

#guardsymposium2026
X @GuardConsortium



GUARD INTERNATIONAL SYMPOSIUM

GU-Alliance for Research and Development

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



16-18 SEPTIEMBRE 2026

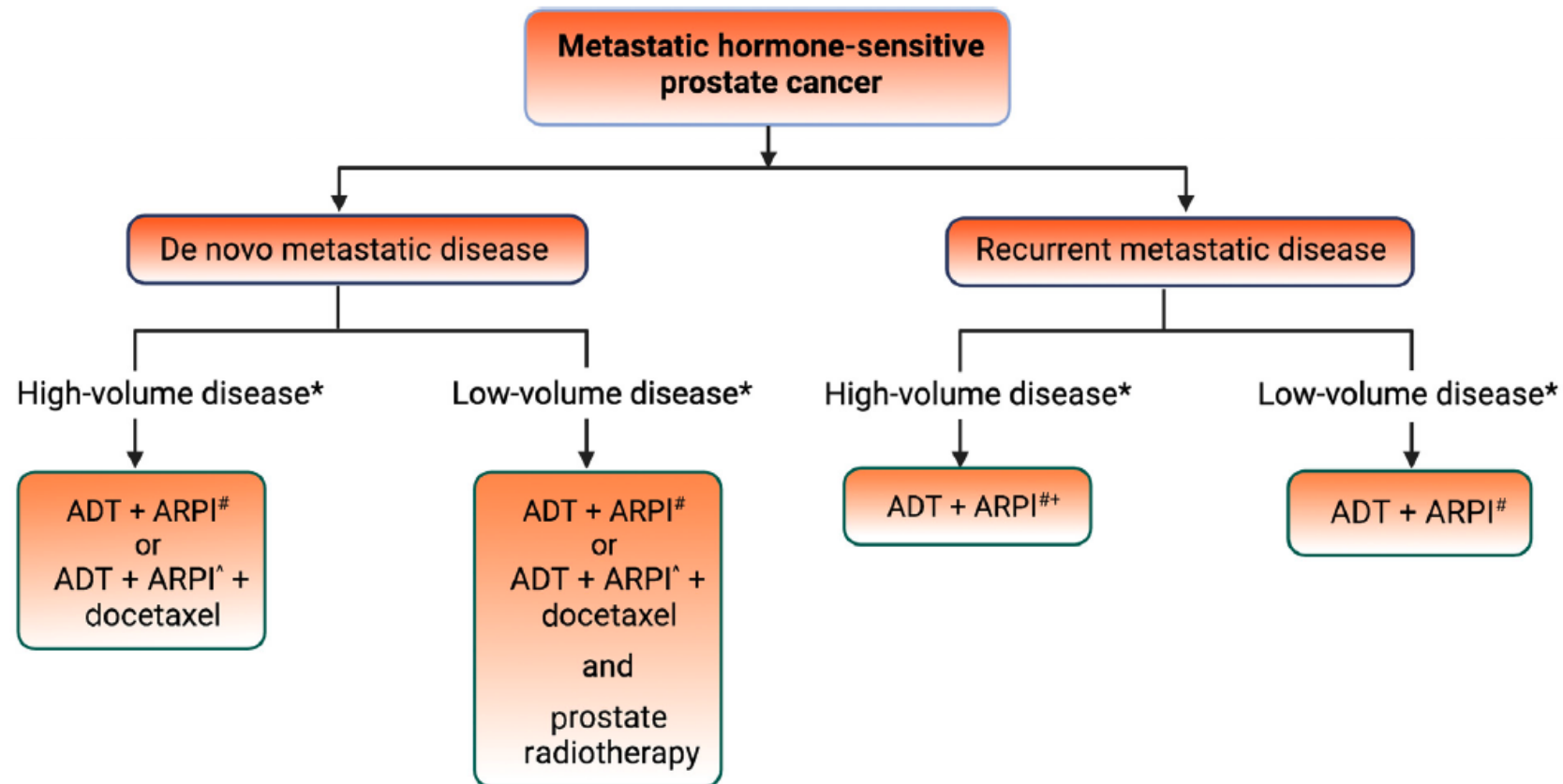
Espacio Maldonado, Madrid

Dissecting new precision medicine ~~clinical trials~~ in mHSPC *treatment strategies*

David Olmos MD PhD

Hospital Universitario 12 de Octubre

Doublets or Triplets according to Volume & Timing



*Volume defined as per CHAARTED criteria;

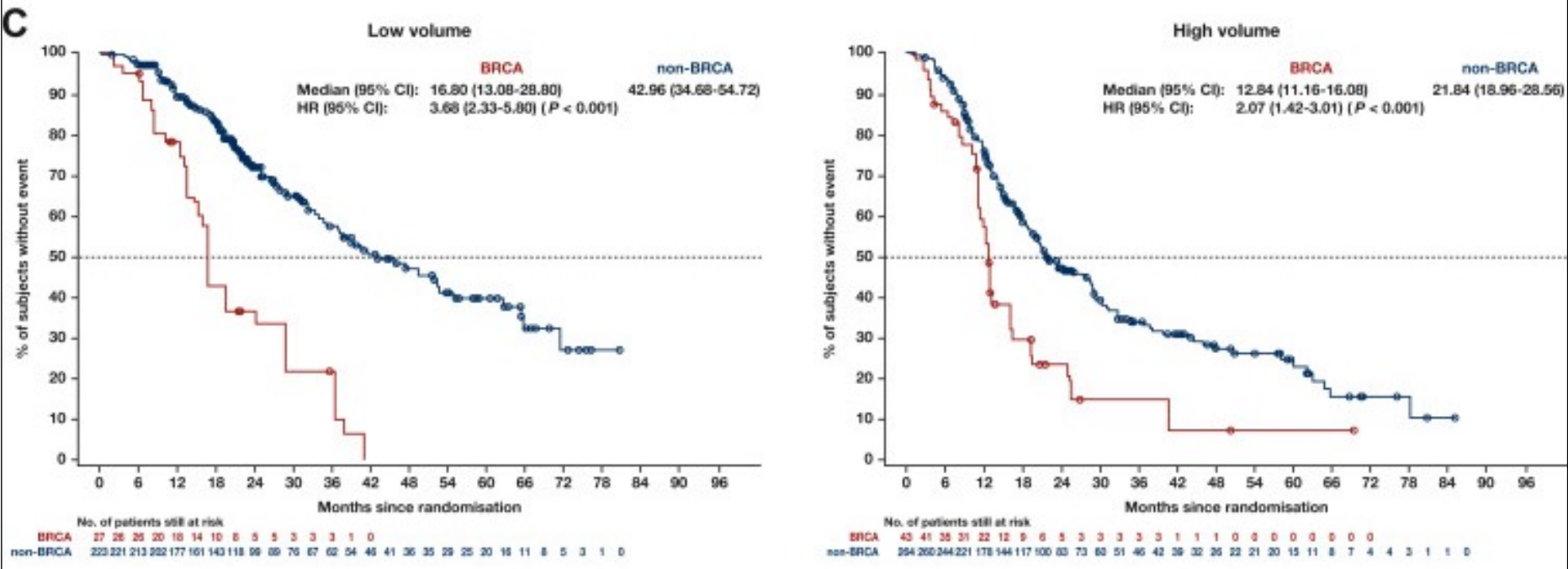
#Enzalutamide, Apalutamide, or Abiraterone; ADT + Docetaxel if an ARPI unavailable and suitable for chemotherapy.

^Enzalutamide, Darolutamide, or Abiraterone. Most evidence supports triplet therapy in de novo high-volume disease.

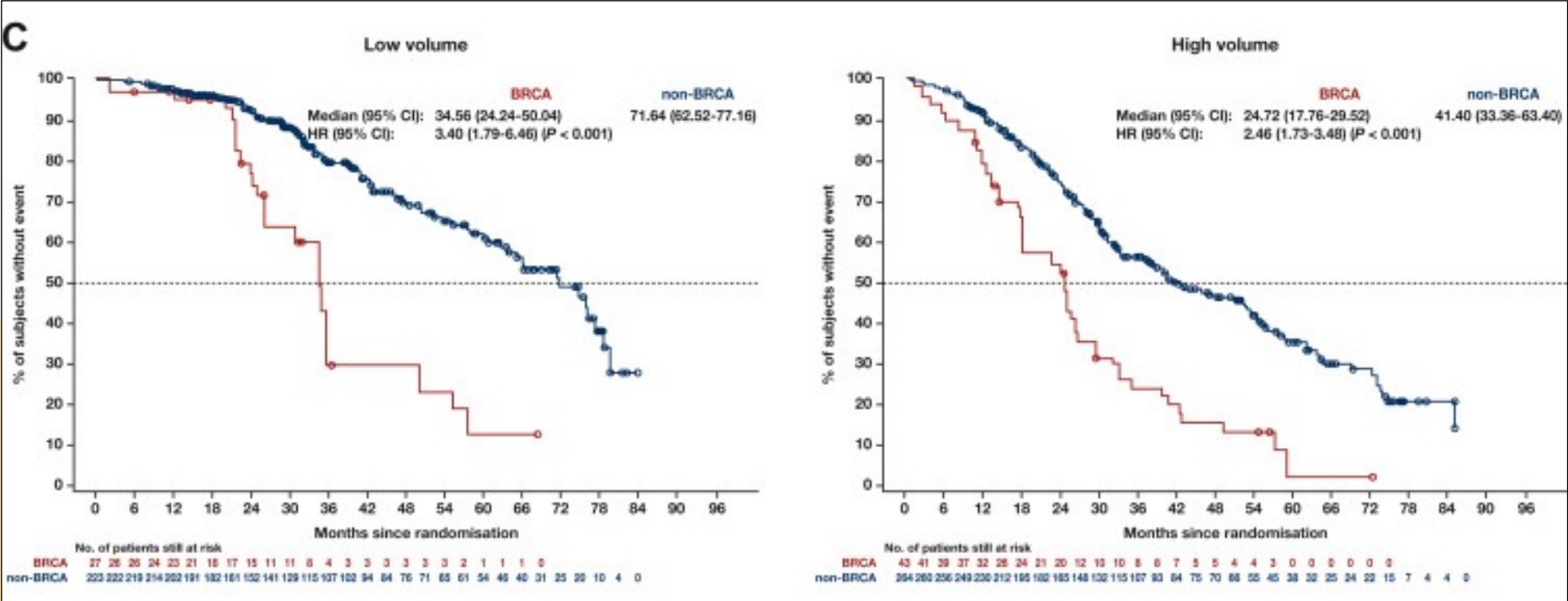
+ADT + ARPI + Docetaxel can be considered for recurrent high-volume disease, however data is limited in this patient cohort.

High vs Low volume
according to HRR

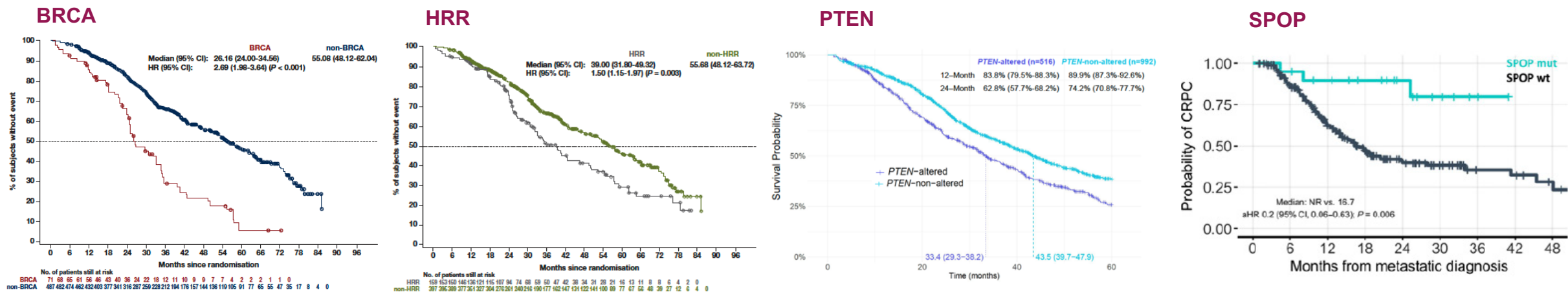
rPFS



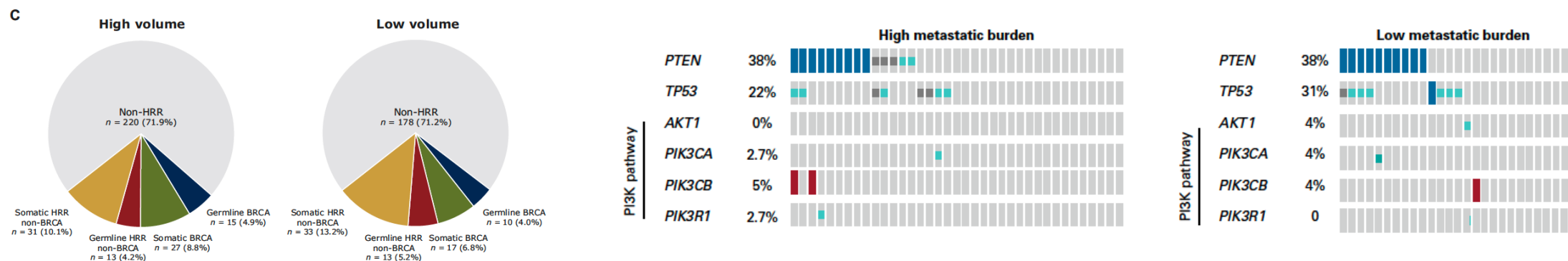
OS



Could volume impact Tx decisions in other genomic backgrounds?



Similar prevalence of BRCA/HRR and PTEN/PIK3 alterations in HV and LV



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

CAPTURE

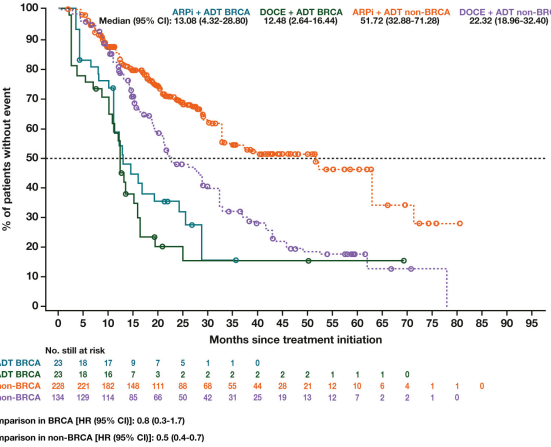
BRCA vs non-BRCA

HRR vs non-HRR

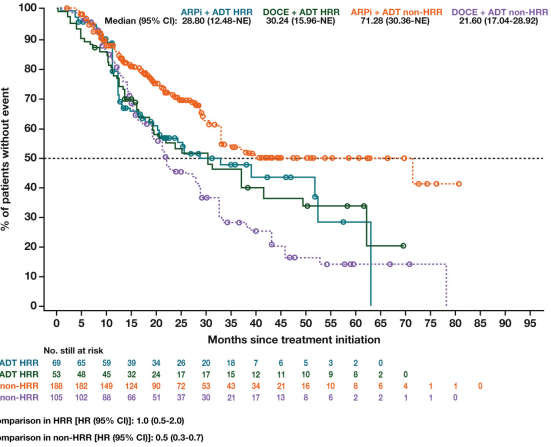
BRCA < HRR non-BRCA < Non-HRR
In BRCA, volume lose prognostic value

rPFS

A

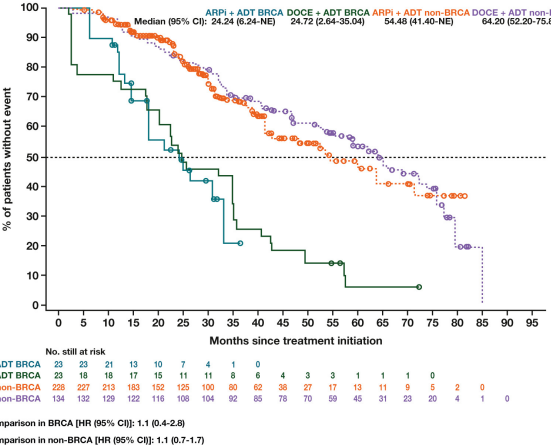


B

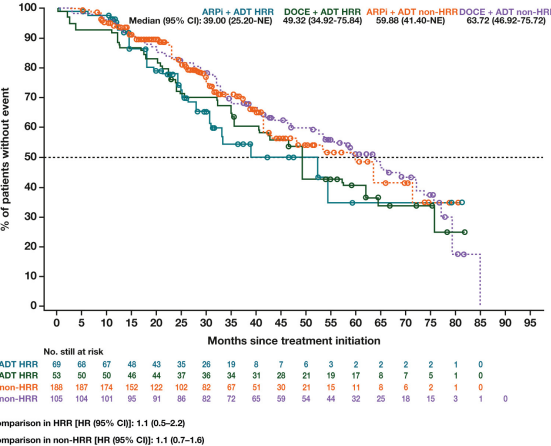


OS

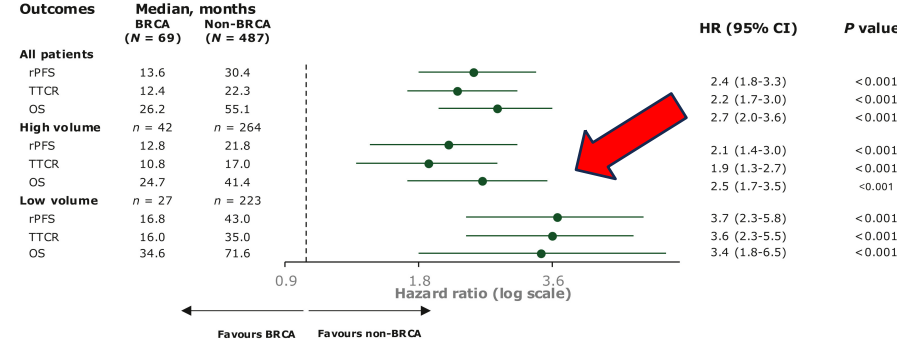
C



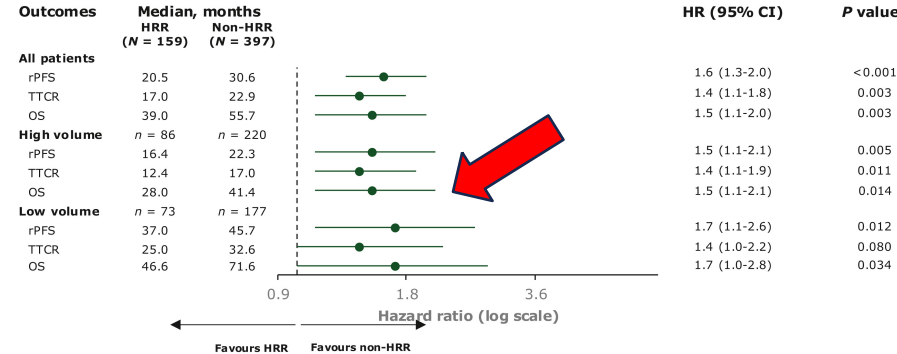
D



A



B



AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Study

7

Clinical data cutoff: January 7, 2025, for the first and final rPFS analysis and first interim analysis of time to symptomatic progression and OS

Key eligibility criteria:

- mCSPC^a
- ≥1 HRR gene alteration: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*
- ECOG PS 0-2

Key exclusion criteria:

- Any prior PARPi
- Any prior ARPI other than AAP

Prior allowed treatments in mCSPC:

- Prior docetaxel (up to 6 cycles)^b
- Prior AAP (up to 45 days)

Randomized
1:1
(N=696)

NIRA + AAP

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

PBO + AAP

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

Stratifications:

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

Primary end point

- rPFS by investigator

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

**Prior Docetaxel → 16% each arm
>75% High volume, 87% *de novo***

- Metachronous mCSPC may be under-represented

- ***BRCA1/2*mut 55% of pts**

^aParticipants with lymph node-only disease are not eligible. ^bLast dose ≤3 month prior to randomization.

ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; NIRA, niraparib; PARPi, PARP inhibitor; PBO, placebo; QD, once daily.

TALAPRO-3: Trial Design → Interim analysis 1

Key eligibility criteria

- mCSPC harboring HRR gene alterations
- Documented metastatic disease by positive bone scan or metastatic lesion on CT or MRI scan
- ECOG PS 0 or 1
- Ongoing ADT
- ≤3 months of ADT with or without ARPI in mCSPC
- Prior docetaxel for mCSPC not permitted^b

Stratification factors

- *De novo* vs relapsed mCSPC
- High vs low-volume disease
- *BRCAm* vs non-*BRCAm* status

1:1

TALA 0.5 mg^a + ENZA 160 mg
once daily

N=599

PBO + ENZA 160 mg,
once daily

Data cutoff date: February 18, 2026

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

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 systemic antineoplastic therapy
- Time to first SSE
- Safety
- PROs

Exploratory endpoint

- PFS2

- Contemporaneous trial against an active ARPi doublet, but:

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

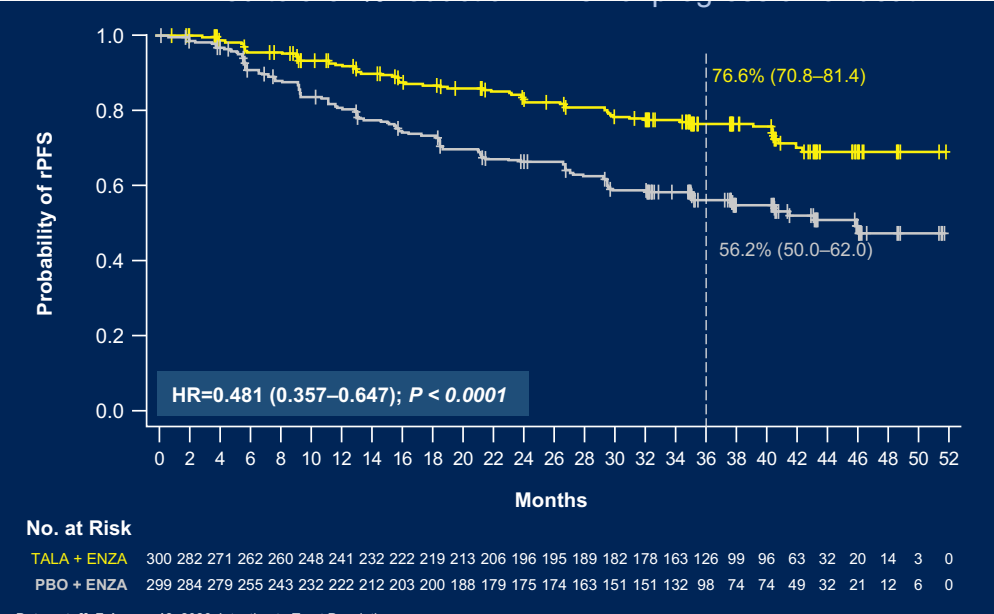
- Metachronous mCSPC may be under-represented
- ***BRCA1/2mut* only 1/3 of pts**
- **Highest number of *ATMmut* cases in PARPi trials (N=157)**

^a0.35 mg once daily if patient has moderate renal impairment. ^bAs per protocol amendment (September 2021). ClinicalTrials.gov identifier: NCT04821622.

ADT=androgen deprivation therapy; *BRCAm*= *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.

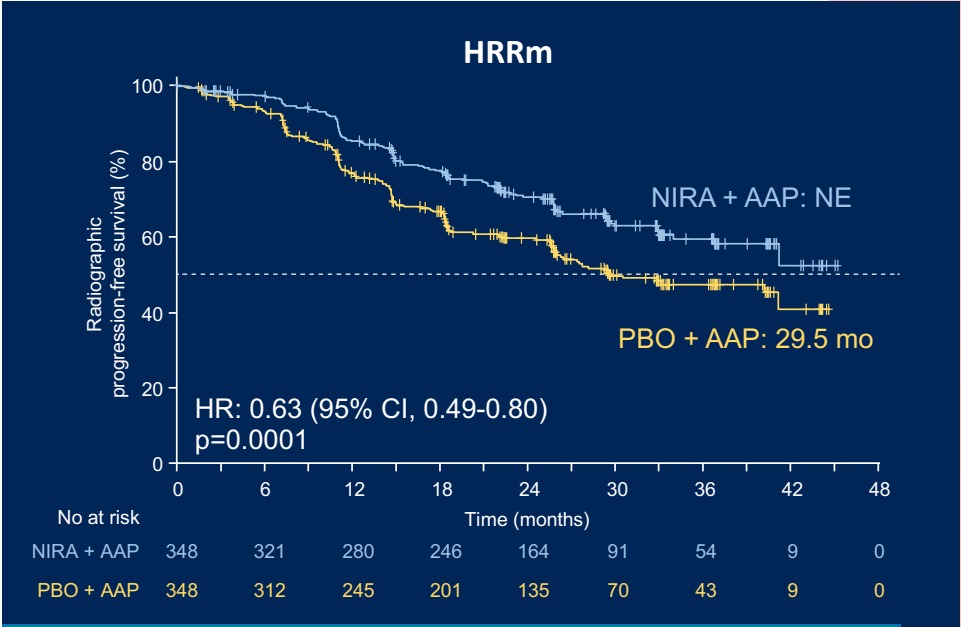
1ry endpointy - rPFS in TALAPRO and AMPLITUDE – Positive Trials

TALAPRO-3



1/3 BRCA1/2 – HR 0.37

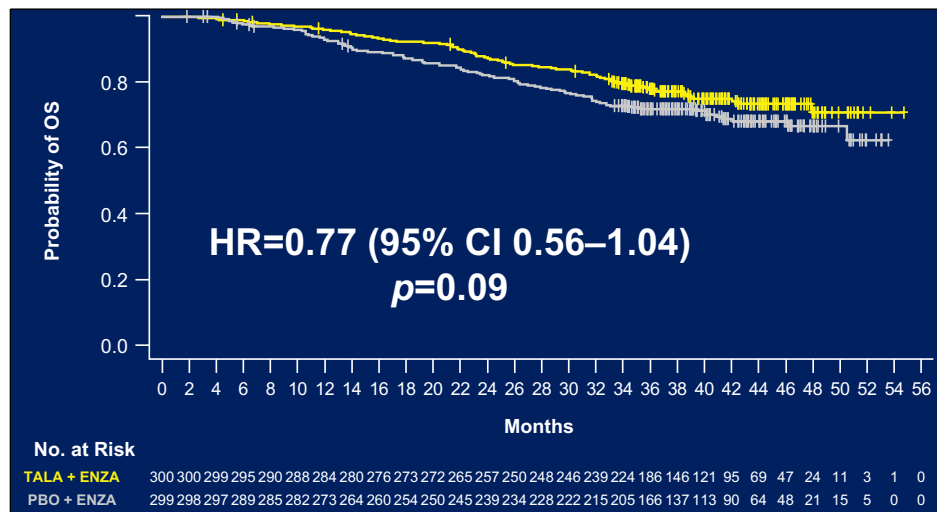
AMPLITUDE



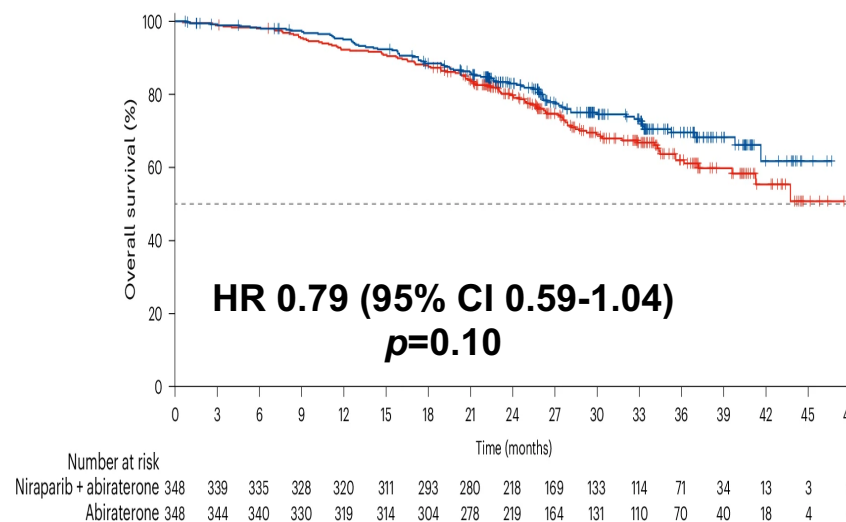
>50% BRCA1/2 – HR 0.52

Overall Survival in TALAPRO-3 & AMPLITUDE Interim analysis

TALAPRO-3



AMPLITUDE



**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

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

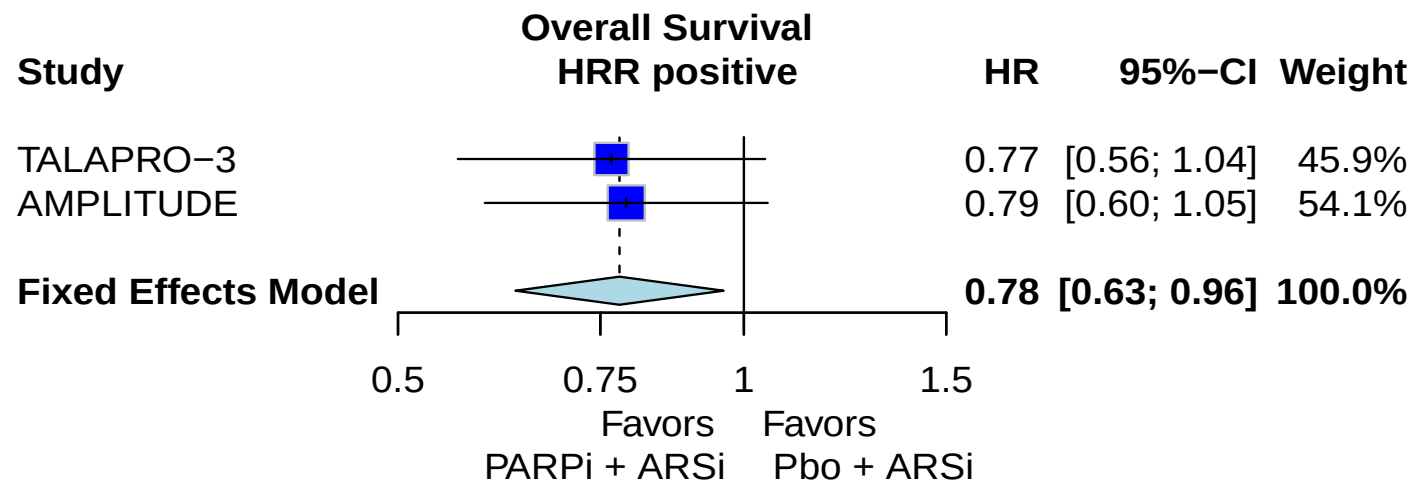
	NIRA + AAP (N=348)	PBO + AAP (N=348)
Events, n	85	108
Median (95% CI), months	NR (NR–NR)	NR (41.3–NR)

Exploratory unpublished analysis performed for this presentation

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



Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.8899$

Test for overall effect: $z = -2.34$ ($p = 0.0191$)

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

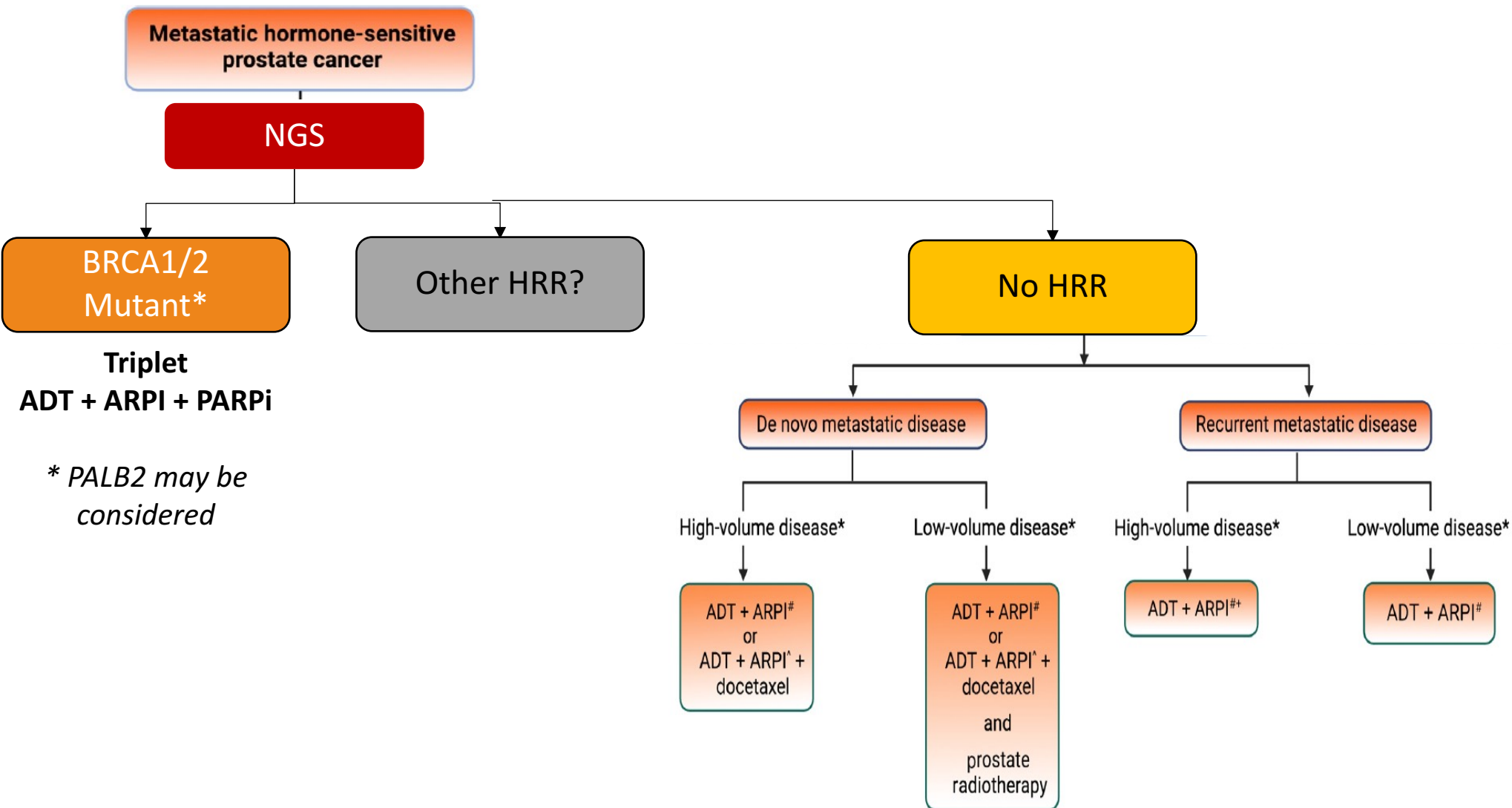
Expected to be higher in BRCA! / 2 pts

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 analyzed together.

Lorente, Attard, Agarwal, Olmos. Submitted

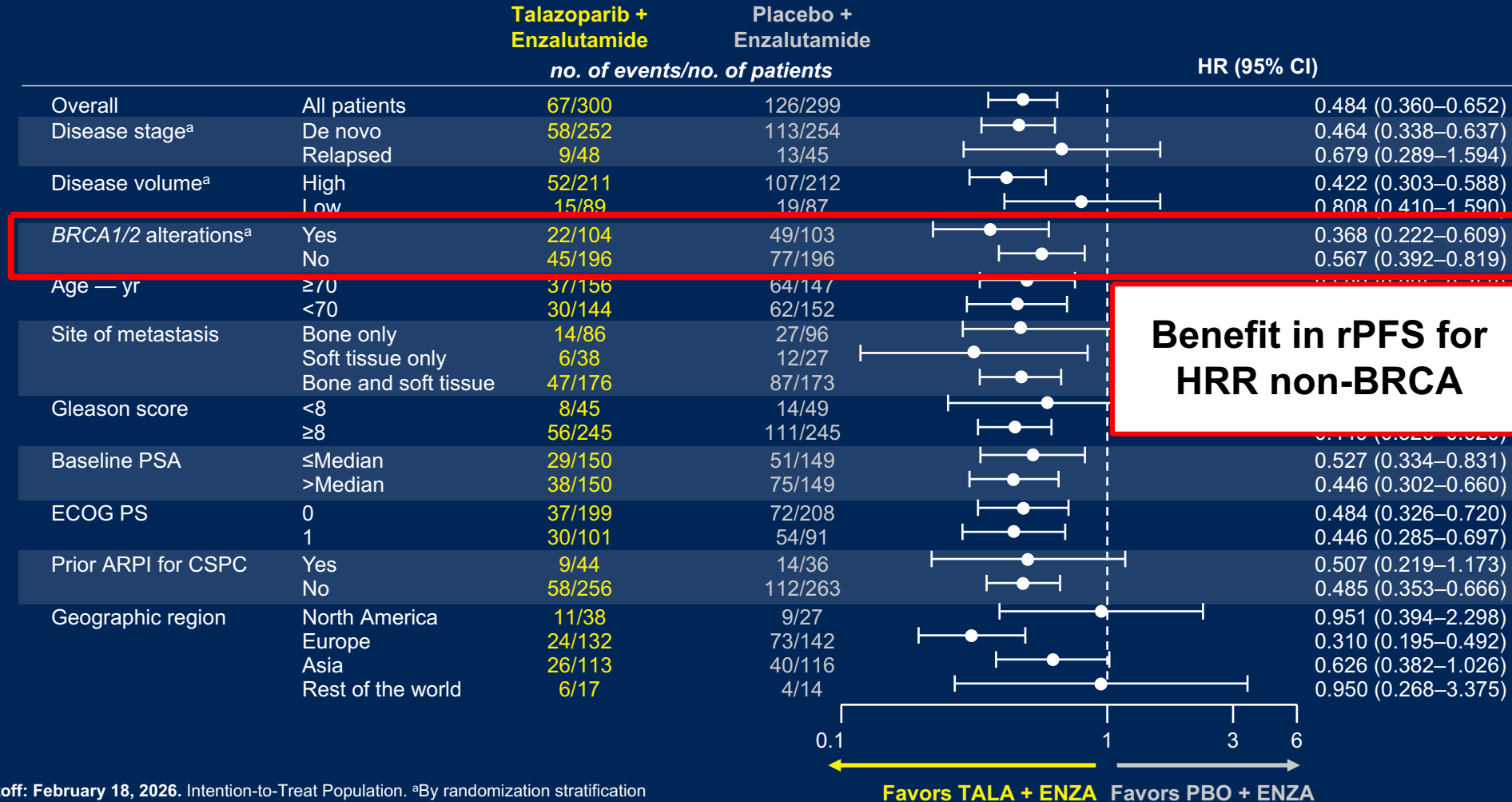
Doublets or Triplets according to Biology, Volume & Timing



Adapted from Azad et al, Eur Urol, 2025

Subgroup Analysis of rPFS

A consistent treatment effect for rPFS was observed across prespecified subgroups

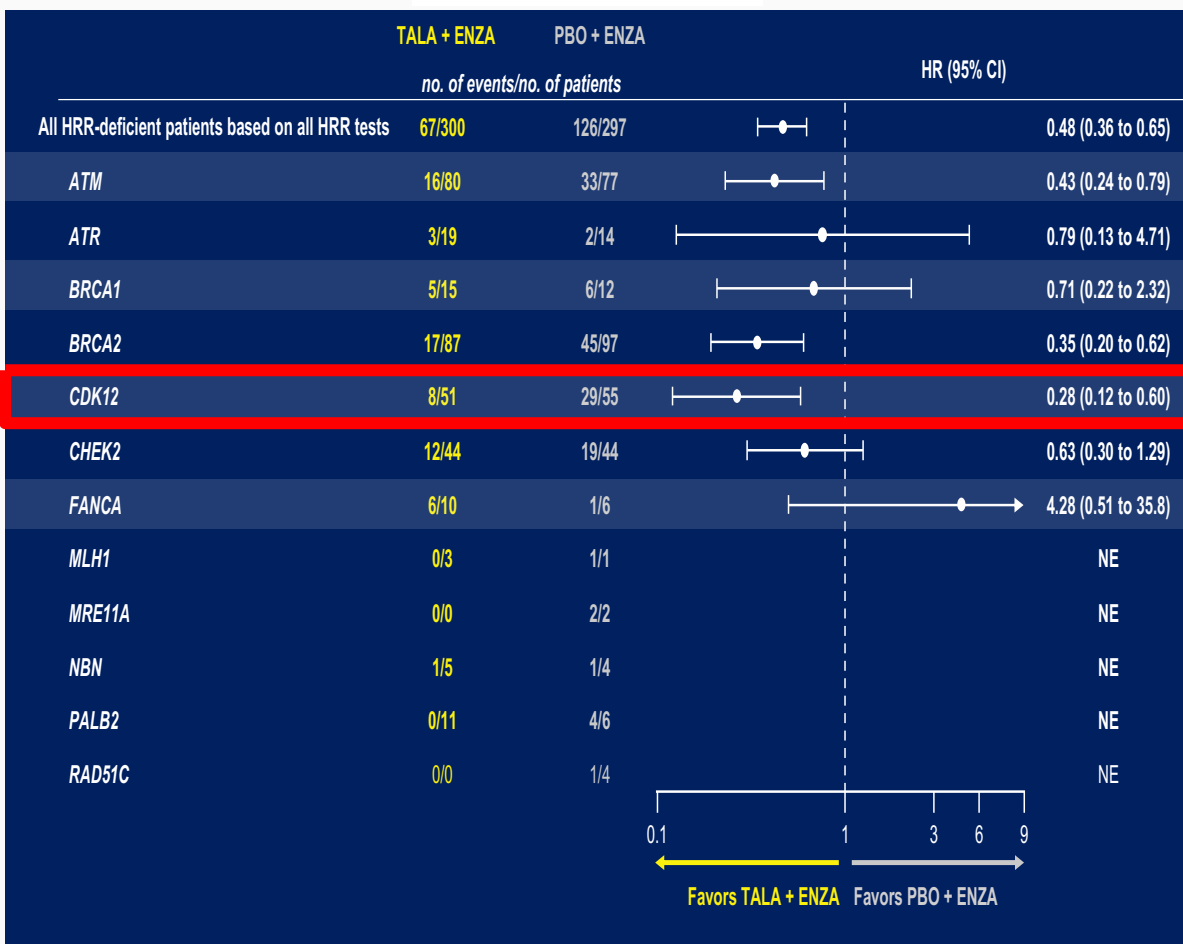


Data cutoff: February 18, 2026. Intention-to-Treat Population. ^aBy randomization stratification
Unstratified hazard ratio based on Cox proportional hazards model. P-value from unstratified log-rank test.

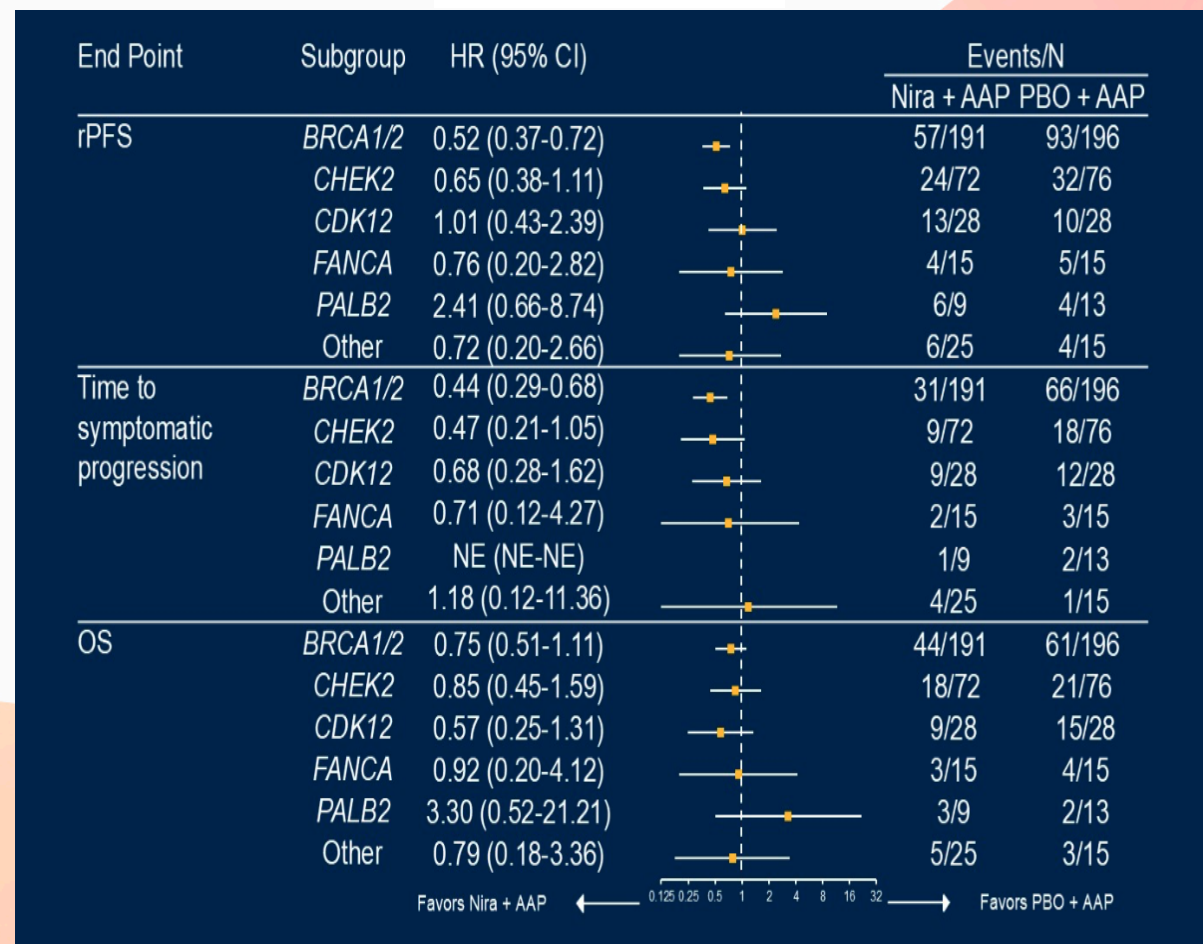
Benefit beyond BRCA

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

TALAPRO-3



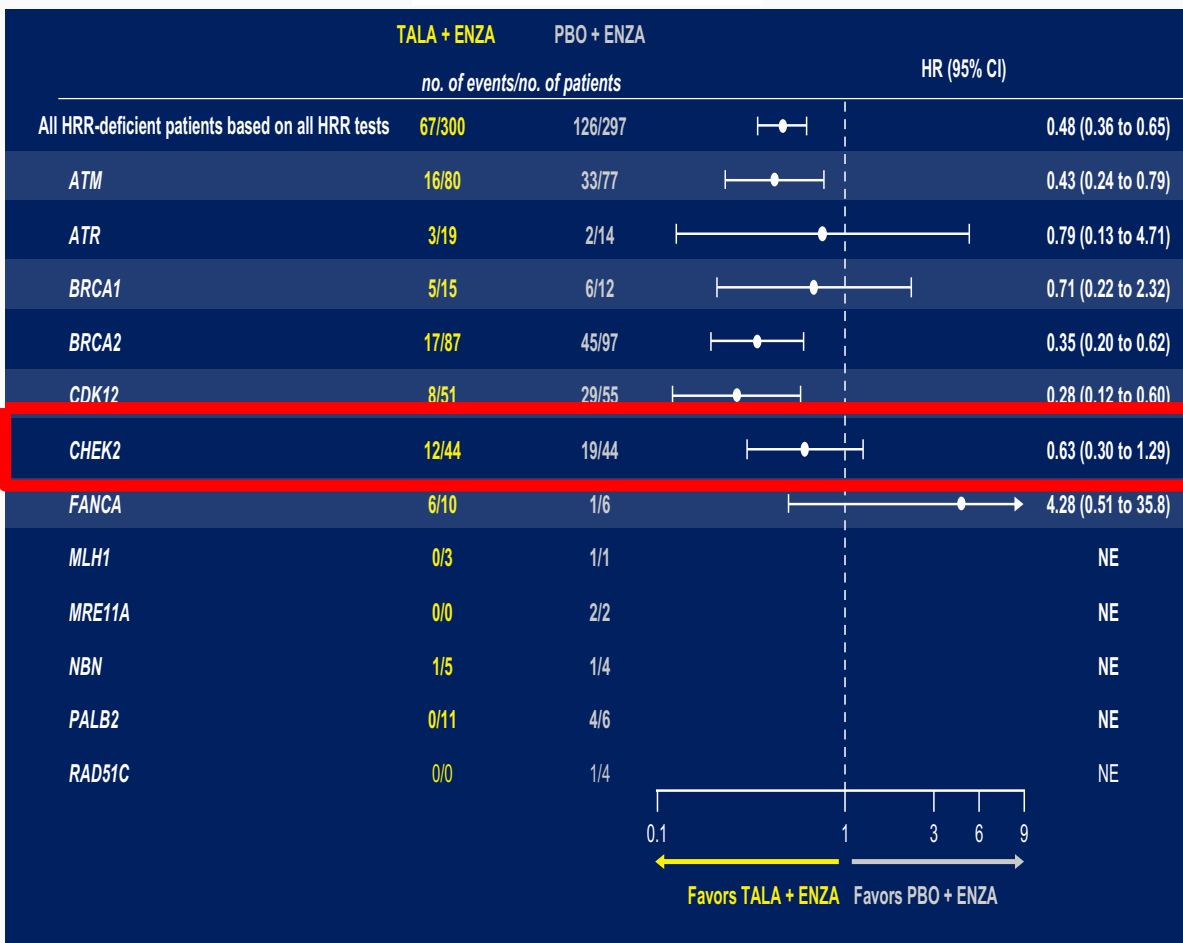
AMPLITUDE



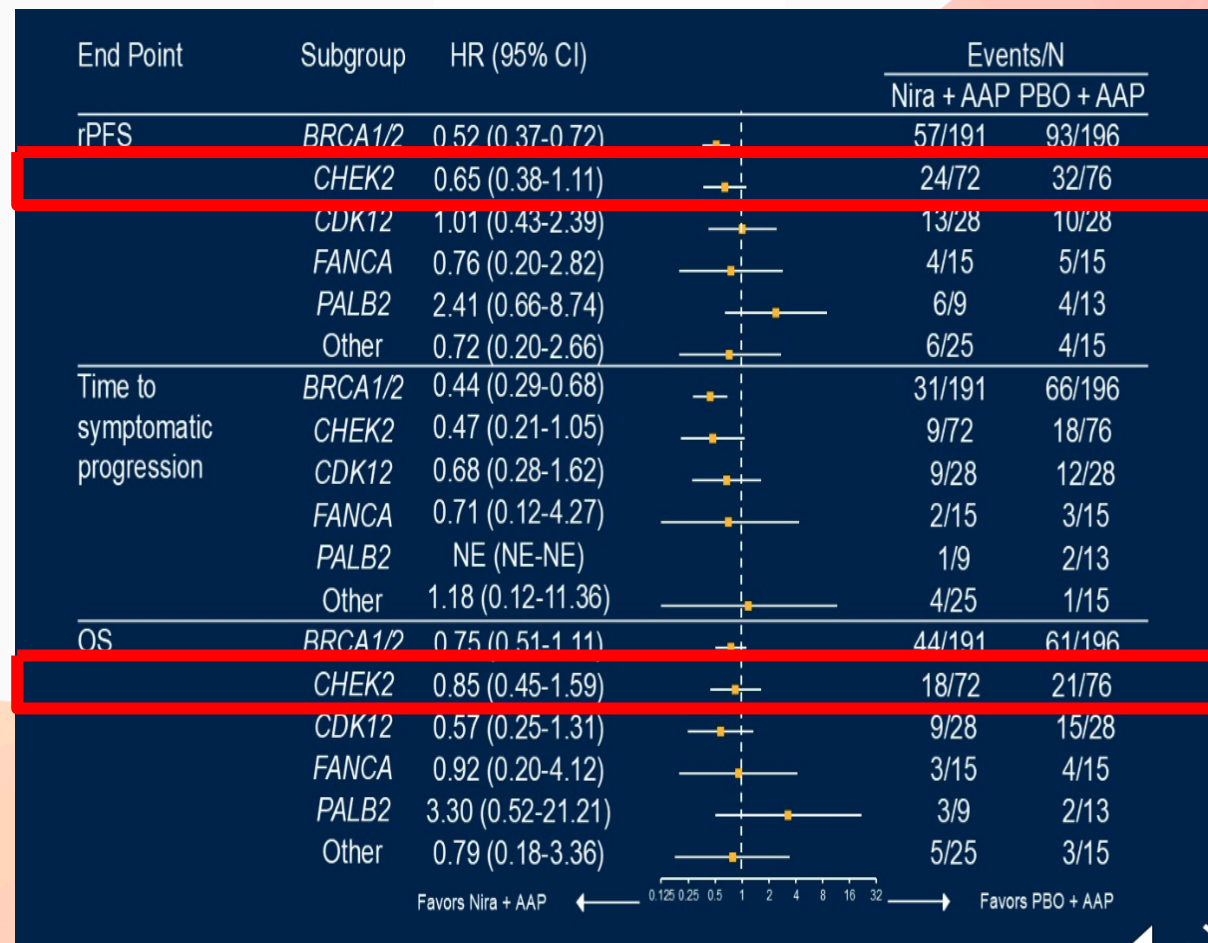
Benefit beyond BRCA

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

TALAPRO-3



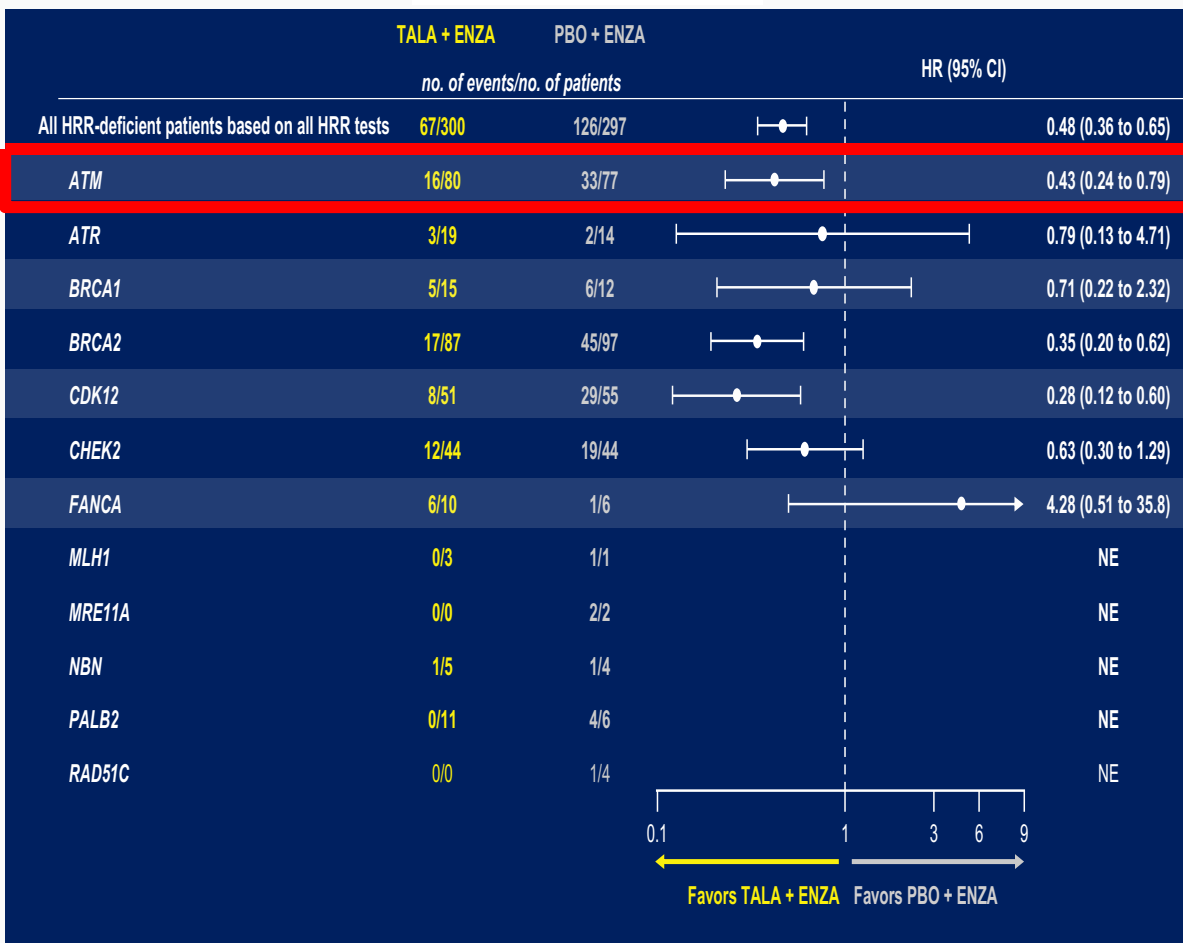
AMPLITUDE



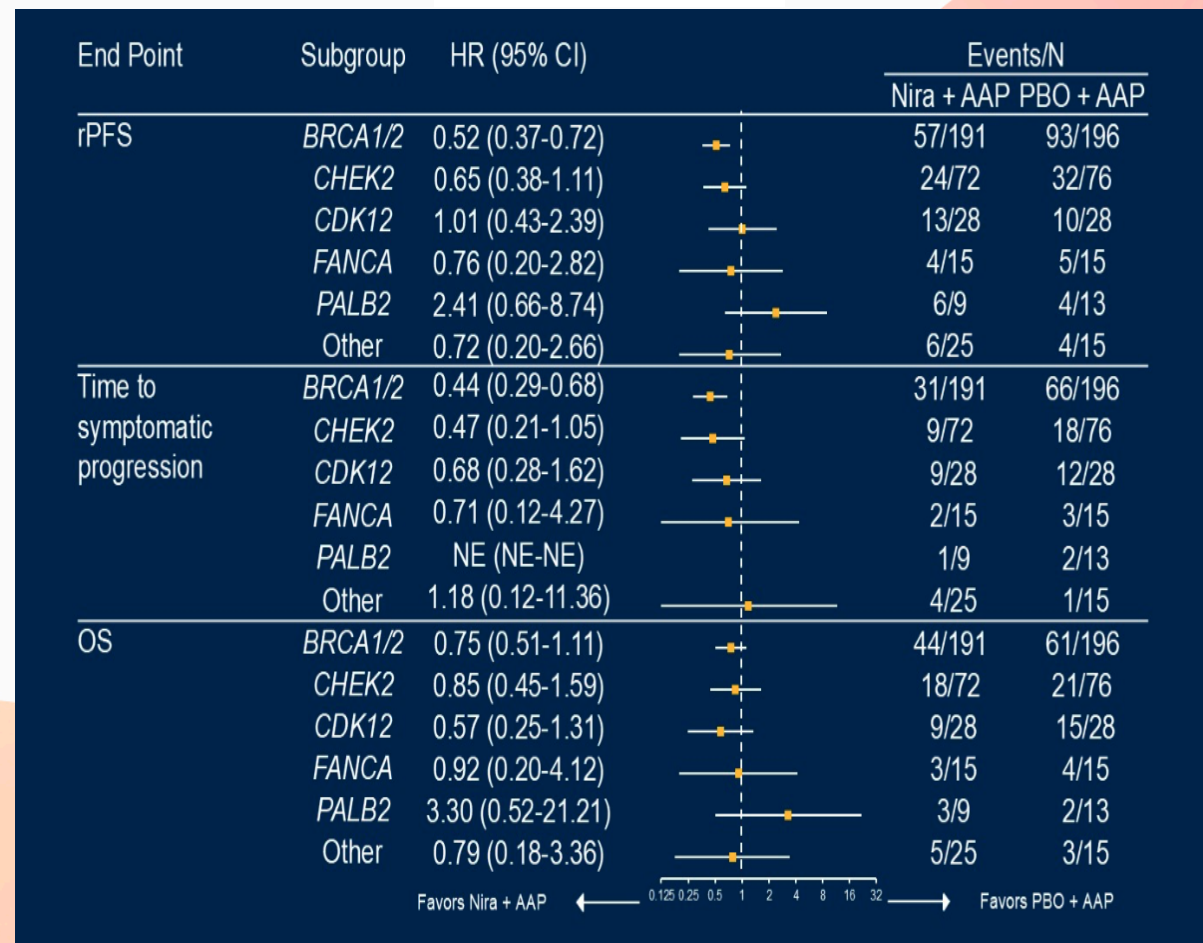
Benefit beyond BRCA

ATM: robust rPFS benefit observed with ENZA+TALA (TALAPOR has the hig

TALAPRO-3

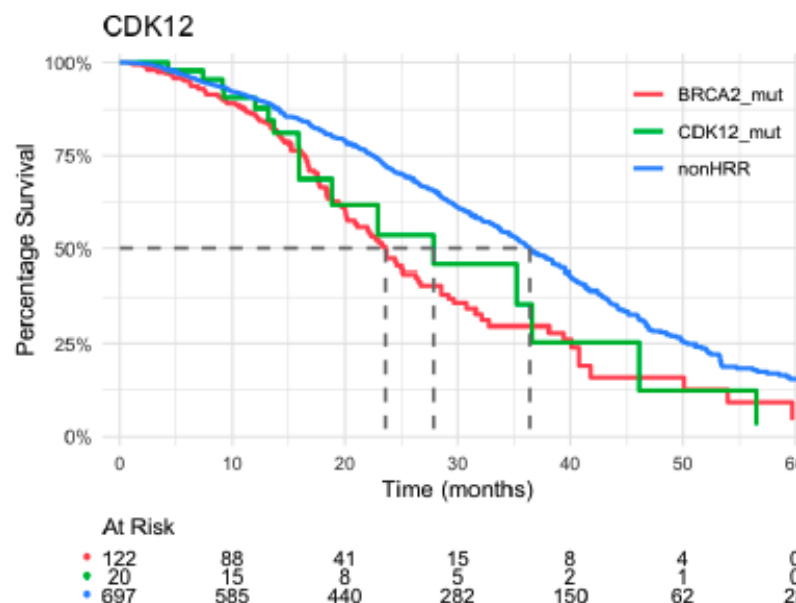


AMPLITUDE

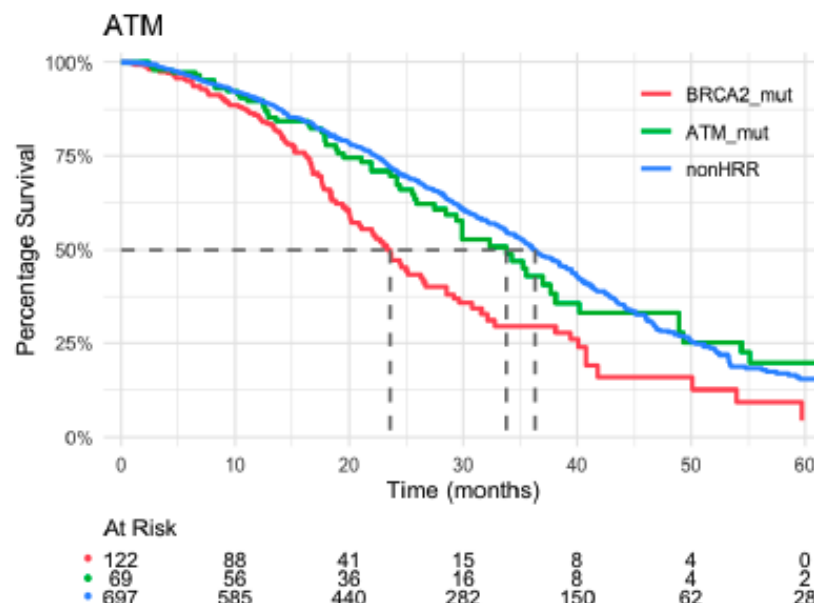


How patients with non-BRCA mutated genes behave with SoC?

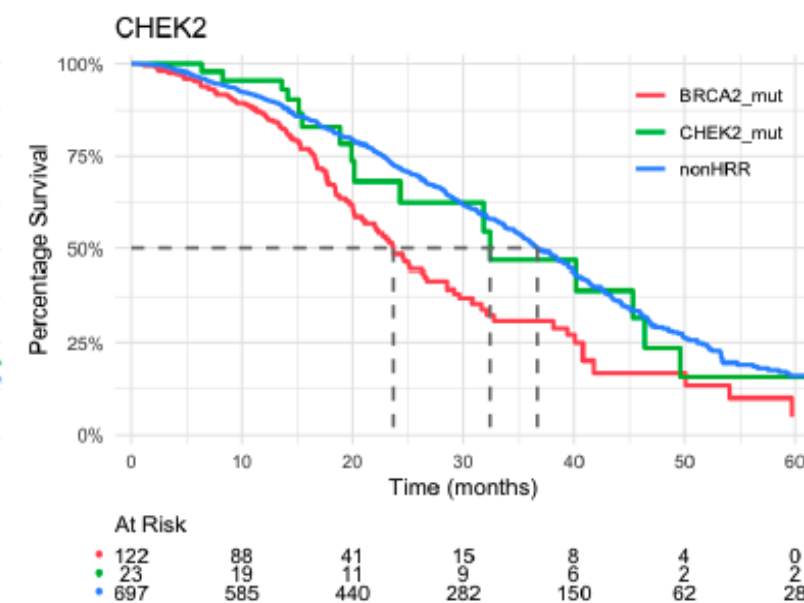
As physicians, we must balance benefit vs risk
Understanding how patients perform on the SoC is therefore essential



CDK12m pts have poor outcomes, similar to BRCA2



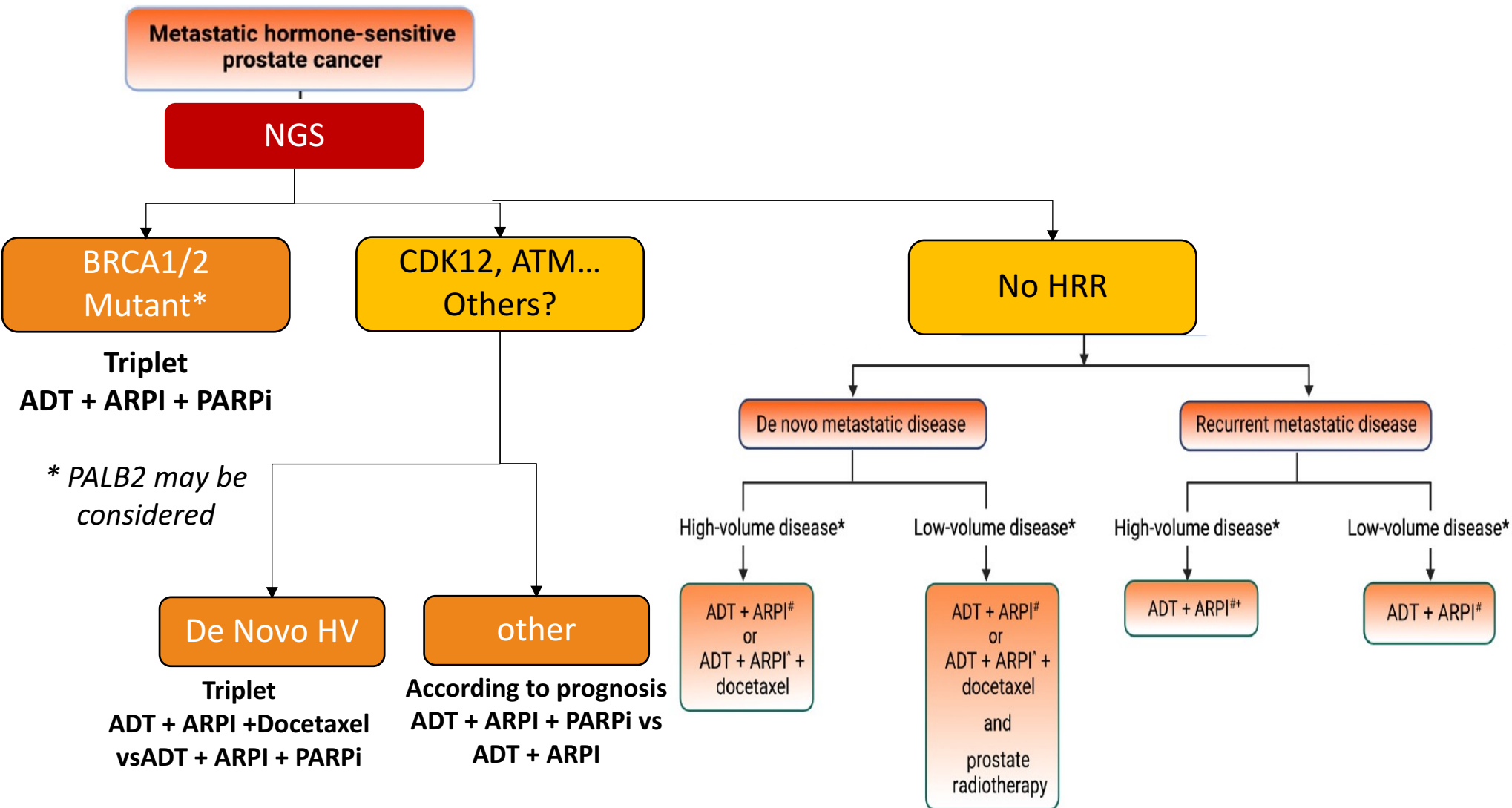
ATMm pts have outcomes similar to non-HRR pts



CHEK2m pts have outcomes similar to non-HRR pts

Is better ADT+ARPI+Docetaxel in these patients?

Doublets or Triplets according to Biology, Volume & Timing



Adapted from Azad et al, Eur Urol, 2025

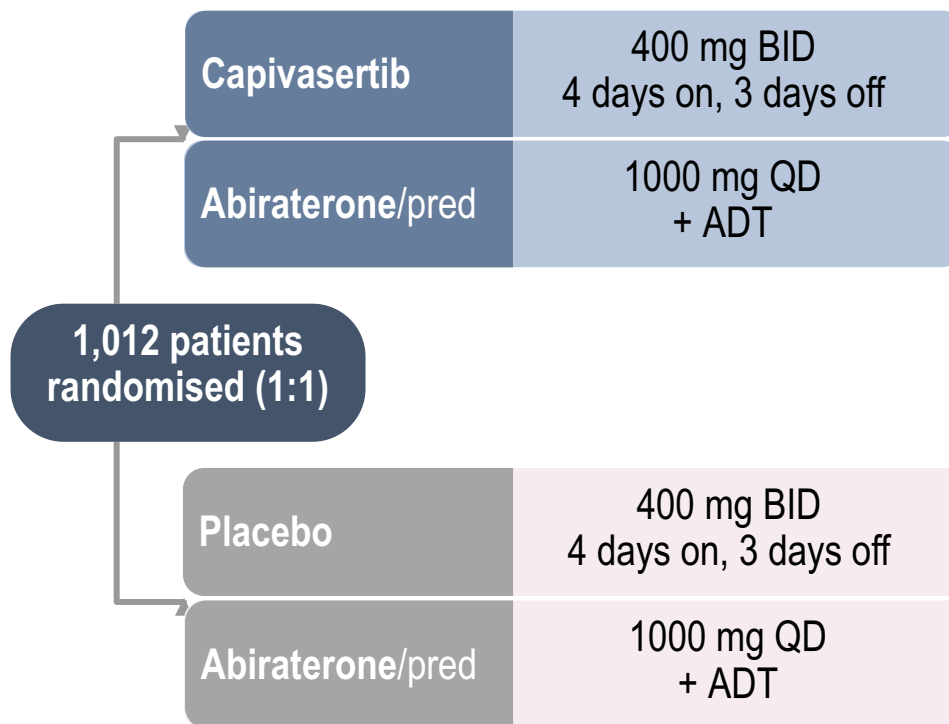
CAPtello-281 Study Design

A global, multicentre, Phase 3, randomized, double-blind study

Patients with PTEN deficient *de novo* mHSPC

- PTEN deficiency: (diagnostic cut-off of $\geq 90\%$ of viable malignant cells with no specific cytoplasmic staining by IHC)*

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



Stratification factors:[†]

- M1 volume (CHAARTED criteria) and visceral mets
- Geography

Primary endpoint

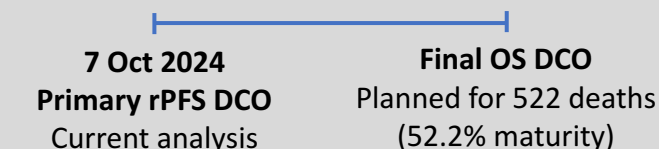
- Investigator assessed rPFS

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

Study timeline



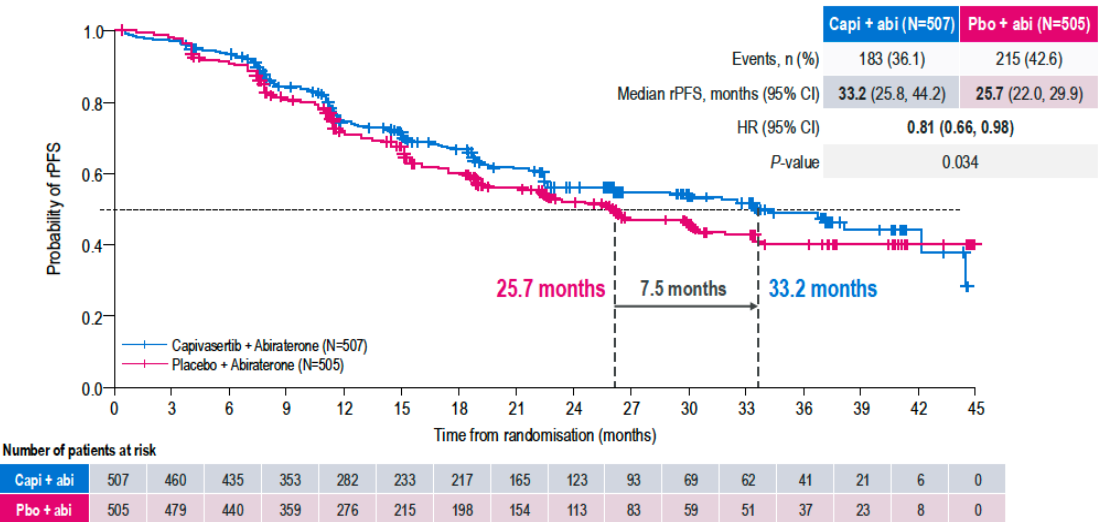
NCT04493853. Full eligibility criteria available in the online article. *Determined using investigational antibody for PTEN (SP218) (Roche Diagnostics).

[†]High-vol. disease with visceral mets, high-vol disease without visceral mets, low-vol. disease; North America; Western Europe and Australia; Latin America and Eastern Europe; Asia.

ADT, androgen deprivation therapy; BID, twice daily; IHC, immunohistochemistry; mHSPC, metastatic hormone-sensitive prostate cancer; pred, prednisone/prednisolone; QD, once daily; rPFS, radiographic progression-free survival

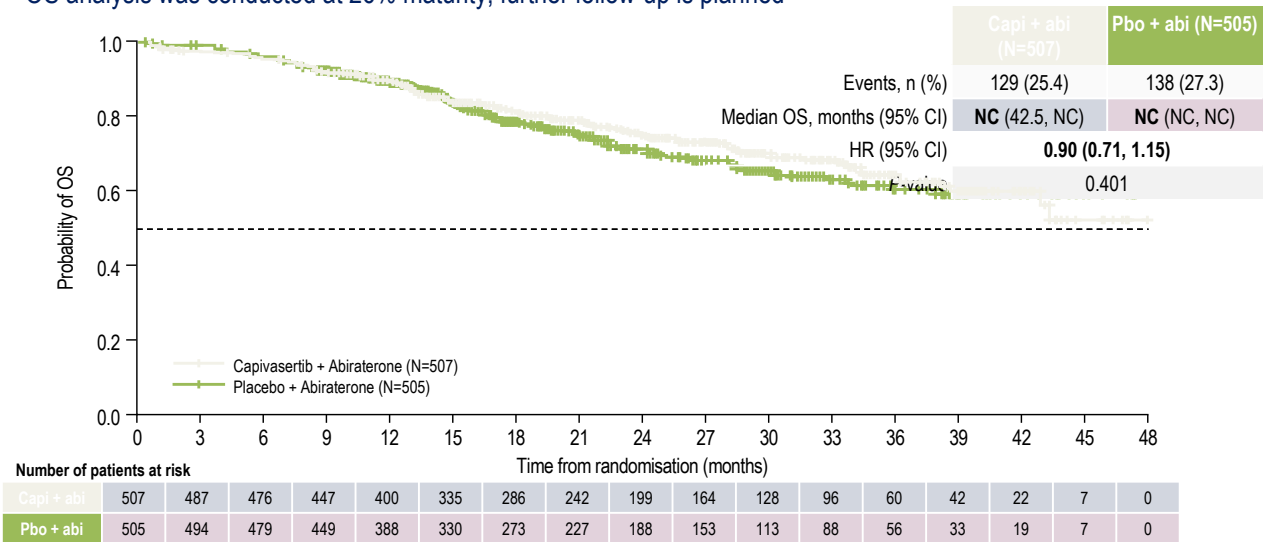
CAPITELLO-281: AA + AKTi

CAPitello-281 Primary endpoint: investigator-assessed rPFS



CAPitello-281: Interim OS

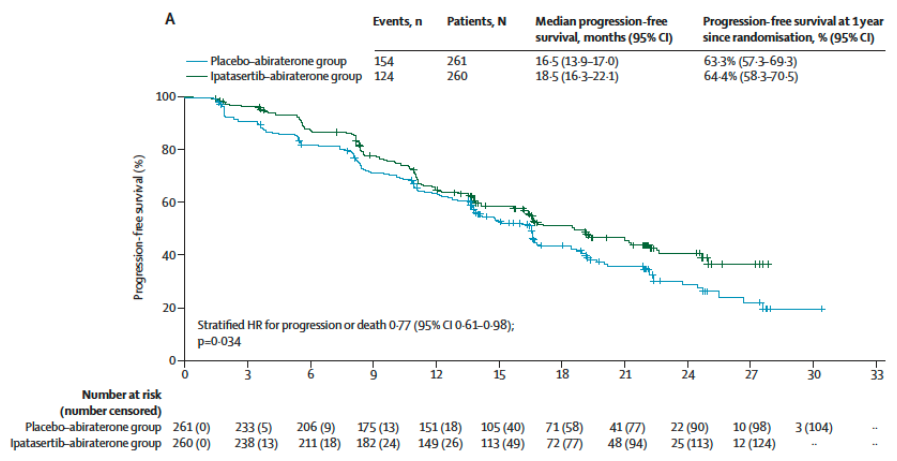
OS analysis was conducted at 26% maturity, further follow-up is planned



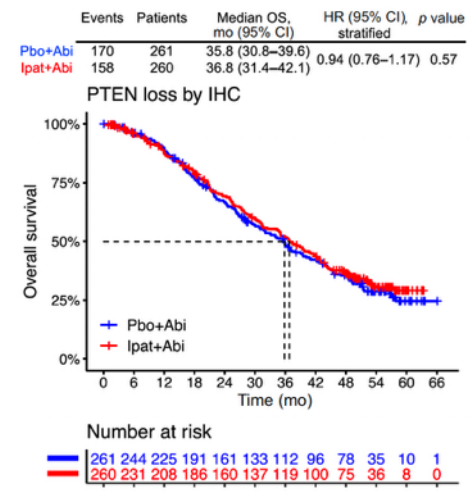
A stratified log-rank test was used to calculate two-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model.
CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; pbo, placebo

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

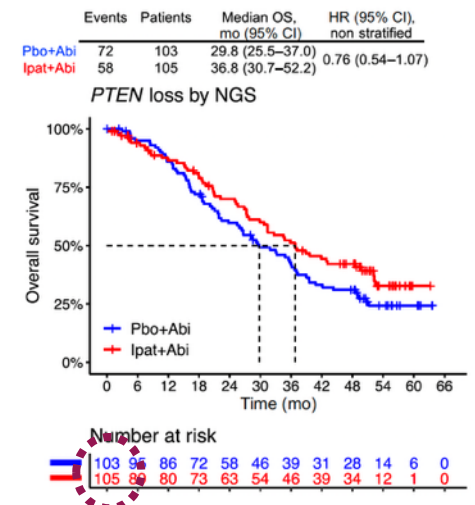
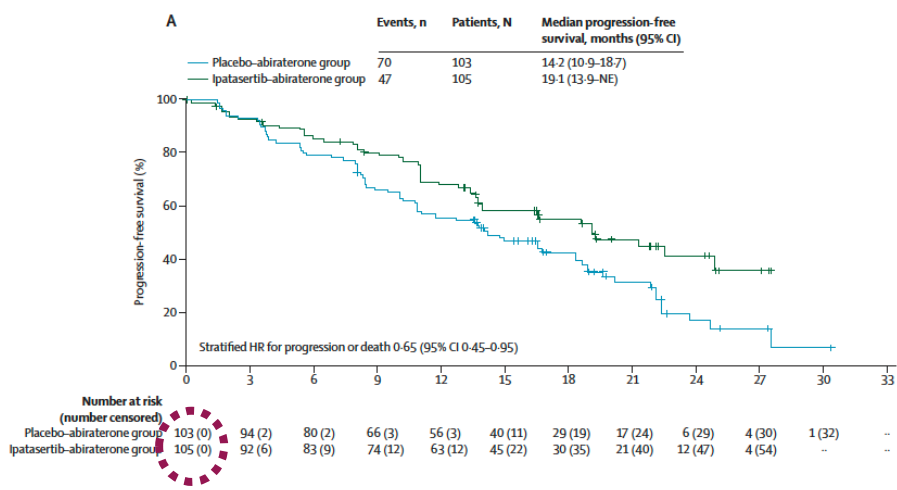
IPATENTIAL150: Identification of PTEN deficiency by NGS was associated with greater benefit from Ipatasertib



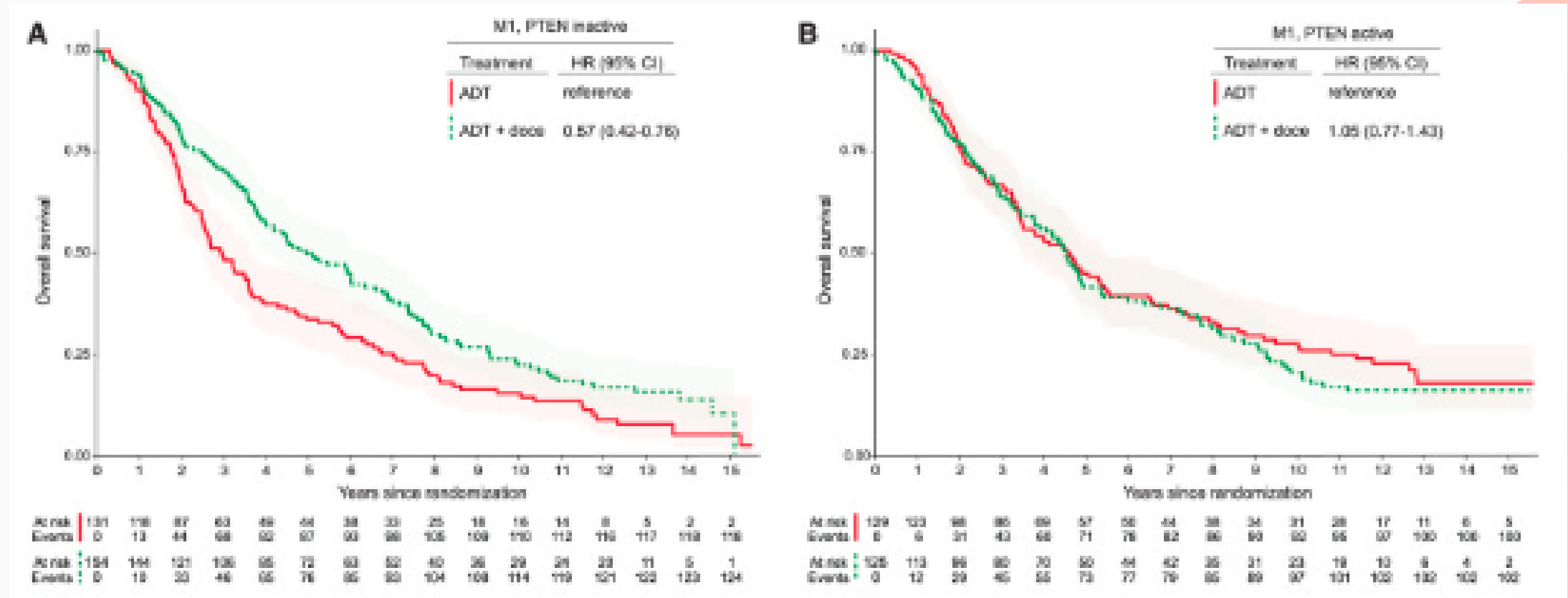
IHC

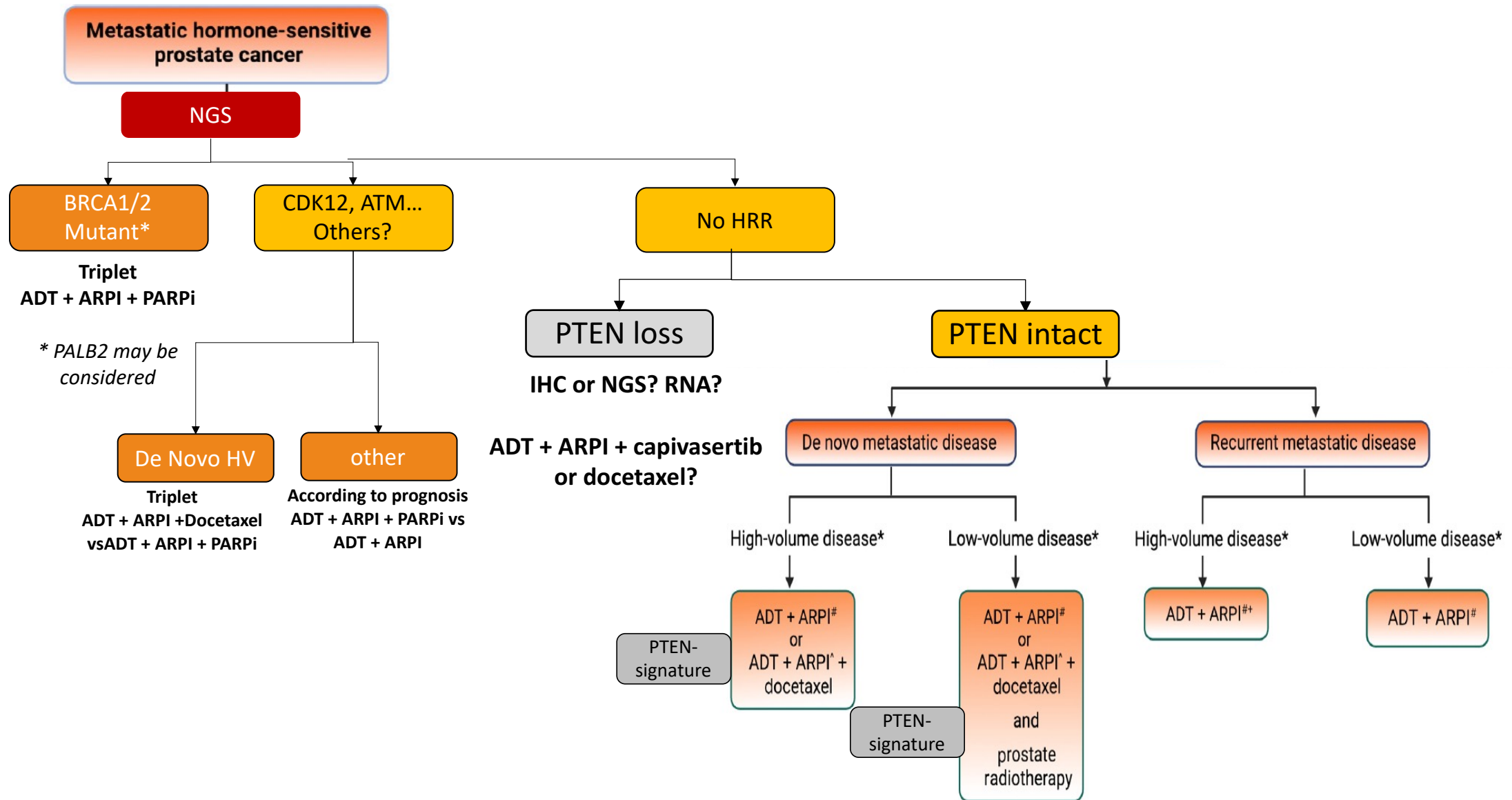


NGS



STAMPEDE: PTEN deficiency transcriptomic signature and Docetaxel benefit

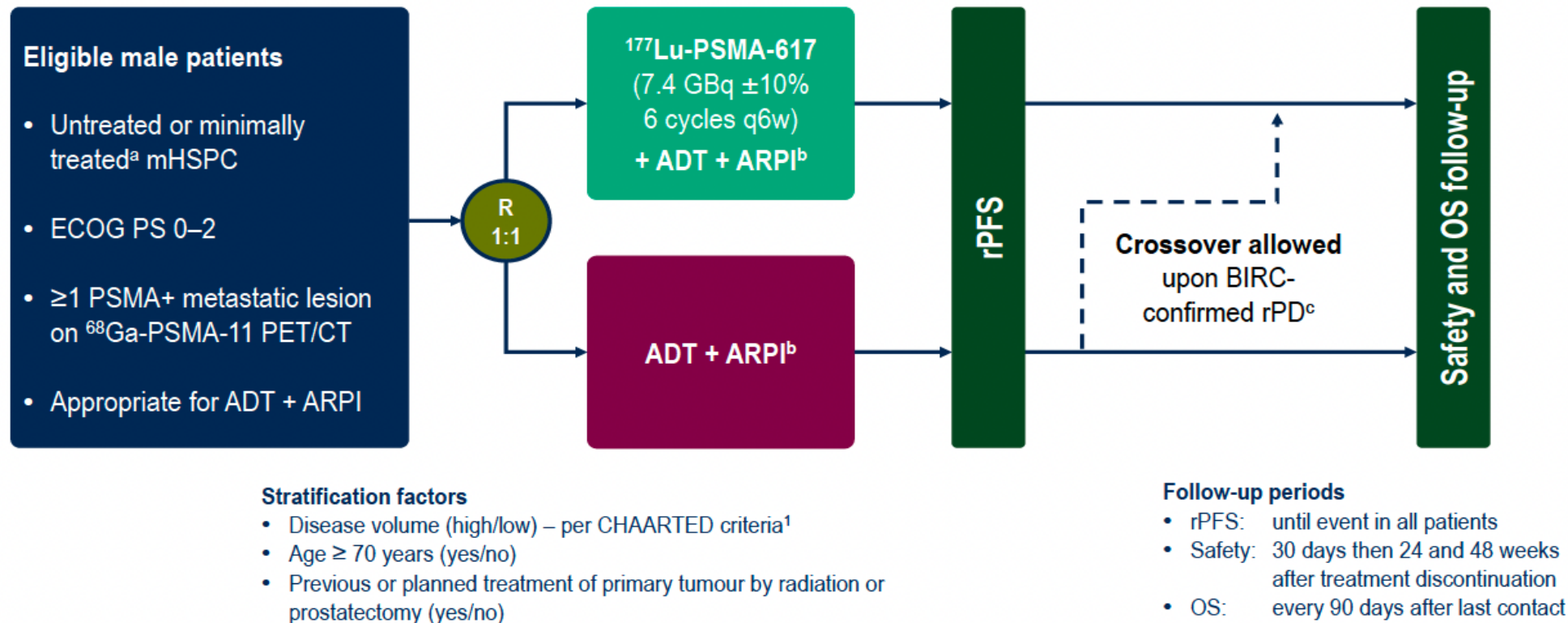




Doublts or Triplets according to Biology, Volume & Timing

triplets with PSMA-Lu177: PSMA Addition in PSMA +

PSMAAddition: randomized phase 3 trial of ^{177}Lu -PSMA-617 in mHSPC



High proportion >50% of Low volume mHPSC

^a ADT in the neo-/adjuvant setting and/or ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PET/CT, positron-emission tomography/computed tomography; q6w, every 6 weeks; rPD, radiographic disease progression; rPFS, radiographic progression-free survival

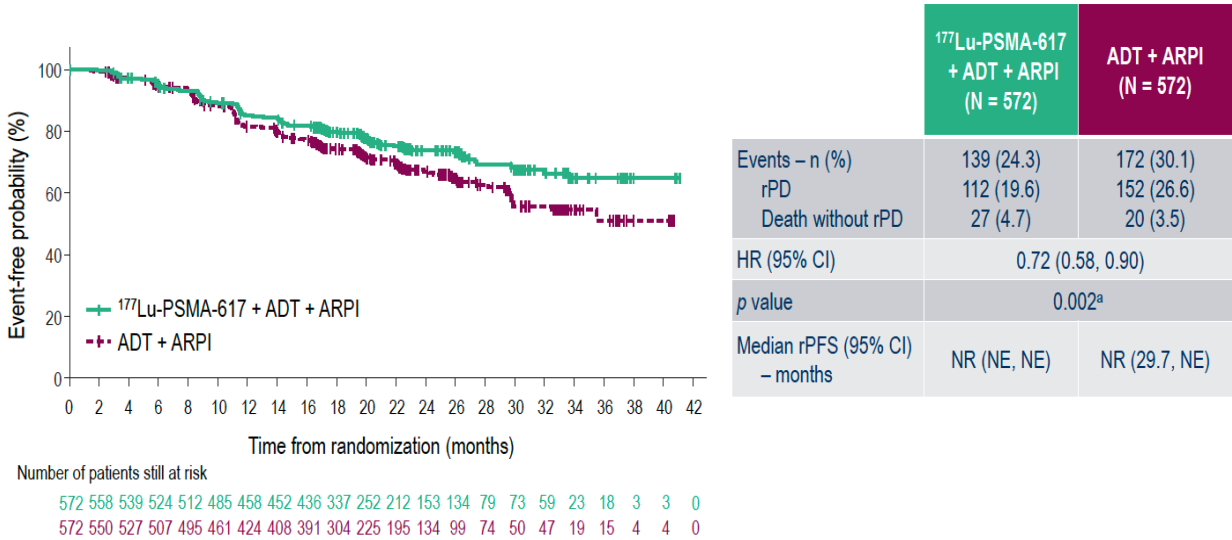
1. Sweeney CT *et al.* *N Engl J Med* 2015;373:737–46

not mandatory after crossover

triplets with PSMA-Lu177: PSMA Addition in PSMA +

rPFS by BIRC – the primary endpoint was met

Data cut-off: 13 January 2025

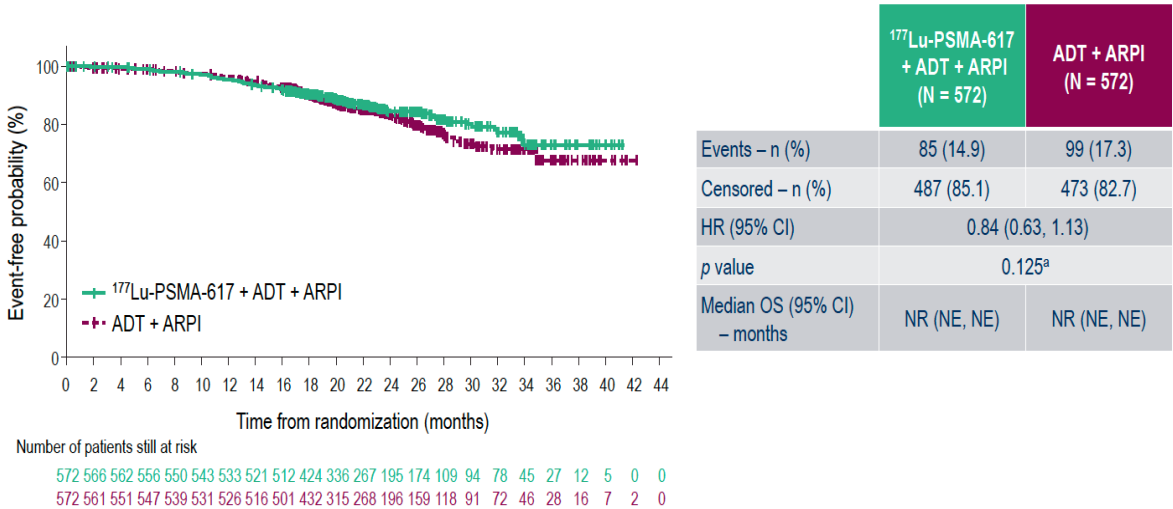


^aSignificance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%
CI, confidence interval; IA, interim analysis; NE, not estimable; NR, not reached



Interim OS (prespecified intent-to-treat analysis – follow-up continues)

Data cut-off: 13 January 2025



^aSignificance threshold at OS IA1: 0.0011 (one-sided; stratified log-rank test); information fraction, 47.3%



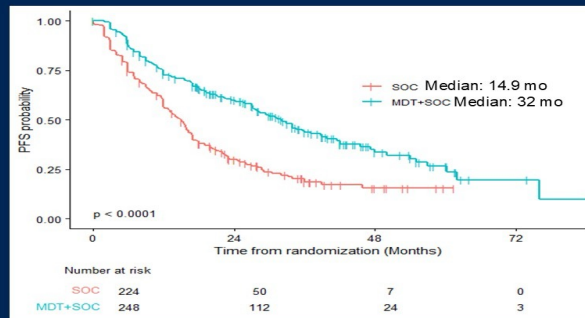
OligoMTS mHSPC: Wolverine

Trial Level Analysis:
Random effects model $P < 0.001$

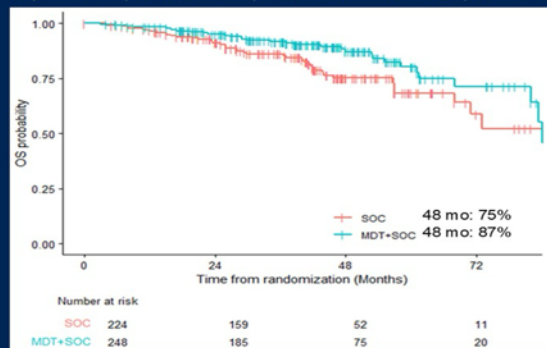
Study	logHR	SE(logHR)	Hazard Ratio	HR	95%-CI
ARTO	-0.9375	0.2399		0.392	[0.245, 0.627]
EXTEND cADT	-0.6596	0.3242		0.517	[0.274, 0.976]
EXTEND iADT	-0.6509	0.2492		0.522	[0.320, 0.850]
Oriole	-0.9696	0.3311		0.379	[0.198, 0.726]
SABR-COMET	-2.4113	1.0096		0.090	[0.012, 0.649]
Stomp	-0.7245	0.2742		0.485	[0.263, 0.829]
Common effect model				0.444	[0.349, 0.565]
Random effects model				0.444	[0.349, 0.565]

Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.0001$, $p = 0.99$

Cox Regression (Stratified by Trial):
MDT (vs SOC) HR: 0.45 (95% CI: 0.35-0.58), $P < 0.001$



Cox Regression (Stratified by Trial):
MDT (vs SOC) HR: 0.64 (95% CI: 0.40-1.01), $P = 0.057$



Effect of MDT (vs SOC) among subgroups

Group	Subgroup	Events/N	HR (95% CI)
Full cohort		300/472	0.50 (0.39, 0.62)
CRPC_baseline	Resistant	113/199	0.45 (0.30, 0.66)
	Sensitive	187/273	0.51 (0.38, 0.68)
Primary_treated	Yes	258/389	0.51 (0.39, 0.65)
	No	39/79	0.41 (0.21, 0.78)
Cancer stage	N1+M1a	131/202	0.52 (0.36, 0.74)
	M1b+M1c	169/269	0.48 (0.36, 0.66)
Imaging type	PSMA PET/CT	19/61	0.24 (0.09, 0.69)
	Conventional	124/189	0.53 (0.37, 0.76)
	Fluciclovine PET/CT	40/58	0.48 (0.26, 0.92)
	Choline PET/CT	117/164	0.52 (0.35, 0.75)
	Other than PSMA PET/CT	281/411	0.51 (0.40, 0.64)
Mets_Number	1-2	202/318	0.50 (0.38, 0.67)
	3-5	98/154	0.48 (0.32, 0.72)
ADT among CSPC	Yes	82/152	0.48 (0.31, 0.74)
	No	104/119	0.42 (0.28, 0.63)

Interaction was tested for all subgroups and were not significant at $P > 0.05$.

START-MET: SbrT Androgen Receptor Therapy METastatic HS prostate cancer.

mHSPC, non-blinded, randomized, phase III, multi center study.

ClinicalTrials.gov Identifier: NCT05209243

Meets following criteria

Inclusion criteria

- Castration sensitive → Local prior treatment allowed
- ECOG PS 0 or 1
- Distant metastatic disease by ≤ 3 lesions based on CT and Bone Scan and ≤ 5 lesions based on Coline or PSMA PET/TC

Stratification factors:

- Prior local treatment
- New Imaging technique (Coline vs PSMA PET/TC)

Exclusion criteria

- Metastases in previously irradiated areas
- Prior docetaxel or second generation hormonal treatments
- Tumor stage T4

N = 266

Randomization 1:1

STANDARD OF CARE + SBRT (all metastatic lesions)

ADT+ RT to the primary tumor (previously not treated) + Second generation hormonal treatment

STANDARD OF CARE

ADT+ RT to the primary tumor (previously not treated) + Second generation hormonal treatment

(ADT+ Abi/Apa/Enza/Daro)

ENDPOINTS

Primary endpoint:

- rPFS

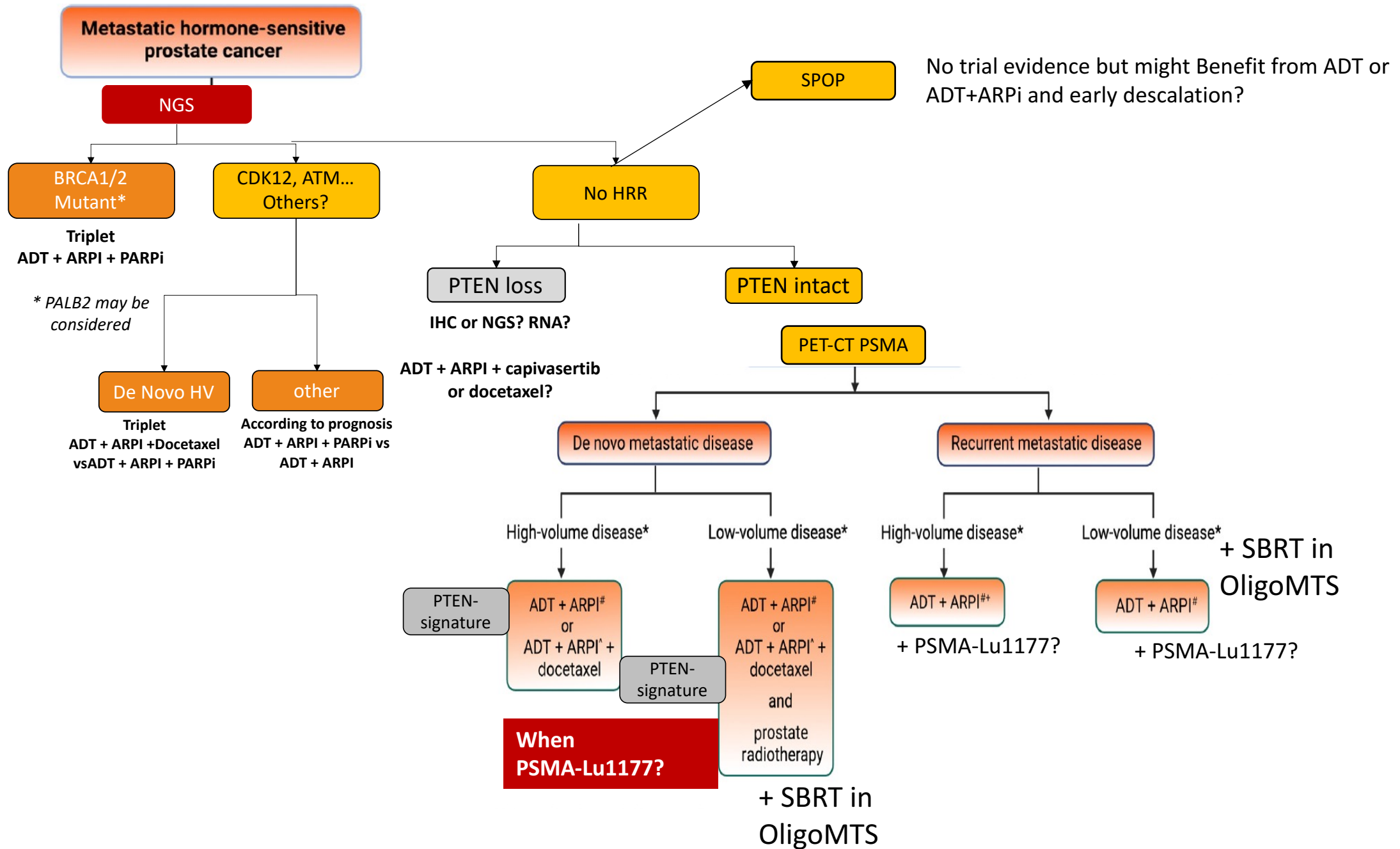
Key Secondary endpoints:

- Overall survival
- Time to cytotoxic chemotherapy
- Time to PSA progression
- Time to pain progression
- Time to castration resistance
- Time to skeletal-related event
- Quality of life and safety profile

Exploratory endpoints:

- Biomarkers assessment
- Local control
- Second progression free survival (PFS2)
- Time to symptomatic progression

PIs: Conde-Moreno, López-Campos, Gómez-Iturriaga
Genomic sub.studies PI: Olmos and López-Campos.



Doublets or Triplets according to Biology, Volume & Timing

Conclusions

- **The greatest evidence from clinical trials to apply personalized treatment approach →**
 - the PARPi trials BRCA1/2 pts benefits the most and have the worse outcomes with SoC → Triplet with PARPi
 - Other HRR: benefit of PARPi addition not extended to all... we lack data of triplet therapy benefit
 - Early access to best-in-class NGS testing for prostate is still a major hurdle
- **IHC PTEN loss in prognostic, adding AKTi is predictive of modest rPFS Benefit but not OS:**
 - Best method to identify Good responders: IHC vs NGS vs RNA signatures
 - PTEN deficiency signature in STAMPEDE associates to Docetaxel Benefit → Triplet therapy?
- **PET PSMA may further stratify patients**
 - To define oligo MTS disease for SBRT intensification
 - No clear OS data for adding Lu177-PSMA

¡Gràcias!