND GENETIC TESTING

TUMOURS CAN DEVELOP IN THE CONTEXT OF GERMLINE OR SOMATIC GENE ALTERATIONS[1-7]

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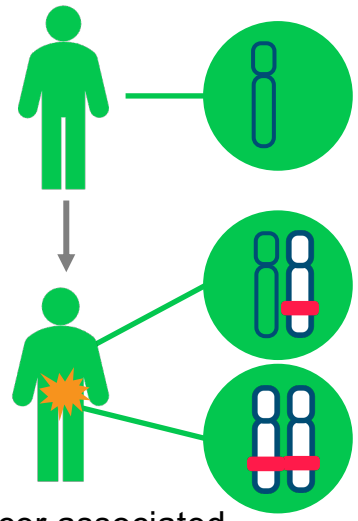
BRCA[a] MUTATIONS PROVIDE A GOOD EXAMPLE OF THIS[1,2]

Germline

BRCAm inherited from parent

All cells have one mutated and one normal BRCA[a] copy
(monoallelic BRCA loss – cells are viable but predisposed to cancer)

Somatic mutation causes loss of normal BRCA copy in a cell
(biallelic BRCA loss is a tumour driver event)

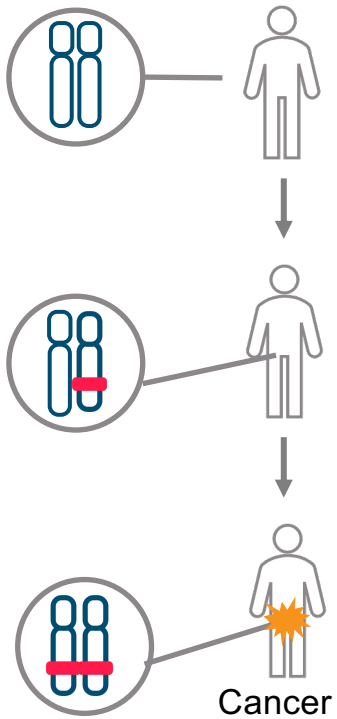


Cancer associated with BRCAm

Non-tumour cells remain with monoallelic BRCA loss
Tumour cells have biallelic BRCA loss[b]

Somatic

No inherited BRCAm



All cells have two 'normal' copies of BRCA gene

Somatic mutation in cell causes monoallelic BRCA loss

Second somatic mutation results in biallelic BRCA loss

Cancer associated with BRCAm

Non-tumour cells remain 'normal'
Tumour cells have biallelic BRCA loss[b]

[a] Can be either *BRCA1* or *BRCA2*. [b] Loss of function can also result from epigenetic and other non-genomic mechanisms
BRCA1/2, breast cancer gene 1/2; BRCAm, breast cancer gene 1/2 mutation

1. Wu H, et al. Gene Ther. 2017;24,601-9; 2. Castro E, et al. Asian J Androl. 2012;14:409-14; 3. Macedo GS, et al. Genet Mol Biol. 2019;42(1 suppl 1):215-31; 4. Ryland GL, et al. BMC Medical Genomics. 2015;8:45; 5. Stoppa-Lyonnet D. Eur J Human Genet. 2016;24:S3-9; 6. Tucker T, et al. J. Clin Genet. 2002;62:345-57; 7. Hunt JL. Cell & Tissue Based Mol Pathol. 2009;5:50-5

FAMILY HISTORY IS THE STRONGEST KNOWN RISK FACTOR FOR PROSTATE CANCER

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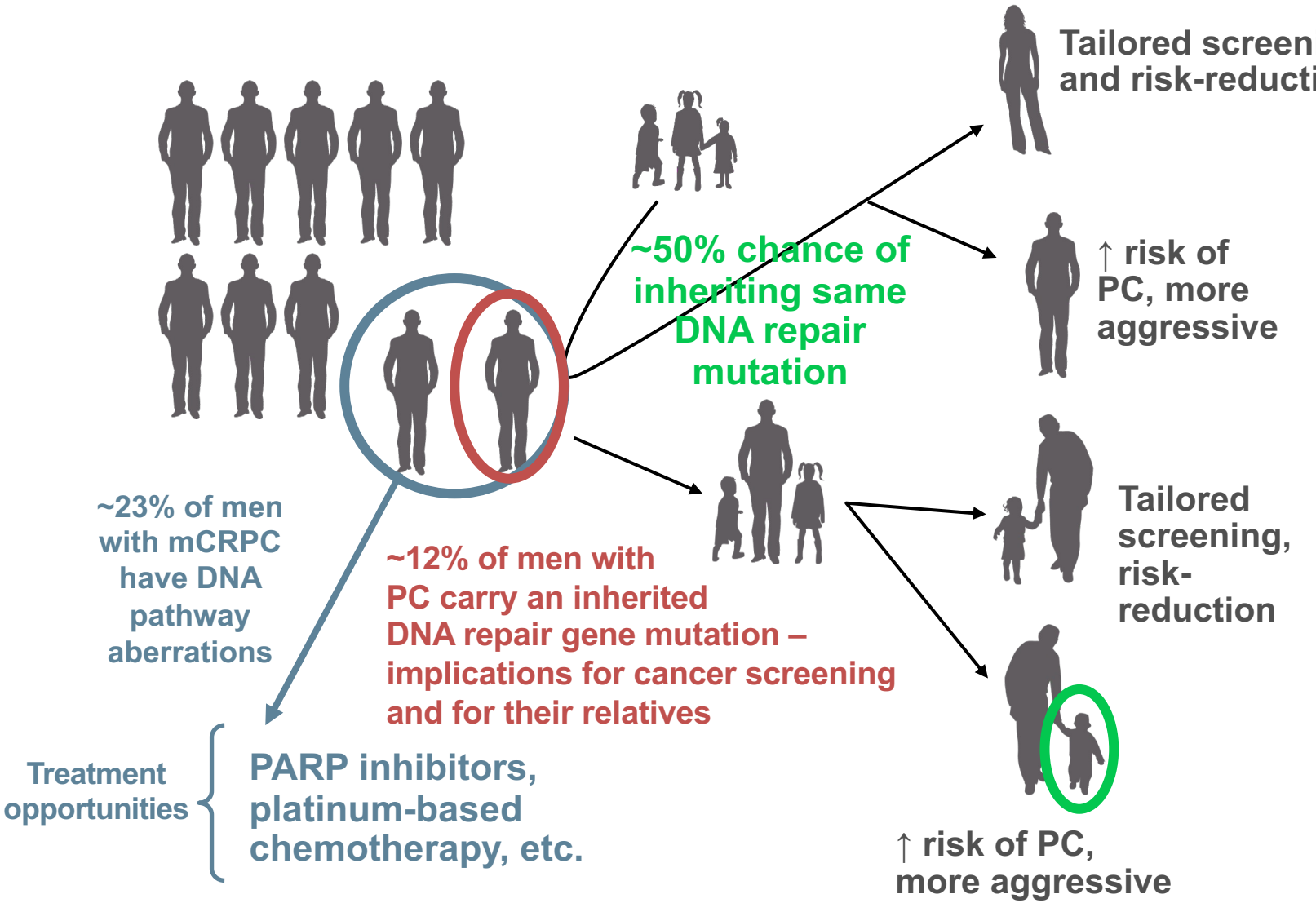
- A father or brother with prostate cancer doubles a man's risk of prostate cancer
- A mother or sister with breast cancer diagnosed before age 50 significantly increases a woman's risk of breast cancer
- A mother or sister with breast cancer can affect a man's risk of prostate cancer

Chen YC, et al. Prostate. 2008;68(14):1582-91; Colditz GA, et al. Breast Cancer Res Treat. 2012;133(3):1097-104

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;17:515-21; Pritchard CC, et al. N Engl J Med. 2016;375:443-53; Szymaniak BM, et al. JCO Oncol Pract. 2020;16:811-9; Antonarakis ES, et al. Eur Urol. 2018;74:218-25

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

GUIDELINE RECOMMENDATIONS FOR GENETIC TESTING

Guideline/consensus	Recommendations for genomic testing	Recommendations for specific genes to test	Recommendations for specimen to test (e.g. tissue, ctDNA)	Recommendations for germline testing
ESMO Clinical Practice Guidelines[1,2]	✓	✓	✓	✓
EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines[3]	✓	✗	✗	✓
NCCN Guidelines[4]	✓	✓	✓	✓
AUA/ASTRO/SUO Guidelines[5]	✓	✗	✗	✓

1. Parker C, et al. Ann Oncol. 2020;31(9):1119-34; 2. Mosele F, et al. Ann Oncol. 2020 Nov;31(11):1491-1505; 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-2022_2022-04-25-063938_yfos.pdf (d56bochluxqnz.cloudfront.net) Accessed Dec 2022); 4. National Comprehensive Cancer Network. Prostate Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed Oct 2022; 5. Lowrance WT, et al. J Urol. 2021; 205(1):22-9

GUIDELINE RECOMMENDATIONS FOR GENETIC TESTING

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INTERNATIONAL GUIDELINE RECOMMENDATIONS FOR GENETIC TESTING			
ESMO[1]	**EAU-EANM-ESTRO-ESUR-ISUP-SIOG[2]**	**NCCN[3]**	**AUA/ASTRO/SUO[4]**
Somatic testing for HRR and MMR defects (or MSI) in patients with mCRPC **Germline** testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer	**Somatic** testing for homologous repair and MMR defects should be offered to all metastatic patients should be offered somatic genomic testing **Germline** testing should be considered for men with a personal or family history of PCa or other cancer types arising from DNA repair gene mutations *(strength rating "weak")*: • Men with mPCa • Men with high-risk PCa and a family member diagnosed with PCa at age < 60 years • Men with multiple family members diagnosed with clinically significant PCa 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	**Somatic** testing in mPCa patients to identify alterations in HRR genes. May be considered in patients with regional PCa. **Germline** testing recommended for patients with prostate cancer and any of the following: • Very-high-risk localized or high-risk localised , very high-risk, regional, or mPCa • Family history of certain cancers • Ashkenazi Jewish ancestry • A known family history of a familial cancer risk mutation • Personal history of breast cancer	**Germline** and **somatic** tumour genetic testing should be offered to identify DNA repair deficiency mutations and MSI status that may inform prognosis in patients with mCRPC and counselling regarding family risk as well as potential targeted therapies

ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; BRCA, breast cancer gene; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; ESTRO, European Society for Radiotherapy and Oncology; ESUR, European Society of Urogenital Radiology; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; MMR, mismatch repair; mPCa, metastatic prostate cancer; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; PARP, poly-ADP ribose polymerase; SIOG, International Society of Geriatric Oncology; SUO, Society of Urologic Oncology

1. Parker C, et al. Ann Oncol. 2020;31(9):1119-34; 2. Mottet N, et al. Guidelines on prostate cancer 2022: EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2022_2022-04-25-063938_yfos.pdf (d56bochluxqnz.cloudfront.net); 3.National Comprehensive Cancer Network. Prostate Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed Oct 2022;
4. Lowrance WT, et al. J Urol. 2021; 205(1):22-9

*BRCA*m ARE ASSOCIATED WITH POOR CLINICAL OUTCOMES

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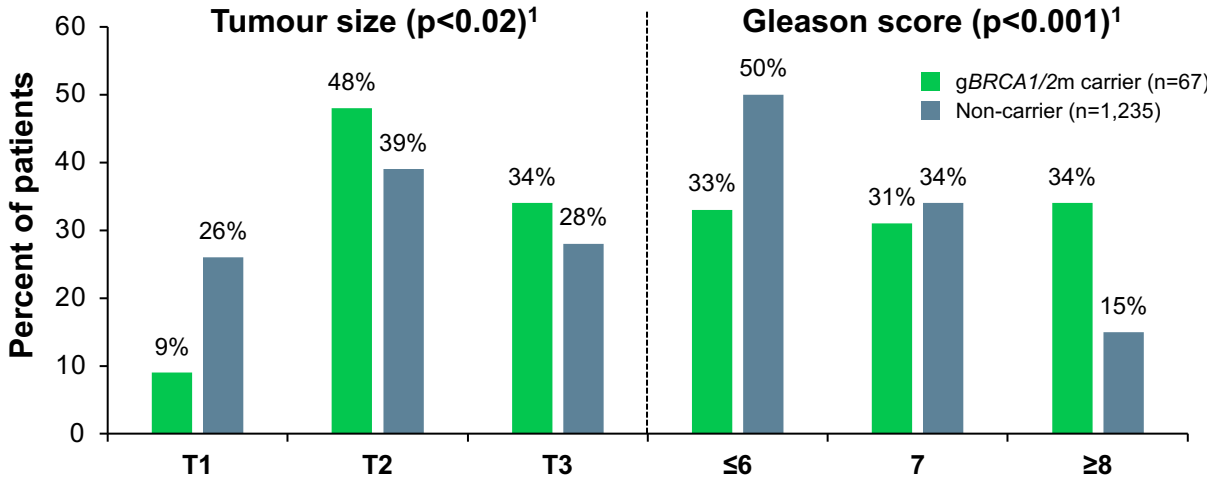
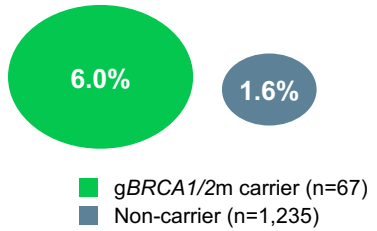
HRRm is associated with an aggressive phenotype, with most data assessing *BRCA*m[1–3]

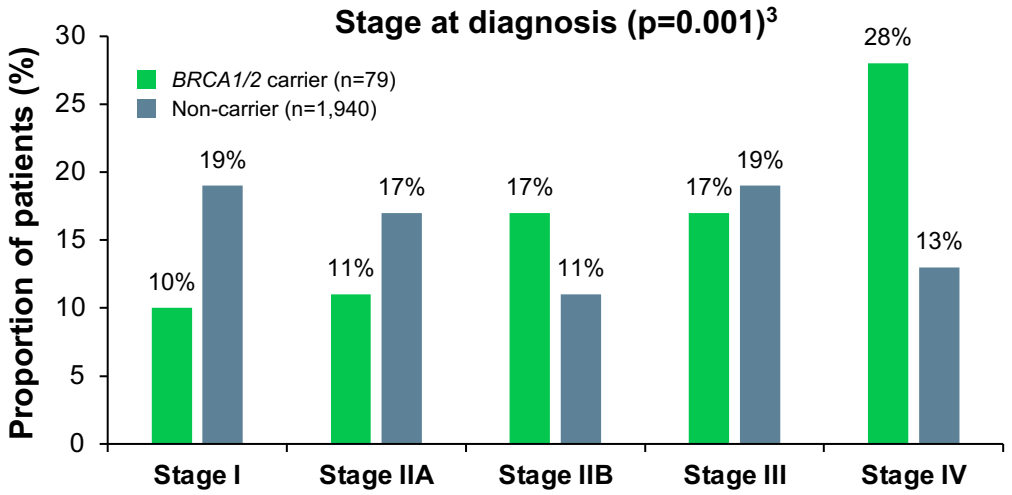
Several large retrospective studies have found an association between *BRCA*m and aggressive disease and rapid progression to metastatic disease[1–3]

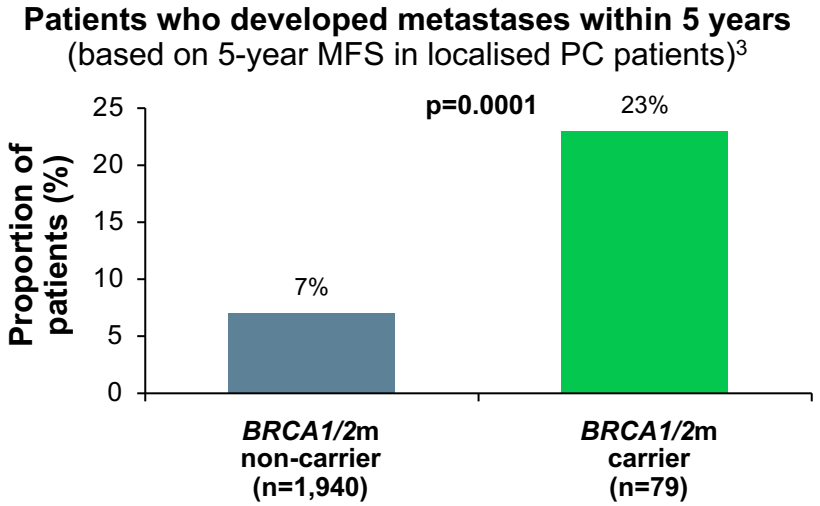
*BRCA2*m tumours are also more likely to show a pattern of intraductal carcinoma which correlates with poor prognosis[2]





g*BRCA2*m tumours are also more likely to show a pattern of ultra-ductal carcinoma which correlates with poor prognosis[2]





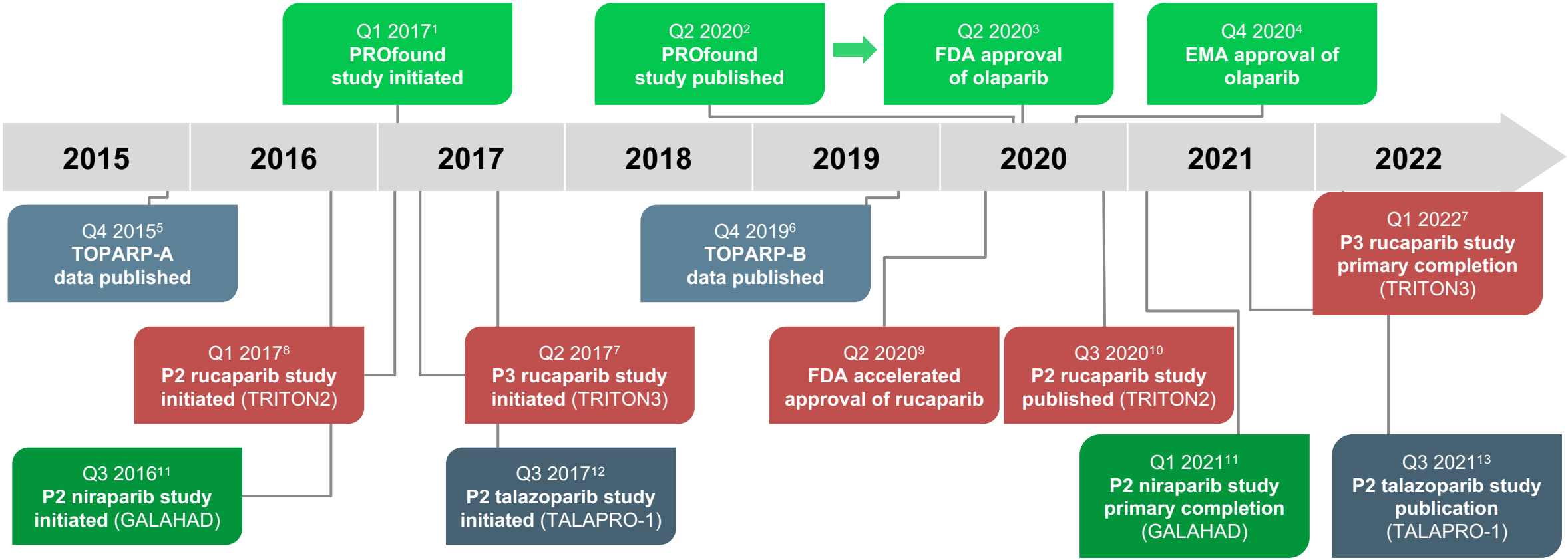
BRCA1/2, breast cancer gene 1/2; BRCAm, BRCA mutated; (g)BRCA2m, (germline) BRCA2 mutation; (g)BRCA1/2m, (germline) breast cancer gene 1/2 mutation; HRRm, homologous recombination repair mutation; MFS, metastasis-free survival; PC, prostate cancer

1. Castro E, et al. Eur Urol. 2015;68:186-93; 2. Taylor RA, et al. Nat Commun. 2017;8:13671; 3. Castro E, et al. J Clin Oncol. 2013;31(14):1748-57

PARPI MONOTHERAPY IN mCRPC: NON-REGISTRATIONAL STUDIES

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

PHASE 2/3 PARP INHIBITOR MONOTHERAPY TRIALS IN mCRPC



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

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

TOPARP TRIALS: PHASE 2 TRIALS OF OLAPARIB IN HEAVILY PRE-TREATED mCRPC PATIENTS

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TOPARP A – UNSELECTED PTS (TEST SET)[1]

- Olaparib 400 mg bid
- **33% response rate** (n=16/49) (95% CI: 20-48%)
- Genomic analysis of prospectively obtained tumour samples revealed:
  - **33% were biomarker positive** (n=16/49)
    - mutations in ***ATM*, *BRCA2* and others**
    - 14 of these patients responded to treatment
  - **67% were biomarker negative** (n=33/49)
    - 2 of these patients responded
- TOPARP A: **identified an association between** somatic alterations in **DDR genes and antitumour activity of olaparib** in mCRPC patients

TOPARP B – BIOMARKER SELECTED PTS (VALIDATION SET)[2]

- Olaparib 300 mg or 400 mg bid
- First prospective clinical trial in a genomically defined population of patients with mPC
- Distribution of DDR mutations in screened patients:
  - 32.7% *BRCA1/2*
  - 21.4% *ATM*
  - 21.4% *CDK12*
  - 7.1% *PALB2*
  - 21.4% Other
- **Study confirmed the antitumour activity of olaparib** against mCRPC with germline or somatic alterations in **DDR genes**

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CI, confidence interval; DDR, DNA damage repair; mCRPC, metastatic castration-resistant prostate cancer; mPC, metastatic prostate cancer; PALB2, partner and localizer of BRCA2; Pts, patients

1. Mateo J, et al. N Engl J Med. 2015;373:1697-1708; 2. Mateo J, et al. Lancet Oncol. 2020;21:162-74

TOPARP-B RESULTS: OLAPARIB HAS ANTITUMOUR ACTIVITY AGAINST mCRPC WITH DDR GENE ALTERATIONS

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- Despite randomisation, ***CDK12*** **aberrations were imbalanced** between the cohorts, which **might explain the inferior response in the 300 mg cohort**

DNA DAMAGE RESPONSE GENE ABERRATION SUBGROUP

Baseline characteristics	Total (N=98)	Dose group	
		300 mg (n=49)	400 mg (n=49)
BRCA1/2	32 (33%)	15 (31%)	17 (35%)
ATM	21 (21%)	10 (20%)	11 (22%)
CDK12	21 (21%)	15 (31%)	6 (12%)
PALB2	7 (7%)	3 (6%)	4 (8%)
OTHER	21 (21%)	10 (20%)	11 (22%)

	Total (N=92[a])			Dose group					
				300 mg (n=46)			400 mg (n=46)		
	Resp/N	%	95% CI	Resp/n	%	95% CI	Resp/n	%	95% CI
Composite response (confirmed)	**43/92**	**46.7%**	**36.3-57.4**	**18/46**	**39.1%**	**25.1-54.6**	**25/46**	**54.3%**	**39.0-69.1**
RECIST 1.1 objective response	14/70	20.0%	11.4-31.3	6/37	16.2%	6.2-32.0	8/33	24.2%	11.1-42.3
PSA response ≥50%	30/89	33.7%	24.0-44.5	13/43	30.2%	17.2-46.1	17/46	37.0%	23.2-52.5
CTC conversion	28/55	50.9%	37.1-64.6	13/27	48.1%	28.7-68.1	15/28	53.6%	33.9-72.5
RECIST or PSA response	32/92	34.8%	25.1-45.4	13/46	28.3%	16.0-43.5	19/46	41.3%	27.0-56.8

[a] 98 randomised, 92 evaluable for primary endpoint analysis (6 found ineligible/not evaluable and excluded)

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CI, confidence interval; CTC, circulating tumour counts; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours

Mateo J, et al. Lancet Oncol. 2020;21:162-74

TOPARP-B: OLAPARIB SIDE EFFECTS

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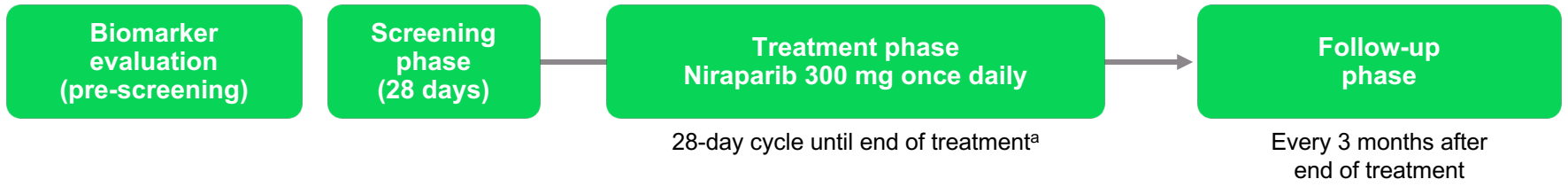
TOPARP-B STUDY: TEAEs INCIDENCE ≥10% (N=98)

N, (%)	300 mg (N=49)			400 mg (N=49)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Anaemia	16 (33)	14 (29)	1 (2)	19 (39)	18 (37)	0
Fatigue	19 (39)	3 (6)	0	27 (55)	4 (8)	0
Back pain	13 (27)	4 (8)	0	11 (22)	3 (6)	0
Nausea	17 (35)	1 (2)	0	13 (27)	0	0
Platelet count decreased	9 (18)	2 (4)	1 (2)	12 (24)	3 (6)	0
Decreased appetite	13 (27)	2 (4)	0	10 (20)	0	0
Vomiting	10 (20)	0	0	15 (31)	0	0
Weight decreased	9 (18)	1 (2)	0	15 (31)	0	0
Diarrhoea	8 (16)	1 (2)	0	10 (20)	1 (2)	0
Arthralgia	8 (16)	1 (2)	0	5 (10)	4 (8)	0
Hypertension	9 (18)	1 (2)	0	4 (8)	4 (8)	0
Neutrophil count decreased	9 (18)	2 (4)	0	4 (8)	2 (4)	1 (2)
Dyspnoea	5 (10)	1 (2)	0	10 (20)	1 (2)	0
Abdominal pain	4 (8)	0	0	6 (12)	5 (10)	1 (2)
Blood creatinine increased	9 (18)	0	0	6 (12)	0	0
Oedema peripheral	6 (12)	0	0	8 (16)	1 (2)	0
Urinary tract infection	3 (6)	3 (6)	0	6 (12)	3 (6)	0
Constipation	7 (14)	0	0	7 (14)	0	0
Cough	3 (6)	0	0	9 (18)	0	0
Musculoskeletal chest pain	3 (6)	0	0	9 (18)	0	0
Musculoskeletal pain	5 (10)	1 (2)	0	5 (10)	1 (2)	0
Hypokalaemia	3 (6)	0	0	8 (16)	0	0
Muscular weakness	4 (8)	0	0	5 (10)	2 (4)	0
White blood cell count decreased	4 (8)	0	0	6 (12)	1 (2)	0
Alkaline phosphatase increased	3 (6)	0	0	5 (10)	1 (2)	0
Dysgeusia	6 (12)	0	0	3 (6)	0	0
Haematuria	5 (10)	0	0	2 (4)	2 (4)	0
Influenza like illness	3 (6)	0	0	6 (12)	0	0
Muscle spasms	3 (6)	0	0	6 (12)	0	0
Spinal cord compression	0	1 (2)	0	0	5 (10)	0

TEAE, treatment emergent adverse event

Mateo J, et al. Lancet Oncol. 2020;21:162-74

GALAHAD: PHASE 2 STUDY OF NIRAPARIB IN PRE-TREATED mCRPC PATIENTS WITH DDRm



Key eligibility criteria

- mCRPC
- Biomarker positive for DRD
- Progressed on ≥1 ARSI therapy and ≥1 taxane-based CTx
- No prior PARP inhibitor or platinum-based CTx
- No prior or current MDS/AML

Primary endpoint

- **Objective response rate** (ORR) of soft tissue (visceral or nodal disease), as defined by RECIST 1.1[b] with no evidence of bone progression according to the PCWG3 criteria in patients with biallelic *BRCA*

Secondary endpoints

- **ORR** (per RECIST 1.1 / PCWG3 criteria) in patients with biallelic non-*BRCA*
- **CTC response:** CTC=0 per 7.5 mL blood at 8 weeks post-baseline in patients with baseline CTC >0
- **OS:** time from enrolment to death from any cause
- **rPFS:** time from enrolment to radiographic progression or death from any cause, whichever occurs first
- **Duration of objective response:** time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first
- **Safety:** adverse events and laboratory tests

[a] Treatment continued until disease progression, unacceptable toxicity or death; [b] Investigator assessed
Non-*BRCA*: *ATM, FANCA, PALB2, CHEK2, BRIP1* or *HDAC2*

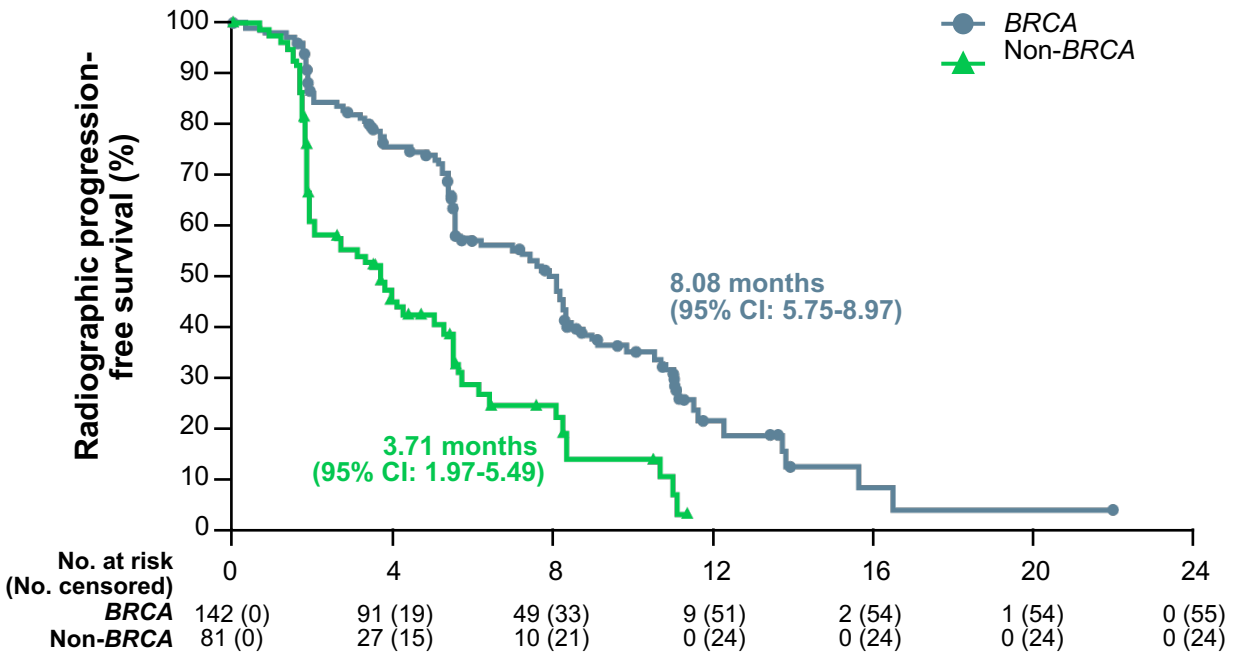
AML, acute myeloid leuameia; ARSI, androgen signalling receptor inhibitors; BRCA, breast cancer gene; CTC, circulating tumour cell; CTx, chemotherapy; DDRm, DNA damage repair mutations; DRD, DNA repair deficiency; mCRPC; metastatic castration resistant prostate cancer; MDS, myelodysplastic syndrome; OS, overall survival; PARP, poly adenosine diphosphate-ribose polymerase; PCWG3, Prostate Cancer Working Group 3; PSA50, ≥50% decline in prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival

Smith M, et al. ESMO 2019, oral presentation

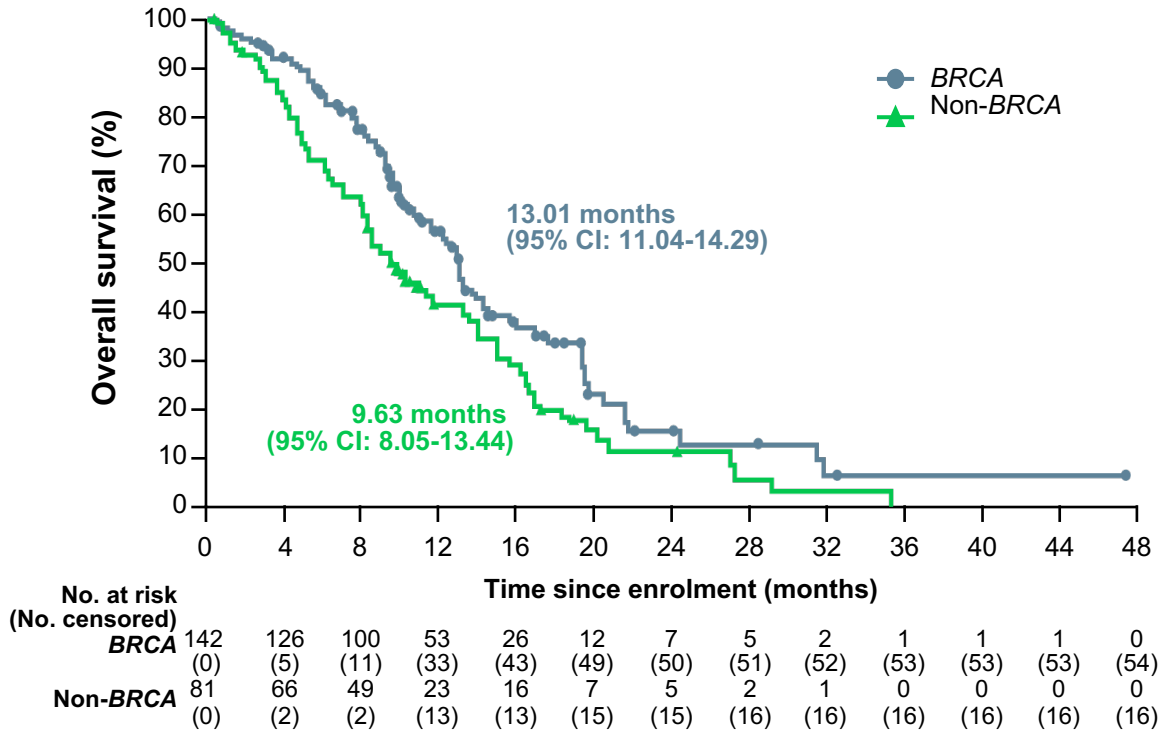
GALAHAD: NIRAPARIB SHOWS ANTI-TUMOUR ACTIVITY IN mCRPC PATIENTS WITH DDRm, PARTICULARLY *BRCA1/2*

OBJECTIVE RESPONSE RATE	*BRCA* cohort[a] (N=76)	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%)

RADIOGRAPHIC PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



CI, confidence interval; DDRm, DNA damage repair mutations; mCRPC, metastatic castration resistant prostate cancer

Smith M, et al. Lancet Oncol. 2022;23:362-73

GALAHAD: NIRAPARIB SIDE EFFECTS

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%.

TEAEs, treatment emergent adverse events

Smith M, et al. Lancet Oncol. 2022;23:362-73

TALAPRO-1: TALAZOPARIB IN PRE-TREATED mCRPC PATIENTS WITH DDR MUTATIONS

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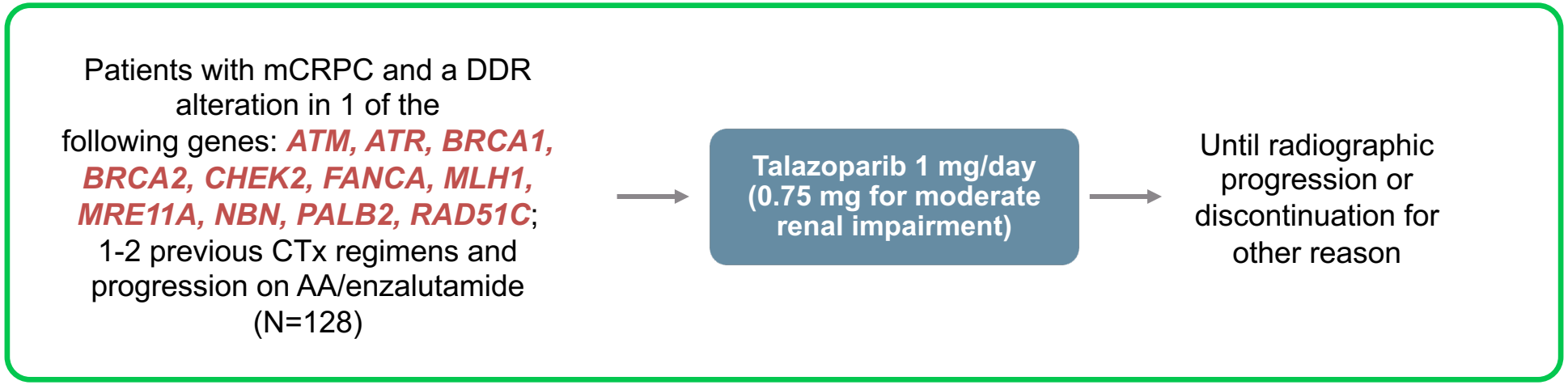
- International open label, phase 2 study



- Primary endpoint: ORR
- Secondary endpoints: TTR, DoR, PSA decrease ≥50%, CTC count conversion, time to PSA progression, rPFS, OS, safety, PROs, pharmacokinetics

AA, abiraterone acetate; BRCA1/2, breast cancer gene 1/2; CTx, chemotherapy; CTC, circulating tumour cells; DDR, DNA damage repair; DoR, duration of response; mCRPC, metastatic castration resistant prostate cancer; ORR, objective response rate; OS, overall survival; PROs, patient-reported outcomes; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; TTR, time to response

de Bono JS, et al. Lancet Oncol. 2021;22:1250-64

TALAPRO-1: TALAZOPARIB SHOWS ANTI-TUMOUR ACTIVITY IN mCRPC PATIENTS WITH DRDs, PARTICULARLY *BRCA1/2*

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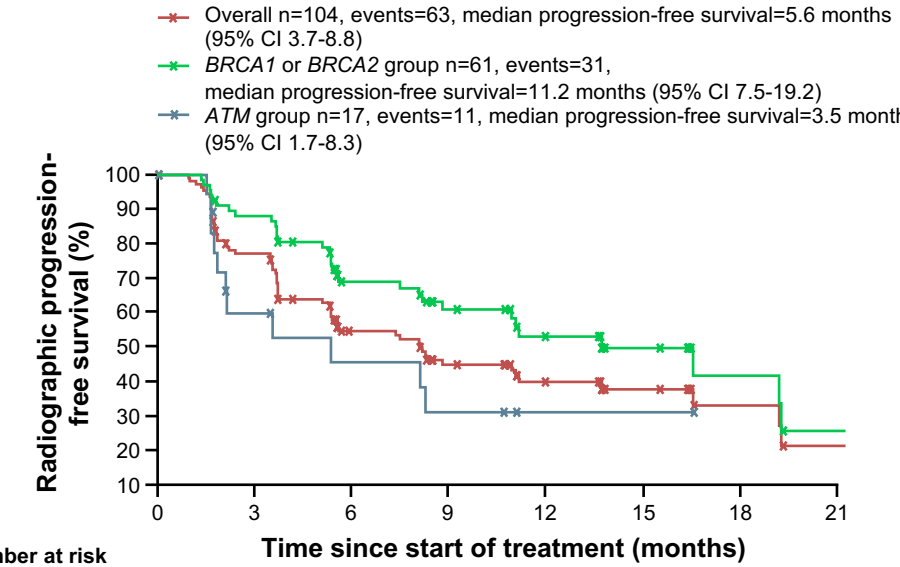
TUMOUR RESPONSE BY HRR GENE ALTERATION

N (%)	*BRCA1* or *BRCA2* (n=61)*	*BRCA2* (n=57)*	*PALB2* (n=4)	*ATM* (n=17)†	Other (N=22)‡	Total (N=104)
Best overall response§						
Confirmed complete response	6 (10)	6 (11)	0 (0)	1 (6)	0 (0)	7 (7)
Confirmed partial response	22 (36)	20 (35)	1 (25)	1 (6)	0 (0)	24 (23)
Stable disease (any duration)	21 (34)	19 (33)	2 (50)	6 (35)	8 (36)	37 (36)
Stable disease for ≥6 months	6 (10)	6 (11)	0 (0)	2 (12)	0 (0)	8 (8)
Non-complete response or non-progressive disease	4 (7)	4 (7)	0 (0)	0 (0)	0 (0)	4 (4)
Progressive disease	4 (7)	4 (7)	0 (0)	8 (47)	10 (46)	22 (21)
Not evaluable	4 (7)	4 (7)	1 (25)	1 (6)	4 (18)	10 (10)
Objective response§	28 (46)	26 (46)	1 (25)	2 (12)	0 (0)	31 (30)

*The BRCA1 or BRCA2 and BRCA2 groups included two patients with both BRCA2 and PALB2 alterations, one patient with both BRCA2 and ATM alterations, one patient with both BRCA2 and CHEK2 alterations, and one patient with both BRCA2 and MLH1 alterations. †The ATM group included one patient with both ATM and FANCA alterations and one patient with both ATM and RAD51C alterations. ‡The other group included patients with HRR gene alterations in ATR, CHEK2, FANCA, MLH1, MRE11A, NBN, or RAD51C. § Only includes patients with measurable disease per investigator assessment

rPFS BY HRR GENE ALTERATION



Number at risk (number censored)								
Overall	104 (0)	72 (7)	38 (18)	26 (22)	16 (29)	10 (34)	4 (39)	1 (40)
BRCA1 or *BRCA2* group	61 (0)	52 (1)	31 (10)	23 (14)	15 (19)	9 (24)	4 (28)	1 (29)
ATM group	17 (0)	8 (2)	5 (3)	3 (3)	1 (5)	1 (5)	0 (6)	0 (6)

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CI, confidence interval; HRR, homologous recombination repair; rPFS, radiographic progression-free survival

de Bono JS, et al. Lancet Oncol. 2021;22:1250-64

TALAPRO-1: TALAZOPARIB SIDE EFFECTS

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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%)

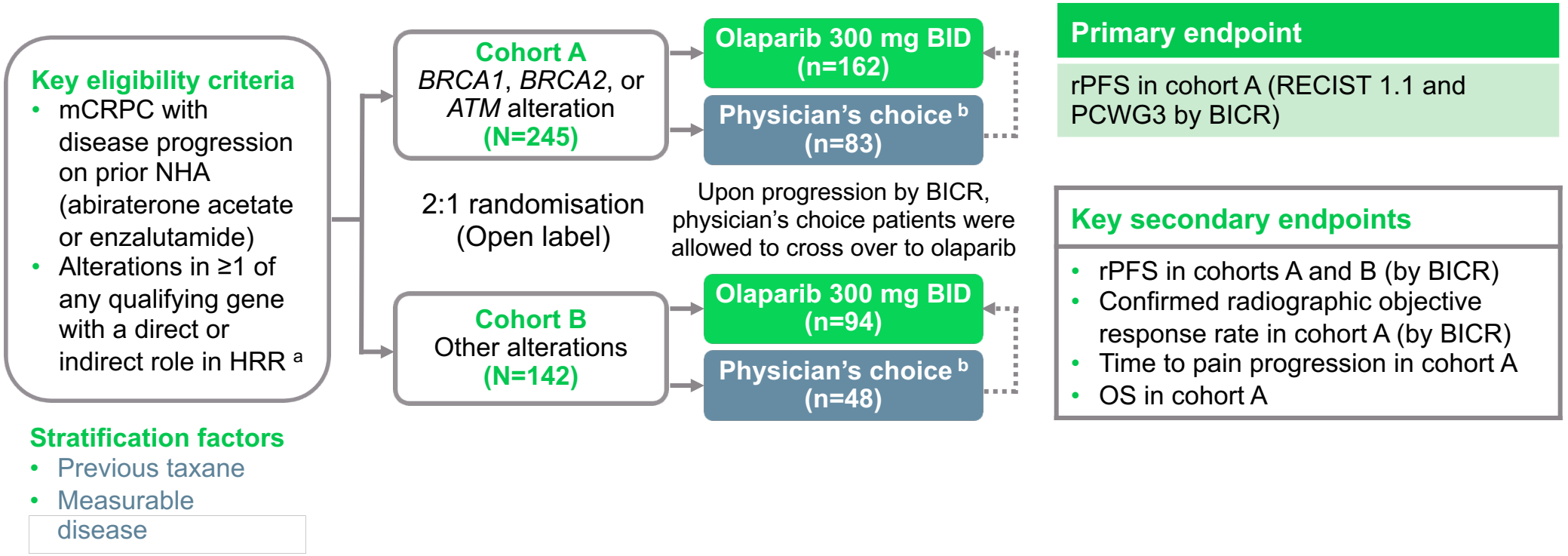
Data are n (%). Data presented are for events reported in at least 10% of patients

de Bono JS, et al. Lancet Oncol. 2021;22:1250-64

PARPi MONOTHERAPY IN mCRPC: STUDIES LEADING TO REGISTRATION

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

PROfound: PHASE 3 OF OLAPARIB VS. SECOND NEW HORMONAL AGENT IN HRRm mCRPC



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

PROfound: OLAPARIB MONOTHERAPY IMPROVES rPFS COMPARED TO NHA RECHALLENGE

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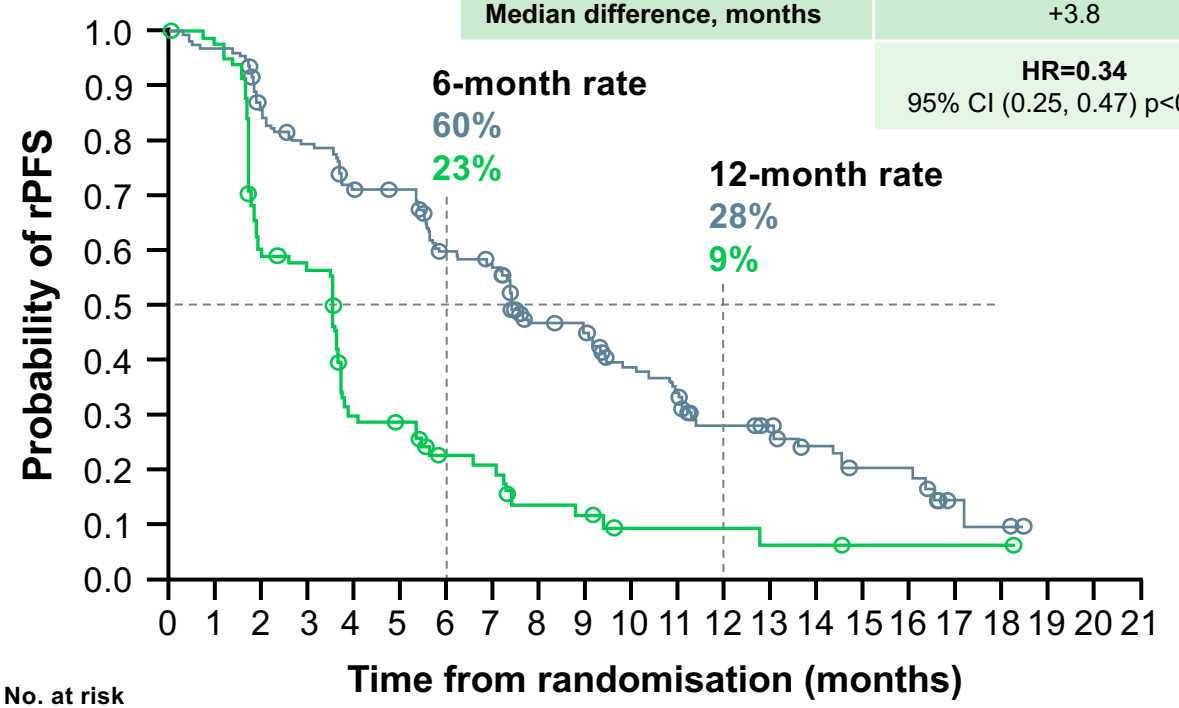
COHORT A: *BRCA1/2* or *ATM*

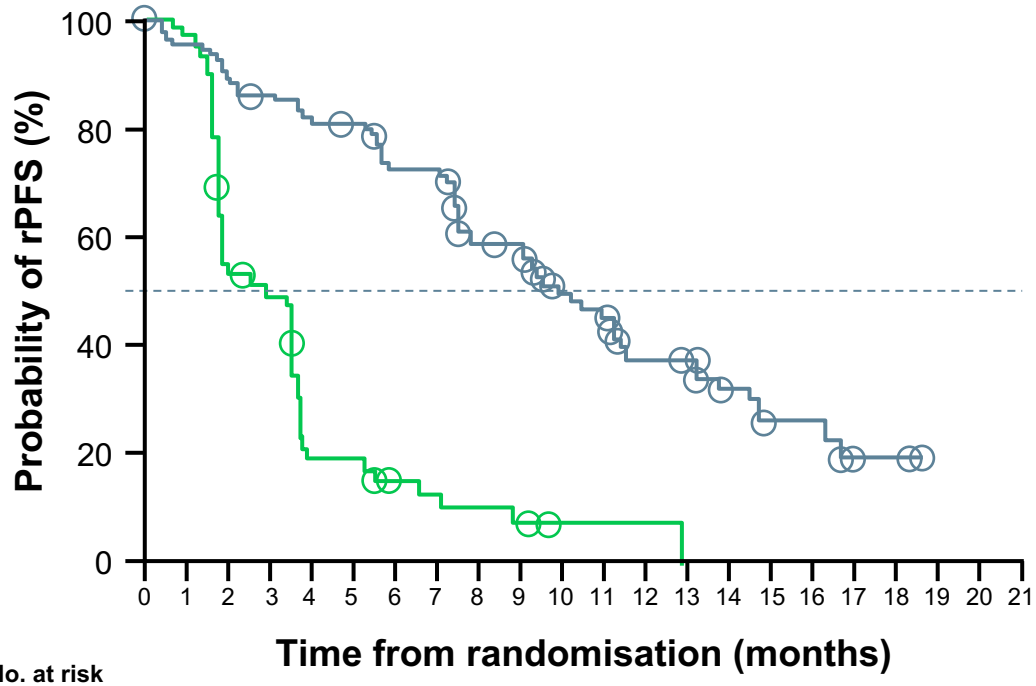
	Olaparib (N=162)	Physician's choice (N=83)
Events, n (%)	106 (65.4)	68 (81.9)
Median PFS, months (BICR)	7.4	3.6
Median difference, months	+3.8	
	HR=0.34 95% CI (0.25, 0.47) p<0.001	



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

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

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

[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; (r)PFS, radiographic progression-free survival

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

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

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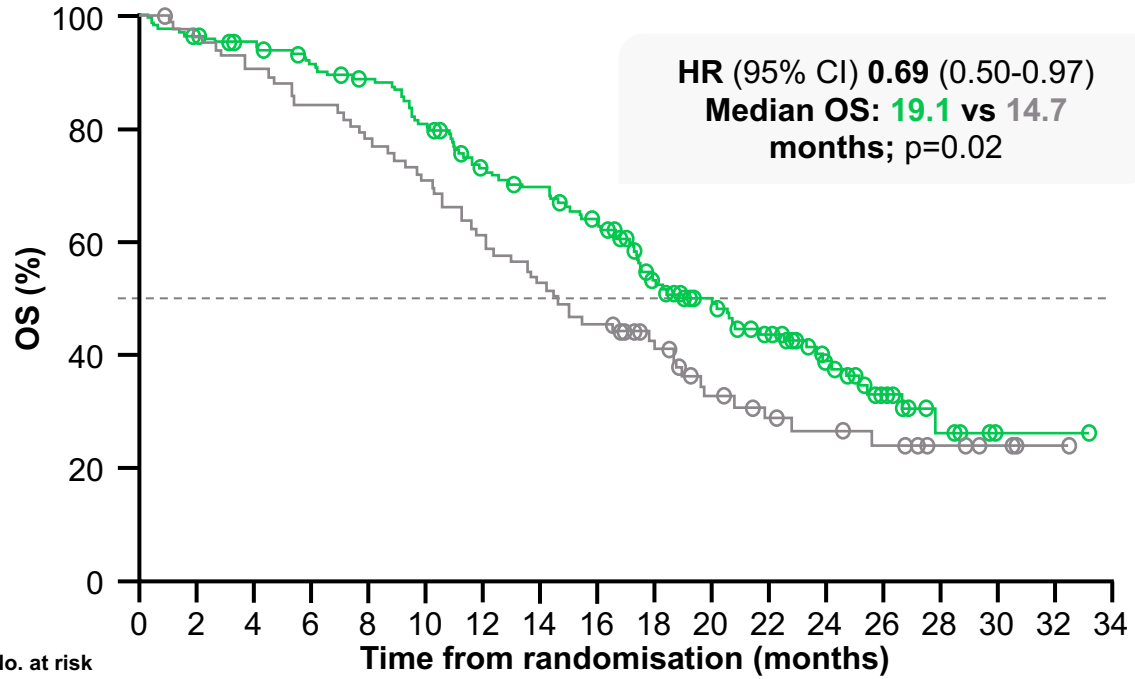
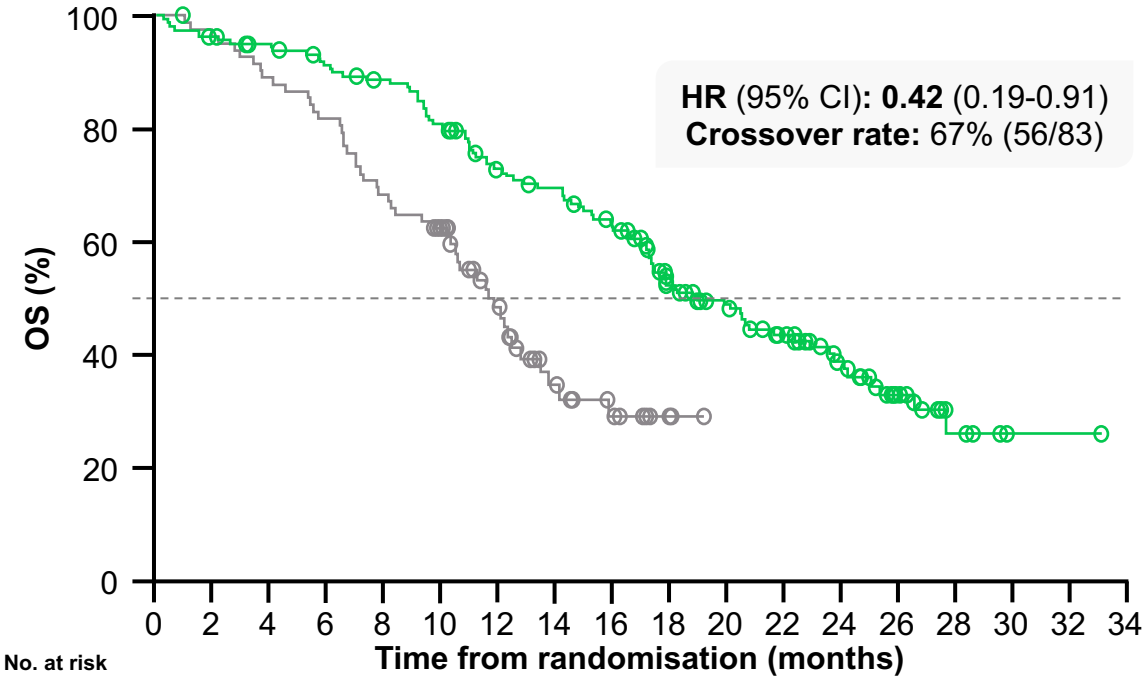
COHORT A: *BRCA1/2* OR *ATM* MUTATIONS



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

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

PROfound: GREATER ACTIVITY WITH OLAPARIB IN *BRCA*m BUT POSITIVE EFFECT SEEN WITH OTHER HRRm

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EXPLORATORY GENE-LEVEL ANALYSES		BRCA1/2 or ATM		All HRRm[a]		*BRCA1* and/or *BRCA2*		*ATM*		*CDK12*	
		Olaparib (N=162)	pcNHA (N=83)	Olaparib (N=256)	pcNHA (N=131)	Olaparib (N=102)	pcNHA (N=58)	Olaparib (N=62)	pcNHA (N=24)	Olaparib (N=61)	pcNHA (N=28)
rPFS	Median, months	7.4	3.6	5.8	3.5	9.8	3.0	5.4	4.7	5.1	2.2
	HR (95% CI)	0.34 (0.25–0.47)		0.49 (0.38–0.63)		0.22 (0.15–0.32)		1.04 (0.61–1.87)		0.74 (0.44–1.31)	
OS	Median OS, months	19.1	14.7	17.3	14.0	20.1	14.4	18.0	15.6	14.1	11.5
	HR (95% CI)	0.69 (0.50–0.97)		0.79 (0.61–1.03)		0.63 (0.42–0.95)		0.93 (0.53–1.75)		0.97 (0.57–1.71)	
ORR	Evaluable patients, n	84	43	138	67	57	33	30	10	34	12
	(%)	33.3	2.3	21.7	4.5	43.9	0	10.0	10.0	5.9	0
PSA	Evaluable patients, n	153	77	243	123	94	54	61	22	58	27
	Confirmed response, %	43.1	7.8	30.0	9.8	61.7	0	13.1	22.7	5.2	3.7
CTC	Evaluable patients, n	52	22	78	32	29	17	25	3	14	5
	Conversion, %	55.8	22.7	52.6	21.9	69.0	23.5	40.0	33.3	50.0	40.0

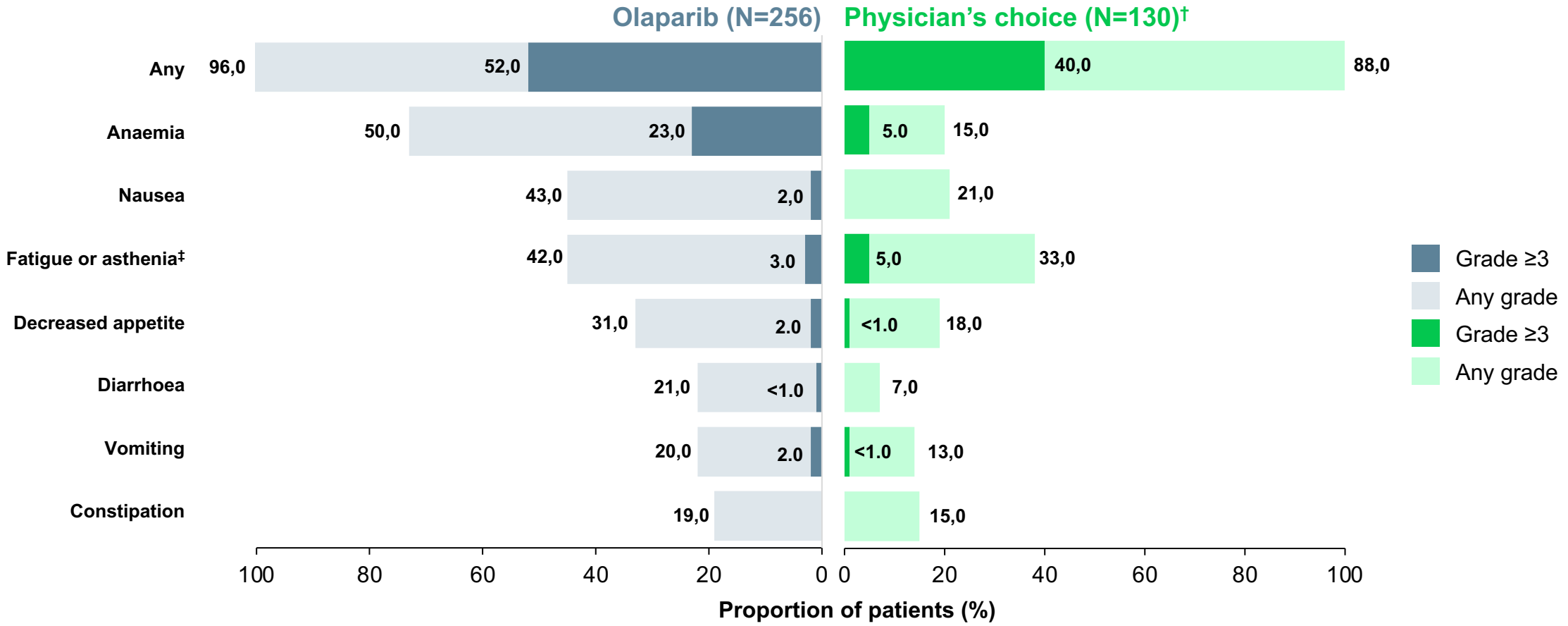
[a]*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; BRCAm, breast cancer gene 1/2 mutation; CI, confidence interval, CTC, circulating tumour count; HR, hazard ratio; ORR, overall response rate; OS, overall survival; pcNHA, physician's choice new hormonal agent; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102; 2. Hussain M, et al. N Engl J Med. 2020;383(24):2345-57; 3. de Bono J, et al. J Clin Oncol. 2021;39 suppl 6:126 (ASCO GU 2021 presentation)

PROfound: MOST COMMON AEs (≥10% ANY GRADE) IN THE OVERALL POPULATION*

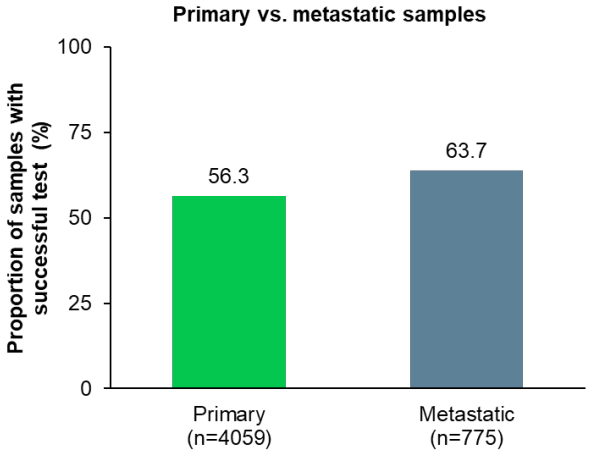
At the final OS DCO, median duration of treatment was 7.6 months in the olaparib arm and 3.9 months in the control arm

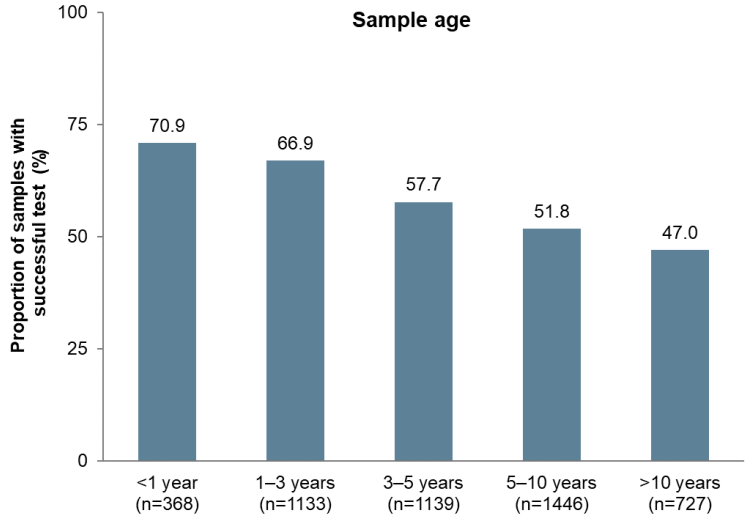


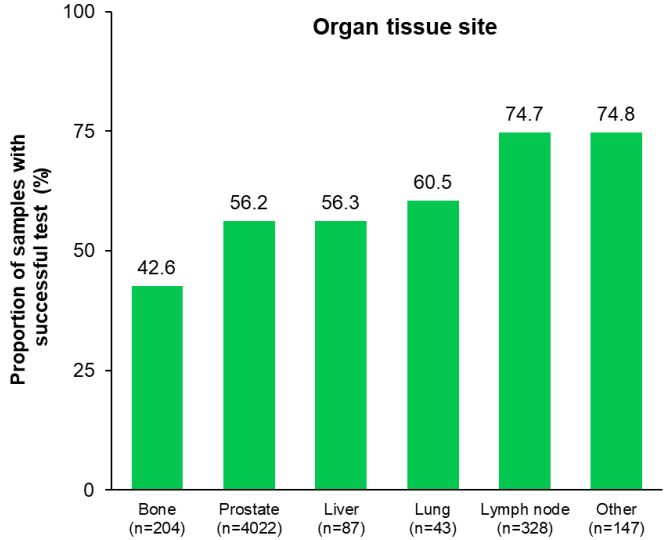
* Most common AEs associated with treatment with PARP inhibitors. Patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D,* and / or *RAD54L*. Note, there were no cases of myelodysplastic syndromes or AML. There has since been one fatal case of AML 54 days after discontinuation of olaparib. † One patient in the control group did not receive treatment. ‡ Grouped term.
AE, adverse event; AML, acute myeloid leukemia; DCO, data cut-off; OS, overall survival.
1. Hussain M, et al. N Engl J Med. 2020;383(24):2345-2357

PROfound: TUMOUR TISSUE USED TO PROSPECTIVELY IDENTIFY PATIENTS WITH HRRm

- A total of 4,858 samples were tested and reported by FMI during screening
- Majority of samples were derived from archived tissue (N=4,365) and from the primary tumour (N=4,059)
- Success rates higher with newly collected vs. archived samples and metastatic sites vs. primary tumour







FMI, Foundation Medicine, Inc

Hussain M, et al. J Clin Oncol. 2020;38 suppl 6:195 (ASCO GU 2020)

PROfound: ~ 30% OF SCREENED PATIENTS WERE IDENTIFIED WITH A QUALIFYING HRRm

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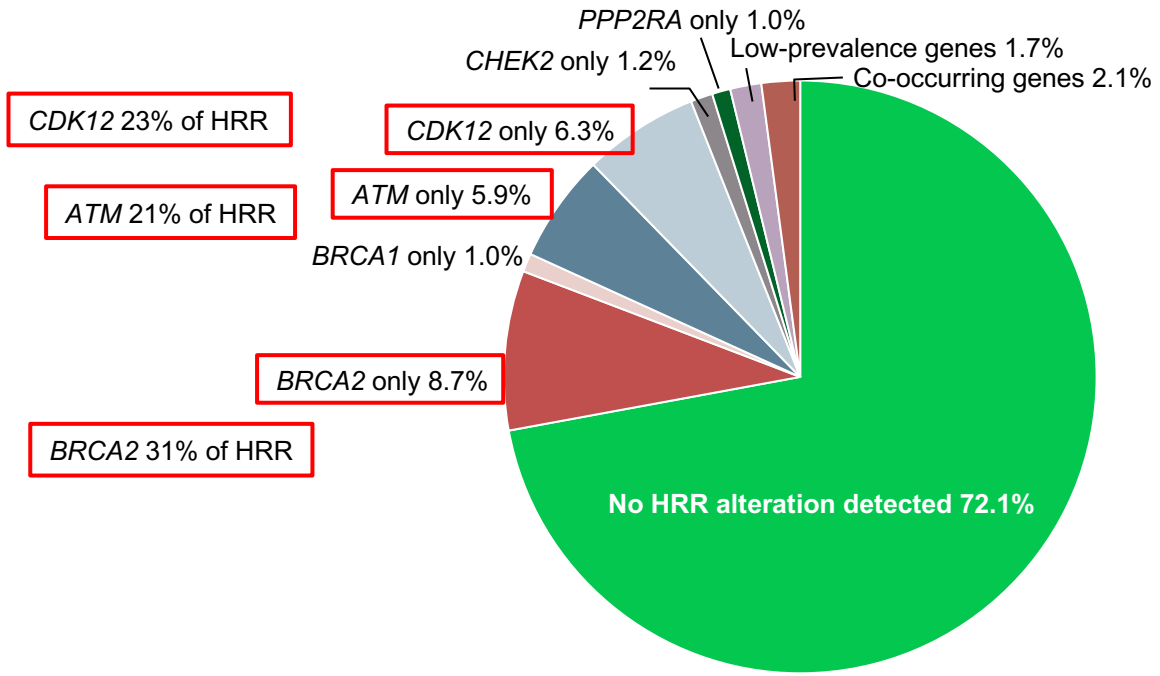
A similar proportion of patients were identified with HRRm, irrespective of whether the tissue was derived from the primary tumour or metastatic deposits

HRR gene alteration prevalence in primary and metastatic tumour samples from screened patients[1]

	HRR gene alteration prevalence (%)
All patients	27.9
All primary tumours	**27.2**
Archived primary	27.1
Newly collected primary	28.9
All metastatic tumours	**31.8**
Archived metastatic	33.2
Newly collected metastatic	29.5

***BRCA2*, *ATM* and *CDK12* were the most prevalent HRRm identified**

Overview of HRR gene profile in patients screened for the PROfound study with a reported biomarker (n=2792)[1a]



[a] Patients with multiple genes are included across more than one gene

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; HRR(m), homologous recombination repair (mutation)

1. de Bono J, et al. Ann Oncol. 2019;30 suppl 5:v328-9 (ESMO 2019, 847PD)

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

GU connect® POWERED BY COR2ED

Screening

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

HRR genes

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

Key eligibility criteria

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

Treatment

28-day cycles

Rucaparib 600 mg BID

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

Treatment until radiographic progression or discontinuation for other reason

Primary endpoints†

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

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

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

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

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

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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 cutoff 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

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

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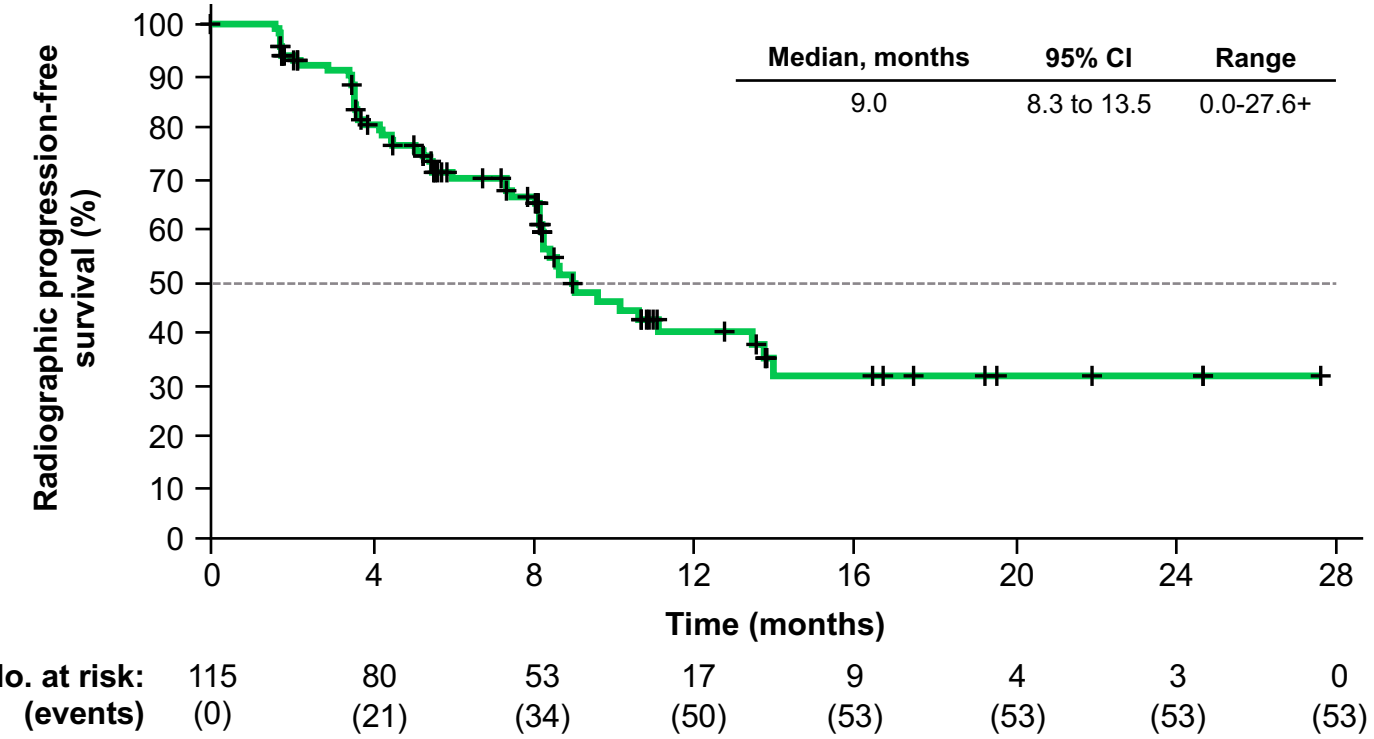
- FDA granted accelerated approval based on data from TRITON2



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

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

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

TRITON2: RUCAPARIB SIDE EFFECTS

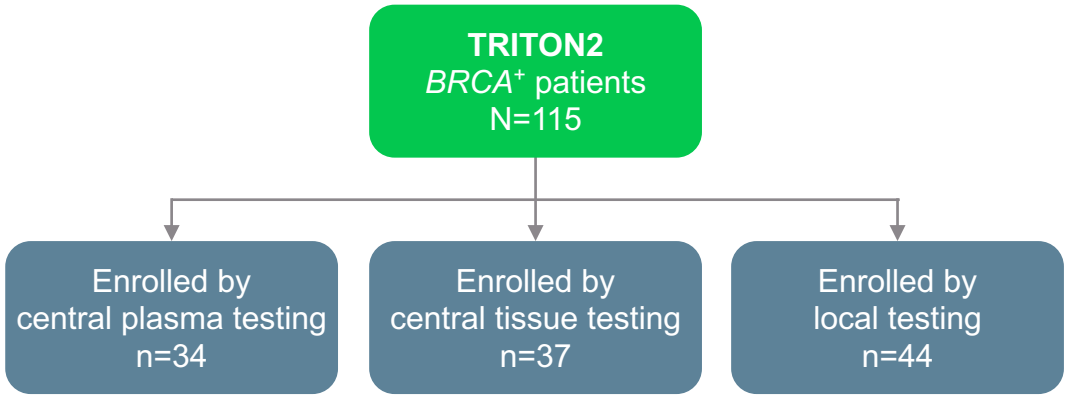
Individual TEAE (preferred terms) occurring in ≥15% of patients	Any grade	Grade ≥3
Asthenia/fatigue	71 (61.7)	10 (8.7)
Nausea	60 (52.2)	3 (2.6)
Anaemia/decreased hemoglobin	50 (43.5)	29 (25.2)
ALT/AST increased	38 (33.0)	6 (5.2)
Decreased appetite	32 (27.8)	2 (1.7)
Constipation	31 (27.0)	1 (0.9)
Thrombocytopenia/decreased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

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

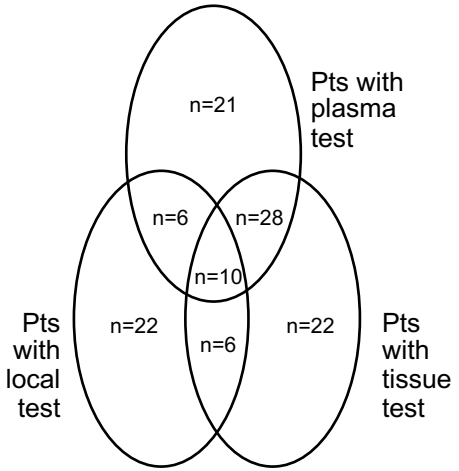
Abida W, et al. J Clin Oncol. 2020;38:3763-72

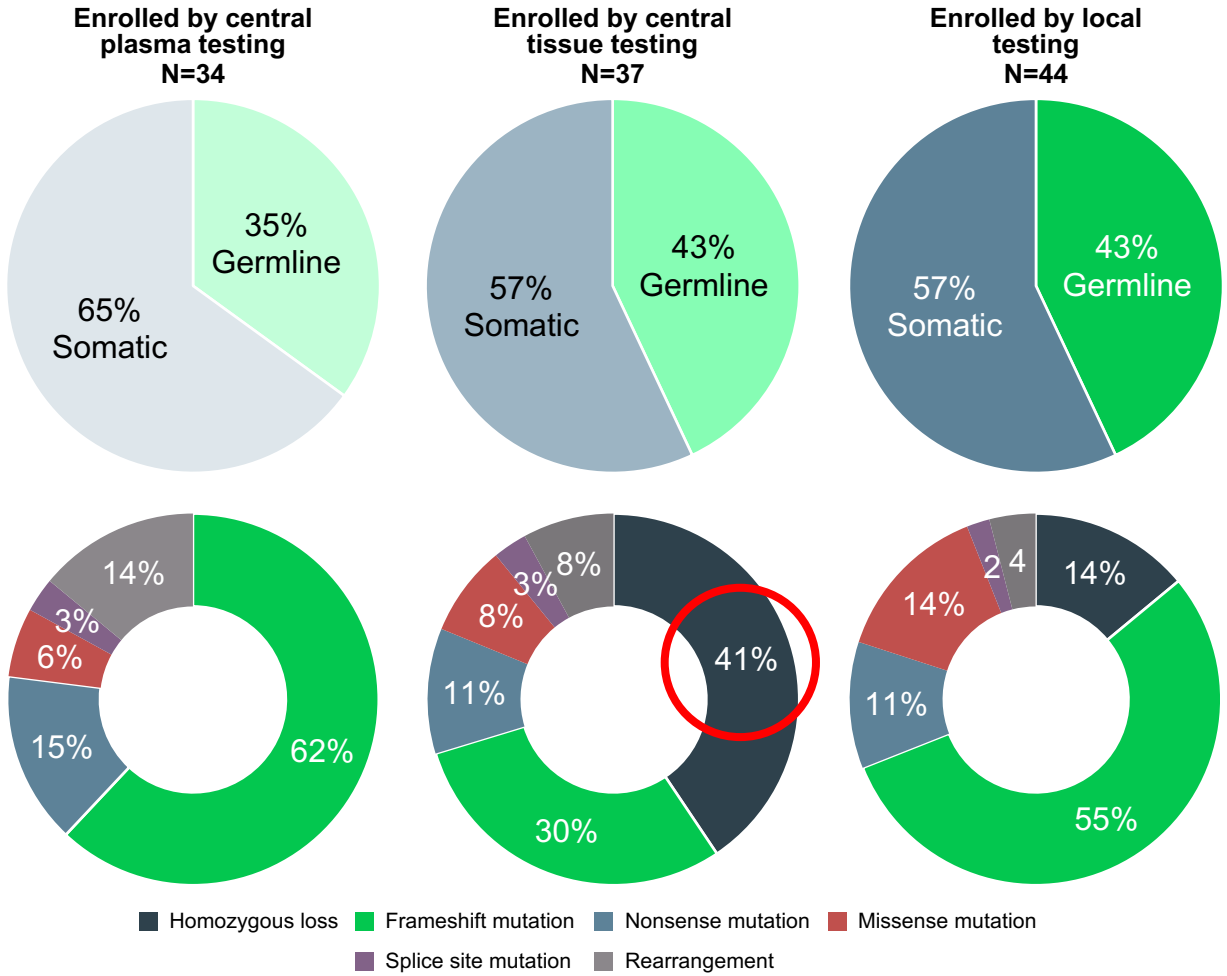
TRITON2: HRRm IDENTIFIED VIA TISSUE OR ctDNA

GENOMIC TESTING BY ASSAY TYPE



	Pts enrolled by	Pts *BRCA*⁺ by
Plasma test	34	61
Tissue test	37	59
Local test	44	44





BRCA, breast cancer gene; ctDNA, circulating tumour DNA; HRRm, homologous recombination repair mutations; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; Pts, patients

Loehr A, et al. Clin Cancer Res. 2021;27:6677-86

TRITON2: CONCORDANCE BETWEEN TISSUE AND ctDNA TESTING

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- There is high concordance between liquid and tissue biopsy

BRCA/*ATM* variant subtype detection sensitivity in ctDNA and tissue

	Sensitivity of detection in tumour tissue			Sensitivity of detection in ctDNA		
	Detected in tumour tissue	Detected in tumour tissue and ctDNA	Detected in tumour tissue only	Detected in ctDNA	Detected in tumour tissue and ctDNA	Detected in ctDNA only
Frameshift/indel	96	83 (86%)	13 (14%)	110	83 (75%)	27 (25%)
Homozygous loss	30	8 (27%)	22 (73%)	7	7 (100%)	0
Large rearrangement	24	15 (63%)	9 (37%)	23	16 (70%)	7 (30%)
Nonsense	28	26 (93%)	2 (7%)	32	26 (81%)	6 (19%)
Splice	15	13 (87%)	2 (13%)	26	13 (50%)	13 (50%)
Missense	4	1 (25%)	3 (75%)	9	1 (11%)	8 (89%)
Total	197	146 (74%)	51 (26%)	207	146 (71%)	61 (29%)

Concordance between tumour tissue and ctDNA testing determined by positive and negative percentage agreements

	Tissue BRCA/*ATM* mutation detected (T^+)	Tissue BRCA/*ATM* mutation not detected (T^-)	Total
Plasma (ctDNA) BRCA/*ATM* mutation detected (P^+)	143 (81%; T^+/P^+)	24 (8%; T^-/P^+)	167
Plasma (ctDNA) BRCA/*ATM* mutation not detected (P^-)	33 (19%; T^+/P^-)	291 (92%; T^-/P^-)	324
Total	176	315	491
	T^+/P^+: 81% (95% CI, 75-87)	T^-/P^-: 92% (95% CI, 89-95)	PPV = 0.68 NPV = 0.96

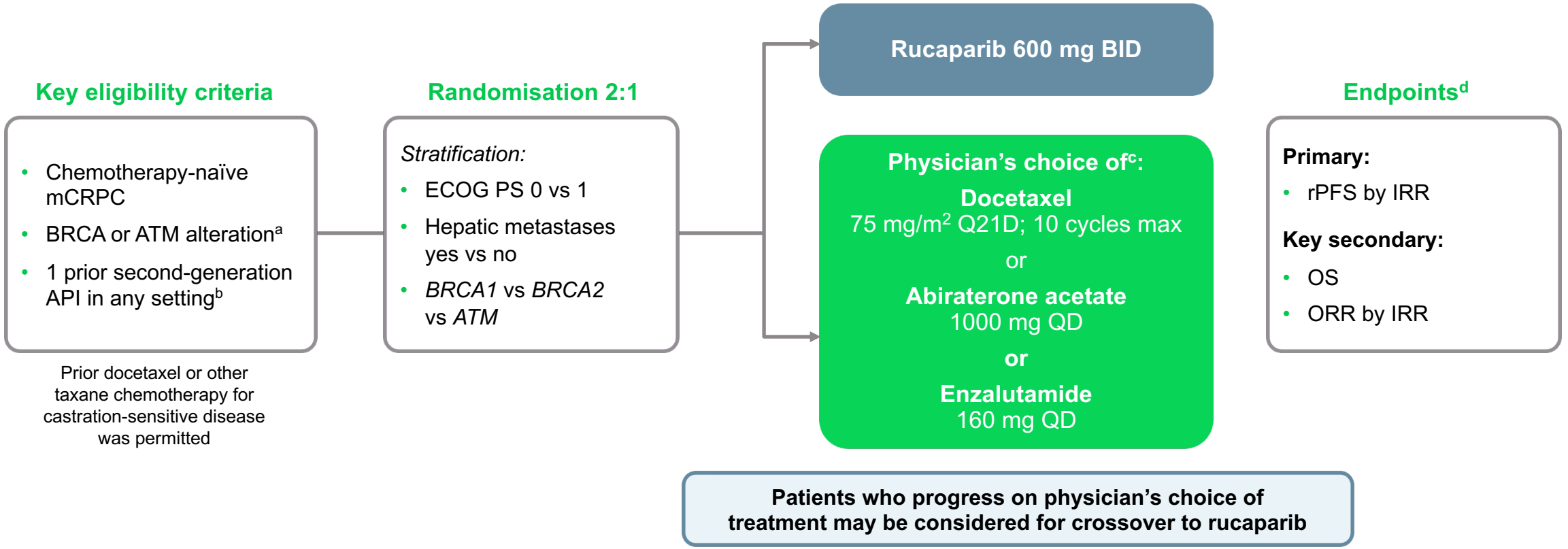
- However, sequencing on ctDNA might miss a significant proportion of *BRCA2* homologous loss

ATM, ataxia telangiectasia mutated; BRCA, breast cancer gene; CI, confidence interval; ctDNA, circulating tumour DNA; NPV, negative predictive value; P, plasma; PPV, positive predictive value; T, tissue

Chi KN, et al. Clin Cancer Res. 2022. DOI: 10.1158/1078-0432.CCR-22-0931

TRITON3 STUDY DESIGN

CONFIRMATORY STUDY FOR ACCELERATED APPROVAL OF RUCAPARIB

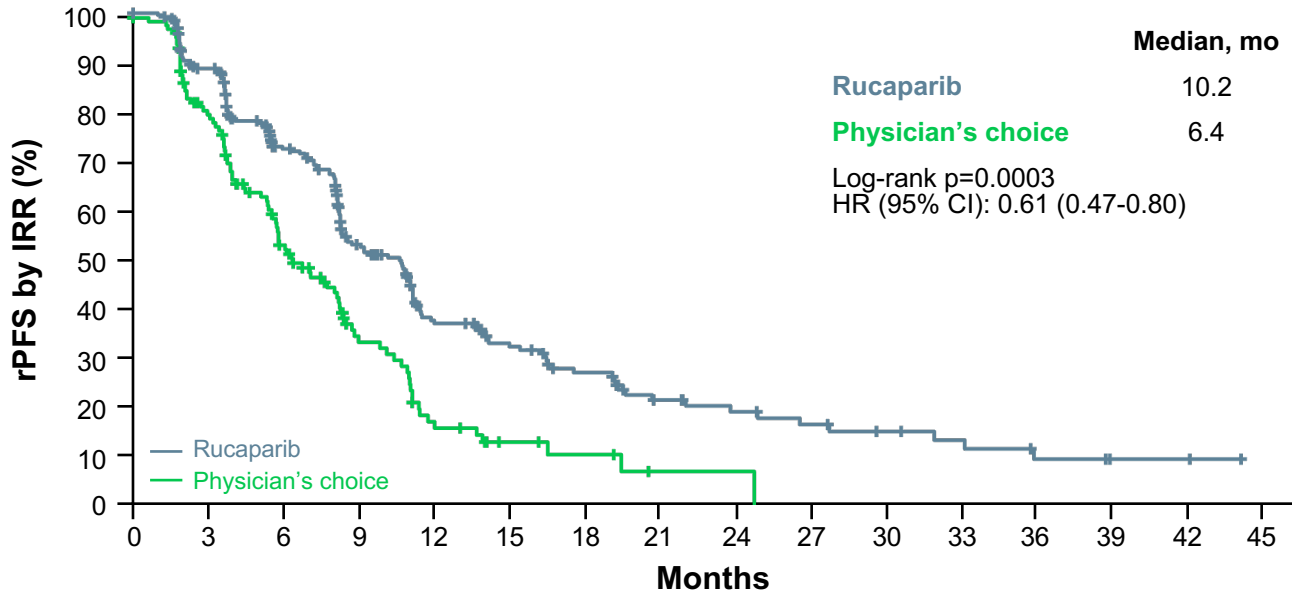


Visit cutoff date: 25 August 2022. [a] Determined by Foundation Medicine testing of tissue or plasma. [b] Protocol amendment June 19, 2018: patients' qualifying second-generation API could be in any setting. [c] If chosen, patients received whichever second-generation API had not yet been received. [d] 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; BRCA, breast cancer gene; 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, daily; rPFS, radiographic progression-free survival

Bryce AL, et al. Prostate Cancer Foundation Retreat 2022

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

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

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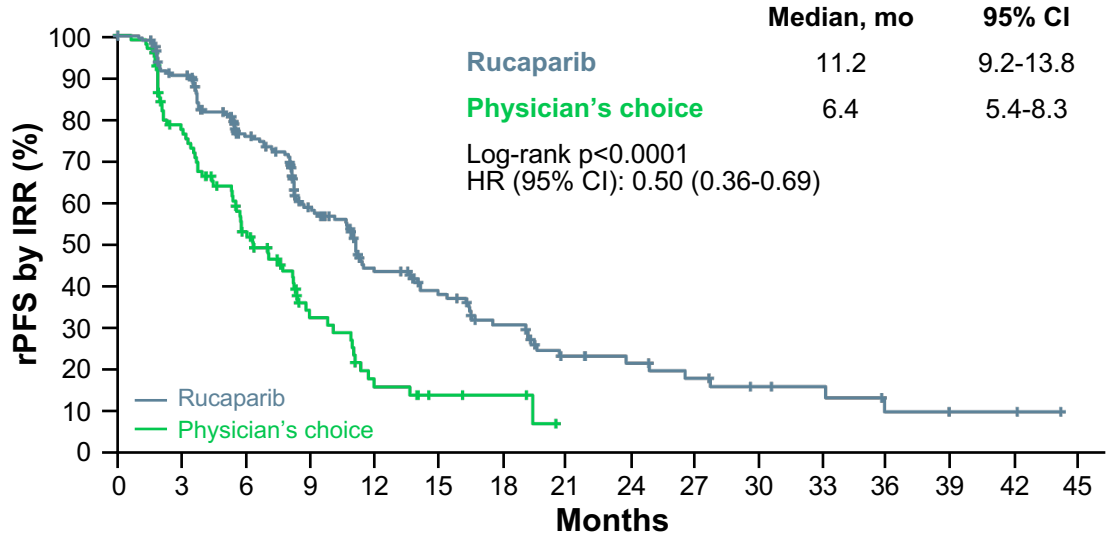
rPFS by IRR in the *BRCA* subgroup



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

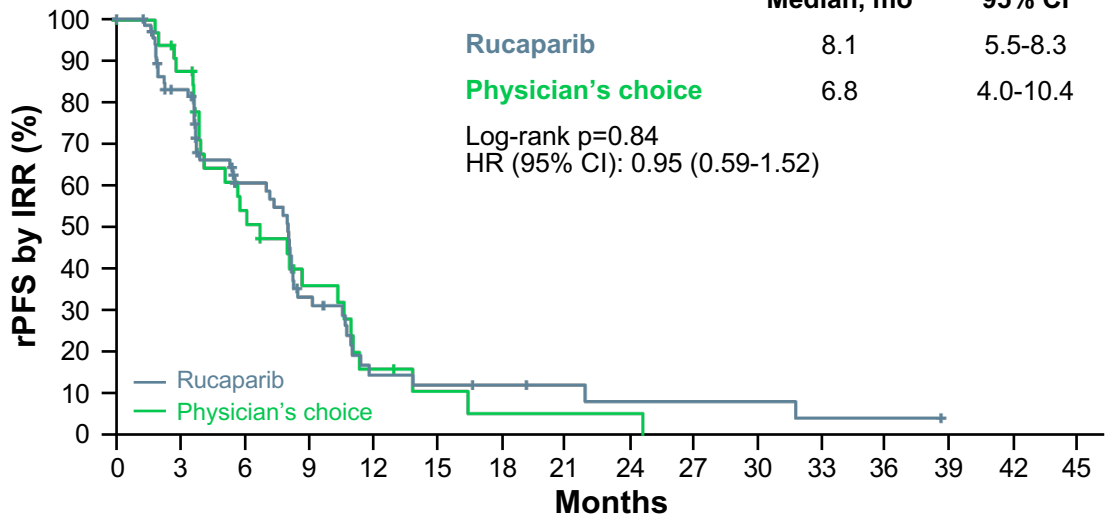
Log-rank p<0.0001
HR (95% CI): 0.50 (0.36-0.69)

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). *BRCA* subgroup, *BRCA1* and *BRCA2*

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)

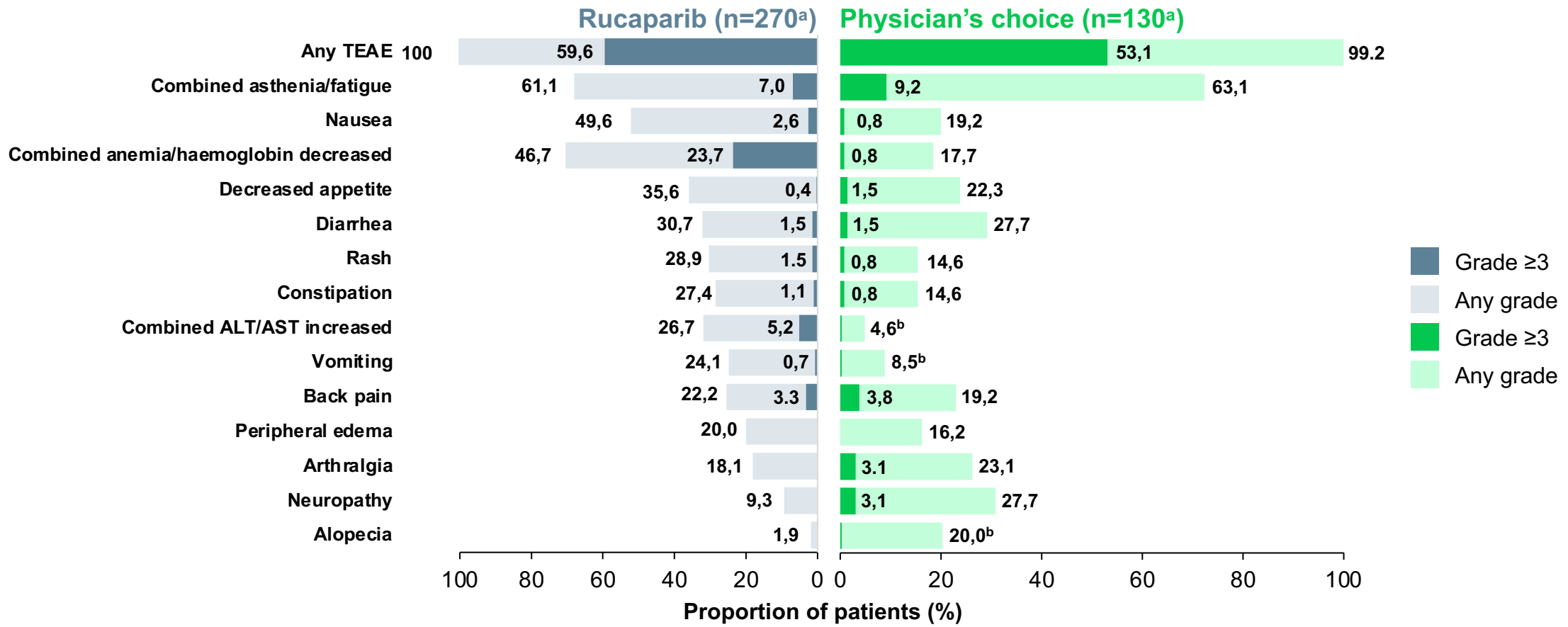
Rucaparib	69 (0)	51 (11)	31 (24)	16 (38)	6 (46)	5 (47)	4 (47)	3 (47)	2 (48)	2 (48)	2 (48)	1 (49)	1 (49)	0 (49)		
Physician's choice	34 (0)	28 (4)	16 (14)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)						

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

ATM, ataxia telangiectasia mutated; BRCA, breast cancer gene; 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

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

WHERE DO PARPI's FIT IN THE mCRPC TREATMENT LANDSCAPE?

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

PARP INHIBITORS ARE APPROVED IN PROSTATE CANCER[1,2]

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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 an **NHA**. Determine *BRCAm* status with a **validated test method**[b]

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]

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

[a]Rucaparib is FDA-approved for the treatment of adult patients with a deleterious *BRCA*m-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (no current approval in prostate cancer in Europe)[3]; [b]olaparib has received a positive recommendation from the EMA CHMP to be used in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated

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 (Sep 2022); 3. Rubraca (rucaparib) US prescribing information; 4. Lynparza: Pending EC decision | European Medicines Agency (europa.eu);

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

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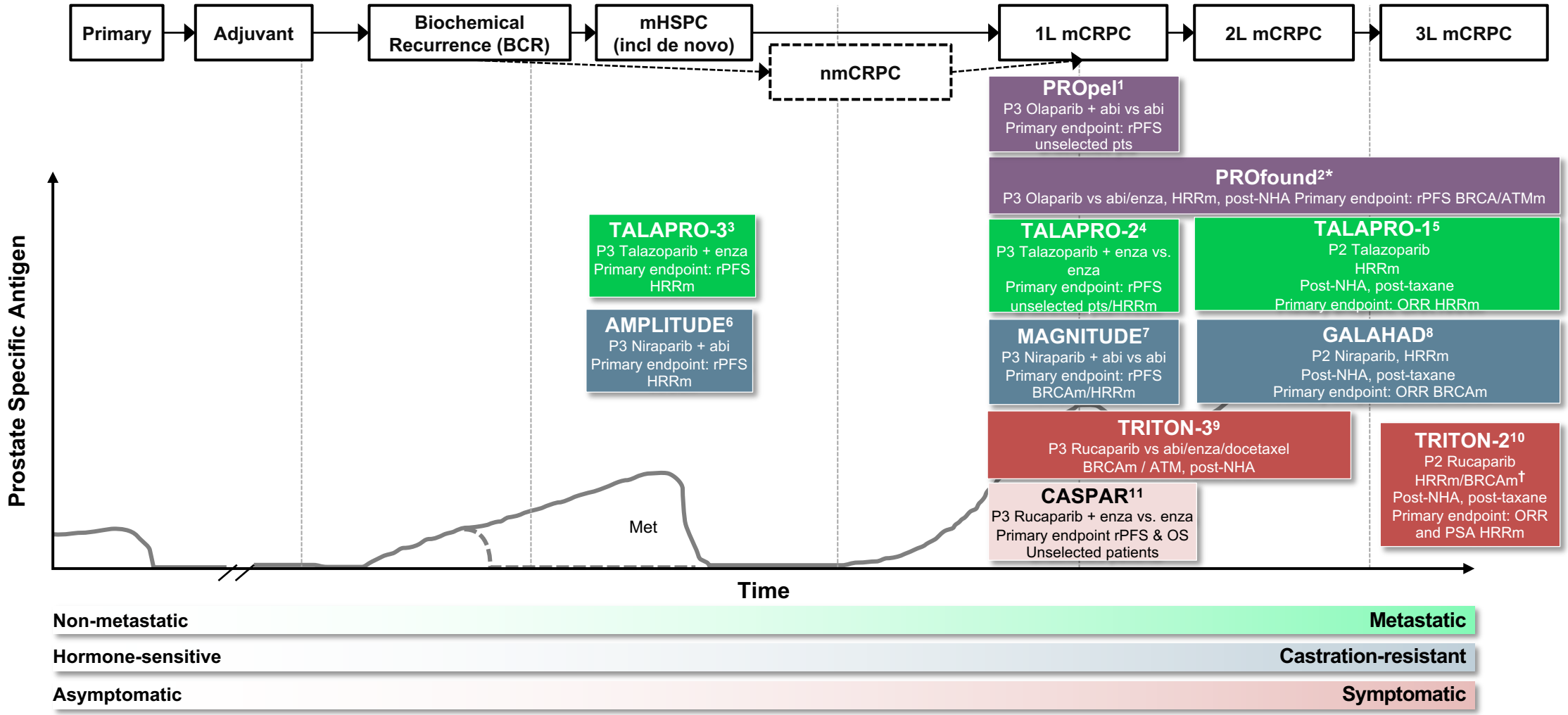

Please see slide notes for references. [a] As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA[12,13; b] As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane[14]

Abi, abiraterone; BCR, biochemical recurrence; Enza, enzalutamide; FDA, US Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, new hormonal agent; nmCRPC, non-metastatic castration-resistant prostate cancer; Ola, olaparib; P, phase; PSA, prostate-specific antigen

PARPi's BEYOND PROSTATE CANCER

PARPi, poly-ADP ribose polymerase inhibitor

AVAILABLE PARP INHIBITORS AND THEIR CURRENT TUMOUR INDICATIONS

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	Olaparib	Rucaparib	Niraparib	Talazoparib
Single-agent dose (approved for olaparib, rucaparib, niraparib, and talazoparib)	300 mg BID	600 mg BID	200/300[d] mg QD	1 mg QD
Tumour indications	Ovarian cancer, breast cancer, pancreatic cancer, prostate cancer[1,2,3,a,b]	Ovarian cancer,[4,5] prostate cancer[5,c]	Ovarian cancer[6,7]	Breast cancer[8,9]

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

[b] Olaparib is EMA-approved as monotherapy for the treatment of adult patients with mCRPC and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included an NHA[2] and has received a positive recommendation from the EMA CHMP to be used in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[3]

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

[d] Niraparib FDA-approved dose is 300 mg QD and EMA approved dose is either 200 or 300 mg QD depending on weight and other factors

AR, androgen receptor; BID, twice daily; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; QD, once daily; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PARP, poly-ADP ribose polymerase

1. Olaparib PI; 2. Olaparib SmPC; 3. Lynparza: Pending EC decision | European Medicines Agency (europa.eu); 4. Rucaparib SmPC; 5. Rucaparib PI; 6. Niraparib PI; 7. Niraparib SmPC; 8. Talazoparib SmPC; Talazoparib PI. All accessed November 2022.

AE PROFILES OF PARPi FROM MONOTHERAPY TRIALS ACROSS DIFFERENT TUMOUR TYPES

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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 of AEs in ovarian and breast cancer trials – All Grade (Grade ≥3)	Olaparib (SOLO-2)[5]	Rucaparib (ARIEL3)[6]	Niraparib (NOVA)[7]	Talazoparib (EMBRACA)[8]
Hypertension %	NR	9.7 (2.4)	19.3 (8.2)	NR
Increased transaminases %	NR	34.7 (10.2)	NR	NR
Insomnia %	NR	14.5 (0.0)	24.3 (0.3)	NR
Alopecia %	NR	NR	NR	25.2 (0.0)

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 red 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; 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; 5. Poveda A, et al. Lancet Oncol. 2021;22(5):620-31; 6. Ledermann A, et al. Lancet Oncol. 2020;21:710-22; 7. Mirza MR, et al. New Engl J Med. 2016;375:2154-64; 8. Litton JK, et al. New Engl J Med. 2018;379:753-63 (supplementary appendix)

HAEMATOLOGICAL AE PROFILES OF PARPi FROM MONOTHERAPY TRIALS ACROSS DIFFERENT TUMOUR TYPES

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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

Frequency and grade of cytopenias in ovarian and breast cancer trials	Olaparib (SOLO-2)[5]	Rucaparib (ARIEL3)[6]	Niraparib (NOVA)[7]	Talazoparib (EMBRACA)[8]
Anaemia Grade ≥3 (%)	21	22	25	39
Neutropenia Grade ≥3 (%)	7	8	20	21
Thrombocytopenia Grade ≥3 (%)	2	5	34	15

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 red if value ≥10%

[a]Frequency of grade 3 AEs not reported but 1% of patients experienced TEAE leading to treatment discontinuation

AE, adverse event; NR, not reported; PARPi, poly-ADP ribose polymerase inhibitor; TEAE, treatment-emergent adverse event

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; 5. Poveda A, et al. Lancet Oncol. 2021;22(5):620-31; 6. Ledermann A, et al. Lancet Oncol. 2020;21:710-22; 7. Mirza MR, et al. New Engl J Med. 2016;375:2154-64; 8. Litton JK, et al. New Engl J Med. 2018;379:753-63 (supplementary appendix)

IN CONCLUSION

- **PARP inhibitors are effective** drugs as monotherapy **in mCRPC patients with HRR alterations**
- **Genetic testing is important** to help with treatment decision making and for understanding inherited risk
- *BRCA* mutations are associated with poor outcomes in mCRPC patients
- Patients with tumours harbouring ***BRCA1/BRCA2* alteration** (especially HomDel) appear to derive the **greatest clinical benefit from PARPi**, but patients with other HRR alterations might also derive benefit
- Further work needed to understand predictive phenotypes (mutational signatures, HRD scores)

HomDel, homologous deletions; HRD, homologous repair deficiency; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARPi, poly-ADP ribose polymerase inhibitors

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GU CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

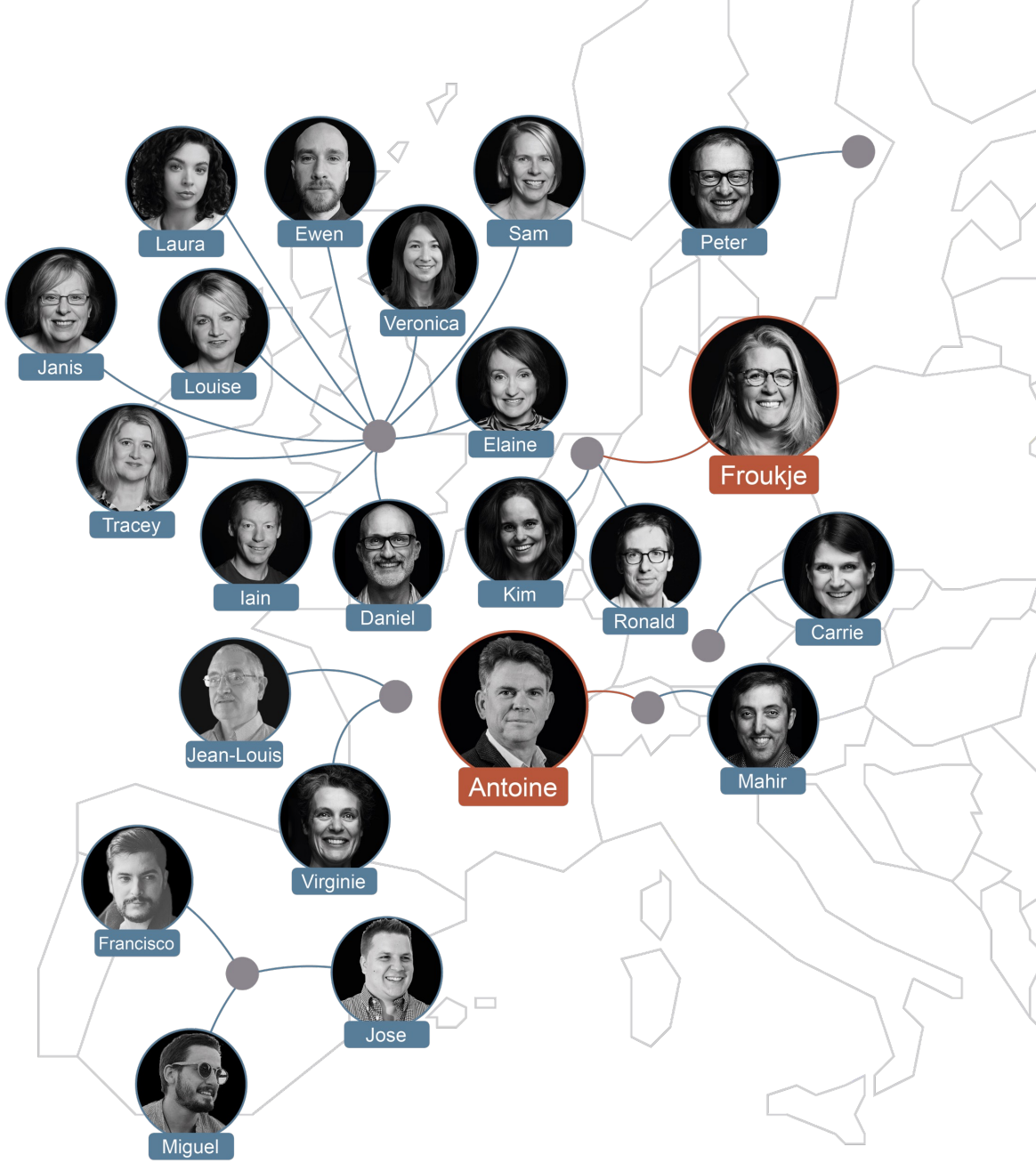
+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com



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