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GUARD INTERNATIONAL SYMPOSIUM

GU-Alliance for Research and Development

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



16-18 SEPTIEMBRE 2026

Espacio Maldonado, Madrid

What is the best treatment option for 1L mCRPC?

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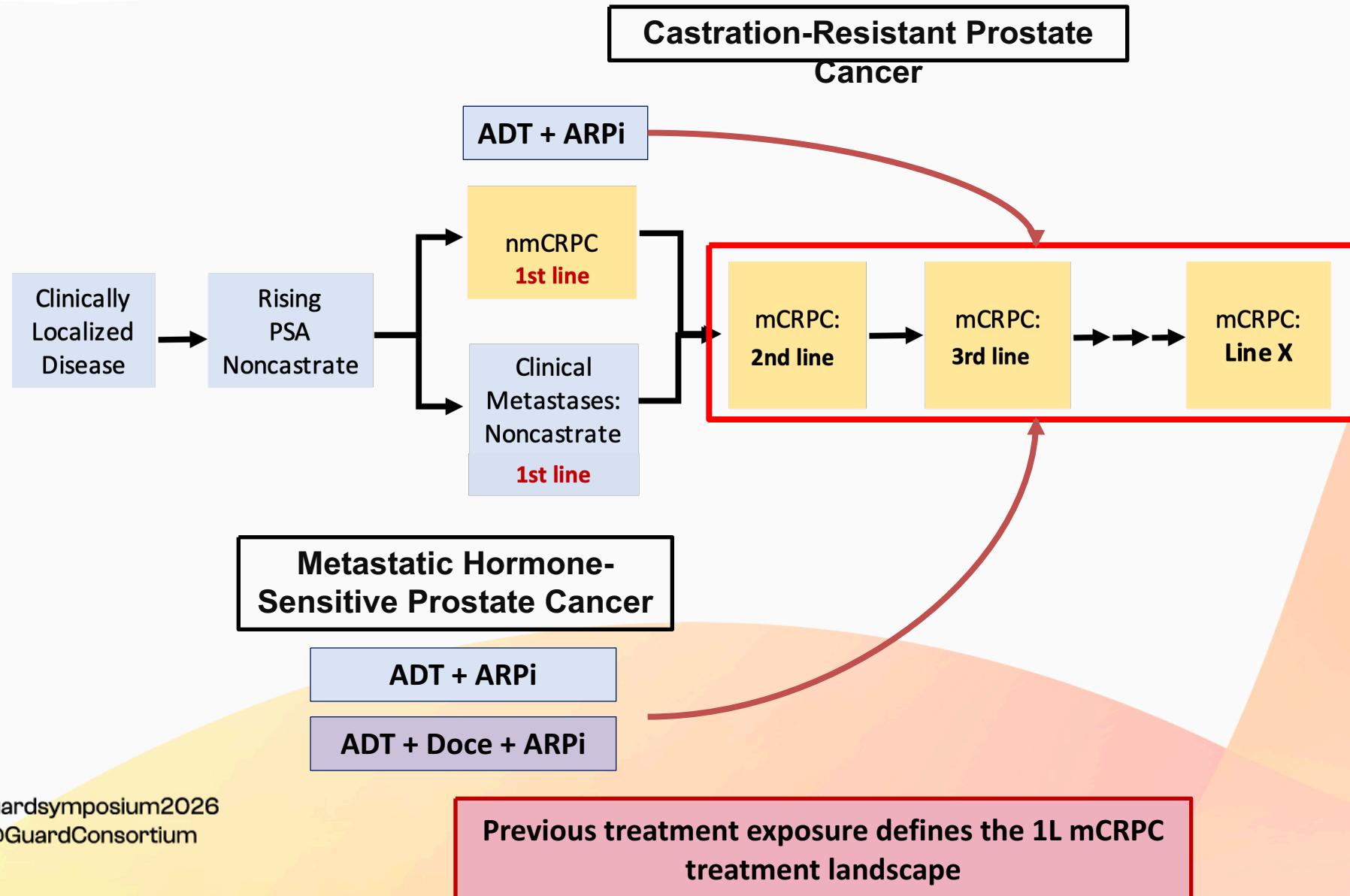
Disclosures

Speaker fees: MSD, Advanced Accelerator Applications (AAA), Johnson & Johnson (J&J), Astellas, Roche, Bayer, Sanofi, IPSEN, AstraZeneca, Pfizer, Gilead

Advisory board: Johnson & Johnson (J&J), Merck/Pfizer, Orion Pharma, Advanced Accelerator Applications (AAA), Astellas

Travel/accommodation: Roche, Astellas, Sanofi, Johnson & Johnson (J&J), MSD, BMS, Merck

First-line mCRPC depends on what came before



Why previous exposure matters?

Sequential AR pathway inhibition

	Abi → Enza	Enza → Abi
N	73	75
PSA response	36%	4%
PSA-PFS	3,5 m	1,7 m

	Population	Control arm	Endpoint	Median PFS
CARD	Post-docetaxel, post-ARSI	Change ARSI	rPFS	3,7 m
PSMAfore	Post-ARSI, Taxane-naïve, PSMA+	Change ARSI	rPFS	5,6 m
PROFOUND	Post-ARSI	Alternate ARSI	rPFS	3.5 m

ARPI → ARPI is a suboptimal strategy

Scenario 1: ADT alone / no prior ARPI

ARPI-näive mCRPC: the “classical” evidence still matters

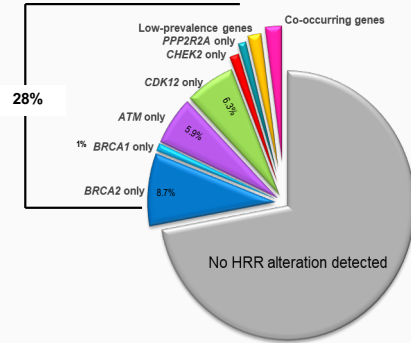
	Overall survival		
	Experim	Control	HR (IC 95%)
TAX-327 Docetaxel vs Mitoxantrona	19,2 m	16,3 m	0,79 (0,67-0,93)
COU-302 Abiraterone/P vs Placebo/P	34,7 m	30,3 m	0,81 (0,70-0,93)
PREVAIL Enzalutamide vs Placebo	35,3 m	31,3 m	0,77 (0,67-0,88)

Several effective 1L options remain in ARPI-näive
mCRPC

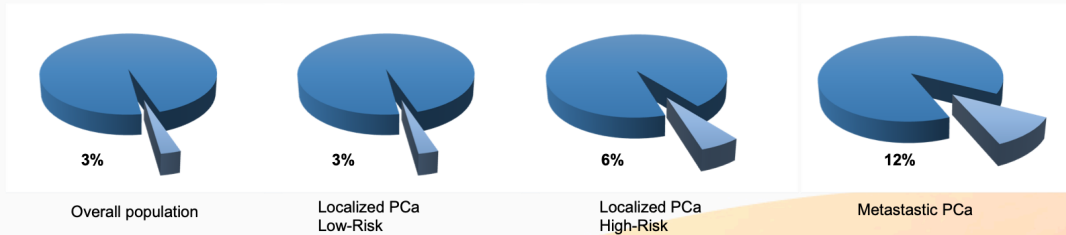
What has changed in ARPI-naïve mCRPC?

Molecular testing is now part of 1L treatment planning

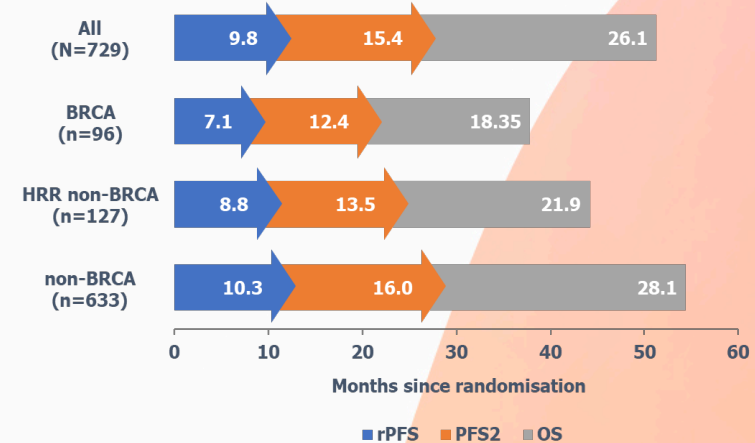
Alterations detected in tumoral tissue



Germline alterations



1L mCRPC



BRCA alterations are associated with poor prognosis

BRCA alterations provides both prognostic and predictive information

Scenario 2: prior docetaxel, no prior ARPI

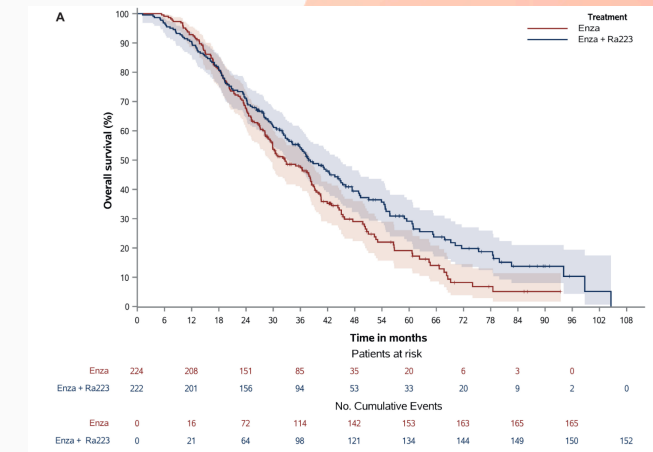
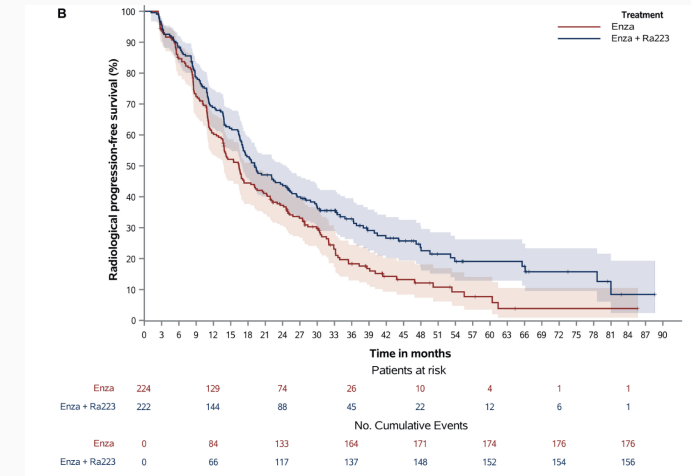
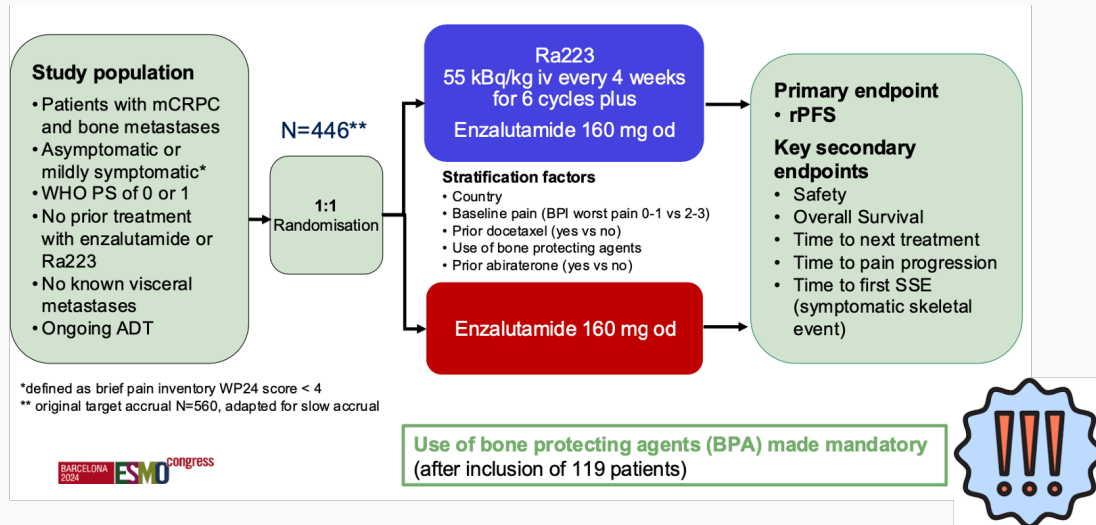
Prior docetaxel → several life-prolonging options remain effective

	Overall survival		
	Experim	Control	HR (IC 95%)
TROPIC Cabazitaxel vs Mitoxantrona	15,1 m	12,7 m	0,70 (0,59-0,83)
COU-301 Abiraterone/P vs Placebo/P	15,8 m	11,2 m	0,74 (0,64-0,86)
AFFIRM Enzalutamide vs Placebo	18,4 m	13,6 m	0,63 (0,53-0,75)
ALSYMPCA Radium-223 vs Placebo	14,9 m	11,3 m	0,70 (0,58-0,83)

These trials were not conducted in patients receiving docetaxel for mHSPC

An additional option: PEACE-3

Enzalutamide + radium-223 Patients without visceral metastases



Prior docetaxel (30%) and abiraterone (3%) were allowed for mHSPC

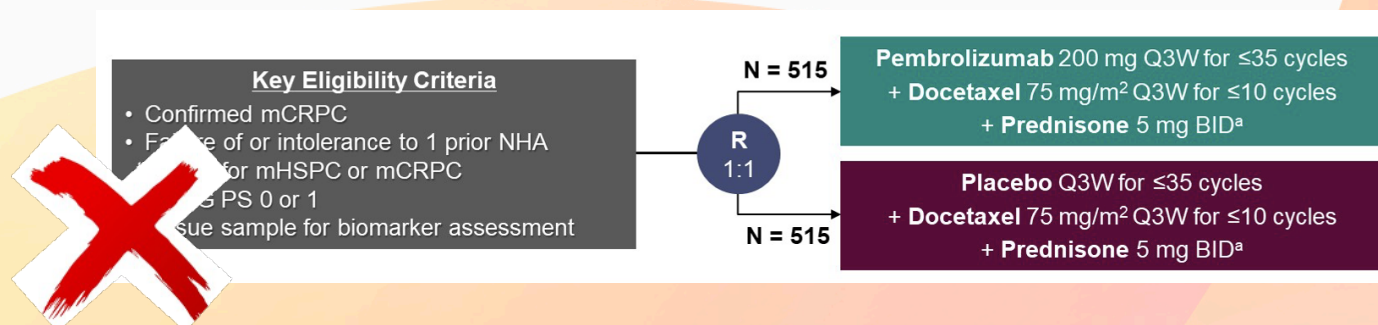
Scenario 3: prior ARPI

After prior ARPi: chemotherapy remains an effective treatment

	N	PSA Resp	PFS	OS
TAX-327	1006	52.4%	NR	19.2 m
ABIDO (Abi → Docetaxel)	47	46.5%	5.5 m	16.9 m
SPARTAN post-hoc analysis	29	NR	7.9 m	18.2 m

KEYNOTE-921	1030	45.7%	8.3 m	19 m
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Modern prospective evidence confirms docetaxel activity after ARPI



A new pre-taxane option?

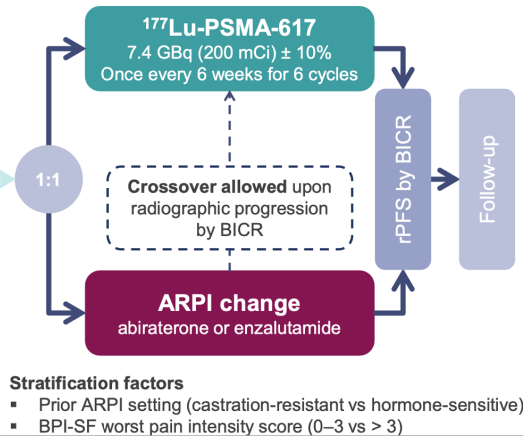
PSMAfore: moving ^{177}Lu -PSMA-617 earlier

PSMAfore: a phase 3, randomized, open-label study

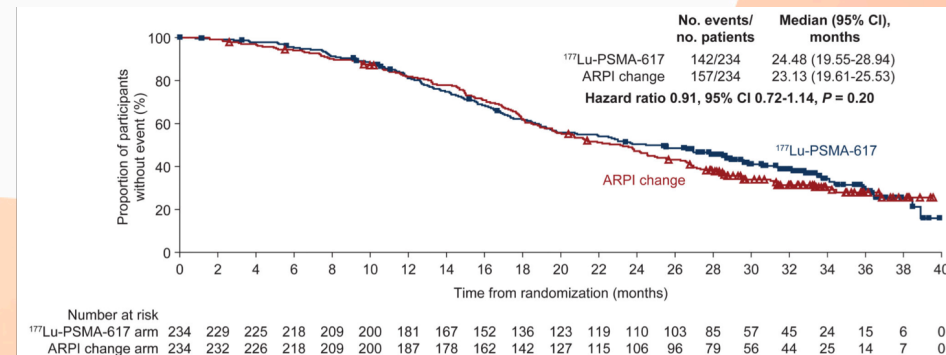
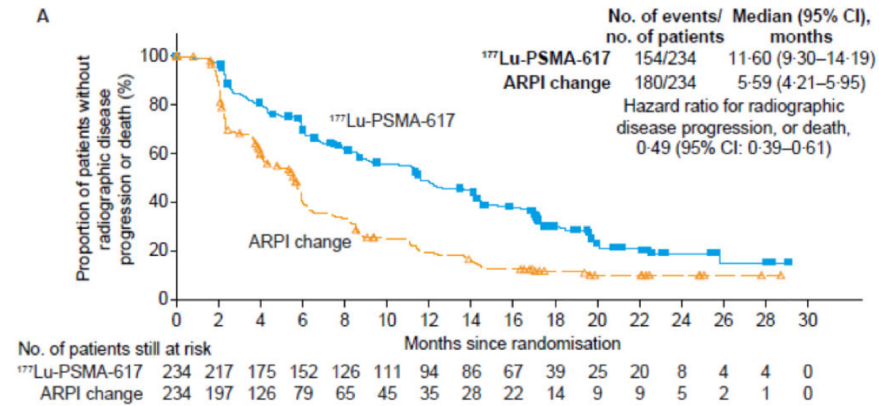
Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
 - Candidates for change in ARPI
- Taxane-naïve (except [neo]adjuvant > 12 months ago)
 - Not candidates for PARPi
- ECOG performance status 0–1

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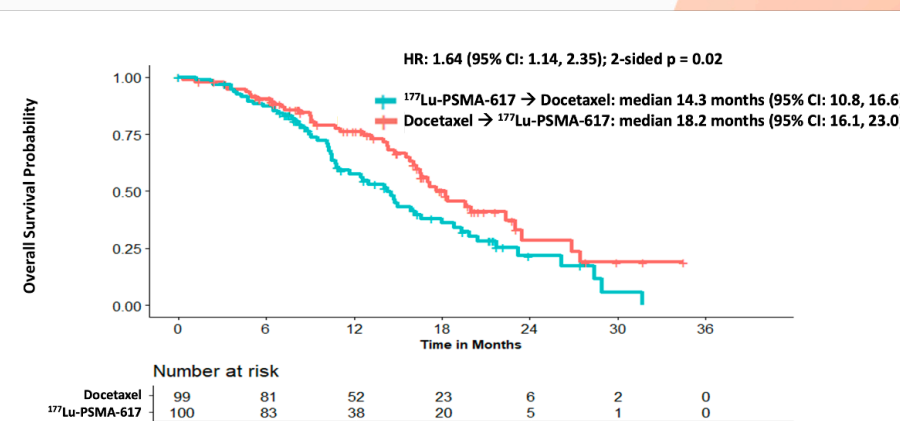
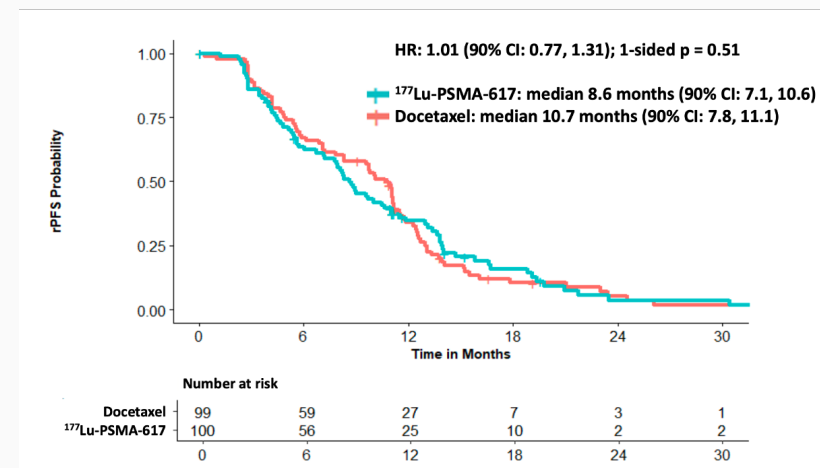
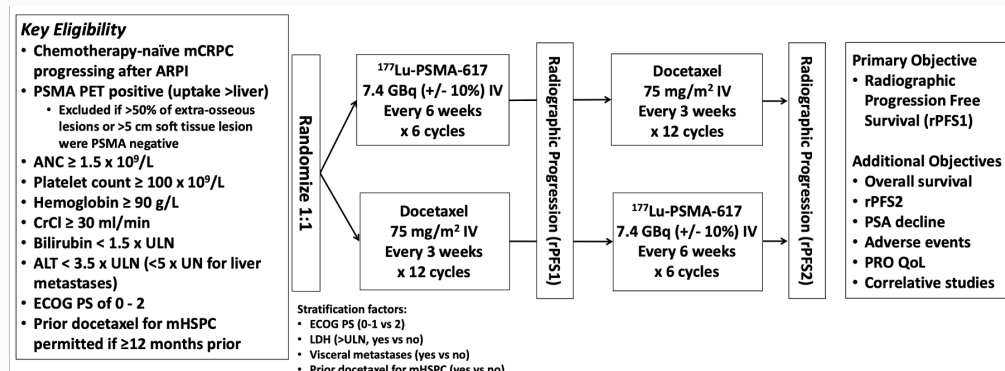


A



But what is the right comparator?

Randomized phase II evidence



Direct randomized phase II comparison: no rPFS advantage over docetaxel; sequencing remains unresolved

Scenario 4: prior ARPi + docetaxel

CARD trial: cabazitaxel beats a second ARPi

CARD -STUDY DESIGN-

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Patients with mCRPC who progressed ≤ 12 months on prior AR-targeted agent (before or after docetaxel)*

N = 255

R
A
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1:1

Cabazitaxel (25 mg/m² Q3W)
+ prednisone + G-CSF^b
n = 129

Abiraterone (1000 mg QD)
+ prednisone
OR
Enzalutamide (160 mg QD)
n = 126

Endpoints

Primary: rPFS

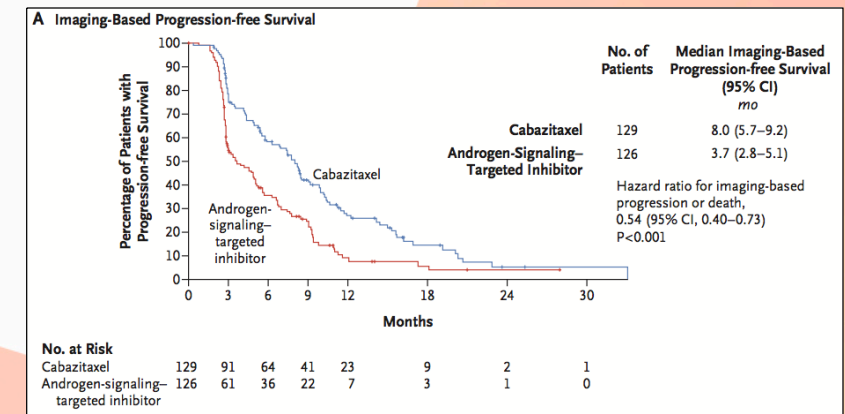
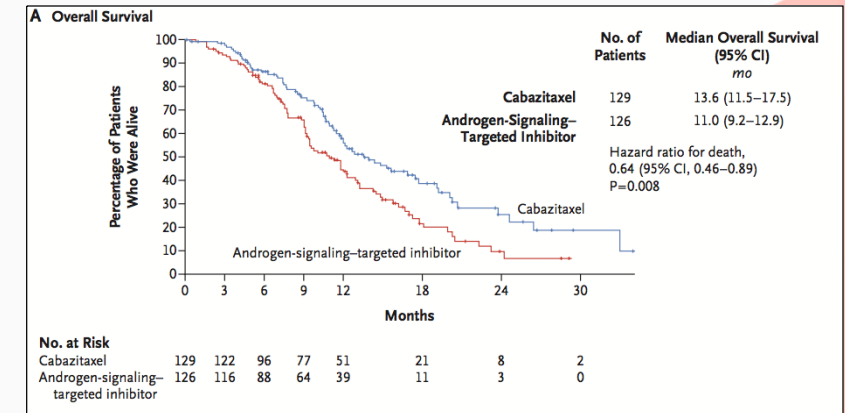
Key secondary: OS, PFS,
PSA response,
tumor response

Other secondary:

Pain response,
time to SSE, safety,
FACT-P, EQ-5D-5L,
biomarkers

Stratification factors:

- ECOG PS (0/1 vs 2)
- time to disease progression (≤ 6 vs $> 6-12$ months)
- timing of previous alternative AR targeted agent (before vs after docetaxel)



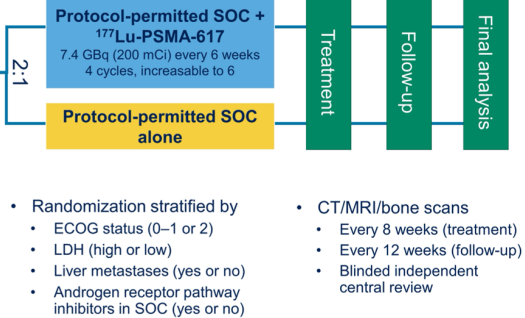
^{177}Lu -PSMA-617 after ARPI + taxane

After ARPI + taxane → more than one evidence-based option

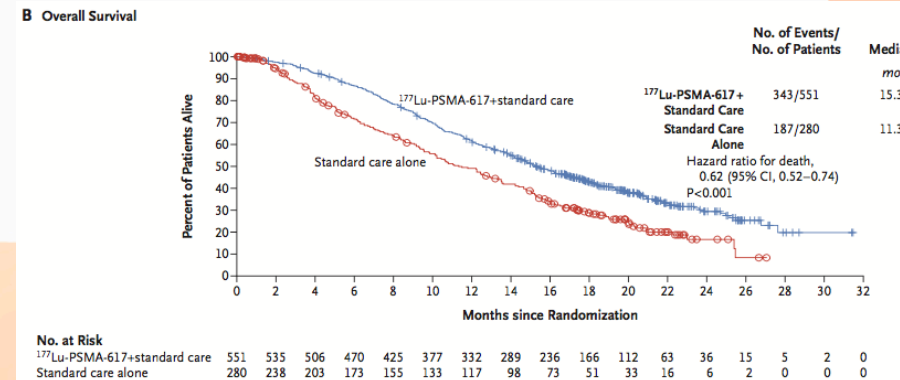
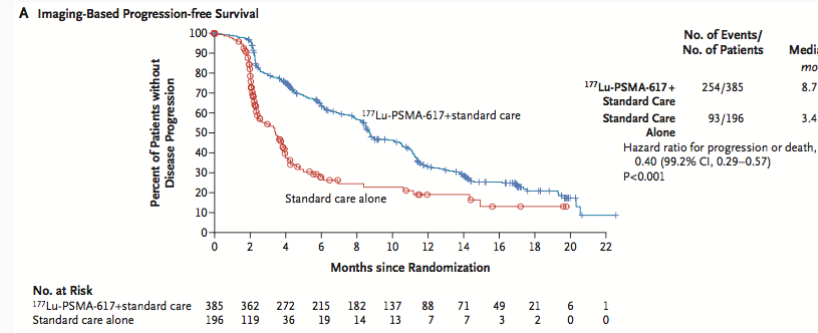
Open-label study of protocol-permitted standard of care ± ^{177}Lu -PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

- Previous treatment with both
 - ≥ 1 androgen receptor pathway inhibitor
 - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
 - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga -PSMA-11



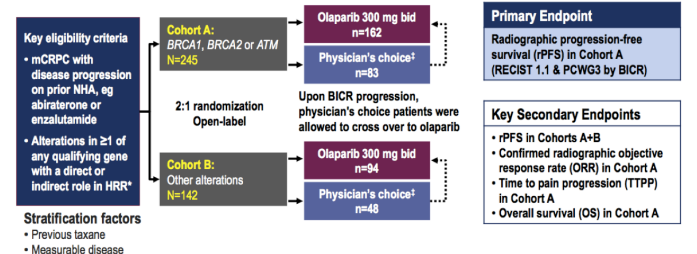
TheraP trial (cabaizatxel vs Lu-PSMA)



Precision medicine changes the sequence

PARPi monotherapy after prior ARPI: benefit is strongly driven by BRCA1/2 alterations

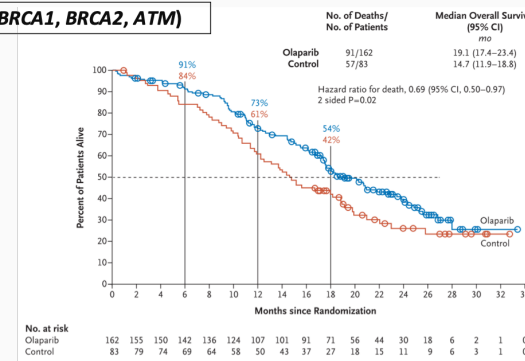
PROfound STUDY DESIGN



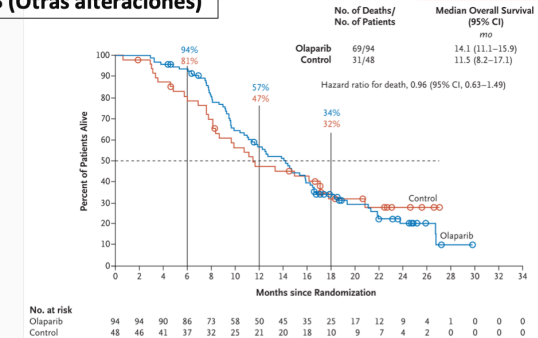
*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/ or RAD54L in their tumor tissue

DOCETAXEL → 65%

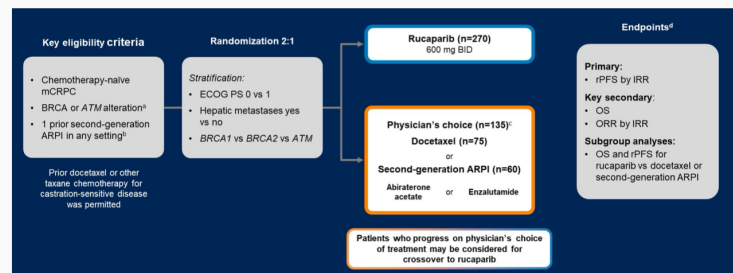
COHORT A (BRCA1, BRCA2, ATM)



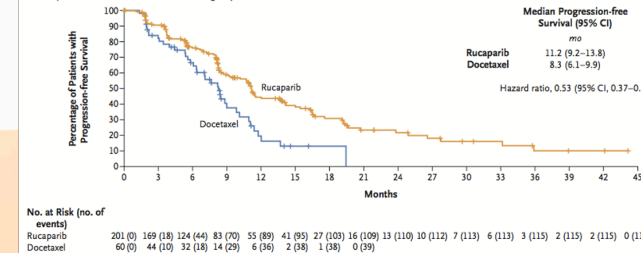
COHORT B (Otras alteraciones)



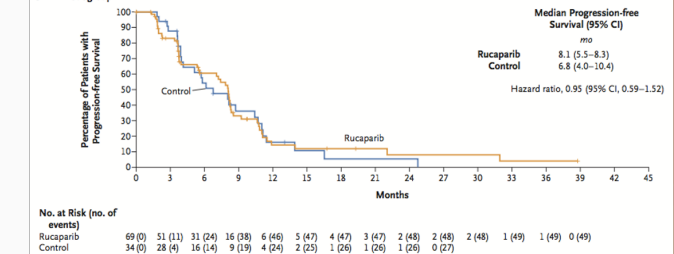
TRITON3 (Phase 3)



A Rucaparib vs. Docetaxel in the BRCA Subgroup

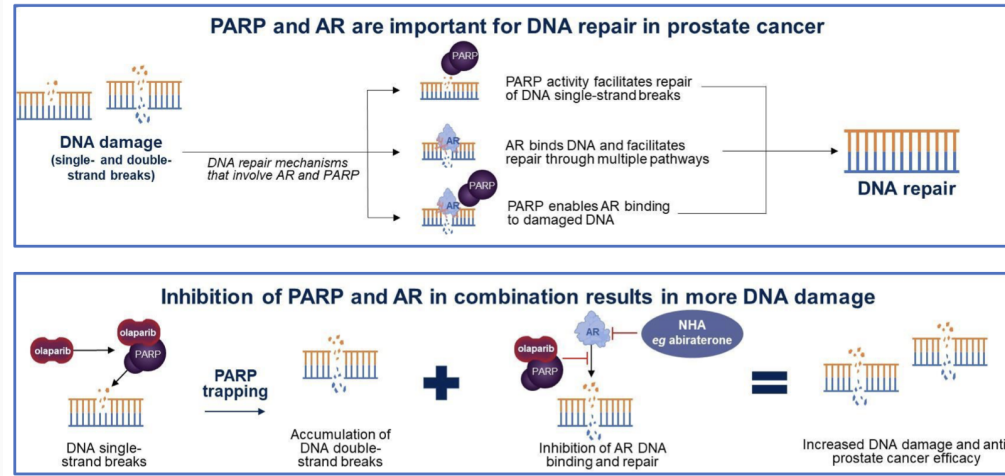


C ATM Subgroup

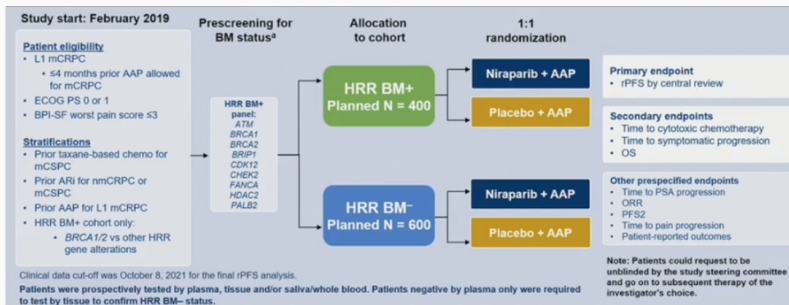


What changes the first-line choice today?

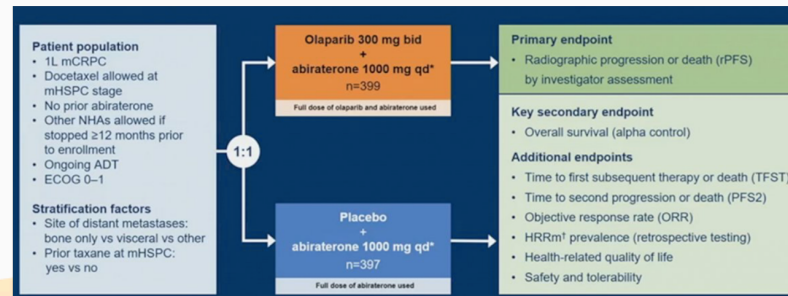
Crosstalk between AR and DDR pathway



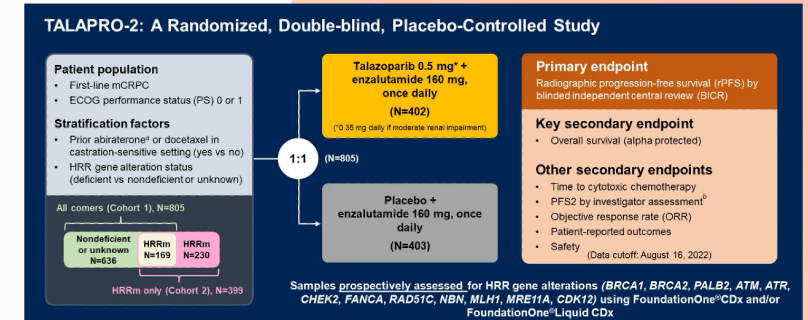
MAGNITUDE



PROpel



TALAPRO-2



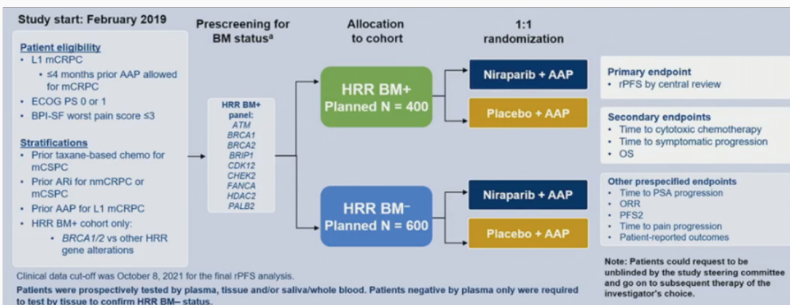
1L mCRPC most patients were ARPI-naïve

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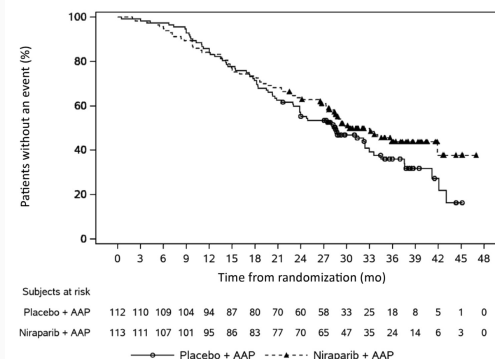


What changes the first-line choice today?

MAGNITUDE

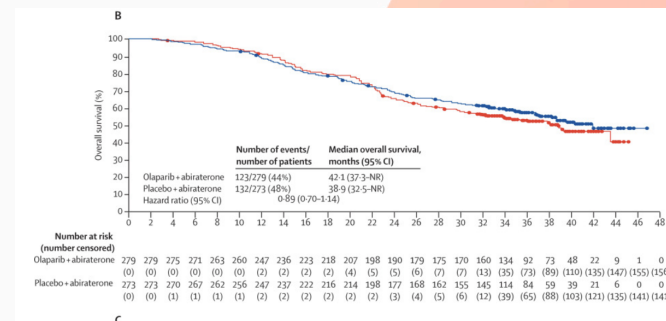
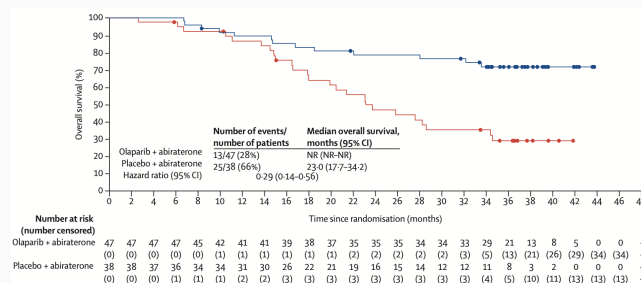
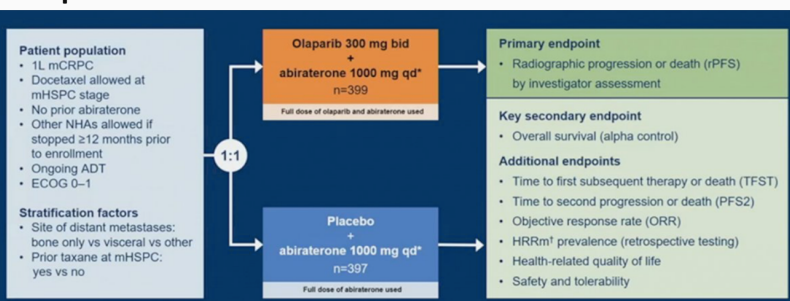


BRCA

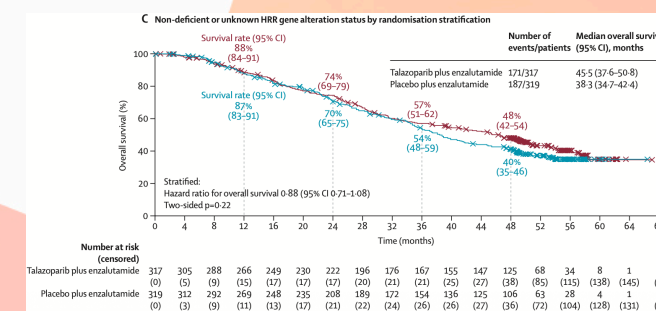
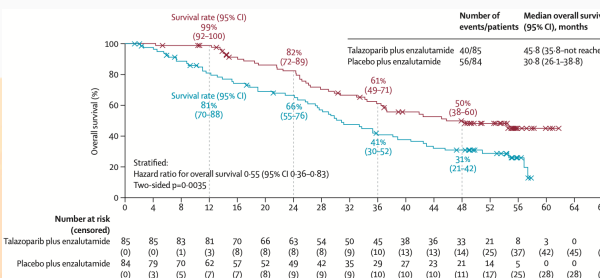
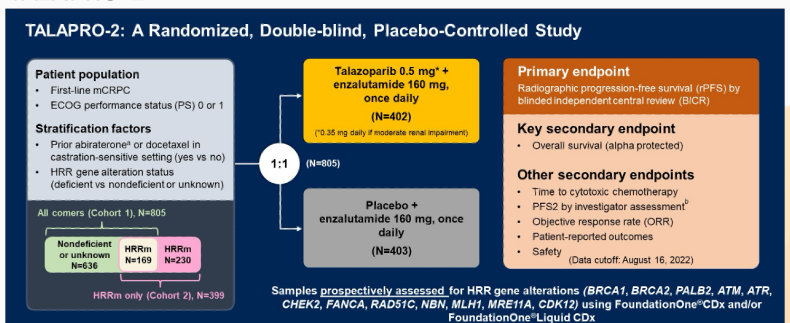


Non-HRR alterations

PROpel



TALAPRO-2



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Benefit: BRCA1/2 > broader HRR > unselected population

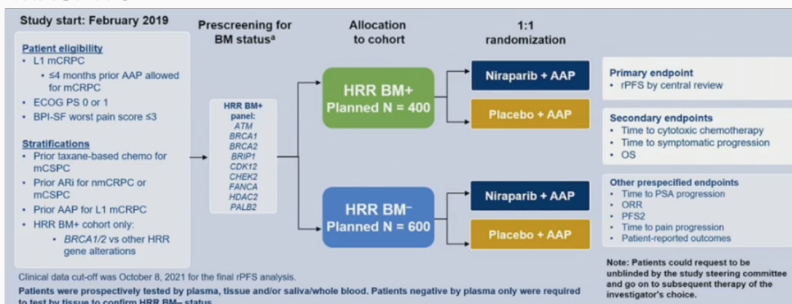


Chi K, et al, J Clin Oncol 2023; Clarke et al, N Engl J Med Evidence 2022; Agarwal N, et al, J Clin Oncol 2023

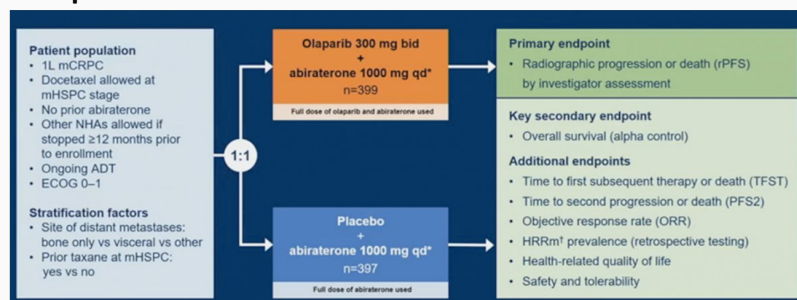
But context matters for PARPi combinations

Can we extrapolate PARPi + ARPI after prior ARPI exposure?

MAGNITUDE



PROpel

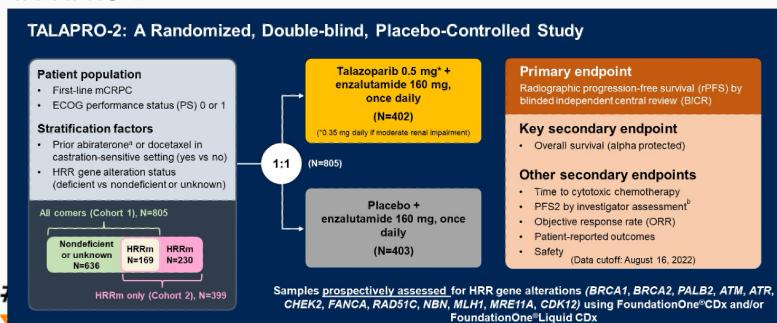


1L mCRPC



Patients with established resistance to a prior ARPI were not represented in the pivotal 1L mCRPC combination trials

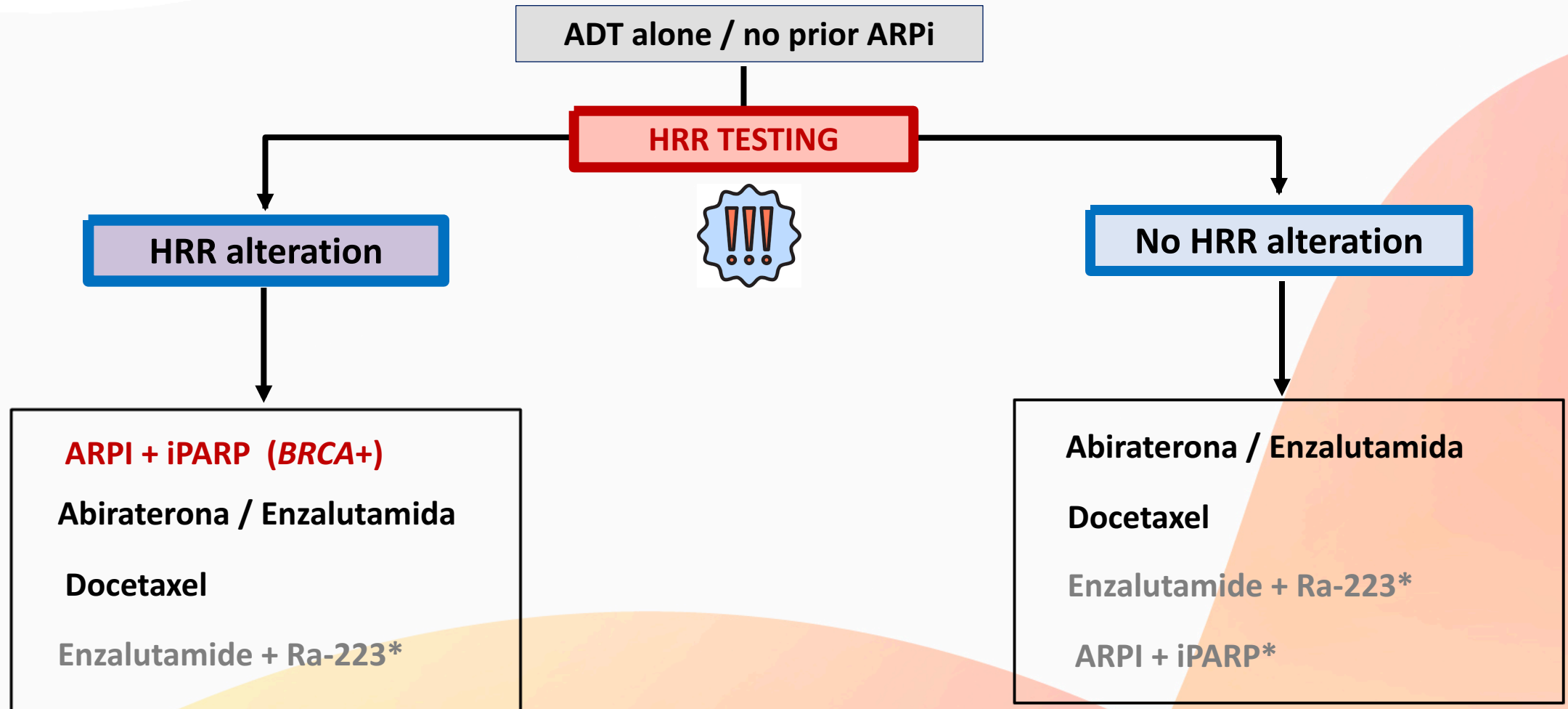
TALAPRO-2



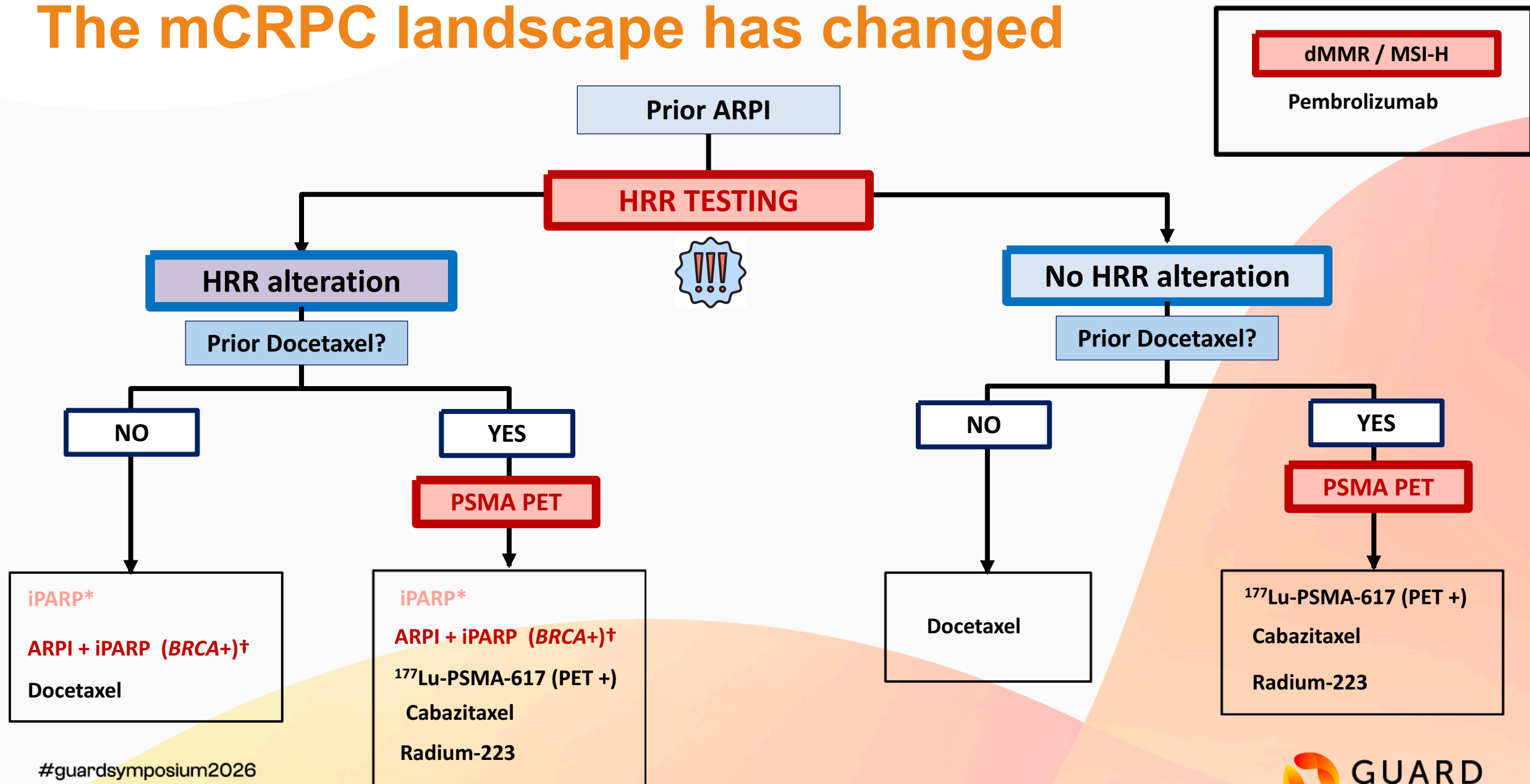
Clinical evidence ≠ current reimbursement landscape



The mCRPC landscape has changed



The mCRPC landscape has changed



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*Not reimbursed in Spain

[†]Limited evidence after prior ARPI exposure

Take-home messages

**Treatment choice depends on what the patient received before,
tumour biology and treatment access**

**There is no universal best first-line treatment – there is a best
next treatment for each patient**



¡Gracias!

