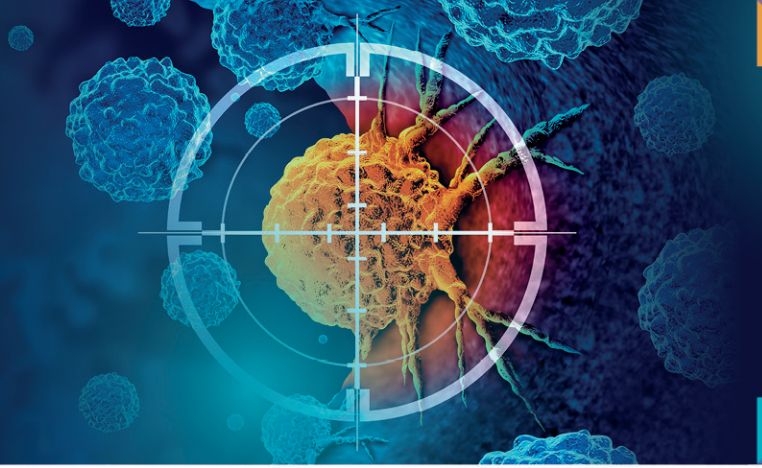
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

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



Cáncer de próstata: ¿hemos entrado en la era de la selección molecular?

Rebeca Lozano Mejorada, MD, PhD

Oncología Médica

Complejo Asistencial Universitario de Salamanca

Instituto de Investigación Biomédica de Salamanca (IBSAL)

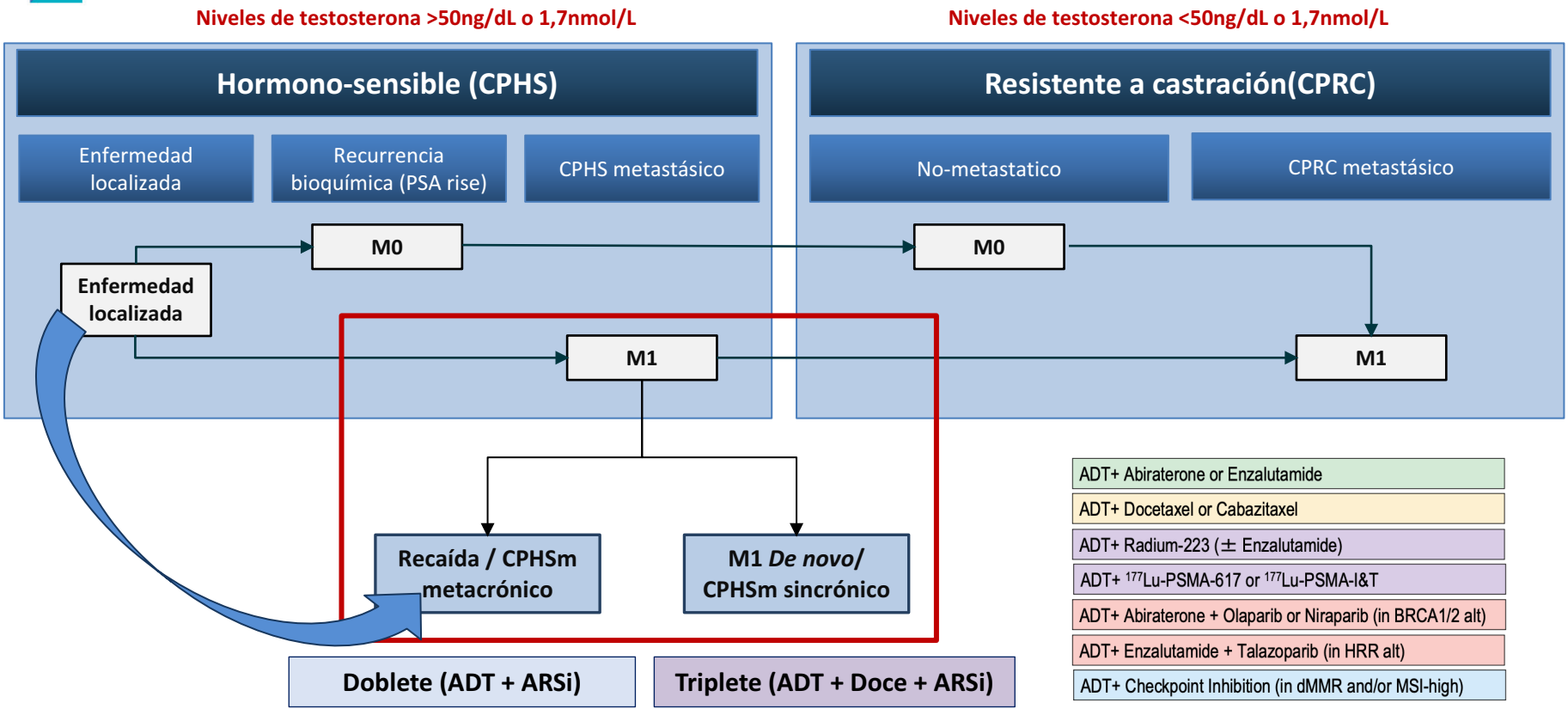
COMPLEJO ASISTENCIAL UNIVERSITARIO DE SALAMANCA | Sacyl | IBSAL Instituto de Investigación Biomédica de Salamanca | EUnetCCC ONEFORALL | DESIGNATED

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), Novartis

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

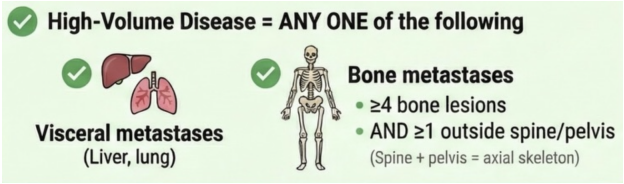


Modificado de Scher et al, J Clin Oncol 2016

Cáncer de Próstata metastásico sensible a castración

ALTO volumen tumoral

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



BAJO volumen tumoral

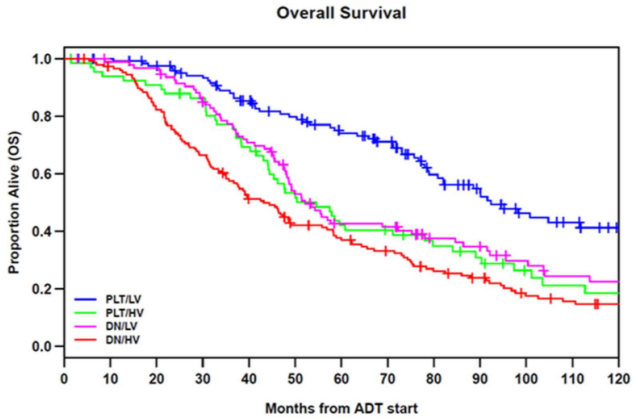
Todo aquel que no cumple criterios de alto volumen

Enfermedad sincrónica / M1 *de novo*

Enfermedad metacrónica / recurrente

Kyriakopoulos et al. J Clin Oncol 2018; Vale CL, ASCO 2022 Abstract 5070

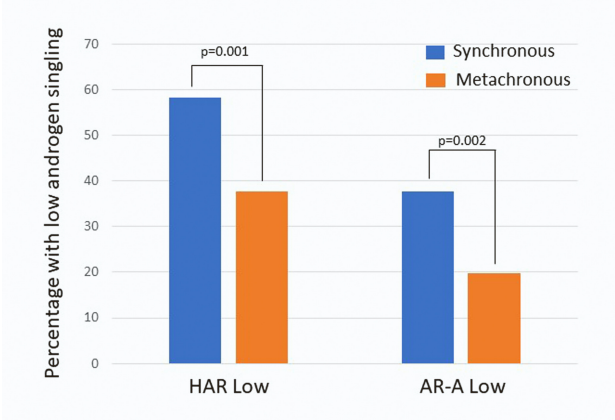
Cáncer de Próstata metastásico sensible a castración



Bajo volumen – recaída M1 →
Mediana OS ~8 años

Alto volumen – diagnóstico M1 de novo →
Mediana OS ~3 años

Biologic difference between timing of metastatic disease

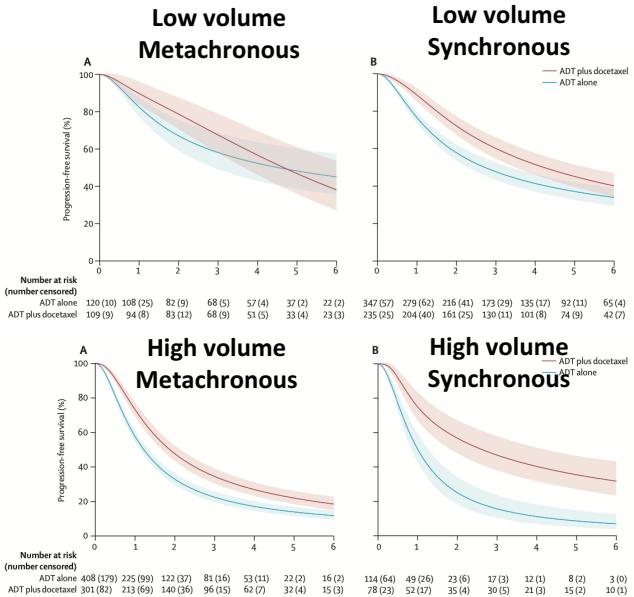


Patients with **synchronous disease** have **lower Androgen Receptor Activity** (AR-A) and **Hallmark Androgen Response** (HAR) gene signature scores in comparison with metachronous disease

Francini E, et al, Prostate 2018; Sutera PA, et al, Ann of Oncol, 2023

Cáncer de Próstata metastásico sensible a castración

No clear benefit of docetaxel in low volumen metachronous disease

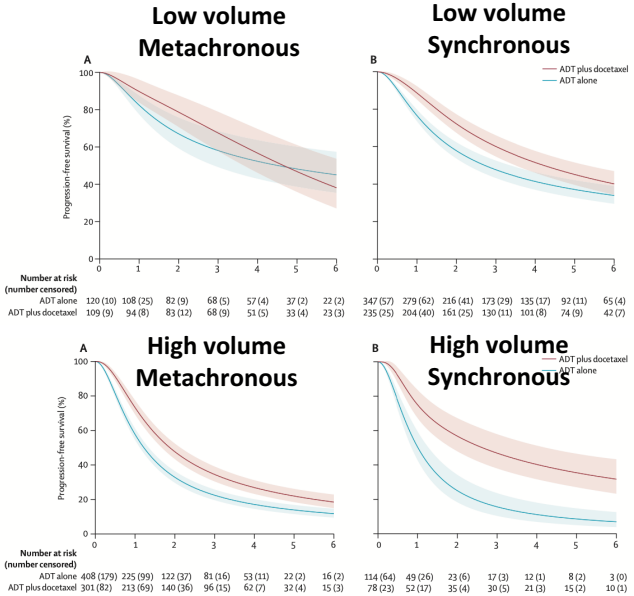


Supervivencia global		SG 5a ADT	SG 5a ADT + Docetaxel
Alto volumen	Sincrónico (n=1044)	26%	39%
	Metacrónico (n=132)	28%	38%
Bajo volumen	Sincrónico (n=582)	52%	60%
	Metacrónico (n=229)	72%	72%

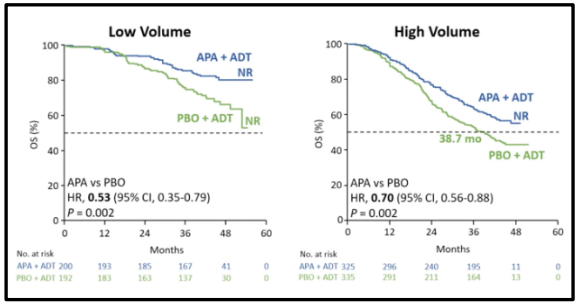
Vale et al, Lancet Oncol 2023; David I, ASCO 2022: LBA 5004; Sweeney et al, Eur Urol 2021

Cáncer de Próstata metastásico sensible a castración

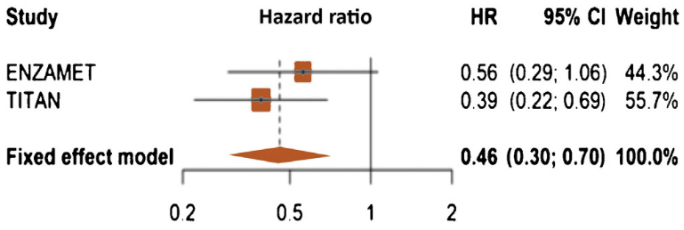
No clear benefit of docetaxel in low volumen metachronous disease



ARSi: Benefit in all patients

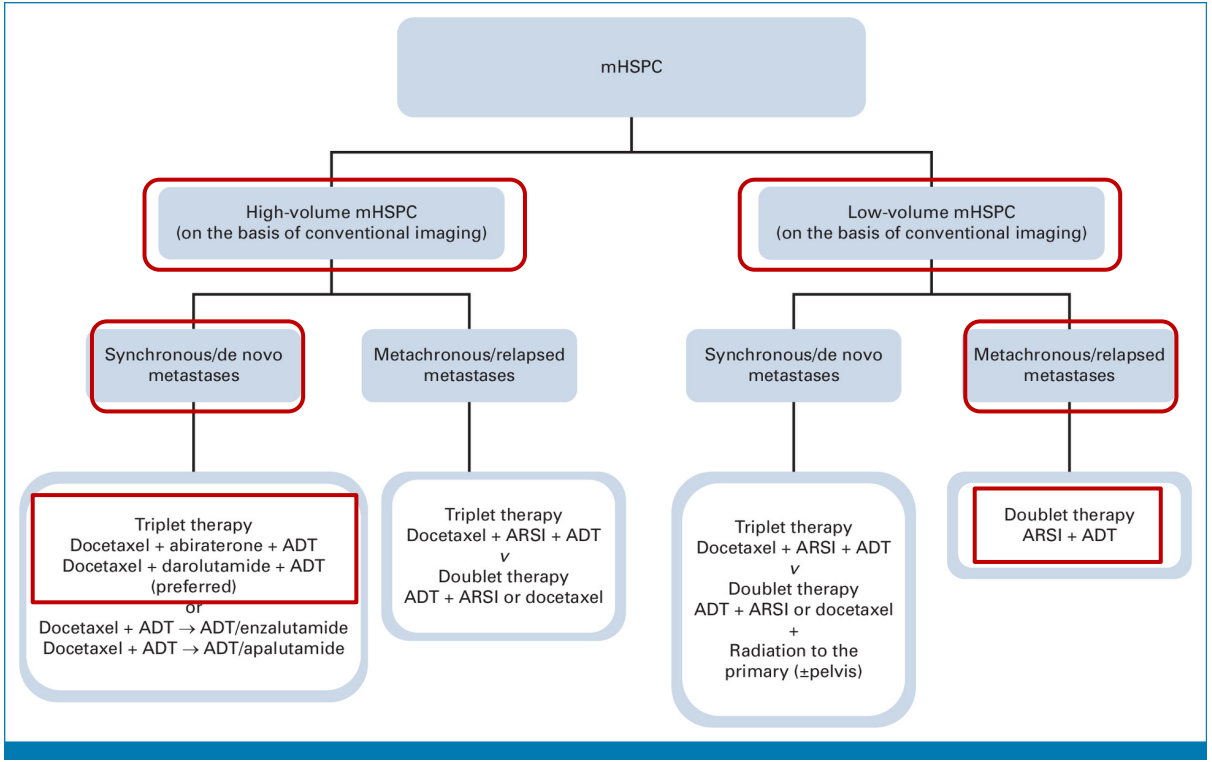


Meta-analysis of OS in metachronous mHSPC



Vale et al, Lancet Oncol 2023; David I, ASCO 2022: LBA 5004; Sweeney et al, Eur Urol 20

Cáncer de Próstata metastásico sensible a castración

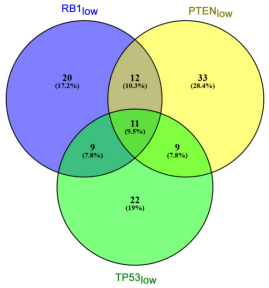


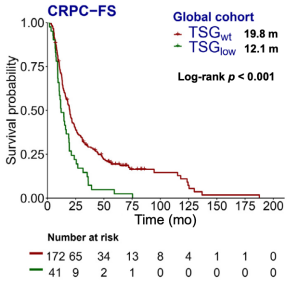
McManus HA, J Clin Oncol, 2023

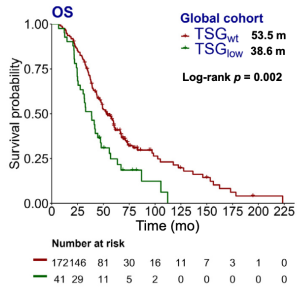
Cáncer de Próstata metastásico sensible a castración

Molecular subgroups with different prognosis

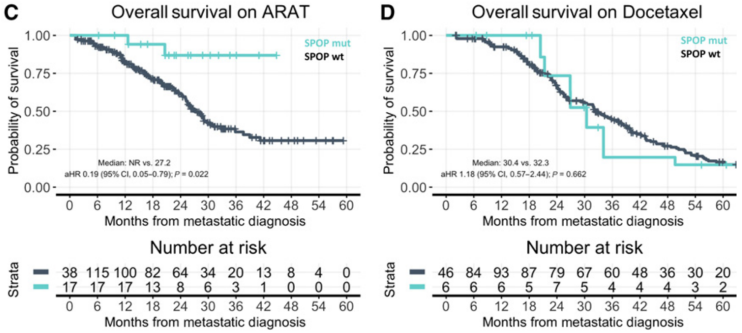
N= 218 mHSPC patients
76% *de novo* metastatic
68% High-volumen







		ARPI (median in months)	Docetaxel (median in months)
mut*SPOP*	TTHRPC	NR[a]	18.5
	OS	NR[a]	30.4
wt*SPOP*	TTHRPC	16.7[a]	15.7
	OS	27.2[a]	32.3

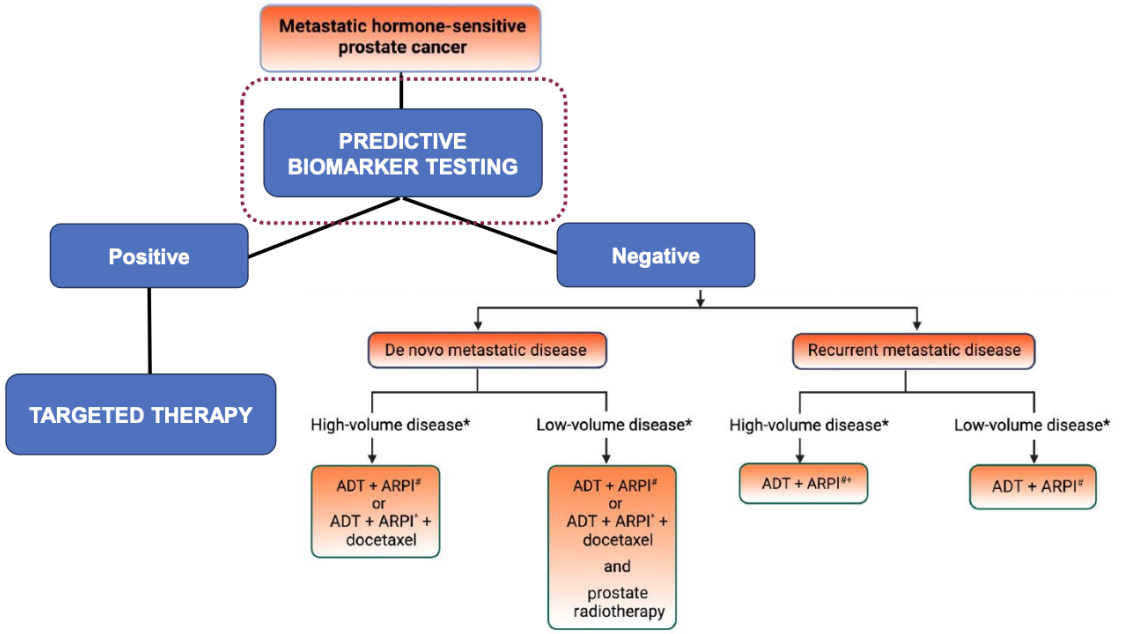


TSG low – low expresión of ≥2 of *RB1*, *PTEN* or *TP53*

Jimenez N, Eur Urol 2024; SWAMI U, Clin Cancer Res 2022

Cáncer de Próstata metastásico sensible a castración

Molecular subgroups with different prognosis

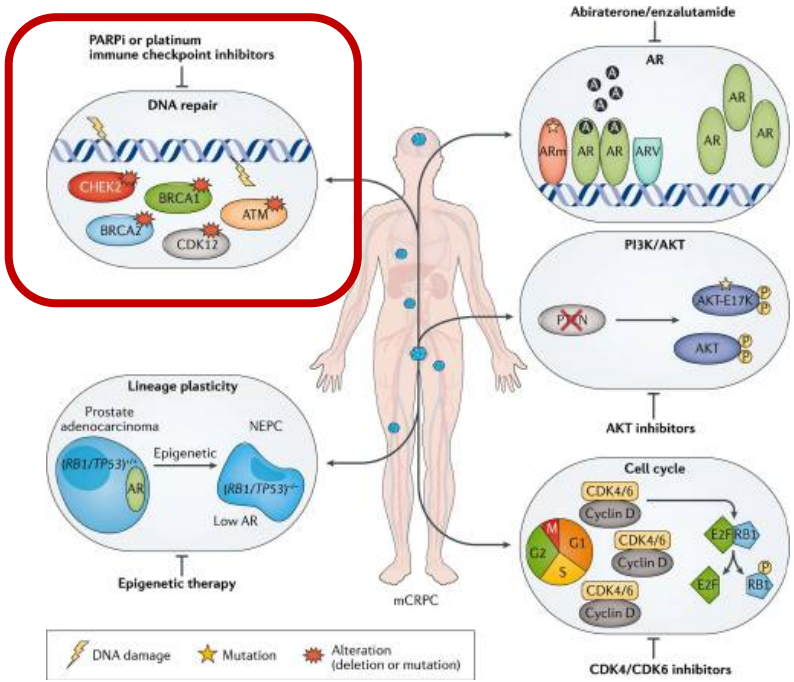


*Volume defined as per CHAARTED criteria;
#Enzalutamide, Apalutamide, or Abiraterone; ADT + Docetaxel if an ARPI unavailable and suitable for chemotherapy.
^Enzalutamide, Darolutamide, or Abiraterone. Most evidence supports triplet therapy in de novo high-volume disease.
+ADT + ARPI + Docetaxel can be considered for recurrent high-volume disease, however data is limited in this patient cohort.

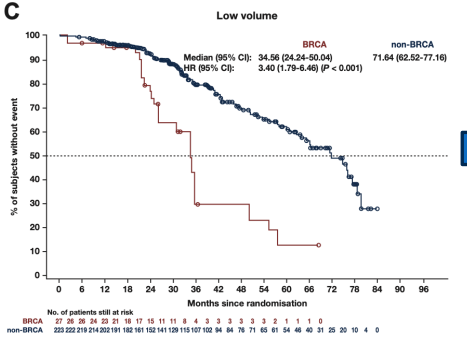
Presented by Elea Castro in ESMO 2025; adpated from Azad, Eur Urol 2025

Cáncer de Próstata metastásico sensible a castración

HRR gene alterations

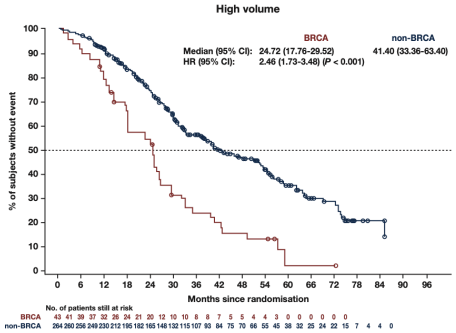


C



LOW VOLUME

(BRCA) 34.6 vs (non-BRCA) 71.6 months
HR 3.4; p<0.001



HIGH VOLUME

(BRCA) 24.7 vs (non-BRCA) 41.4 months
HR 2.4; p<0.001

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

Ku et al, Nat Rev Urol 2019º Olmos D, Ann Oncol , 2024

Cáncer de Próstata metastásico sensible a castración

AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC

First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival. Median follow-up: 30.8 months

Key inclusion criteria:
- mCSPC[a]
- Alteration in ≥1 HRR eligible gene: *BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L*[b]
- ECOG PS 0-2

Key exclusion criteria:
- Any prior
  - PARPi
  - ARPI other than AAP

Prior allowed treatments in mCSPC:
- ADT ≤6 months
- Docetaxel ≤6 cycles[c]
- AAP ≤45 days
- Palliative RT

Randomized 1:1 (N=696)

Nira (200 mg QD) + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

PBO + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

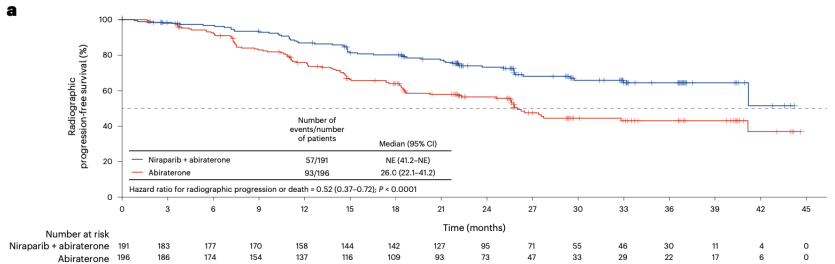
Primary end point
- rPFS by investigator review

Key secondary end points
- Time to symptomatic progression
- OS
- Safety

Stratification factors:
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Clinical data cutoff: January 7, 2025

[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.



TALAPRO-3: Trial Design

Key eligibility criteria
- HRR gene-altered mCSPC
- Metastatic disease confirmed by positive bone scan or metastatic lesion by CT or MRI scan
- ECOG PS 0 or 1
- Ongoing ADT
- ≤3 months of prior ADT with/without ARPI for mCSPC
- Prior docetaxel for mCSPC not permitted†

Stratification factors
- De novo vs relapsed mCSPC
- High- vs low-volume disease
- *BRCA*m vs non-*BRCA*m

TALA 0.5 mg* + ENZA 160 mg QD

1:1 N=599

PBO + ENZA 160 mg QD

Data cutoff: February 18, 2026

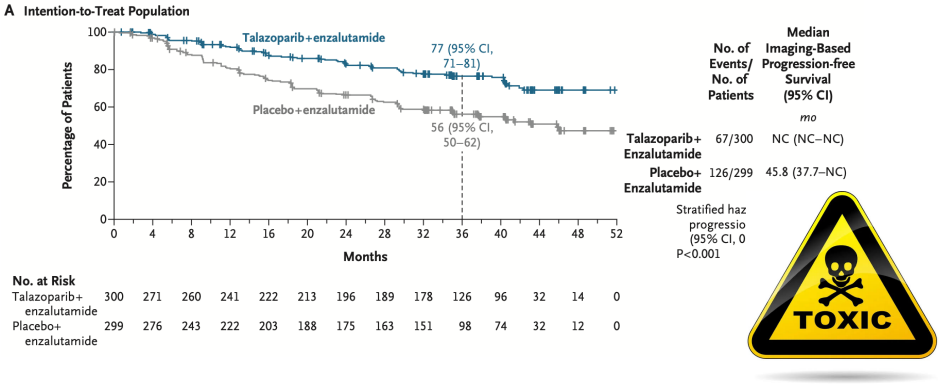
Primary endpoint
- rPFS by investigator assessment

Key secondary endpoint
- OS (alpha-protected)

Other secondary endpoints
- ORR per RECIST v1.1
- Duration of soft tissue response
- PSA response
- Time to PSA progression
- Time to subsequent antineoplastic therapy
- Time to first SSE
- Safety
- PROs

Exploratory endpoint
- PFS2

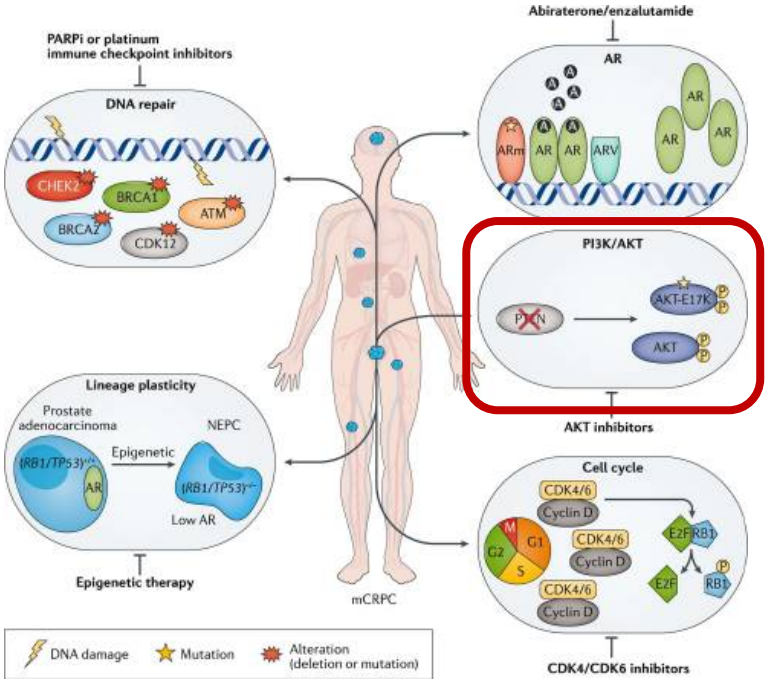
HRRm: *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*‡

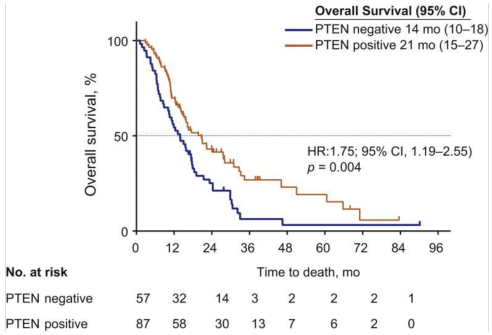


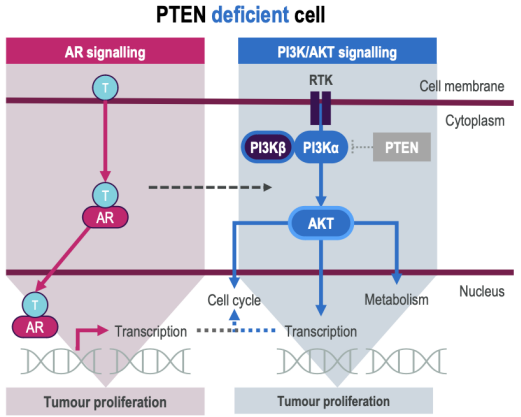
Attard G, ASCO 2025, Attard G, Nature Medicine 2025; Agarwal N, NEJM, 2026

Cáncer de Próstata metastásico sensible a castración

PTEN loss predicts lethal Prostate Cancer







Ku et al, Nat Rev Urol 2019;; Robinson, Cell 2014; Ferraldeschi, Eur Urol 2016; Rescigno P, Eur Urol 2018

Cáncer de Próstata metastásico sensible a castración

Patients with PTEN deficient *de novo* mHSPC

- PTEN deficiency: (diagnostic cut-off of **≥90%** of viable malignant cells with **no specific cytoplasmic staining** by IHC)*
  - i.e. ≤10% of cells expressing PTEN by IHC

Of ~6,200 patients submitting tumour tissue **97%** had a valid IHC result and **25%** were **PTEN deficient**

1,012 patients (R 1:1)

Capivasertib	400 mg BID 4 days on, 3 days off
Abiraterone/pred + ADT	1000 mg/5 mg QD + ADT
Placebo	400 mg BID 4 days on, 3 days off
Abiraterone/pred + ADT	1000 mg/5 mg QD + ADT

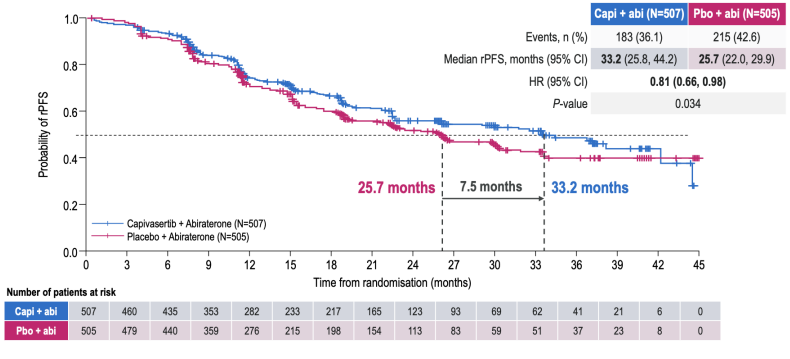
Primary endpoint

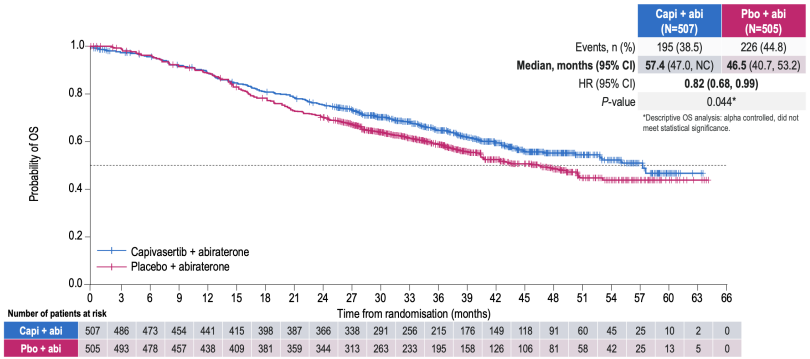
- **Investigator assessed rPFS**

Secondary endpoints

- Overall survival
- Time to first subsequent therapy
- Symptomatic skeletal-event free survival
- Time to pain progression
- Time to castration resistance
- Time to PSA progression

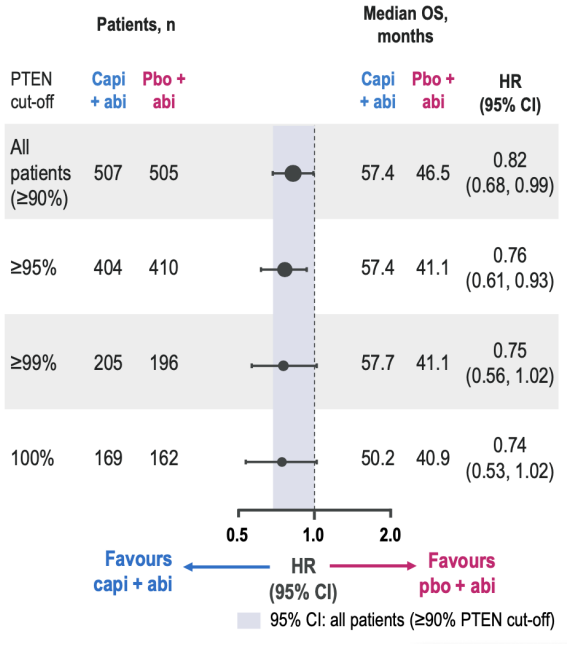
Exploratory *post-hoc* PTEN deficiency subgroups





Fizazi K, ESMO 2025; Fizazi K, Annals of Oncol 2026; Fizazi K, ESMO 2026

Cáncer de Próstata metastásico sensible a castración



Estimated prevalence of PTEN deficiency by IHC cut-off

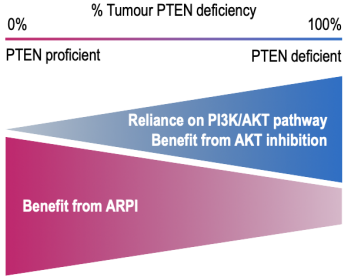
Cut-off ≥ 90%: 25%

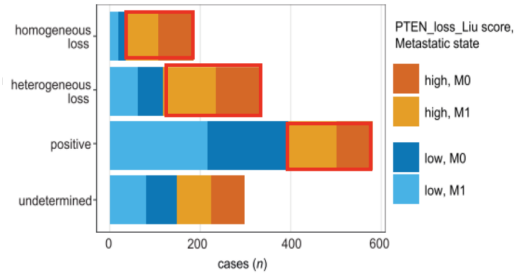
Cut-off ≥ 95%: ≈ 20%

Cut-off ≥ 99%: ≈ 10%

Cut-off ≥ 100%: ≈ 8%

This gradient effect is supported by biologic rationale[2]





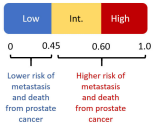
Fizazi K, ESMO 2025; Fizazi K, Annals of Oncol 2026; Castro E, Presented. In ESMO 2025; Grist et al, Cell 2025

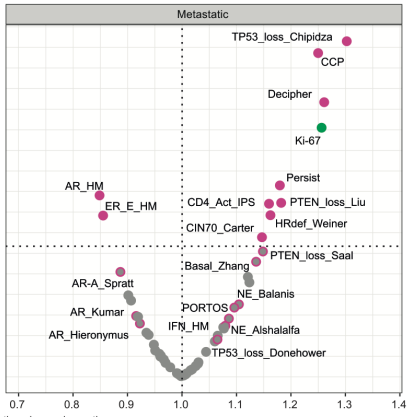
Cáncer de Próstata metastásico sensible a castración

Transcriptome gene expresión values from 1523 patients (M1 832)

Decipher
PROSTATE GENOMIC CLASSIFIER
veracyte

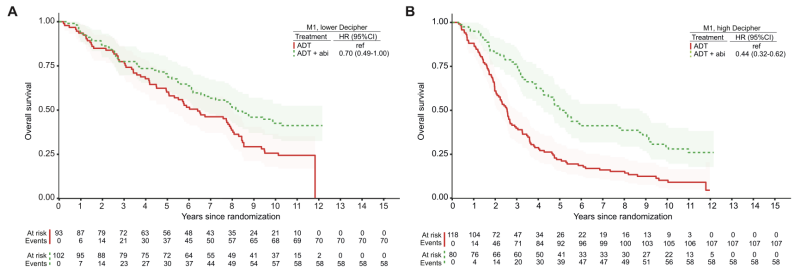
DECIPHER SCORES



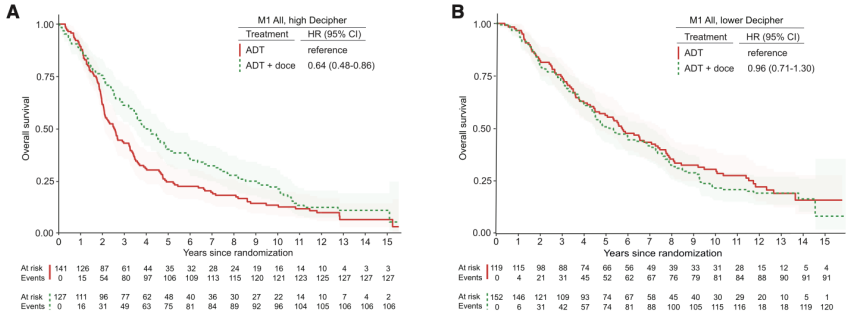


High Decipher → worse prognosis

Benefit with ADT + abiraterone in high & low Decipher patients



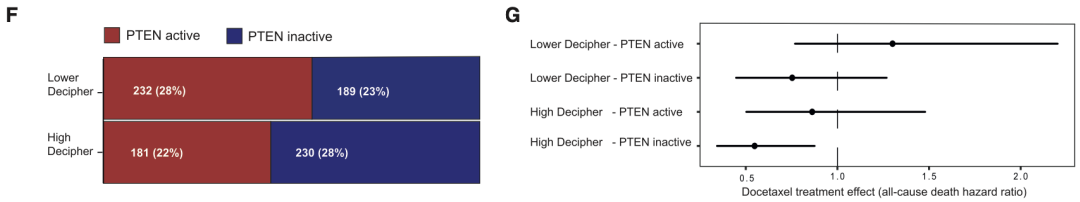
Benefit from ADT + docetaxel only in High Decipher patients



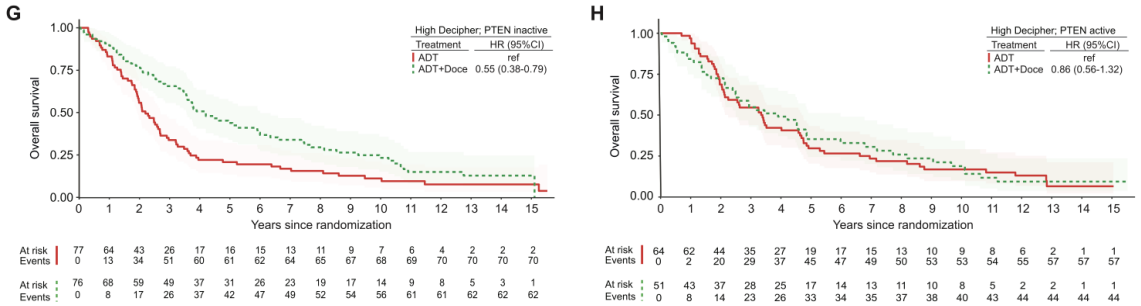
Grist E, Cell, 2025

Cáncer de Próstata metastásico sensible a castración

PTEN inactivation & Decipher high risk



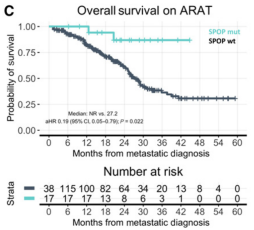
PTEN inactivation may further refine prediction of docetaxel benefit

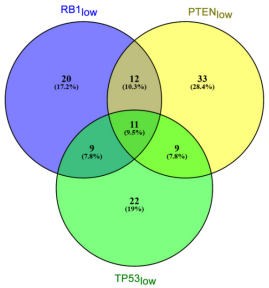


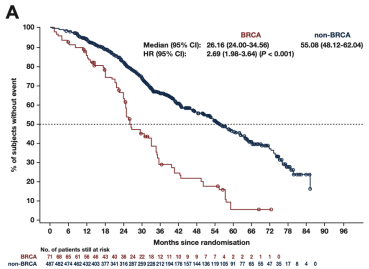
Grist E, Cell, 2025

¿Qué nos aporta la biología molecular?

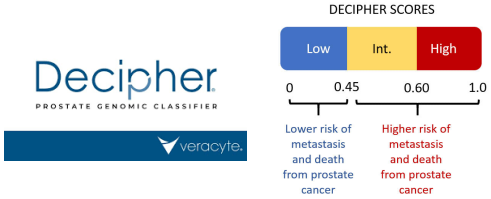
Información pronóstica

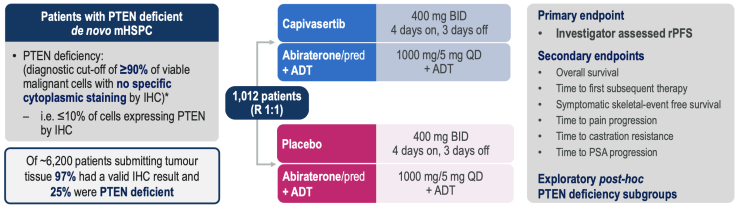


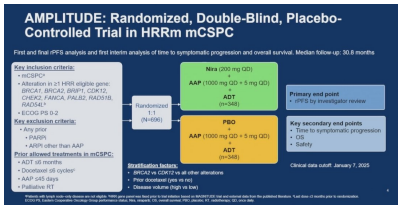


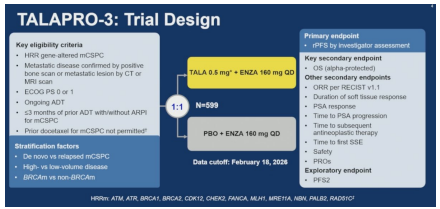


Información predictiva









¿Estamos preparados para seleccionar el tratamiento?

BRCA2 **mutado + alto volumen + de novo: ¿triplete con docetaxel o ARPI + iPARP?**

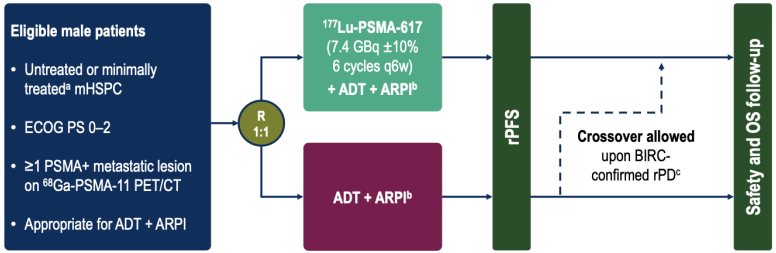
PTEN loss: ¿qué pacientes obtienen un beneficio suficiente con capivasertib para compensar la toxicidad?

Decipher alto: ¿podría apoyar la indicación de docetaxel incluso en pacientes de bajo volumen?

Cáncer de Próstata metastásico sensible a castración

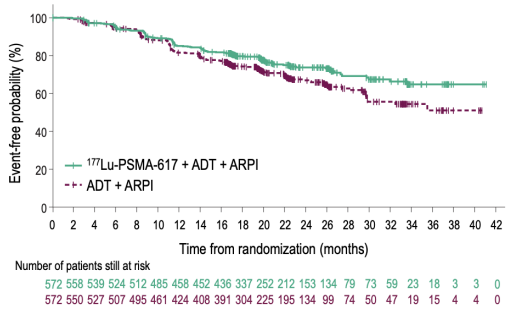
Más allá de la selección genómica…

PSMAddition TRIAL - mHPSC

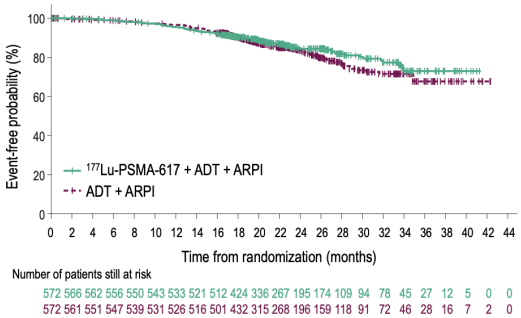


Stratification factors
- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

Follow-up periods
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	85 (14.9)	99 (17.3)
Censored – n (%)	487 (85.1)	473 (82.7)
HR (95% CI)	0.84 (0.63, 1.13)	
p value	0.125[a]	
Median OS (95% CI) – months	NR (NE, NE)	NR (NE, NE)

Tagawa S, Presented in ESMO 2025

Mensajes finales

- El **volumen tumoral** y la **presentación de la enfermedad** siguen siendo fundamentales para orientar el tratamiento del CPHSm, pero **no reflejan** completamente su **heterogeneidad biológica.**

- La **selección molecular** tiene ya **implicaciones terapéuticas** en CPHSm: BRCA/HRR y PTEN identifican poblaciones candidatas a nuevas estrategias de intensificación.

- **Decipher** tiene **potencial** para **individualizar el beneficio de docetaxel,** pero requiere validación prospectiva.

- La **integración de los biomarcadores** en la toma de decisiones aún presenta **incertidumbres,** especialmente sobre la estrategia óptima de intensificación y la secuencia de tratamientos.

- La medicina de precisión va más allá de la genómica: la **imagen molecular mediante PET-PSMA** permite seleccionar pacientes para **tratamientos dirigidos** con **radioligandos**.



FIND A PRACTICAL SENSE



Tenemos cada vez más piezas del puzzle. Ahora debemos aprender a combinarlas para ofrecer el mejor tratamiento a cada paciente

¡Gracias!



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