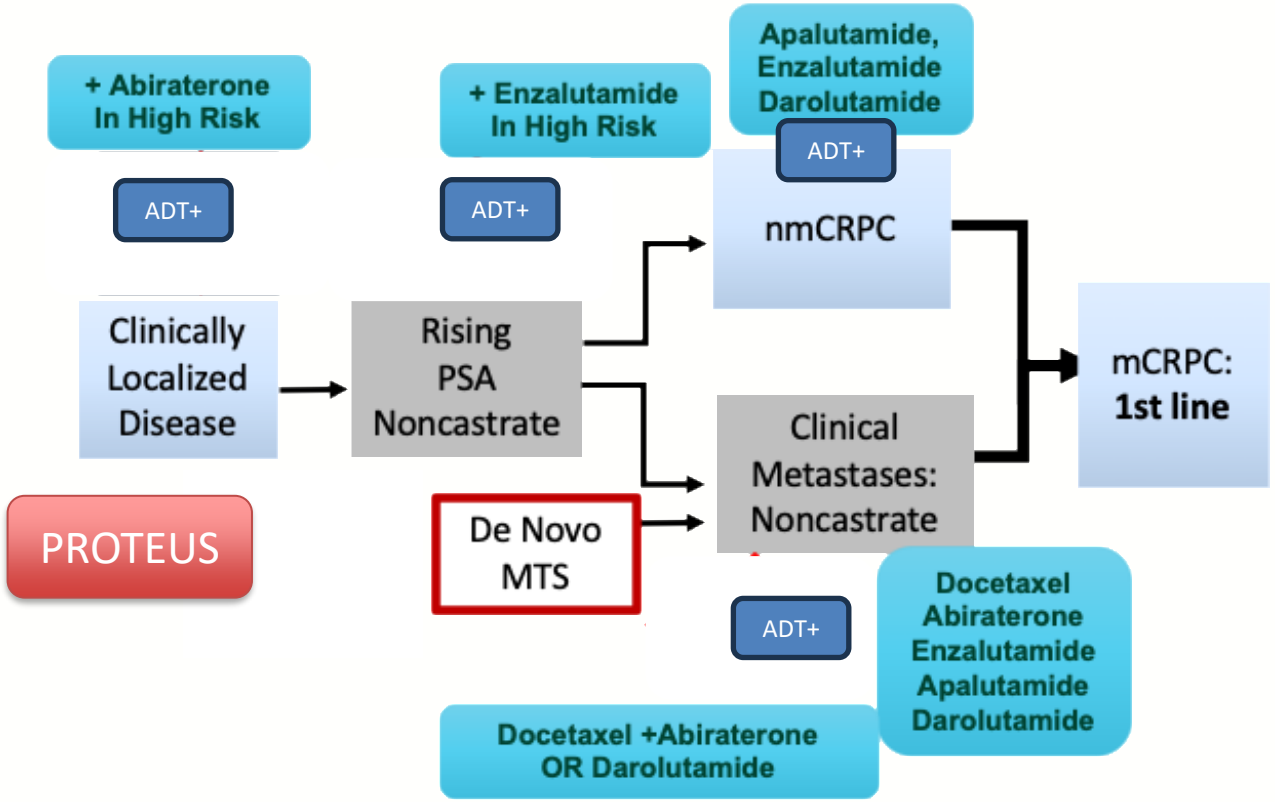
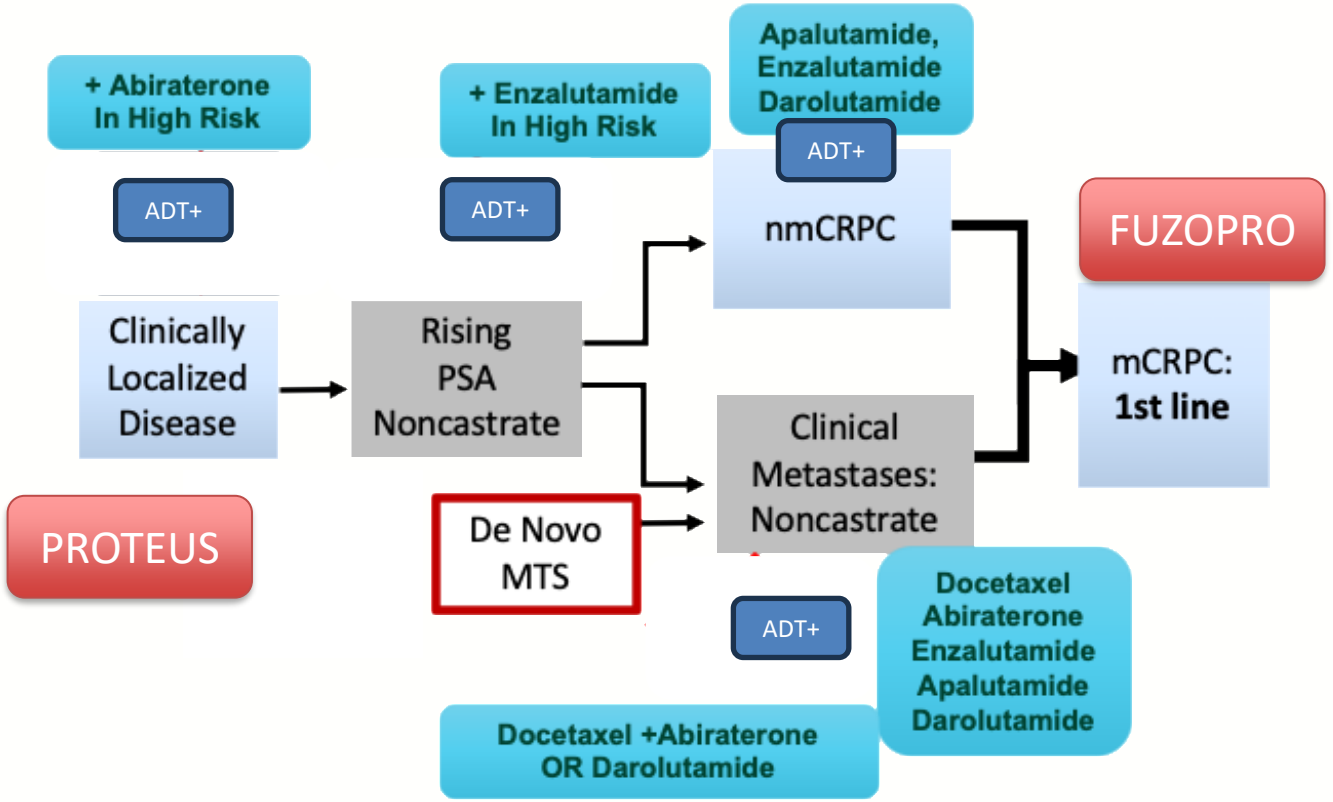
GONORTE
Grupo Oncológico

Presentaciones más destacadas en cáncer de próstata

Dr. David Olmos

Hospital Universitario 12 de Octubre - Madrid


+ Abiraterone
In High Risk
ADT+
+ Enzalutamide
In High Risk
ADT+
Apalutamide,
Enzalutamide
Darolutamide
ADT+
nmCRPC
Clinically
Localized
Disease
Rising
PSA
Noncastrate
mCRPC:
1st line
Clinical
Metastases:
Noncastrate
PROTEUS
De Novo
MTS
ADT+
Docetaxel
Abiraterone
Enzalutamide
Apalutamide
Darolutamide
Docetaxel +Abiraterone
OR Darolutamide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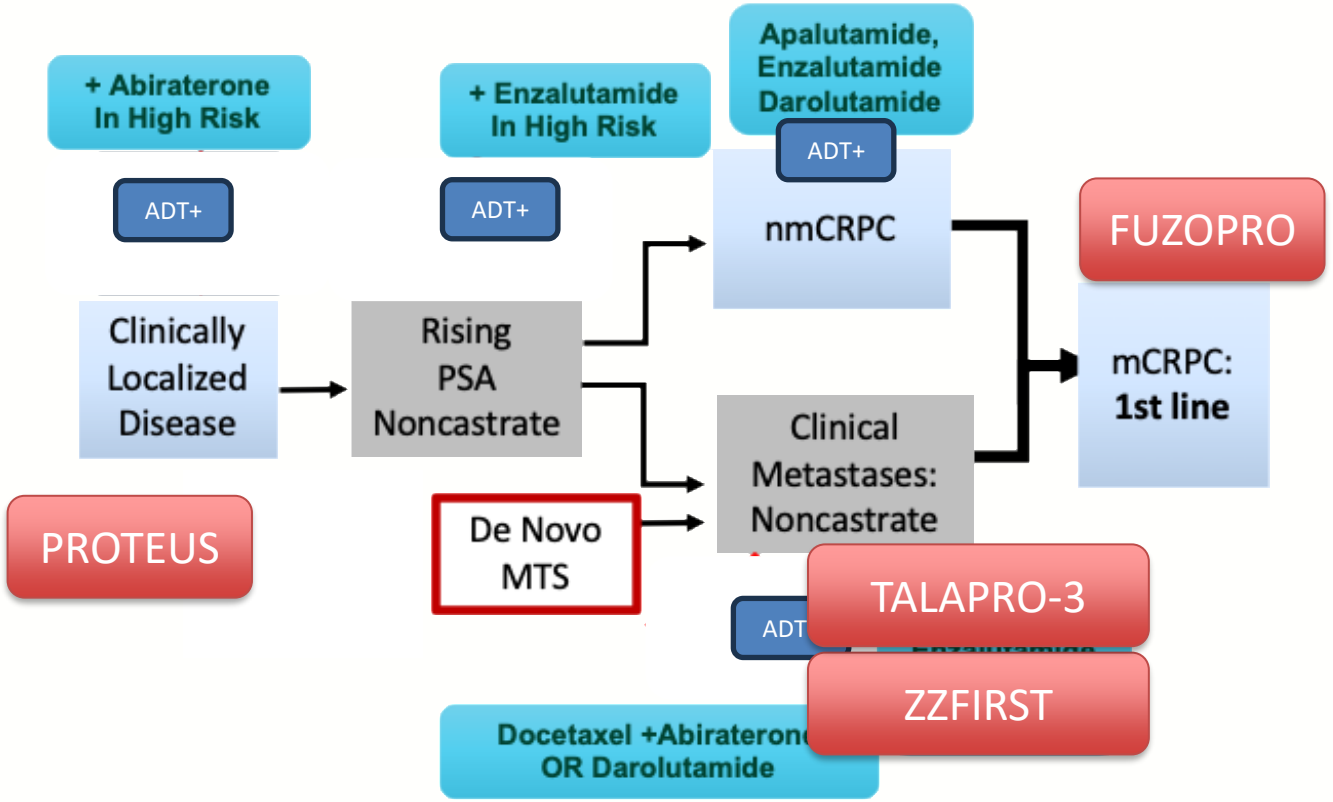
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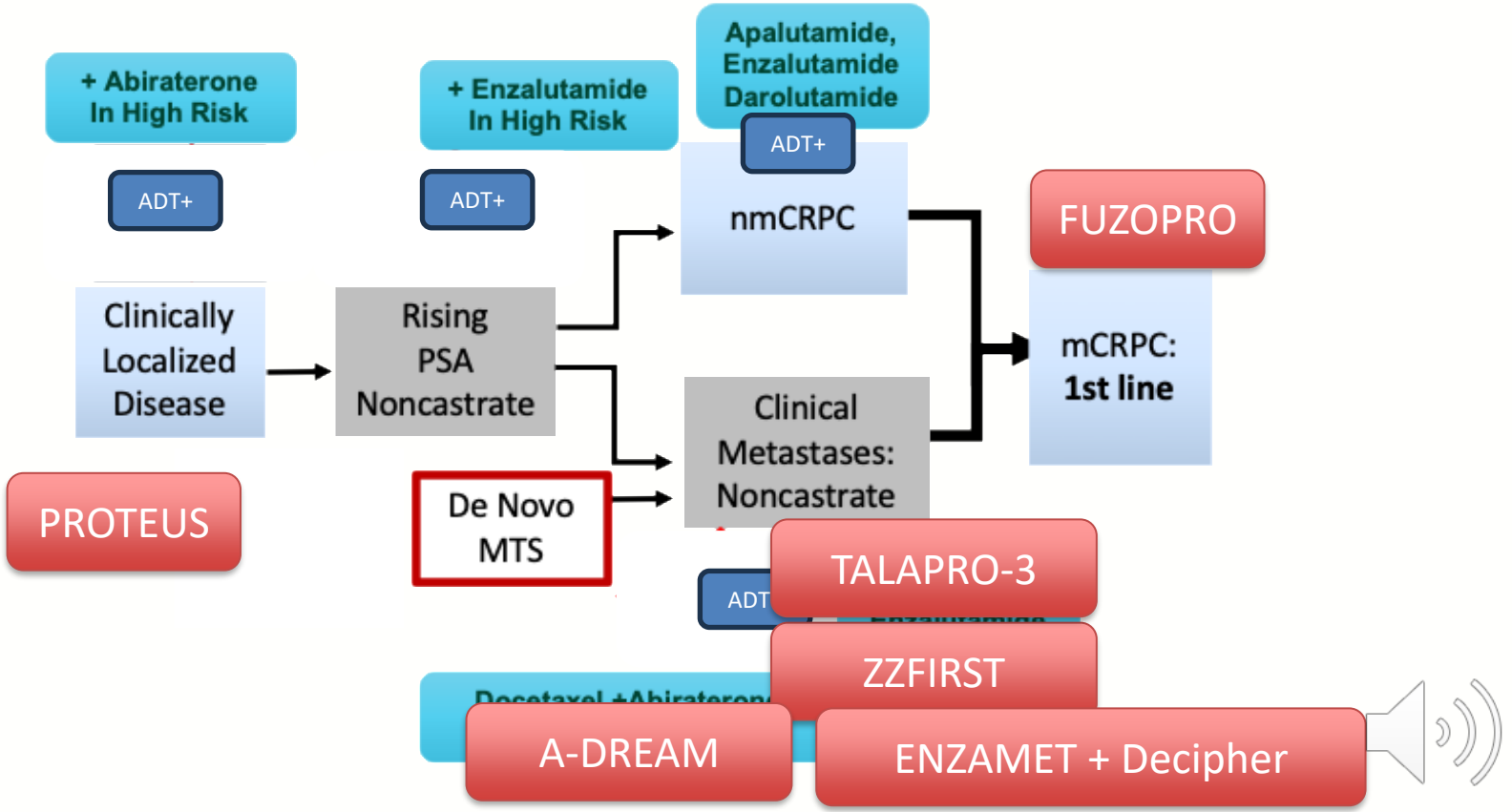
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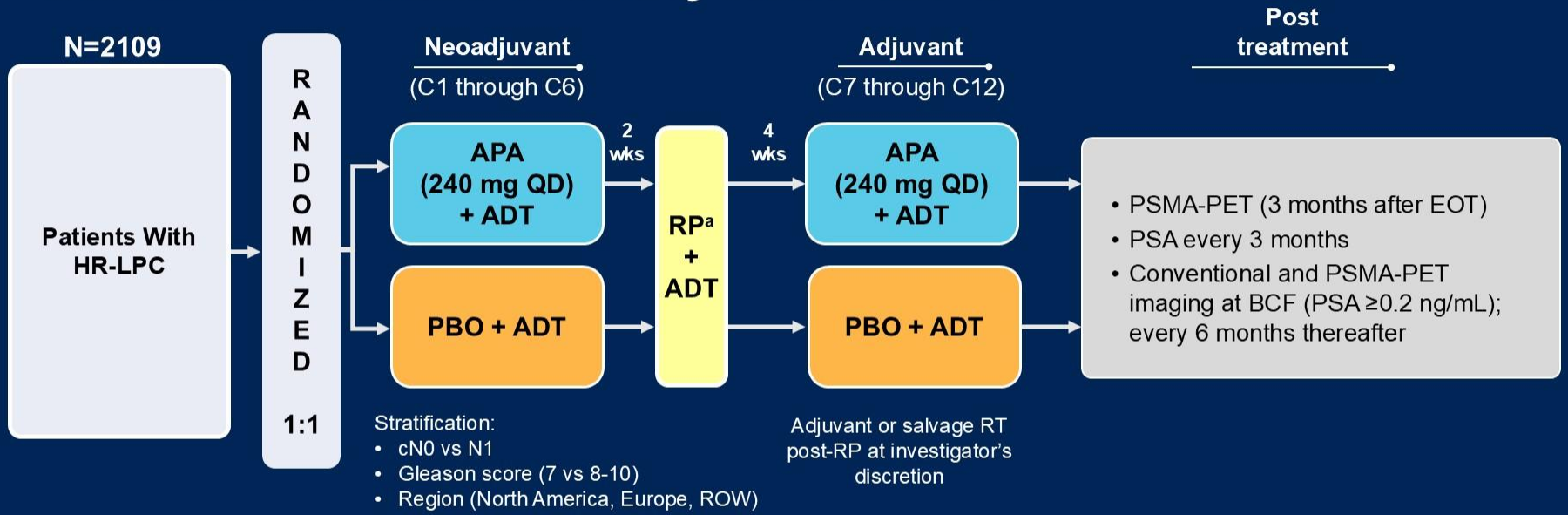
PROTEUS
De Novo
MTS
TALAPRO-3
ZZFIRST
A-DREAM
ENZAMET + Decipher

PROTEUS: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in HR-LPC



- To complement these data, a substudy is ongoing to further inform on the role of APA + ADT + RP versus RP alone

Patients randomized from July 15, 2019, to June 30, 2022.
Protocol Amendment 7 for including PSMA-PET into MFS assessment (April 14, 2022).

APA, apalutamide; BCF, biochemical failure; C, cycle; EOT, end of treatment; PBO, placebo; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron emission tomography; QD, daily; ROW, rest of the world; RT, radiation therapy.
[a]APA/PBO is stopped 2 weeks prior to planned RP and then resumed 4 weeks after RP. Cardiovascular risk prophylaxis and venous thromboembolism prophylaxis given based on risk.

PROTEUS Statistical Analysis Plan

Based on 2000 Accrued Patients

Dual Primary End Points	pCR/MRD	MFS
Alpha (2 sided)	0.01	0.04
Power	94%	85%
Number of events needed at final analysis	≥5% difference between arms	477 (Actual 472)

- pCR/MRD and MFS were to be tested at
  recycled to test MFS when pCR/MRD an
- As pCR/MRD and EFS were significant a

COMPOSITE:
* pCR-pT0 or
* MRD-≤pT2 or ≤5% residual T

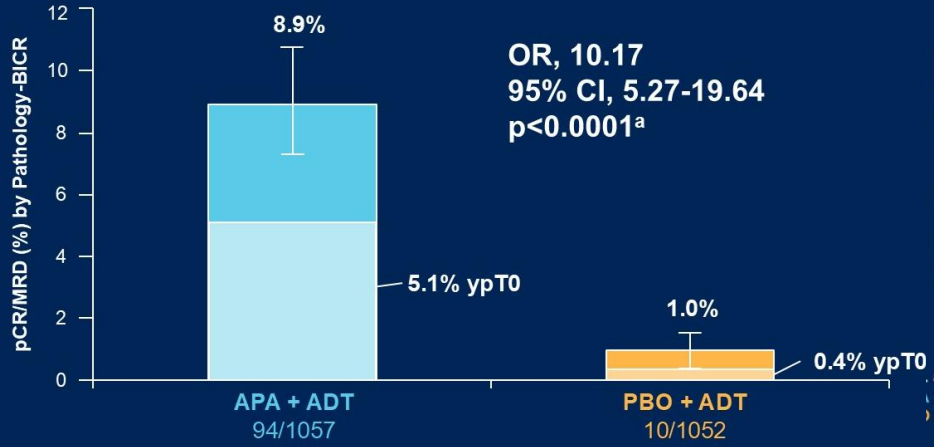
COMPOSITE:
* MFS convencional
* MFS PET
* MTS por biopsia

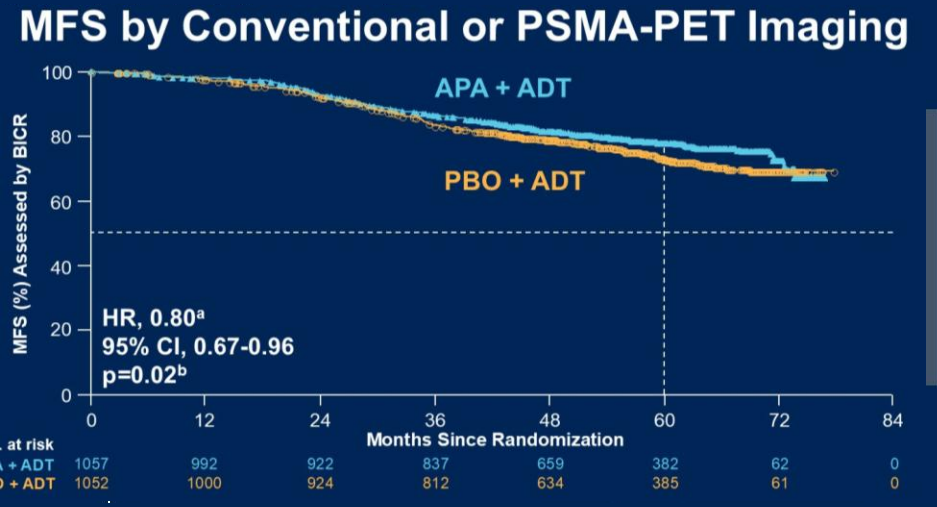
Power for MFS analysis was based on assumption of HR=0.75
Power for pCR/MRD was based on assumption of 5% pCR/MRD rate in PBO + ADT arm.

The independent data monitoring committee recommended continuing blinding until the final analysis.

PRESENTED BY: Mary-Ellen Taplin, MD, FASCO

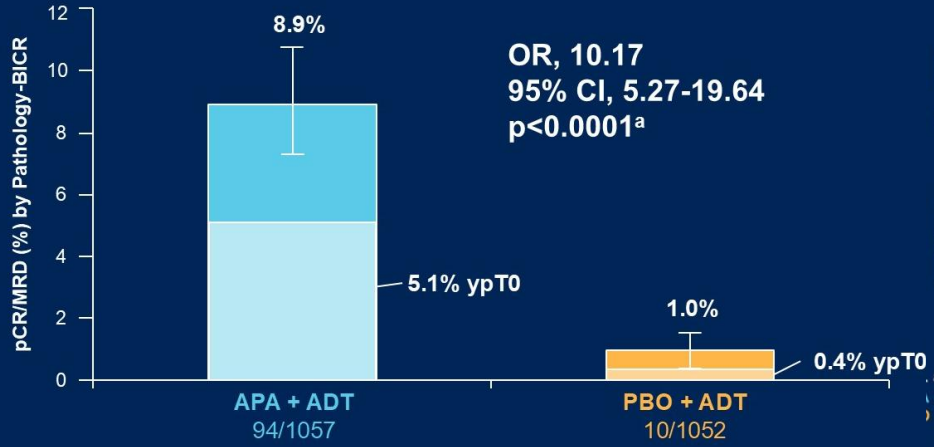
Dual Primary End Point Met:

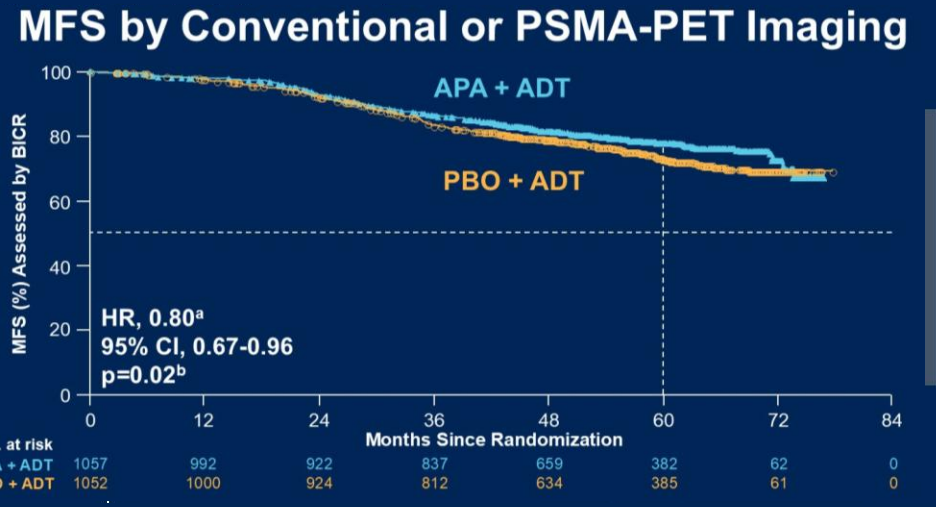




Positive study according to their pre-specified ENDPOINTS boundaries

Dual Primary End Point Met:

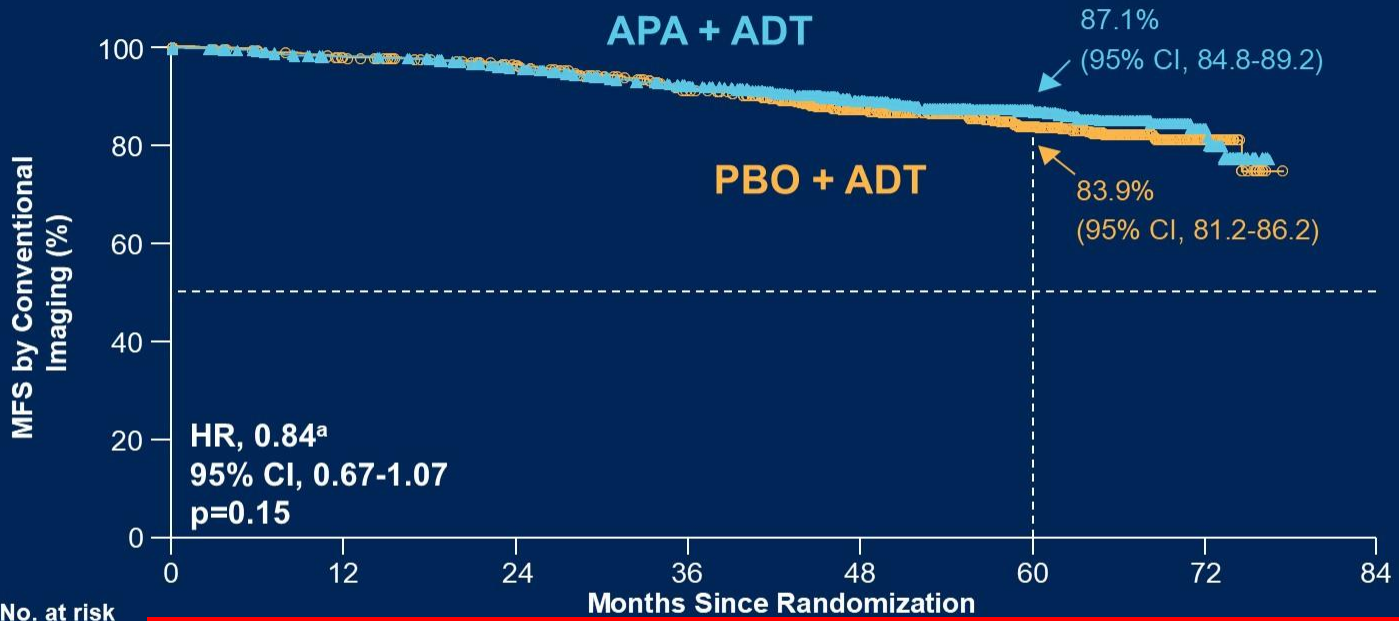




Aprox. x10 FOLD
INCREASED IN pCR/MDR

Only 5% MFS increase
What does PET-PSMA MFS means?
PSA-driven, major % not basal PET

MFS by Conventional Imaging



MFS: Time to
Patients prog
imaging

NS, not significa
[a]HR is from stra

Use of PSMA-PET with potential early detection of metastasis and subsequent therapy may impact MFS by conventional imaging

NNT for 5 yrs Conventional MFS

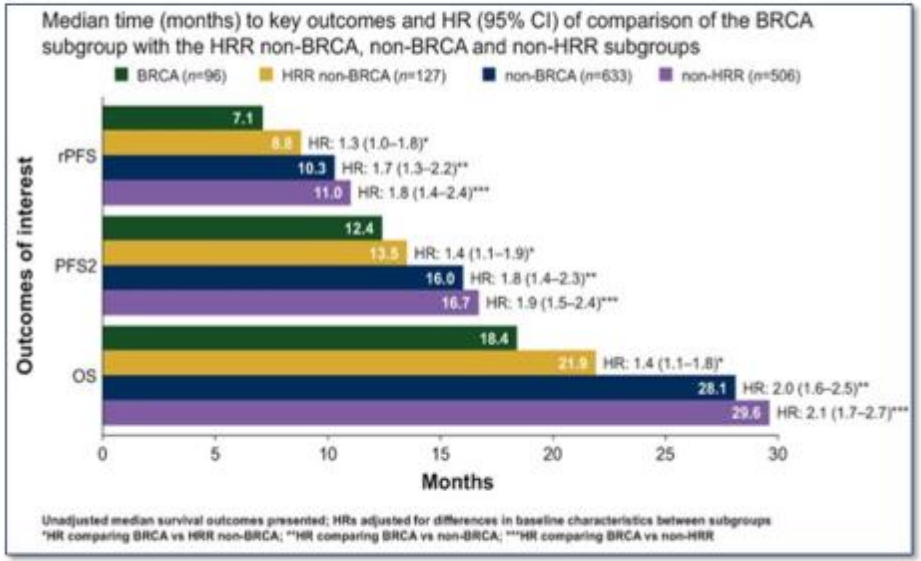
I need to treat 32 patients to avoid a MTS at 5 years!

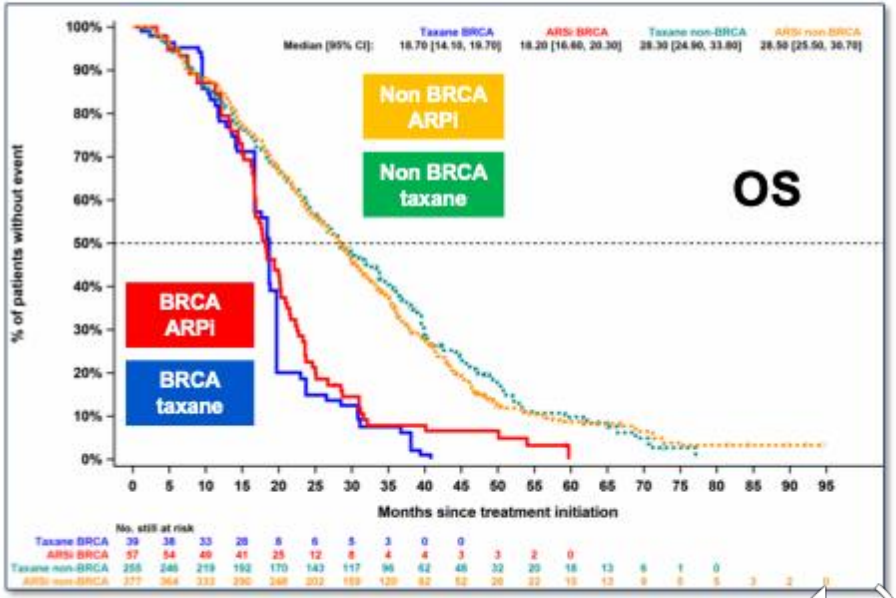
How many I need to terat to avoid a OS?

Outcomes with SoC 1L mCRPC differ by BRCAm/HRRm/non-HRR status

***BRCA1/2m* pts tend to progress earlier to 1L**, either taxanes or ARPi

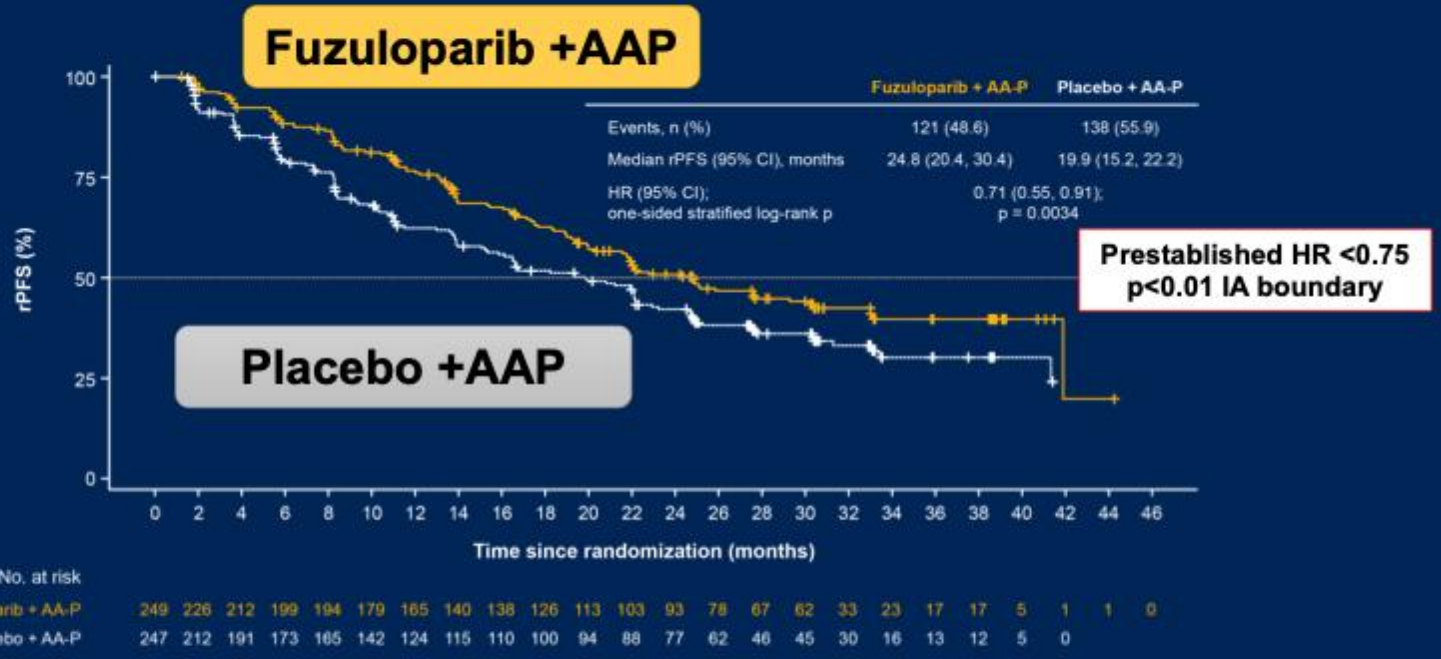
BRCA < HRR non-BRCA< Unselected < Non-HRR





Olmos D et al. A[illegible]co) 2024

rPFS by BICR in the overall population – *Interim Analysis Cohort 1 per Nov 2024 amendment*

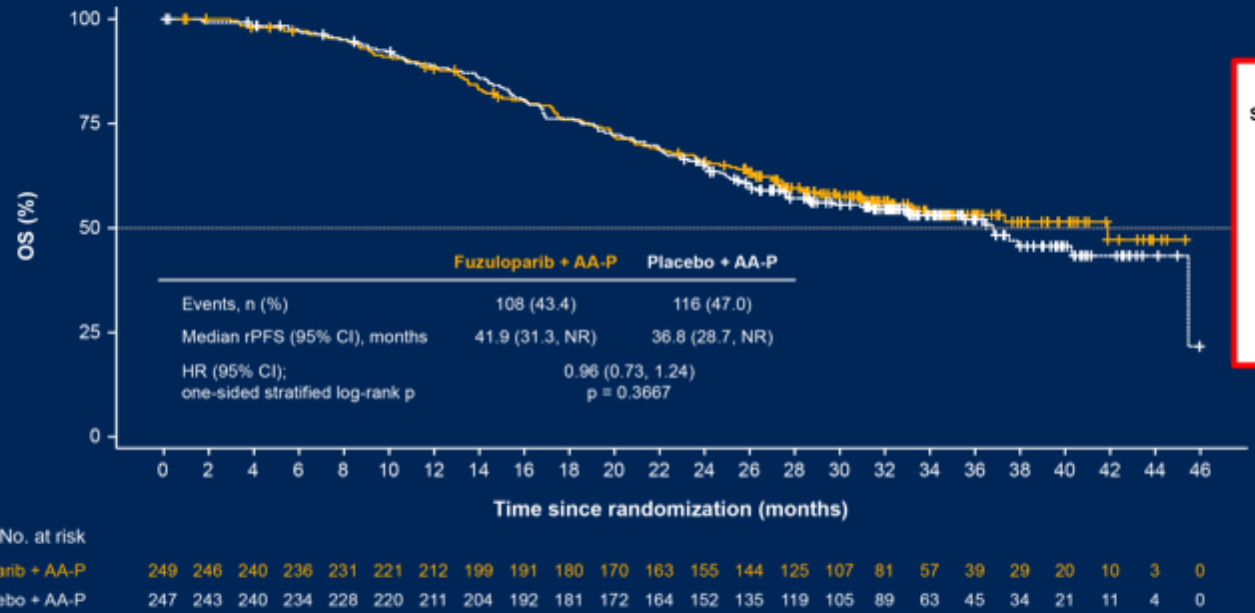


The interim rPFS analysis met the prespecified efficacy boundary, confirming the study as positive for its primary endpoint

PRESENTED BY: D. Olmos MD PhD @dolmos77

OS in the overall population → 83% maturity for final OS

224 of 270 OS events



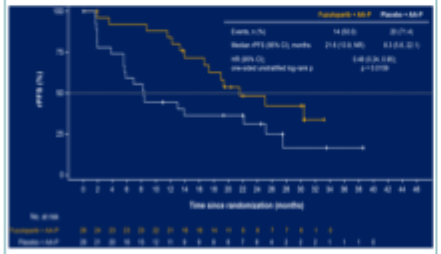
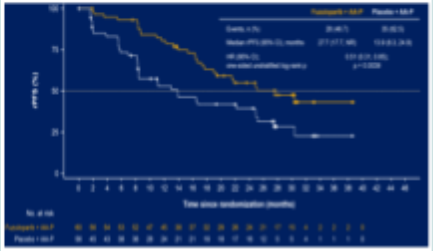
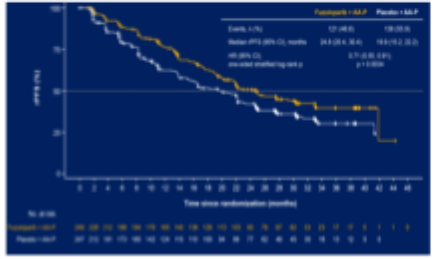
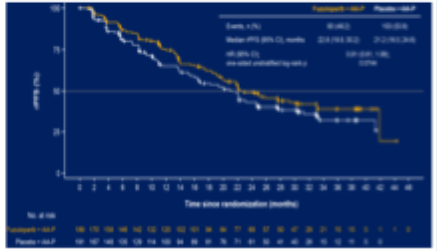
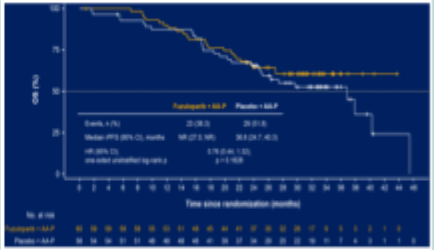
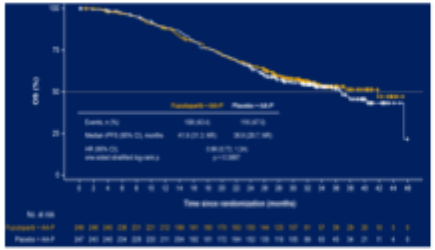
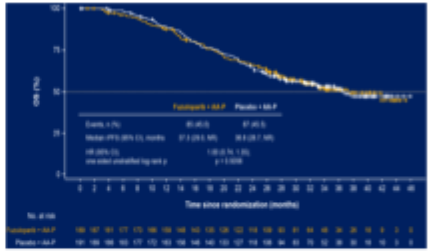
Crossing OS curves suggest non-proportional hazards

HR≈0.96 with 83% of events → very low probability that any non-proportional hazard model will change the conclusion

With 83% OS maturity in this analysis, it is highly unlikely that the final OS analysis will change the result

Similarly to TALAPRO-2 and PROPEL

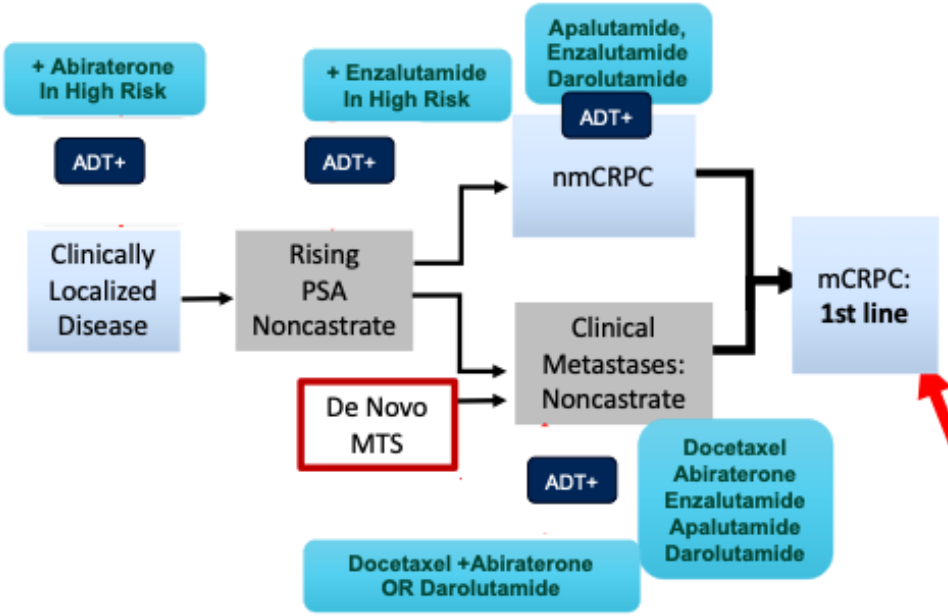
In FUZUPRO we see the same hierarchical benefit aligned with biology

	BRCA	>> HRRm	>> Unselected pts	> non-HRRm
rPFS				
	HR 0.48 (0.24-0.95)	**HR 0.51** (0.31-0.85)	**HR 0.71** (0.55-0.95)	**HR 0.81** (0.61-1.08)
OS	?			
	Unknown	**HR 0.76** (0.32-1.32)	**HR 0.96** (0.73-1.24)	**HR 1.00** (0.74-1.35)

Ye et al. ASCO 2026

PRESENTED BY: D. Olmos MD PhD @dolmos77

FUZUPRO in Post-ARPi → similar lack of data as other PARPi-ARPi combinations



	28 BRCA 56 HRR	28 BRCA 60 HRR
	Fuzuloparib + AA-P (N = 249)	Placebo + AA-P (N = 247)
DRD status		
Positive	60 (24.1)	56 (22.7)
Negative/unknown	189 (75.9)	191 (77.3)
BRCA1/2 mutations		
Positive	28 (11.2)	28 (11.3)
Negative/unknown	221 (88.8)	219 (88.7)
Presence of visceral metastases (excluding lymph nodes)	35 (14.1)	41 (16.6)
Presence of high tumor burden	153 (61.4)	155 (62.8)
Baseline PSA level, median (IQR)	13.7 (4.7, 50.6)	14.2 (4.6, 51.2)
Baseline PSA level		
<median	126 (50.6)	121 (49.0)
≥median	122 (49.0)	125 (50.6)
Use of cytotoxic chemotherapy or novel AR-targeted therapy at HSPC stage	43 (17.3)	43 (17.4)

Note: in FUZUPRO 20 pts in the experimental arm have <3m run-in AAP before randomization
In MAGNITUDE longer AAP exposition to AAP before randomisation was associated to worse outcomes in BRCA/HRR patients (Castro et al. ASCO GU 2023)

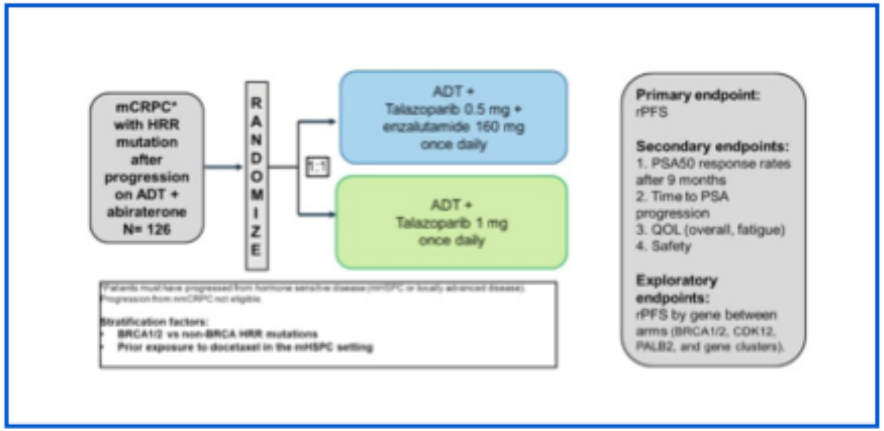
1 patient previously exposed to Abiraterone in mHSPC*
**Data provided by investigators/Sponsor*

ADT – Androgen Deprivation Therapy; CRPC – Castration Resistant Prostate Cancer

Further evidence of the ARPI+PARPi combos is required in Post-ARPi setting

Post-AAP

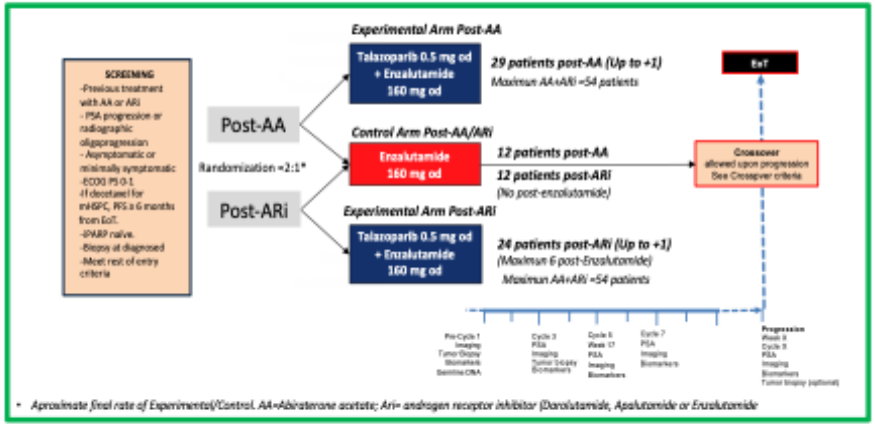
TALENT (NCT06844383): Talazop + Enza vs Talazo in **HRR**



A. Morgans / K. Autio

Post-AAP or Post-"amide"/ARi

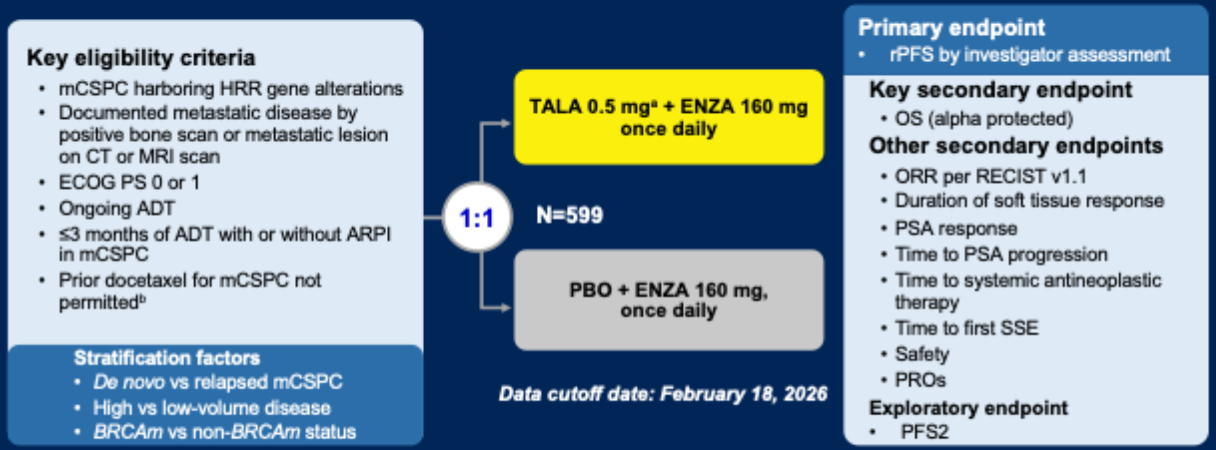
TEAM PC (NCT06582628): Talazop + Enza vs Enza in **all**



E. Castro / G. Roubaud / D. Olmos

PRESENTED BY: D. Olmos MD PhD @dolmos77

TALAPRO-3: Trial Design → Interim analysis 1



HRR gene alterations: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C* (using FoundationOne/FoundationOne®CDx and FoundationOne®Liquid CDx)

- **Contemporaneous trial** against an active ARPi doublet, but:

No triplet with Docetaxel →
70% High volume, 84% *de novo*

- Metachronous mCSPC may be under-represented
- ***BRCA1/2*mut only 1/3 of pts**
- **Highest number of *ATM*mut cases** in PARPi trials (N=157)

[a]0.35 mg once daily if patient has moderate renal impairment. [b]As per protocol amendment (September 2021). ClinicalTrials.gov identifier: NCT04821622.
ADT=androgen deprivation therapy; *BRCA*m= BRCA alterations; CT=computed tomography; NRI=magnetic resonance imaging; ORR=objective response rate; PBO=placebo; PFS2=time to second progression or death; PRO=Patient-reported outcomes; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; SSE=symptomatic skeletal event.

PRESENTED BY: Neeraj Agarwal

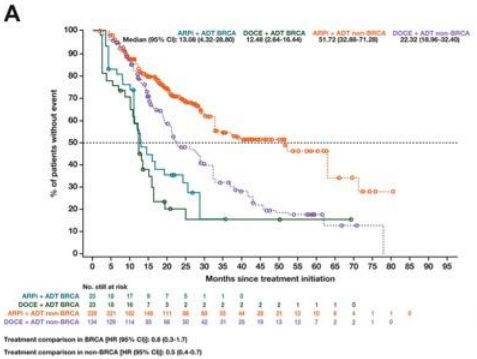
Clinical outcomes of mCSPC according to BRCA/HRR/Non-HRR status

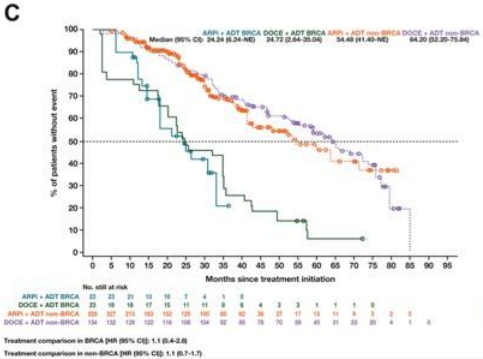
CAPTURE mCSPC

rPFS

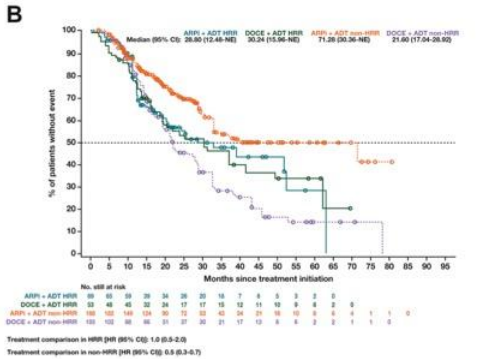
OS

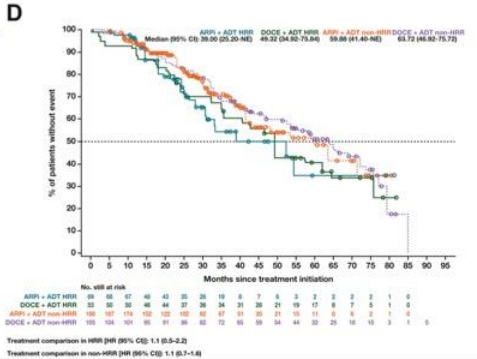
BRCA vs non-BRCA





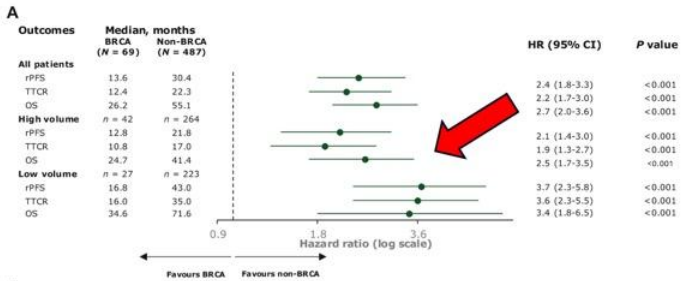
HRR vs non-HRR

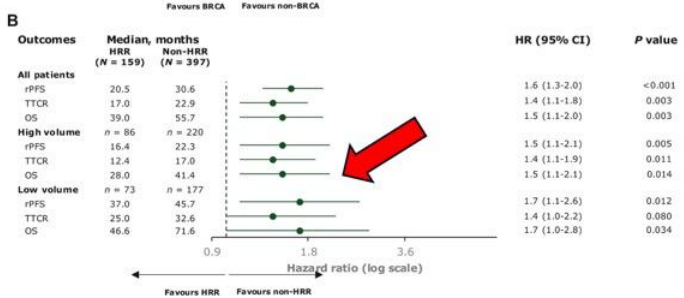




BRCA < HRR non-BRCA < Non-HRR

In BRCA, volume lose prognostic value



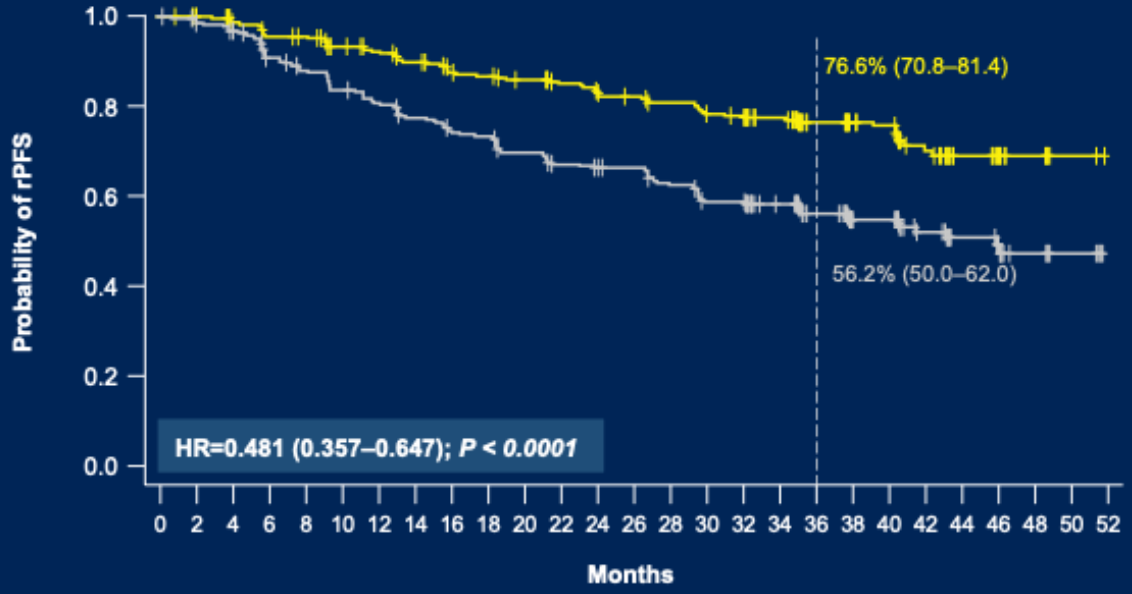


Olmos et al. Ann O 025

PRESENTED BY: D. Olmos MD PhD @dolmos77

Primary Endpoint: rPFS by Investigator

TALA + ENZA led to a 52% reduction in risk of progression or death



No. at Risk

TALA + ENZA	300	282	271	262	260	248	241	232	222	219	213	206	196	195	189	182	178	163	126	99	96	63	32	20	14	3	0
PBO + ENZA	299	284	279	255	243	232	222	212	203	200	188	179	175	174	163	151	151	132	98	74	74	49	32	21	12	6	0

	TALA + ENZA (N=300)	PBO + ENZA (N=299)
Events, n	67	126
Median (95% CI), months	NR (NR–NR)	45.8 (37.7–NR)

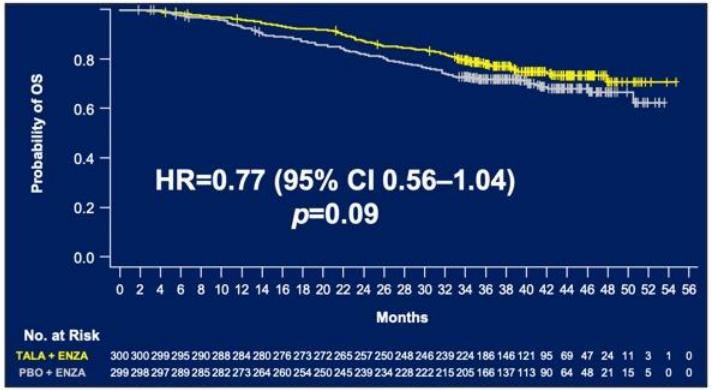
Median follow-up for rPFS was 37.6 and 37.7 months, respectively

POSITIVE STUDY
For its 1ry endpoint

Data cutoff: February 18, 2026. Intention-to-Treat Population.
Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated. CI=confidence interval; HR=hazard ratio; NR=not reached

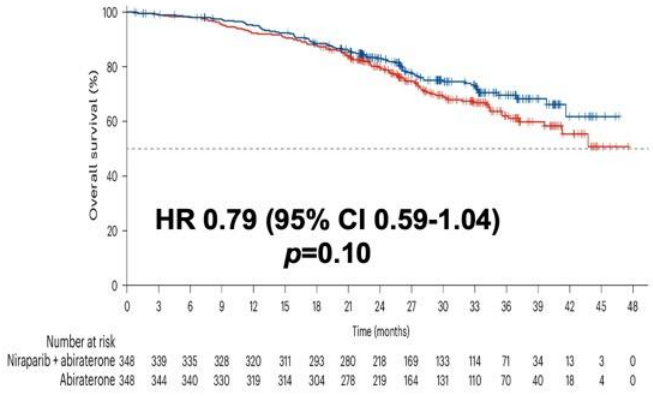
Overall Survival in TALAPRO-3 & AMPLITUDE Interim analysis

TALAPRO-3



	TALA + ENZA (N=300)	PBO + ENZA (N=299)
Events, n	74	91
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)

AMPLITUDE



	TALA + ENZA (N=300)	PBO + ENZA (N=299)
Events, n	74	91
Median (95% CI), months	NR (NR–NR)	NR (NR–NR)

PARPi/Platinum in control arm

- Similar, 1/3 in both AMPLITUDE & TALAPRO

BRCA vs non-BRCA

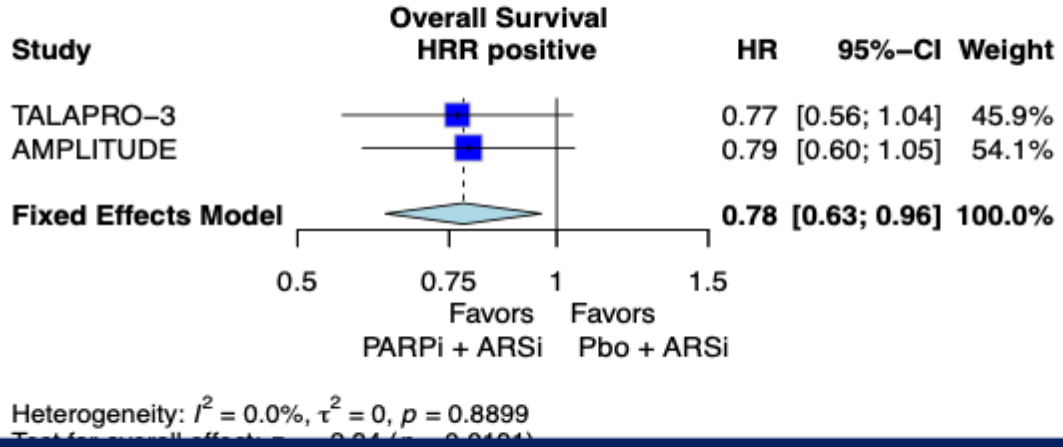
- 1/3 *BRCA1/2* in TALAPRO-3
- >50% *BRCA1/2* AMPLITUDE

Agarwal et al. ASCO 2026; Attard et al. Nat Med 2025

AMPLITUDE & TALAPRO-3 Meta-analysis

Olmos. ASCO 2026; Lorente et al. Submitted EUO 2026

METHODOLOGY:
A fixed-effects model is appropriate given the minimal effect heterogeneity between AMPLITUDE and TALAPRO-3
Data source: Agarwal et al. ASCO 2026; Attard et al. Nat Med 2025



Both trials analysed together show a significant OS effect for ARPi+PARPi in HRRm mCSPC

- NOTE/CAUTION:

No OS stratified data for BRCA vs non-BRCA HRR subgroups across trials; unequal BRCA distribution (higher in AMPLITUDE) may overestimate the HRR non-BRCA effect when analy[illegible]ge th[illegible]r.

Subgroup Analysis of rPFS

A consistent treatment effect for rPFS was observed across prespecified subgroups

		Talazoparib + Enzalutamide	Placebo + Enzalutamide	HR (95% CI)
		no. of events/no. of patients		
Overall	All patients	67/300	126/299	0.484 (0.360–0.652)
Disease stage[a]	De novo	58/252	113/254	0.464 (0.338–0.637)
	Relapsed	9/48	13/45	0.679 (0.289–1.594)
Disease volume[a]	High	52/211	107/212	0.422 (0.303–0.588)
	Low	15/89	19/87	0.808 (0.410–1.590)
BRCA1/2 alterations[a]	Yes	22/104	49/103	0.368 (0.222–0.609)
	No	45/196	77/196	0.567 (0.392–0.819)
Age — yr	≥70	37/156	64/147	
	<70	30/144	62/152	
Site of metastasis	Bone only	14/86	27/96	
	Soft tissue only	6/38	12/27	
	Bone and soft tissue	47/176	87/173	
Gleason score	<8	8/45	14/49	
	≥8	56/245	111/245	
Baseline PSA	≤Median	29/150	51/149	0.527 (0.334–0.831)
	>Median	38/150	75/149	0.446 (0.302–0.660)
ECOG PS	0	37/199	72/208	0.484 (0.326–0.720)
	1	30/101	54/91	0.446 (0.285–0.697)
Prior ARPI for CSPC	Yes	9/44	14/36	0.507 (0.219–1.173)
	No	58/256	112/263	0.485 (0.353–0.666)
Geographic region	North America	11/38	9/27	0.951 (0.394–2.298)
	Europe	24/132	73/142	0.310 (0.195–0.492)
	Asia	26/113	40/116	0.626 (0.382–1.026)
	Rest of the world	6/17	4/14	0.950 (0.268–3.375)

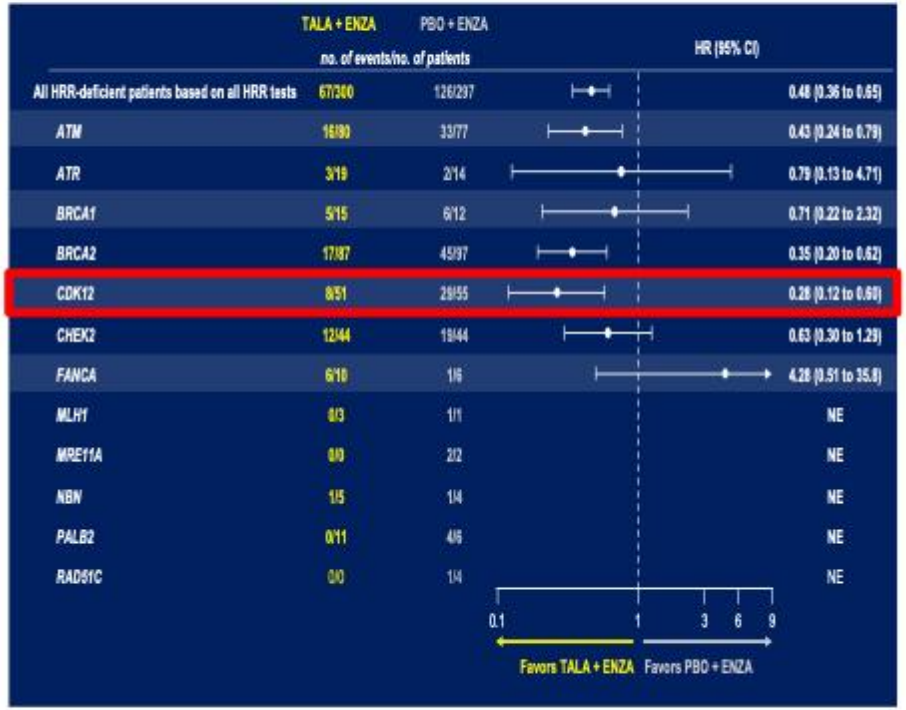
Benefit in rPFS for HRR non-BRCA

Data cutoff: February 18, 2026. Intention-to-Treat Population. [a]By randomization stratification
Unstratified hazard ratio based on Cox proportional hazards mode. P-value from unstratified log-rank test.

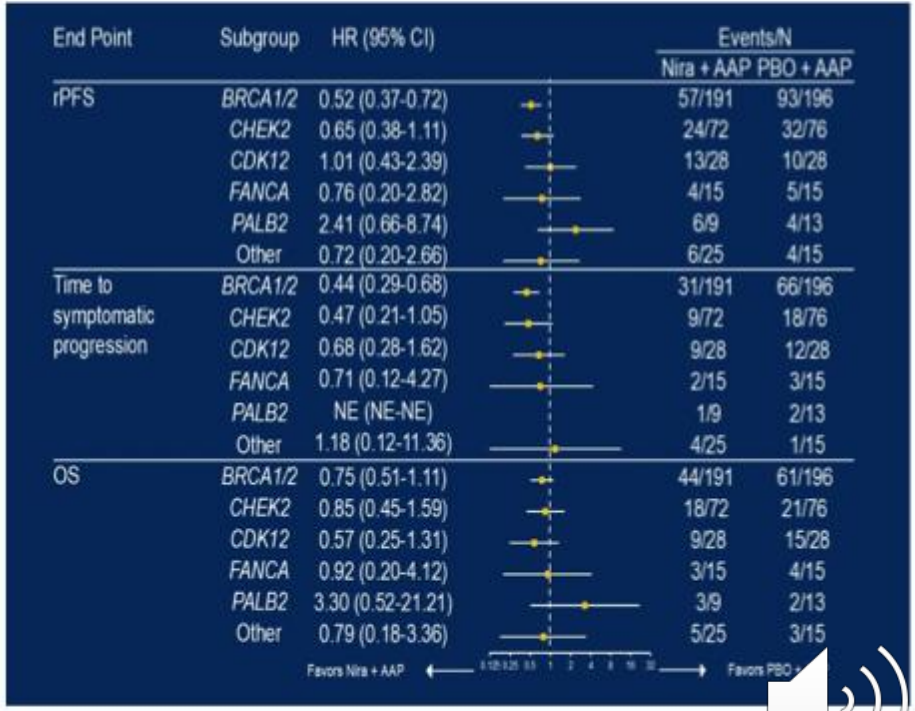
Benefit beyond BRCA

CDK12: Benefit in rPFS supports ENZA+TALA, which was already seen in mCRPC

TALAPRO-3



AMPLITUDE

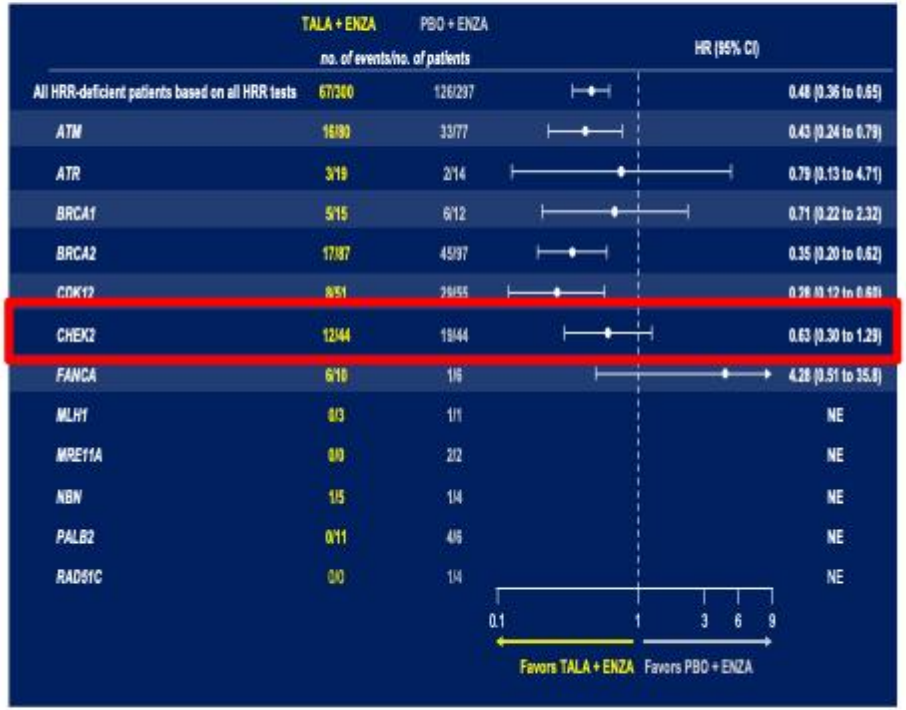


Agarwal et al. ASCO 2026; Attard et al. ASCO 2025

Benefit beyond BRCA

CHEK2: Benefit trends in rPFS with NIRA+AAP or ENZA+TALA may not translate into OS advantage

TALAPRO-3



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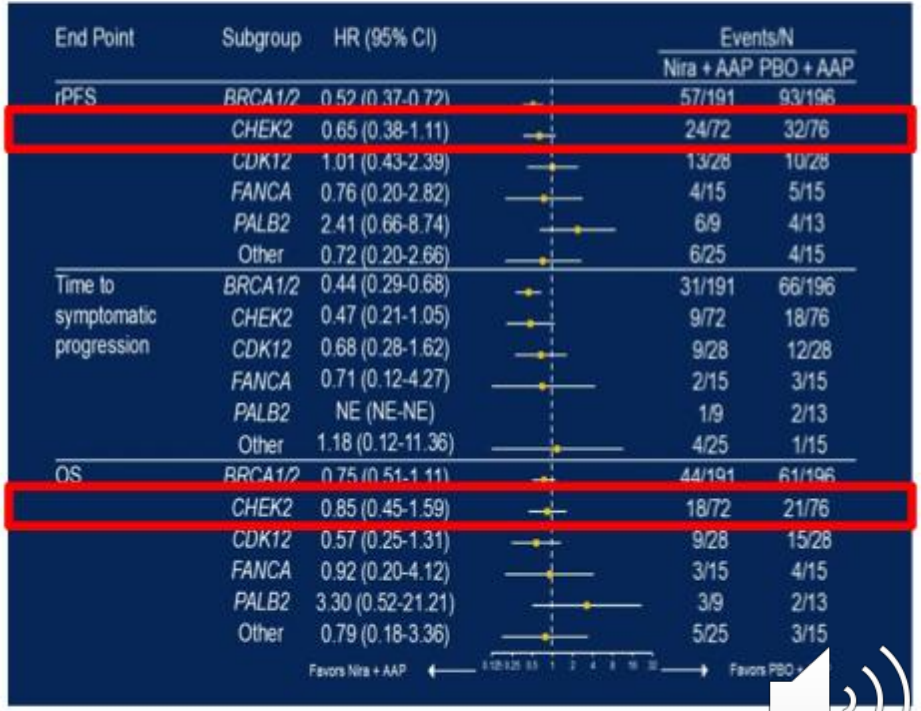
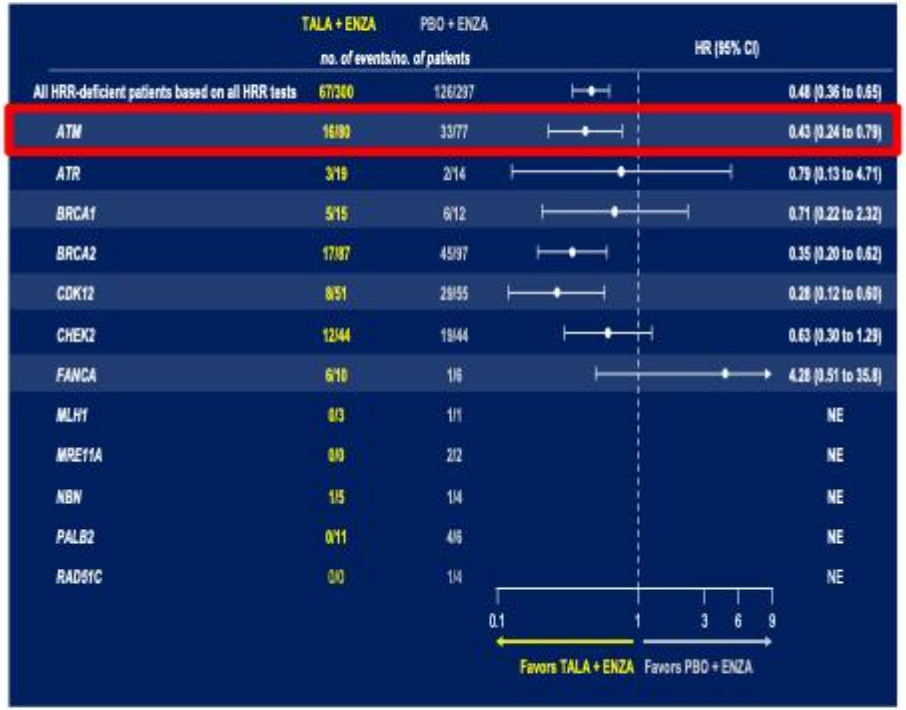


Agarwal et al. ASCO 2026; Attard et al. ASCO 2025

Benefit beyond BRCA

ATM: robust rPFS benefit observed with ENZA+TALA

TALAPRO-3



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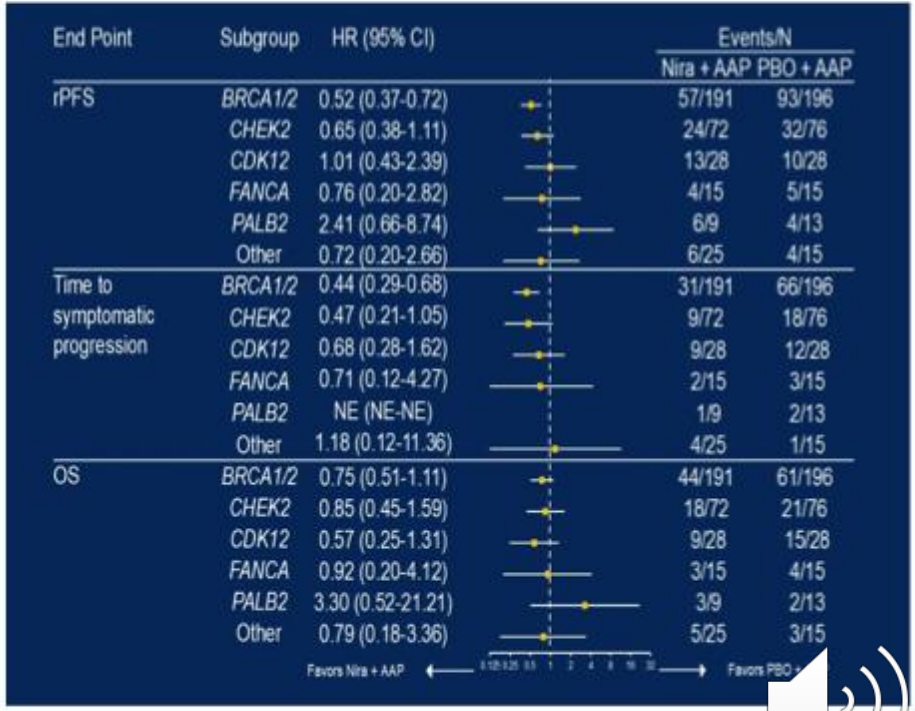
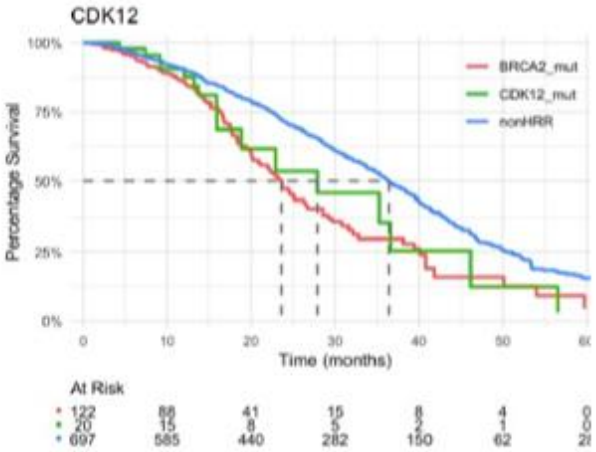


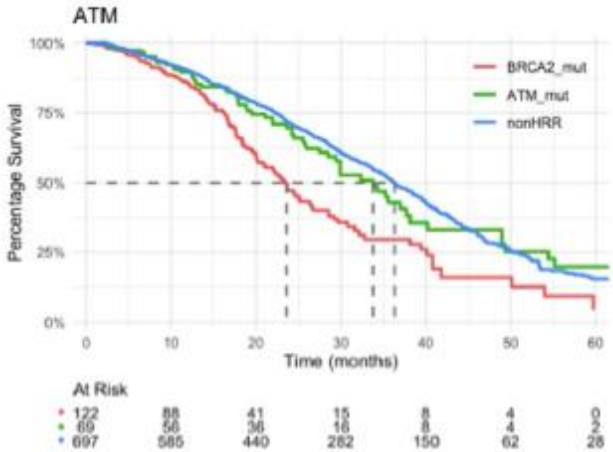
Agarwal et al. ASCO 2026; Attard et al. ASCO 2025

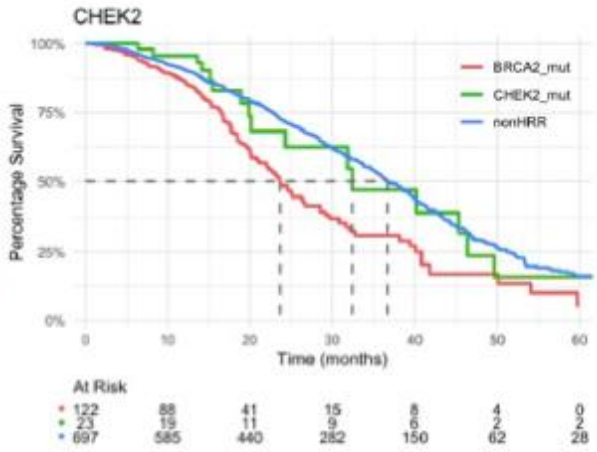
How patients with non-BRCA mutated genes behave with SoC?

As physicians, we must balance benefit vs risk

Understanding how patients perform on the SoC is therefore essential







***CDK12m* pts have poor outcomes, similar to BRCA2**

***ATMm* pts have outcomes similar to non-HRR pts**

***CHEK2m* pts have outcomes similar to non-HRR pts**

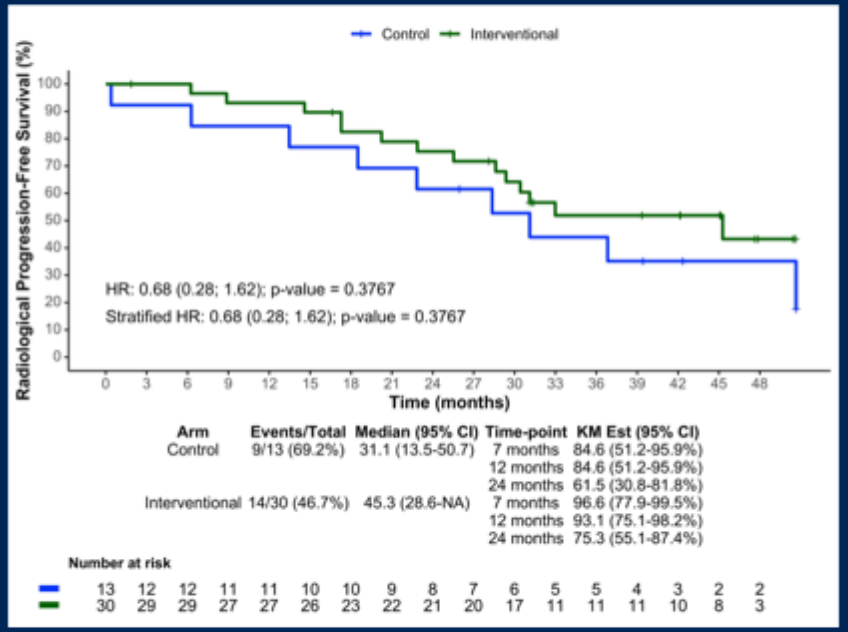
PRESENTED BY: D. Olmos MD PhD @dolmos77

Lorente et al. ESMO 2025; Submitted Eur Urol Oncol

ZZFIRST shows potential activity of ENZA+TALA in HV non-HRRm mCSPC

Radiographic PFS – HRR WT (n = 43)

Wild-type/non deficient HRR by NGS panel



Arm	Events/Total	Median (95% CI)	Time-point	KM Est (95% CI)
Control	9/13 (69.2%)	31.1 (13.5-50.7)	7 months	84.6 (51.2-95.9%)
			12 months	84.6 (51.2-95.9%)
			24 months	61.5 (30.8-81.8%)
Interventional	14/30 (46.7%)	45.3 (28.6-NA)	7 months	96.6 (77.9-99.5%)
			12 months	93.1 (75.1-98.2%)
			24 months	75.3 (55.1-87.4%)

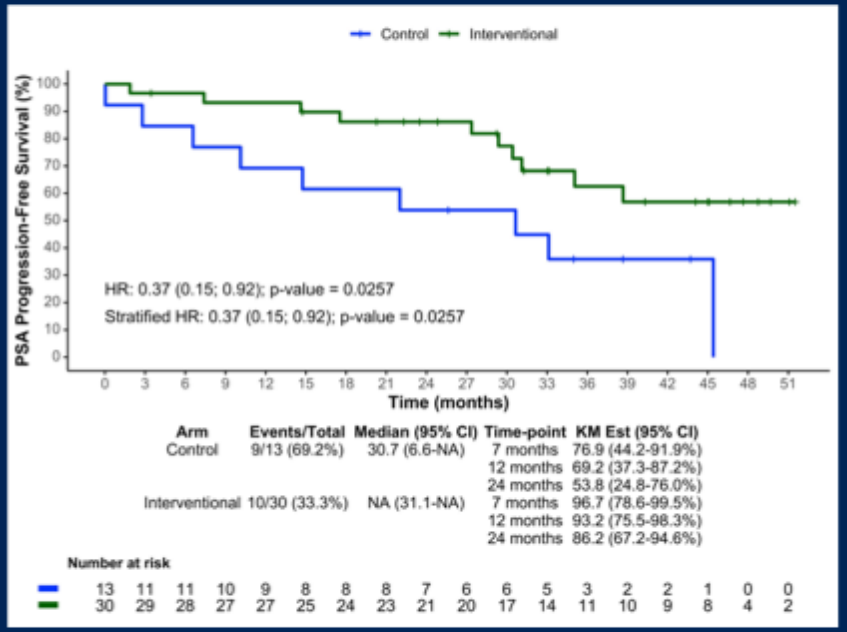
Number at risk

13	12	12	11	11	10	10	9	8	7	6	5	5	4	3	2	2
30	29	29	27	27	26	23	22	21	20	17	11	11	11	10	8	3

HRR WT (n = 43), HRRmut (n = 7), HRR status unknown/failed targeted NGS (n = 4).

PSA PFS – HRR WT (n = 43)

Wild-type/non deficient HRR by NGS panel



Arm	Events/Total	Median (95% CI)	Time-point	KM Est (95% CI)
Control	9/13 (69.2%)	30.7 (6.6-NA)	7 months	76.9 (44.2-91.9%)
			12 months	69.2 (37.3-87.2%)
			24 months	53.8 (24.8-76.0%)
Interventional	10/30 (33.3%)	NA (31.1-NA)	7 months	96.7 (78.6-99.5%)
			12 months	93.2 (75.5-98.3%)
			24 months	86.2 (67.2-94.6%)

Number at risk

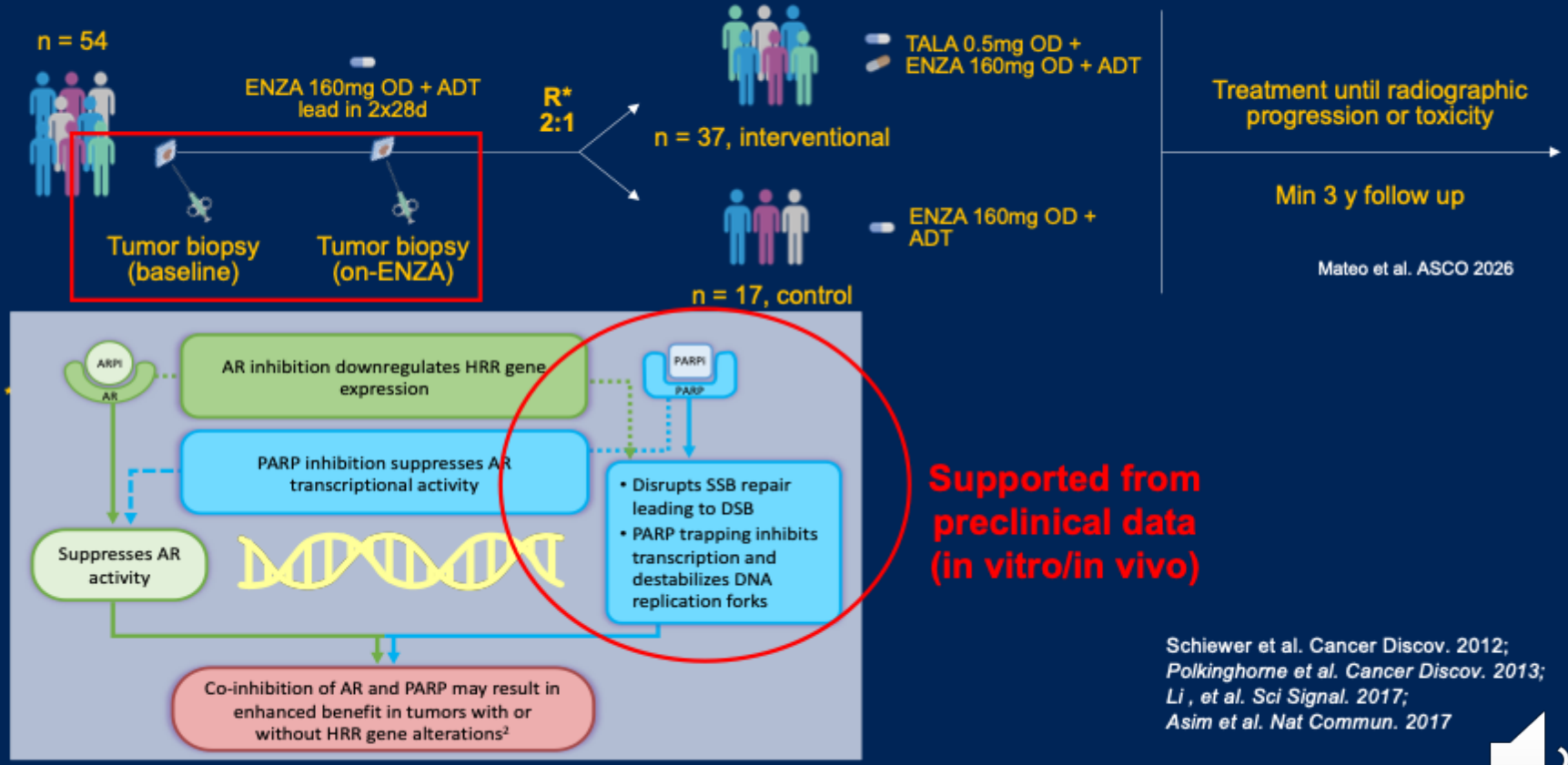
13	11	11	10	9	8	8	8	7	6	6	5	3	2	2	1	0	0
30	29	28	27	27	25	24	23	21	20	17	14	11	10	9	8	4	2

median follow-up: 3.6 years

Mateo et al. ASCO 2026

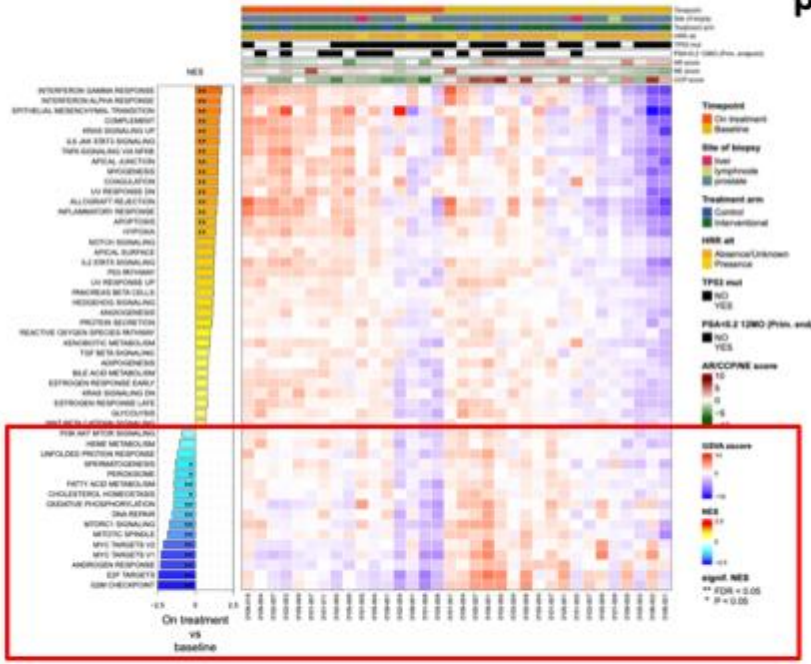
PRESENTED BY: D. Olmos MD PhD @dolmos77

Does ARinh induce BRCAness in HRR WT hormone-sensitive PCa cells?



Schiewer et al. Cancer Discov. 2012;
Polkinghorne et al. Cancer Discov. 2013;
Li , et al. Sci Signal. 2017;
Asim et al. Nat Commun. 2017

What is ENZA causing in these HRR wt hormonosentive PCa cells?



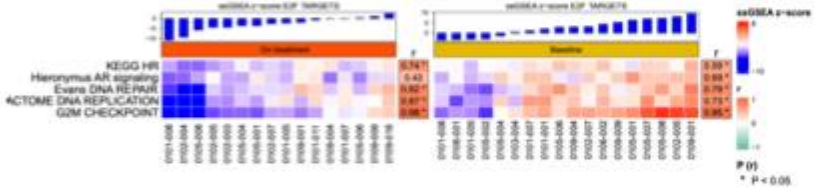
Using RNAseq for comparing Expression Profiles in paired pre- & post-ENZA tumour biopsies they found:

Global decrease in Transcriptional activity

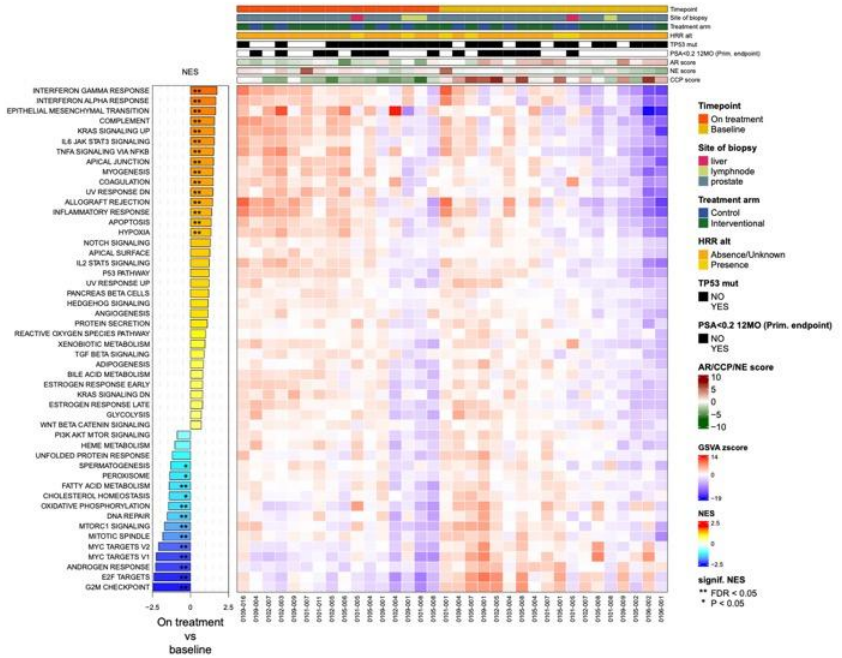
A decrease in proliferation/survival signals

A decrease in downstream AR-signalling pathways

A decrease expression DNA-repair genes, non-HRR specific



Does this global transcriptional down-regulation translate in true HRR deficiency?



Decrease in proliferation signals

Decrease in all downstream AR-signalling pathways

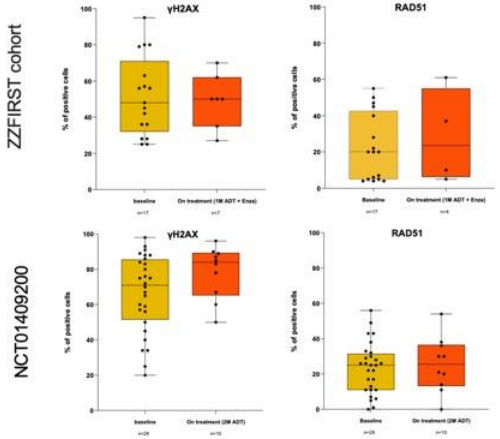
Using a Functional assay for HRR in tumour biopsies:

H2AX → Double Strand Breaks

RAD51 → final effector of HRR

Geminin* → Diving cells

**HRR is active only during the S and G2 phases of the cell cycle*



Validation cohort from MD Anderson

AR INHIBITION DOES NOT IMPAIR HRR

Mateo et al. ASCO 2026

Overall ENZAMET cohort: DGC > 0.85 was associated with poorer OS

STRATIFICATION

- Volume of metastases*
  - -High vs Low
- Planned Early Docetaxel
  - Yes vs No
- ECOG PS
  - - 0-1 vs 2
- Anti-resorptive therapy
  - -Yes vs No
- Comorbidities
  - ACE-27**: 0-1 vs 2-3
- Study Site

RANDOMIZE

ARM A ("Control"): Testosterone Suppression + standard NSAA → Evaluate every 12 weeks → CRPC therapy at investigator's discretion at progression

ARM B ("Enzalutamide"): Testosterone Suppression + Enzalutamide (160 mg/d) → Evaluate every 12 weeks → Follow for time to progression and overall survival

Participants enrolled *(N = 1,125)*

↓

Participants consented for biomarker analyses *(N = 1,071)*

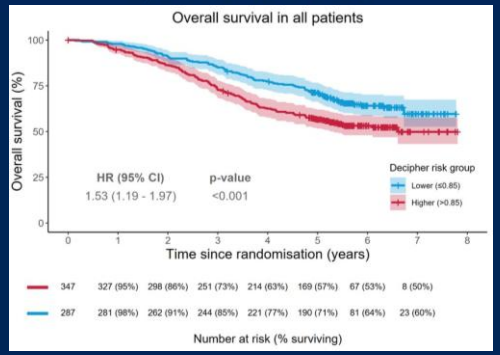
↓

Gene expression profilig (GEP) in CLIA* laboratory *(N = 764)** *(Final Biomarker Cohort^ (N = 634)*

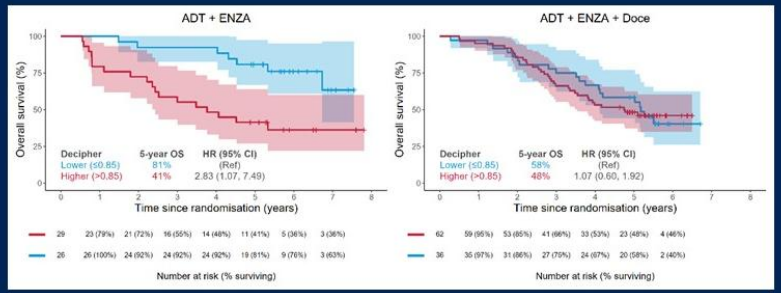
↓

ADT + ENZA ± Docetaxel Cohort (N=320)

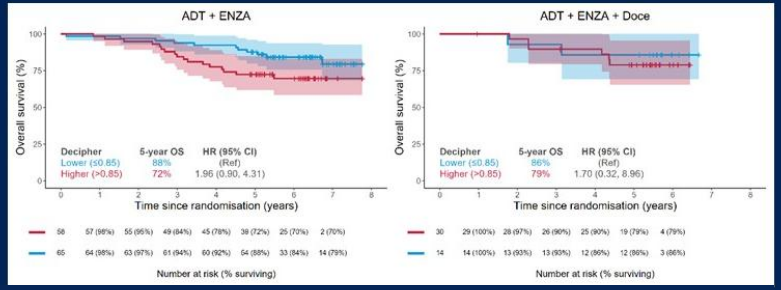
Also more prognostic features in patients treated with docetaxel

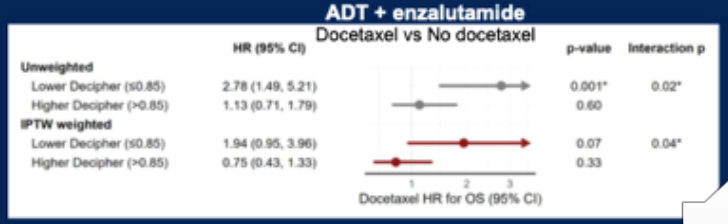


High Volume



Low Volume





What does it mean for individual-patient base decisions?

Study Design

mAPMS on ADT + ARPI
PSA<0.2 (stable/falling) after 18-24 mo ADT
(at least 12 mo ARPI)

N=75

Interrupt ADT + ARPI

Re-initiation triggers:
- *PSA ≥ 5 ng/ml*
- *Radiographic change (PCWG3)*
- *PrCa-related sx*

PSA / T q3 mo
Scans at least q6 mo (q3mo w/ rising PSA)
QOL q6 mo

Primary Endpoint: Treatment-free (w/ eugonadal T ≥ 150 ng/dl) at 18 months

Secondary Endpoints:
- Time to eugonadal T
- Duration off-tx
- QOL

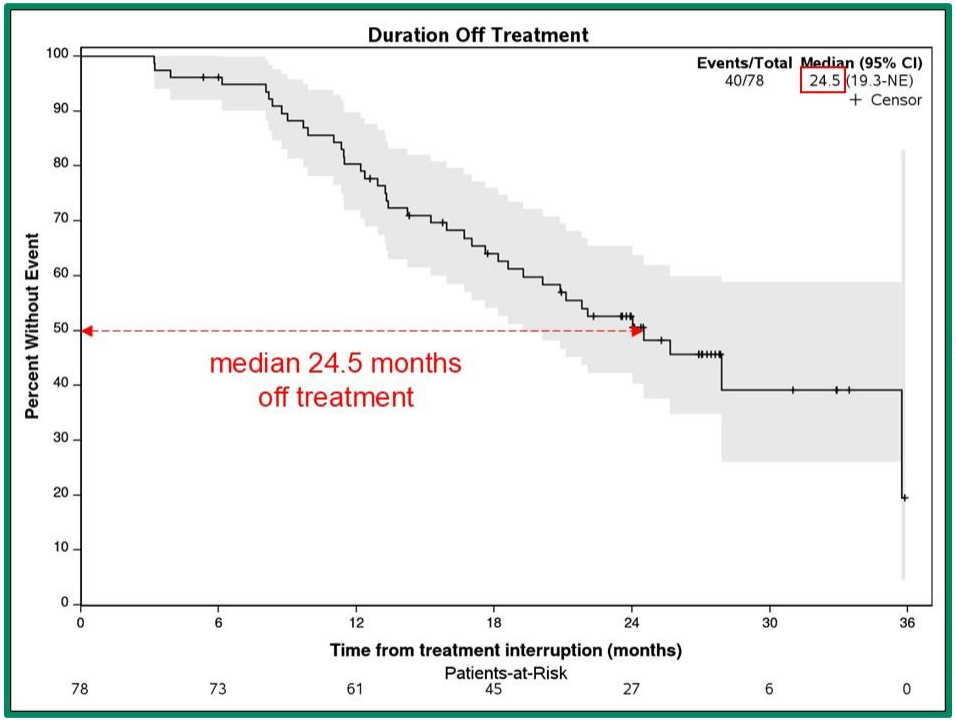
Physician Discretion

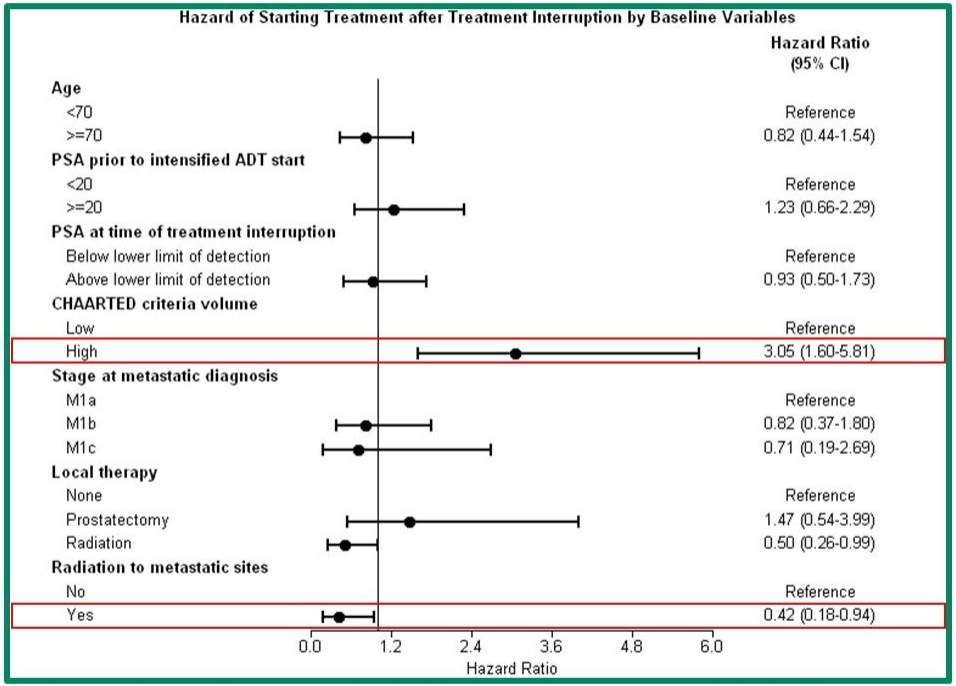
Exploratory Endpoints:
- rPFS, TTNT
- OS (CSS/NCSS)
- Cost

PCWG3=prostate cancer working group 3; QOL=quality of life questionnaire; rPFS=radiographic progression-free survival; TTNT=time to next treatment; (N)CSS=(non-)cancer-specific survival

PRESENTED BY: Atish D. Choudhury, MD PhD

Duration Off Treatment





Low volume disease and prior RT to mets were associated with lower likelihood of requiring cancer-directed therapy (including ADT, ARPI resumption) after treatment interruption

PRESENTED BY: Atish D. Choudhury, MD PhD

KEY TAKEHOME MESSAGES

Talazoparib + Enzalutamida + ADT e un nuevo SoC en mCSPC, con posible actividad en otros HRR

Apalutamida añadida a ADT perioperatorio tiene actividad y retrasa las MTS en pacientes, pero no e un nuevo SoC aún

La discontinuación del tratamiento con ADT+ARPi podría ser una opción en pacienets selccionados con poco volumen/oligoMTS y máximo control