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# GU CONNECT MICRO-LEARNING

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

## MODULE ONE

**UPDATED DECEMBER 2023**

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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# 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

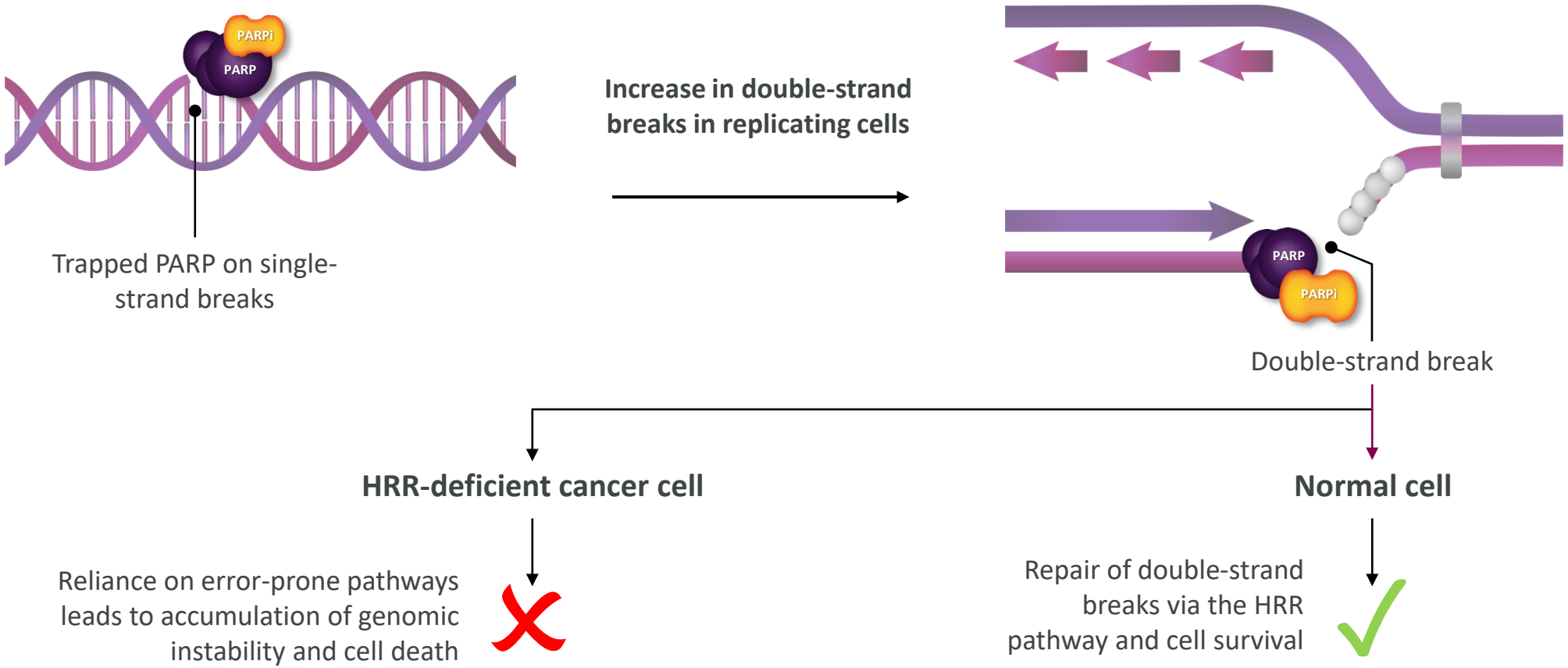
- PARP inhibitors are effective drugs as monotherapy in mCRPC patients with HRR alterations
- Genetic testing is important to help with treatment decision making and for understanding inherited risk
- *BRCA* mutations are associated with poor outcomes in mCRPC patients
- Patients with tumours harbouring *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]

## 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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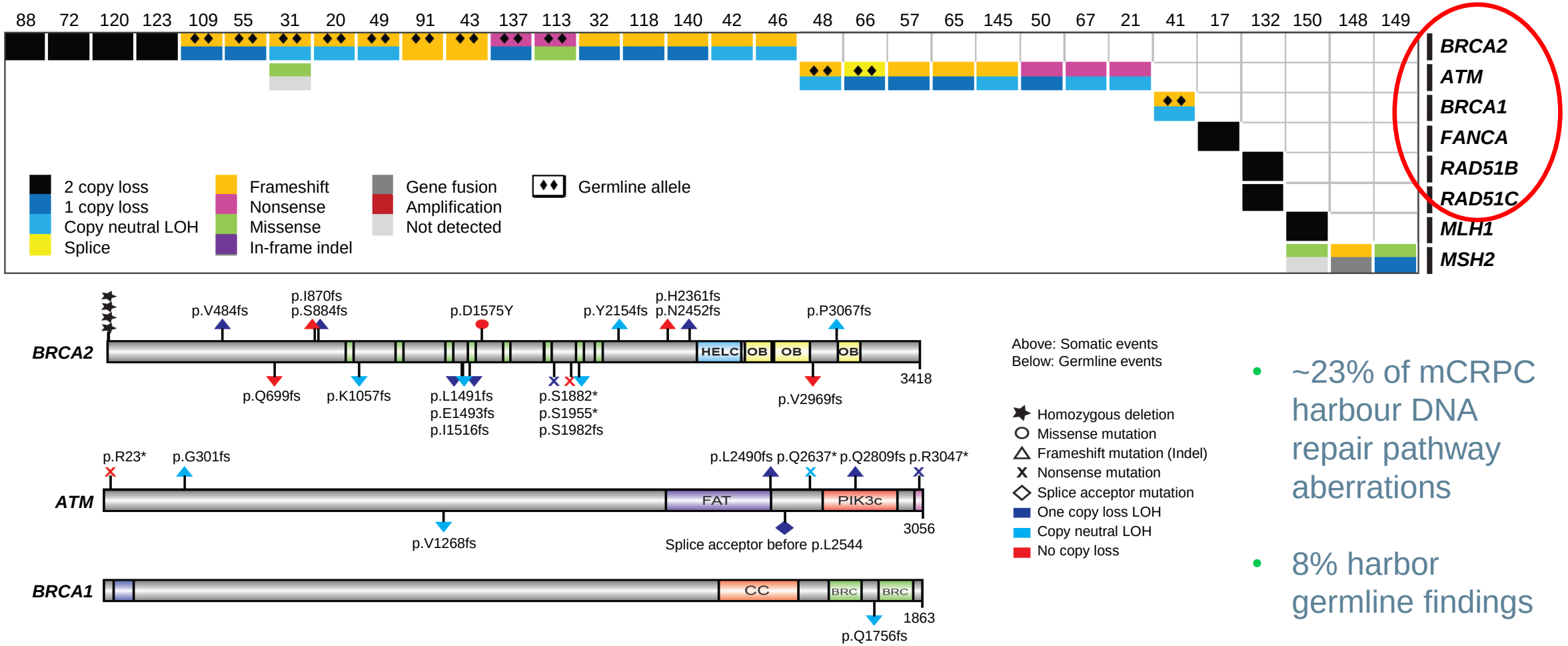


- ~23% of mCRPC harbour DNA repair pathway aberrations
- 8% harbor germline findings

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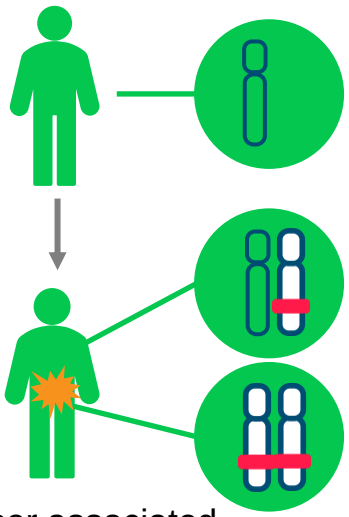
## *BRCA*[a] MUTATIONS PROVIDE A GOOD EXAMPLE OF THIS[1,2]

### 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)

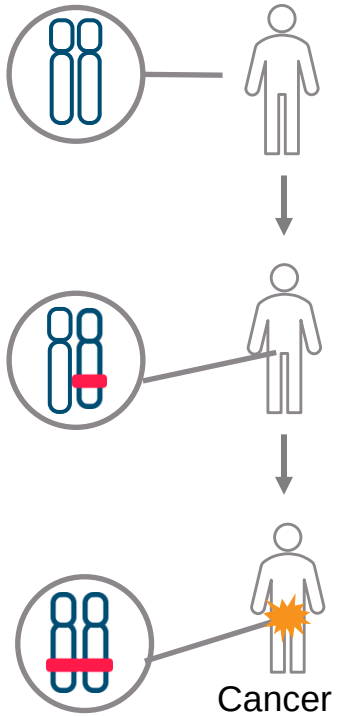


Cancer associated with BRCAm

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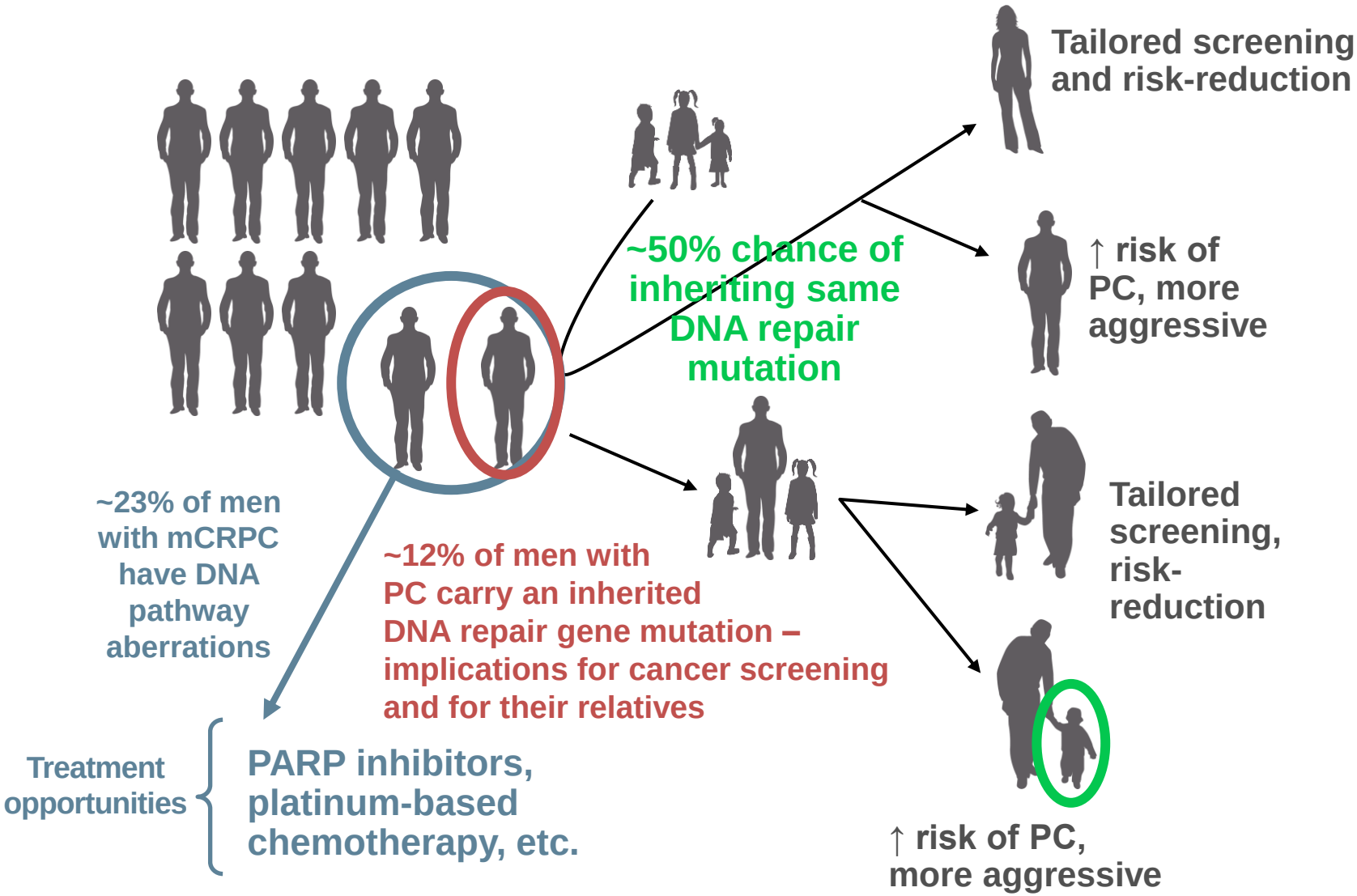
- A father or brother with prostate cancer doubles a man's risk of prostate cancer
- A mother or sister with breast cancer diagnosed before age 50 significantly increases a woman's risk of breast cancer
- A mother or sister with breast cancer can affect a man's risk of prostate cancer

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



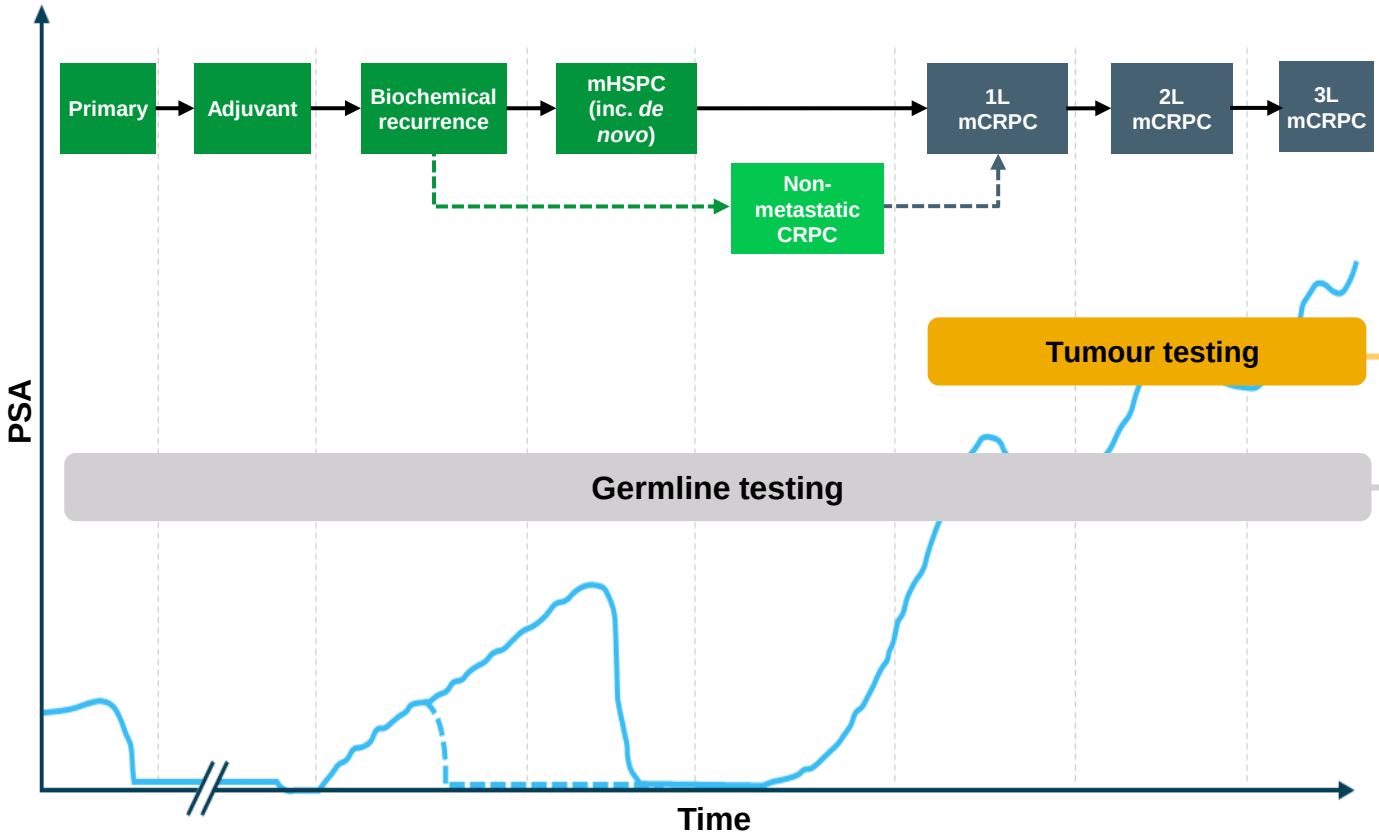

- Full family history should be collected:
  - 3 or 4 generation pedigree
  - Ancestry and consanguinity information
  - Any prior genetic testing
- Family history:
  - Guides choice of broad vs narrow gene panel
  - Determines a patient's criteria for testing
  - Identifies the most appropriate family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

# 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

- Recommend **HRRm** testing in patients with **mPC.** Consider for regional PC
- Recommend testing for **MSI-H, dMMR for mCRPC.** Consider for regional or CSPC
- Consider **TMB** testing for **mCRPC**

## 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

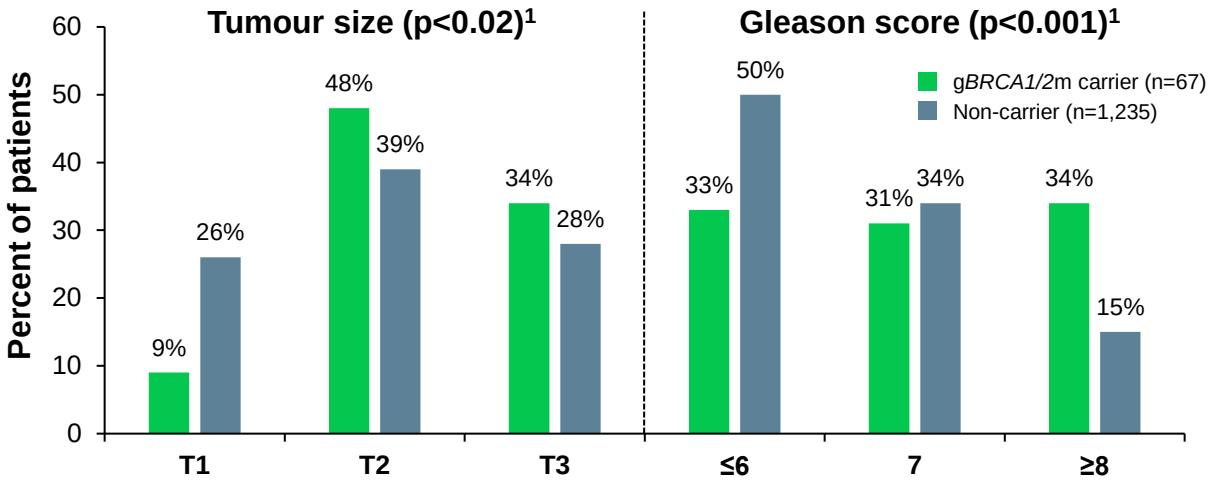
1. Parker C, et al. Annals of Oncology 2020; 31(9): 1119-34; 2. Fizazi K, et al. Annals of Oncology 2023 https://doi.org/10.1016/j.annonc.2023.02.015 ; 3. Mottet N, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf (d56bochluxqnz.cloudfront.net) Accessed May 2023); 4. National Comprehensive Cancer Network. Prostate Cancer (Version 4.2023). prostate.pdf (nccn.org). Accessed Nov 2023; 5. Lowrance W, et al. J Urol. 2023; 209(6):1082-1090; 6. Scher HI, et al. J Clin Oncol 2016; 34 (12): 1402-1418

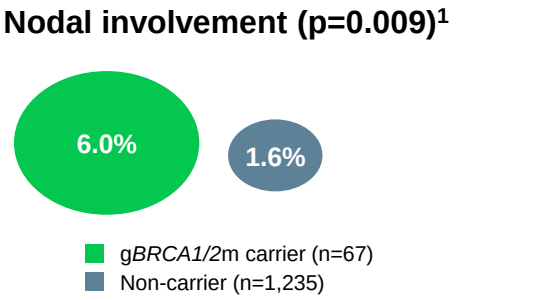
# *BRCA*m ARE ASSOCIATED WITH POOR CLINICAL OUTCOMES

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

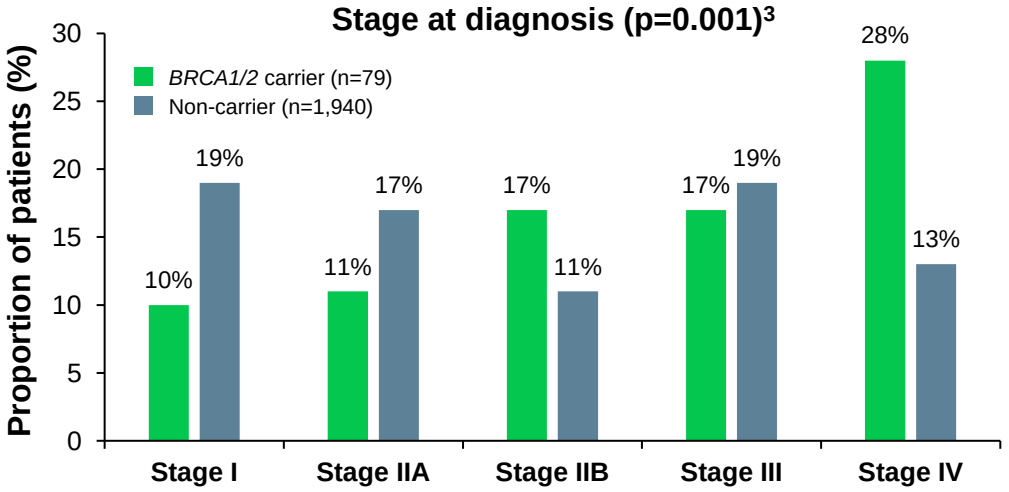
Several large retrospective studies have found an association between *BRCA*m and aggressive disease and rapid progression to metastatic disease[1–3]

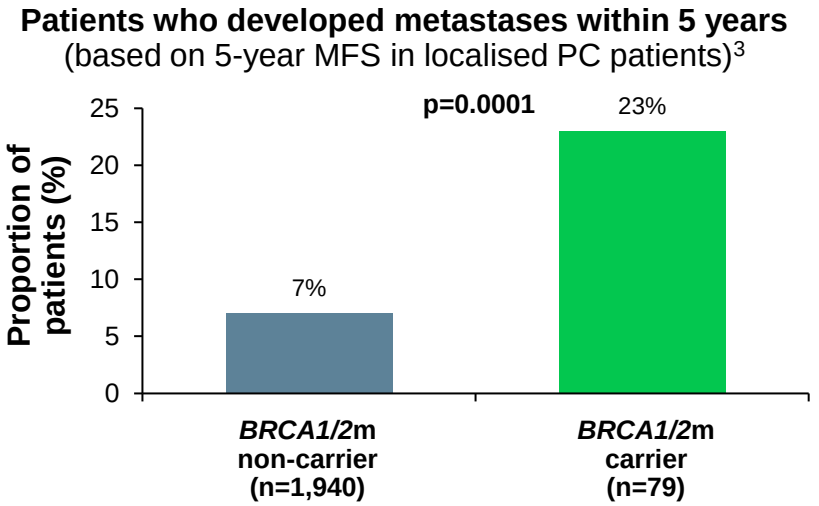
*BRCA2*m tumours are also more likely to show a pattern of intraductal carcinoma which correlates with poor prognosis[2]




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



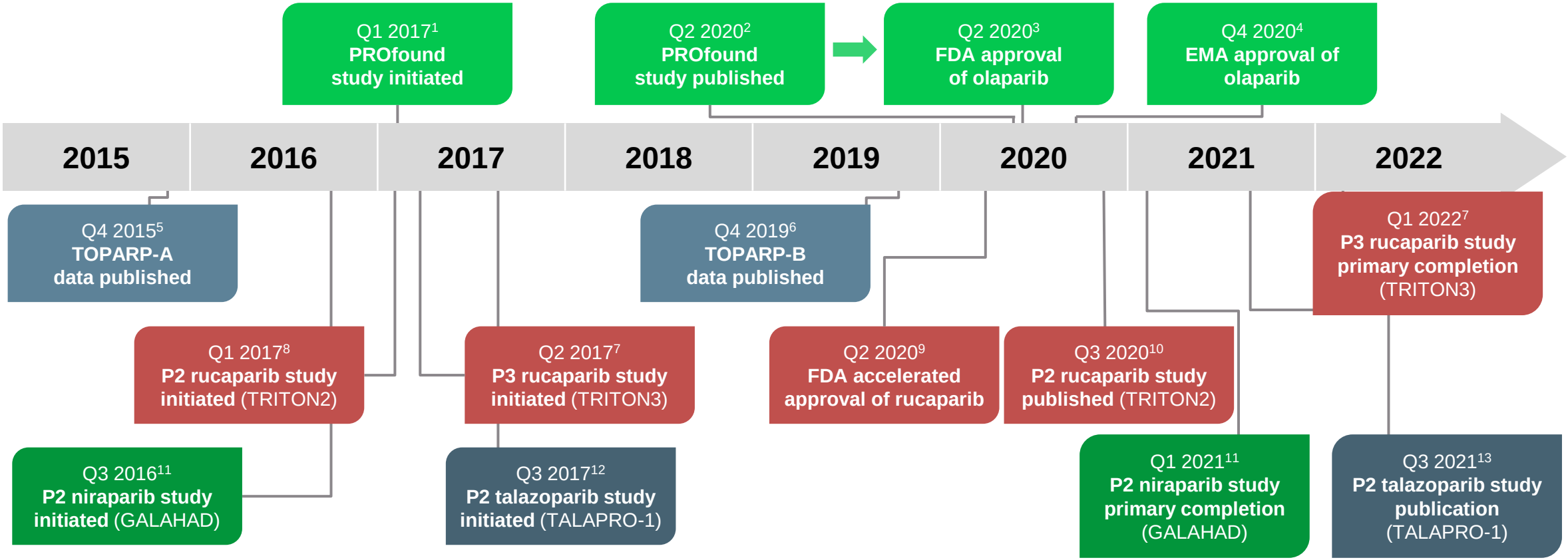

BRCA1/2, breast cancer gene 1/2; BRCAm, BRCA mutated; (g)BRCA2m, (germline) BRCA2 mutation; (g)BRCA1/2m, (germline) breast cancer gene 1/2 mutation; HRRm, homologous recombination repair mutation; MFS, metastasis-free survival; PC, prostate cancer

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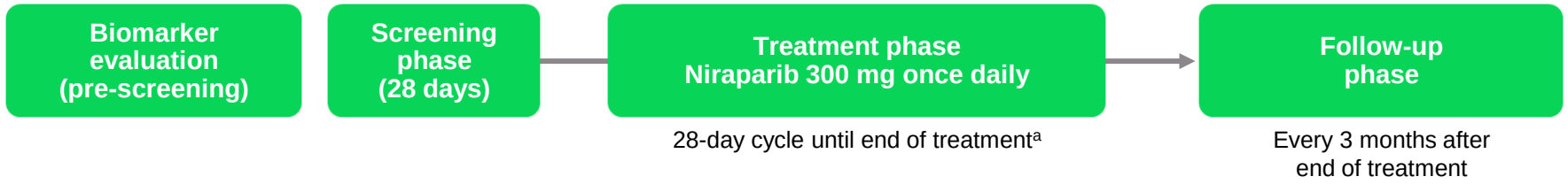
## TOPARP-B STUDY: TEAEs INCIDENCE ≥10% (N=98)

| 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*

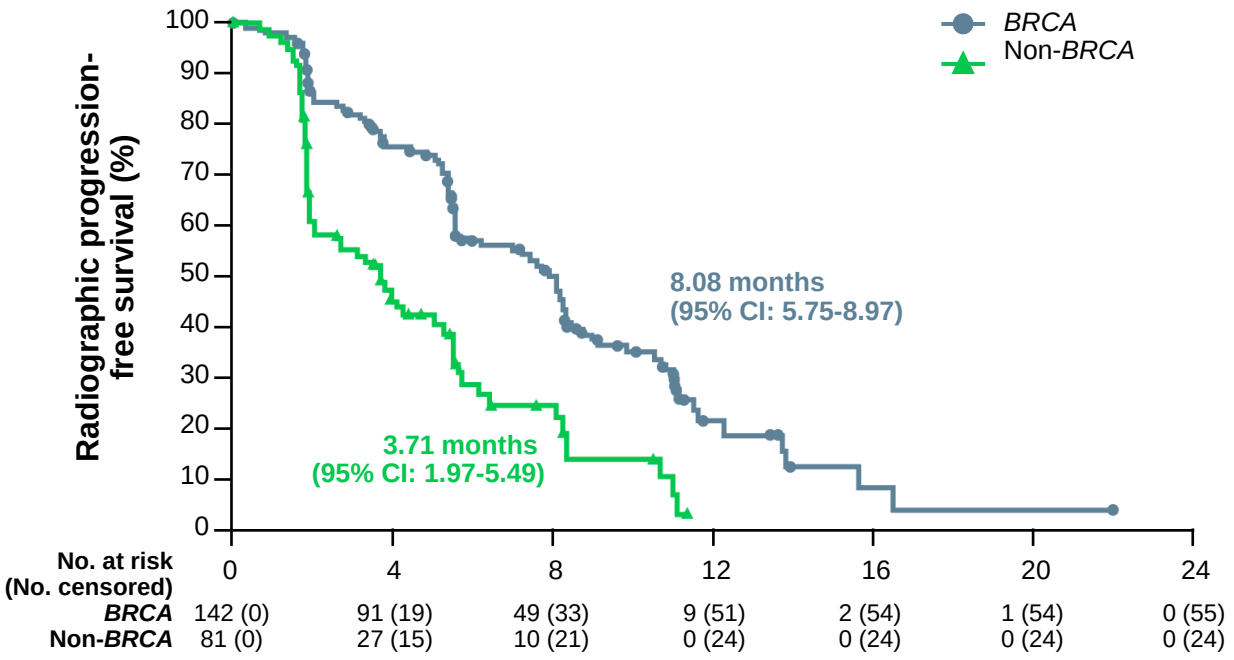
AML, acute myeloid leuameia; ARSI, androgen signalling receptor inhibitors; BRCA, breast cancer gene; CTC, circulating tumour cell; CTx, chemotherapy; DDRm, DNA damage repair mutations; DRD, DNA repair deficiency; mCRPC; metastatic castration resistant prostate cancer; MDS, myelodysplastic syndrome; 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

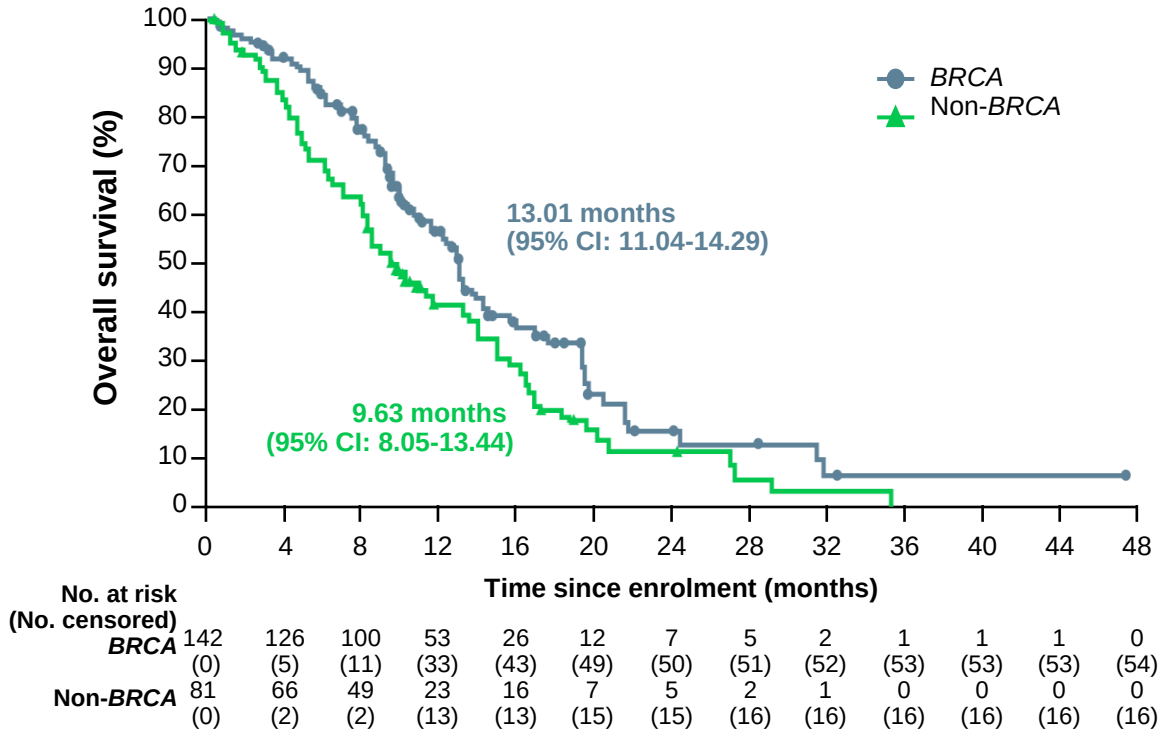
# GALAHAD: NIRAPARIB SHOWS ANTI-TUMOUR ACTIVITY IN mCRPC PATIENTS WITH DDRm, PARTICULARLY *BRCA1/2*

| 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%) |

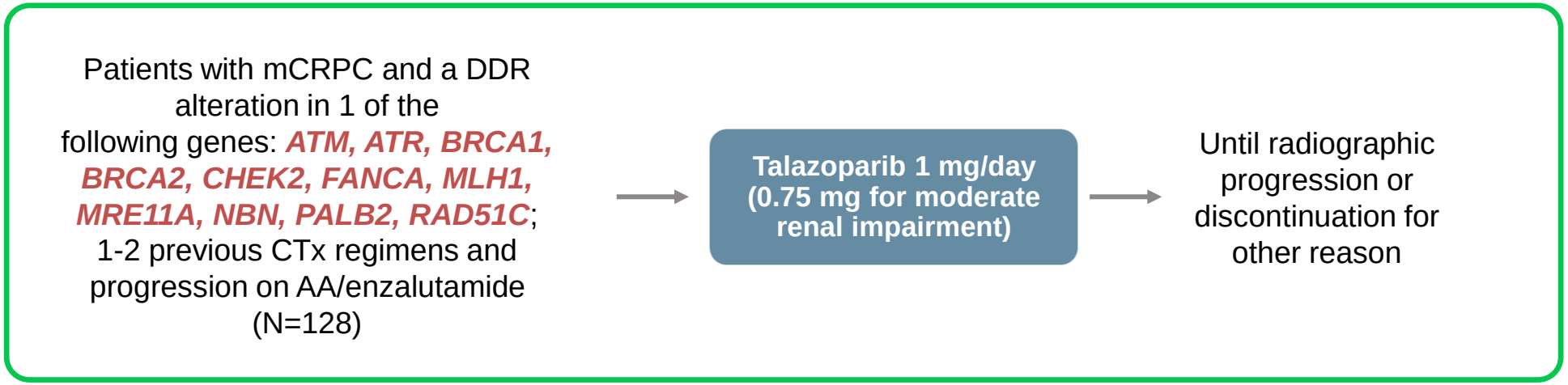
Data are n (%). Data are presented for grade 1-2 treatment-emergent adverse events with a combined incidence of ≥20% or any higher-grade (grade 3-5) treatment-emergent adverse events with an incidence of ≥2%.

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

- 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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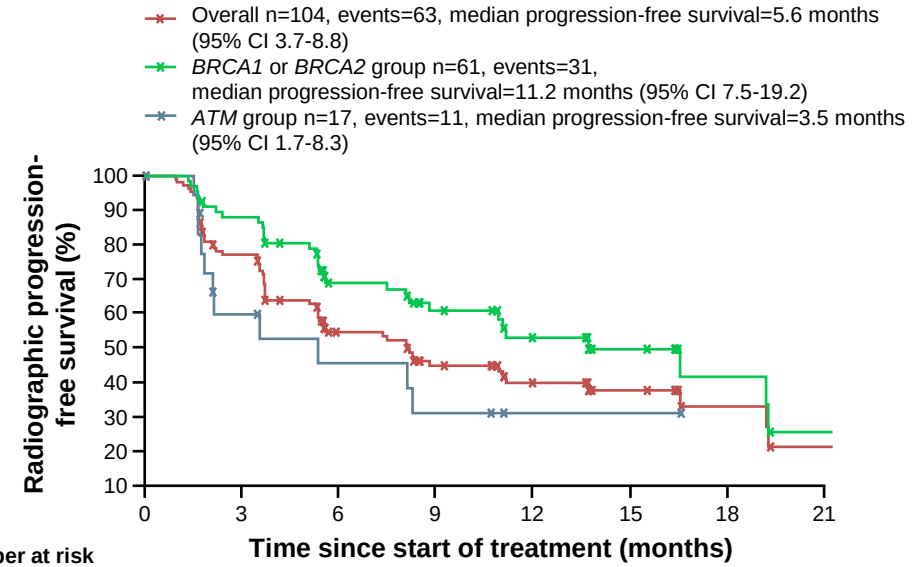
## TUMOUR RESPONSE BY HRR GENE ALTERATION

| 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

## 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%) |

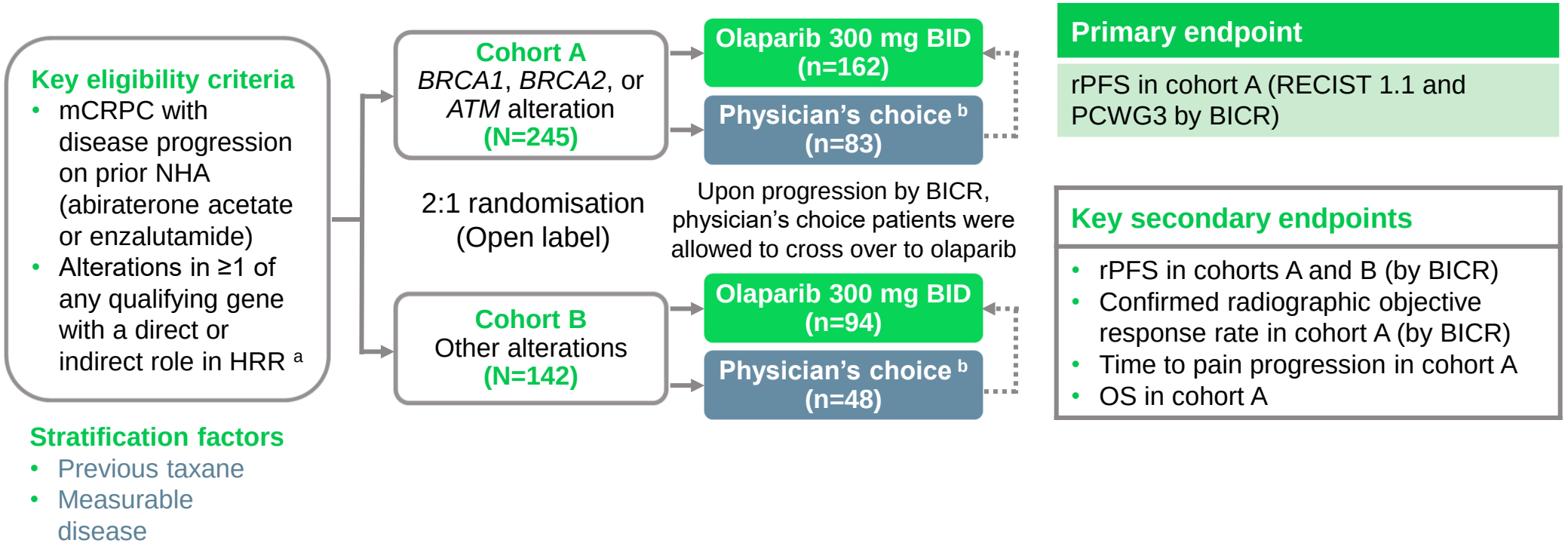
Data are n (%). Data presented are for events reported in at least 10% of patients

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

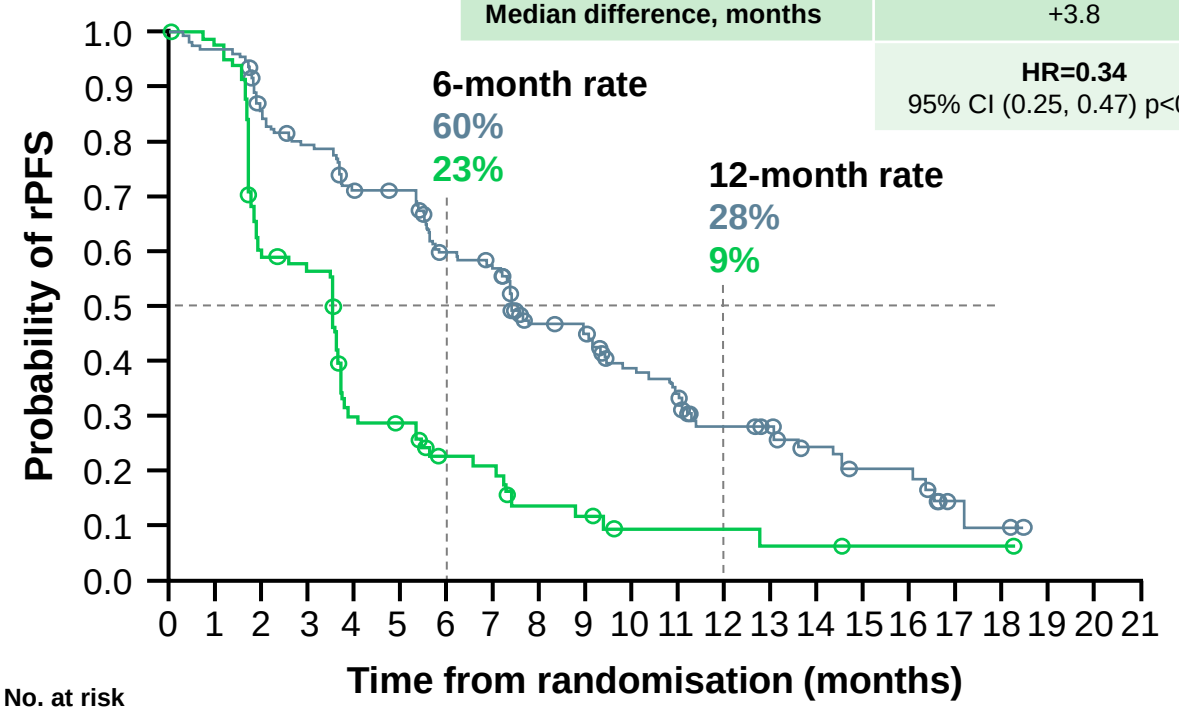
ATM, ataxia telangiectasia mutated; BICR, blinded independent central review; BID, twice daily; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PCWG3, Prostate 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

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

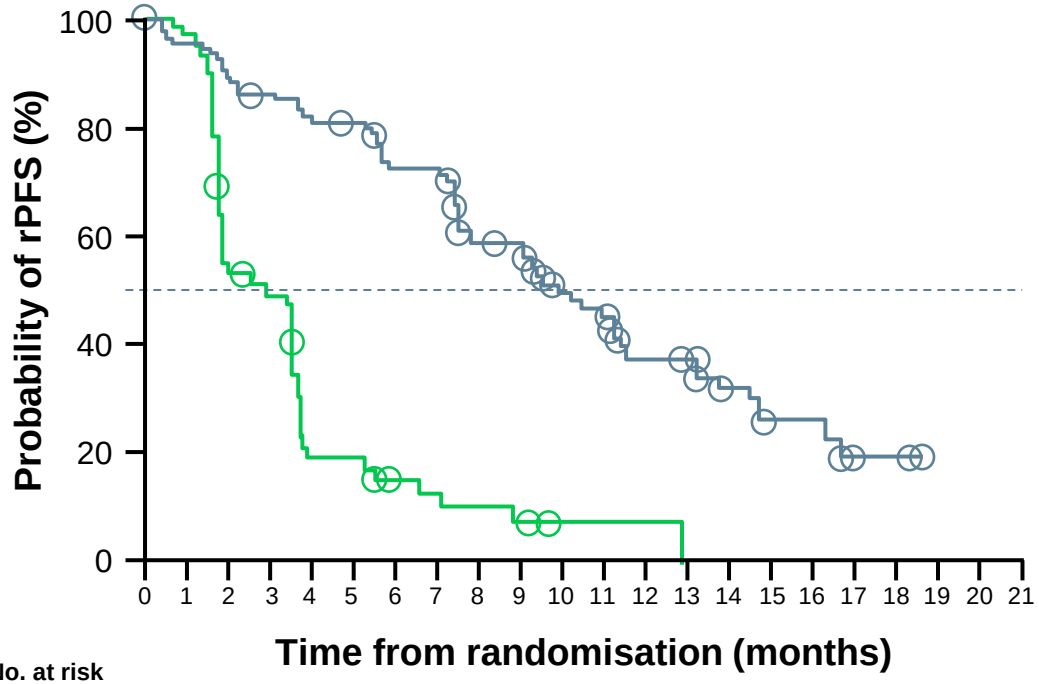
| | Olaparib (N=162) | Physician's choice (N=83) |
|---|---|---|
| Events, n (%) | 106 (65.4) | 68 (81.9) |
| Median PFS, months (BICR) | 7.4 | 3.6 |
| Median difference, months | +3.8 | |
| | HR=0.34<br>95% CI (0.25, 0.47) p<0.001 | |




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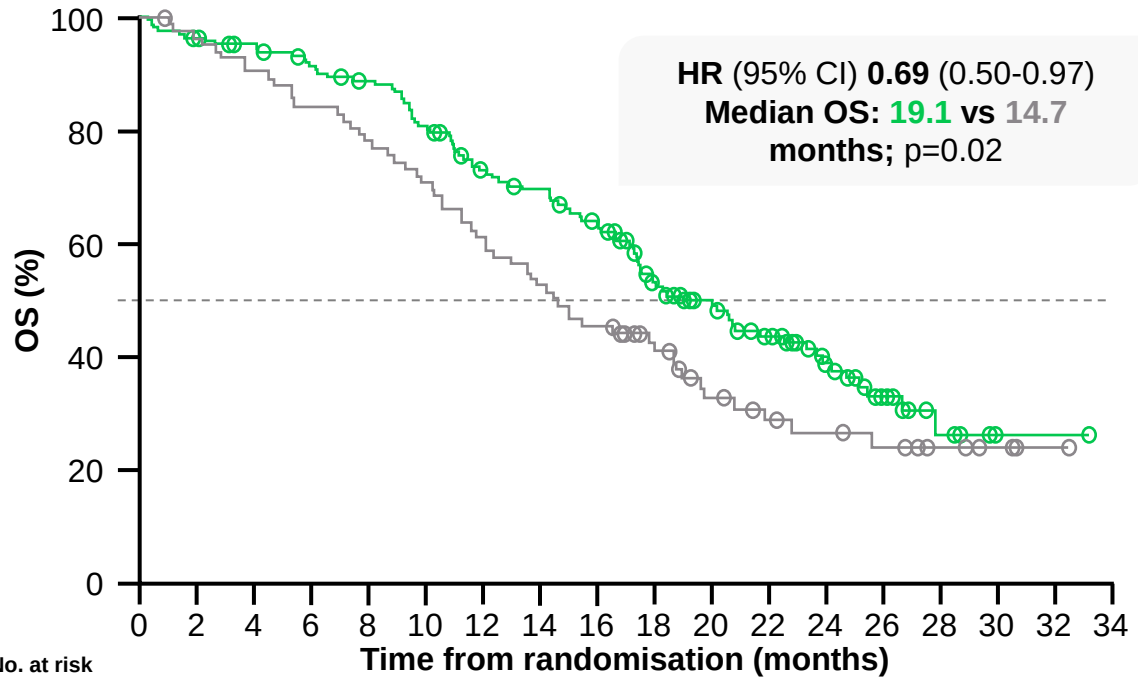
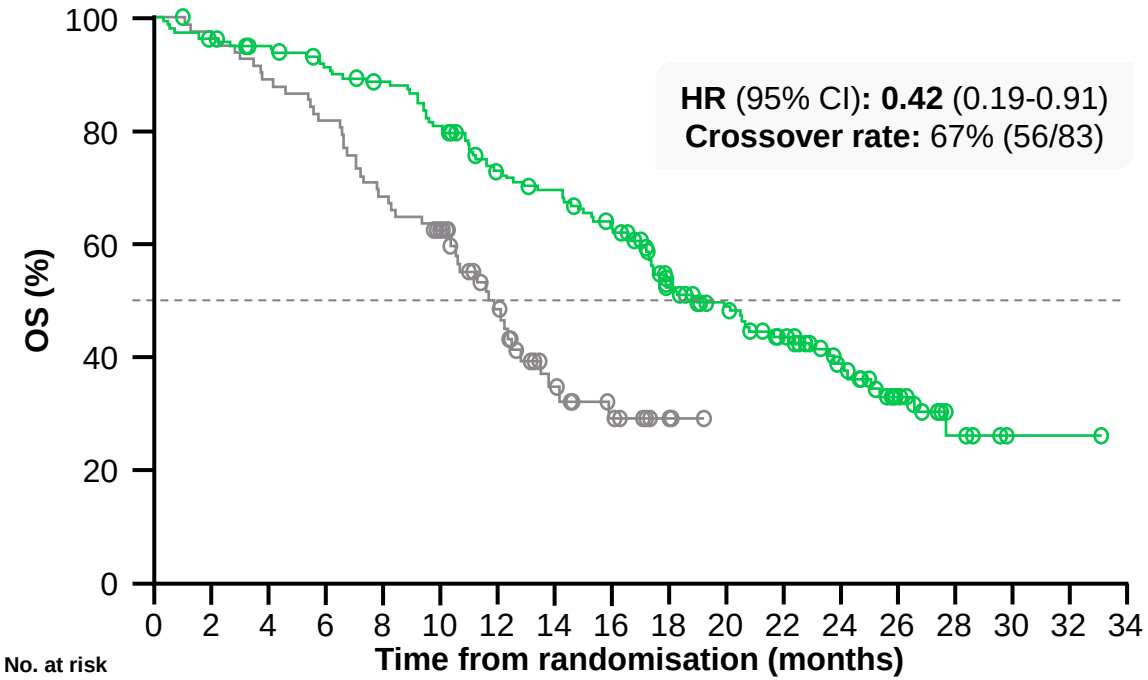
## COHORT A: *BRCA1/2* OR *ATM* MUTATIONS




No. at risk

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

## COHORT A WITH ADJUSTMENT FOR CROSSOVER[A]




No. at risk

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

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

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

CI, confidence interval; HR, hazard ratio; 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]

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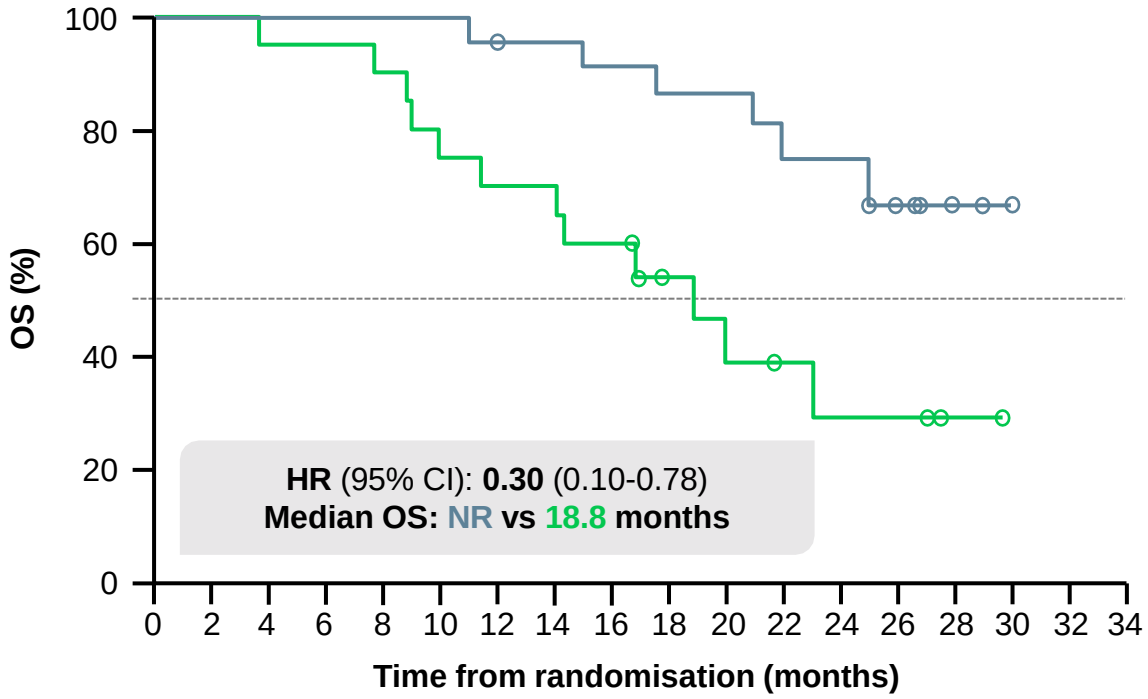
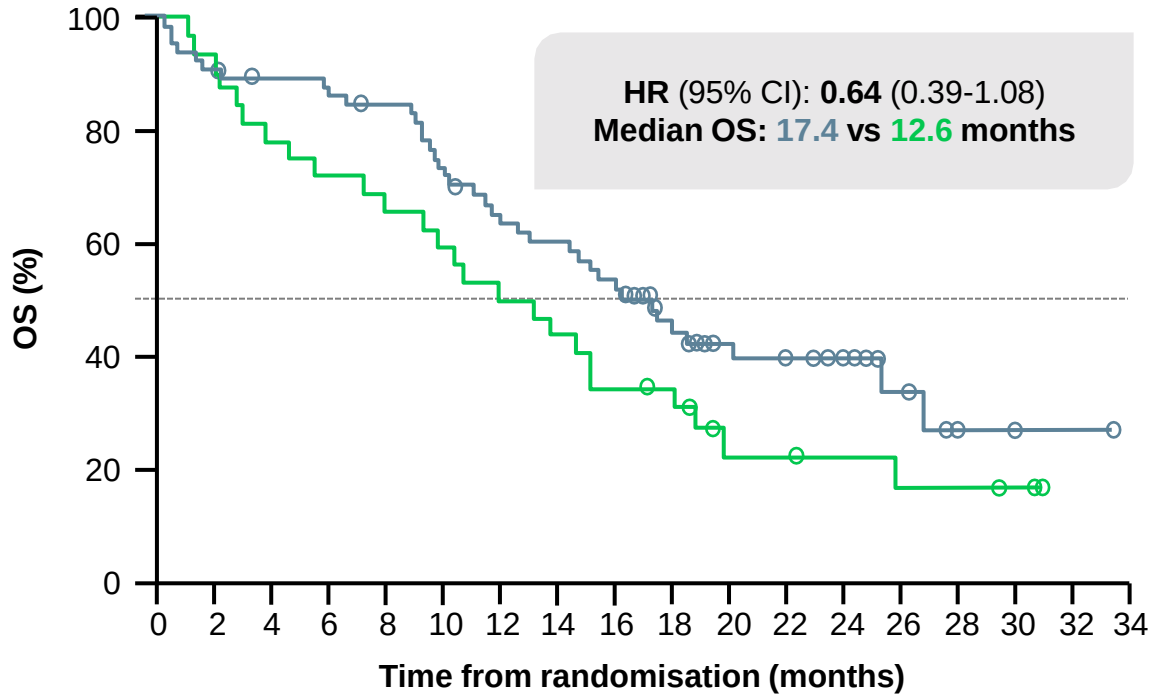
## NO PRIOR TAXANE




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

## PRIOR TAXANE




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

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

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: 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 |

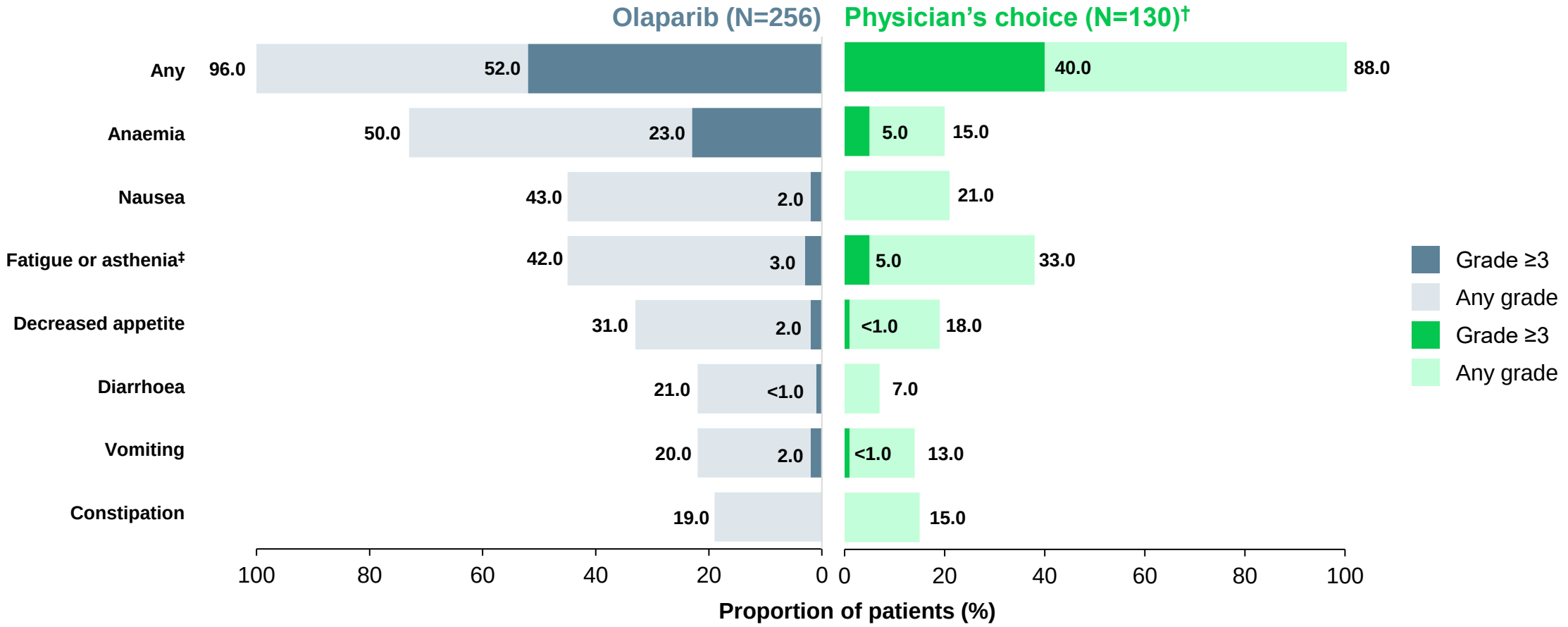
[a]*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*

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*

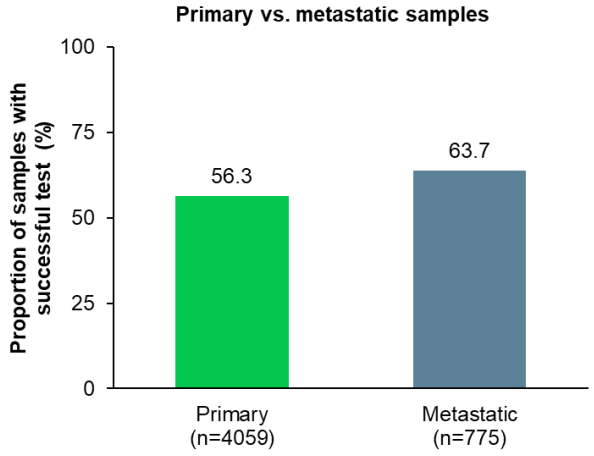
At the final OS DCO, median duration of treatment was 7.6 months in the olaparib arm and 3.9 months in the control arm

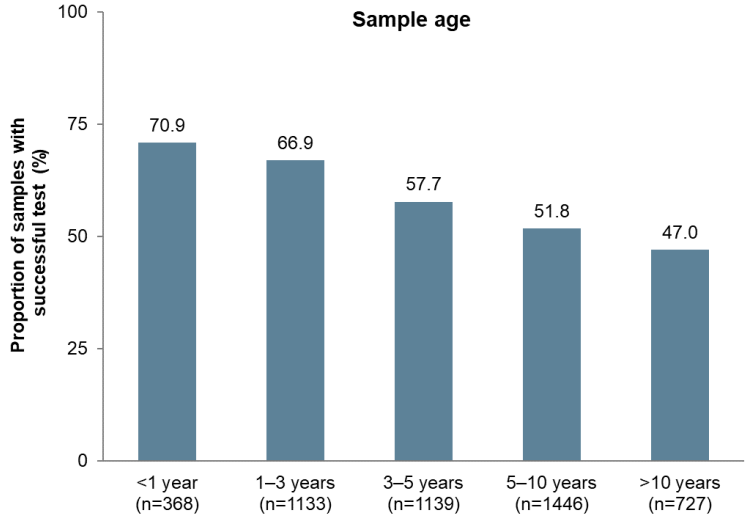


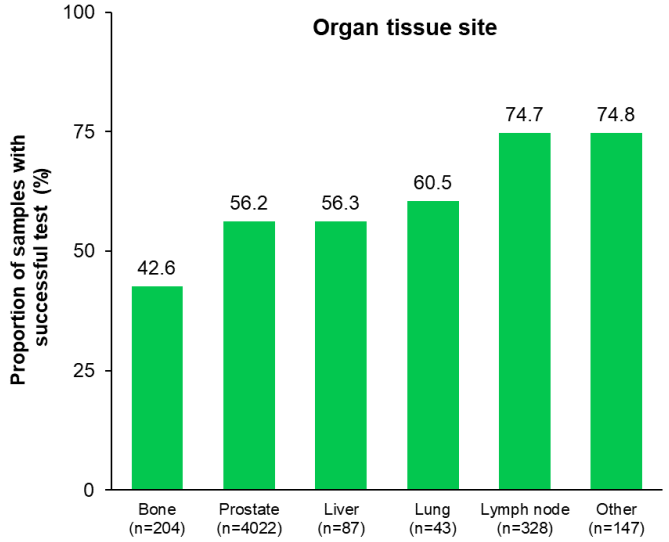

* Most common AEs associated with treatment with PARP inhibitors. Patients had alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and / or *RAD54L*. Note, there were no cases of myelodysplastic syndromes or AML. 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

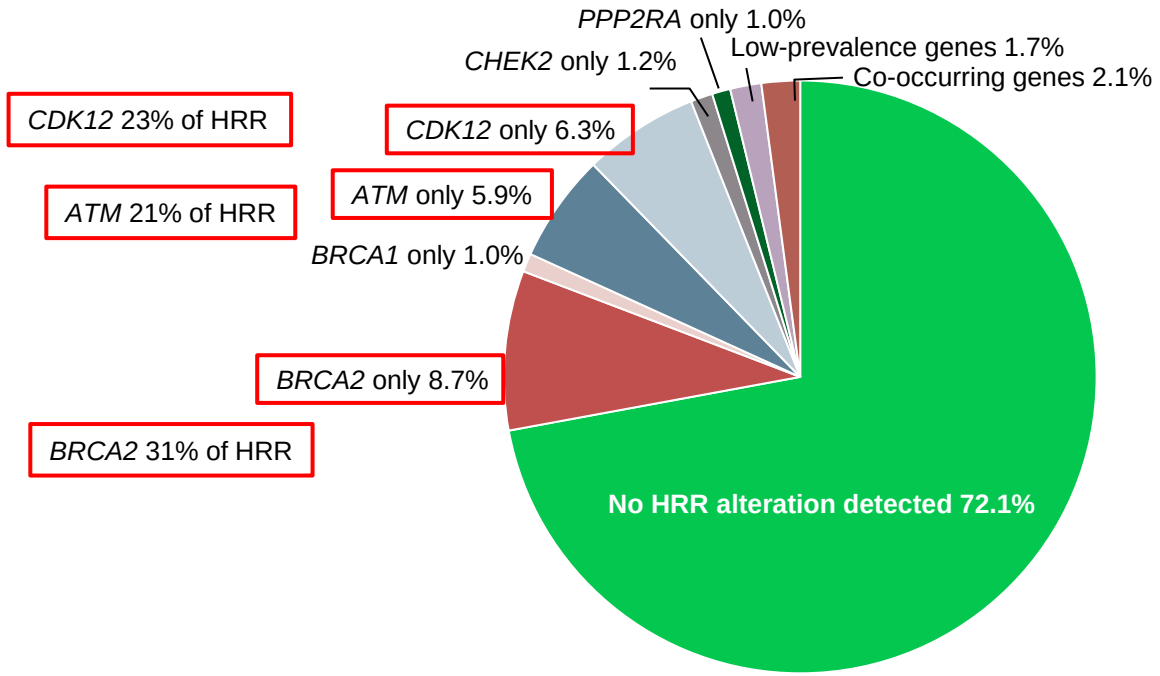
**A similar proportion of patients were identified with HRRm, irrespective of whether the tissue was derived from the primary tumour or metastatic deposits**

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]

GU connect® POWERED BY COR2ED

| 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.

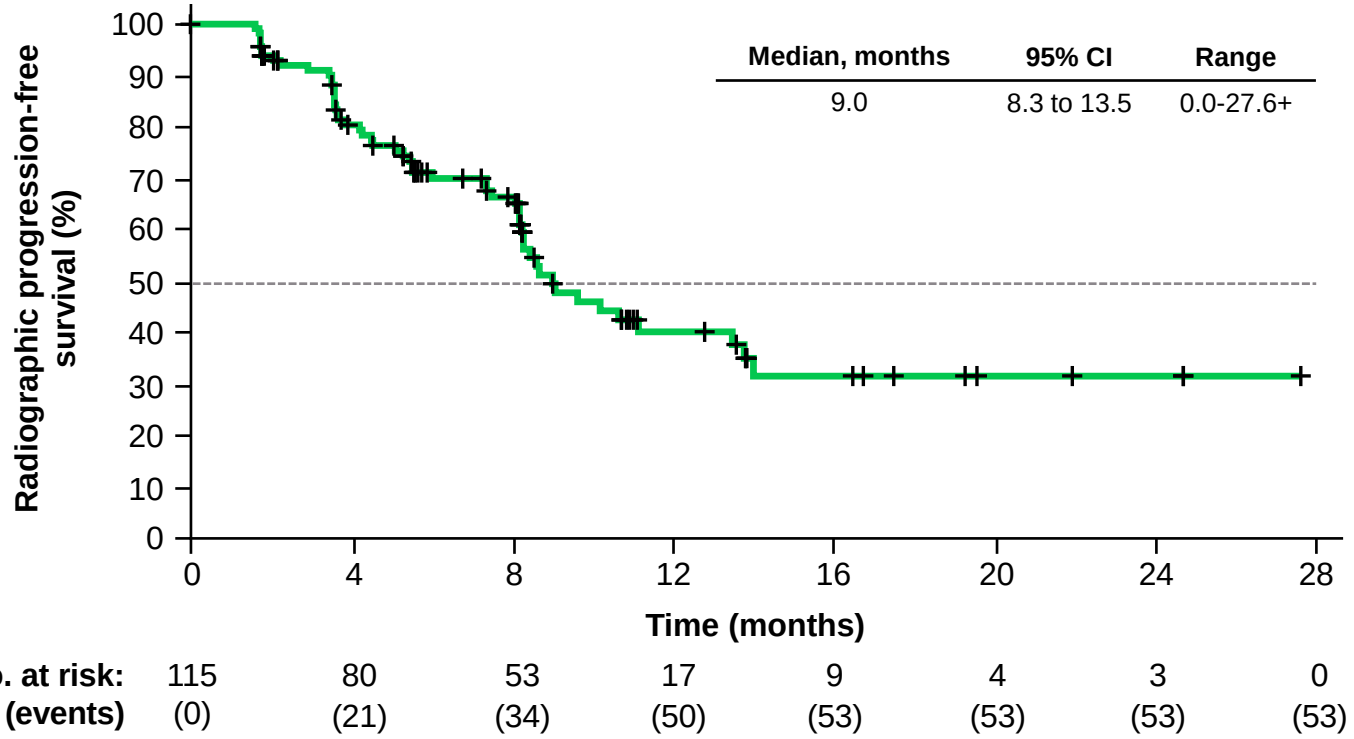
- Patients harbouring an ATM or CDK12 alteration did not receive significant benefit[2]

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

- 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

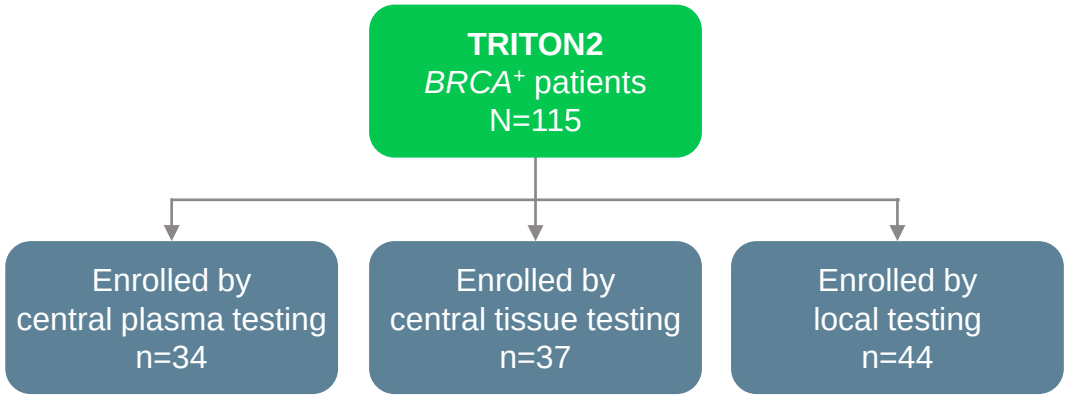
| Individual TEAE (preferred terms) occurring in ≥15% of patients | Any grade | Grade ≥3 |
|---|---|---|
| Asthenia/fatigue | 71 (61.7) | 10 (8.7) |
| Nausea | 60 (52.2) | 3 (2.6) |
| Anaemia/decreased hemoglobin | 50 (43.5) | 29 (25.2) |
| ALT/AST increased | 38 (33.0) | 6 (5.2) |
| Decreased appetite | 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

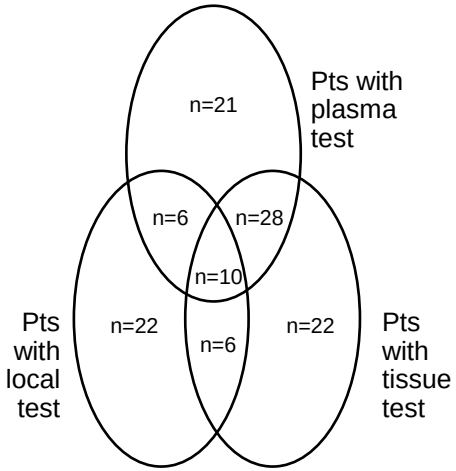
Abida W, et al. J Clin Oncol. 2020;38:3763-72

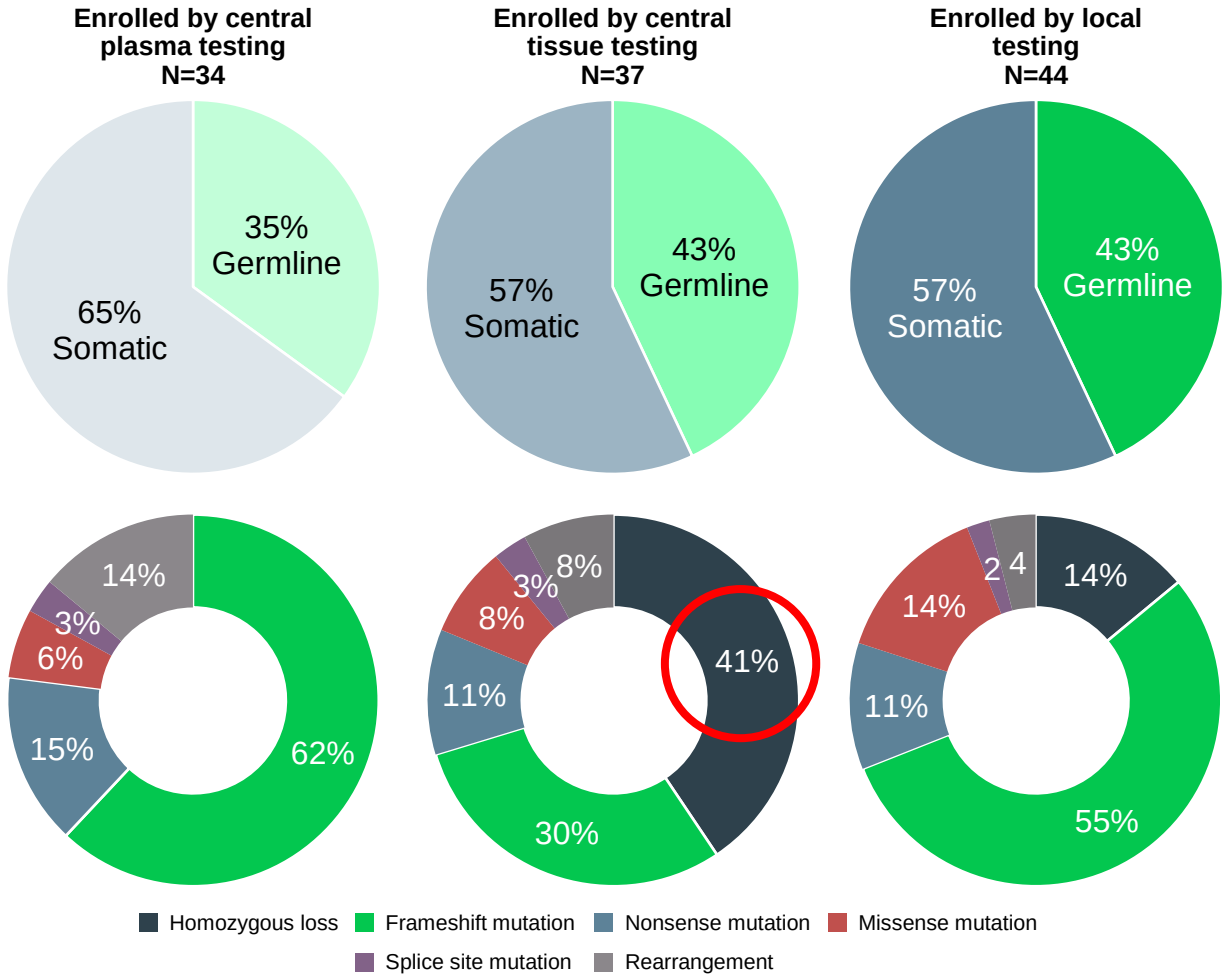
# TRITON2: HRRm IDENTIFIED VIA TISSUE OR ctDNA

## 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

- 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<br>NPV = 0.96 |

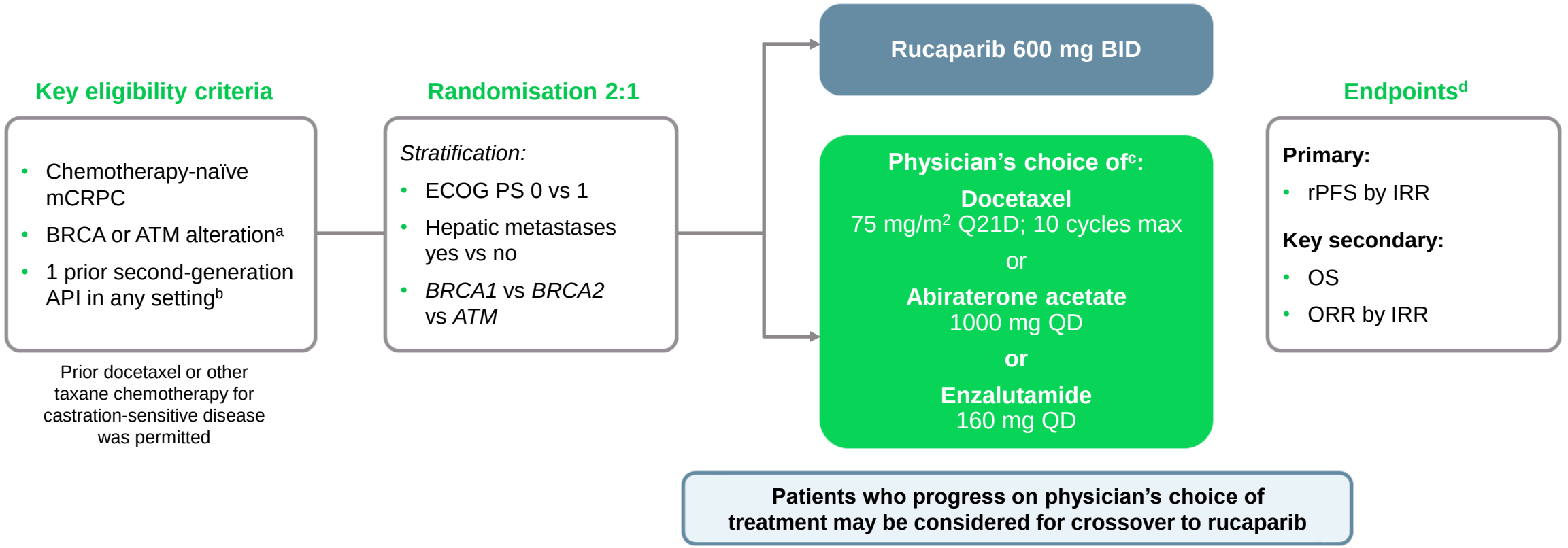
- However, sequencing on ctDNA might miss a significant proportion of *BRCA2* homologous loss

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

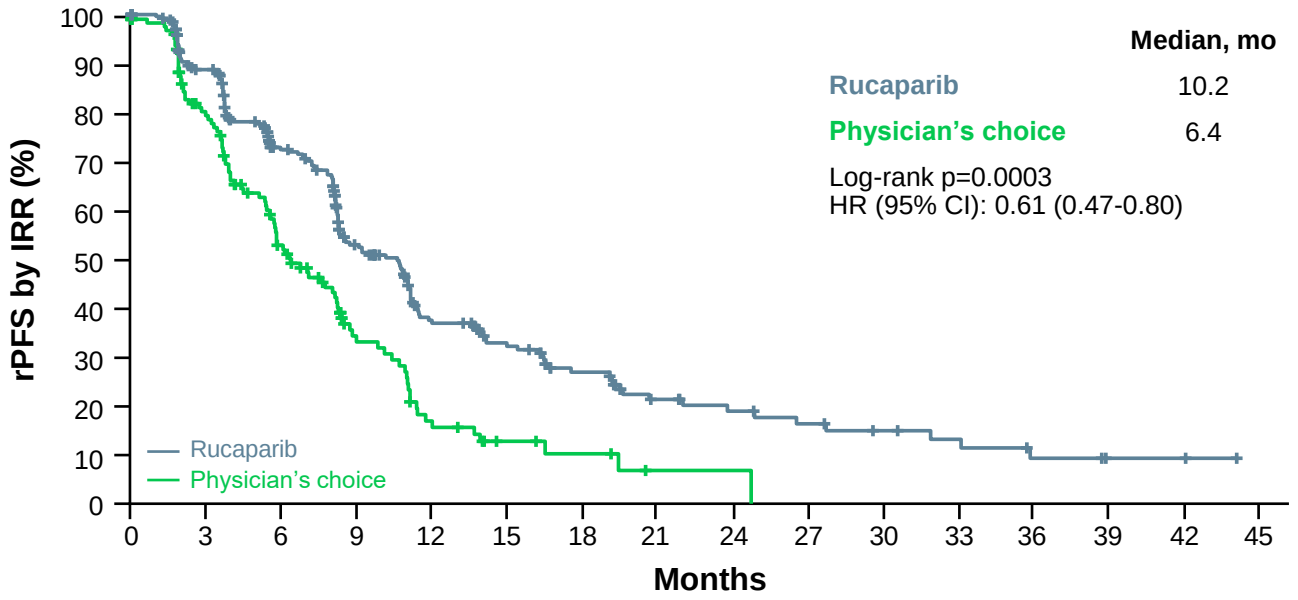



Visit cutoff date: 25 August 2022. [a] Determined by Foundation Medicine testing of tissue or plasma. [b] Protocol amendment June 19, 2018: patients' qualifying second-generation API could be in any setting. [c] If chosen, patients received whichever second-generation API had not yet been received. [d] 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) | | | | | | |

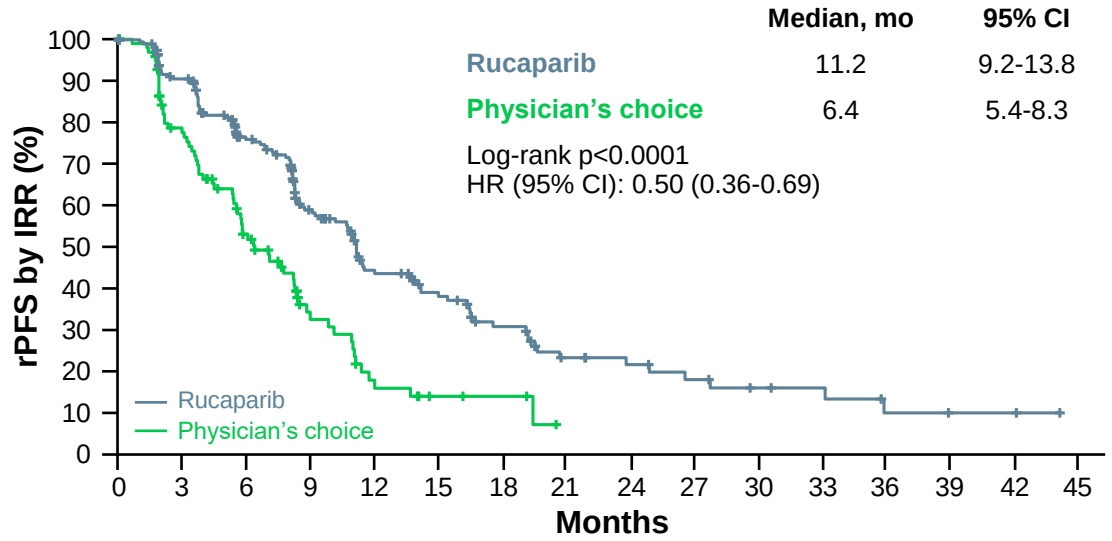
Data maturity: 64% (258/405). The *ATM* subgroup completed enrolment in December 2019

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; 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 |

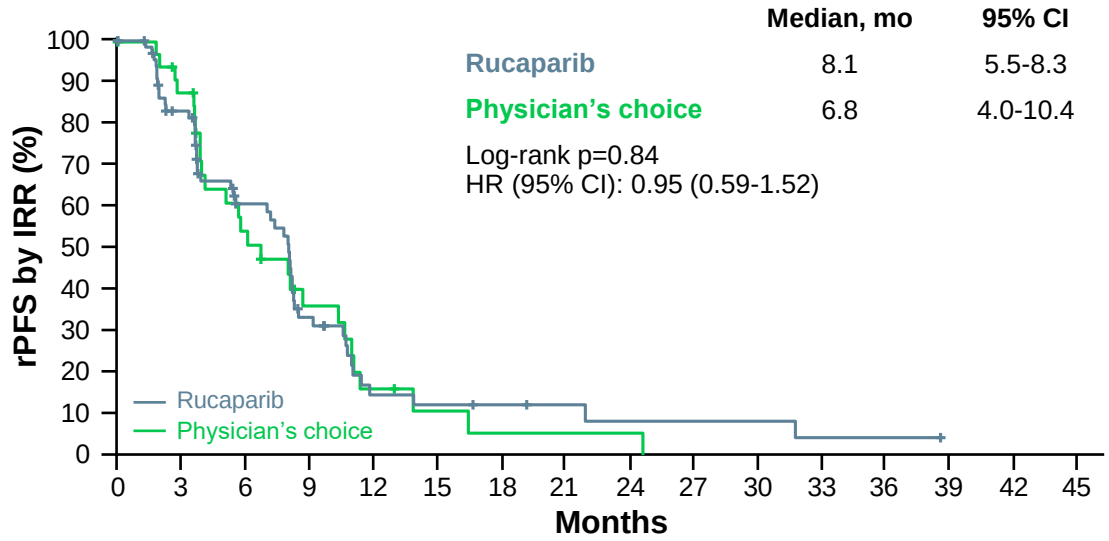
Log-rank p<0.0001
HR (95% CI): 0.50 (0.36-0.69)

**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). *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)**

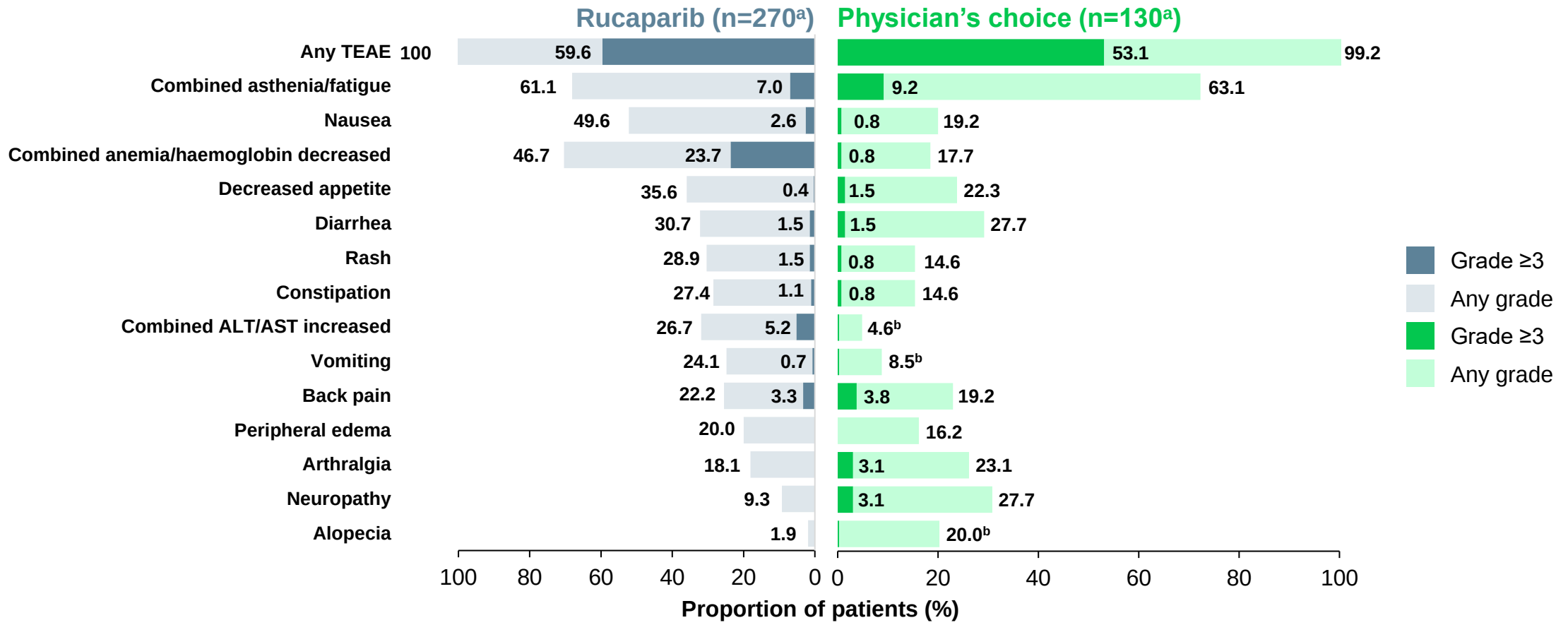
| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rucaparib | 69 (0) | 51 (11) | 31 (24) | 16 (38) | 6 (46) | 5 (47) | 4 (47) | 3 (47) | 2 (48) | 2 (48) | 2 (48) | 1 (49) | 1 (49) | 0 (49) | | |
| Physician's choice | 34 (0) | 28 (4) | 16 (14) | 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; 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

# 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

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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
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with ***BRCAm*** **mCRPC**

***Niraparib FDA-approved indication[3]***

- Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone for the treatment of adult patients with ***BRCAm*** **mCRPC**

***Rucaparib FDA-approved indication[5]***

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

***Talazoparib FDA-approved indication[6]***

- In combination with enzalutamide for the treatment of adult patients with HRRm **mCRPC[b]**

***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**
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with **mCRPC in whom chemotherapy is not clinically indicated**

***Niraparib EMA-approved indication[4]***

- 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**

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

**[b]Talazoparib has no current approval in prostate cancer in Europe**

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 (Sep-2023); 2. Lynparza (olaparib) summary of product characteristics (Mar 2023); 3. FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer | FDA; 4. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate; 5. Rubraca (rucaparib) US prescribing information (Jun 2022); 6. Talzenna (talazoparib) summary of product characteristics (Jun 2023)

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

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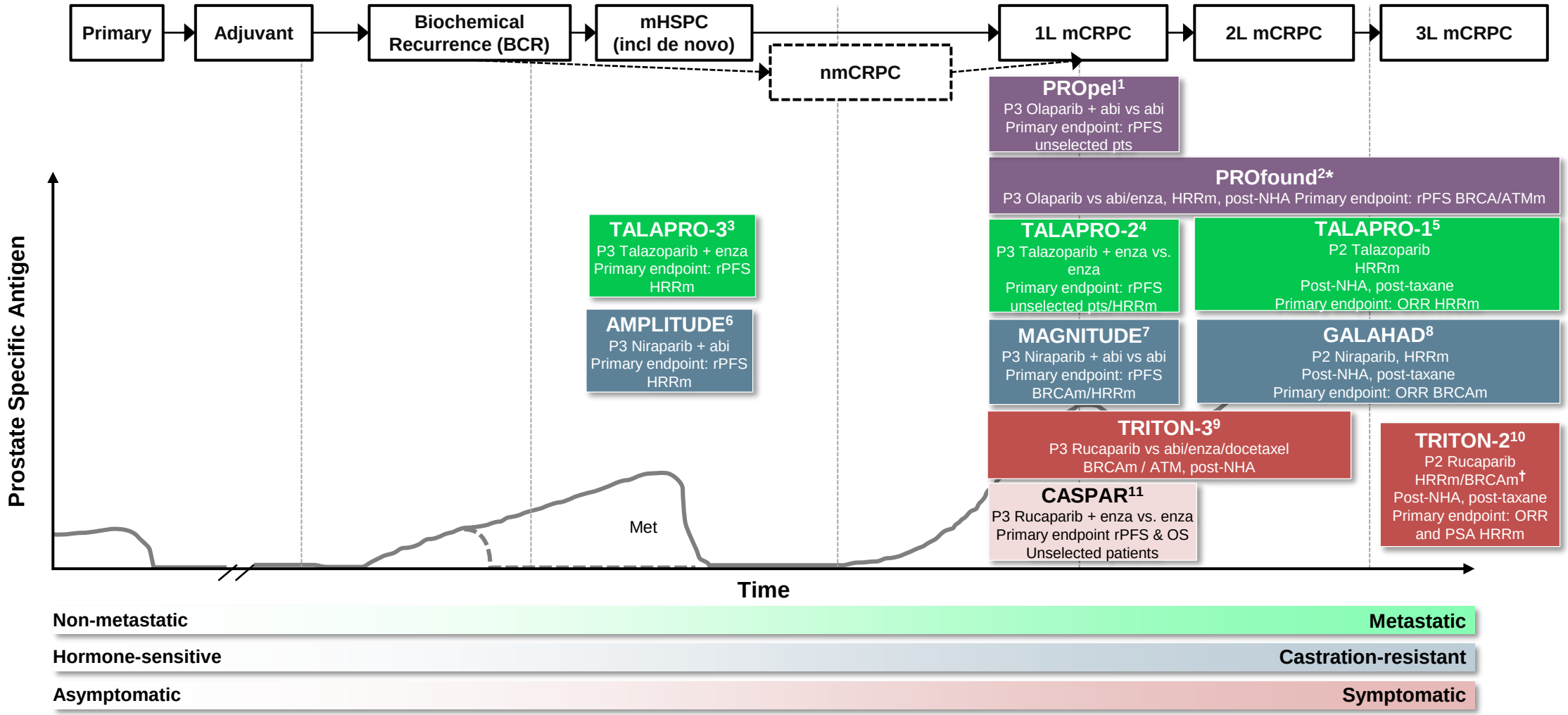


Please see slide notes for references. [a] As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA [b] As a result of the data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

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

| | 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,a,b] | Ovarian cancer,[3,4] prostate cancer[4,c] | Ovarian cancer,[5,6] prostate cancer[7,8,e] | Breast cancer, prostate cancer[9,10,f] |

[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 and is approved by the EMA in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated[2]

[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.

[e] Approved as a fixed dose combination of niraparib/abiraterone acetate with prednisone by the FDA for: the treatment of adult patients with deleterious or suspected deleterious BRCAmutated (BRCAm) metastatic castration-resistant prostate cancer; and by the EMA for the treatment of adult patients with mCRPC and BRCA1/2 gene mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated

[f] Talazoparib is approved by the FDA in combination with enzalutamide for the treatment of adult patients with HRRm mCRPC (no current approval in prostate cancer in Europe)

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. Rucaparib SmPC; 4. Rucaparib PI; 5. Niraparib PI; 6. Niraparib SmPC; 7. Akeega PI; 8. Akeega SmPC; 9. Talazoparib SmPC; 10. Talazoparib PI. All accessed November 2023.

# 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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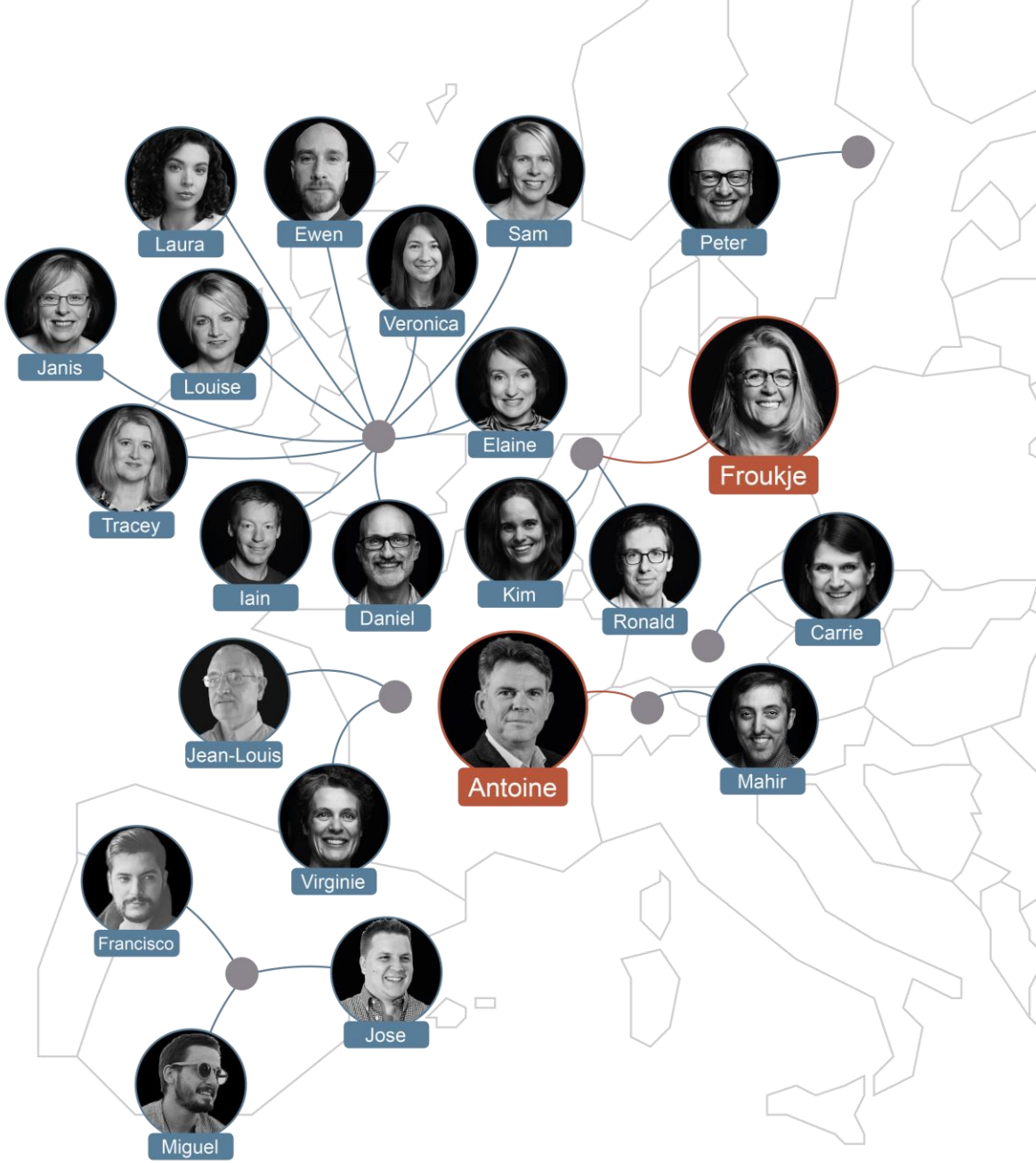


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