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# GUARD INTERNATIONAL SYMPOSIUM

## GU-Alliance for Research and Development

PRESENCIAL RETRANSMITIDO EN DIRECTO
FACE-TO-FACE AND LIVE STREAMING

26-27 JUNIO 2025

Espacio Maldonado, Madrid

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# Talapro-2

## ¿A qué pacientes debemos testar?

## ¿Cuáles son candidatos a tratamiento?

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# TALAPRO-2. Who should we test? Who is the ideal candidate for treatment?

**Who to test?**

**Do PARPi – NHA combinations eliminate the need for testing?**

**Who is the ideal candidate for treatment?**

**What, where and when to test?**

# Who to test? Test everybody!!

## Testing has prognostic implications (outcome)

Testing has implications for the family risk of cancer

Testing has predictive implications (treatment selection)

## Do PARPi – NHA combinations eliminate the need for testing?

## Who is the ideal candidate for treatment?

The ideal candidate is the one that reflects the clinical trial population

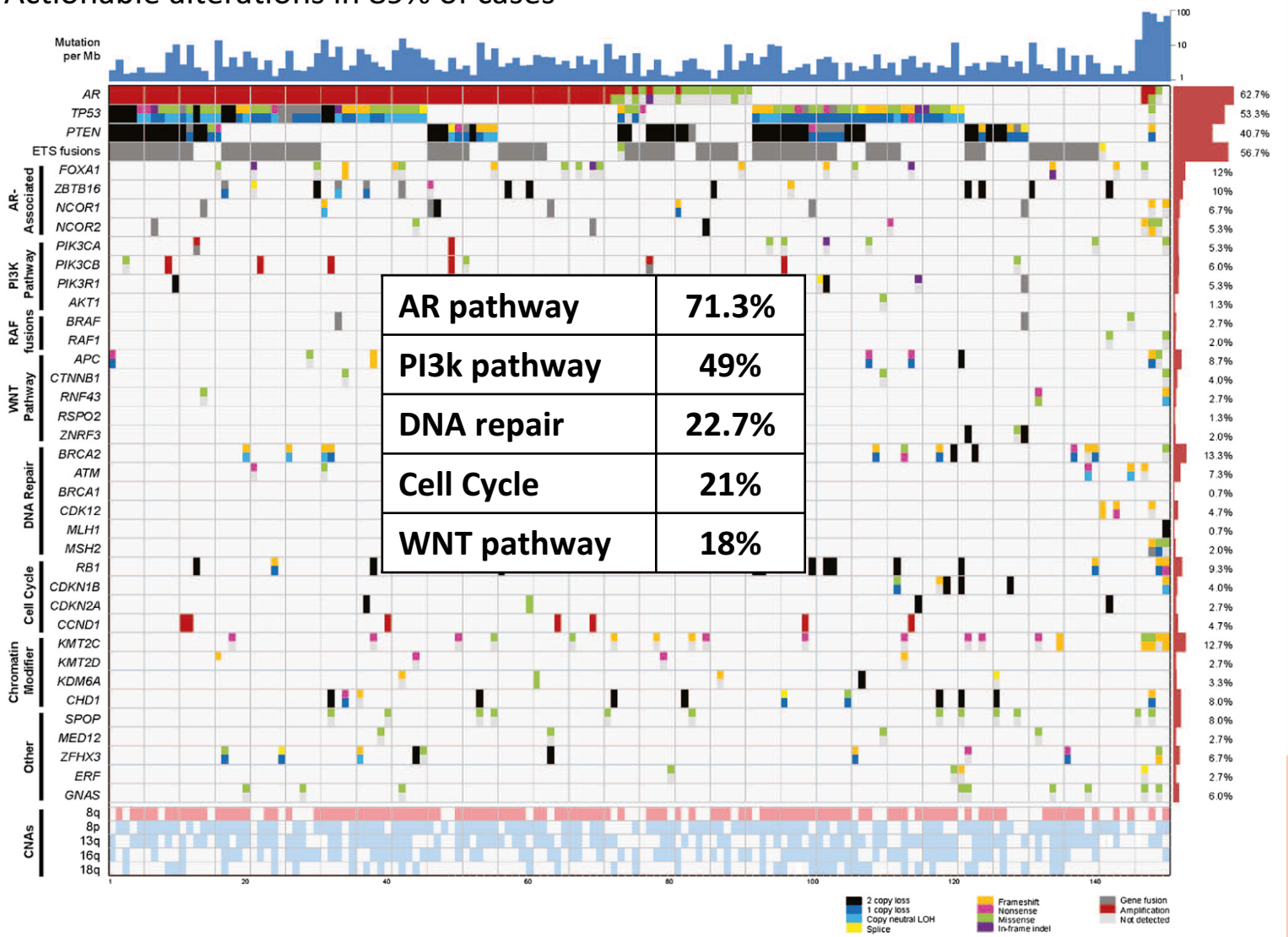
expected benefit is greater than anticipated toxicity (disease burden)

*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

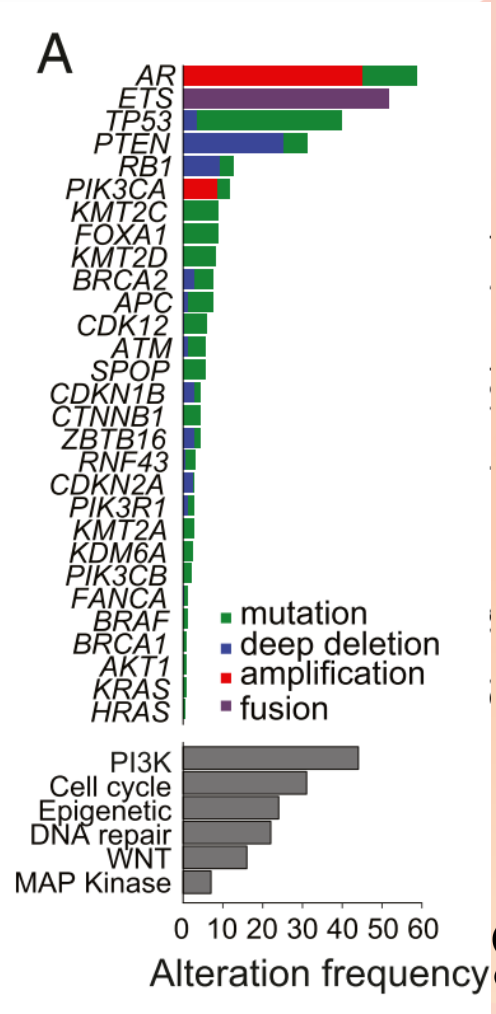
## What, where and when to test?

# Molecular characterization in advanced prostate cancer

Actionable alterations in 89% of cases




| | |
|---|---|
| **AR pathway** | **71.3%** |
| **PI3k pathway** | **49%** |
| **DNA repair** | **22.7%** |
| **Cell Cycle** | **21%** |
| **WNT pathway** | **18%** |

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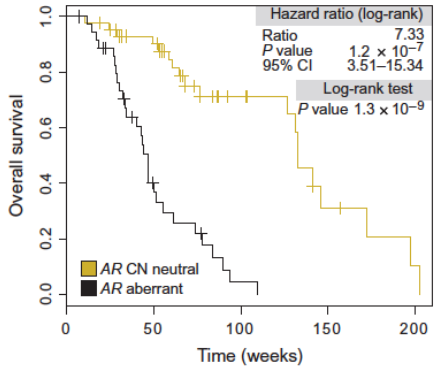
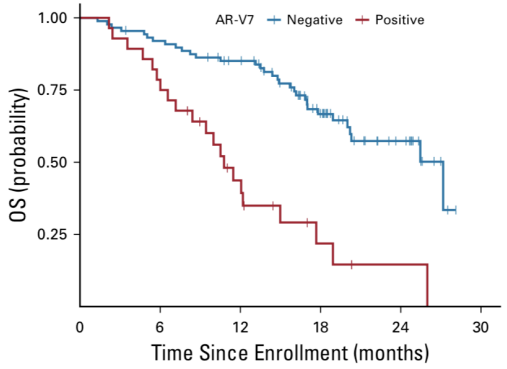
Robinson et al. Cell 2015. Abida et al. PNAS 2019

# Clinical utility of genomic profiling in mCRPC

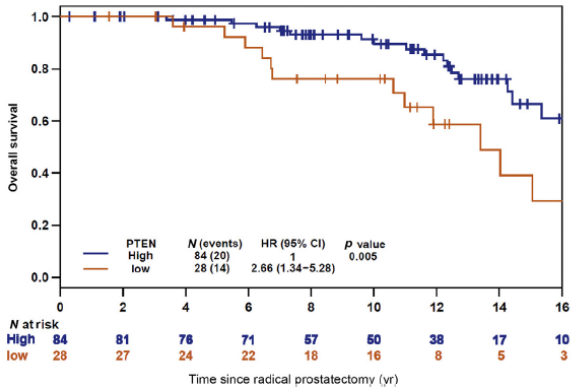
AR aberrations, loss of tumor suppressors (TP53, RB1, PTEN), DNA repair alterations…
all **associated with adverse prognosis**



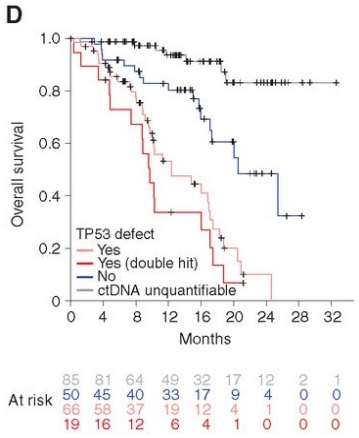

**AR aberrations**



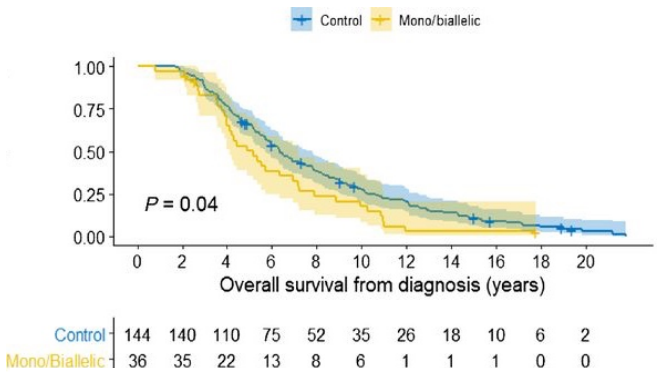

**AR-V7 splice variant**



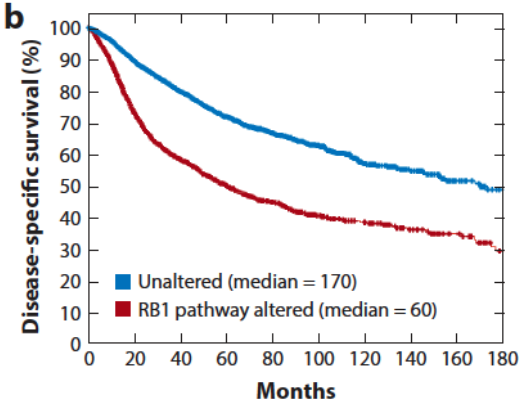

**PTEN loss**




**TP53 mutations**

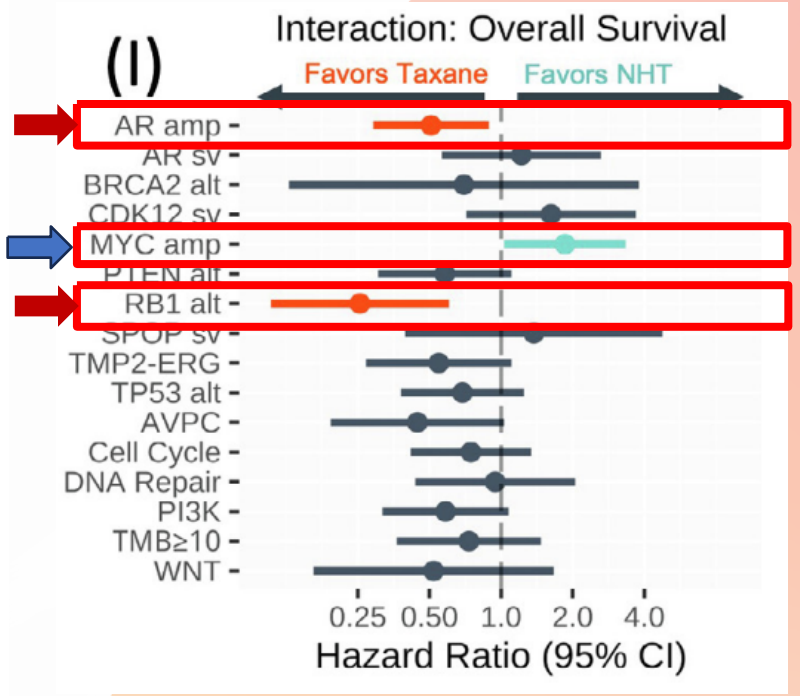



**CDK12 mut**




**RB1 loss**

Some alterations **could be associated** with **differential benefit** from ARSi / taxanes in mCRPC

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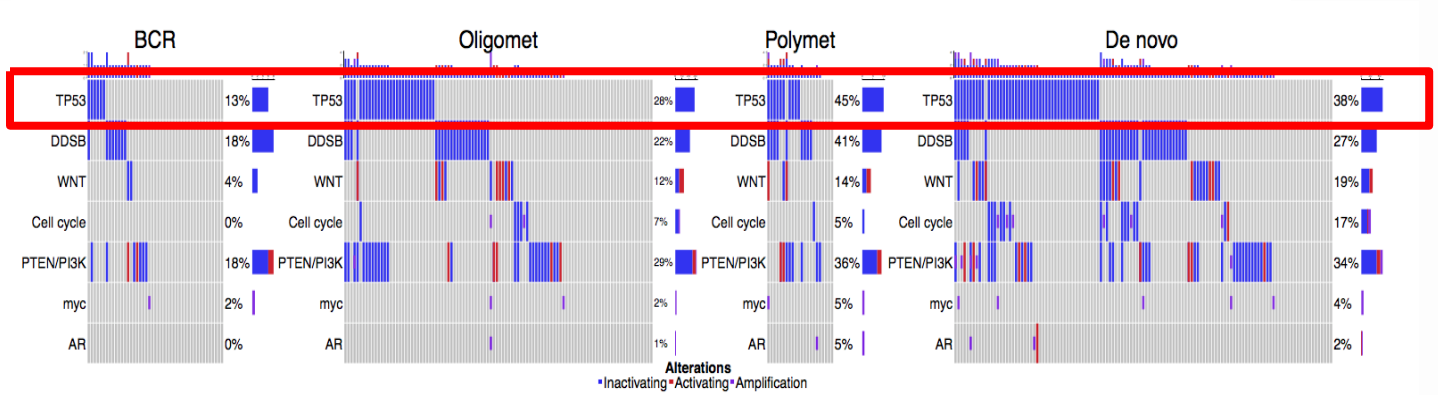
Romanel et al Sci Trans Med, 2015; Annala et al Cancer Discovery, 2019; Armstrong et al JCO 2019; Ferraldeschi, Eur Urol, 2015; Rescigno et al Clin Cancer Res 2021, Graf et al. Eur Urol 2021

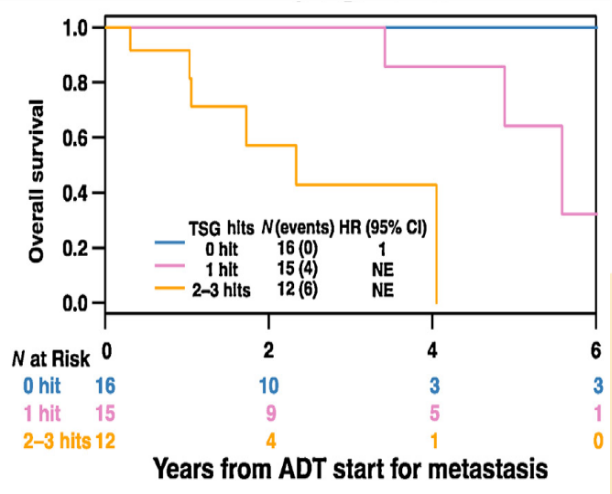
# Genomic alterations and prognosis in mHSPC

## Loss of function of tumor supressors is associated with adverse prognosis

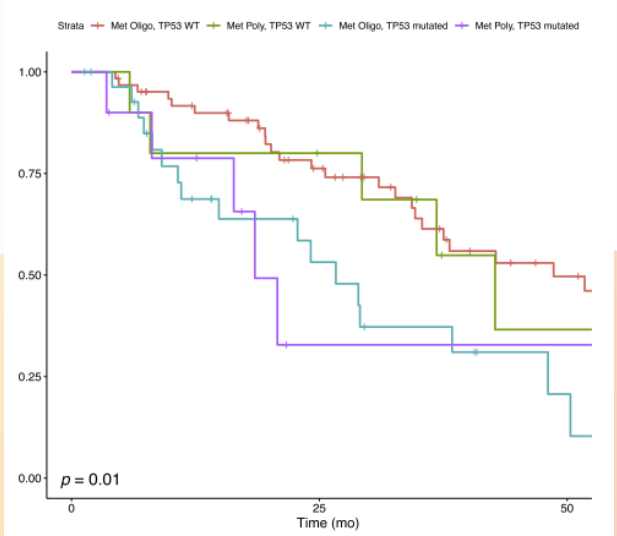
*Increased TP53 alterations with higher volume of metastatic disease*




*Mutations in the TP53, RB1 and PTEN suppressor genes associated with adverse outcome*

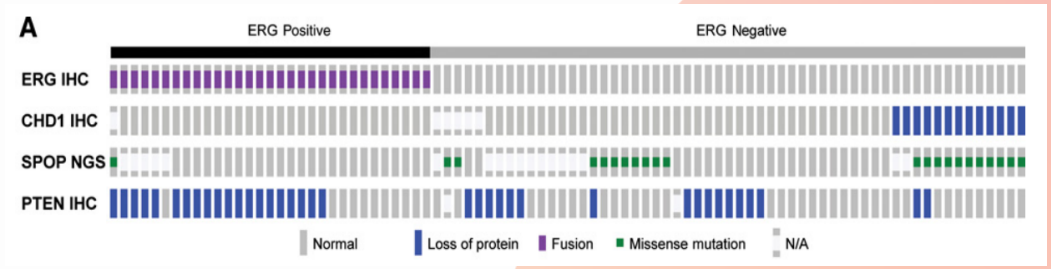



*TP53 mutations associated with adverse prognosis in both oligo- and polymetastatic disease*

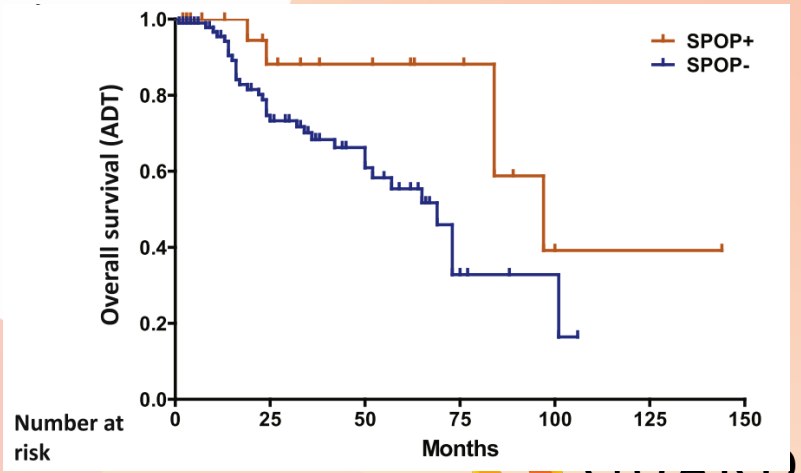



## SPOP mutations associated with favorable prognosis

Most frequently mutated gene in prostate cancer
Mutations in the MATH domain




*SPOP mutation associated with higher response rate and time on abiraterone in mCRPC*

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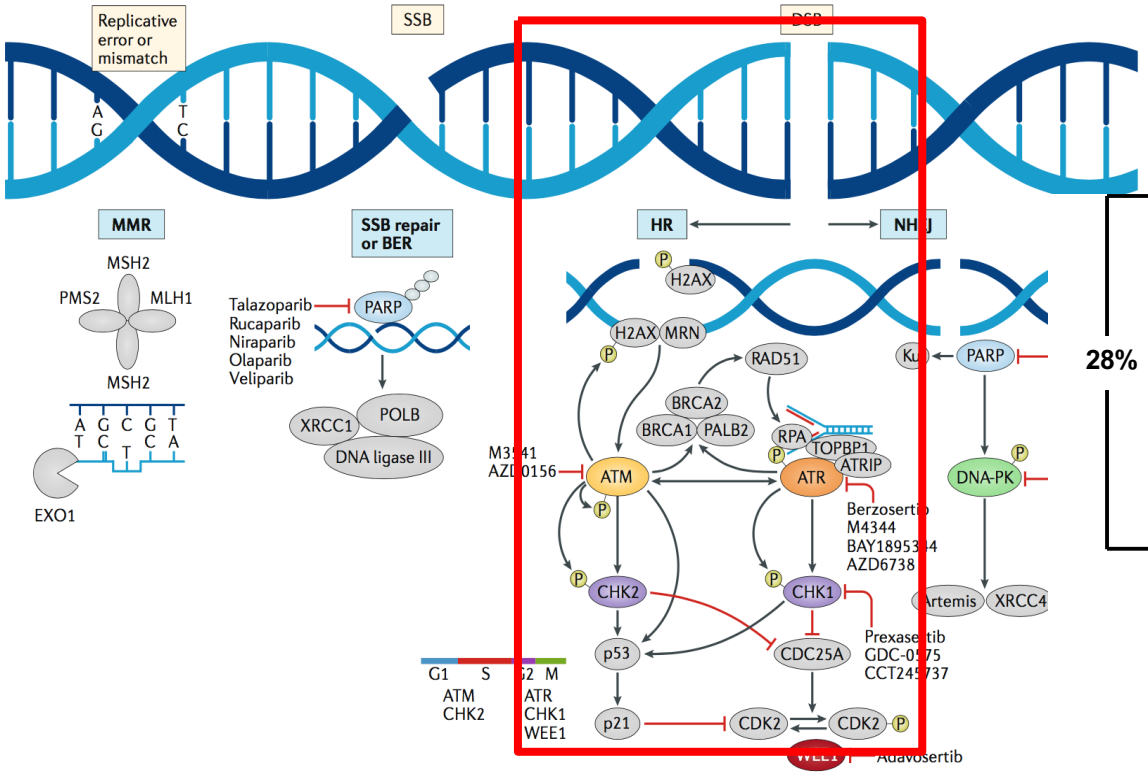
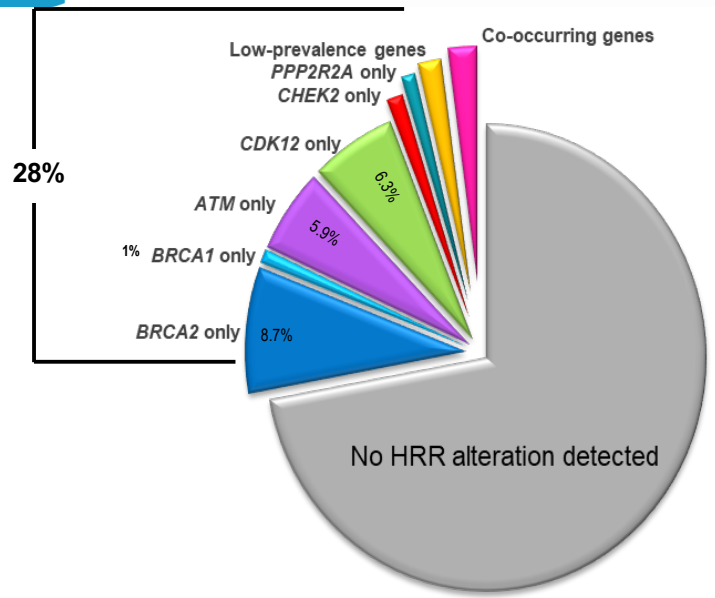
Abida et. PNAS 2019;166(23):11428-11436. Hamid et al. Eur Urol 2019;76(1):89-97. Deek et al. Eur Urol 2021;80(5)632-640.

# DNA repair alterations in advanced prostate cancer




25-30% of patients with mCRPC harbor HRR alterations




BRCA genes are the most frequently mutated

| | mCRPC | mHSPC |
|---|---|---|
| ATM | 8.4% | 7.9% |
| BRCA1 | 2.6% | 1.1% |
| BRCA2 | 10.7% | 11.3% |
| BRIP1 | 1.9% | 1.6% |
| CDK12 | 2.1% | 2% |
| CHEK2 | 1.5% | 3% |
| FANCA | 5.2% | 3.6% |
| HDAC | 2.9% | 2.9% |
| PALB2 | 0.5% | 1.3% |
| RAD51B | 0.4% | 1.1% |
| RAD54L | 0.7% | 1.3% |

**Mismatch Repair**

**Base Excision Repair (BER)**

**Non-homologous end-joining**

**Homologous recombination (HR)**

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Yap et al. Nat Rev Oncol 2019. De Bono et al. N Eng J Med 2020.
Olmos et al Ann Oncol 2024. Olmos et al Ann Oncol 2025.

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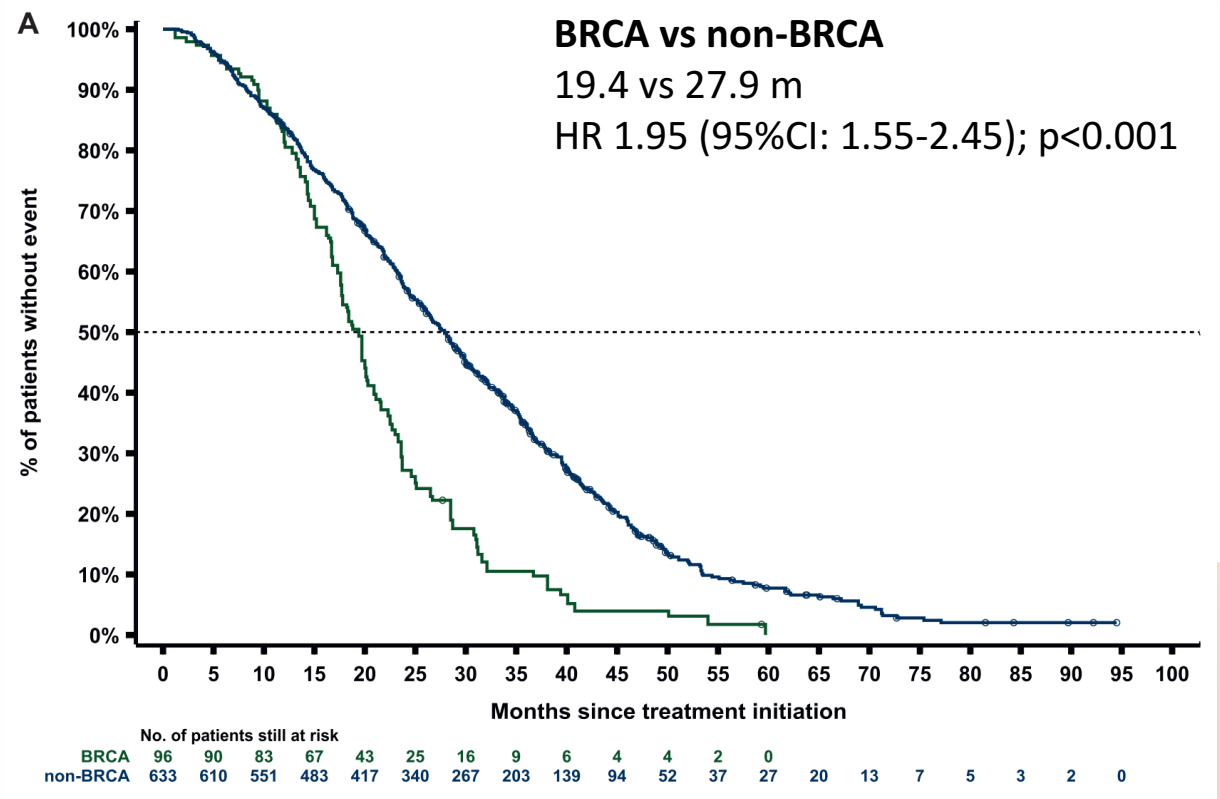
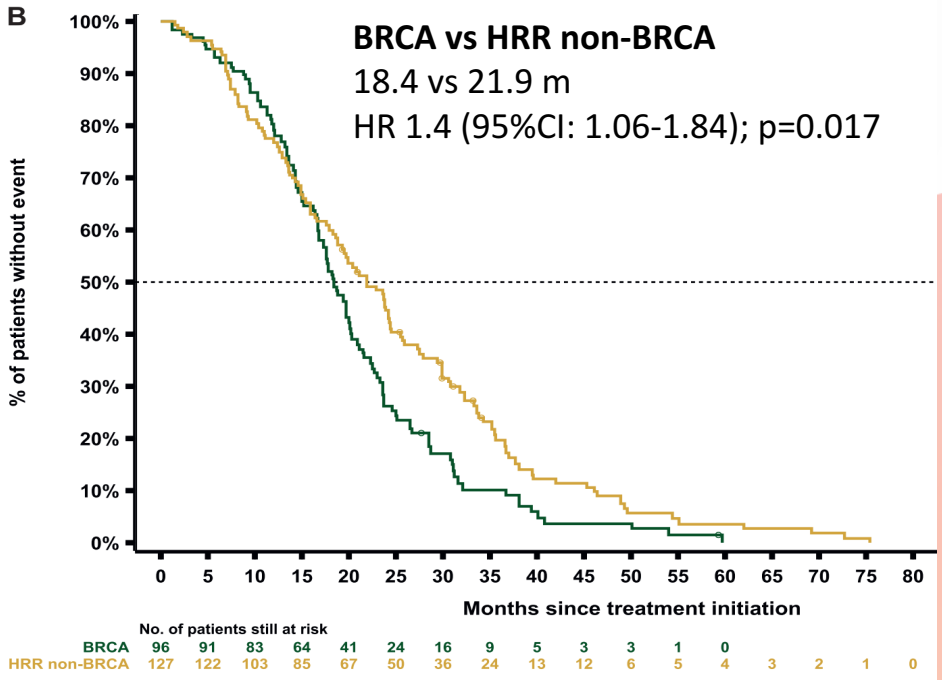
# HRR alterations and prognosis

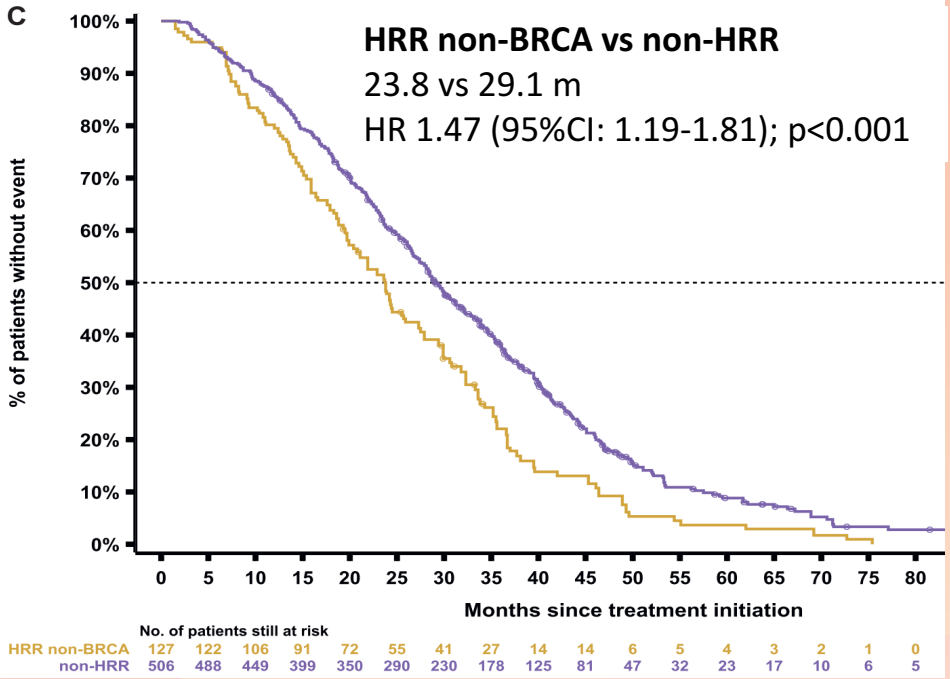
## The CAPTURE study – Cohort 1 (mCRPC)

N=729. mCRPC undergoing 1st L therapy.
1L ARSi (64.6%)
1L Taxanes (35.4%)

| BRCA | Non-BRCA HRR | Non-HRR |
|---|---|---|
| 13.2% | 17.4% | 69.4% |






Olmos et al. Ann Oncol 2024

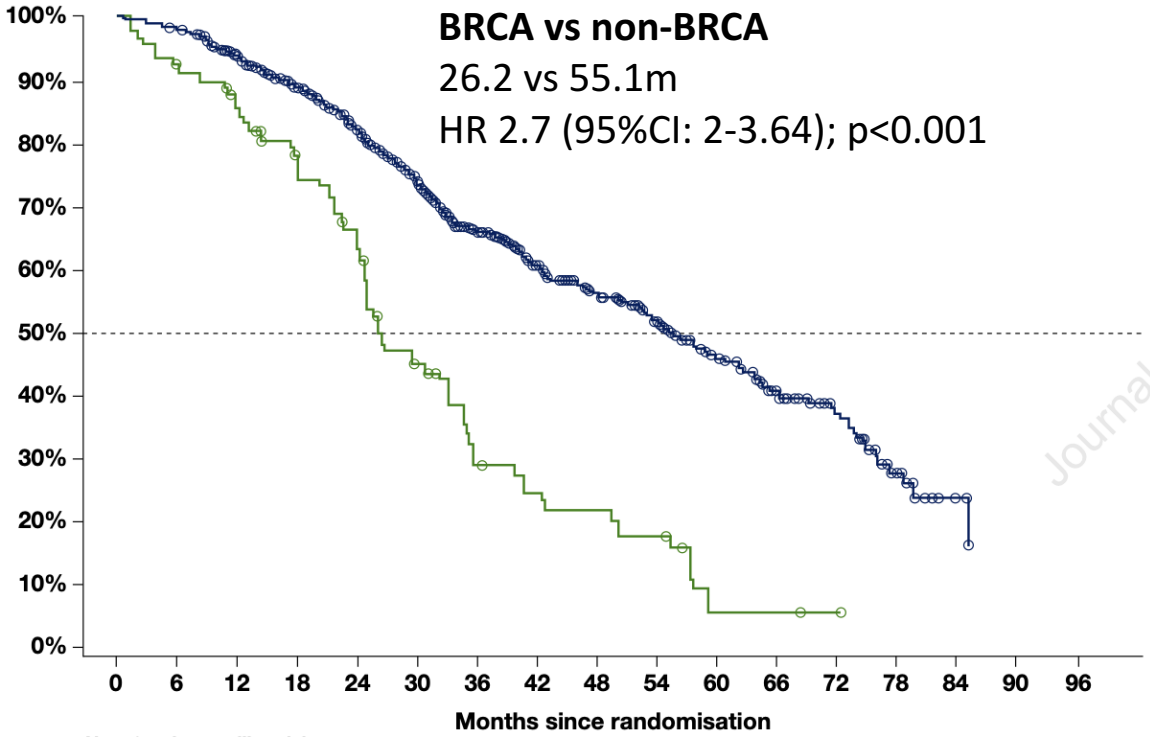
# HRR alterations and prognosis

## The CAPTURE study – Cohort 2 (mHSPC)

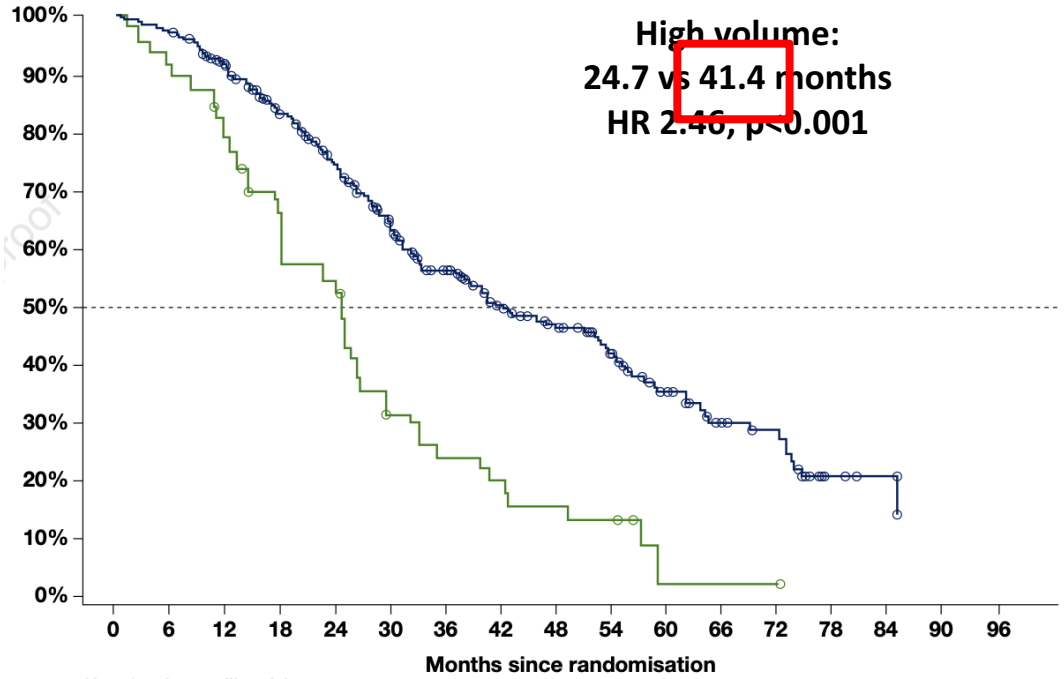
### The CAPTURE study

N=556. mHSPC patients. Hi Vol 55%.
ADT alone (13%), ADT + ARSi (45%),
ADT + Docetaxel (30%),
ADT + ARSi + Docetaxel (11%)

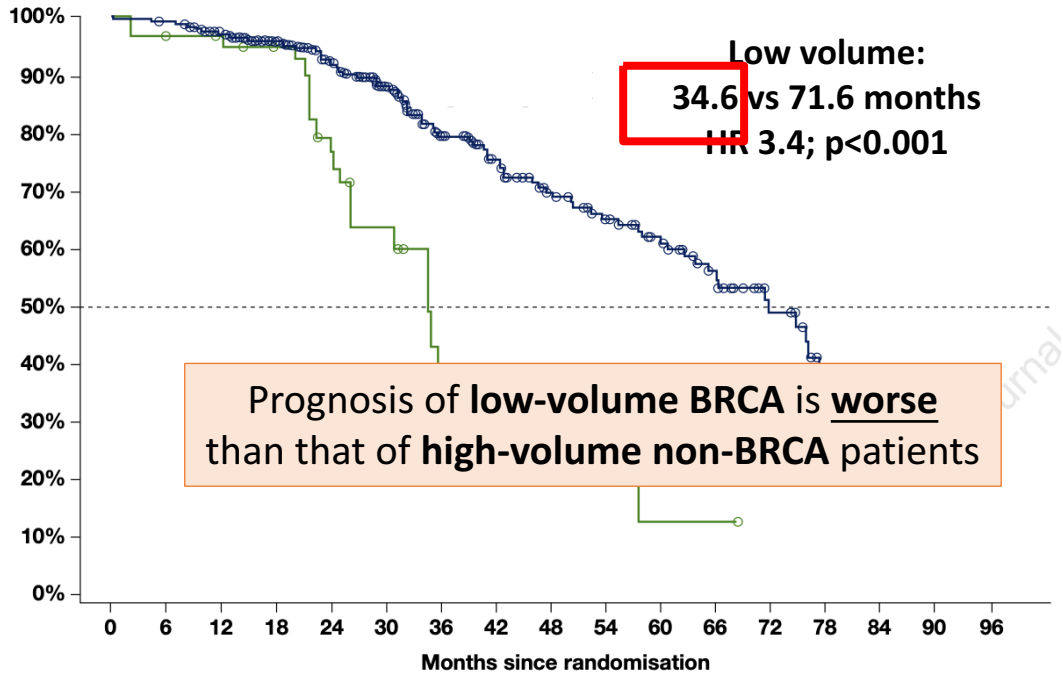
| | All pts | Hi Vol | Low Vol |
|---|---|---|---|
| **BRCA** | 13.3% | 13.7% | 12.8% |
| **HRR** | 28.4% | 28.1% | 28.8% |




**BRCA vs non-BRCA**
26.2 vs 55.1m
HR 2.7 (95%CI: 2-3.64); p<0.001




**High volume:**
**24.7 vs 41.4 months**
**HR 2.46; p<0.001**



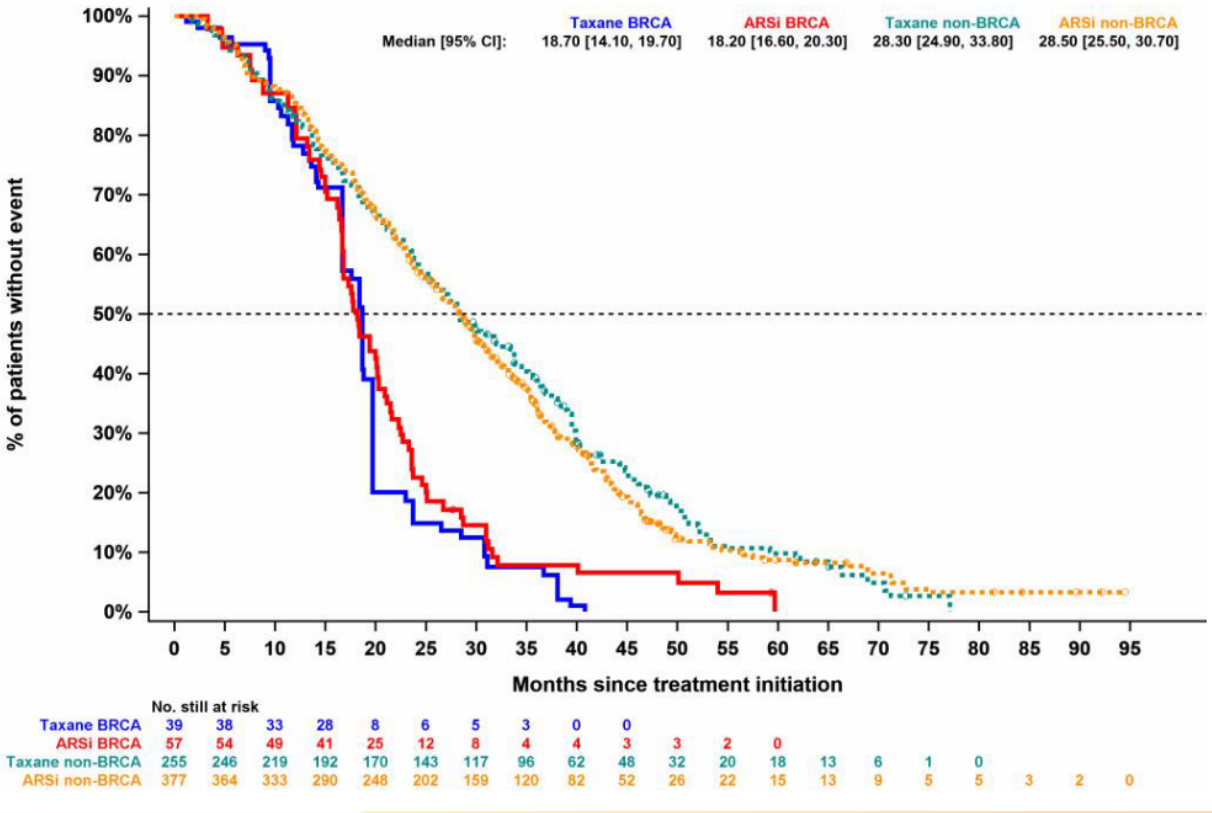

**Low volume:**
**34.6 vs 71.6 months**
**HR 3.4; p<0.001**

Prognosis of **low-volume BRCA** is **worse** than that of **high-volume non-BRCA** patients

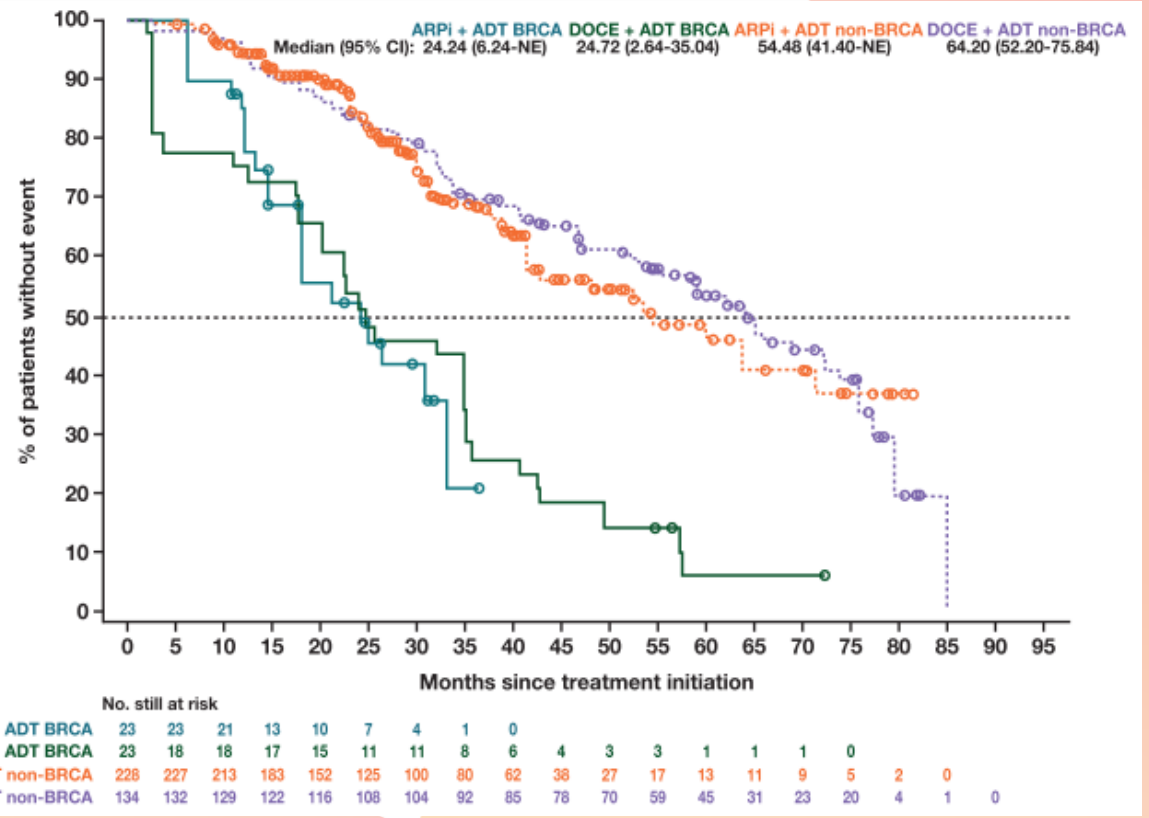
Olmos et al. Ann Oncol 2025

# Conventional therapy is ineffective in BRCA mutants

mCRPC: no OS difference 1st line taxane vs ARSi




mHSPC: no OS difference ADT+ARSi vs ADT+Taxane

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Olmos et al. Ann Oncol 2024; Olmos et al. Ann Oncol 2025

# Non-BRCA HRR is a heterogeneous subgroup

Impact of **individual non-BRCA HRR alterations** on outcome in patients treated with ARSIs or taxanes as first-line therapy for mCRPC (CAPTURE Cohort 1)

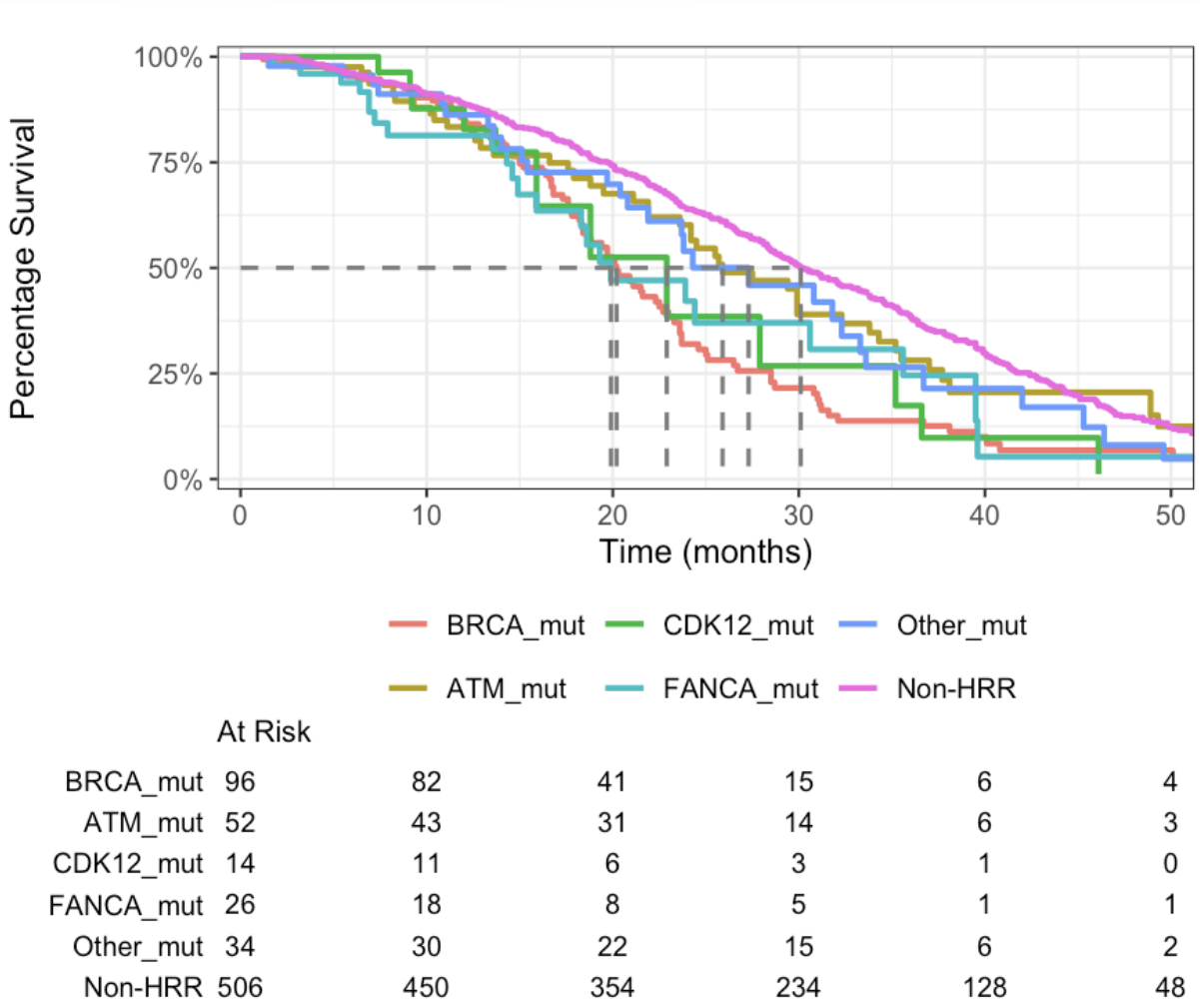



**TABLE 1. PATIENT CHARACTERISTICS**

| | | Non-HRR (N=506) | BRCA (N=96) | ATM (N=52) | CDK12 (N=14) | FANCA (N=26) | Other (N=34) |
|---|---|---|---|---|---|---|---|
| Age (yr) | <65 | 114 (23%) | 16 (17%) | 18 (35%) | 5 (36%) | 7 (27%) | 5 (15%) |
| | 65-75 | 201 (40%) | 41 (43%) | 20 (39%) | 2 (14%) | 11 (42%) | 14 (41%) |
| | >=75 | 191 (38%) | 39 (41%) | 14 (27%) | 7 (50%) | 8 (31%) | 15 (44%) |
| Stage IV at diagnosis | | 244 (48%) | 41 (43%) | 22 (42%) | 5 (36%) | 18 (69%) | 13 (38%) |
| Albumin < 4 g/dL | | 181 (36%) | 46 (48%) | 13 (25%) | 5 (36%) | 12 (46%) | 14 (41%) |
| ALP ≥ ULN | | 237 (47%) | 58 (60%) | 35 (67%) | 6 (43%) | 15 (58%) | 13 (38%) |
| Hb ≤ 12.5 | | 185 (37%) | 40 (42%) | 16 (31%) | 6 (43%) | 10 (39%) | 11 (32%) |
| LDH ≥ ULN | | 225 (45%) | 46 (48%) | 31 (60%) | 7 (50%) | 14 (54%) | 17 (50%) |
| PSA > 50 ng/dL | | 180 (36%) | 41 (43%) | 23 (44%) | 8 (57%) | 13 (50%) | 11 (32%) |
| ECOG | >=1 | 268 (53%) | 52 (54%) | 28 (54%) | 8 (57%) | 14 (54%) | 16 (47%) |
| | 0 | 238 (47%) | 44 (46%) | 24 (46%) | 6 (43%) | 12 (46%) | 18 (53%) |
| Gleason Score >= 8 | | 318 (63%) | 63 (66%) | 33 (64%) | 11 (79%) | 22 (85%) | 15 (44%) |
| Bone metastases > 10 | | 86 (17%) | 18 (19%) | 8 (15%) | 3 (21%) | 9 (35%) | 4 (12%) |
| Visceral metastases | | 70 (14%) | 9 (9%) | 3 (6%) | 5 (36%) | 4 (15%) | 6 (18%) |
| Time to mCRPC ≥ median | | 268 (53%) | 42 (44%) | 20 (39%) | 8 (57%) | 8 (31%) | 20 (59%) |
| 1st line therapy | Taxanes | 200 (40%) | 34 (35%) | 25 (48%) | 5 (36%) | 13 (50%) | 12 (35%) |
| | ARSIs | 306 (60%) | 62 (65%) | 28 (52%) | 9 (64%) | 13 (50%) | 22 (65%) |

**TABLE 2. IMPACT OF NON-BRCA MUTATION STATUS ON OS AND RPFS (MULTIVARIABLE MODEL)**

| | Median (95%CI) | HR (95%CI) vs BRCA | HR (95%CI) vs non-HRR |
|---|---|---|---|
| **OVERALL SURVIVAL** | | | |
| Non-HRR | 29.6 m (27.9-32.1) | - | - |
| BRCA | 18.4 m (16.7-20.2) | - | - |
| ATM | 24.2 m (17.9-29.4) | 0.65 (0.43-0.97); p=0.035 | 1.25 (0.9-1.7); p=0.17 |
| CDK12 | 17.4 m (9.2-35.2) | 1.38 (0.68-2.8); p=0.37 | 2.1 (1.2-3.6); p=0.015 |
| FANCA | 17.1 m (7.9-23.9) | 0.97 (0.58-1.62); p=0.91 | 1.9 (1.2-2.9); p=0.003 |
| Other | 24 m (15-33) | 0.66 (0.4-1); p=0.07 | 1.3 (0.9-1.9); p=0.139 |
| **RADIOGRAPHIC PROGRESSION-FREE SURVIVAL** | | | |
| Non-HRR | 11 m (10.1-12) | - | - |
| BRCA | 7.1 m (6.2-8.5) | - | - |
| ATM | 7.7 m (6.4-10.3) | 0.76 (0.5-1.2); p=0.194 | 1.37 (0.98-1.9); p=0.07 |
| CDK12 | 9.2 (3.1-12.2) | 1.33 (0.6-2.9); p=0.48 | 1.54 (0.8-2.9); p=0.167 |
| FANCA | 7.1 (3.6-11) | 1.1 (0.64-1.8); p=0.77 | 1.9 (1.2-3); p=0.004 |
| Other | 11 (7.3-15.2) | 0.81 (0.5-1.3); p=0.386 | 1.4 (0.97-2.1); p=0.07 |

Lorente et al. ESMO 2024

# Who to test? Test everybody!!

**Testing has prognostic implications (outcome)**

**Testing has implications for the family risk of cancer**

**Testing has predictive implications (treatment selection)**

## Do PARPi – NHA combinations eliminate the need for testing?

## Who is the ideal candidate for treatment?

**The ideal candidate is the one that reflects the clinical trial population**

**expected benefit is greater than anticipated toxicity (disease burden)**

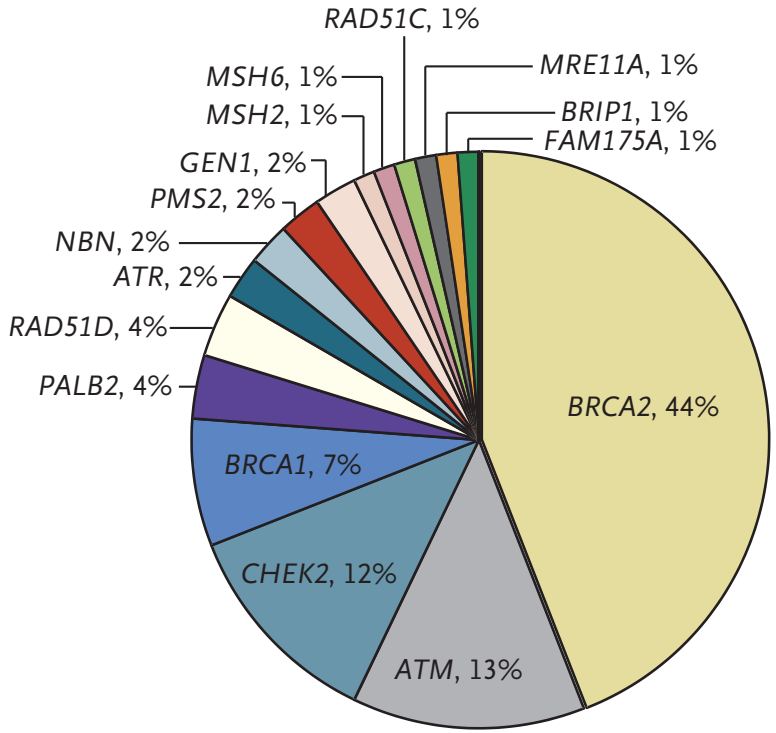
*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

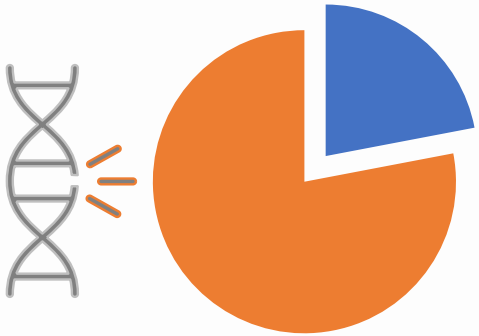
## What, where and when to test?

# Germline BRCA alterations

**692 men** with metastatic prostate cancer unselected for family history of cancer or age at diagnosis were assessed for mutations in 20 DNA repair genes

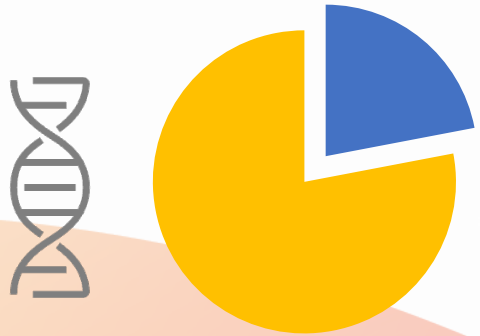
84/692 (11,8%) with germline alterations



Among 72 men with germline DNA-repair mutations

**22% had a family history of PC**



Among 537 men without germline DNA-repair mutations

**22% had a family history of PC**

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Pritchard et al. N Eng J Med 2016

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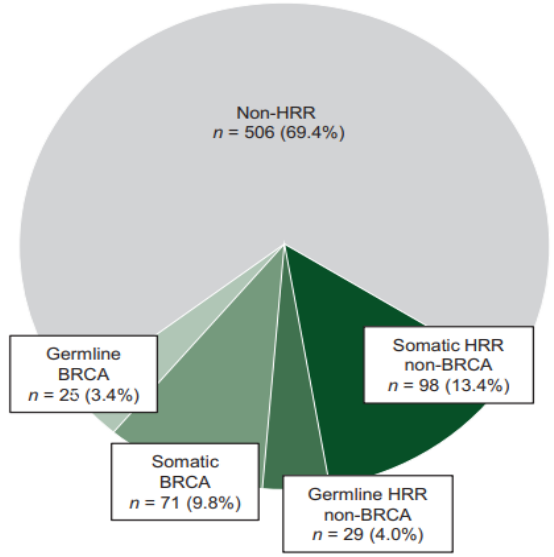
# Germline alterations vary across populations

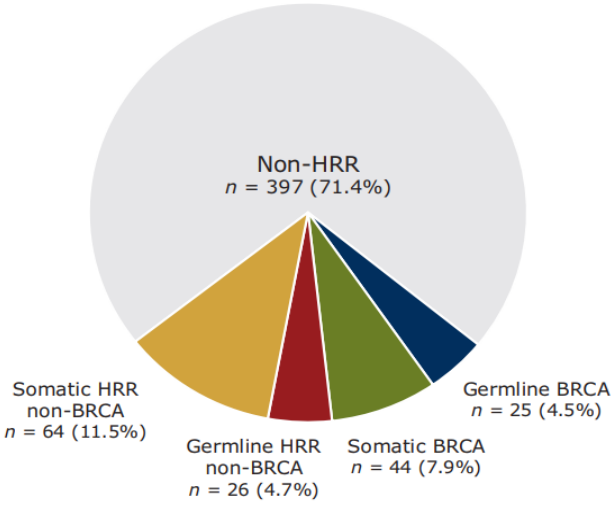
| Gene | European Ancestry N=692 | Spanish N=419 | African-American N=2669 | Chinese N=1836 | LATAM N=379 |
|---|---|---|---|---|---|
| ATM | 1.6 | 1.9 | 0.97 | 1.04 | 0.8 |
| ATR | 0.3 | 0 | - | 0.29 | 0 |
| BRCA1 | 0.9 | 0.9 | 1.41 | 0.21 | 0.3 |
| BRCA2 | 5.3 | 3.3 | 2.8 | 4.3 | **0.8** |
| BRIP1 | 0.14 | 0 | 0 | 0.06 | 0.5 |
| CHEK2 | 1.4 | 0.5 | 0.48 | 0.17 | 1 |
| MLH1 | 0 | 0 | 0 | - | - |
| MSH2 | 0.14 | 0.2 | 0 | 0.45 | - |
| MSH6 | 0.14 | 0 | 0 | 0.17 | - |
| NBN | 0.3 | 0 | 0 | 0.06 | 0 |
| PALB2 | 0.4 | 0 | 1.1 | 0.67 | 0 |
| PMS2 | 0.3 | 0 | 0.47 | 0.06 | - |
| RAD51C | 0.14 | 0 | 0.68 | 0.06 | 0 |
| RAD51D | 0.4 | 0 | 0 | 0.25 | 0 |

**Metastatic prostate cancer (CAPTURE, spanish population)**

| mCRPC | |
|---|---|
| BRCAg | 3.4% |
| Non-BRCAg | 4% |




| mHSPC | |
|---|---|
| BRCAg | 4.5% |
| Non-BRCAg | 4.7% |

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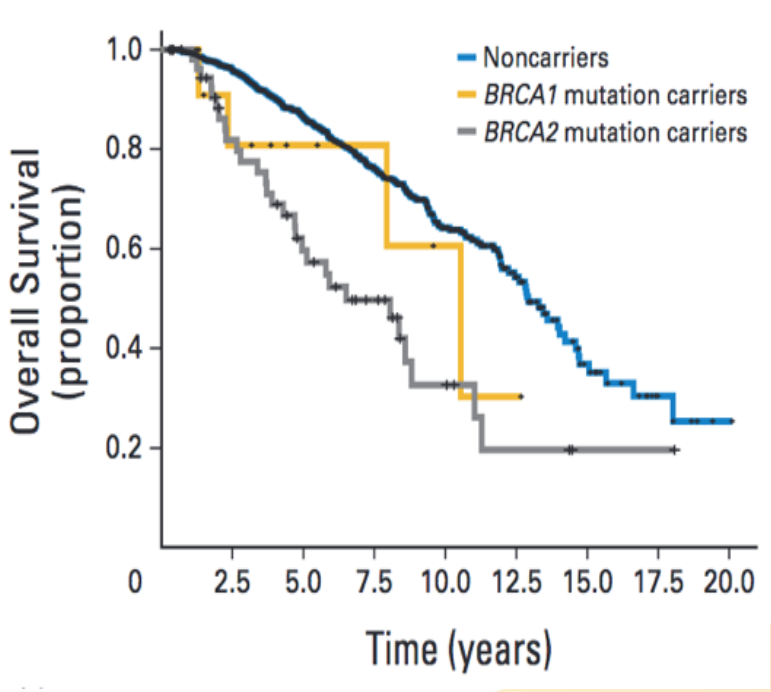
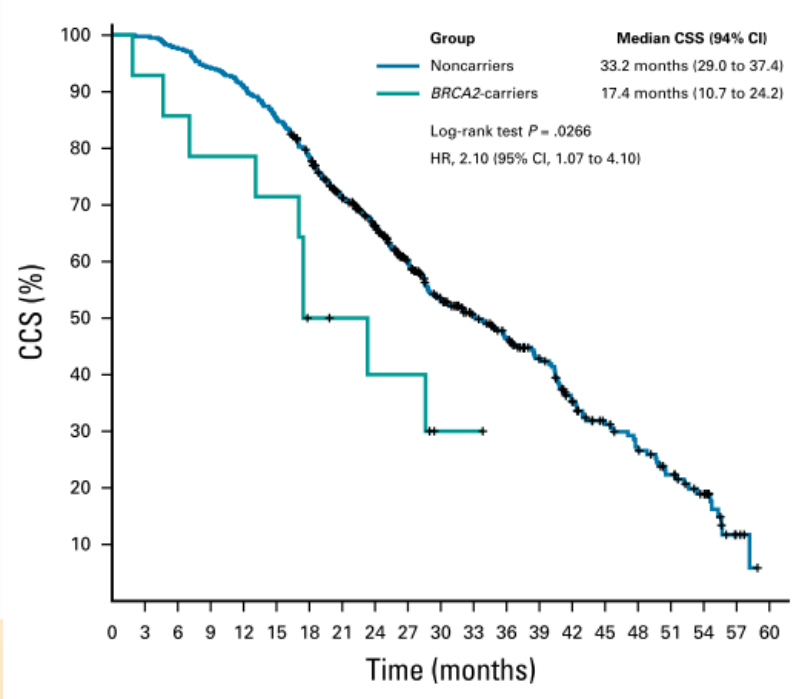
Pritchard et al. N Eng J Med 2016; Castro et al J Clin Oncol 2019, Sartor et al Oncotarget 2022, Zhu et al JNCCN 2022, Manneh et al JCO Precis Oncol 2024, Olmos et al Ann Oncol 2024, Olmos et al Ann Oncol 2025

# Germline BRCA mutations are associated with adverse prognosis

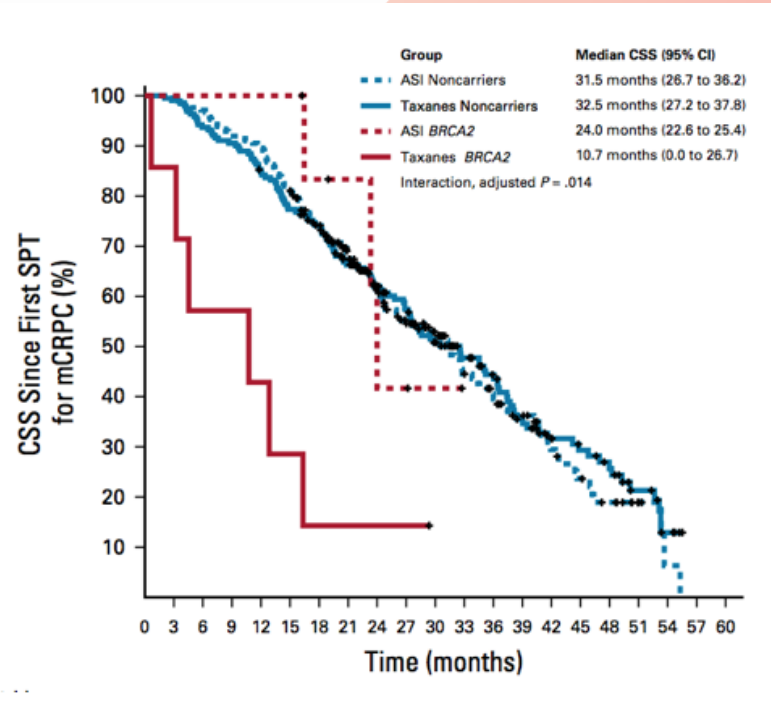
***Localized prostate cancers***




***mCRPC***




***mCRPC: worse outcome in pts treated with taxanes***






Castro et al. J Clin Oncol 2013. Castro et al. J Clin Oncol 2019.

# Who to test? Test everybody!!

**Testing has prognostic implications (outcome)**
**Testing has implications for the family risk of cancer**
**Testing has predictive implications (treatment selection)**

## Do PARPi – NHA combinations eliminate the need for testing?

## Who is the ideal candidate for treatment?

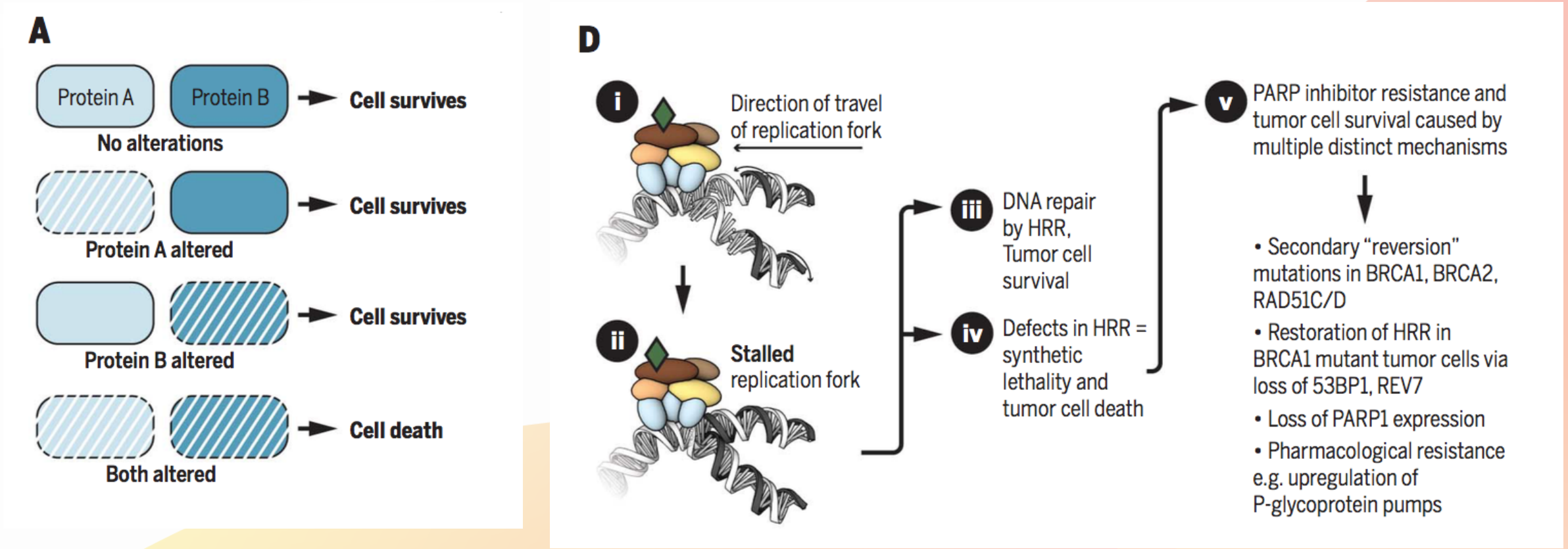
The ideal candidate is the one that reflects the clinical trial population
expected benefit is greater than anticipated toxicity (disease burden)

*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

## What, where and when to test?

# Patients with BRCA/HRR alterations are sensitive to PARPi

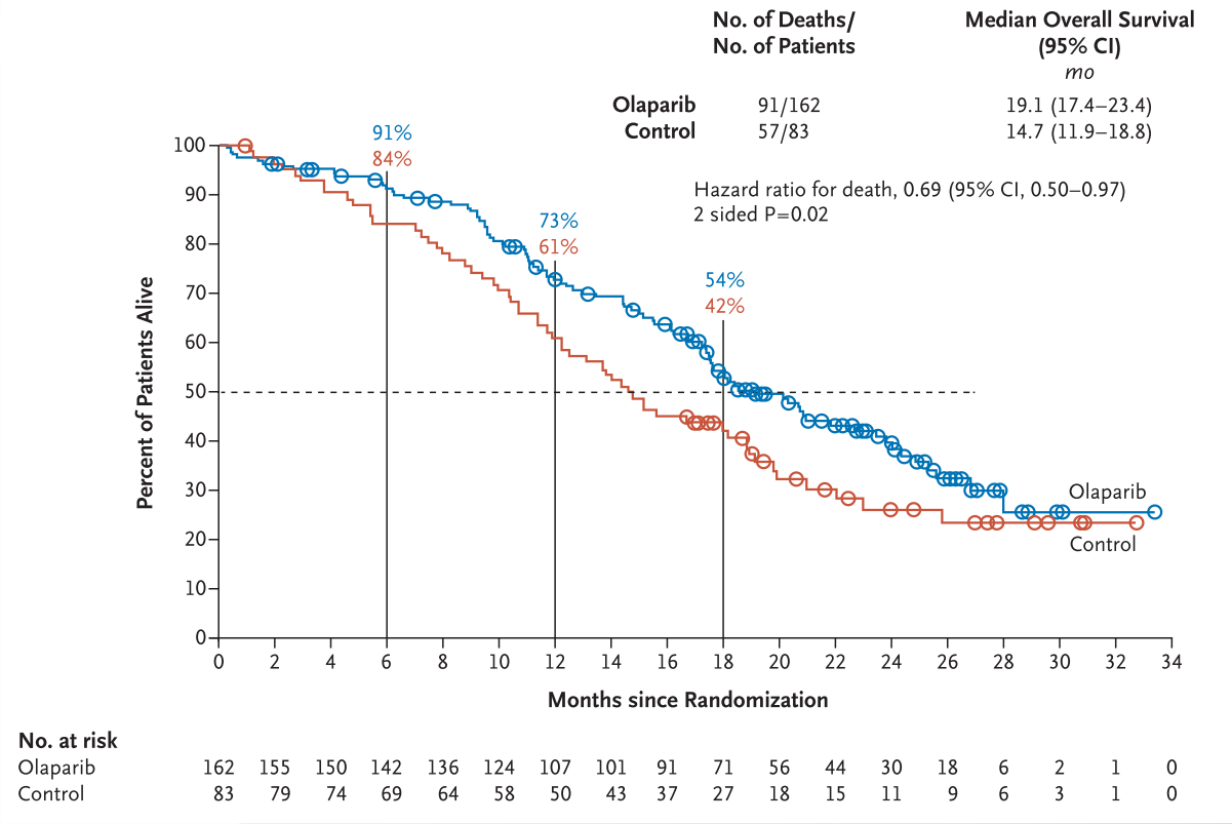
*Synthetic letality*



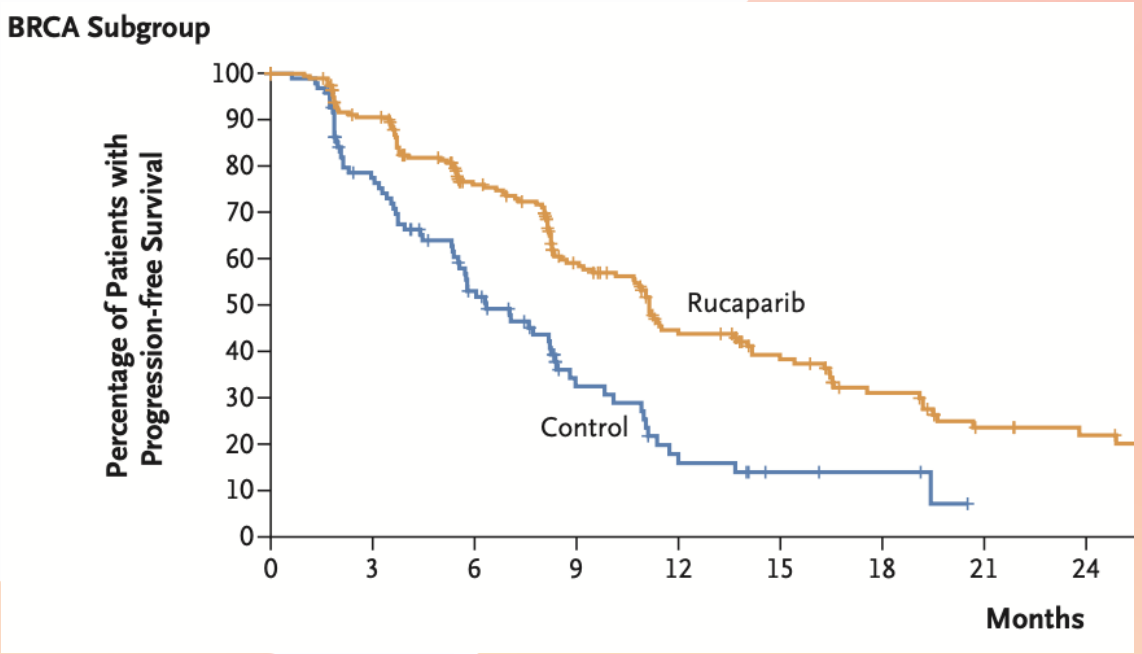

Lord & Ashworth. Science 2017

# BRCA alterations are predictive biomarkers of PARPi efficacy

**PROFOUND (randomized phase III):**
**Olaparib** improves OS vs 2nd hormonal agent in BRCA/ATM pts




**TRITON2 (randomized phase III):**
**Rucaparib** improves rPFS vs 2nd hormonal agent or Docetaxel in BRCA mutant pts

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Hussain et al. N Eng J Med 2020; Fizazi et al. N Eng J Med 2023

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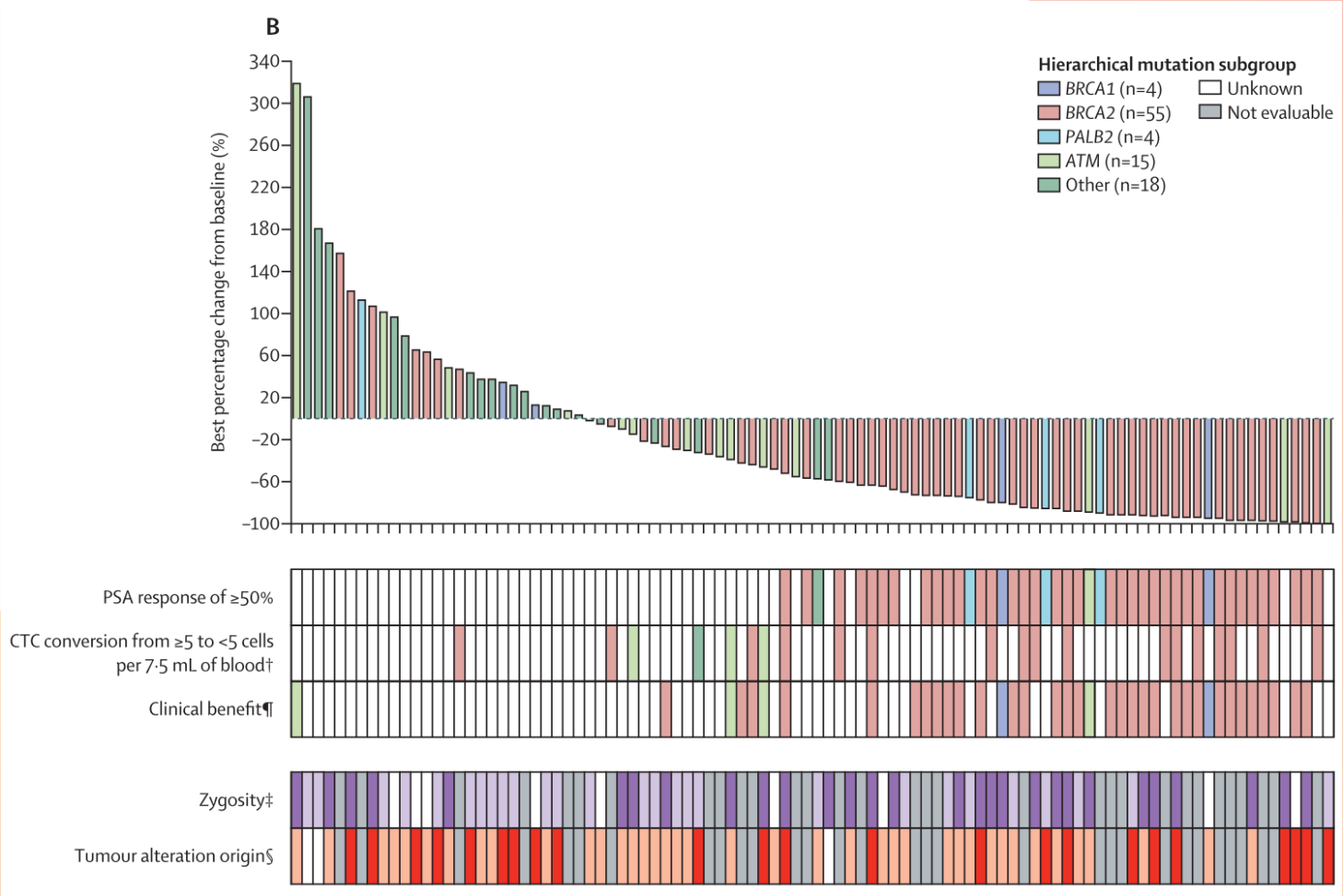
# BRCA alterations are predictive biomarkers of PARPi efficacy

**Antitumor activity in BRCA mutated patients of PARPi in monotherapy**

| | PSA-50 RR | RECIST | rPFS |
|---|---|---|---|
| Olaparib (PROFOUND) | 61.7% | 43.9% | 9.8 m |
| Rucaparib (TRITON3) | 55% | 45% | 11.2 m |
| Talazoparib (TALAPRO-1) | 66% | 46% | 11.2 m |
| Niraparib (GALAHAD) | 43% | 34% | 8.1 m |

TALAPRO-1 trial: Talazoparib monotherapy 1 mg c/24h

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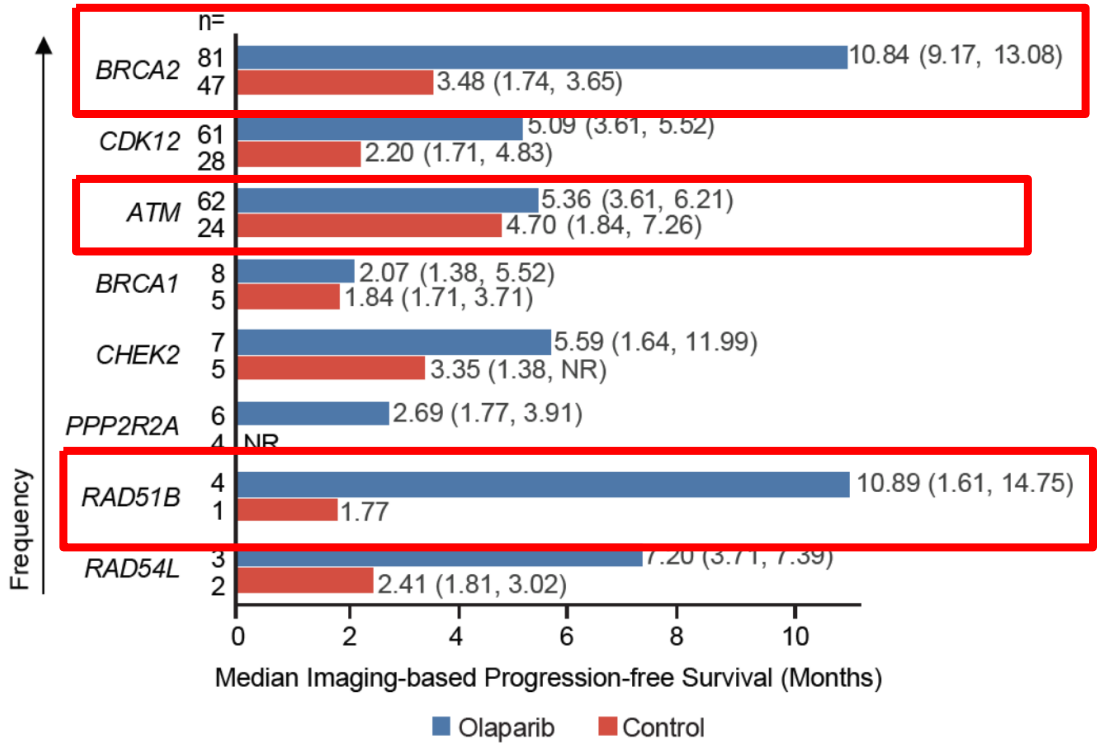
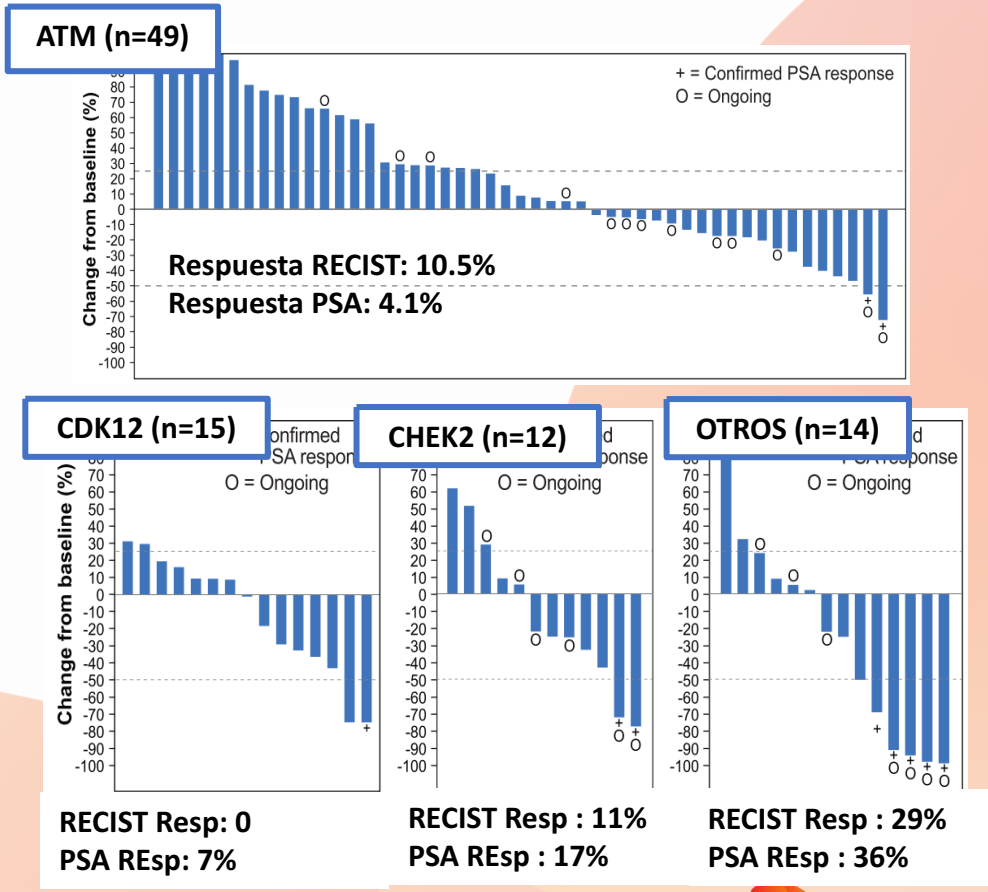
De Bono et al. N Eng J Med 2020; Fizazi et al. N Eng J Med 2023; de Bono et al Lancet Oncol 2021; Smith et al Lancet Oncol 2022

# Non-HRR is heterogeneous

***PROFOUND: OS with different genomic alterations***




***Antitumor activity of Rucaparib in the non-BRCA cohort of the TRITON2 trial***

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Hussain et al. N Eng J Med 2020. Abida et al. Clin Cancer Res 2020.

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# Who to test? Test everybody!!

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**Testing has predictive implications (treatment selection)**

# Do PARPi – NHA combinations eliminate the need for testing?

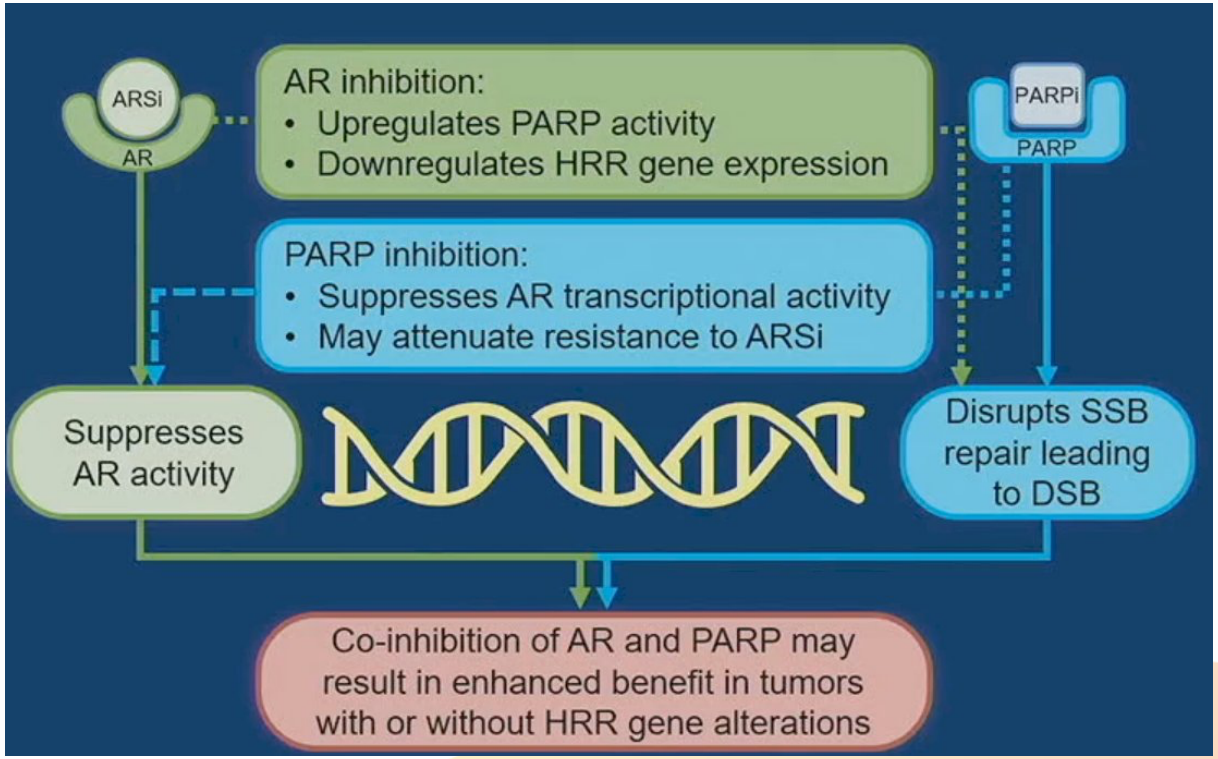
## Who is the ideal candidate for treatment?

**The ideal candidate is the one that reflects the clinical trial population**
**expected benefit is greater than anticipated toxicity (disease burden)**

*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

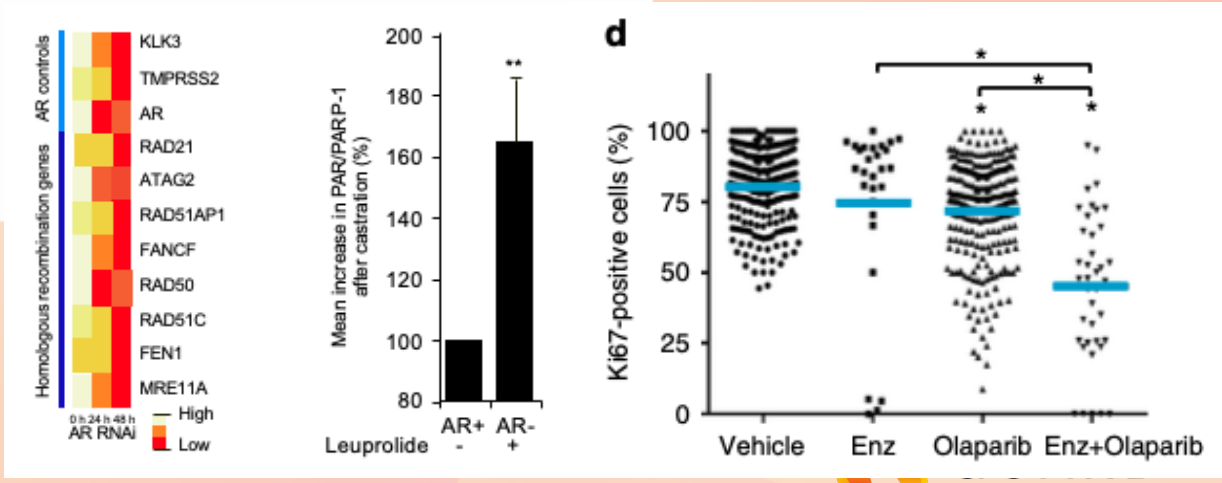
## What, where and when to test?

# Do PARPi + ARSi doublets abrogate the need for testing?




- **ADT can inhibit homologous recombination**
  Upregulation of DNA repair pathways dependent on PARP with androgen deprivation

- **PARP-1 activity is critical for chromatin occupation by the androgen receptor**
  *In vivo PARP* inhibition is sufficient to supress AR activity








Schiewer et al. Cancer Discov 2012; Asim et al. Nature Comm 2017;8:1.

# What is the evidence?

## PROPEL

*rPFS in all comers*
*Retrospective HRR assessment*

**Elegibility**
Metastatic CRPC
No prior therapy for mCRPC
ADT + Docetaxel in mHSPC allowed

- Abiraterone 1000 mg/24h + Olaparib 300 mg/12h (n=399)
- Abiraterone 1000 mg/24h + Placebo/12h (n=397)

Primary endpoint:
Investigator-assessed ibPFS

## MAGNITUDE

*rPFS in BM+ and BM-*
*Prospective HRR assessment*

**Elegibility:**
First-line mCRPC
ECOG PS 0-1
BPI-SF worst pain ≤ 3

- **HRR BM+**
  - Abi 1000 mg/24h Nira 200 mg/12h (n=162)
  - Abi 1000 mg/24h Placebo/12h (n=83)
- **HRR BM-**
  - Abi 1000 mg/24h Nira 200 mg/12h (n=162)
  - Abi 1000 mg/24h Placebo/12h (n=83)

Primary endpoint:
rPFS by central review

## TALAPRO-2

*rPFS in all comers*
*Prospective HRR assessment*

**Elegibility**
mCRPC
First line
ECOG PS 0-1

- Talzaoparib 0,5 mg + Enzalutamide 160 mg/24h (n=402)
- Placebo + Enzalutamide 160 mg/24h (n=403)

**Primary endpoint:**
rPFS (independent evaluation)

**Prospective genomic assessment:**
BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA RAD51C, NBN, MLH1, MRE11A, CDK12



Clarke et al. N Eng J Med Evid 2022; Chi et al. J Clin Oncol 2023; Agarwal Lancet Oncol 2023

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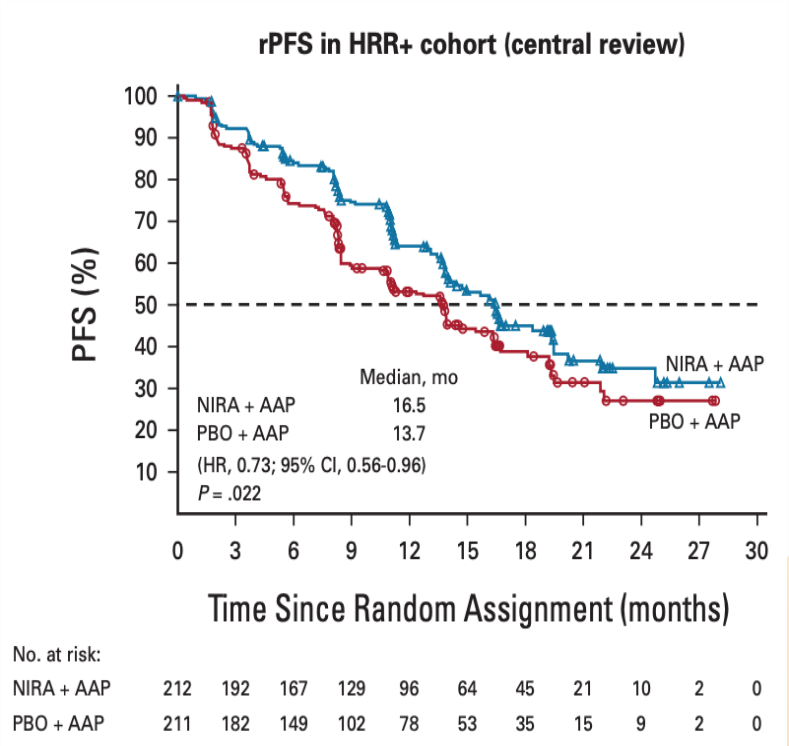
# 3 positive trials (primary endpoint)

## MAGNITUDE

***All HRRm: rPFS***

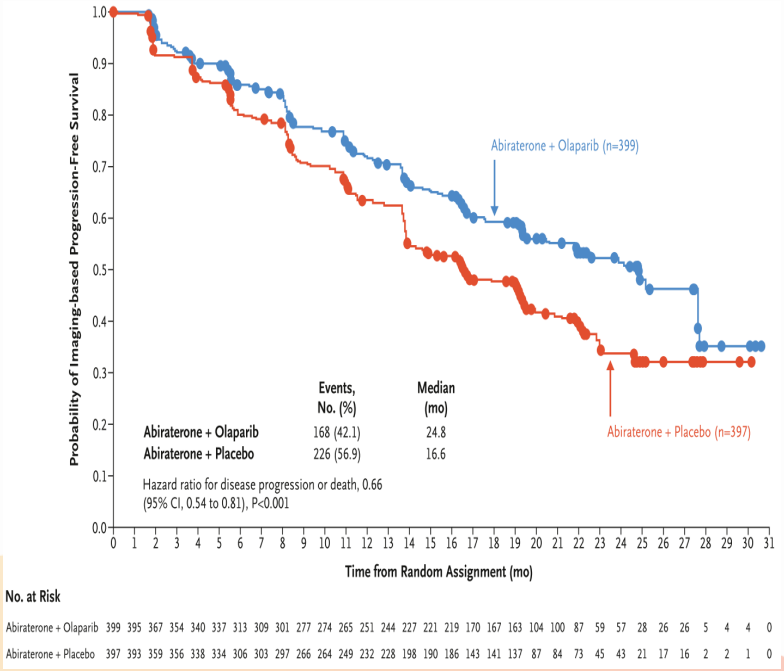
***HR 0.73 (95%CI: 0.56-0.96)***




## PROPEL

***All comers: rPFS***

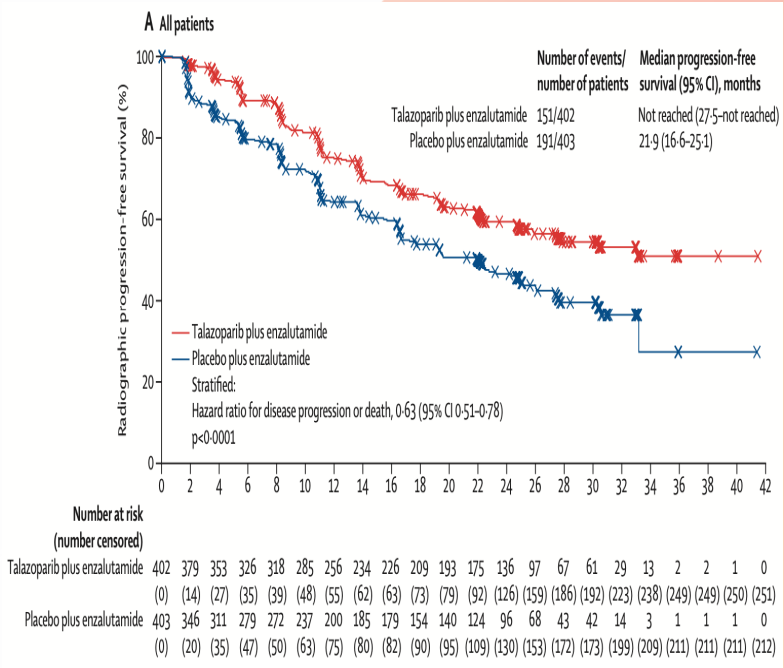
***HR 0.73 (95%CI: 0.56-0.96)***




## TALAPRO-2

***All comers: rPFS***

***HR 0.63 (0.51-0.78); p<0.001***

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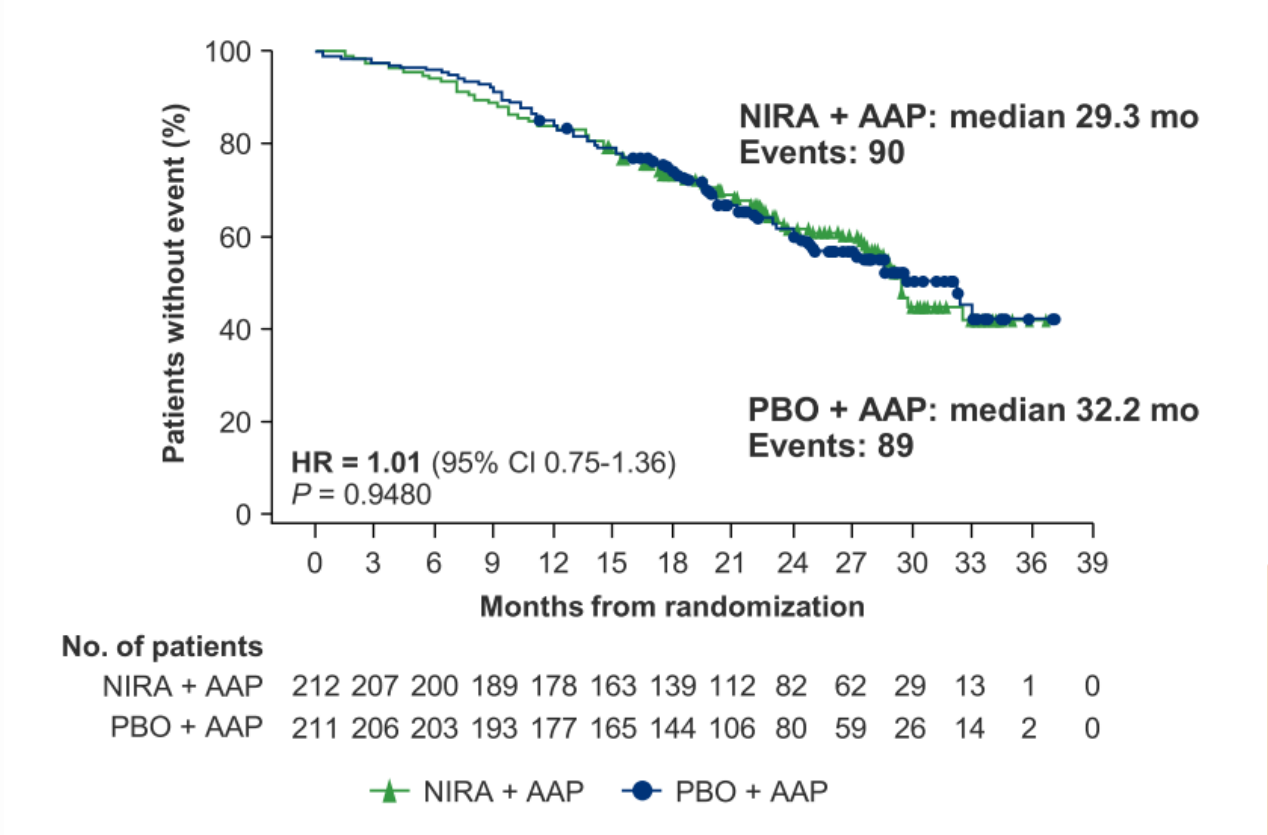
Clarke et al. N Eng J Med Evidence 2022; Chi et al. J Clin Oncol 2023; Agarwal et al. Lancet 2023.

# Overall survival

MAGNITUDE HRR+

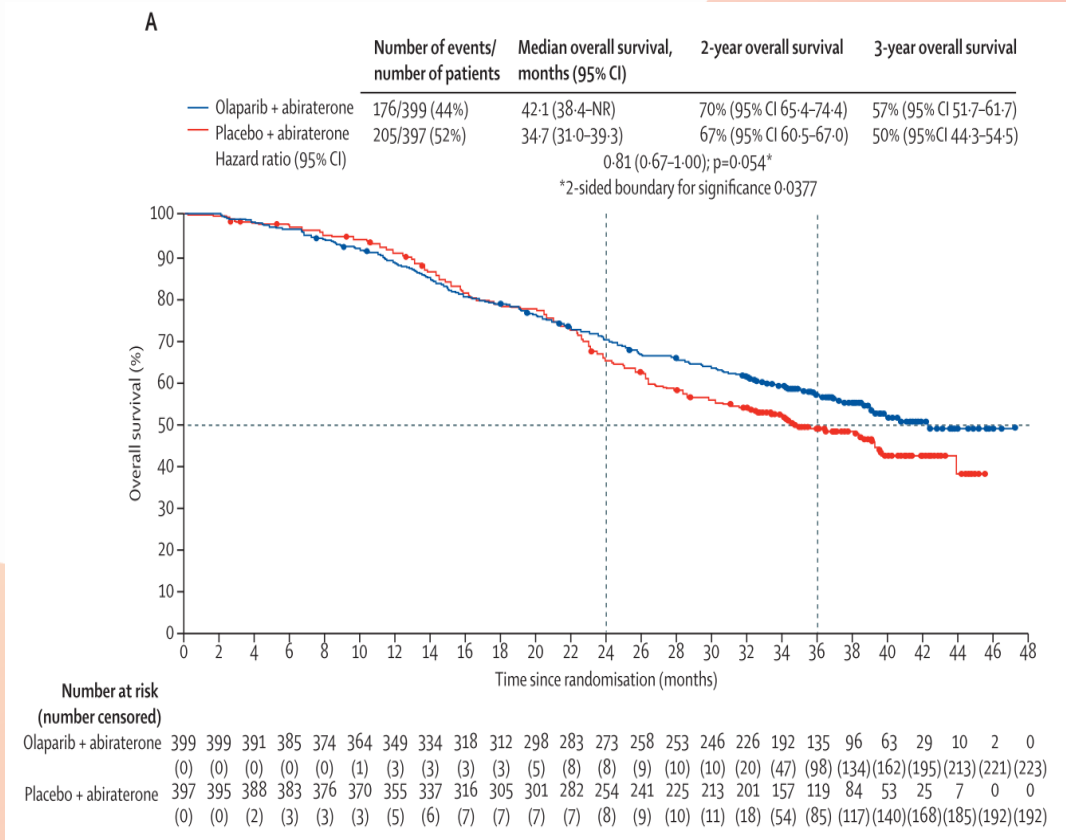
***HR 1.01 (95%CI: 0.75-1.36)***




PROPEL All comers

***HR 0.81 (95%CI 0.67-1); p=0.054***

*2-sided boundary for significance: 0.037*




Chi et al. Ann Oncol 2023, Saad et al. Lancet Oncol 2023

# The TALAPRO-2 trial

**Elegibility**
mCRPC
First line
ECOG PS 0-1

Talzaoparib 0,5 mg + Enzalutamide 160 mg/24h (n=402)

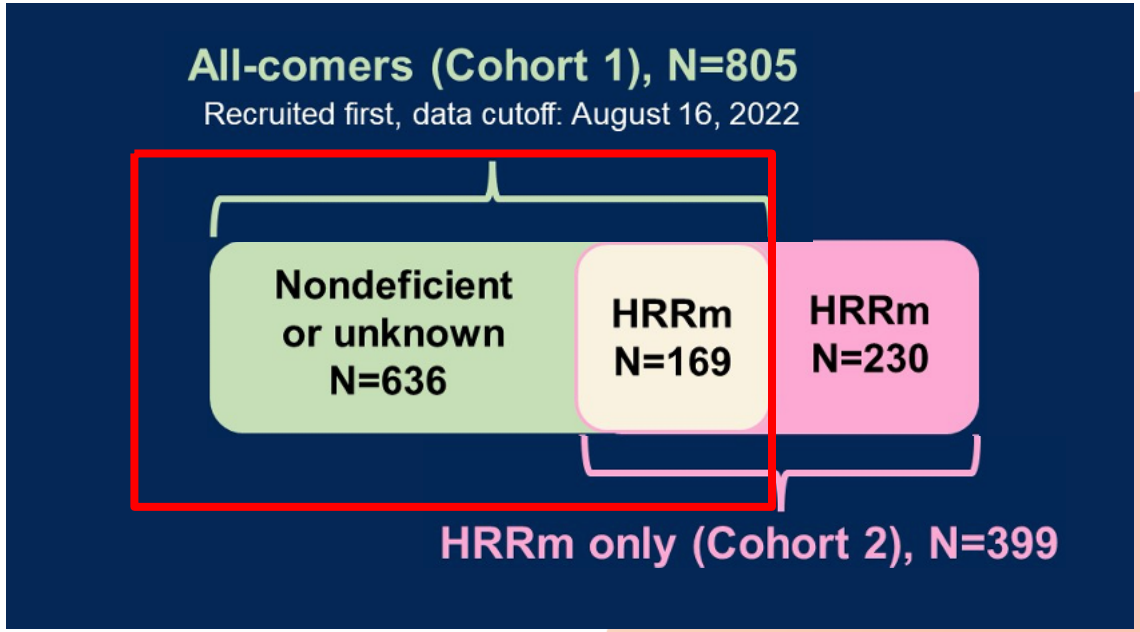
Placebo + Enzalutamide 160 mg/24h (n=403)

**Primary endpoint:**
rPFS (independent evaluation)

**Secondary endpoints:**
Time to chemotherapy
PFS2
Response rate
*Patient-reported outcomes*
Safety

**Stratification**:
- Treatment with Docetaxel or hormonal agents in CPHSm
- HRR alteration (present vs absent vs unknown)

**Prospective genomic assessment:**
BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA RAD51C, NBN, MLH1, MRE11A, CDK12




| | Enza + Talazo | Enza + Placebo |
|---|---|---|
| **Docetaxel mHSPC** | 86 (21%) | 93 (23%) |
| **Prior NHA** | 23 (6%) | 27 (7%) |
| **HRRm status** | | |
| **HRRm** | 85 (21%) | 20.8% |
| **Non-HRRm** | 207 (51%) | 53.1% |
| **HRRm unk** | 110 (27%) | 26.1% |
| **BRCA1/2 alteration** | 27 (7%) | 32 (8%) |

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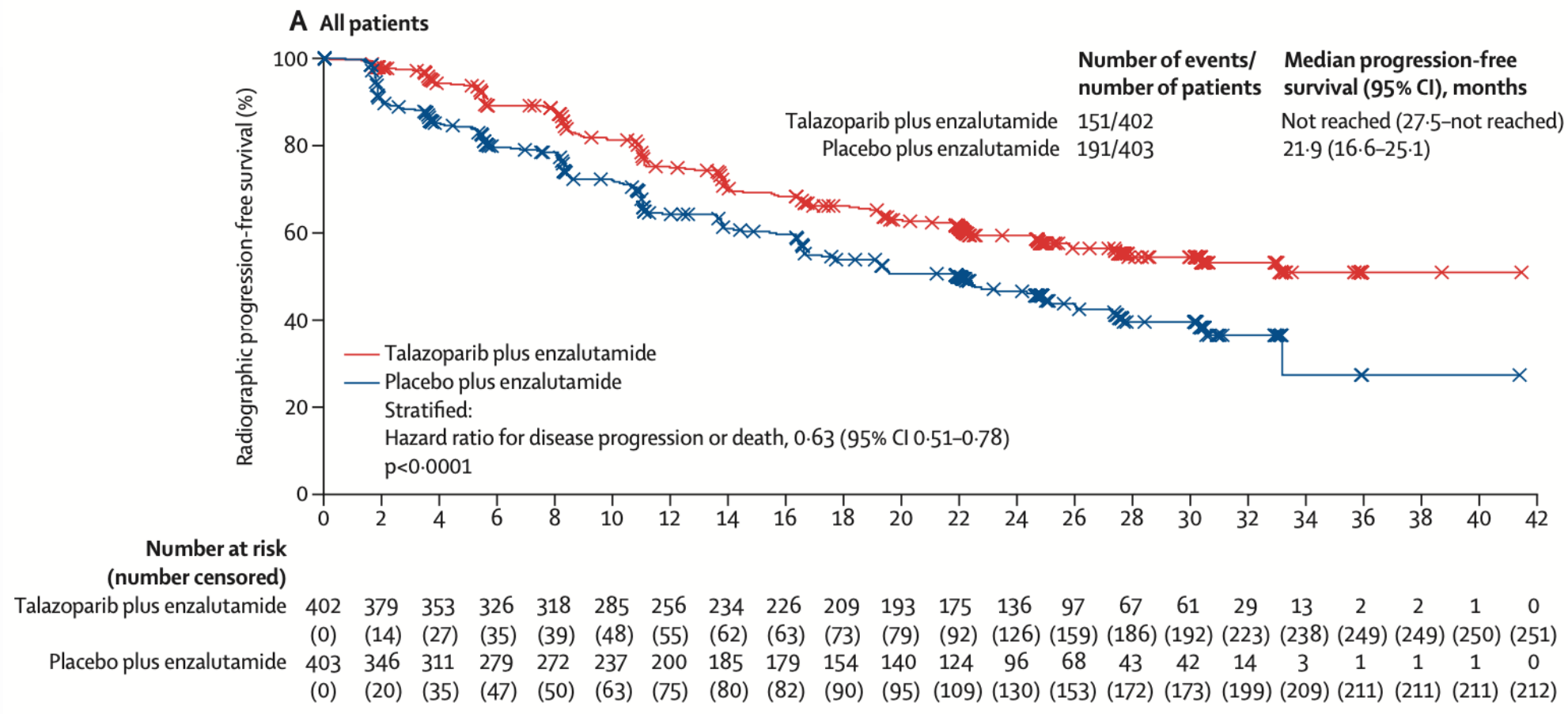
Agarwal et al. ASCO GU 2023. Agarwal et al. Lancet 2023.

# Primary endpoint: significant increase in rPFS (all comers)

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Agarwal et al. Lancet 2023.

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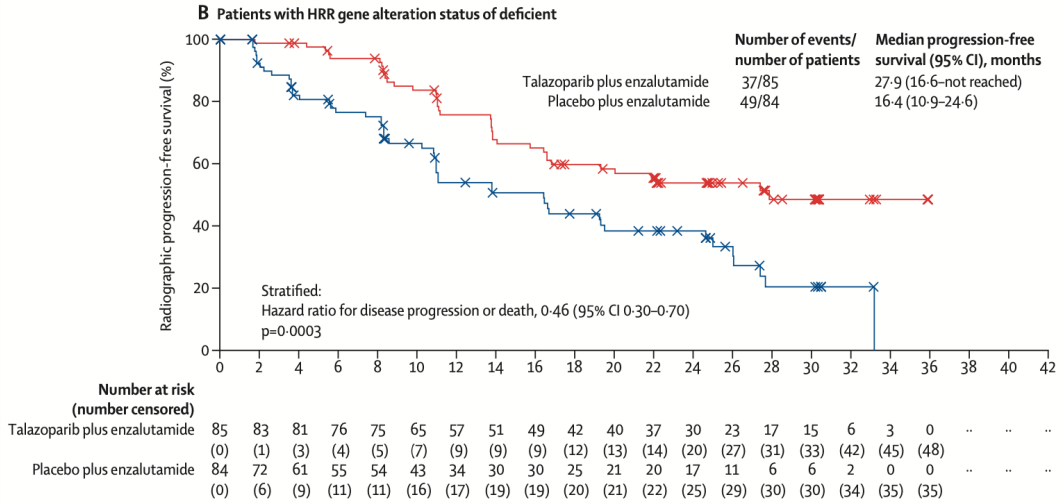
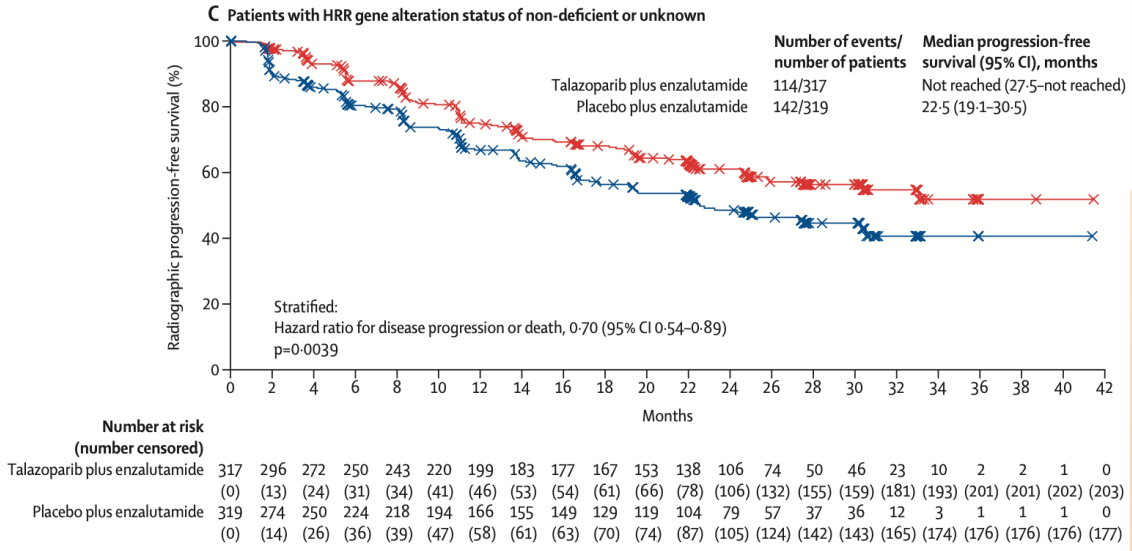
## HRR biomarker positive:

HR 0.45 (95%CI 0.30-0.70); p=0.003



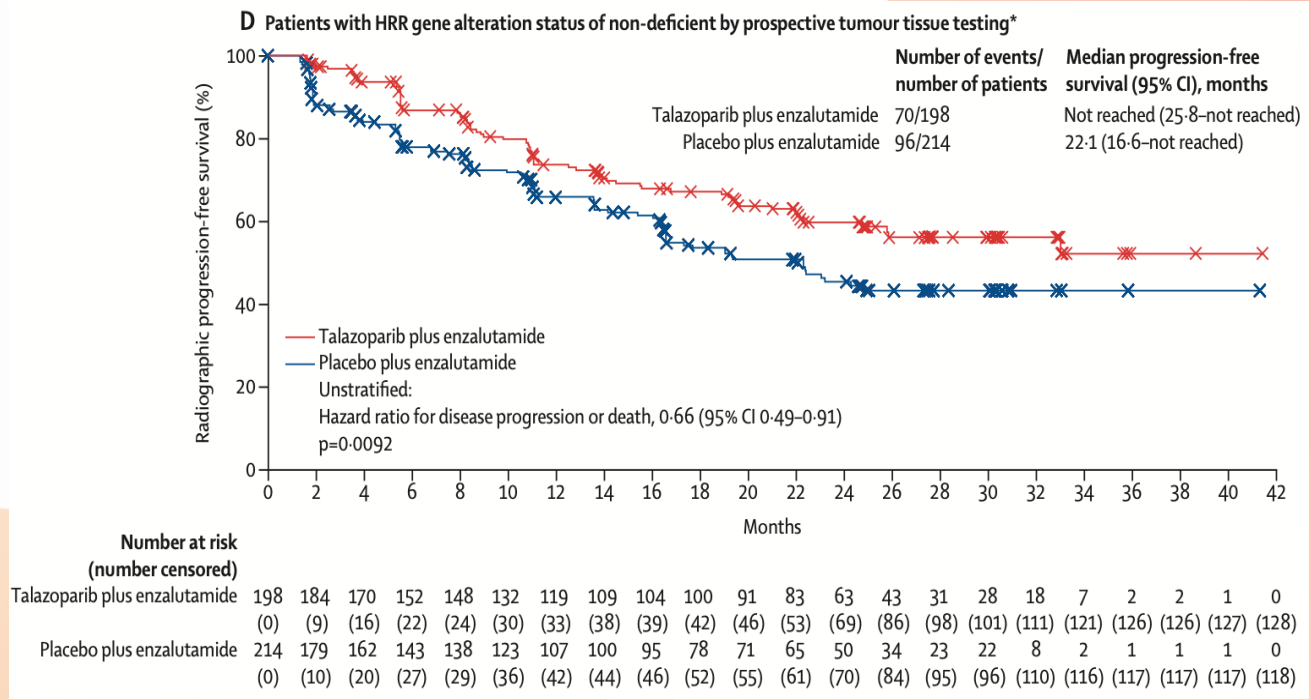

## HRR biomarker negative/unknown:

HR 0.70 (95%CI 0.54-0.89); p=0.004




## HRR biomarker negative (excluding unknown status):

HR 0.66 (95%CI 0.49-0.91); p=0.009

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Agarwal et al. Lancet 2023.

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ECOG PS 0-1

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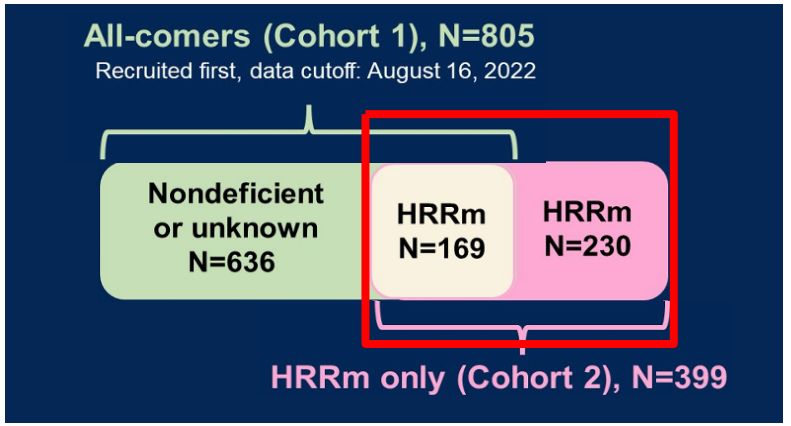


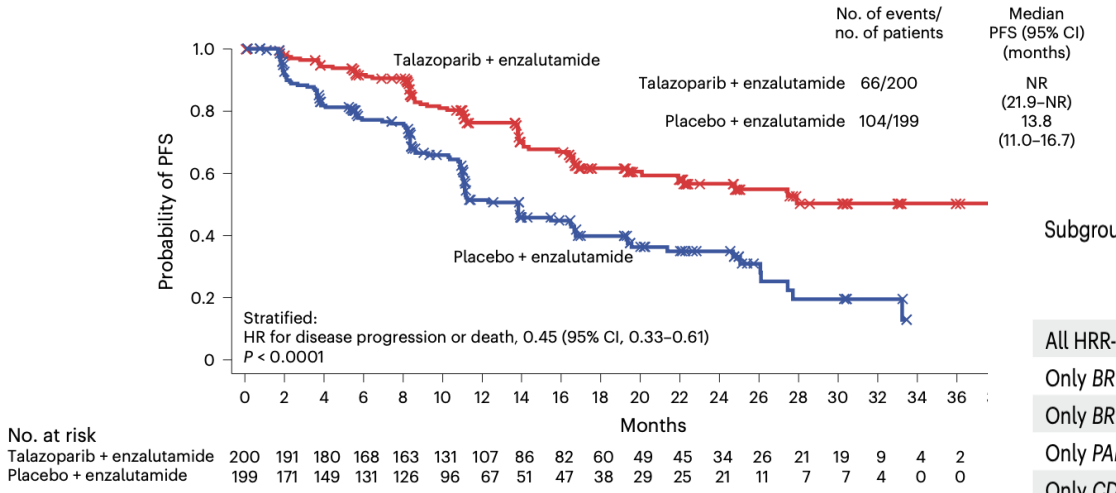

| | Enza + Talazo | Enza + Placebo |
|---|---|---|
| **Docetaxel mHSPC** | 57 (28.5%) | 60 (30.2%) |
| **Prior NHA** | 16 (8%) | 16 (8%) |
| **Tissue source** | | |
| **Tissue only** | 76 (38%) | 80 (40.2%) |
| **Tissue & ctDNA** | 121 (60.5%) | 115 (57.8%) |
| **ctDNA only** | 3 (1.5%) | 4 (2%) |
| **BRCA1 mutant** | 5.5% | 6% |
| **BRCA2 mutant** | 31% | 36.7% |

Fizazi et al. Nature Med 2023

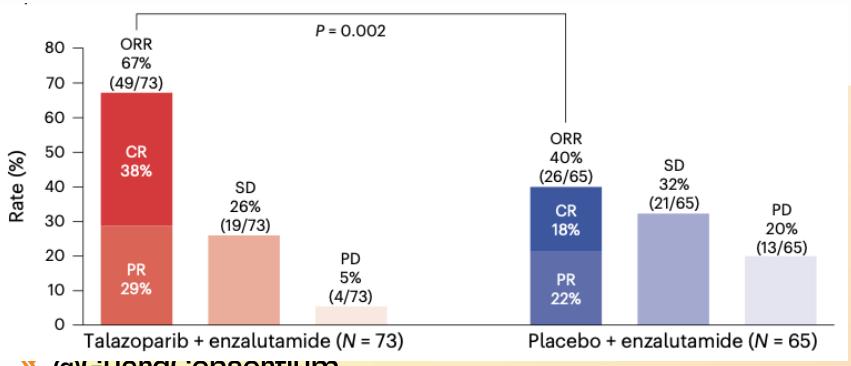
# TALAPRO-2: Cohort 2 results

## HRR gene alteration: rPFS

HR 0.45 (95%CI 0.30-0.70); p=0.003




## Objective response rate

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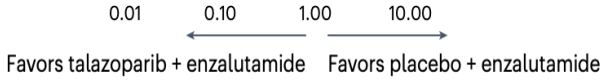
## *Subgroup analysis (rPFS) by gene alteration*

| Subgroup | Talazoparib + enzalutamide | Placebo + enzalutamide | Talazoparib + enzalutamide | Placebo + enzalutamide | Hazard ratio (95% CI) | Two-sided *P* value |
|---|---|---|---|---|---|---|
| | No. of events/no. of patients | | Median (months) | | | |
| All HRR-deficient | 65/198 | 104/197 | NR | 13.8 | 0.44 (0.32–0.60) | <0.0001 |
| Only *BRCA1* | 2/8 | 5/9 | 20.0 | 11.7 | 0.17 (0.02–1.51) | 0.07 |
| Only *BRCA2* | 11/55 | 40/60 | NR | 11.0 | 0.19 (0.10–0.38) | <0.0001 |
| Only *PALB2* | 3/6 | 4/5 | NR | 8.6 | 0.56 (0.12–2.51) | 0.44 |
| Only *CDK12* | 12/28 | 18/30 | 21.9 | 13.8 | 0.49 (0.23–1.02) | 0.05 |
| Only *ATM* | 12/35 | 7/22 | NR | 27.7 | 0.76 (0.30–1.94) | 0.58 |
| Only *CHEK2* | 8/24 | 8/24 | 22.1 | NR | 0.90 (0.34–2.39) | 0.83 |
| *BRCA* cluster | 15/71 | 54/84 | NR | 11.0 | 0.20 (0.11–0.36) | <0.0001 |
| *PALB2* cluster | 3/7 | 6/8 | NR | 8.3 | 0.46 (0.12–1.87) | 0.27 |
| *CDK12* cluster | 13/35 | 23/36 | 21.9 | 13.8 | 0.38 (0.19–0.76) | 0.004 |
| *ATM* cluster | 16/43 | 9/29 | 27.9 | 27.7 | 0.90 (0.39–2.04) | 0.80 |
| Other gene cluster | 18/42 | 12/40 | 22.1 | NR | 1.51 (0.73–3.15) | 0.26 |

Hierarchy

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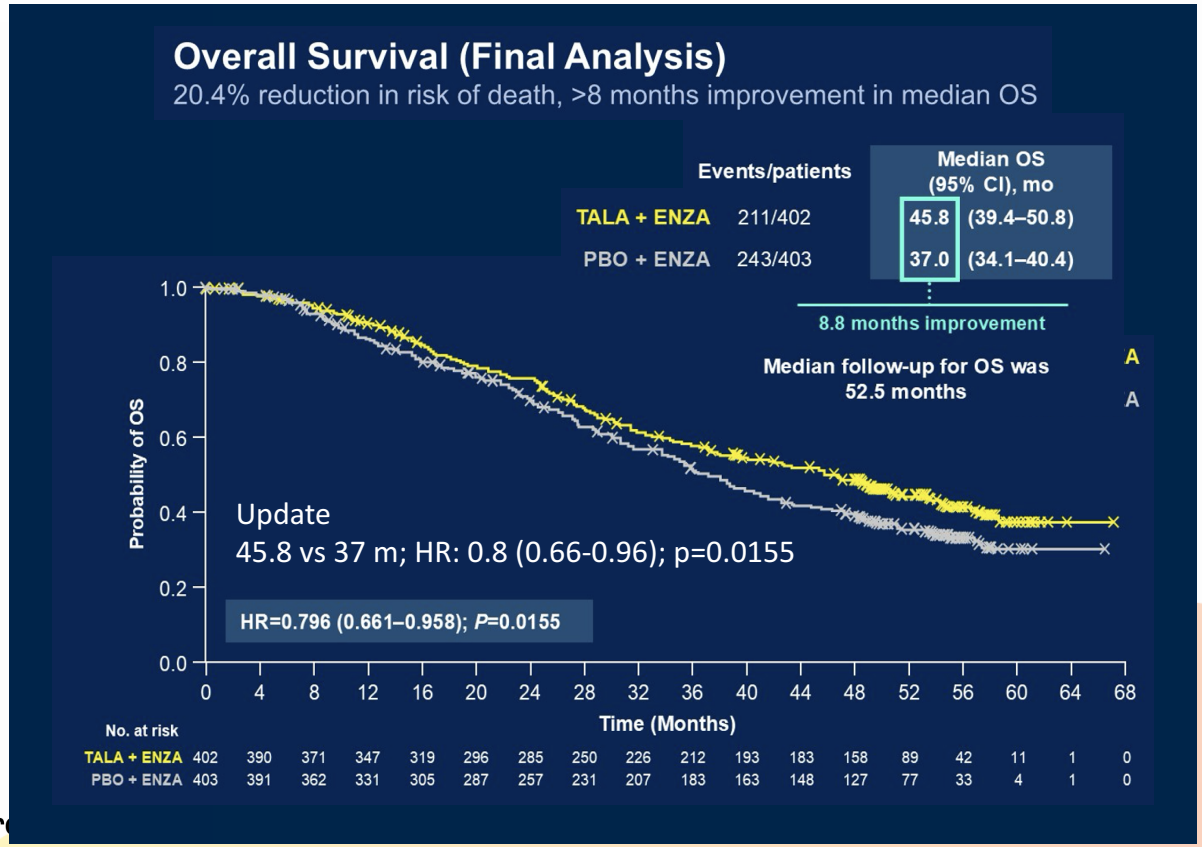
Fizazi et al. Nature Med 2024

# TALAPRO-2: Updated Overall Survival
## (ASCO GU 2025)

### Cohort A (all comers)

Primary analysis (Aug 16 2022)
NR vs 36.4m; HR: 0.89 (0.69-1.14); p=0.35

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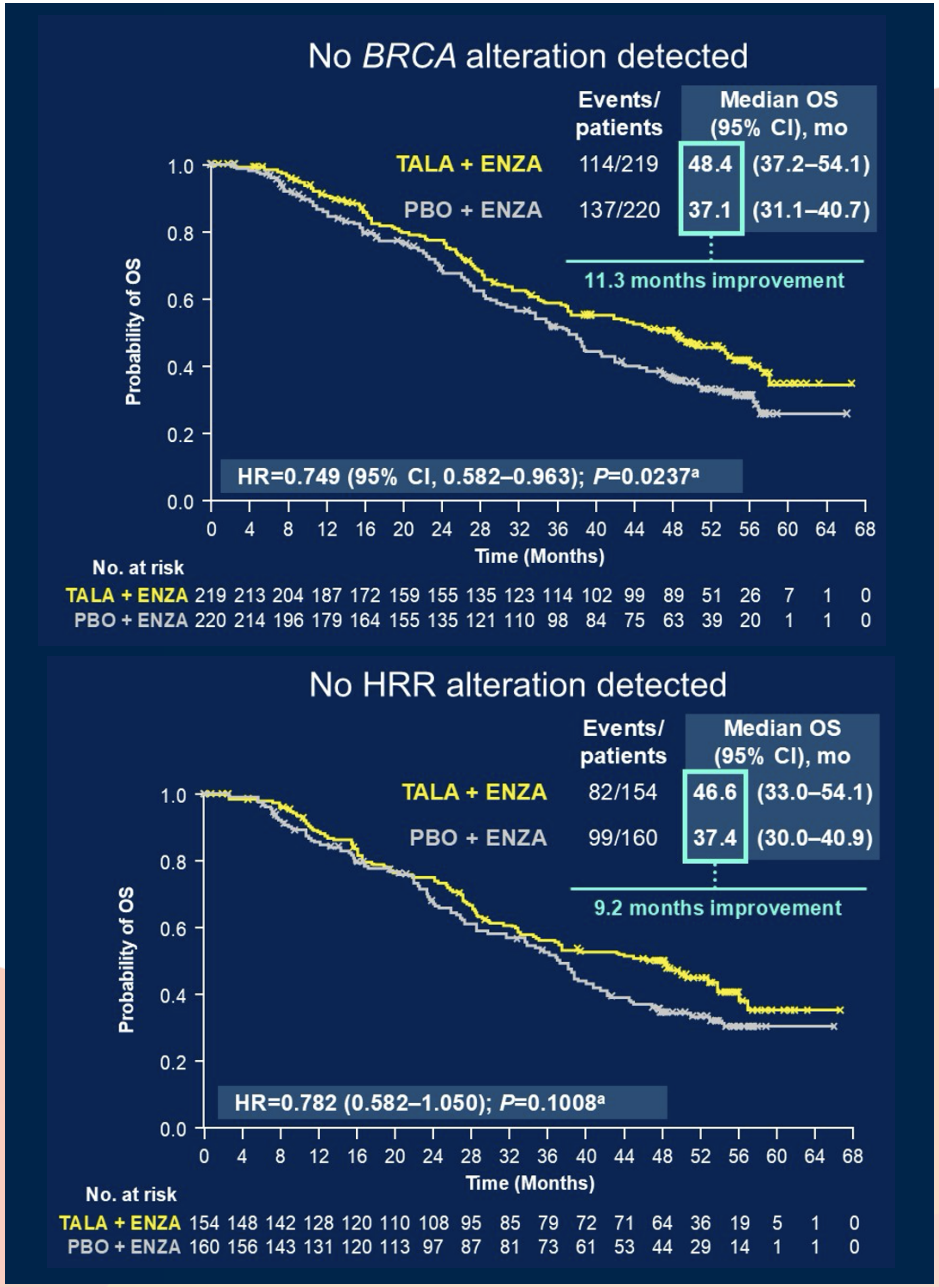
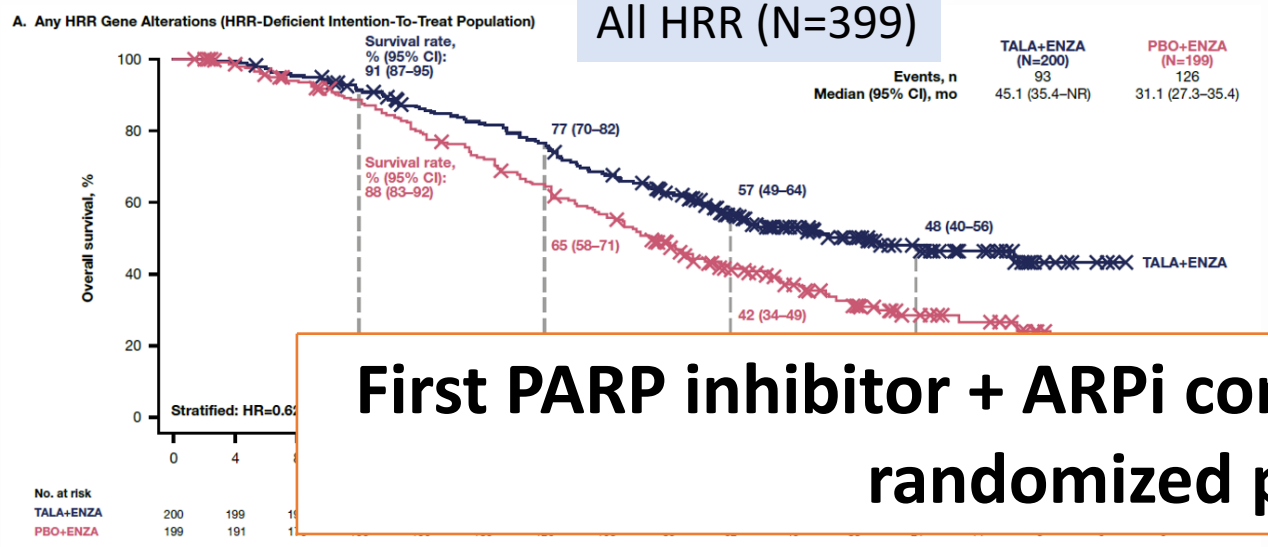
Agarwal et al. ASCO GU 2025

**Overall Survival in Subgroups With No Alterations Detected by Both ctDNA and Tumor Tissue (prospective & retrospective)**



# TALAPRO-2: Updated Overall Survival – Cohort B (HRR +)
## (ASCO GU 2025)

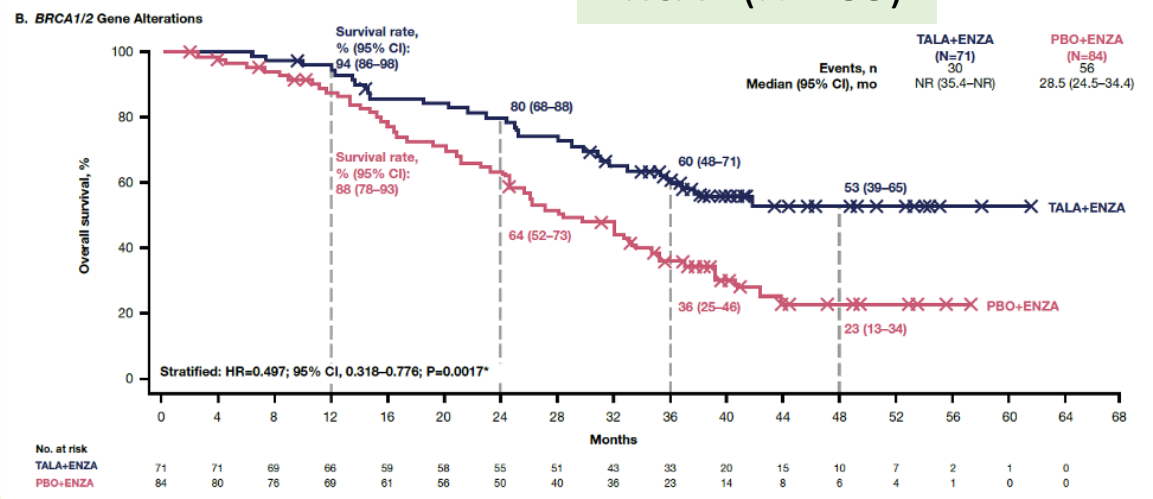
All HRR (N=399)



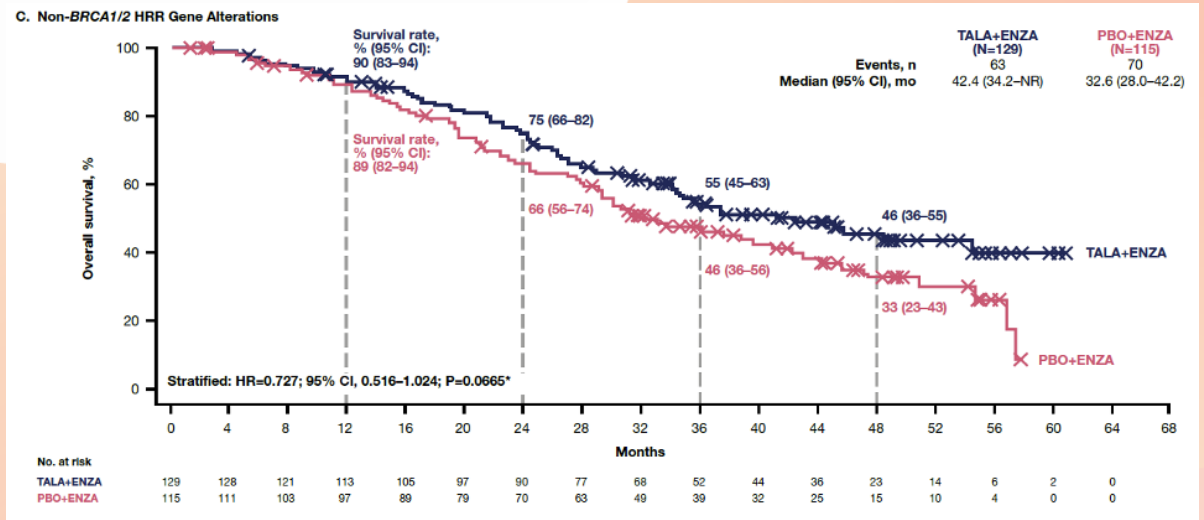

| | Talazo-Enza | Enza | HR (95%CI); p-val |
|---|---|---|---|
| **All HRR** | *N=200* 45.1 m | *N=199* 31.1 m | 0.62 (0.48-0.81); p=0.0006 |
| **BRCA +** | *N=71* NR | *N=84* 28.5 m | 0.50 (0.32-0.78); p=0.0017 |

**First PARP inhibitor + ARPi combo with overall survival in a randomized phase III trial**

BRCA+ (N=155)

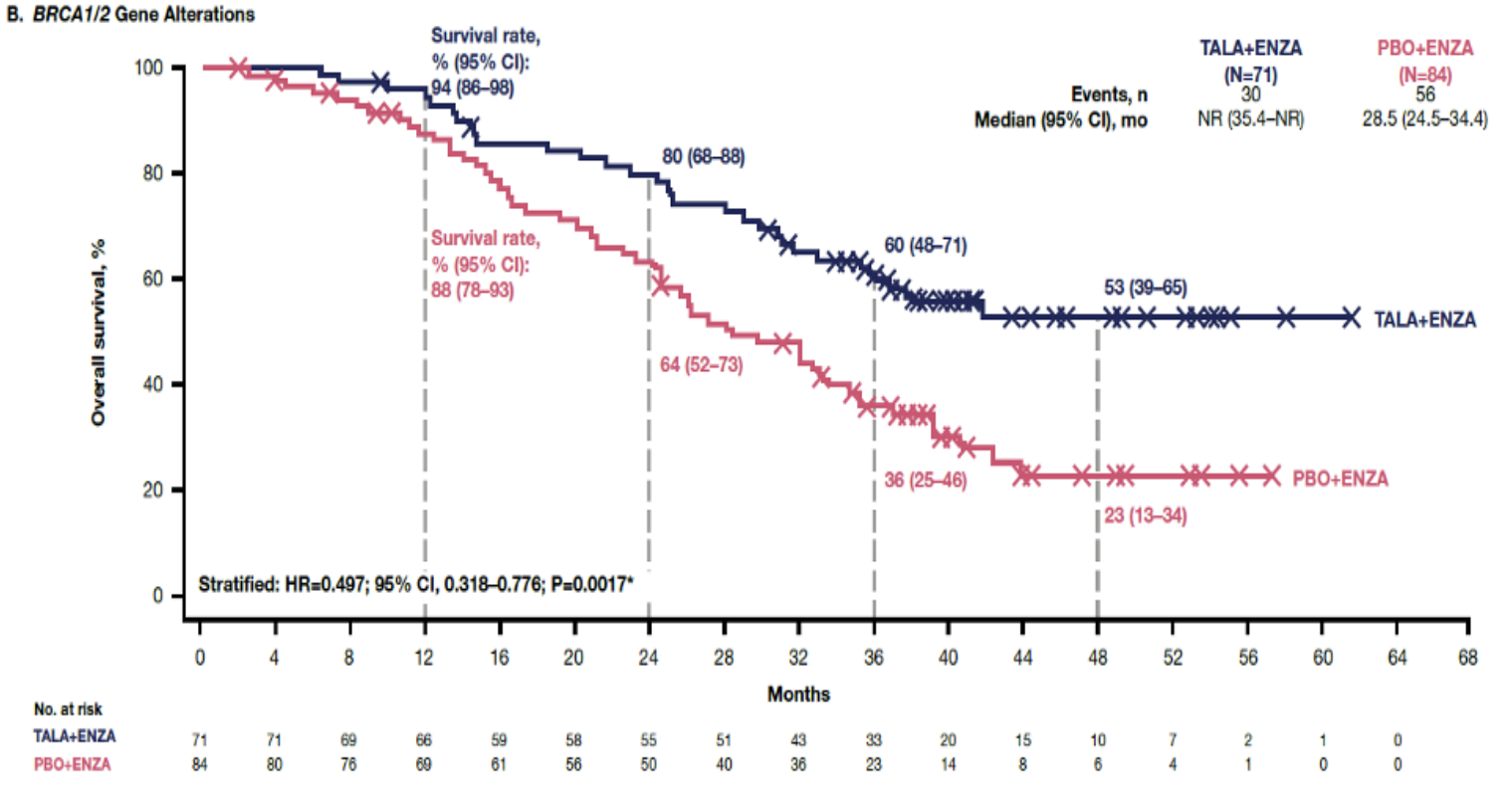



HRR non-BRCA (N=244)




Fizazi et al. ASCO GU 2025

# Benefit is greatest in patients with BRCA mutations




| | Talazo-Enza | Enza | HR (95%CI); p-val |
|---|---|---|---|
| **OS median** | NR | *28.5*m | 0.50 (0.32-0.78); p=0.0017 |
| **2-yr OS** | 80% | 64% | ΔOS: 16% |
| **3-yr OS** | 60% | 36% | ΔOS: 24% |
| **4-yr OS** | 53% | 23% | ΔOS: 30% |
| **PSA50 resp** | 88.7% | 56.2% | - |

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# Toxicity

*Toxicity outcomes in the TALAPRO-2 trial*

| All-grade toxicity | | TALAPRO-2 | |
|---|---|---|---|
| | | Tala + Enza | Enza |
| Anemia | | 65% | 16% |
| Neutropenia | | 32% | 7% |
| Thrombopenia | | 23% | 3% |
| Fatigue | | 33% | 27% |
| Nausea | | 21% | 17% |
| Hypertension | | 18% | 19% |
| Thromboembolic events | | - | - |
| | | | |
| Interruption. | PARPi/Pbo | 58% | 17% |
| | ARSi | 34% | 16% |
| Dose red | PARPi/Pbo | 52% | 6% |
| | ARSi | 14% | 6% |
| Discont | PARPi/Pbo | 10% | 7% |
| | ARSi | 8% | 7% |

#

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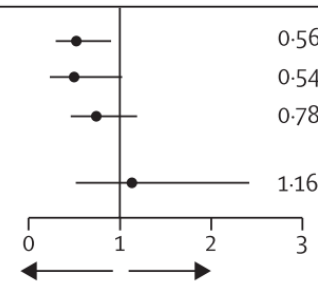
*Improved quality of life*

**A** EORTC QLQ-C30

| | Number of events/number of patients | | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| | Talazoparib plus enzalutamide | Placebo plus enzalutamide | | |
| GHS/QoL | 64/197 | 71/197 | 0·69 (0·49–0·97) | 0·032 |
| Physical functioning | 60/197 | 82/197 | 0·57 (0·41–0·80) | 0·0010 |
| Role functioning | 67/197 | 69/197 | 0·77 (0·55–1·08) | 0·12 |
| Emotional functioning | 39/197 | 57/197 | 0·48 (0·32–0·72) | 0·0004 |
| Cognitive functioning | 66/197 | 73/197 | 0·70 (0·50–0·97) | 0·033 |
| Social functioning | 61/197 | 68/197 | 0·75 (0·53–1·06) | 0·10 |
| Fatigue | 88/197 | 88/197 | 0·85 (0·63–1·14) | 0·27 |
| Nausea and vomiting | 24/197 | 32/197 | 0·56 (0·33–0·95) | 0·030 |
| Pain | 52/197 | 74/197 | 0·56 (0·39–0·79) | 0·0011 |
| Dyspnoea | 45/197 | 50/197 | 0·68 (0·45–1·02) | 0·063 |
| Insomnia | 39/197 | 40/197 | 0·77 (0·50–1·21) | 0·26 |
| Appetite loss | 52/197 | 64/197 | 0·60 (0·41–0·87) | 0·0061 |
| Constipation | 33/197 | 48/197 | 0·52 (0·34–0·82) | 0·0037 |
| Diarrhoea | 19/197 | 21/197 | 0·61 (0·32–1·15) | 0·12 |

**B** EORTC QLQ-PR25

| | | | | |
|---|---|---|---|---|
| Urinary symptoms | 28/197 | 37/197 | 0·56 (0·34–0·93) | 0·022 |
| Bowel symptoms | 16/197 | 21/197 | 0·54 (0·28–1·05) | 0·064 |
| Hormonal treatment-related symptoms | 43/197 | 41/197 | 0·78 (0·50–1·20) | 0·25 |
| Incontinence aid | 16/197 | 14/197 | 1·16 (0·56–2·41) | 0·69 |




Agarwal et al. Lancet Oncol 2023. Fizazi et al. Nature Med 2024. Fay et al. Lancet Oncol 2025

Who to test? Test everybody!!

Do PARPi – NHA combinations eliminate the need for testing?

# Who is the ideal candidate for treatment?

The ideal candidate is the one that reflects the clinical trial population

expected benefit is greater than anticipated toxicity (disease burden)

*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

What, where and when to test?

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What about non-BRCA HRR alterations?

What, where and when to test?

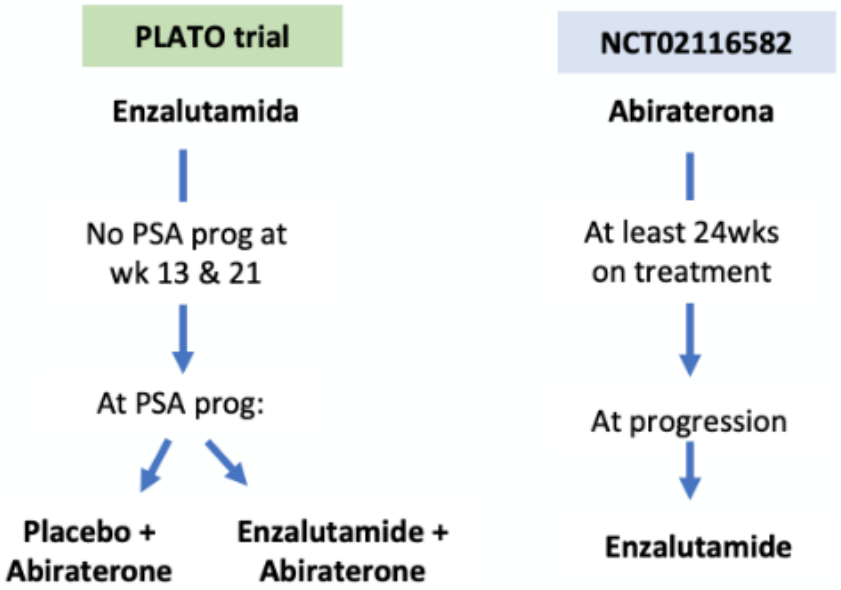
# Prior therapy in PARPi + ARSi trials

| | Prior ADT only | Prior Docetaxel | Prior ARPi |
|---|---|---|---|
| **PROPEL** | 77.2% | 22.5% | 0.3% |
| **MAGNITUDE** | 76.8% | 20.1% | 3.1% |
| **TALAPRO-2** | 71% | 22% | 7% |

PARPi + NHA combinations

# Are results applicable to patients treated with ARPIs in the mHSPC or nmCRPC setting?

*Activity of sequential ARPIs is substantially lower than on first-line*



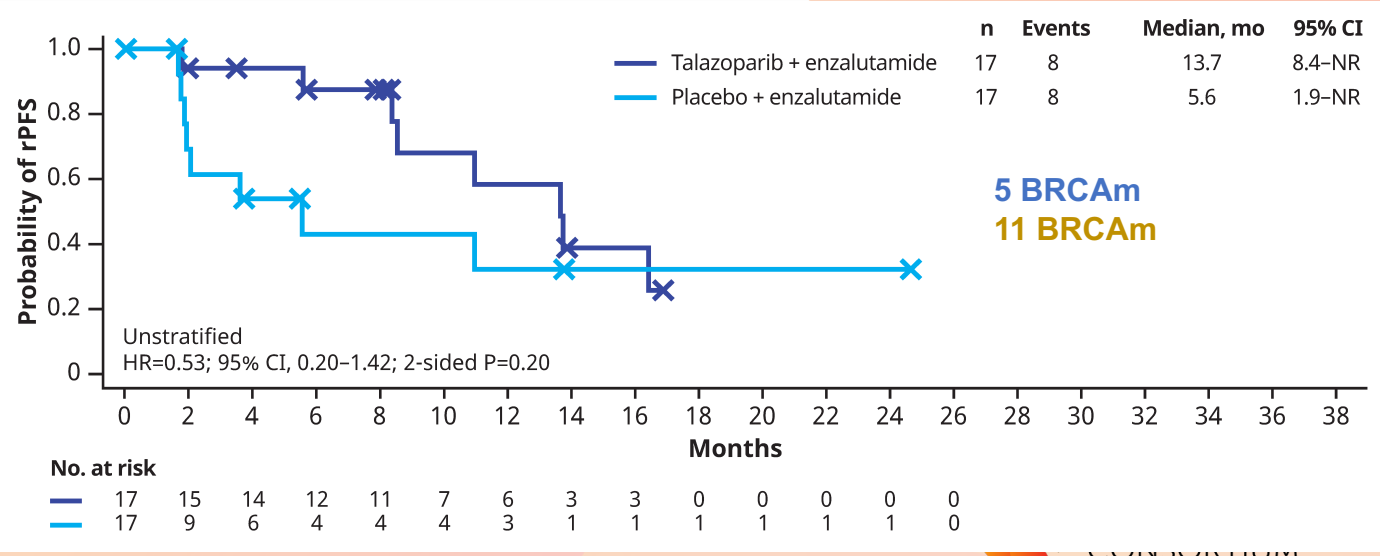

| | Enz→ Abi | Abi→ Enz |
|---|---|---|
| **N** | 251 | 145 |
| **PSA resp** | 2% | 26% |
| **PSA-PFS** | 2.8 m | 5.7 m |
| **rPFS** | 7 m | 8.1 m |

**TALAPRO-2: 50 pts received prior ARSI (abi or orteronel) in mHSPC**

Table 4. rPFS by Previous Treatment With a Second-Generation Androgen Receptor Pathway Inhibitor or With Docetaxel (All-Comers ITT Population)

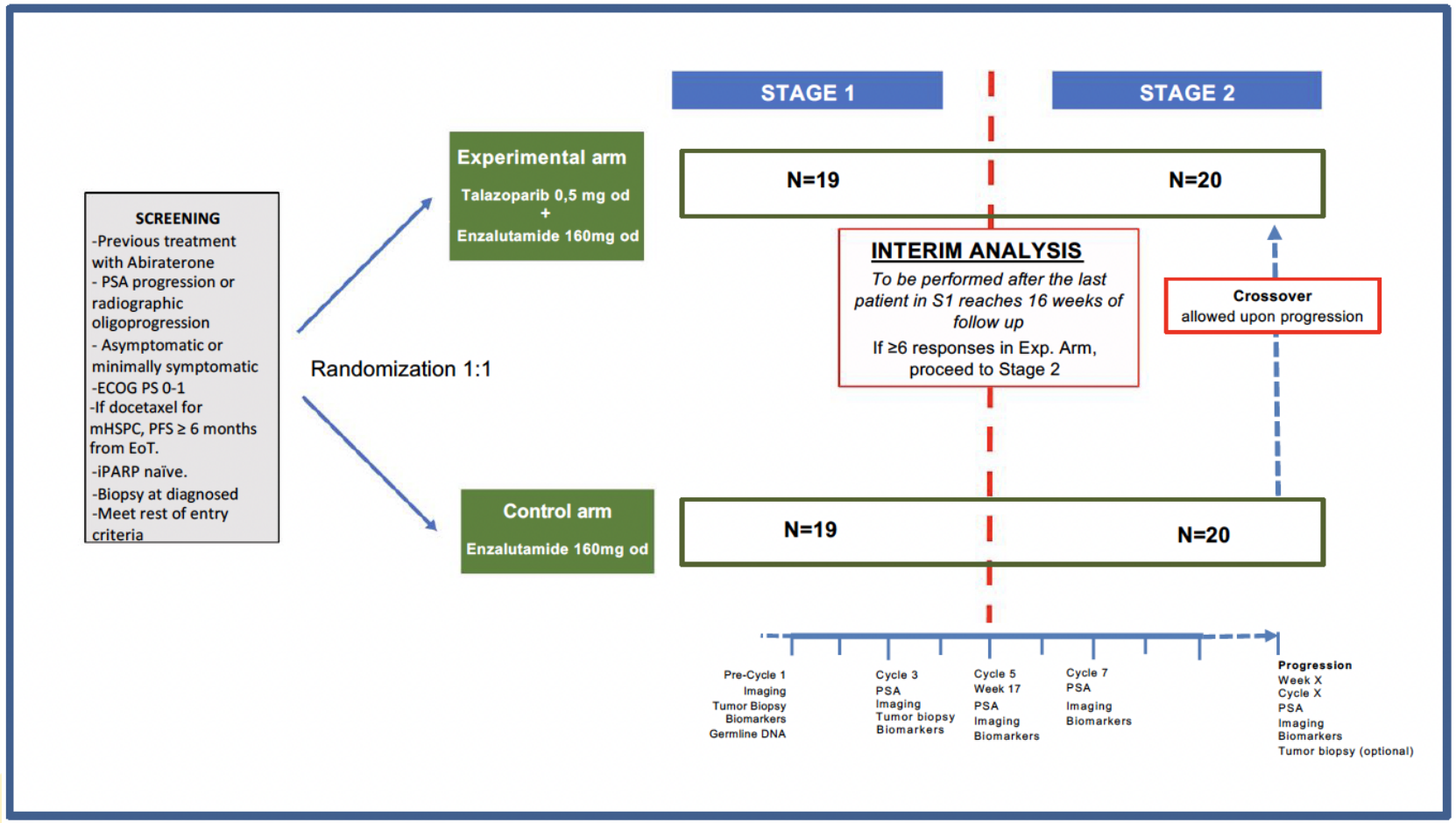
| | TALA + ENZA | PBO + ENZA | TALA + ENZA | PBO + ENZA | | |
|---|---|---|---|---|---|---|
| | Events*/N | | Median (95% CI) | | HR (95% CI) | P Value |
| Prior abiraterone† | | | | | | |
| Yes | 15/23‡ | 16/27§ | 11.0 (5.6–16.4) | 1.9 (1.8–11.0) | 0.57 (0.28–1.16) | 0.12 |
| No | 135/376 | 172/373 | NR (30.4–NR) | 22.5 (17.7–26.1) | 0.64 (0.51–0.80) | 0.0001 |

**Prior ARPI**




Attard et al. J Clin Oncol 2018. De Bono et al. Eur Urol 2018. Fizazi et al. Nature Med 2024

# A multicenter, open label, randomized phase II trial to evaluate the efficacy of Talazoparib plus Enzalutamide as first line treatment for patients with Metastatic castration resistant Prostate Cancer following progression on Abiraterone: TEAM PC study

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Courtesy of dr Elena Castro

# Prior therapy in PARPi +/- ARSi trials

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| **TALAPRO-2** | 71% | 22% | 7% |
| **PROFOUND** | 0 | 65% | 100% |
| **TRITON-3** | 0 | 22% | 100% |
| **TALAPRO-1** | 0 | 99% | 99% |
| **GALAHAD** | 0 | 100% | 100% |

PARPi + NHA combinations

PARPi monotherapy



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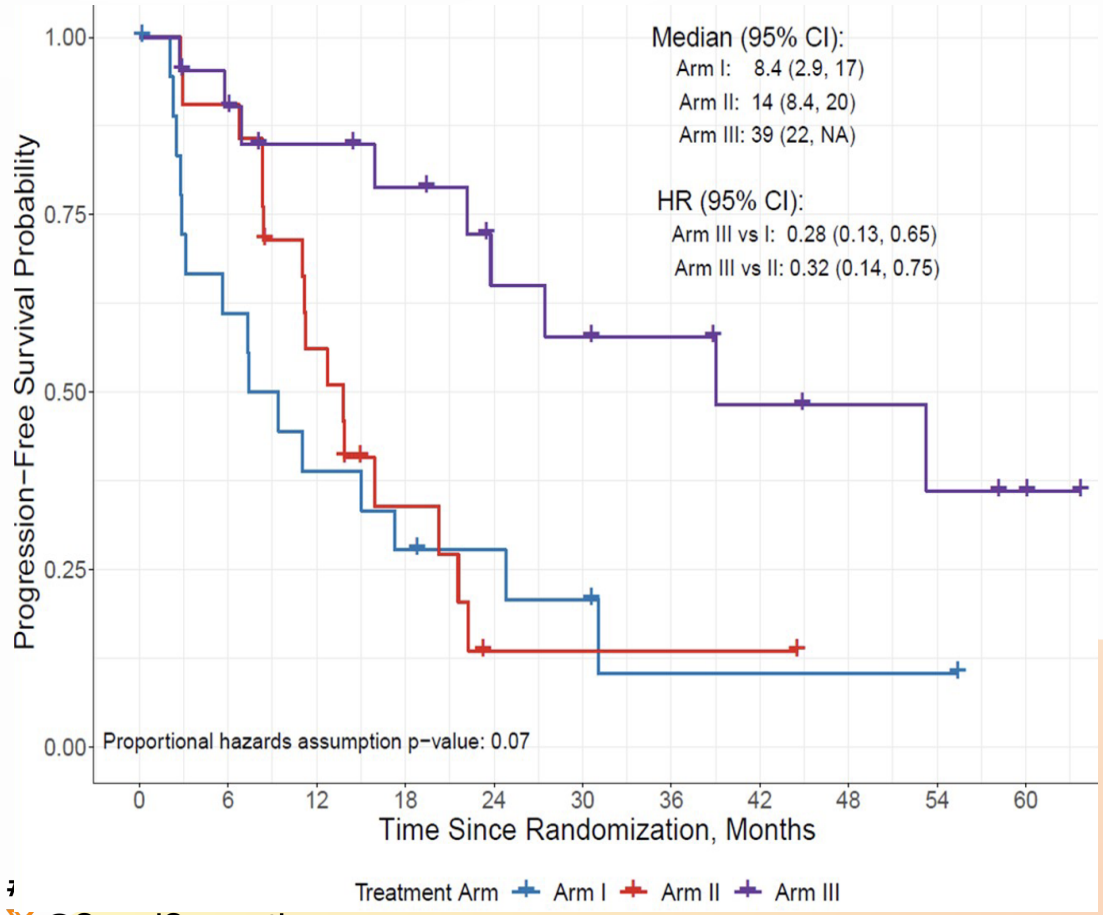
# PARPi monotherapy & PARPi +/- NHT
# Combination or sequential therapy?

**BRCAAWAY** Abiraterone + Olaparib upfront vs Abiraterone → Olaparib vs Olaparib → Abiraterone




**Primary endpoint**: radiographic PFS

| | Arm I (n = 19) | Arm II (n = 21) | Arm III (n = 21) |
|---|---|---|---|
| Median PFS, months (95% CI) | **8.4 (2.9, 17)** | **14 (8.4, 20)** | **39 (22, NR)** |
| Objective RR, % (95% CI) | **22** (6.4, 48) | **14** (3, 36) | **33** (15, 57) |
| PSA RR, % (95% CI) | **61** (36, 83) | **67** (43, 85) | **95** (76, 100) |
| Undetectable PSA RR, % (95% CI) | **17** (3.6, 41) | **14** (3, 36) | **33** (15, 57) |

**16 patients crossed over at progression**

| | Crossover to Olaparib (n = 8) | Crossover to Abiraterone (n = 8) |
|---|---|---|
| Median PFS from crossover, months (95% CI) | **8.3 (5.5, 15)** | **7.2 (2.8, NR)** |
| Median PFS from randomization, months (95% CI) | **16 (7.8, 25)** | **16 (11, NR)** |



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Hussain et al. ASCO GU 2024. Hussain et al. J Clin Oncol 2024.

Who to test? Test everybody!!

Do PARPi – NHA combinations eliminate the need for testing?

# Who is the ideal candidate for treatment?

**The ideal candidate is the one that reflects the clinical trial population**
**expected benefit is greater than anticipated toxicity (disease burden)**

*ECOG PS 0-1, adequate hematic-renal function, metastases defined by CT/Bone scan*

**What about non-BRCA HRR alterations?**

What, where and when to test?

## Benefit is **greatest** with **BRCA mutations**

| | |
|---|---|
| PROPEL | HR 0.23 (95%CI 0.12-0.43) |
| MAGNITUDE | HR 0.53 (95%CI 0.36-0.79) |
| TALAPRO-2 | HR 0.20 (95%CI0.11-0.36) |

## **Intermediate** with **HRR mutations**

| | |
|---|---|
| PROPEL | HR 0.50 (95%CI 0.34-0.73) |
| MAGNITUDE | HR 0.64 (95%CI 0.49-0.86) |
| TALAPRO-2 | HR 0.45 (0.33-0.61) |

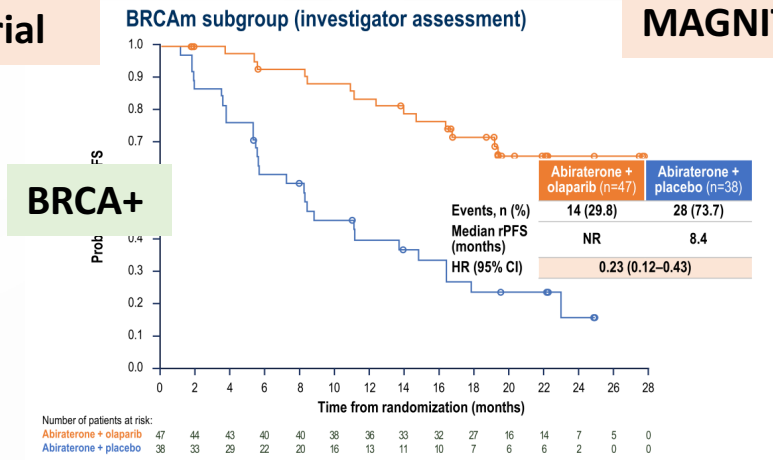
## **Lowest** in patients **without HRR alterations**

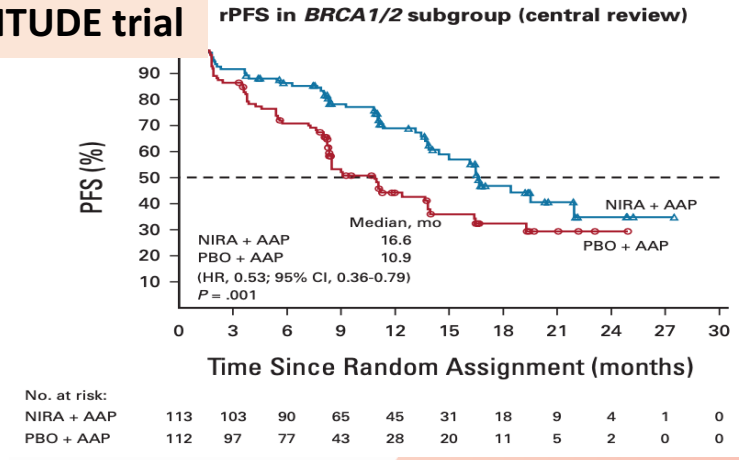
| | |
|---|---|
| PROPEL | HR 0.76 (95%CI: 0.60-0.97) |
| MAGNITUDE | HR 1.03 (95%CI 0.63-1.67) |
| TALAPRO-2 | HR 0.66 (95%CI: 0.49-0.91) |

**PROPEL trial**

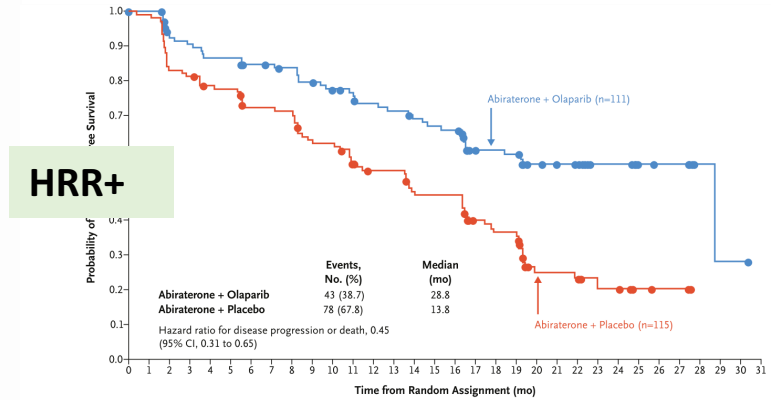
**MAGNITUDE trial**

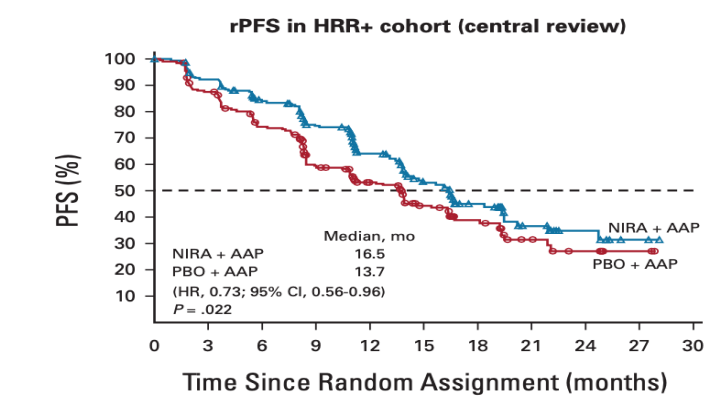
**BRCA+**



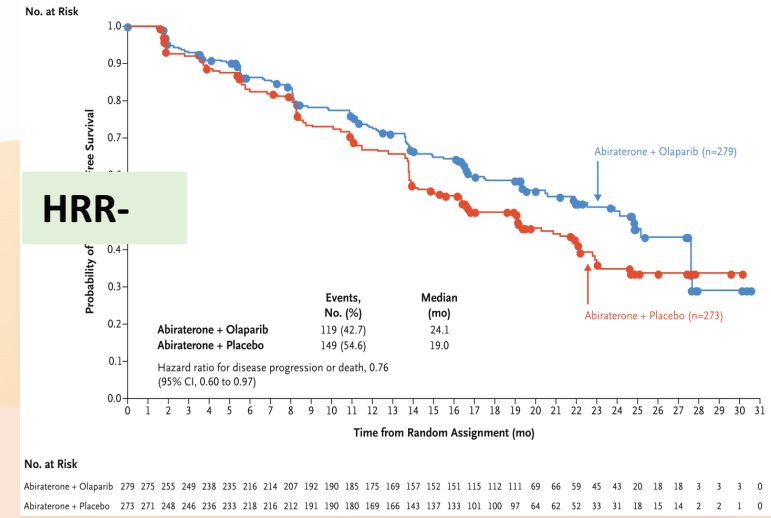



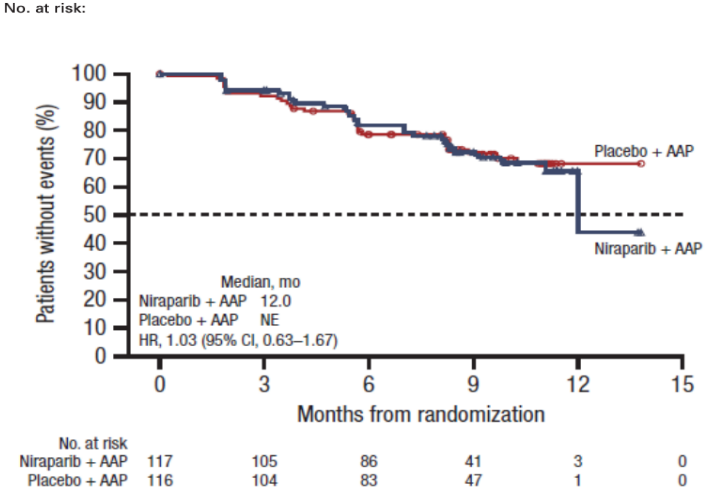

**HRR+**




**HRR-**

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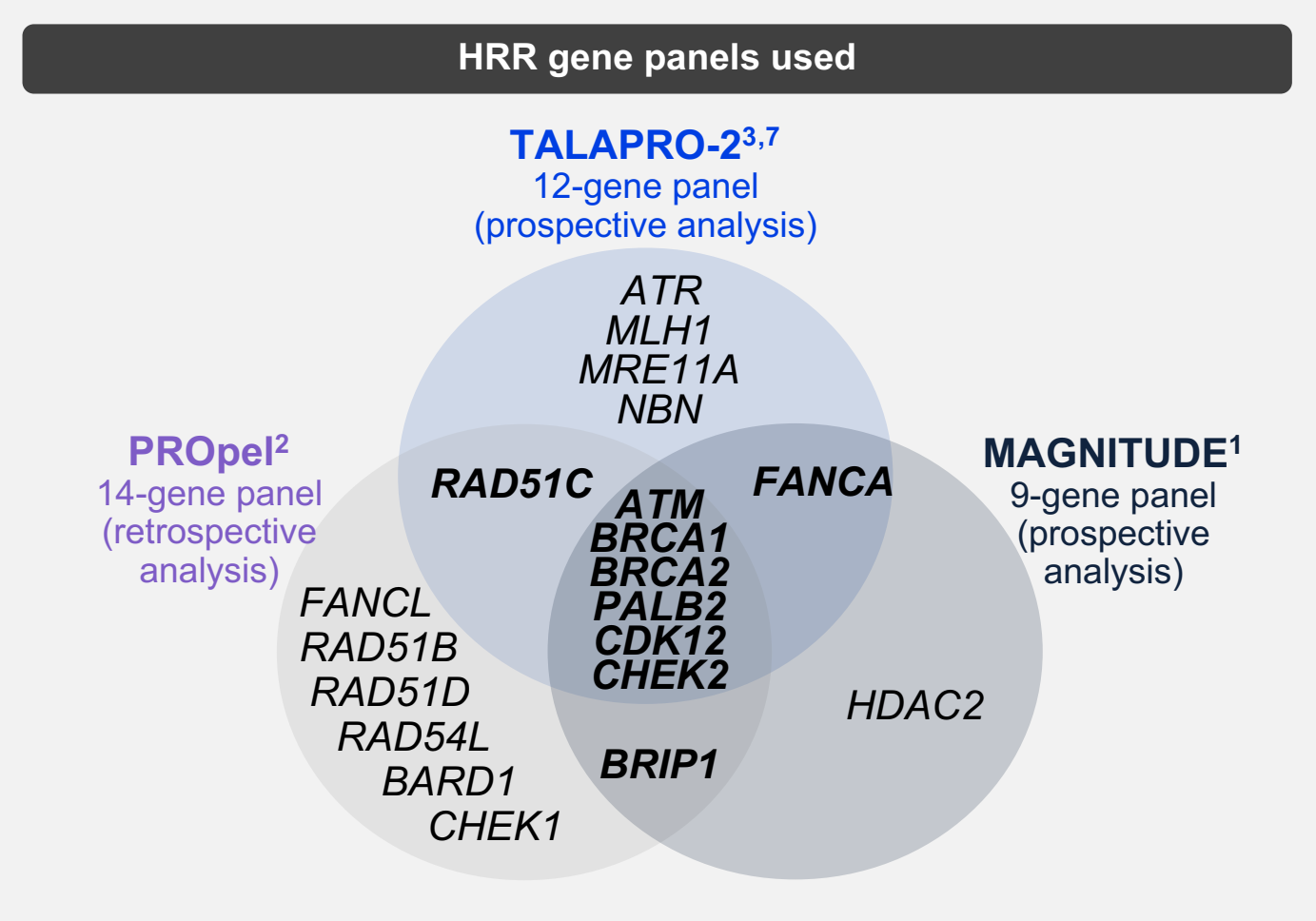
Clarke et al. NEJM Evidence 2023. Saad et al. Lancet Oncol 2023.
Chi et al. J Clin Oncol 2023. Chi et al. Ann Oncol 2023.
Agarwal et al. Lancet Oncol 2023. Fizazi et al. Nature Med 2024.

# Non-BRCA HRR is an elusive term

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**1.** Chi KN, et al. *J Clin Oncol.* 2023;41(18)3339-3351. **2.** Clarke NW, et al. *NEJM Evidence* 2022;1(6):1-16. **3.** Agarwal N, et al. *Lancet*. 2023;402(10398):291-303. **4.** Azad A, et al. ASCO 2023. Abstract 5056. **5.** Chi KN, et al. *Clin Cancer Res*. 2023;29(1):81-91.
**6.** Tukachinsky H, et al. *Clin Cancer Res.* 2021;27(11):3094-3105. **7.** Fizazi K, et al. *Nat Med*. 2024;30(1):257-264.


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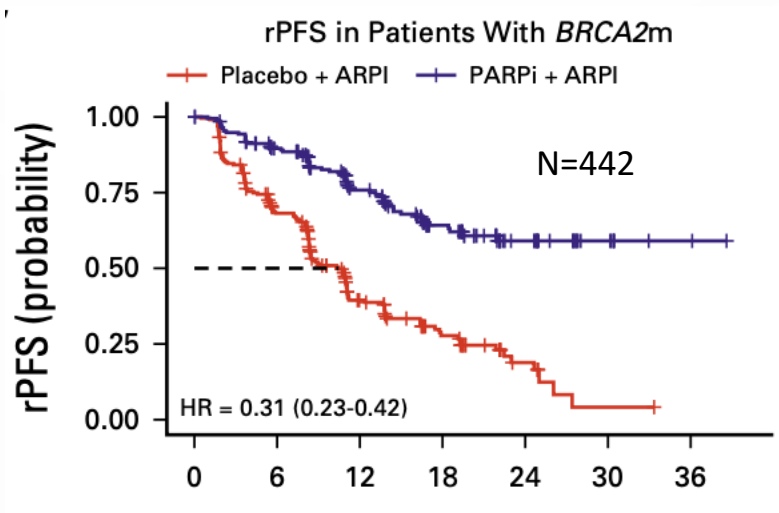
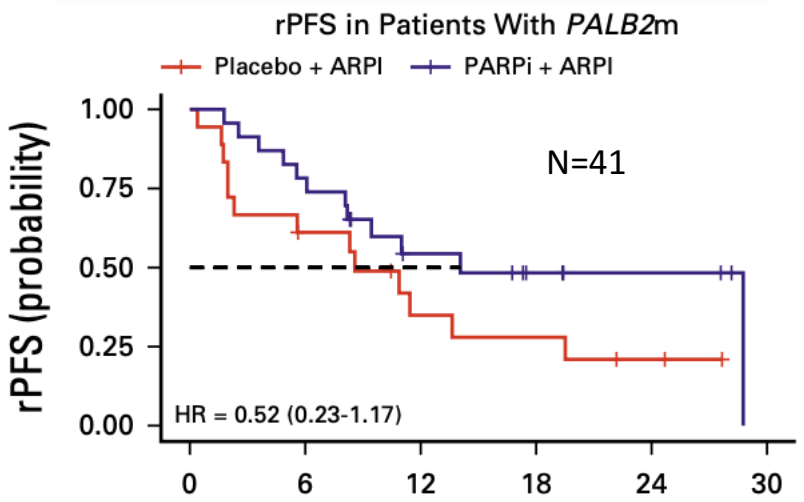
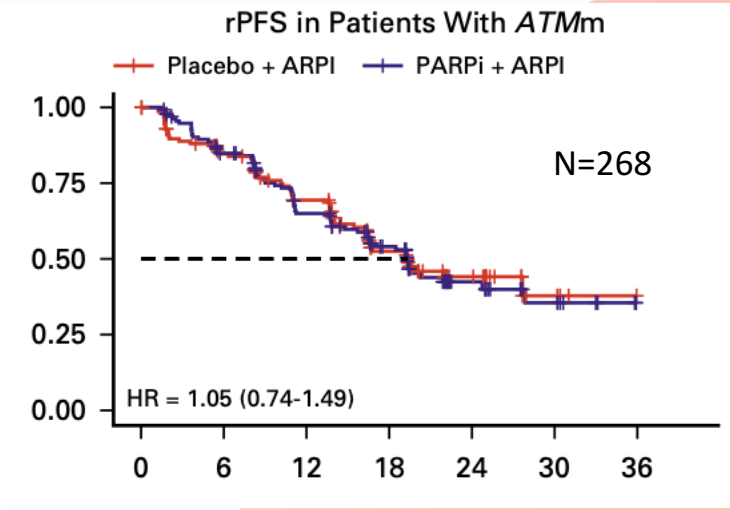
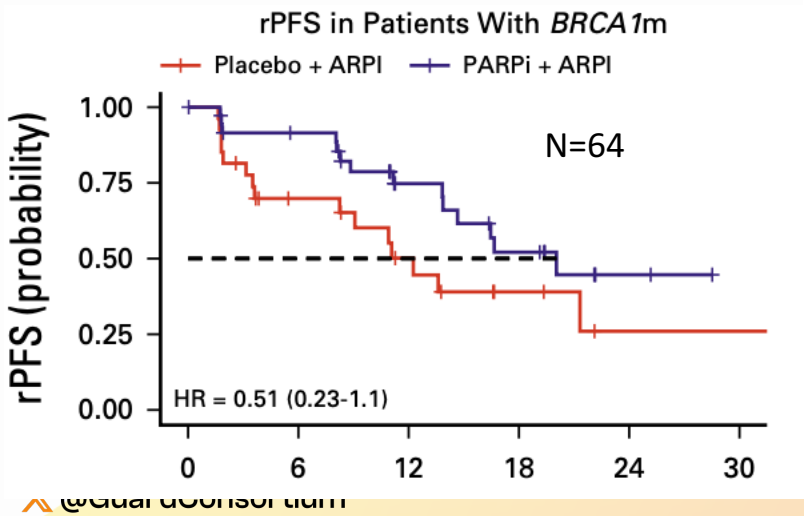
# Patient selection for non-BRCA HRR

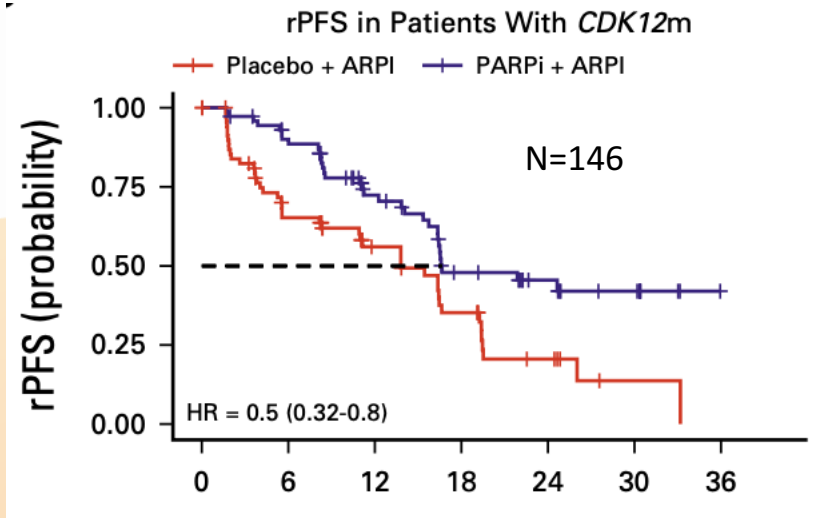
FDA pooled analysis of three trials of PARPi + ARPi combination + 3 trials of PARPi monotherapy

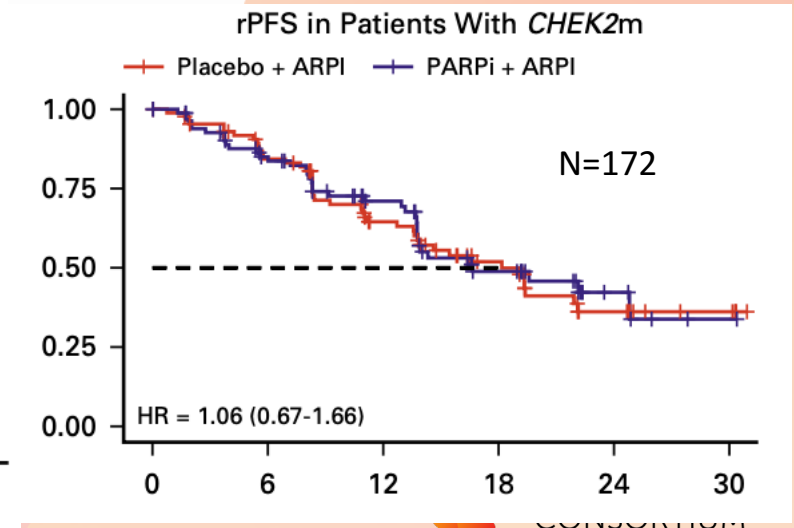


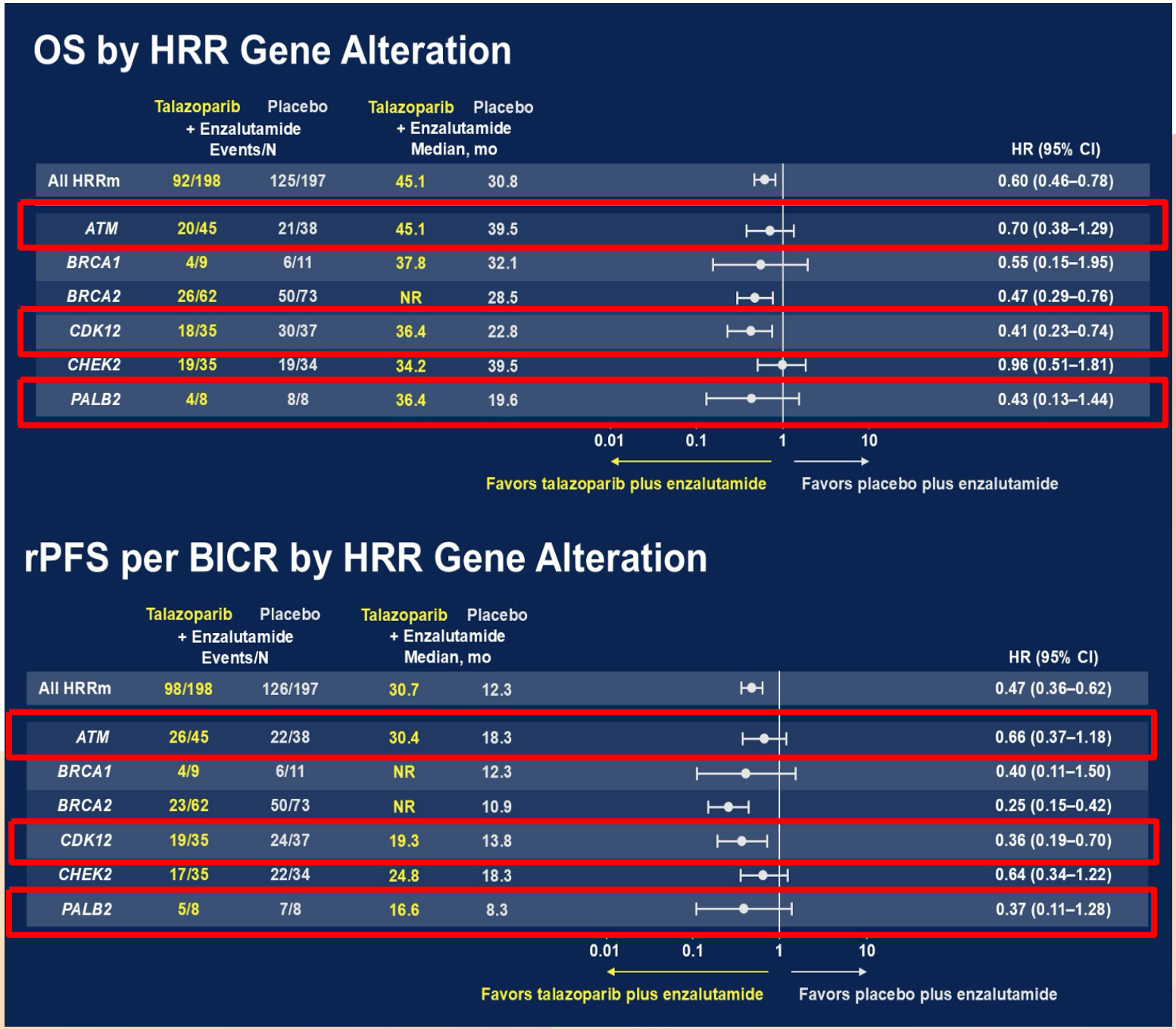




Fallah et al. J Clin Oncol 2024

# TALAPRO-2: Benefit in individual non-BRCA HRR alterations

Benefit in some non-BRCA HRR alterations

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Who to test? Test everybody!!

Do PARPi – NHA combinations eliminate the need for testing?

Who is the ideal candidate for treatment?

# What, where and when to test?

# Assessing DNA repair defects on tumor tissue

- Tumor testing is the **gold standard (high clinical sensitivity)**
- DNA repair alterations are **early events**
- Fresh or achival tumor samples can be used (older samples have lower success rates)
- **Can capture both germline and somatic mutations**

| *PROFOUND study: primary vs metastatic tissue* | HHR gene alteration prevalence % |
|---|---|
| All patients | 27.9% |
| All primary tumors<br>Archived primary<br>Newly collected primary | 27%<br>27%<br>26.5% |
| All metastatic tumors<br>Archived metastatic<br>Newly collected metastatic | 32.3%<br>33.9%<br>29.7% |

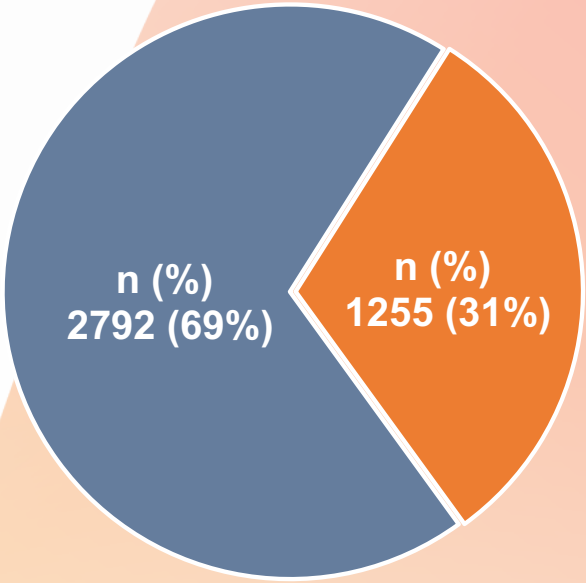
## High failure rates (~30%)

*Sample selection and optimisation of tissue collection is critical*

***Rates of tissue failure***

| Trial | (%) |
|---|---|
| PROFOUND | 31% |
| TRITON2 | 32% |
| IPATENTIAL 150 | 33% |

***PROFOUND study***




**Single-site biopsies do not capture intra-individual heterogeneity**

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De Bono et al. ESMO 2019. Green et al. AACR 2019. De Bono et al. ASCO GU 2021.

# Assessing DNA repair defects in ctDNA

Circulating tumor DNA assessment

**Non-invasive**, safer, serial analysis
Useful where **no tissue is available**
Can detect both **germline and somatic** mutations
Capture relative **contribution of metastases** in different anatomical sites

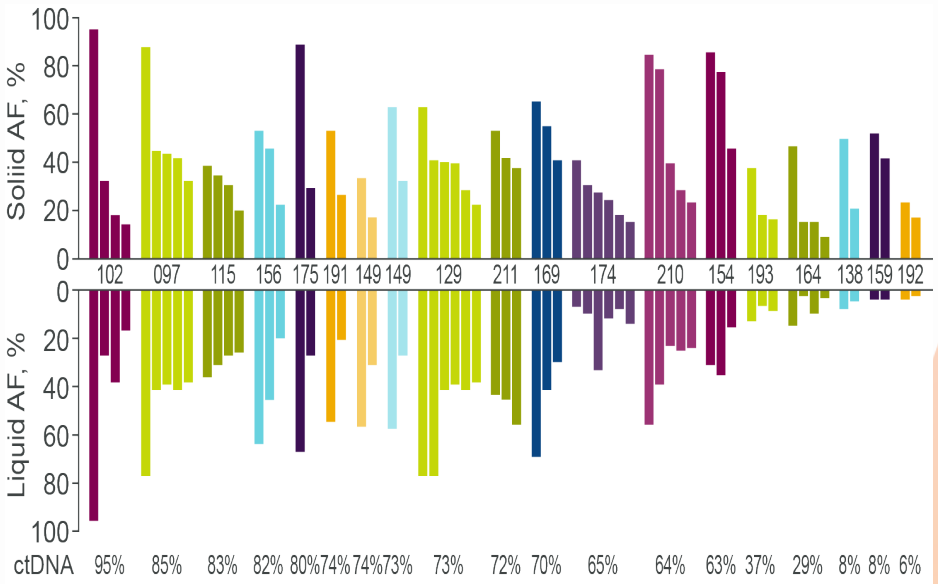
## But…

Biallelic deletions associated with greatest benefit to PARP inhibitors

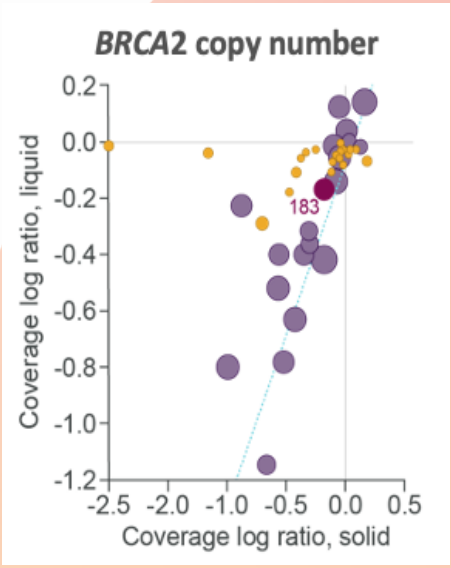
***% pts with ctDNA fraction >20% was*** 47% (401/856) in TRITON2 & 28% (233/818) in TRITON3

ctDNA fraction may sharply decline only weeks after initial ADT (in mHSPC)

***Similar mutation profiles***




***Similar copy number alterations***




| | Mutations | Monoallelic deletions | Biallelic deletions | Amplific |
|---|---|---|---|---|
| **ctDNA, %** | >0.1 | >5–10 | >10–15 | >2-5 |
| **% mCRPC Pts** | >80% | 50% | 40% | CN dependent |

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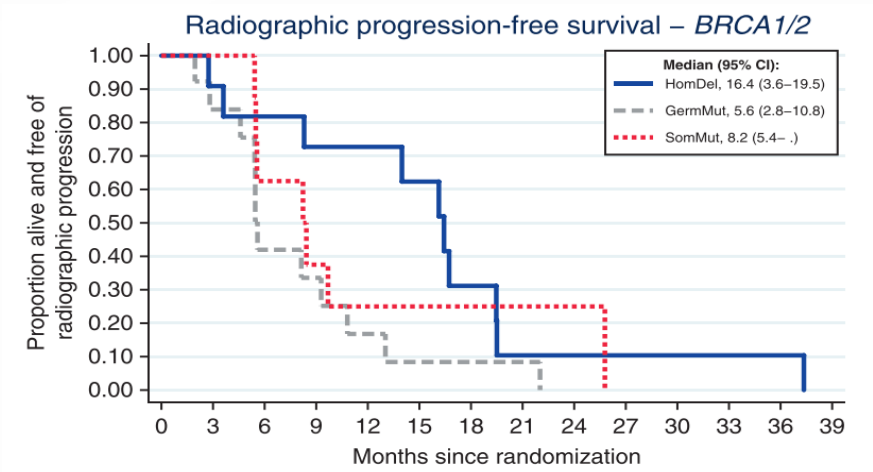
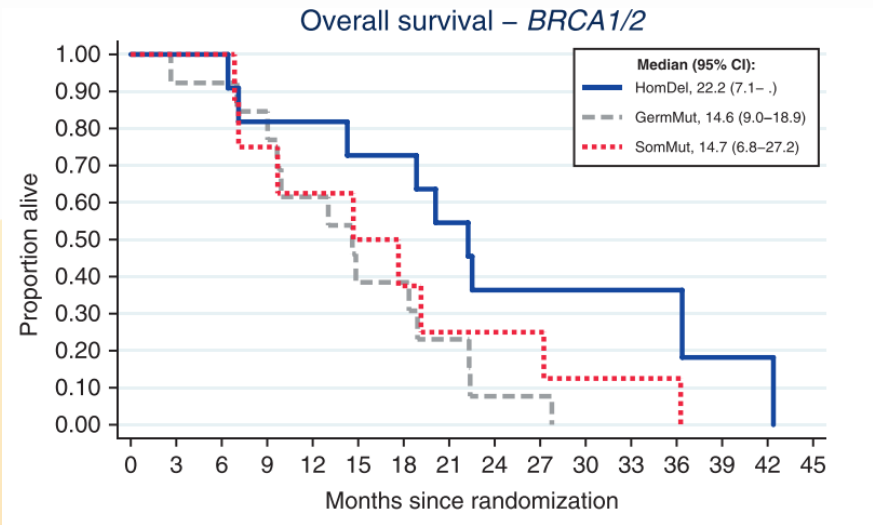
Wyatt AW et al. J Natl Cancer Inst 2017. Annala M et al. Cancer Discov 2018. Carreira et al. Cancer Discov 2021. Tukachinsky et al. Clin Cancer Res 2021. Vandekerkhove et al. Eur Urol 2019. Carreira et al. Cancer Discov 2021. Jensen et al. JAMA Oncol 2021

# Not all BRCA mutants are the same

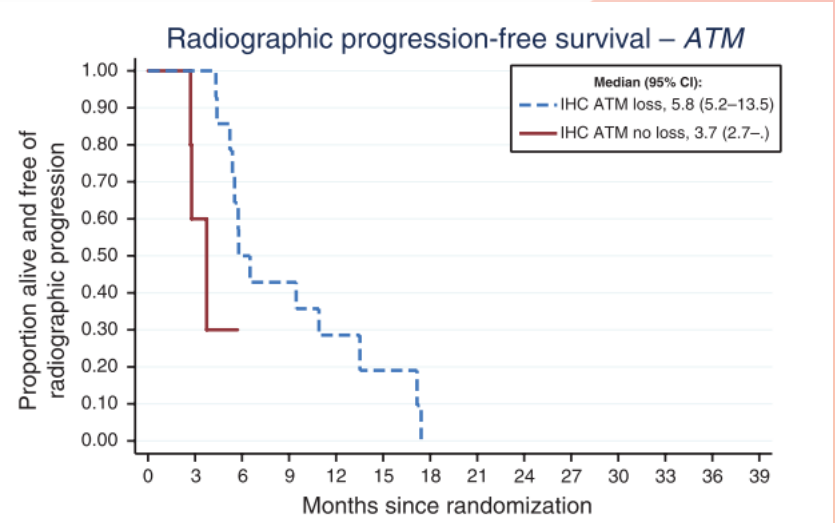
*Biallelic BRCA2 mutations derive the greatest benefit from PARP inhibition*

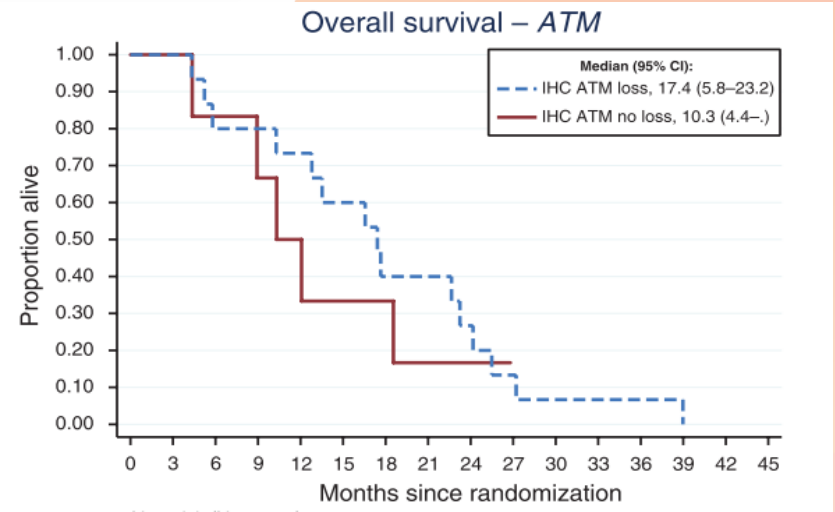
***Homozygous BRCA deletions***




***ATM loss by IHC***

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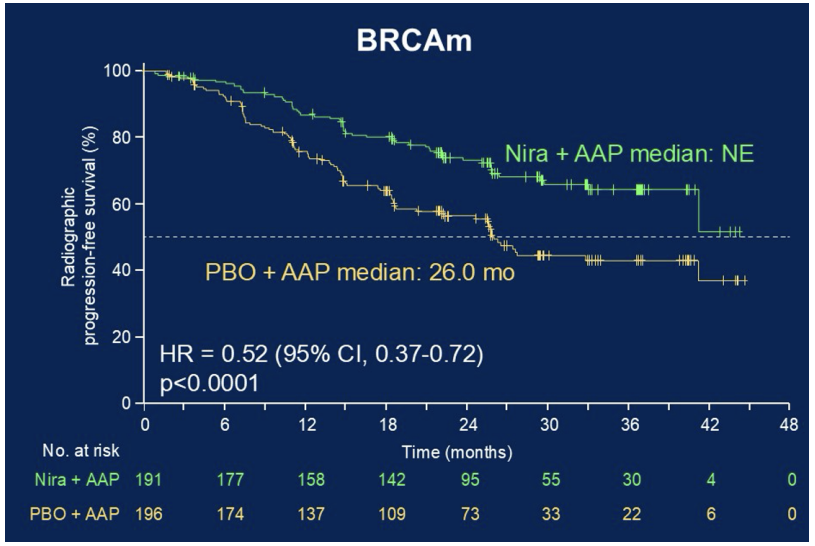
Carreira et al. Cancer Discov 2021

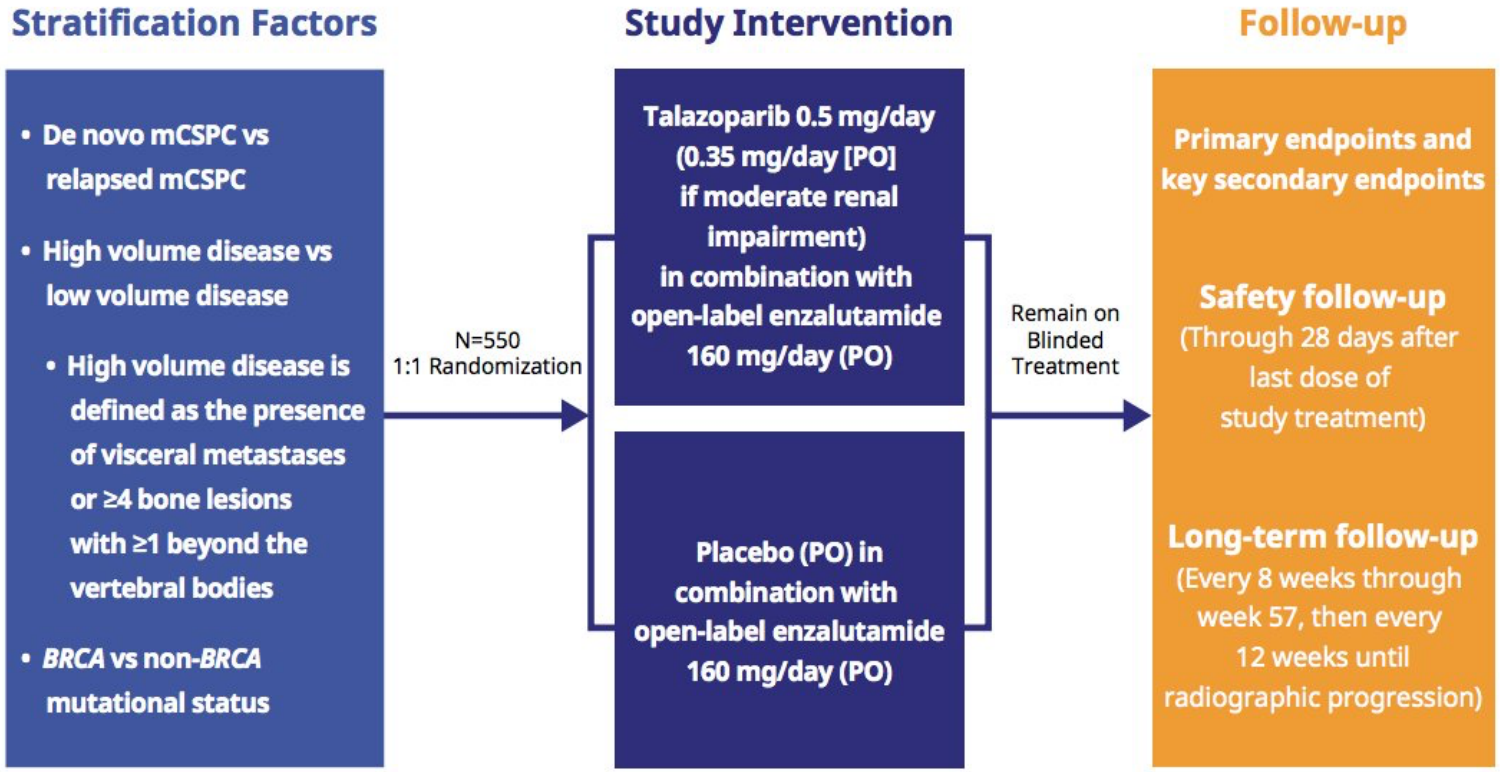
# When to test?

ASCO 2025: Niraparib + Abiraterone improves rPFS in mHSPC HRR mutant population




**TALAPRO-3**: talazoparib plus enzalutamide versus placebo plus enzalutamide in men with mCSPC with DDR/HRR alterations.

- Alterations in 12 DDR/HRR genes (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)
- Metastatic disease (no brain metastases)




Attard et al. ASCO 2025. Agarwal et al. ESMO 2021

# TALAPRO-2. Who should we test? Who is the ideal candidate for treatment?

- Test **all metastatic patients** because testing has **prognostic, predictive and family risk** implications
  Test as soon as possible (currently mCRPC, implications for mHSPC therapy coming soon)

- Alterations in **HRR genes** identify candidates for treatment with PARP inhibitors (monotherapy or in combination with NHAs)

- **Talazoparib + Enzalutamide** is the only **PARPi + NHA combo** that has proven **overall survival benefit** in a randomized phase III trial
  Greatest benefits in **BRCA** mutants but evidence of **benefit with other alterations**

- Outstanding issues when **finding the ideal candidate for treatment**
  What is the HRR alteration? What type of alteration (point mutation, biallelic deletion…)
  What was the patient's prior therapy? Was the prior ARPi abiraterone or apa/enza/daro?
  What is the patient's general status? What is the burden of disease?
  What are the goals of treatment?

# Thank you!

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# ¡Gracias!

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