

# XVII SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN  
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

## Cáncer de Próstata Avanzado: un escenario en continua evolución

**Rebeca Lozano Mejorada, MD, PhD**

Oncología Médica

Complejo Asistencial Universitario de Salamanca

Instituto de Investigación Biomédica de Salamanca (IBSAL)

Complejo Asistencial  
Universitario  
de Salamanca



## DISCLOSURES

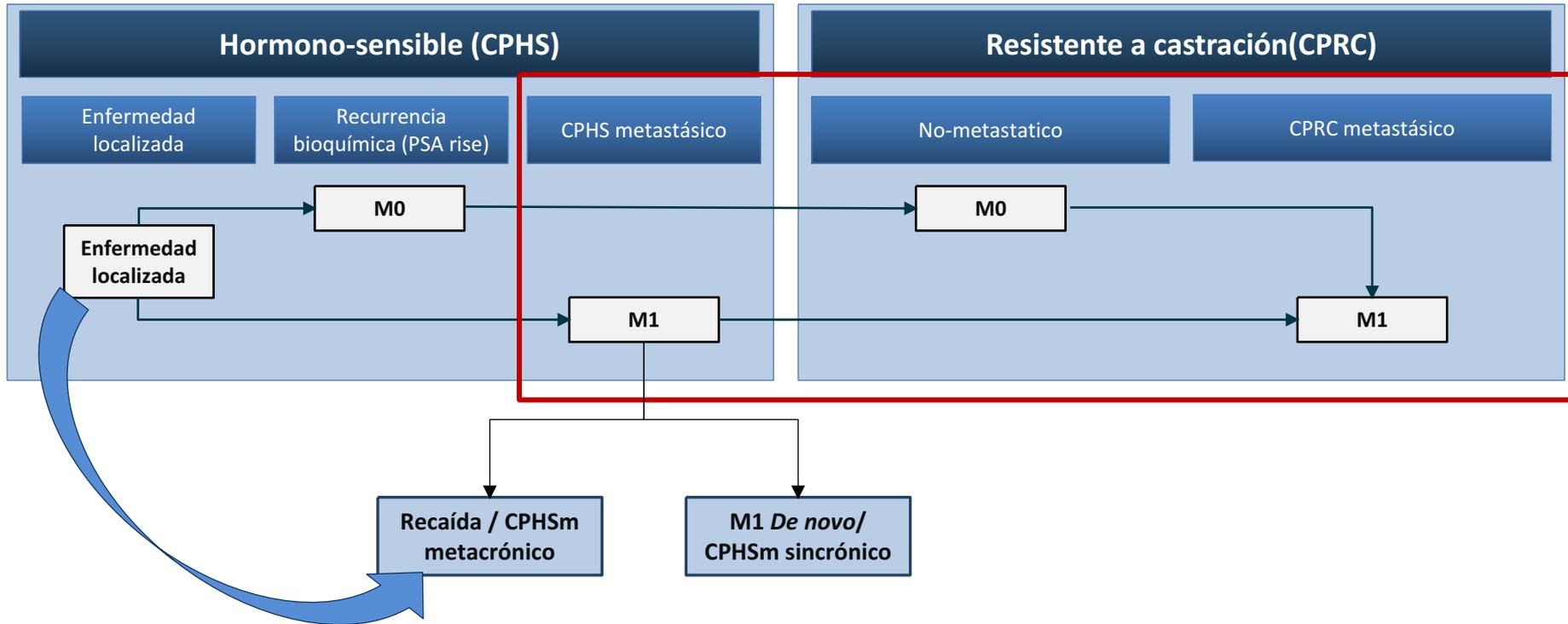
**Speaker fees:** Advanced Accelerator Applications (AAA); Johnson & Johnson, Astellas, Roche, Bayer, Sanofi, IPSEN, AstraZeneca, Pfizer

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

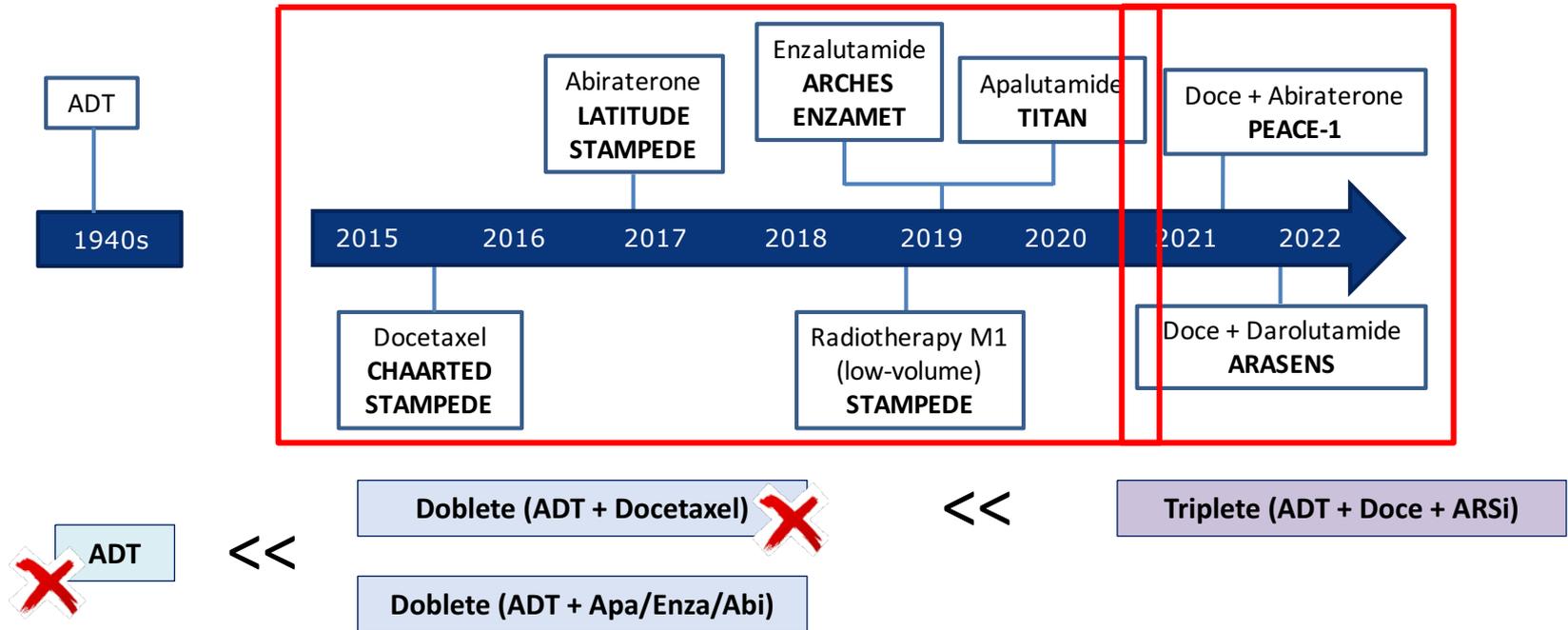
**Travel/accommodation:** Roche, Astellas, Sanofi, Janssen, MSD, BMS, Merck, Novartis

Niveles de testosterona >50ng/dL o 1,7nmol/L

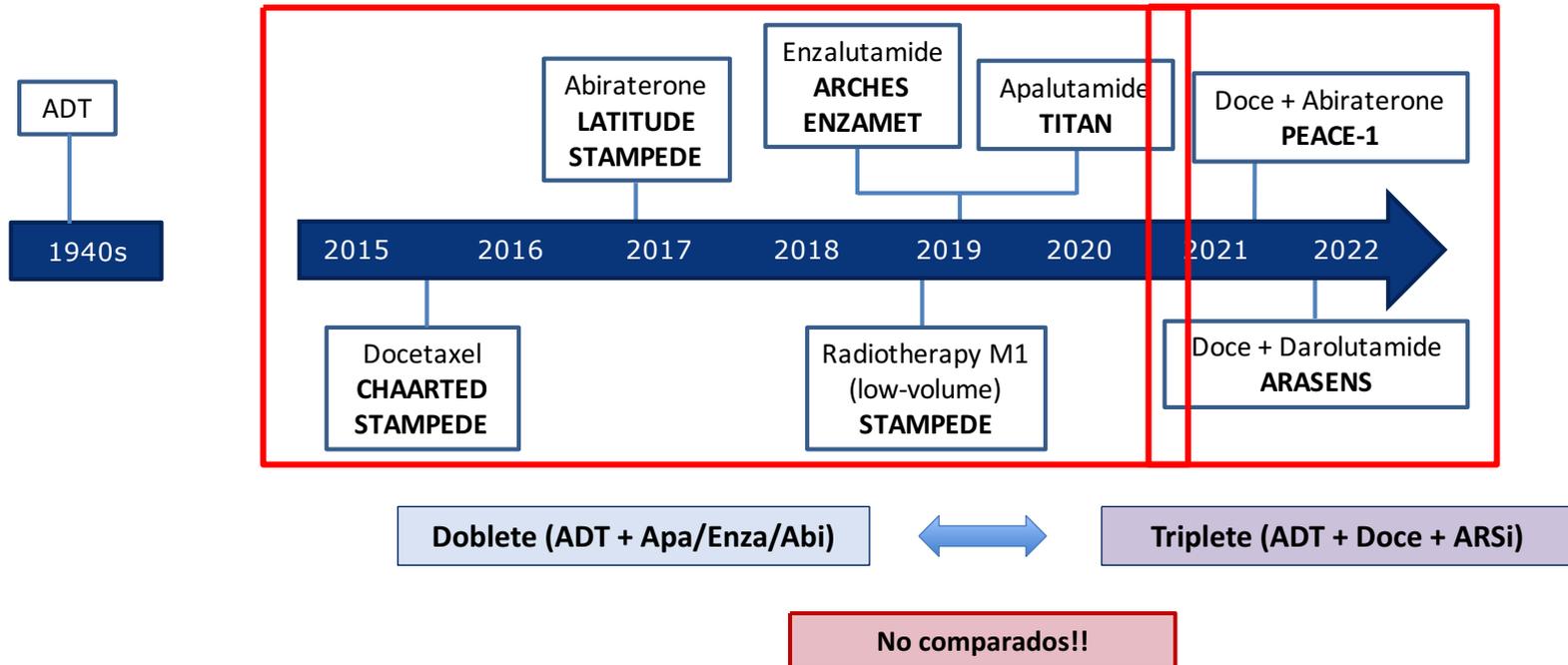
Niveles de testosterona <50ng/dL o 1,7nmol/L



## Cáncer de Próstata Hormonosensible metastásico



## Cáncer de Próstata Hormonosensible metastásico



## Cáncer de Próstata Hormonosensible metastásico

**ALTO** volumen  
tumoral

Metástasis viscerales y/o  $\geq 4$  metástasis óseas (al menos una fuera del esqueleto axial)

**BAJO** volumen  
tumoral

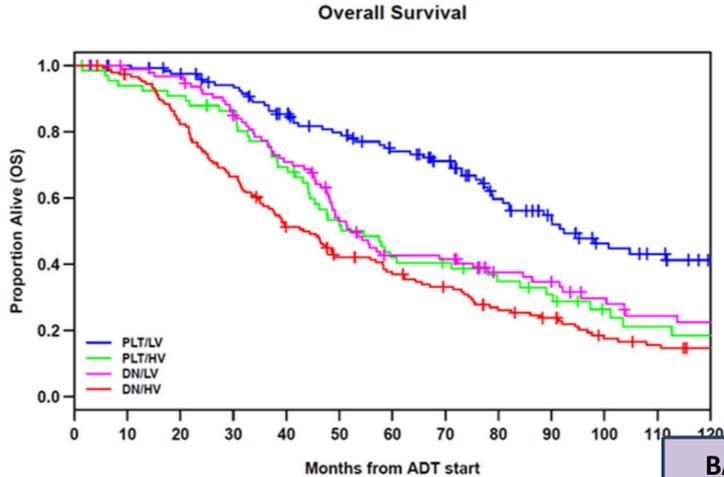
Todo aquel que no cumple criterios de alto volumen

Enfermedad sincrónica / M1 *de novo*

Enfermedad metacrónica / recurrente

Pruebas de imagen convencionales  
(TC, GGO, RM)

## Cáncer de Próstata Hormonosensible metastásico



**Bajo volumen - recaída M1** →

Mediana OS ~8 años

BAJO volumen tumoral

Enfermedad metacrónica / recurrente

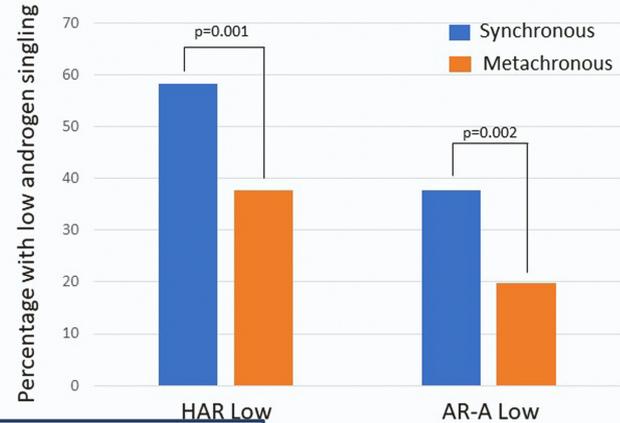
**Alto volumen - diagnóstico M1 de novo** →

Mediana OS ~3 años

ALTO volumen tumoral

Enfermedad sincrónica / M1 de novo

## Biologic difference between timing of metastatic disease



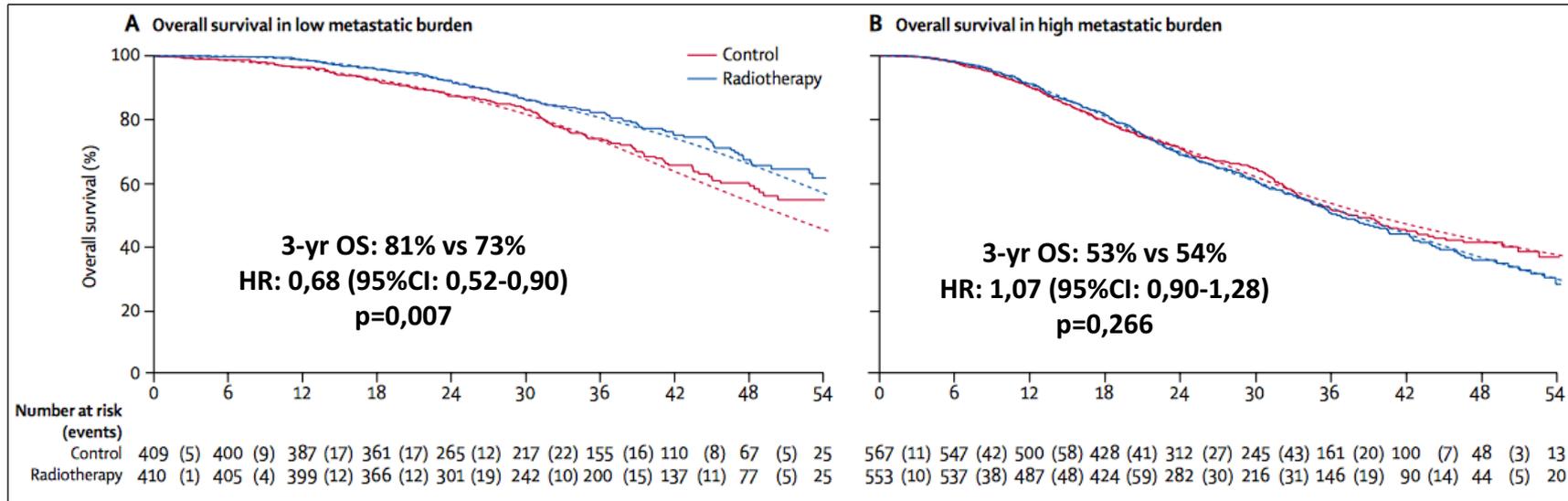
Patients with **synchronous disease** have **lower Androgen Receptor Activity (AR-A)** and **Hallmark Androgen Response (HAR)** gene signature scores in comparison with **metachronous disease**

## ¿TRATAMIENTO LOCAL en mHSCP *de novo*?

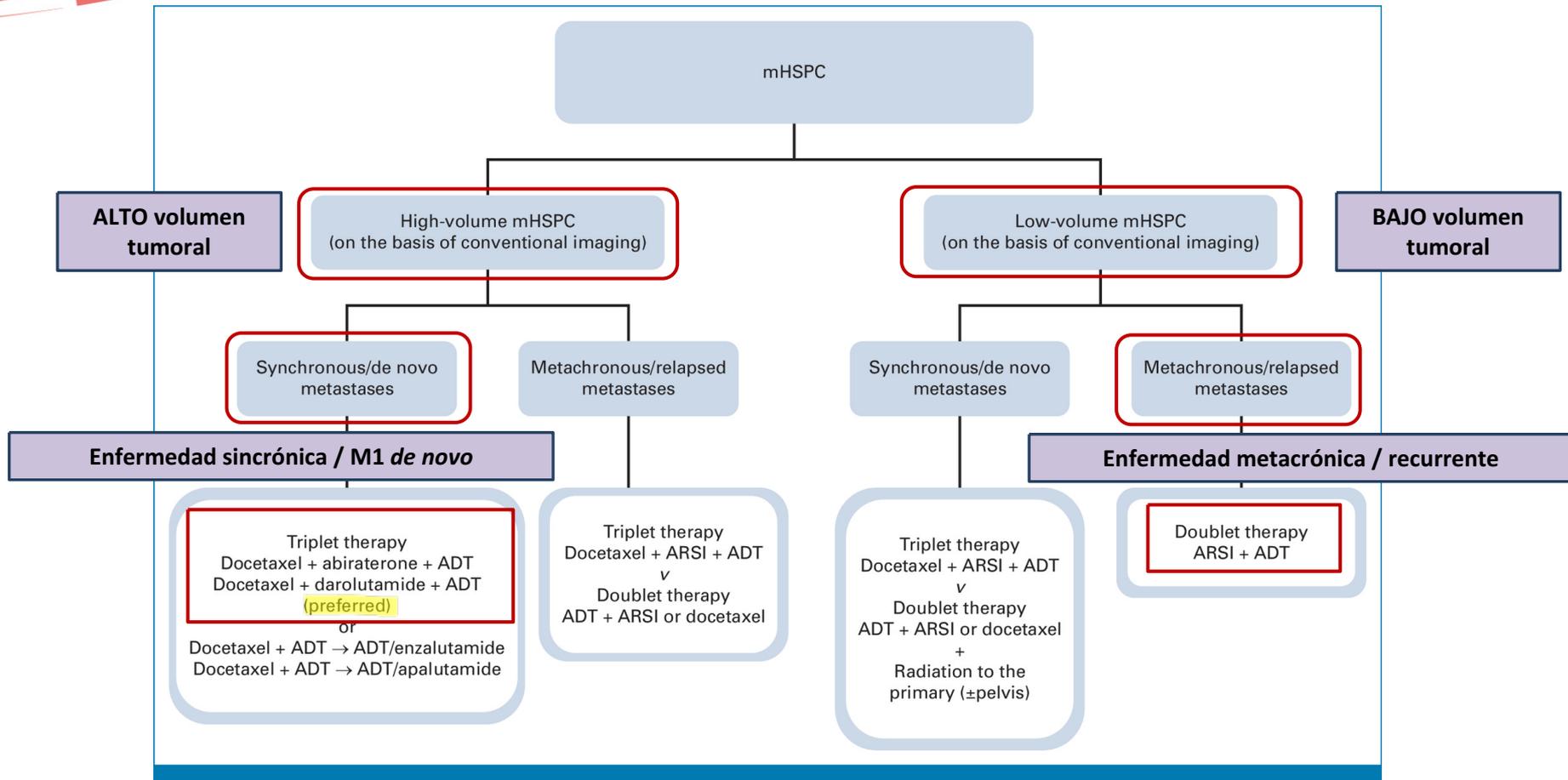
### ENSAYO STAMPEDE

Brazo H → Radioterapia en Cáncer Próstata Hormonosensible metastásico

#### RT + TDA vs TDA



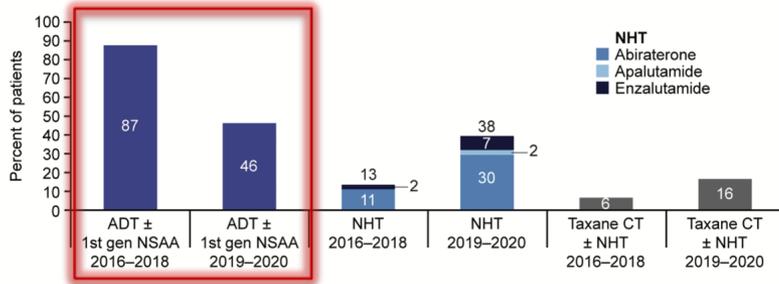




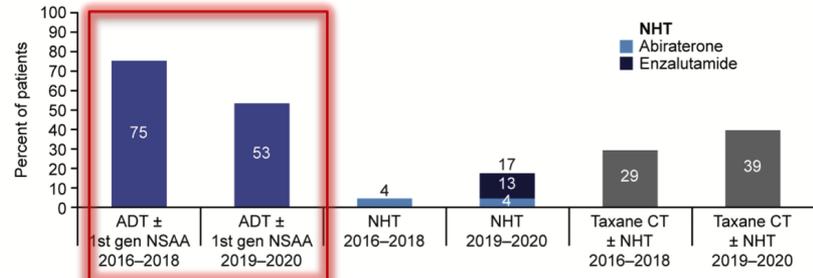
## Real-World Treatment Trends Among Patients with Metastatic Castration-Sensitive Prostate Cancer: Results from an International Study

2016 – 2018  
2019 – 2020

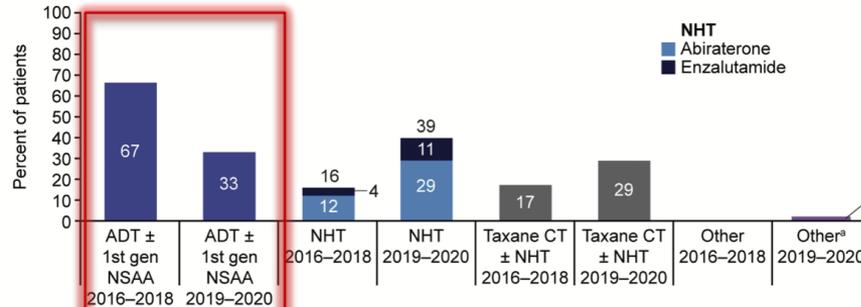
### FRANCIA



### UK



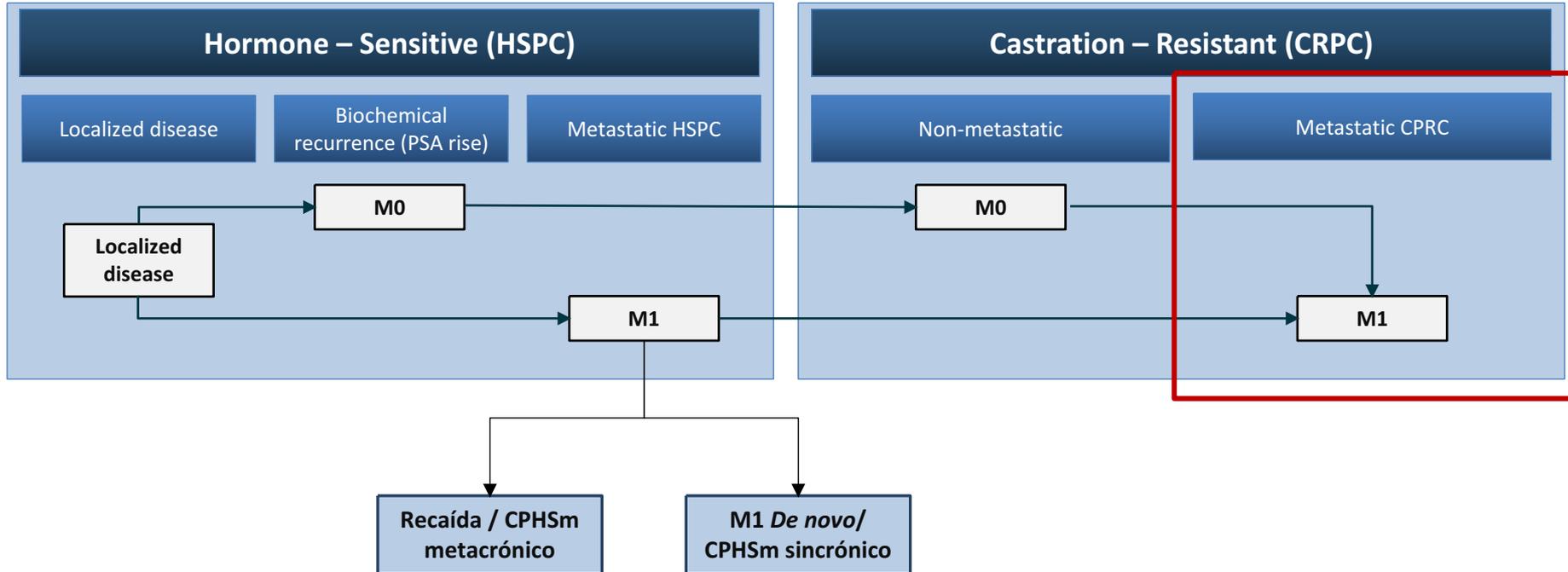
### ESPAÑA



# Cáncer de Próstata Avanzado

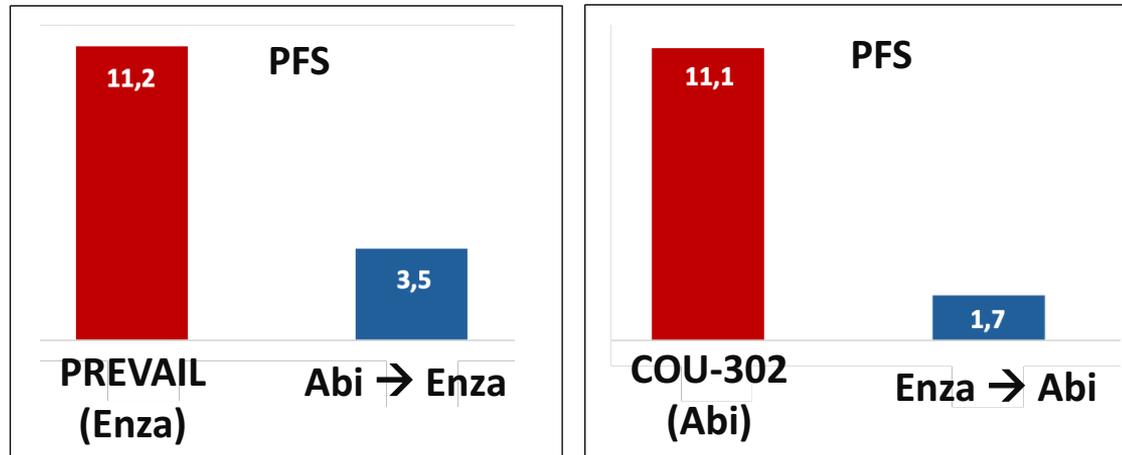
Niveles de testosterona >50ng/dL o 1,7nmol/L

Niveles de testosterona <50ng/dL o 1,7nmol/L



## CROSS-RESISTANCE

### ARSi after ARSi



**Estrategia subóptima**

## CPSH metastásico

ADT monoterapia 

Doblete (ADT + Docetaxel) 

Doblete (ADT + ARSi)

Triplete (ADT + Doce + ARSi)

## CPRC metastásico

ARSI [Abiraterona / Enzalutamida]  
Docetaxel

ARSI [Abiraterona / Enzalutamida]  
Cabazitaxel  
Ra-223



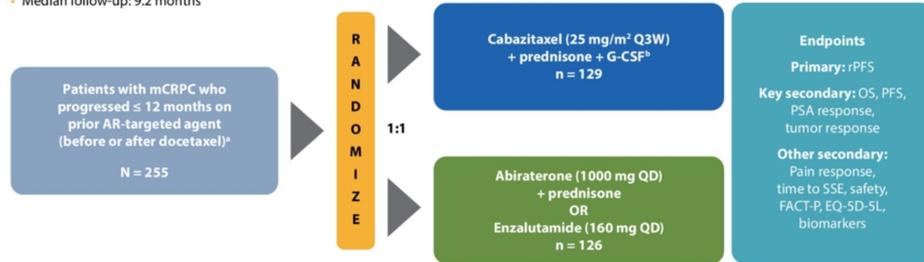
	Supervivencia Global			
	Experim	Control	HR (IC 95%)	p-valor
<b>TAX-327</b> Docetaxel vs Mitoxantrona	19,2 m	16,3 m	0,79 (0,67-0,93)	0,004
<b>COU-302</b> Abiraterona/P vs Placebo/P	34,7 m	30,3 m	0,81 (0,70-0,93)	0,003
<b>PREVAIL</b> Enzalutamida vs Placebo	35,3 m	31,3 m	0,77 (0,67-0,88)	<0,001

	Supervivencia Global			
	Experim	Control	HR (IC 95%)	p-valor
<b>TROPIC</b> Cabazitaxel vs Mitoxantrona	15,1 m	12,7 m	0,70 (0,59-0,83)	<0,001
<b>COU-301</b> Abiraterona/P vs Placebo/P	15,8 m	11,2 m	0,74 (0,64-0,86)	<0,001
<b>AFFIRM</b> Enzalutamida vs Placebo	18,4 m	13,6 m	0,63 (0,53-0,75)	<0,001
<b>ALSYMPCA</b> Radium-223 vs Placebo	14,9 m	11,3 m	0,70 (0,58-0,83)	<0,001

## Beneficio de cabazitaxel tras docetaxel & ARSI

### CARD -STUDY DESIGN-

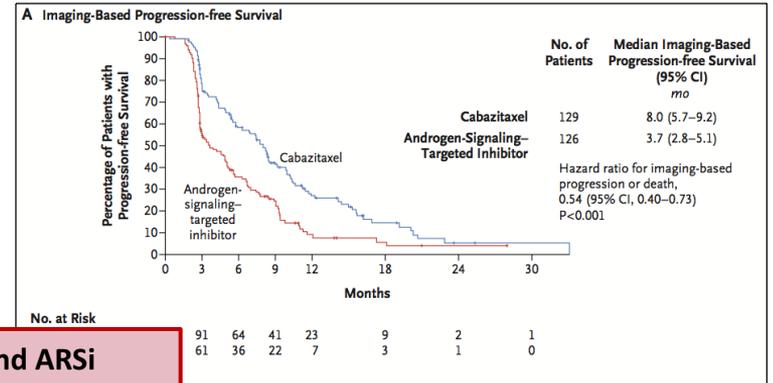
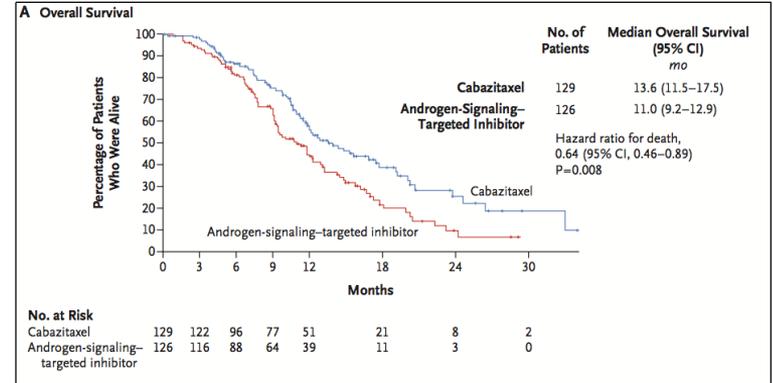
- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months



#### 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)

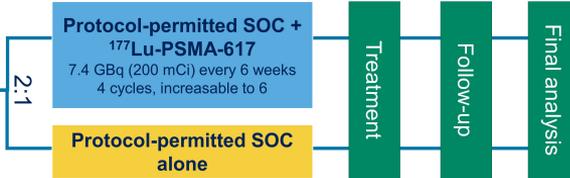
**Standard of care after docetaxel and ARSI**



## Open-label study of protocol-permitted standard of care ± <sup>177</sup>Lu-PSMA-617 in adults with PSMA-positive mCRPC

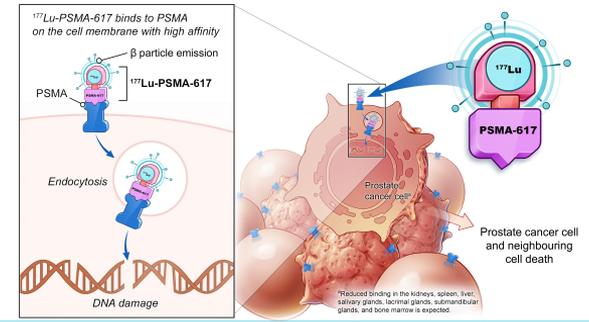
### Eligible patients

- 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 <sup>68</sup>Ga-PSMA-11



- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

### <sup>177</sup>Lu-PSMA-617 targeted radioligand therapy

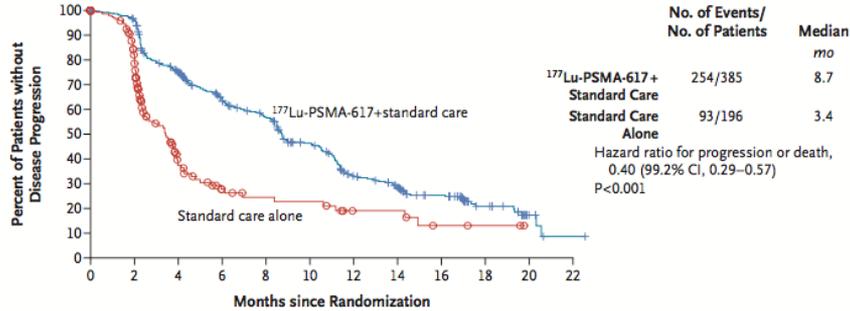


### Centrally read PSMA PET imaging criteria

- ≥ 1 PSMA-positive metastatic lesion
  - Positive = <sup>68</sup>Ga uptake > liver
- No PSMA-negative metastatic lesions
  - Bone with soft tissue component ≥ 1.0 cm
  - Lymph node ≥ 2.5 cm
  - Solid organ ≥ 1.0 cm

PSMA criteria met	869/1003 (86.6%)
PSMA criteria not met	126/1003 (12.6%)

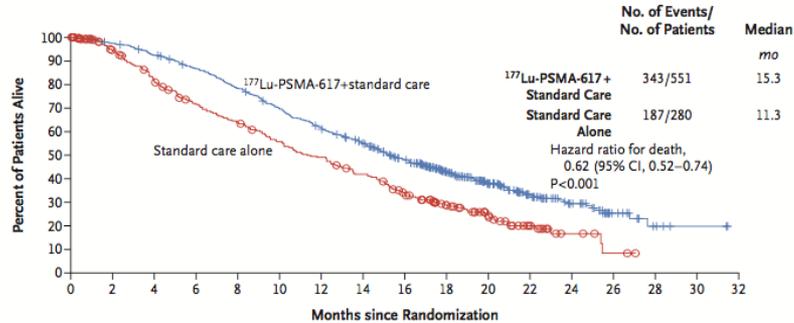
## A Imaging-Based Progression-free Survival



### No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22
<sup>177</sup> Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

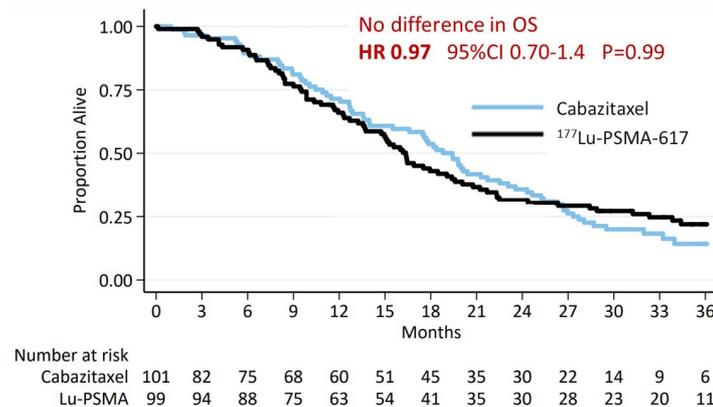
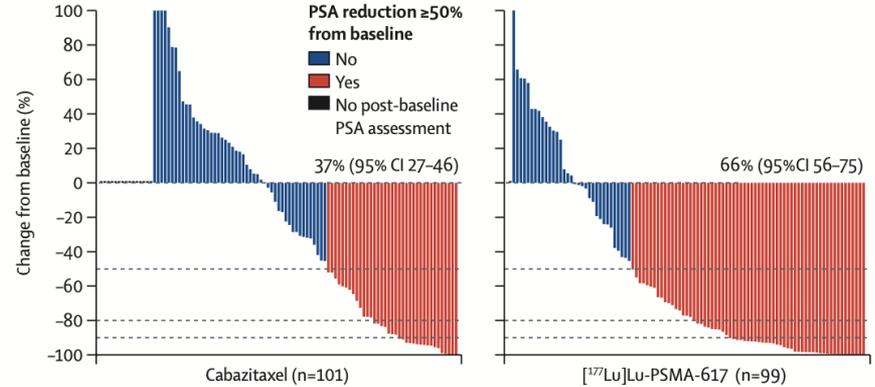
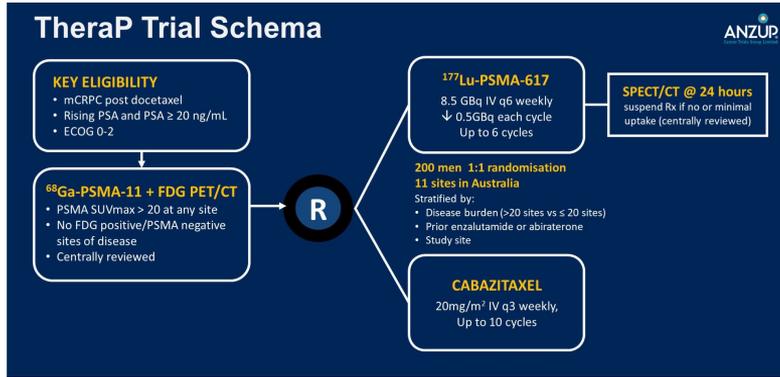
## B Overall Survival



### No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
<sup>177</sup> Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Cabazitaxel or <sup>177</sup>Lu-PSMA-617 ??



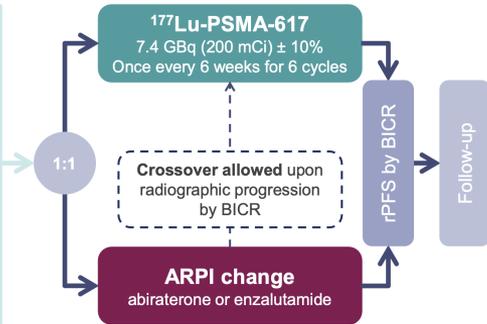
**Cabazitaxel or  $^{177}\text{Lu-PSMA-617}$  ??**

## Before docetaxel ...

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

#### Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [<sup>68</sup>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

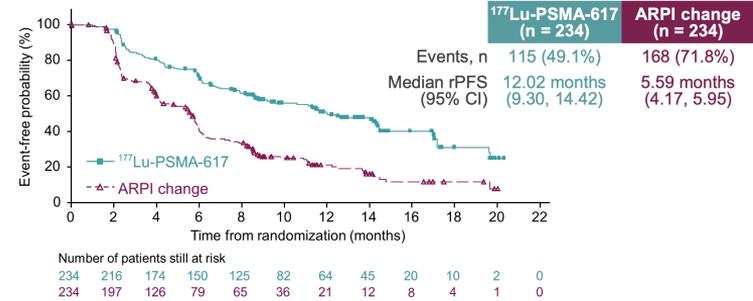


#### Stratification factors

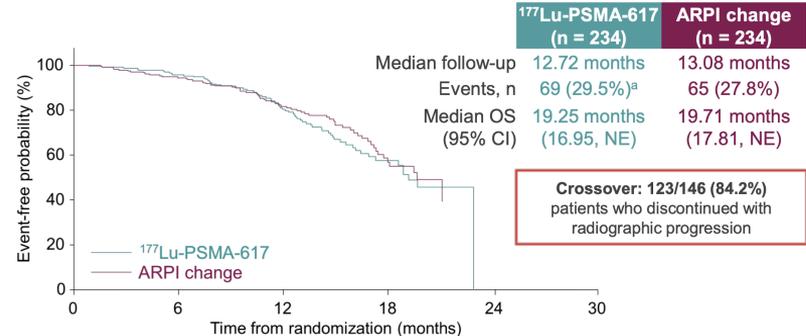
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)



Updated HR: 0.43 (95% CI: 0.33, 0.54)

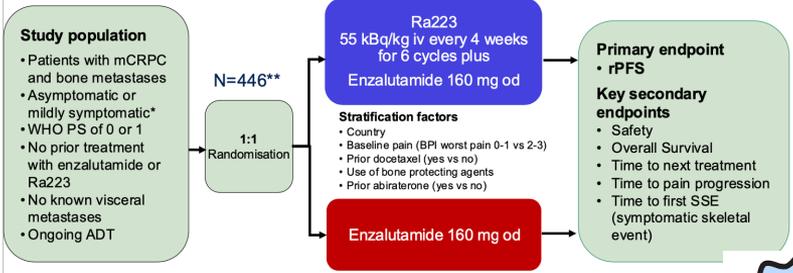
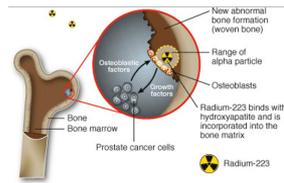


HR: 1.16 (95% CI: 0.83, 1.64)



## After ADT or ADT + docetaxel

### Radium-223



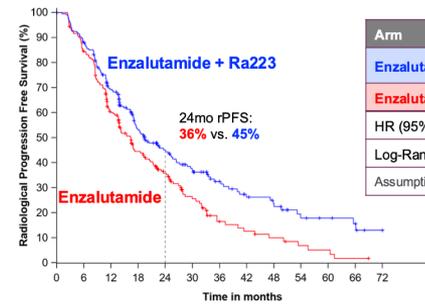
\*defined as brief pain inventory WP24 score < 4  
 \*\* original target accrual N=560, adapted for slow accrual



**Use of bone protecting agents (BPA) made mandatory (after inclusion of 119 patients)**



**ADT 70%**  
**Prior docetaxel (30%) and abiraterone (3%) was allowed for mHSPC**

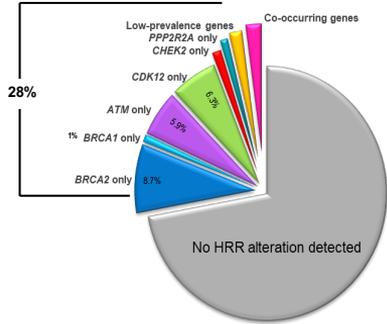


Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	19.4 (17.1-25.3) mo
Enzalutamide	160/224	16.4 (13.8-19.2) mo
HR (95%CI)	0.69 (0.54-0.87)	
Log-Rank p-value	0.0009	
Assumption of proportional hazard achieved		

Patients-at-Risk (No. Cumulative Events)

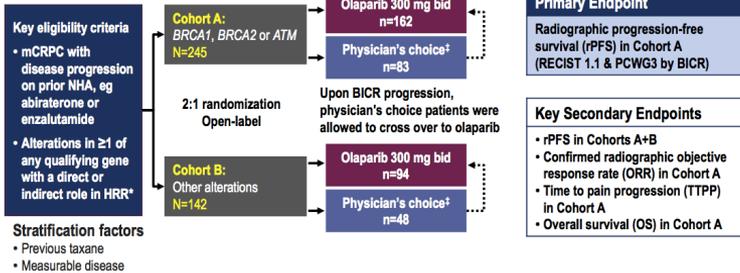
Time (months)	Enza-	Enza+Ra223-
0	224 (0)	222 (0)
6	122 (84)	138 (65)
12	52 (128)	64 (107)
18	13 (150)	32 (123)
24	7 (155)	19 (131)
30	3 (158)	9 (135)
36	0 (160)	3 (137)

Patients	Enza+Ra223	Enza
	N (%)	N (%)
Adverse events (AEs)	218 (100)	216 (96)
Drug-related AEs	183 (84)	158 (71)
Serious AEs	93 (43)	66 (30)
Serious drug-related AEs	18 (8)	3 (1)
Grade 3-5 AEs	143 (66)	125 (56)
Grade 3-5 drug-related AEs	61 (28)	42 (19)
Death due to AE	7 (3)	4 (2)
Death due to a drug-related AE	0	0
Treatment discontinuation due to toxicity		
Enzalutamide	13 (8)	12 (7)
RA223	7 (3)	



**ATM**  
**BRCA1**  
**BRCA2**  
**BARD1**  
**BRIP1**  
**CDK12**  
**CHEK1**  
**CHEK2**  
**RAD51B**  
**RAD51C**  
**RAD51D**  
**FANCL**  
**PALB2**  
**PPP2R2A**  
**RAD54L**

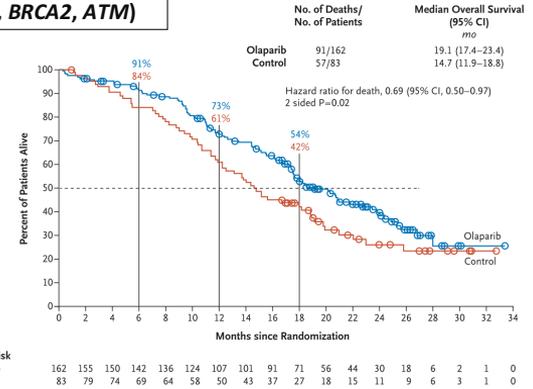
## PROfound STUDY DESIGN



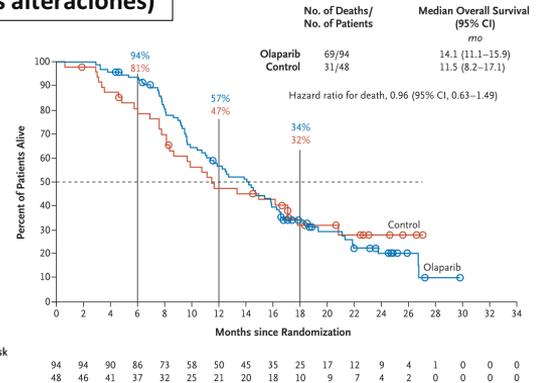
\*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A,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

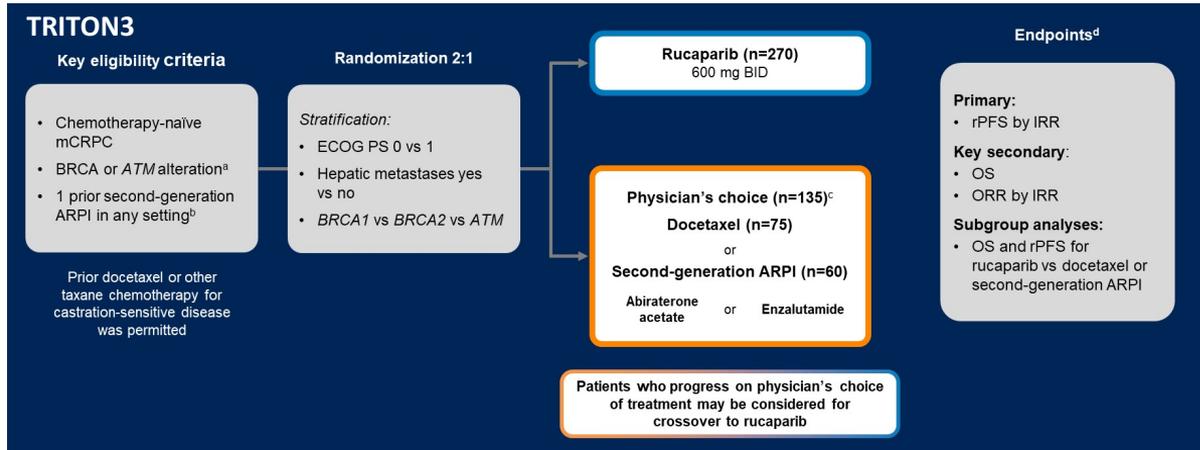
DOCETAXEL → 65%

## COHORT A (BRCA1, BRCA2, ATM)

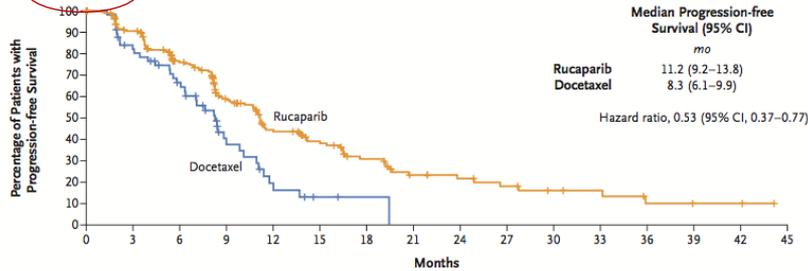


## COHORT B (Otras alteraciones)





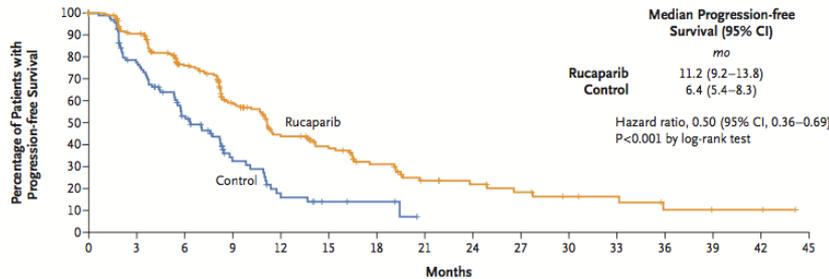
**A Rucaparib vs. Docetaxel in the BRCA Subgroup**



No. at Risk (no. of 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)
Docetaxel	60 (0)	44 (10)	32 (18)	14 (29)	6 (36)	2 (38)	1 (38)	0 (39)								

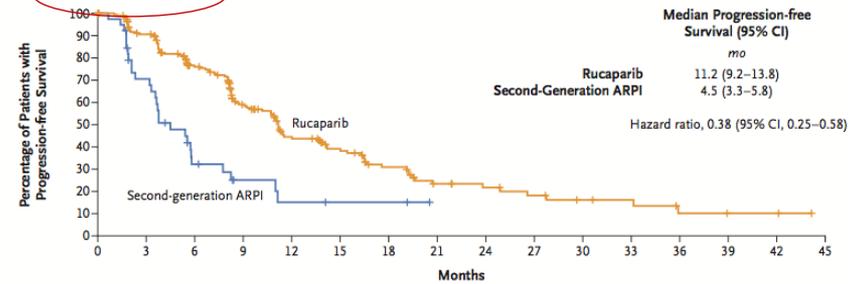
**A BRCA Subgroup**



No. at Risk (no. of 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)
Control	101 (0)	69 (21)	42 (42)	19 (55)	9 (64)	4 (66)	3 (66)	0 (67)								

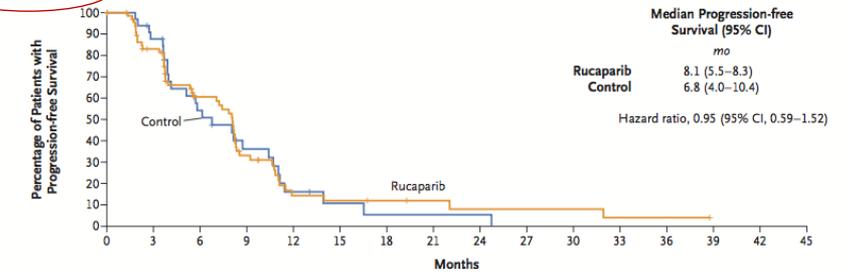
**B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup**



No. at Risk (no. of 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)
Second-generation ARPI	41 (0)	25 (11)	10 (24)	5 (26)	3 (28)	2 (28)	2 (28)	0 (28)								

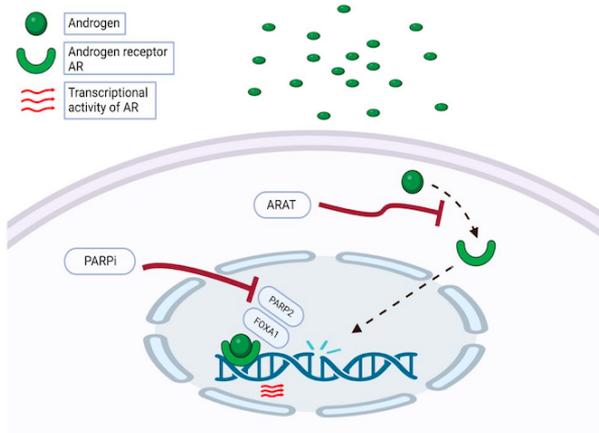
**C ATM Subgroup**



No. at Risk (no. of 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)
Control	34 (0)	28 (4)	16 (14)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)				

## Crosstalk between Androgen Receptor and DDR pathway



## The rationale for combining PARPi with NHT

NHTs induce a phenotype resembling HRR deficiency

Suppressed AR function causes an upregulation of PARP

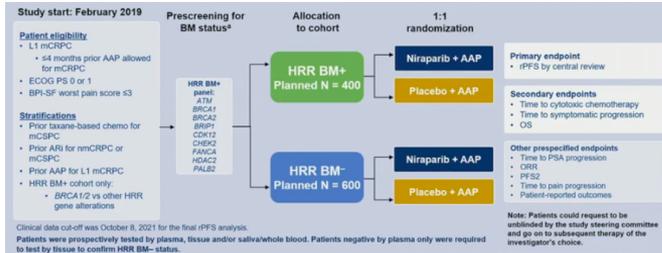
NHTs prime tumor cells for PARP inhibition

PARP augments AR activity

PARP inhibitors may attenuate resistance to NHTs

PARP inhibitors extend the benefits of NHTs

## MAGNITUDE



### • Tratamiento:

iPARP + ARSi vs placebo + ARSi

### • Población de pacientes:

1L CPRCm

Permitido docetaxel y otros ARSi en CPHm / CPRCnm

80% de los pacientes incluidos → TDA monoterapia

### • Diseño del estudio

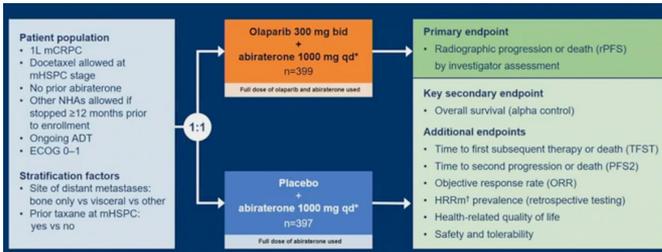
MAGNITUDE: Pre-screening molecular → HRR+ vs HRR-

PROpel y TALAPRO-2 → población no seleccionada (*all comers*)

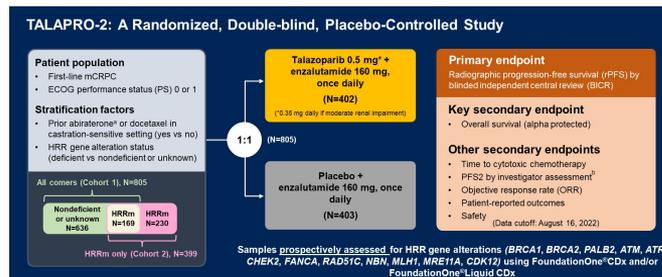
Análisis retrospectivo (PROpel) y **prospectivo** (TALAPRO-2) de alteraciones en genes

HRR

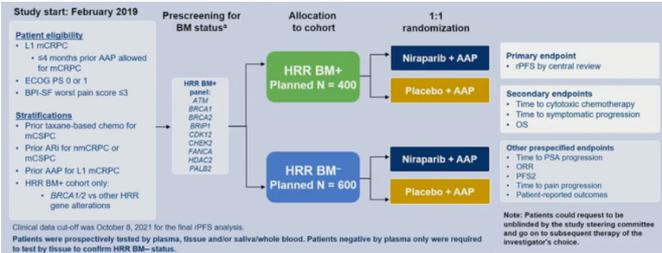
## PROpel



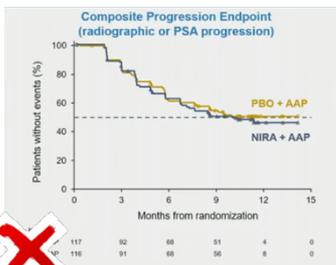
## TALAPRO-2



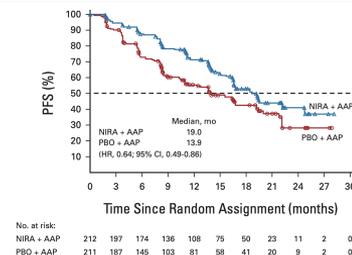
## MAGNITUDE



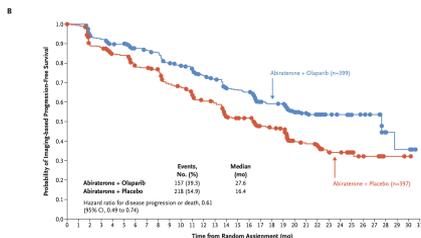
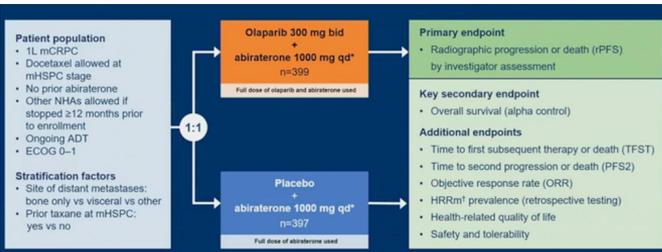
## HRR Negativo



## HRR Positivo

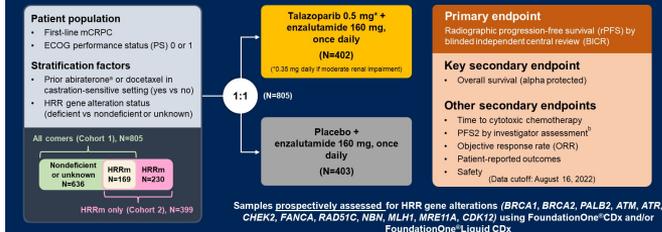


## PROpel

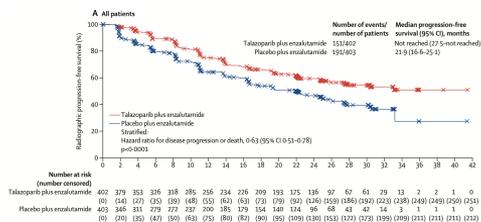


## TALAPRO-2

### TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

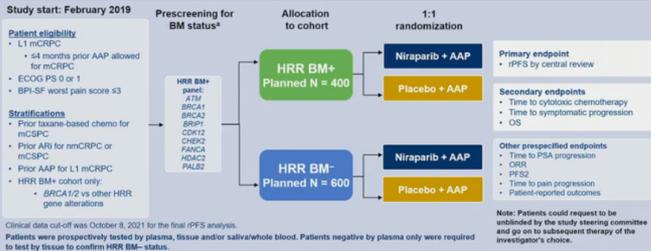


## ALL COMERS

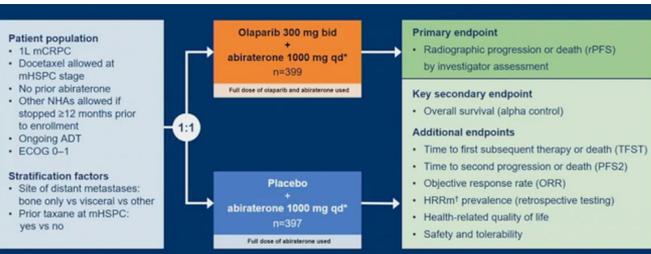




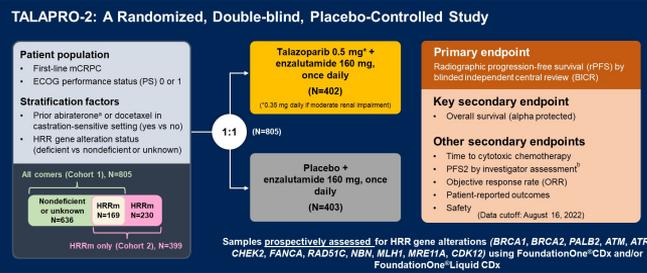
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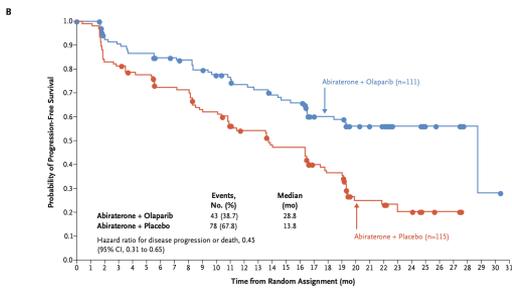
## PROpel



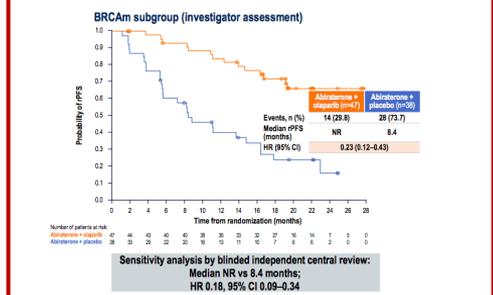
## TALAPRO-2



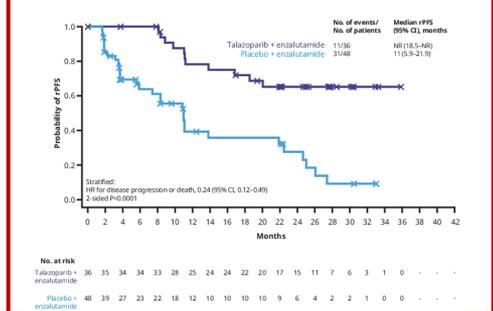
## HRR Positivo



## BRCA carriers

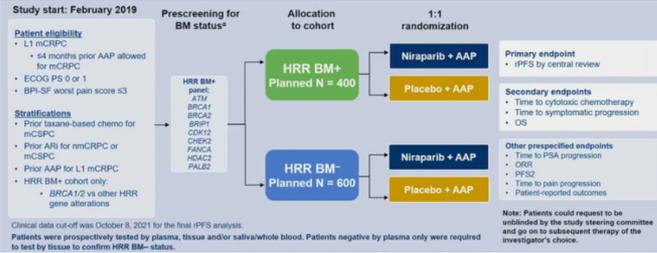


## A. BRCAm

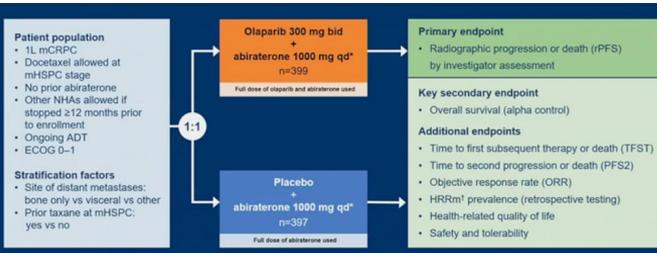


# Cáncer de Próstata Avanzado

## MAGNITUDE

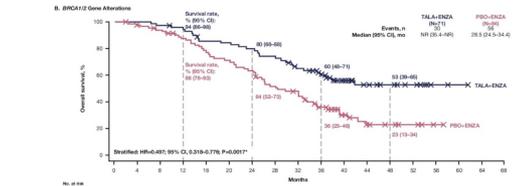
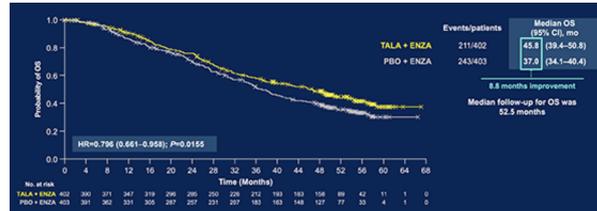
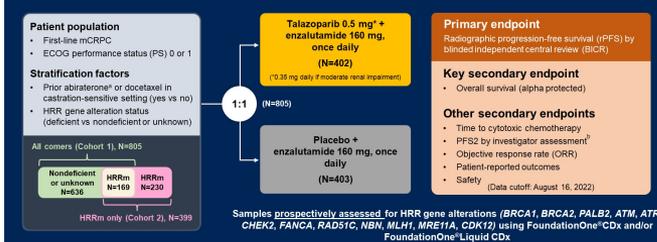


## PROpel



## TALAPRO-2

### TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study



## CPSH metastásico

ADT monoterapia



## CPRC metastásico

ARSI [Abiraterona / Enzalutamida]

Docetaxel

Abiraterona / Enzalutamida + iPARP (BRCA +)  
Enzalutamida + Ra223

Doblete (ADT + Docetaxel)



ARSI [Abiraterona / Enzalutamida]

Cabazitaxel

Ra-223

Abiraterona / Enzalutamida + iPARP (BRCA +)  
Enzalutamida + Ra223

Doblete (ADT + ARSi)

Docetaxel

Ra223

Triplete (ADT + Doce + ARSi)

Cabazitaxel

<sup>177</sup>Lu-PSMA-617

iPARP (BRCA+)

Ra-223

# Reflexiones finales

- ❖ En **cáncer de próstata hormonosensible metastásico** → combinación de **doblete** (TDA + Apalutamida/Enzalutamida/Abiraterona) o **tripleto** (TDA + Docetaxel + Abi/Daro) deben considerarse tratamiento de **elección**.
  - ❖ No comparados → toma de decisiones en base a factores clínicos
  - ❖ **Radioterapia** sobre tumor primario en bajo volumen (alto volumen¿?)
- ❖ En **cáncer de próstata resistente a castración metastásico**:
  - ❖ **Cabazitaxel** tras docetaxel / ARSi
  - ❖ <sup>177</sup>**Lu-PSMA-617** tras docetaxel / ARSi (PET-PSMA +)
  - ❖ La combinación de **Ra-223** y **enzalutamida** (+ agente protector del hueso) → potencial tratamiento en 1L (tarde¿?)
- ❖ Los **inhibidores de PARP** han demostrado beneficio en **supervivencia global** en pacientes con CPRCm portadores de mutaciones en **BRCA1/2**.
  - ❖ ¿Qué ocurre con otras alteraciones? No beneficio en pacientes con alteraciones en **ATM**
- ❖ Existe evidencia que demuestra que la **inhibición del RA y PARP** puede ser **sinérgica**, aunque es preciso definir mejor el contexto en el que podemos aplicarlo (más allá de **BRCA2**).
  - ❖ **BRCA2** >> déficit HRR >> CPRCm no seleccionados >> sin alteraciones en HRR
  - ❖ El **escenario de tratamiento ha cambiado** → ARSi se emplean en etapas más tempranas (CPHSm / CPRCnm)

# Cáncer de Próstata Avanzado: un escenario en continua evolución

DATA



SORTED



ARRANGED



PRESENTED VISUALLY



FIND A PRACTICAL SENSE



# XVII SIMPOSIUM

## BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN  
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Complejo Asistencial  
Universitario  
de Salamanca



UNIVERSIDAD  
DE SALAMANCA  
CAMPUS DE EXCELENCIA INTERNACIONAL



*¡Gracias!*



@rebecaLozMe

rebecalozano@saludcastillayleon.es