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GUARD INTERNATIONAL SYMPOSIUM

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



16-18 SEPTIEMBRE 2026

Espacio Maldonado, Madrid

Charla Magistral – Current Status of PARP inhibitor Management in mHSPC

Charles Ryan, M.D
Memorial Sloan Kettering Cancer Center
New York , NY

Current State of Knowledge

HRR Mutations Confer a poor prognosis in prostate cancer

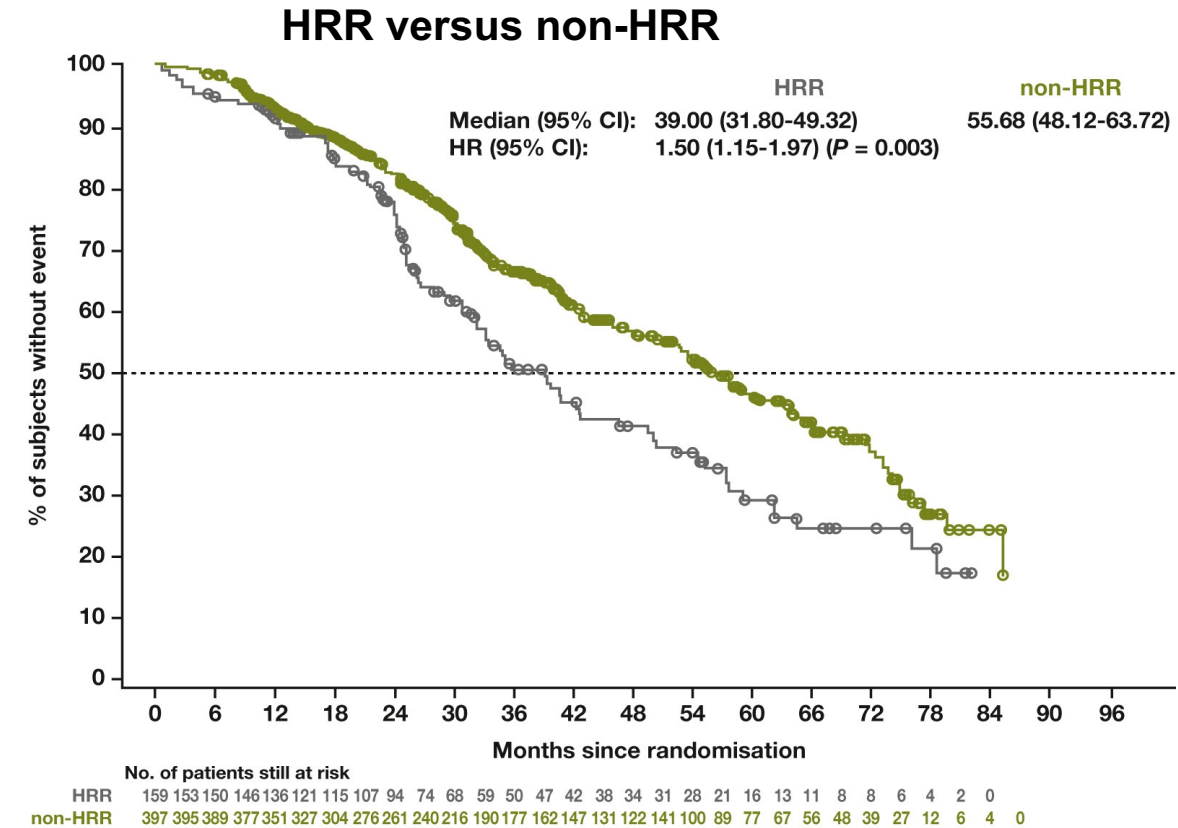
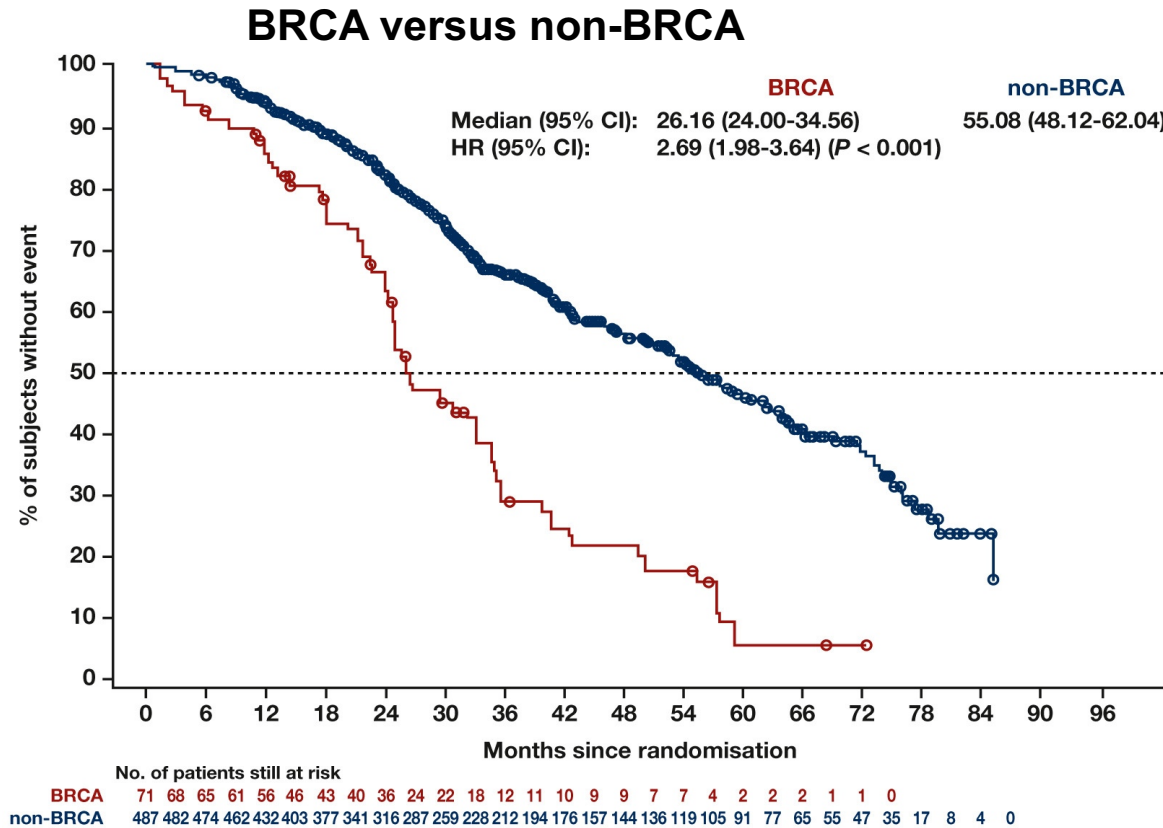
Parpi mono-therapy in CRPC

- approx 50% of BRCAm patients benefit**
- demonstrating the extent, and limits, of single agent therapy**

There is a biological rationale for combination with ARPI

Many details and gaps in our knowledge that need to be addressed

HRRm is a Predictor of Poor Outcome.



Of 556 patients, 28.6% had HRR gene alterations: ~50% involving *BRCA1/2*

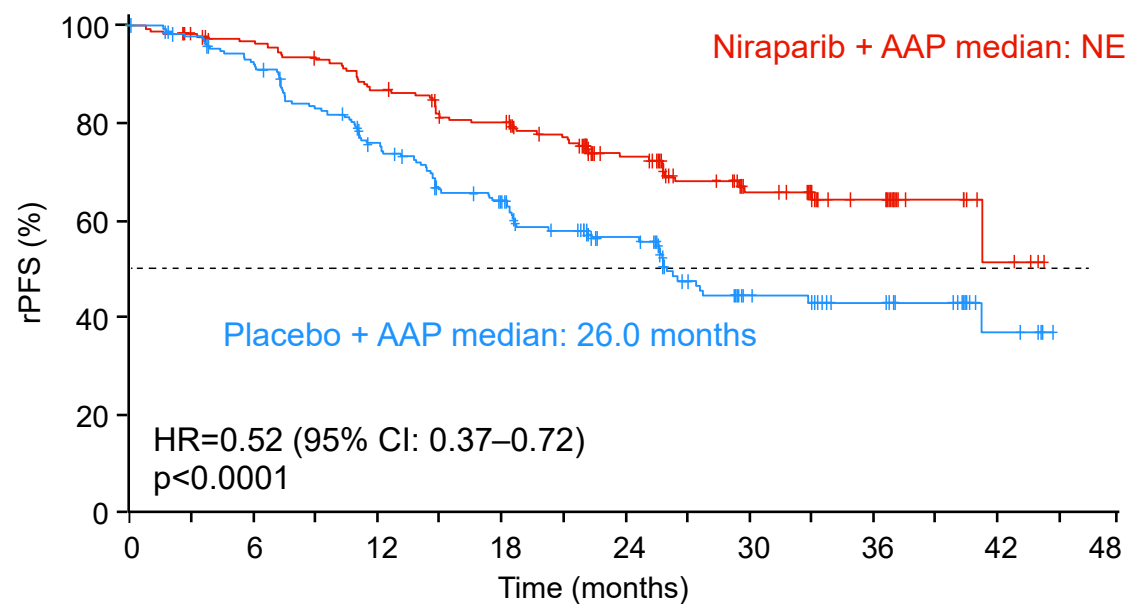
Adapted from Olmos D, et al. Ann Oncol. 2025 May 28:S0923-7534(25)00739-2.

*Results are from IPTW analysis.

BRCA, breast cancer gene; HRR, homologous recombination repair; IPTW, inverse probability treatment weighting.

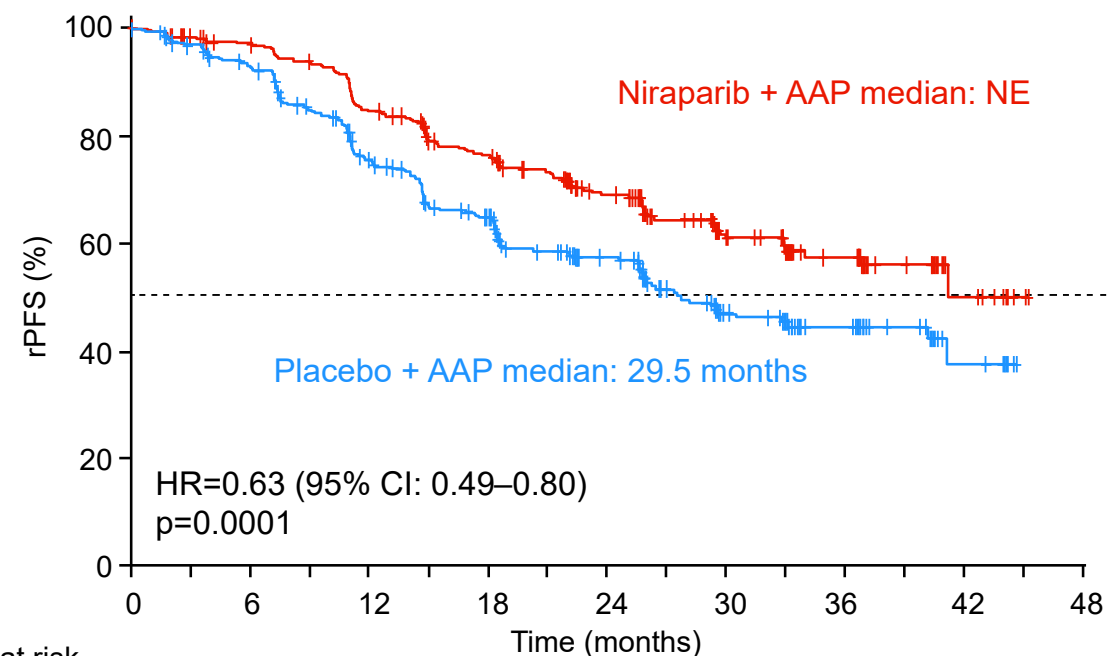
Trial #1 Niraparib plus Abiraterone/Prednisone vs Abiraterone alone

BRCA sub-group



Number at risk									
Niraparib + AAP	191	177	158	142	95	55	30	4	0
Placebo + AAP	196	174	137	109	73	33	22	6	0

HRRm (ITT)

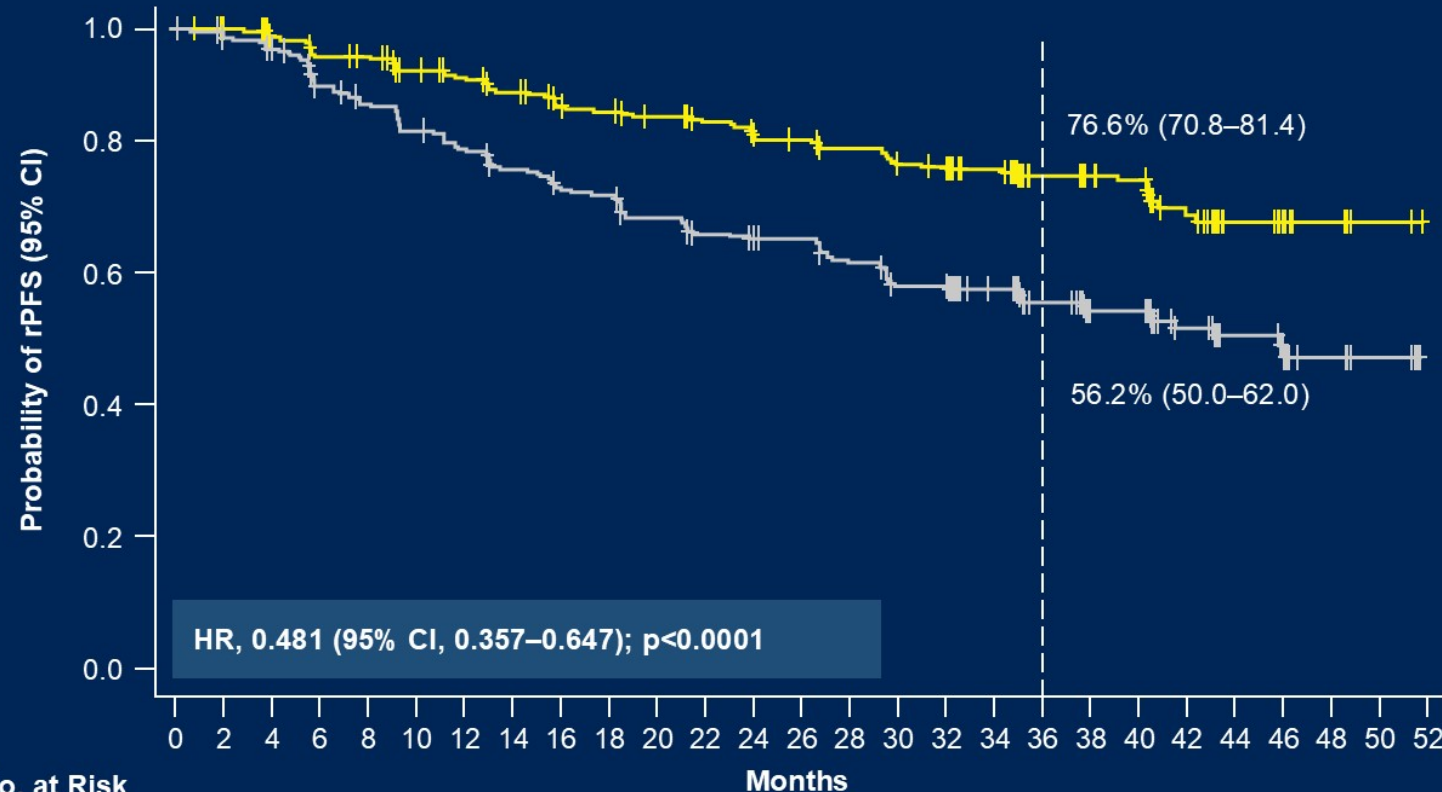


Number at risk									
Niraparib + AAP	348	321	280	246	164	91	54	9	0
Placebo + AAP	348	312	245	201	135	70	43	9	0

AMPLITUDE met the primary end point: Niraparib + AAP significantly reduced the risk of radiographic progression^a or death by 48% in BRCAm group and by 37% in HRRm population

Primary Endpoint: Investigator-Assessed rPFS

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



	TALA + ENZA (n=300)	PBO + ENZA (n=299)
No. of events	67	126
Median (95% CI), mo	NR (NR–NR)	45.8 (37.7–NR)

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

No. at Risk

Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
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

Data cutoff: February 18, 2026 (ITT population). Stratified HRs and 2-sided p values are reported throughout this presentation unless otherwise stated.
NR=not reached.

Pivotal questions

#1. Do we really need the combination of PARPI and ARPI?

#2. What constitutes appropriate selection for HRM?

#3. Does the PARPI matter?

#4 What is the best *management strategy* for these patients?

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PARPI + ARPI CONSIDERATIONS in APMS

Pro

Additive (at a minimum)

Synergistic (at a maximum)

In mHSPC/APMS it is the first strike against the cancer

Ties to the mechanism of disease onset....

WE HAVE TWO POSITIVE PHASE III STUDIES!

Con

Pill Burden

Drug Drug Interactions

Toxicity Management- how do we separate the benefits/risks

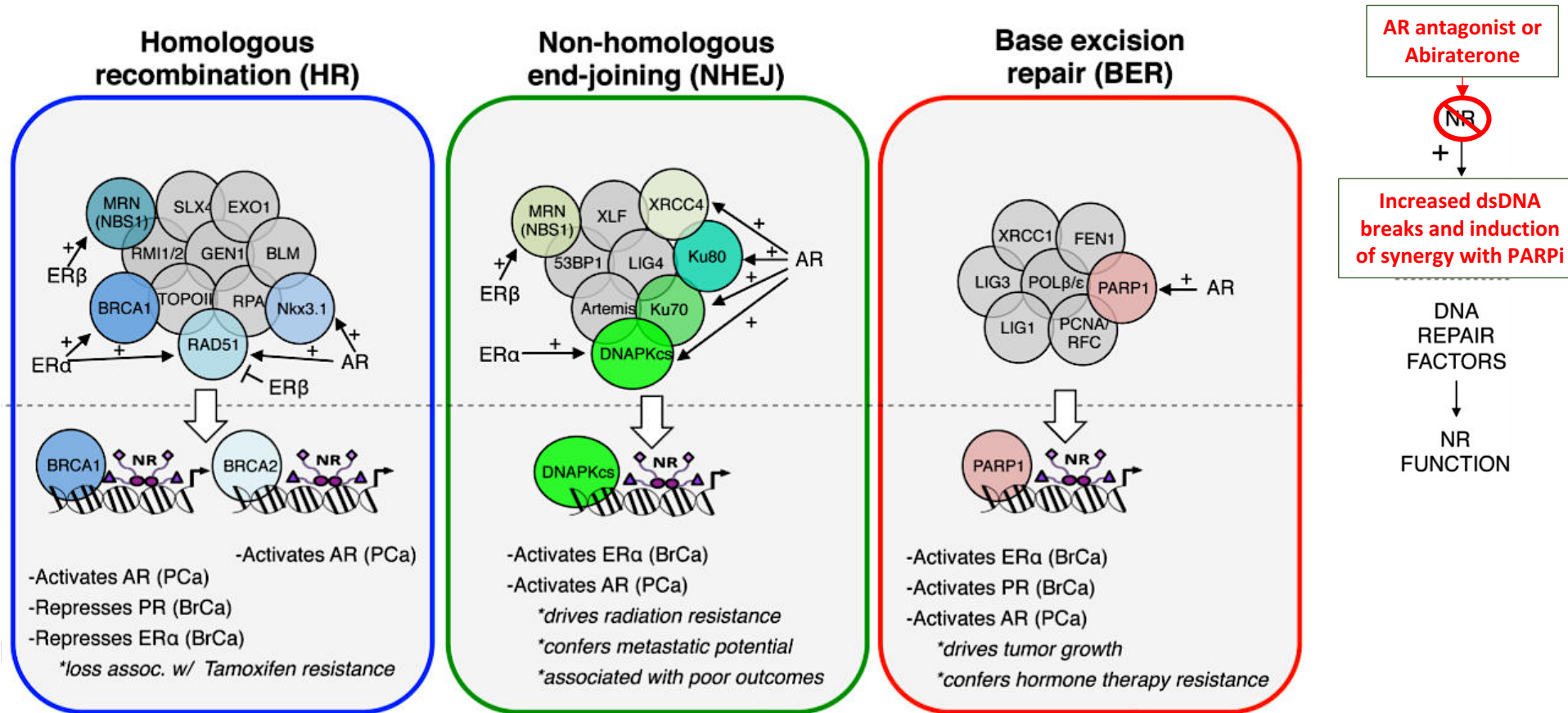
Duration of Rx may be long – years?

Cost

Phase III Studies not positive for OS

In 2016 we asked...

Synergy between AR signaling and PARP: Do we need BRCA2 alterations at all?



Adopted from Linking DNA damage and hormone signaling pathways in cancer by Schiewer and Knudsen.

Trends Endocrinol Metab. 2016 Apr; 27(4): 216–225.

Mechanistic rationale for arpi/parpi combinations

Mechanism 1 — ARPIs induce "BRCAness" by downregulating HRR/DDR genes

--ARPIs (abiraterone, enzalutamide, apalutamide) downregulate RAD51, reduce RAD51 foci at DSB sites, and impair repair capacity, creating a BRCAness-like phenotype that sensitizes to PARP inhibition

Mechanism 2 — PARP1 is a coactivator of AR transcription

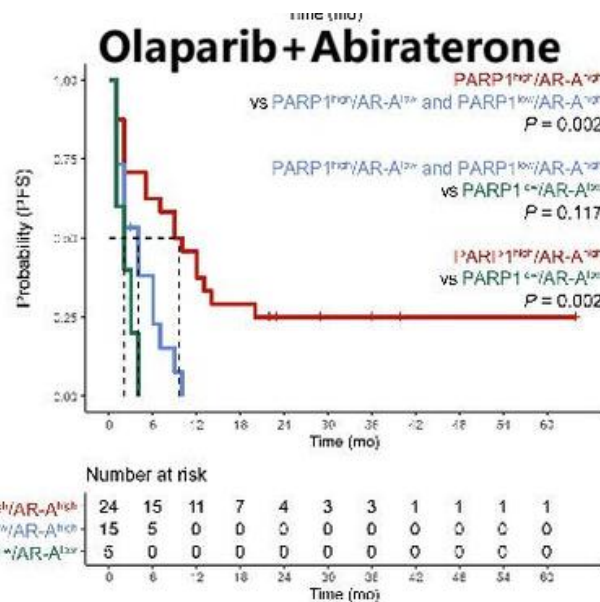
--PARP1 recruited to sites of AR function, promotes AR occupancy and transcription of AR target genes (PSA, TMPRSS2, ERG) (Schiwer CA Discovery 2012)

Higher AR activity + Higher Parp expression = Better response to the combination

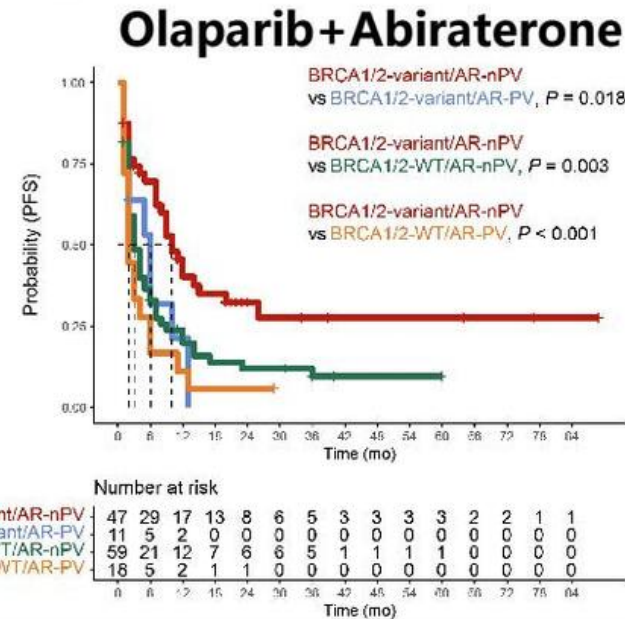
Abstract #523272: Heterogeneity and Synergistic Inhibition of the Poly(ADP-ribose) Polymerase and Androgen Receptor Signaling Pathway in Patients with Metastatic Castration-resistant Prostate Cancer

Bin Yang, Li Ding, Yiqun Zhang, Wei Chen, Baijun Dong, Hanxu Guo, Chengqi Jin, Jing Xu, Wentao Luo, Shiyu Mao, Changcheng Guo, Bo Peng, Xudong Yao, Bing Shen

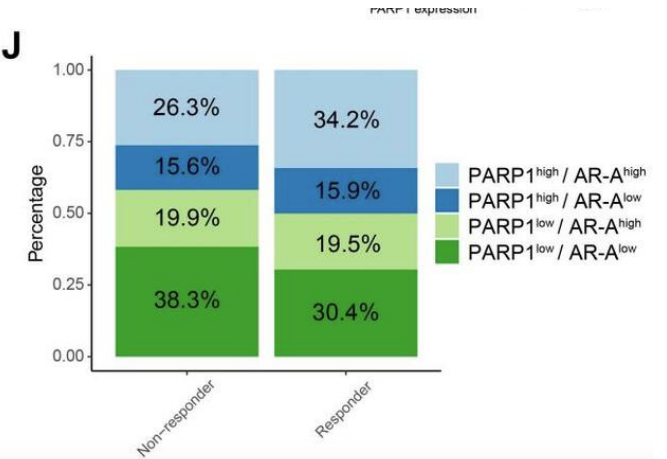
ASCO Genitourinary Cancers Symposium



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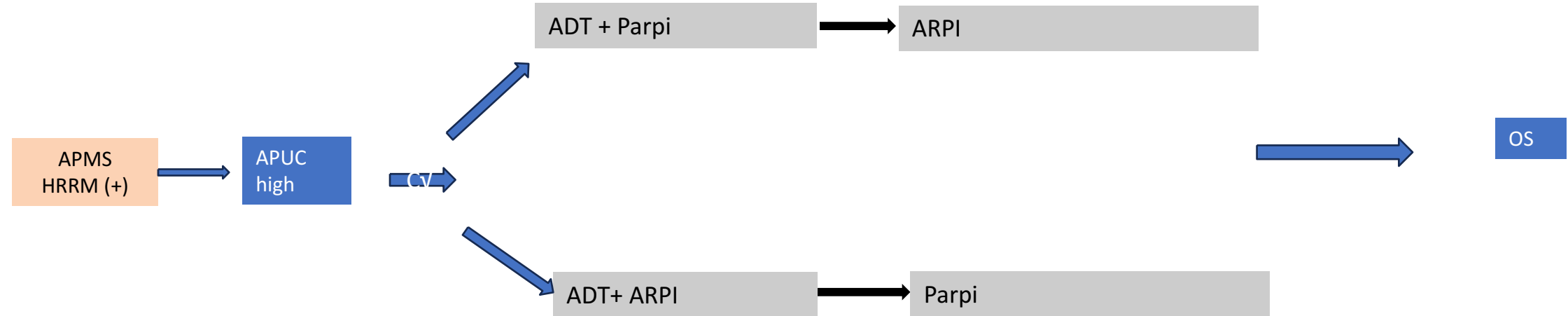


Results: PARP1 and AR-A exhibited marked heterogeneity in mCRPC (Fig.1). Compared with olaparib monotherapy, olaparib combined with abiraterone significantly improved progression-free survival (PFS) and overall survival (OS) in mCRPC patients, particularly among those harboring a PARP1^{high}/AR-A^{high} signature or a BRCA-variant/AR-nPV signature (Fig.2-3).

Conclusions: Biomarkers reflecting DNA damage repair deficiency and AR signaling have potential value in guiding the selection of mCRPC patients for olaparib treatment, particularly in the context of combination therapy. Patients harboring a PARP1^{high}/AR-A^{high} signature or a BRCA-variant/AR-nPV signature are more likely to benefit from olaparib combined with abiraterone or olaparib monotherapy. These findings warrant further validation through prospective clinical trials.

Associated with better rPFS = Wildtype AR, High AR expression, Higher Parp Expression, BRCA1/2 Variant

Ideally....



This trial would never happen
Unethical to withhold ARPI

Pivotal questions

#1. Do we really need the combination of PARPI and ARPI?

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Inter- HRRM Variability

Three PARPI and arpi combinations in APMR



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 7.2026 Prostate Cancer

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PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Table 1. PARP Inhibitors with or without ARPIs

Treatment	FDA-Approved Disease State Indication	Biomarker Pathogenic variant or mutation in gene (germline and/or somatic)	Clinical Trial
Olaparib	mCRPC that has progressed following prior treatment with enzalutamide or abiraterone.	<i>BRCA2, BRCA1, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L</i>	PROfound ¹
Rucaparib	mCRPC that has been treated with androgen receptor-directed therapy and taxane-based chemotherapy	<i>BRCA2, BRCA1</i>	TRITON2 ^{2,3}
Olaparib/ Abiraterone	mCRPC	<i>BRCA2, BRCA1</i>	PROpel ⁴
Talazoparib/ Enzalutamide	mCRPC	<i>BRCA2, BRCA1, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C</i>	TALAPRO-2 ^{5,6}
Niraparib/ Abiraterone	mCRPC	<i>BRCA2, BRCA1</i>	MAGNITUDE ^{7,8}

Inter HRRm Variability – Niraparib + Abi

AMPLITUDE (NIRAPARIB PLUS ABIRATERONE) SUBGROUP ANALYSIS BY BRCA AND NON-BRCA ALTERATIONS

End Point	Subgroup	HR (95% CI)	Events/N	
			Nira + AAP	PBO + AAP
rPFS	BRCA1/2	0.52 (0.37-0.72)	57/191	93/196
	CHEK2	0.65 (0.38-1.11)	24/72	32/76
	CDK12	1.01 (0.43-2.39)	13/28	10/28
	FANCA	0.76 (0.20-2.82)	4/15	5/15
	PALB2	2.41 (0.66-8.74)	6/9	4/13
	Other	0.72 (0.20-2.66)	6/25	4/15
Time to symptomatic progression	BRCA1/2	0.44 (0.29-0.68)	31/191	66/196
	CHEK2	0.47 (0.21-1.05)	9/72	18/76
	CDK12	0.68 (0.28-1.62)	9/28	12/28
	FANCA	0.71 (0.12-4.27)	2/15	3/15
	PALB2	NE (NE-NE)	1/9	2/13
	Other	1.18 (0.12-11.36)	4/25	1/15
OS	BRCA1/2	0.75 (0.51-1.11)	44/191	61/196
	CHEK2	0.85 (0.45-1.59)	18/72	21/76
	CDK12	0.57 (0.25-1.31)	9/28	15/28
	FANCA	0.92 (0.20-4.12)	3/15	4/15
	PALB2	3.30 (0.52-21.21)	3/9	2/13
	Other	0.79 (0.18-3.36)	5/25	3/15

Favors Nira + AAP ← 0.125 0.25 0.5 1 2 4 8 16 32 → Favors PBO + AAP

Non-BRCA subgroups were not statistically powered for formal testing in this exploratory analysis. Hazard ratios stratified by disease volume (high vs low).
Other: RAD54L, BRIP1, RAD51B.

Highlights

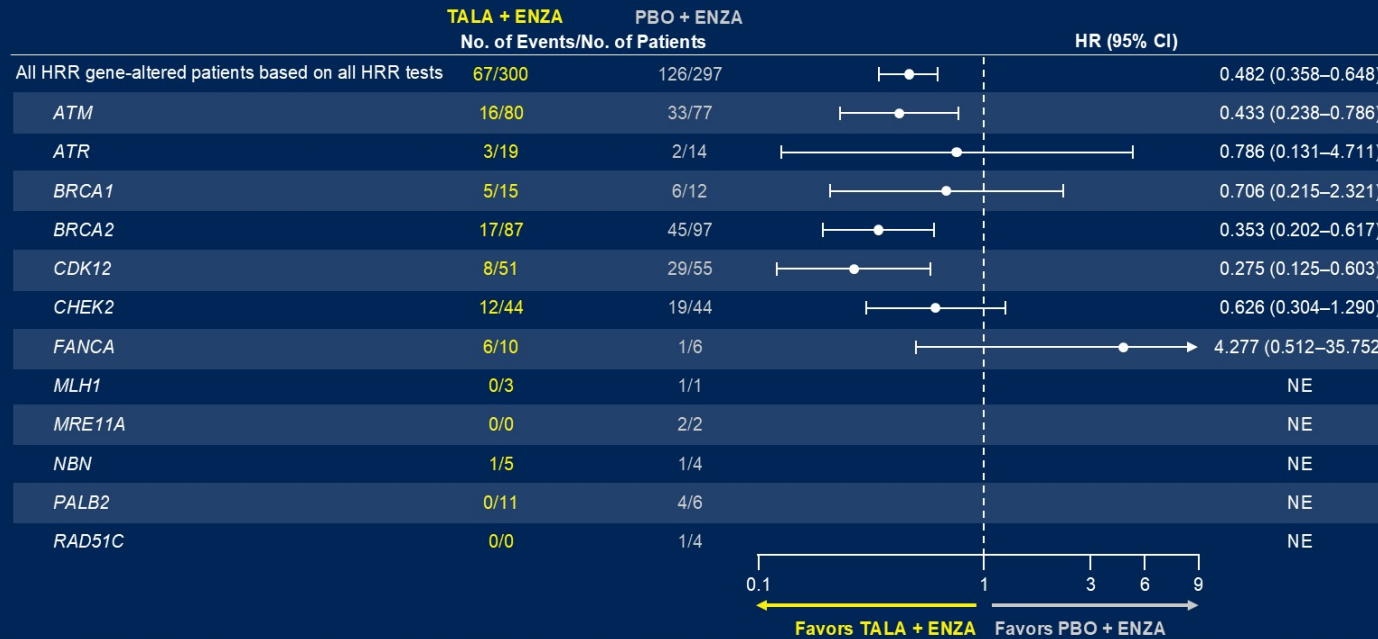
1. Strong signal for BRCA2, Chek2
2. BRCA2 OS
3. No ATM patients

Inter HRRm Variability – TALA +ENZA

By Gene Analysis of rPFS

In post hoc analyses, rPFS generally favored TALA + ENZA across HRR gene subgroups

11



Data cutoff: February 18, 2026 (ITT population). Analyses included all available tumor and baseline ctDNA records. For non-BRCAm, those with co-occurring BRCA1/2m were excluded. For BRCA1m, those with co-occurring BRCA2m were excluded. Unstratified HRs are based on a Cox proportional hazards model, with treatment as the only covariate. ctDNA=circulating tumor DNA; NE=not evaluable.

Highlights

1. Strong signal for BRCA2, ATM, CDK12
2. No data on OS by individual mutation

illustrates proportion of response

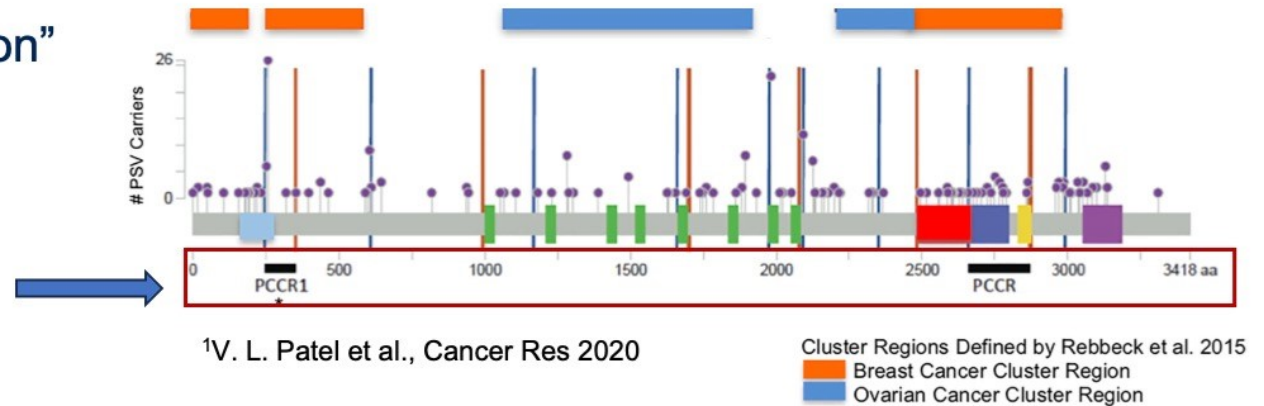
Best Change from Baseline in PSA (n=84)



***Intra- BRCA* Variability**

BRCA2 alterations: The same or different?

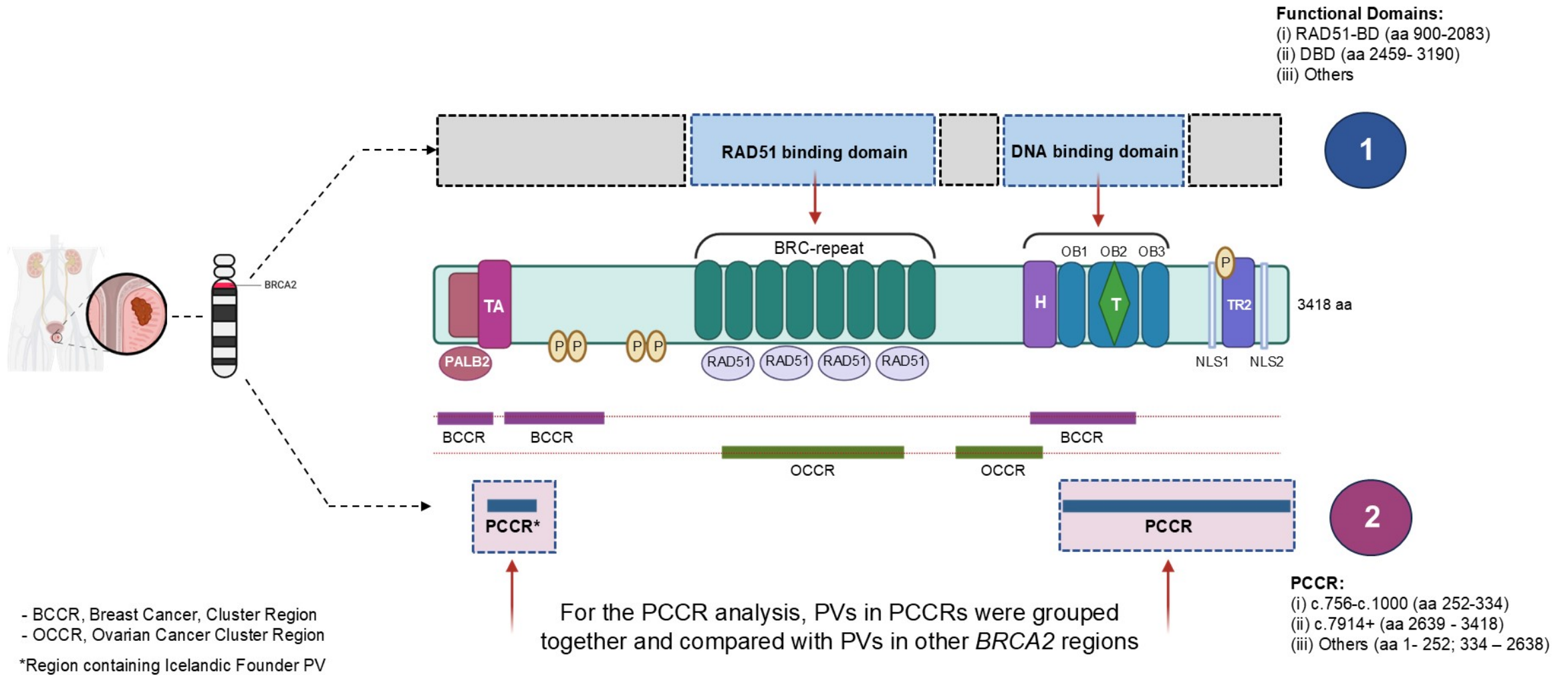
- In *BRCA2*, a “Prostate Cancer Cluster Region” (PCCR) in which PVs were associated with increased PC risk and more aggressive features was recently identified¹
- The PCCR included PVs in the 3' region of *BRCA2* (c.7914+) and c.756-c.1000¹



Study Objective:

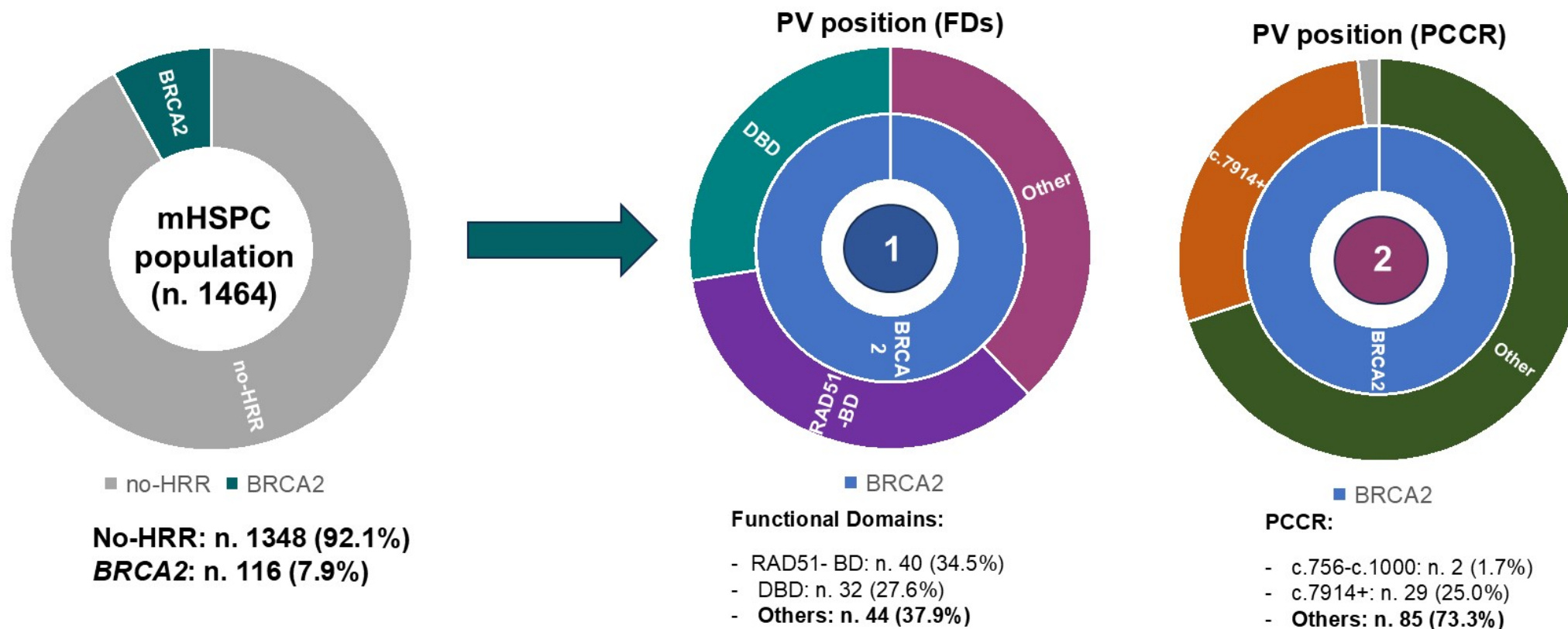
To investigate clinical outcomes in patients with mPC according to *BRCA2* PV position and type across mHSPC and mCRPC settings

Methods: *BRCA2* PV position



Metastatic Hormone-Sensitive PC, *BRCA2*, 1L treatment

PV distribution according to FDs and PCCR

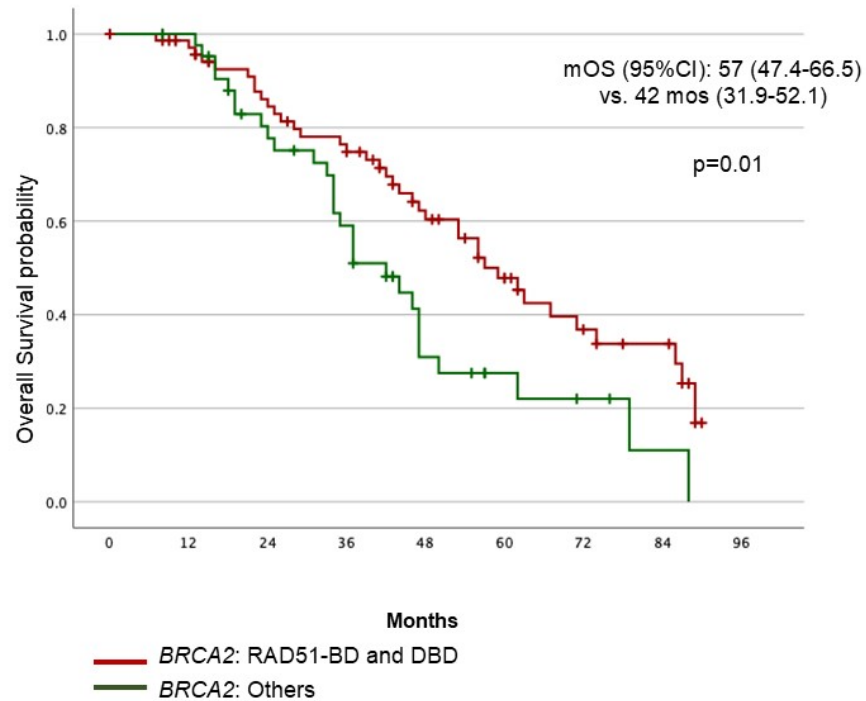


The largest groups were represented by “other” regions: outside the FDs and outside the PCCRs

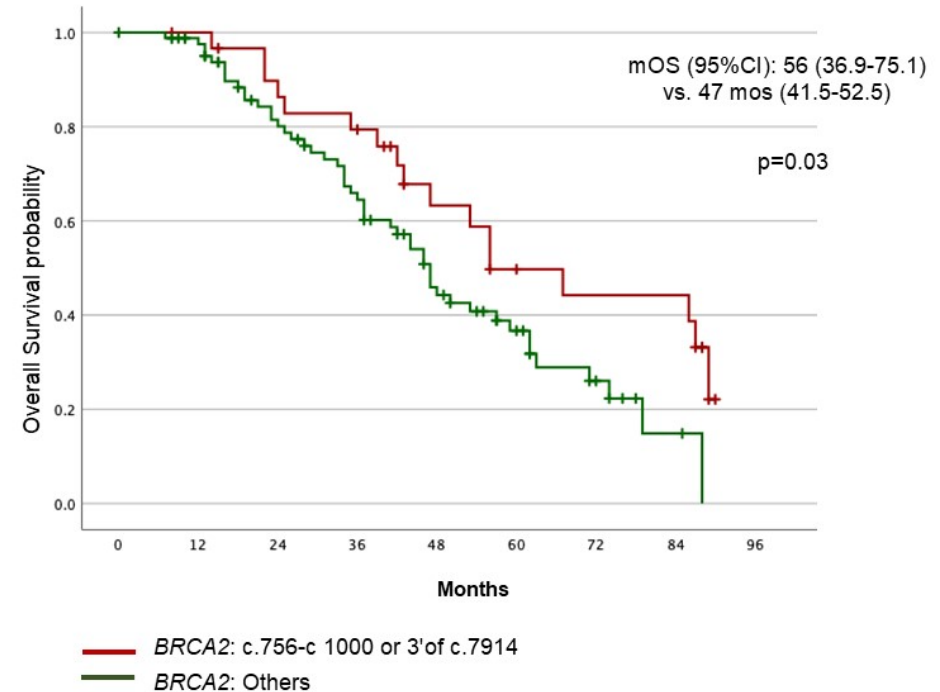
Metastatic Hormone-Sensitive PC, *BRCA2*

1L treatment

***BRCA2* Functional Domains:** RAD51-BD and DBD vs. Others



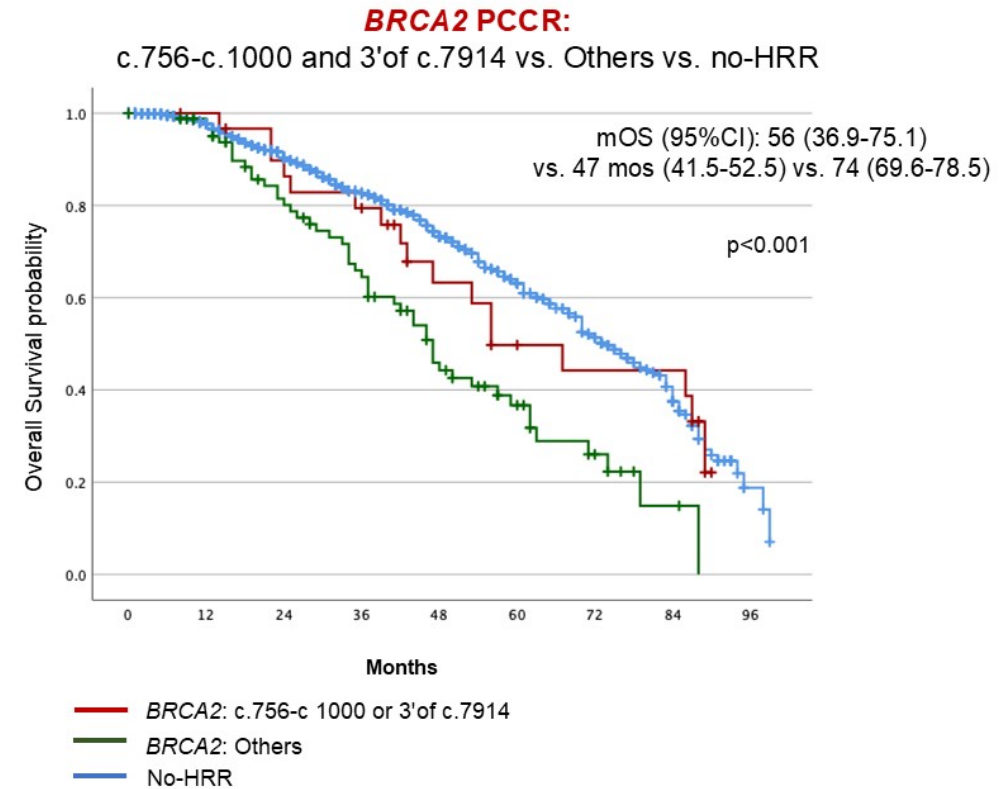
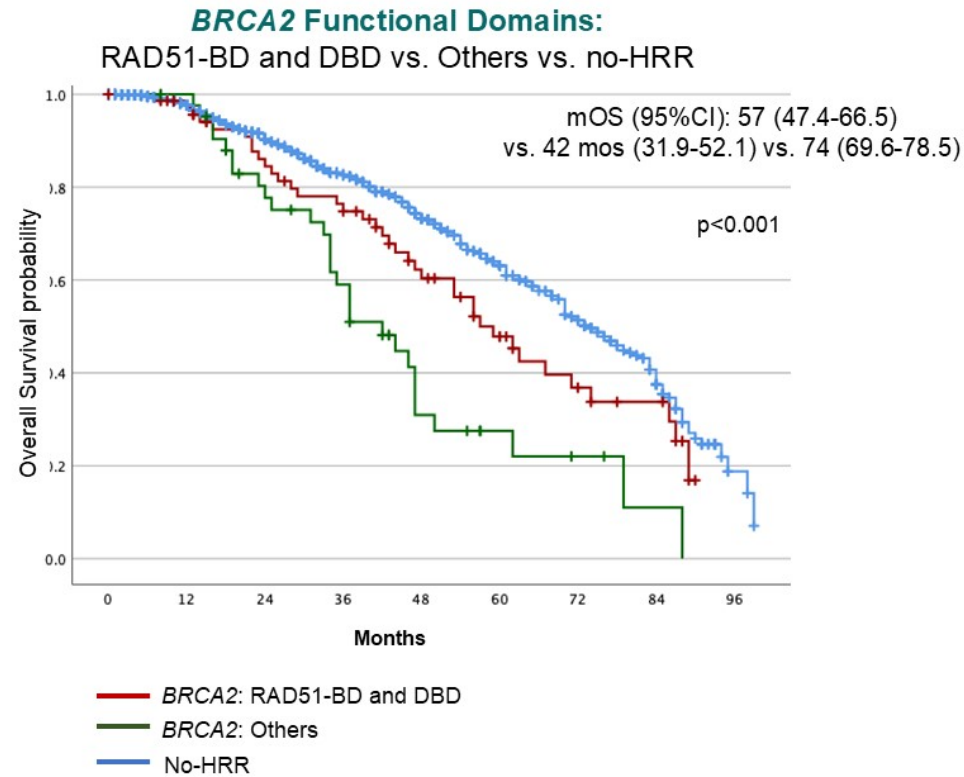
***BRCA2* PCCR:** c.756-c.1000 and 3' of c.7914 vs. Others



In the hormone-sensitive setting, the position of genetic alteration in the *BRCA2* gene (RAD51-BD/DBD-outside and PCCR outside) was associated with shorter OS

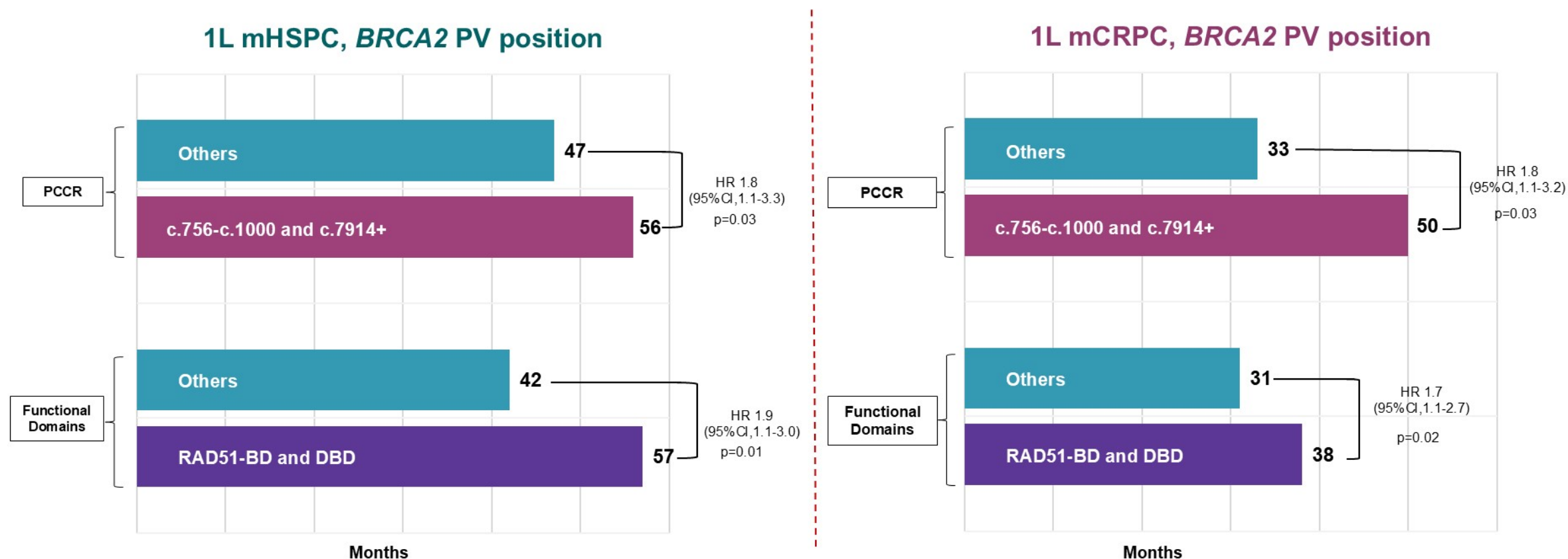
Metastatic Hormone-Sensitive PC, *BRCA2* vs. no-HRR alterations

1L treatment



Both *BRCA2* subgroups had shorter OS. *BRCA2* PVs located in RAD51-BD/DBD or PCCR appear to identify smaller subgroups with a trend toward a more favorable prognosis and longer OS compared with their respective “other” subgroups

Summary of Overall Survival by *BRCA2* subgroups



The consistency of the pattern observed in mHSPC and mCRPC, support the hypothesis that *BRCA2* PV location captures underlying biological heterogeneity that may influence clinical outcome

Intra –BRCA Variability

- 1. Requires further study in relation to efficacy of PARP inhibitors.**
- 2. May be driven by location of mutation within BRCA**
- 3. May be driven by other mutational factors (e.g. homozygous deletion etc)**
- 4. May be a driver of variability in response in both CRPC/CSPC**

Pivotal questions

#1. Do we really need the combination of PARPI and ARPI?

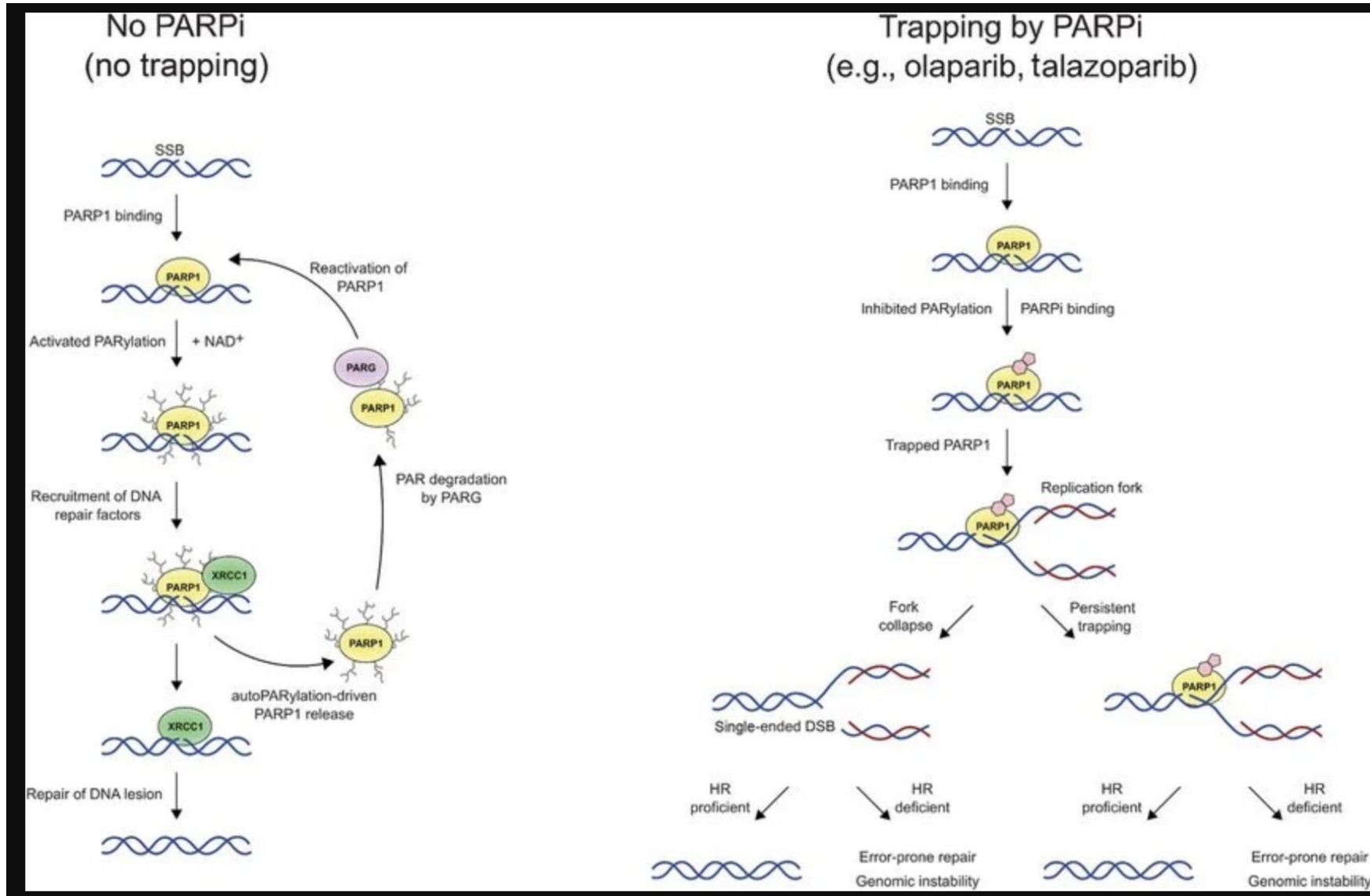
#2. What constitutes appropriate selection for HRM?

#3. Does the PARPI matter?

#4 What is the best *management strategy* for these patients?

PARP Trapping

Talazaparib > Other Parpi



Talazaparib is the most potent PARP1/2 trapper

Approx 50–100× more potent at trapping than olaparib, niraparib, and rucaparib

More trapper than catalytic (PARylation) inhibition

Explains single-agent cytotoxicity, its low approved dose, and its hematologic toxicity.

AMPLITUDE: Randomised, double-blind, placebo-controlled trial in HRRm mHSPC

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:

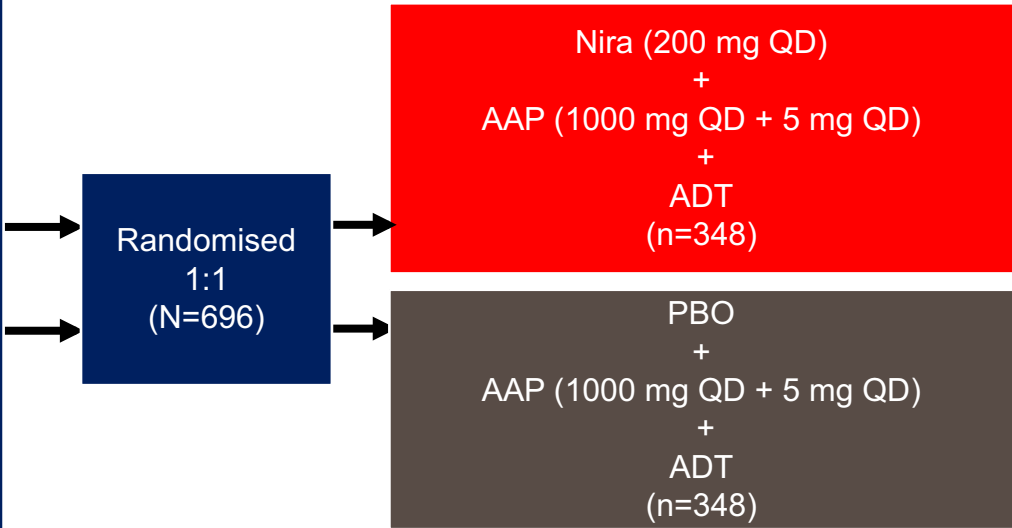
- mCSPC^a
- Alteration in ≥1 HRR eligible gene: BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L^b
- ECOG PS 0–2

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



Stratification factors:

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

Primary end point

- rPFS by investigator review

Key secondary end points

- Time to symptomatic progression
- OS
- Safety

Clinical data cutoff: January 7, 2025

Adapted from Attard G, et al. 2025.¹ ^aPatients with lymph node-only disease were not eligible.¹ ^bHRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature.¹ ^cLast dose ≤3 months prior to randomisation.¹
BRCA, breast cancer gene; BRIP1, BRCA1 interacting protein C-terminal helicase 1; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; FANCA, Fanconi anaemia complementation group A; Nira, niraparib; OS, overall survival; PALB2, partner and localiser of BRCA2; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PBO, placebo; RAD51B, RAD51 paralogue B; RAD54L, radiation sensitive 54-like; rPFS, radiographic progression-free survival; RT, radiotherapy; QD, once daily.
¹. Attard G, et al. Oral Presentation at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, IL.

Baseline characteristics

		Niraparib + AAP (n=348)	Placebo + AAP (n=348)
Median age (range), years		68 (40-88)	67 (40-92)
Median prostate-specific antigen (PSA) at initial diagnosis (range), ng/mL		112.3 (0.1-17,475) ^a	101.6 (0.1-15,900) ^b
ECOG PS score, n (%)	0 ≥1	242 (70) 106 (30)	218 (63) 130 (37)
Gleason score at initial diagnosis, n (%)	≥8	276 (79)	262 (75)
Metastatic stage at diagnosis, n (%)	M1 (synchronous)	301 (86)	302 (87)
Disease volume, n (%)	High	269 (77)	271 (78)
Prior docetaxel use in mHSPC, n (%)		54 (16)	56 (16)
Site of metastases ^c , n (%)	Bone only Visceral Lymph nodes	146 (42) 57 (16) 173 (50)	154 (44) ^d 54 (16) ^d 161 (46) ^d
BRCA alteration, n (%)		191 (55)	196 (56)

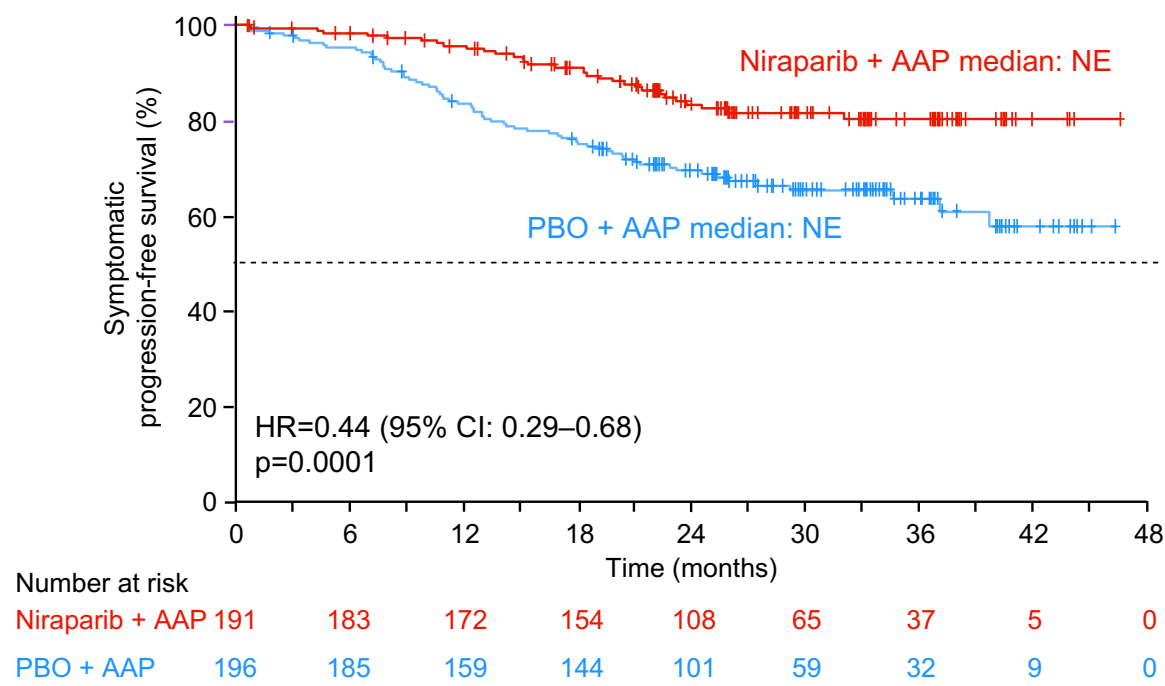
Primary end point: radiographic progression-free survival

BRCA sub-group

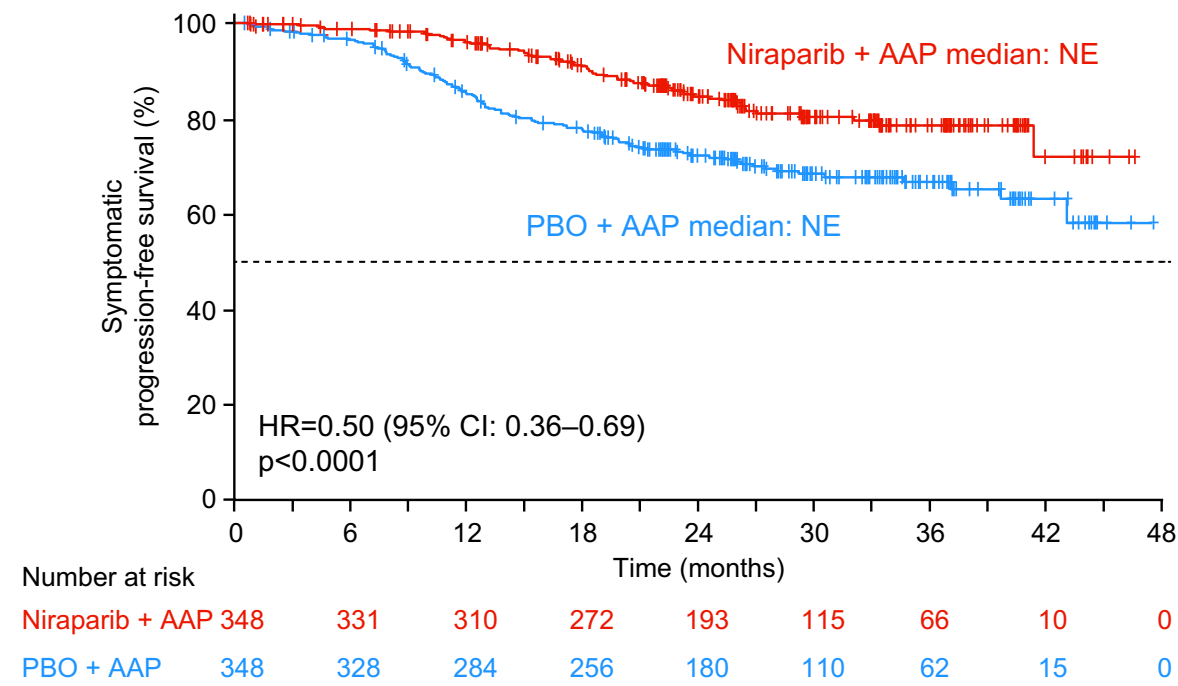
AMPLITUDE met the primary end point: Niraparib + AAP significantly reduced the risk of radiographic progression^a or death by 48% in BRCAm group and by 37% in HRRm population

2^{ary} end point: symptomatic progression-free survival

BRCA sub-group



HRRm (ITT)



Niraparib + AAP significantly reduced the risk of symptomatic progression by 56% in BRCAm group and by 50% in HRRm group

Adverse events of special interest

Selected categories of TEAEs of interest, n (%)		Nira + AAP (n=347)		PBO + AAP (n=348)	
		All grades	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 AE of interest		306 (88)	217 (63)	261 (75)	132 (38)
Hematologic	Anemia	179 (52)	101 (29)	83 (24)	16 (5)
	Neutropenia	76 (22)	33 (10)	28 (8)	7 (2)
	Thrombocytopenia	66 (19)	24 (7)	20 (6)	1 (<1)
	MDS	1 (<1)	1 (<1)	0	0
Cardiovascular	Hypertension	155 (45)	93 (27)	113 (33)	64 (18)
	Arrhythmia	68 (20)	19 (5)	28 (8)	11 (3)
	Cardiac failure	20 (6)	9 (3)	6 (2)	4 (1)
Other	Hypokalemia	92 (27)	40 (12)	70 (20)	38 (11)
	Hepatotoxicity	46 (13)	8 (2)	71 (20)	19 (5)

Other common AEs of any grade: constipation (35% vs 16%), nausea (31% vs 14%), fatigue (26% vs 18%), and arthralgia (21% vs 21%) in the Nira +AAP vs placebo + AAP arms, respectively

Adapted from Attard G, et al. Nat Med. 2025 Oct 7. doi: 10.1038/s41591-025-03961-8.
Predefined adverse events of special interest. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event: the event with the worst toxicity is used.

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
- *BRC*Am vs non-*BRC*Am

1:1

N=599

TALA 0.5 mg* + ENZA 160 mg QD

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*‡

*0.35 mg QD if the patient has moderate renal impairment; †As per the protocol amendment (September 2021). ClinicalTrials.gov identifier: NCT04821622. ‡HRR testing using FoundationOne®/FoundationOne®CDx and FoundationOne®Liquid CDx. *BRC*Am=*BRCA* alterations; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; HRRm=HRR gene alterations; MRI=magnetic resonance imaging; ORR=objective response rate; OS=overall survival; PFS2=time to second progression or death; PRO=patient-reported outcome; PSA=prostate-specific antigen; QD=once daily; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SSE=symptomatic skeletal event.

Statistical Considerations

Planned sample size ~ 550

rPFS (Primary Endpoint)

197 rPFS events provide ~90% power to detect HR of 0.63 using 2-sided log-rank test with 5% level of significance



*Hierarchical Testing Approach to control for Type I error
Formal OS testing conducted only if rPFS was statistically significant*

OS (Key Secondary Endpoint)*

197 deaths provide 85% power to detect HR of 0.65 using a 2-sided log-rank test with a 5% level of significance and a 2-look group sequential design with a Lan–DeMets (O’Brien–Fleming) α -spending function

- Efficacy of TALA + ENZA vs. PBO + ENZA assessed in all randomized participants (ITT population)
- TEAEs assessed in all participants with ≥ 1 dose of study treatment
- K-M analysis used to estimate time-to-event endpoints and a log-rank test to compare treatments
- Cox proportional hazards model used to estimate HRs and associated 95% 2-sided CIs, with the proportionality assumption assessed

*A formal interim analysis of OS will be performed at the time of the final analysis of rPFS.
CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; TEAE=treatment emergent adverse event.

Baseline Characteristics

Baseline characteristics were well balanced

		TALA + ENZA (n=300)	PBO + ENZA (n=299)
Median age (range), y		70 (45–89)	69 (44–86)
Median PSA level (range), ng/mL		3.6 (0–1483)	3.6 (0–2282)
HRR gene alteration,* n (%)	BRCA1/2	104 (35)	103 (34)
	Other	196 (65)	196 (66)
Disease status,* n (%)	De novo	252 (84)	254 (85)
	Relapsed	48 (16)	45 (15)
Disease volume,* n (%)	High	211 (70)	212 (71)
	Low	89 (30)	87 (29)
Gleason score, n (%)	<8	45 (15)	49 (16)
	≥8	245 (82)	245 (82)
Disease site, n (%)	Bone only	86 (29)	96 (32)
	Soft tissue only	38 (13)	27 (9)
	Bone and soft tissue	176 (59)	173 (58)
ECOG PS, n (%)	0	199 (66)	208 (70)
	1	101 (34)	91 (30)

Data cutoff: February 18, 2026 (ITT population).

*By randomization stratification.

HRR Gene Alterations

The prevalence of *BRCA1/2*m was consistent with expectations for advanced prostate cancer^{1,2}

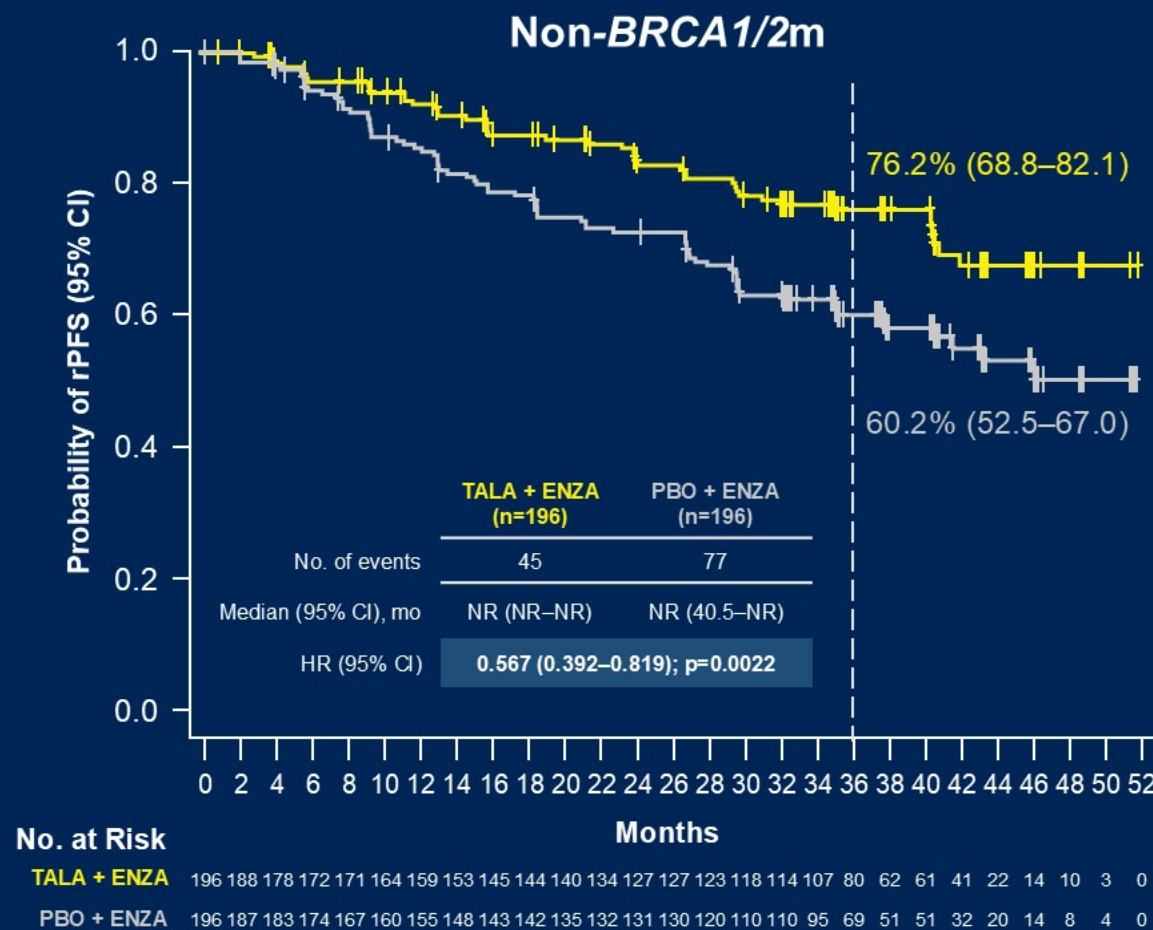
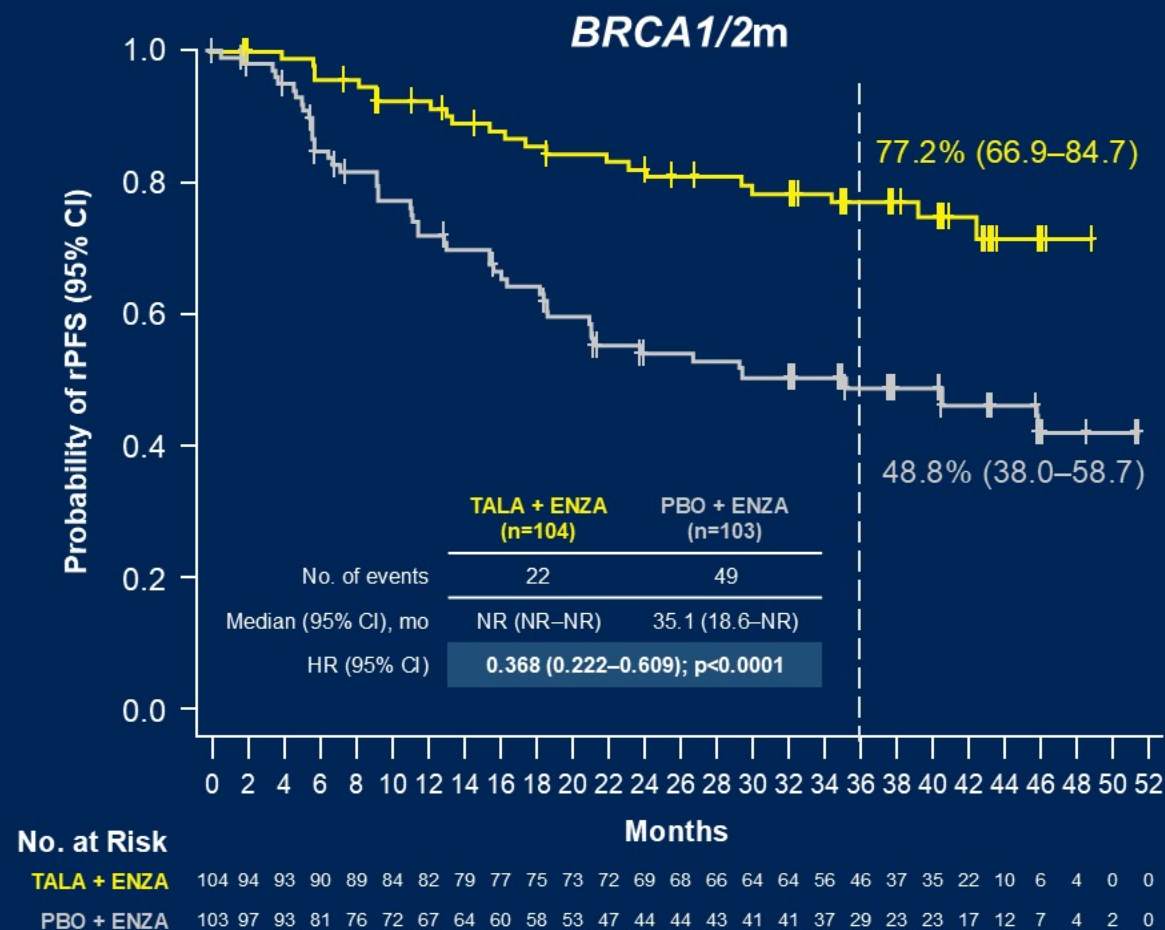
		TALA + ENZA (n=300)	PBO + ENZA (n=299)
HRR gene alteration*, n (%)	<i>BRCA1/2</i>	104 (35)	103 (34)
	Other	196 (65)	196 (66)
Tissue source for HRR gene alteration testing, n (%)	Tumor tissue only	39 (13)	45 (15)
	Blood only	58 (19)	41 (14)
	Tumor tissue and blood	203 (68)	213 (71)
≥1 alteration in the corresponding HRR gene†, n (%)	<i>ATM</i>	87 (29)	80 (27)
	<i>ATR</i>	23 (8)	18 (6)
	<i>BRCA1</i>	16 (5)	11 (4)
	<i>BRCA2</i>	86 (29)	92 (31)
	<i>CDK12</i>	55 (18)	60 (20)
	<i>CHEK2</i>	44 (15)	44 (15)
	<i>FANCA</i>	10 (3)	6 (2)
	<i>MLH1</i>	1 (<1)	1 (<1)
	<i>MRE11A</i>	3 (1)	2 (1)
	<i>NBN</i>	6 (2)	6 (2)
	<i>PALB2</i>	11 (4)	7 (2)
	<i>RAD51C</i>	0	4 (1)

Data cutoff: February 18, 2026 (ITT population). *By randomization stratification; †Prospectively assessed results from blood (liquid biopsy) using FoundationOne®Liquid CDx and/or de novo or archival tumor tissue using FoundationOne® or FoundationOne®CDx.

1. Olmos D et al. *Ann Oncol*. 2025;36:1190-1202; 2. Chung JH et al. *JCO Precis Oncol*. 2019;3:PO.18.00283.

rPFS in the *BRC*Am vs non-*BRC*Am Subgroups

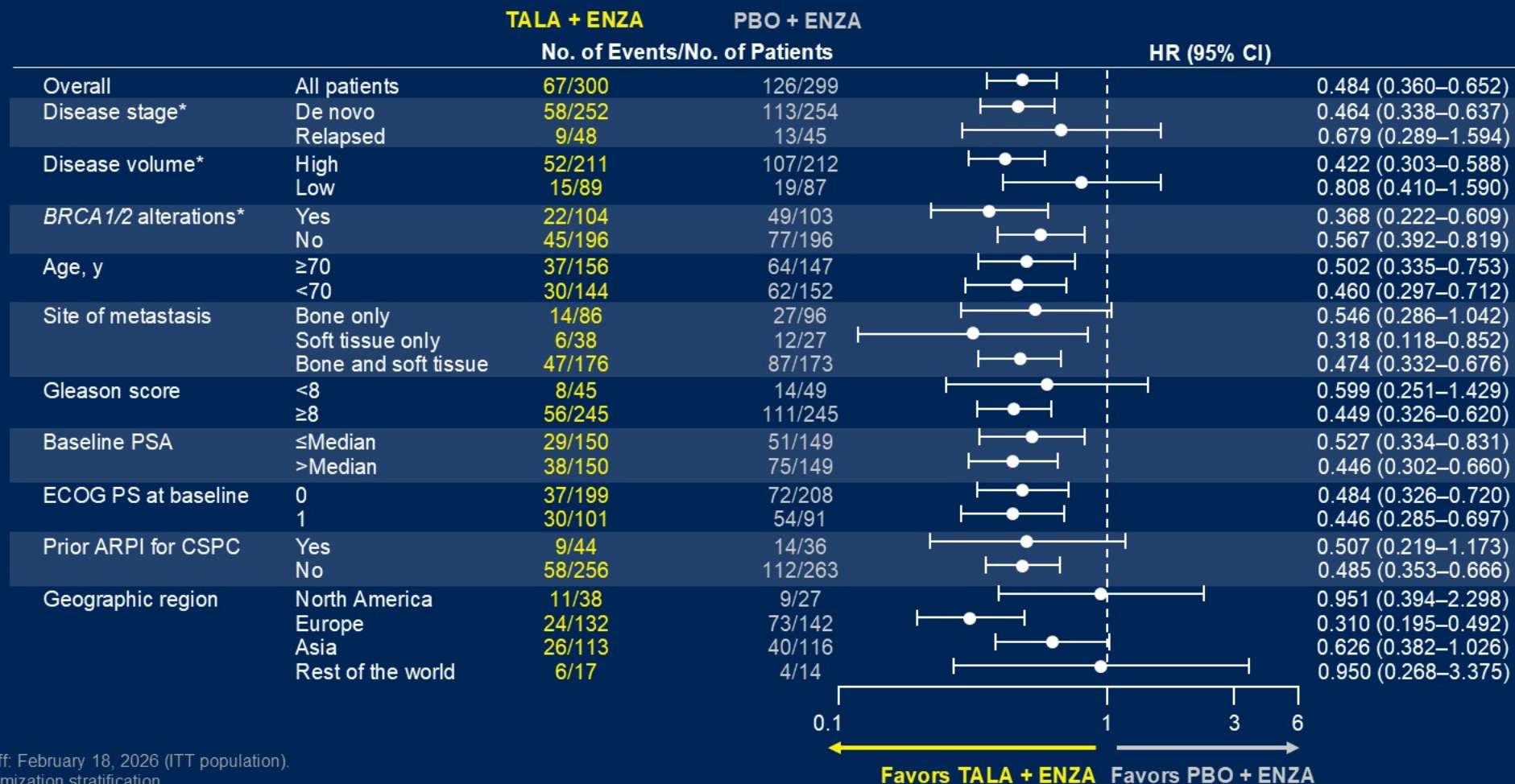
A 63% risk reduction was observed in the *BRC*Am subgroup and 43% in the non-*BRC*Am subgroup



Data cutoff: February 18, 2026 (ITT population). The *BRC*Am and non-*BRC*Am subgroups by randomization stratification. HRs are unstratified.

Subgroup Analysis of rPFS

A consistent treatment effect for rPFS was observed across prespecified subgroups



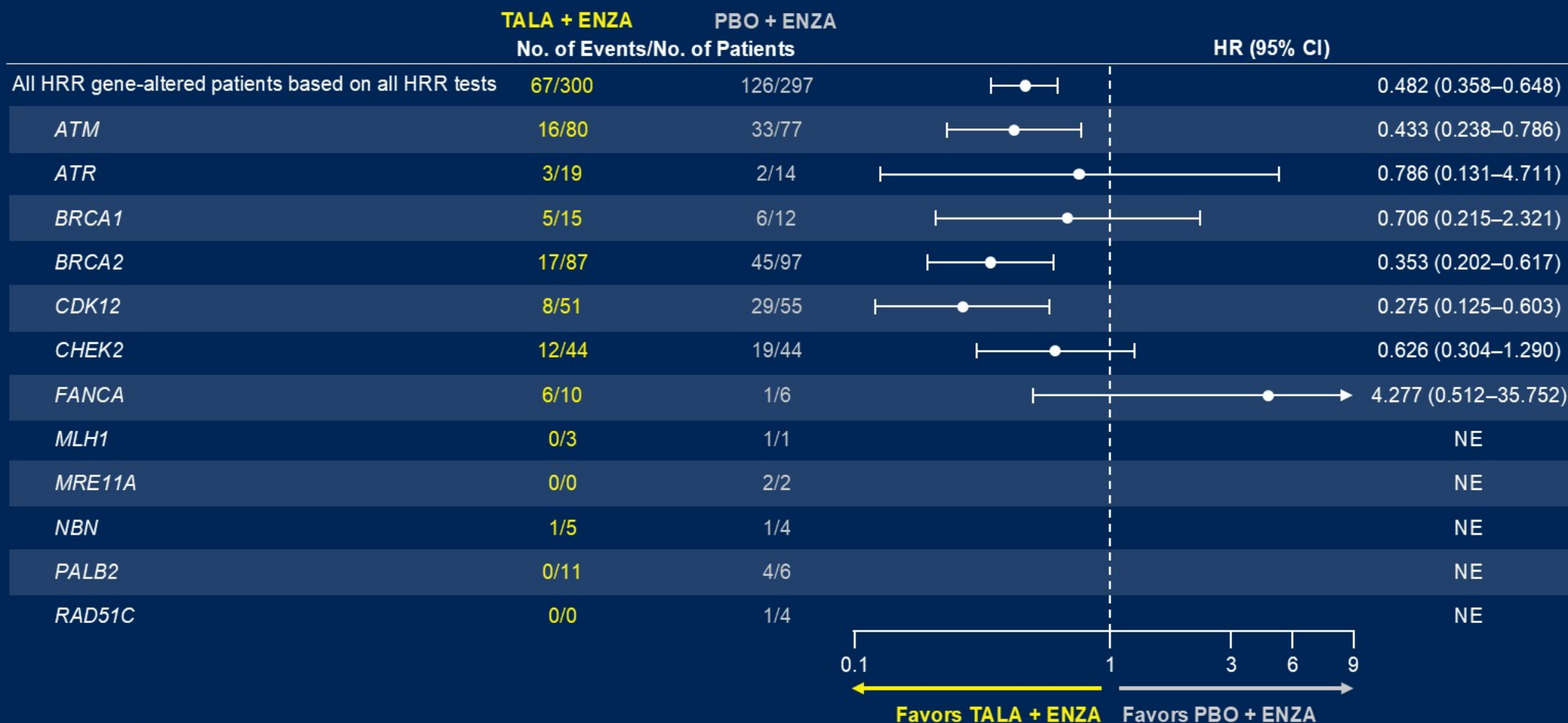
Data cutoff: February 18, 2026 (ITT population).

*By randomization stratification.

Unstratified HRs are based on a Cox proportional hazards model.

By Gene Analysis of rPFS

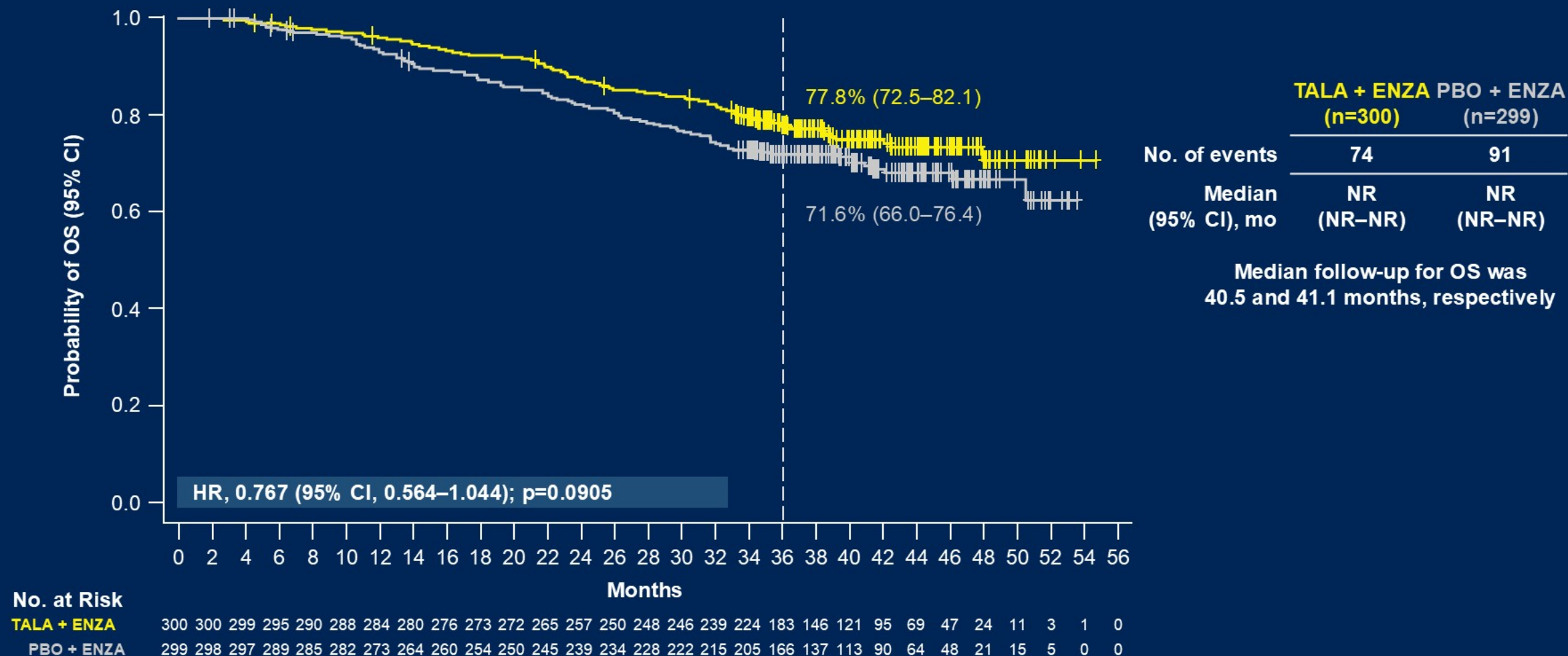
In post hoc analyses, rPFS generally favored TALA + ENZA across HRR gene subgroups



Data cutoff: February 18, 2026 (ITT population). Analyses included all available tumor and baseline ctDNA records. For non-*BRCA*m, those with co-occurring *BRCA1/2*m were excluded. For *BRCA1*m, those with co-occurring *BRCA2*m were excluded. Unstratified HRs are based on a Cox proportional hazards model, with treatment as the only covariate. ctDNA=circulating tumor DNA; NE=not evaluable.

Overall Survival (Interim Analysis)

Interim OS trend favors TALA + ENZA



Data cutoff: February 18, 2026. ITT Population.

Subsequent Systemic Antineoplastic Therapy

Docetaxel was the most common subsequent antineoplastic therapy received in both arms

	TALA + ENZA (n=300) n (%)	PBO + ENZA (n=299) n (%)
Any subsequent systemic anticancer treatment*	66	112
Docetaxel	30 (45)	65 (58)
Abiraterone	19 (29)	29 (26)
Olaparib	6 (9)	30 (27)
Enzalutamide	11 (17)	15 (13)
Cabazitaxel	4 (6)	19 (17)
Carboplatin	3 (5)	12 (11)
Apalutamide	3 (5)	4 (4)
Blinded therapy	0	6 (5)
Lutetium-177	2 (3)	4 (4)
Radium-233	2 (3)	4 (4)
Investigational drug	1 (2)	7 (6)
Etoposide	1 (2)	6 (5)

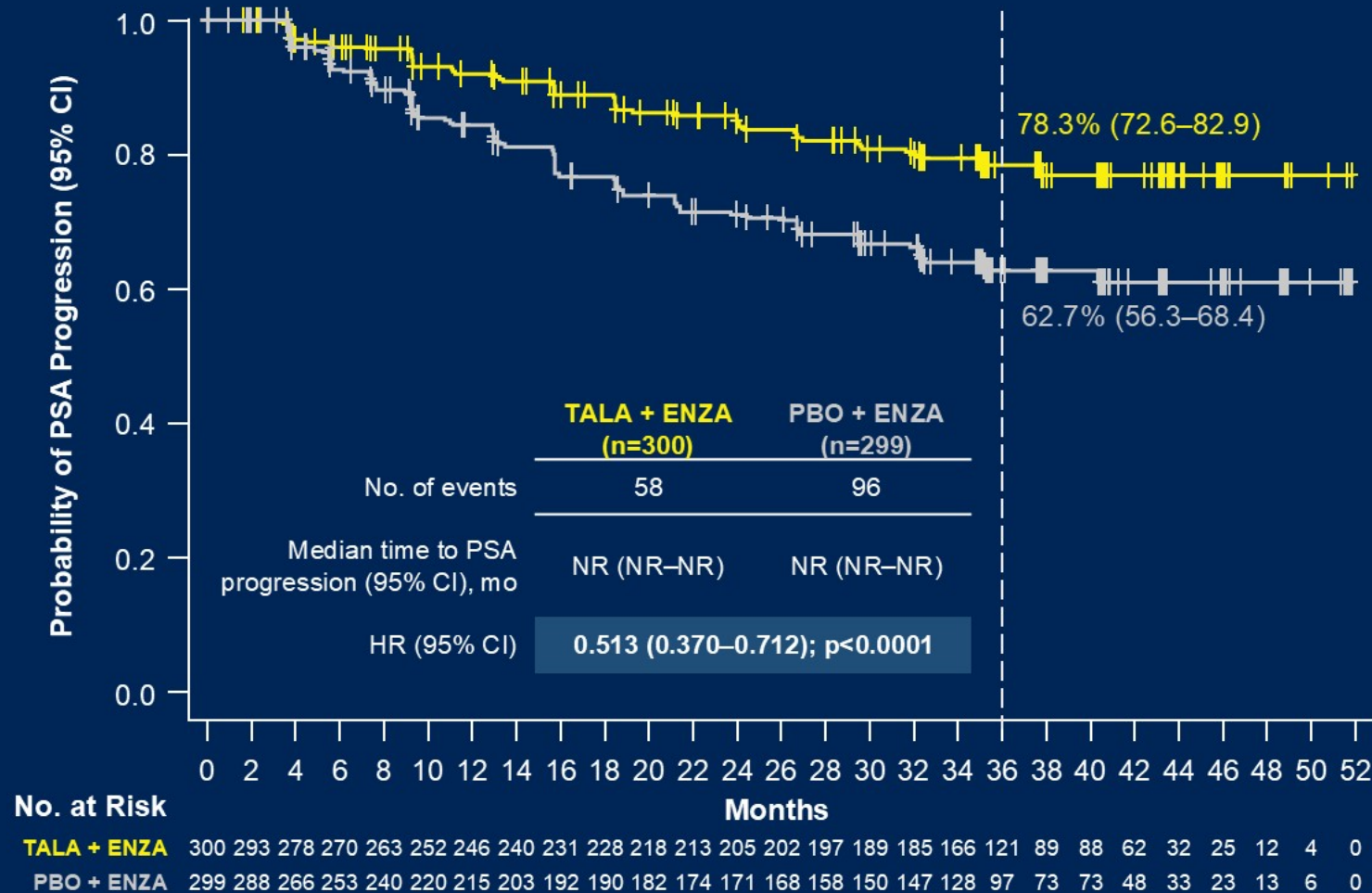
- 55 patients in the TALA arm and 113 patients in the control arm had progressive disease as their rPFS event

Data cutoff: February 18, 2026 (ITT population).

*Shown are subsequent treatments that were received by ≥1% of patients in the intention-to-treat population. Patients could receive multiple subsequent treatments. All patients had discontinued study treatment prior to starting the subsequent therapies, with the following exceptions: two patients in the placebo arm started subsequent therapies without discontinuing placebo, and one patient in each arm started subsequent therapies before discontinuing enzalutamide. Percentages are calculated using number of participants with any subsequent systemic anticancer treatment as the denominator.

Time to PSA Progression

Treatment with TALA + ENZA significantly improved the time to PSA progression



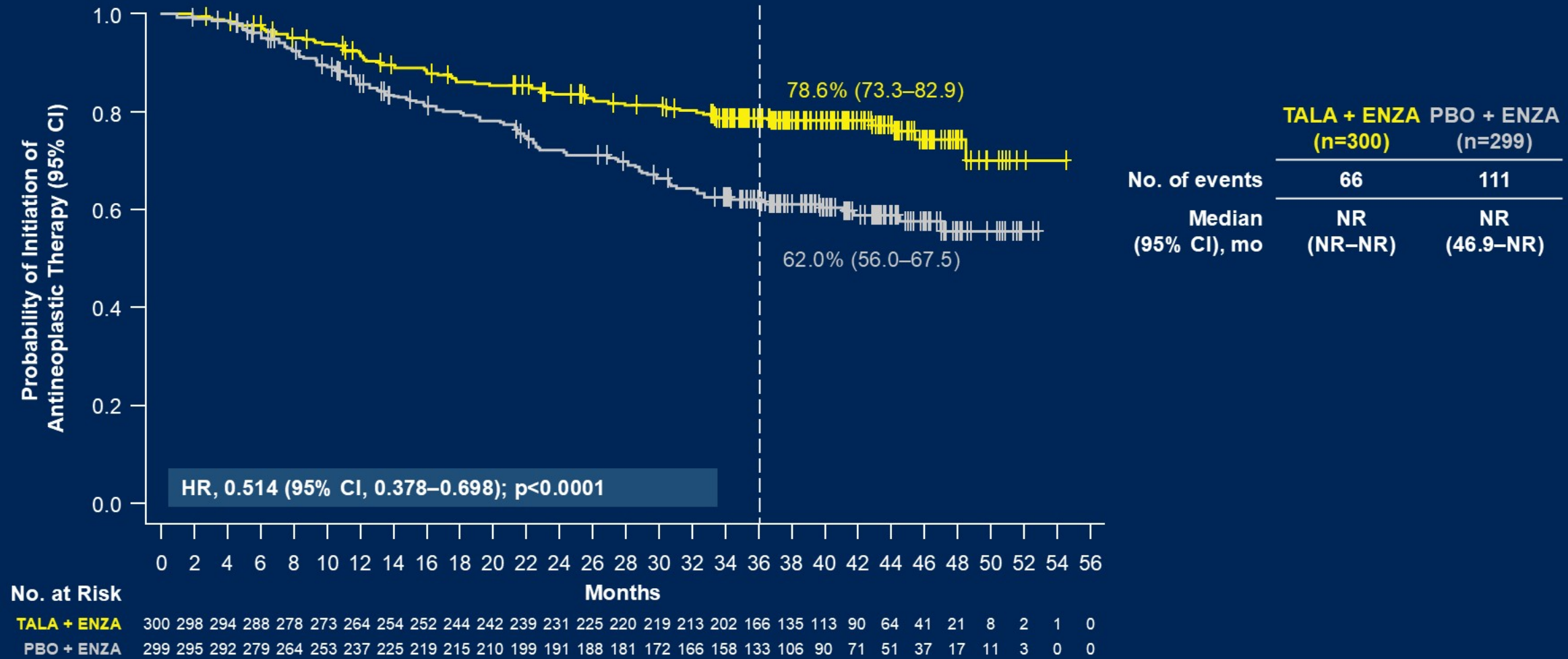
PSA Response Rate

	TALA + ENZA (n=300)	PBO + ENZA (n=299)
PSA response ≥50%, n/N*	268/296	257/297
PSA response rate (95% CI), %	90.5 (86.5–93.5)	86.5 (82.0–90.1)
	p=0.1194	

Data cutoff: February 18, 2026 (ITT population). *The PSA response rate was evaluated in patients with 1 baseline and ≥1 post-baseline PSA assessment. For patients with a decline in PSA, the PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, confirmed by a second consecutive value obtained ≥21 days later.

Time to Subsequent Systemic Antineoplastic Therapy

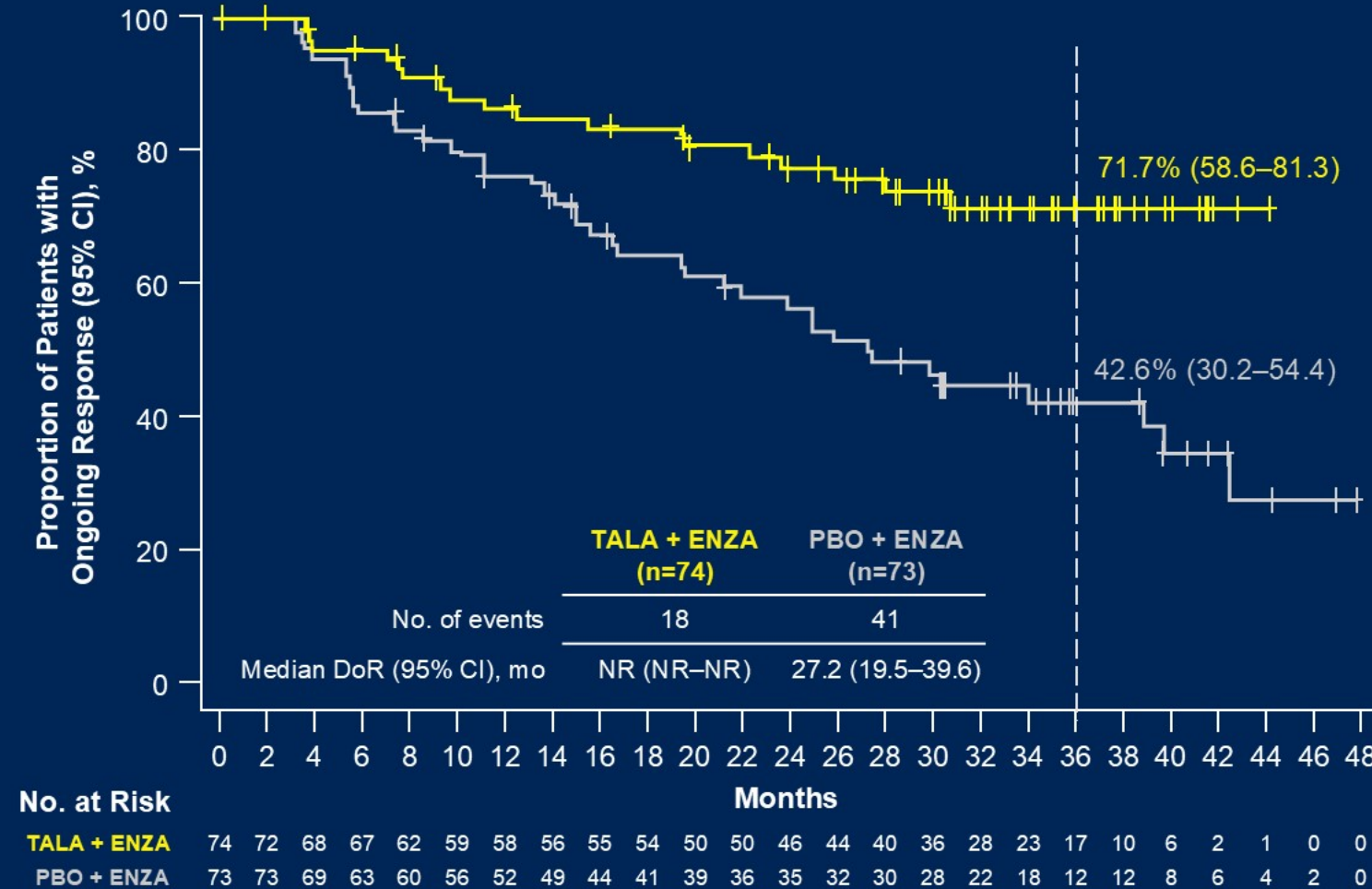
TALA + ENZA significantly improved the time to initiation of subsequent antineoplastic therapy



Data cutoff: February 18, 2026 (ITT population).

Tumor Response in Patients With Measurable Disease

The TALA + ENZA arm had a prolonged duration of response



Objective Response

	TALA + ENZA (n=99)	PBO + ENZA (n=109)
CR, n (%)	23 (23)	15 (14)
PR, n (%)	51 (52)	58 (53)
SD, n (%)	22 (22)	29 (27)
PD, n (%)	0	6 (6)
ORR, % (95% CI)	74.7 (64.8–82.7)	67.0 (57.2–75.5)
P=0.2925		

Data cutoff: February 18, 2026. ORR was assessed in the ITT population with measurable soft tissue disease at baseline. DoR was assessed in patients only with a confirmed complete or partial response. CR=complete response; DoR=duration of response; PD=progressive disease; PR=partial response; SD=stable disease.

Summary of TEAEs

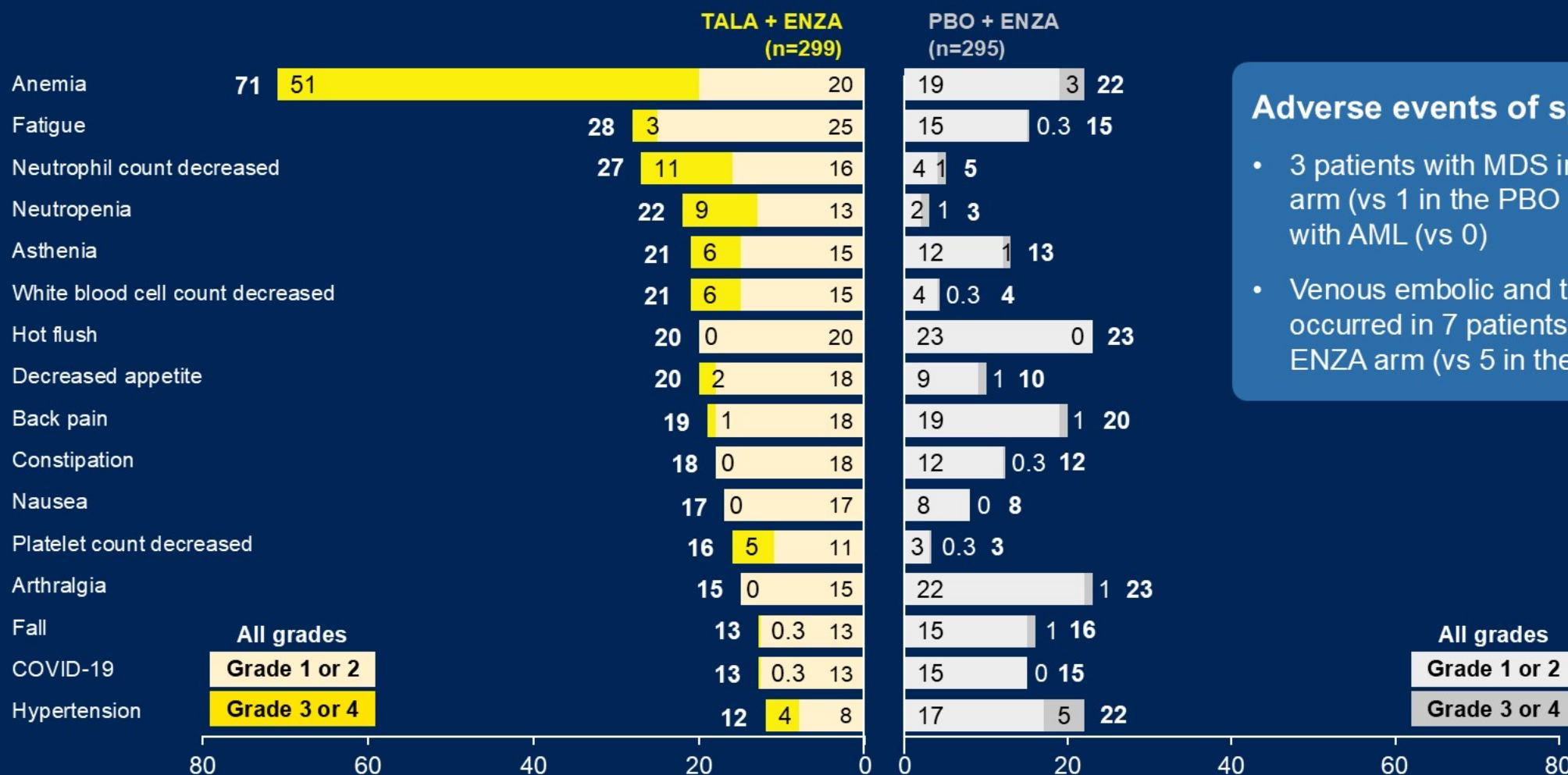
TEAE		TALA + ENZA (n=299)	PBO + ENZA (n=295)
Any TEAE		297 (99)	286 (97)
SAEs		126 (42)	93 (32)
Grade 3–4 TEAEs		235 (79)	121 (41)
Grade 5 TEAEs		8 (3)	9 (3)
Treatment-related*		2 (<1)	0
AE resulting in dose interruption of:	TALA or PBO†	207 (69)	90 (31)
	ENZA‡	140 (47)	85 (29)
AE resulting in dose reduction of:	TALA or PBO†	178 (60)	22 (7)
	ENZA‡	53 (18)	25 (8)
AE resulting in permanent drug discontinuation of:	TALA or PBO†	56 (19)	29 (10)
	ENZA‡	32 (11)	26 (9)
Median duration of treatment, mo (range)	TALA or PBO	35.0 (0.5–54.5)	32.9 (0.1–52.9)
	ENZA	35.9 (0.9–54.5)	32.9 (0.1–52.9)
Median relative dose intensity,% (range)	TALA or PBO	71.6 (23.0–142.9)	100 (52.6–142.9)
	ENZA	99.5 (33.9–100)	100 (35.7–101.6)

Data cutoff: February 18, 2026 (Safety population, i.e, patients treated with ≥1 dose of study treatment). Data are n (%) unless otherwise specified.

*Treatment-related deaths occurred in 2 patients (<1%; 1 death was due to pancytopenia and 1 was due to worsening of idiopathic pulmonary fibrosis) in the TALA + ENZA arm and 0 in the PBO + ENZA arm. †Dose interruption/dose reduction/permanent discontinuation of TALA or PBO regardless of dose modification of ENZA. ‡Dose interruption/dose reduction/permanent discontinuation of ENZA regardless of dose modification of TALA or PBO.

AE=adverse event; SAE=serious AE.

Most Common ($\geq 15\%$) All-Cause TEAEs



Adverse events of special interest

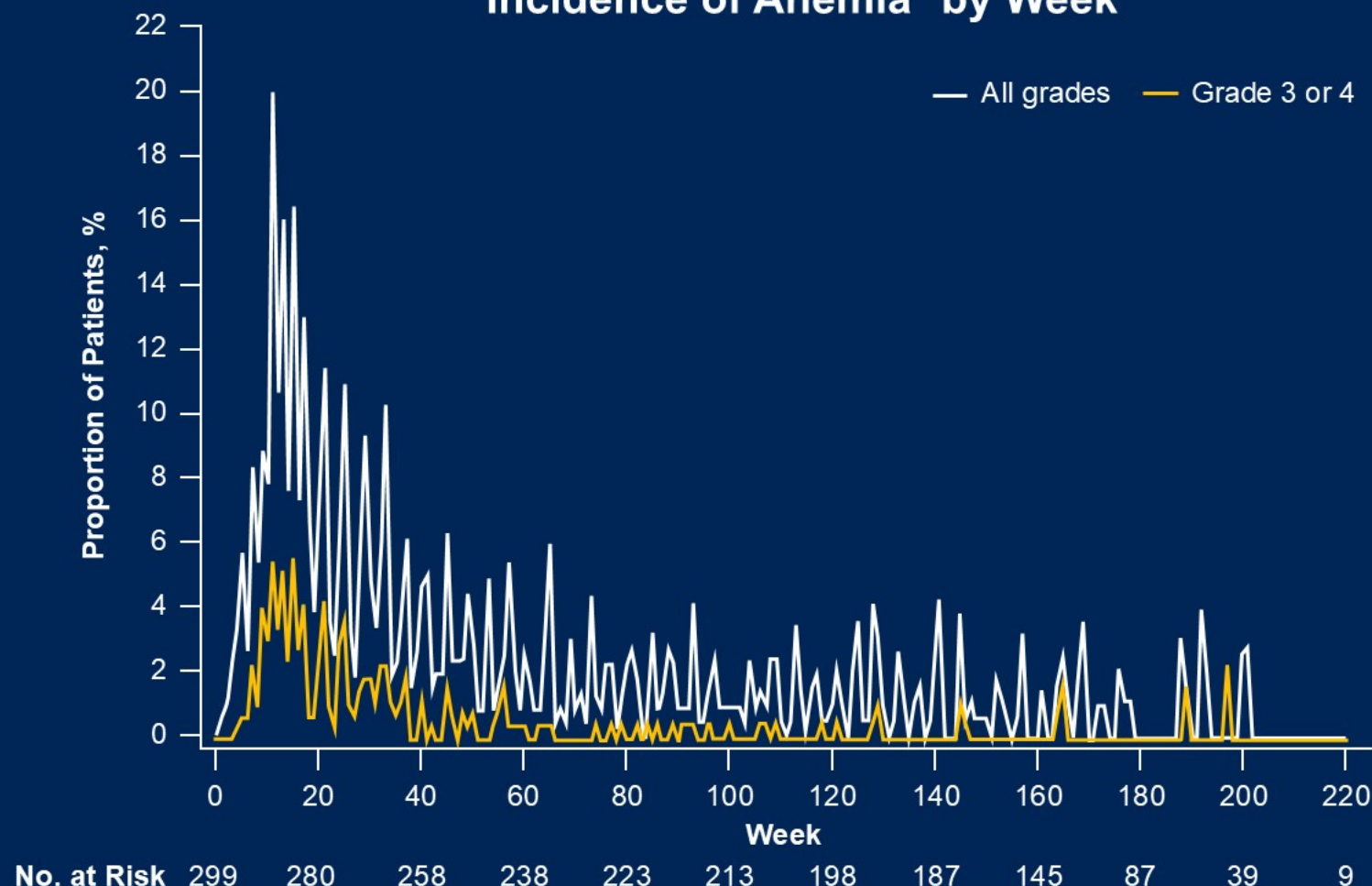
- 3 patients with MDS in the TALA + ENZA arm (vs 1 in the PBO + ENZA arm) and 2 with AML (vs 0)
- Venous embolic and thrombotic events occurred in 7 patients in the TALA + ENZA arm (vs 5 in the PBO + ENZA arm)

Data cutoff: February 18, 2026 (Safety population). Includes AEs occurring from the time of the first dose of study treatment through 28 days after the last dose of study treatment or before initiation of new systemic antineoplastic therapy, excluding ADT, whichever occurs first. TEAEs were graded according to NCI CTCAE v4.03.

AESI=AE of special interest; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; NCI CTCAE v4.03=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Anemia in the Talazoparib Arm

Incidence of Anemia* by Week



Data cutoff: February 18, 2026 (Safety population). Period from the first dose through 28 days after the last dose of study treatment or before initiation of new systemic antineoplastic therapy, excluding ADT, whichever comes first.

*Cluster term of ANEMIA that includes anemia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased.

RBC=red blood cell.

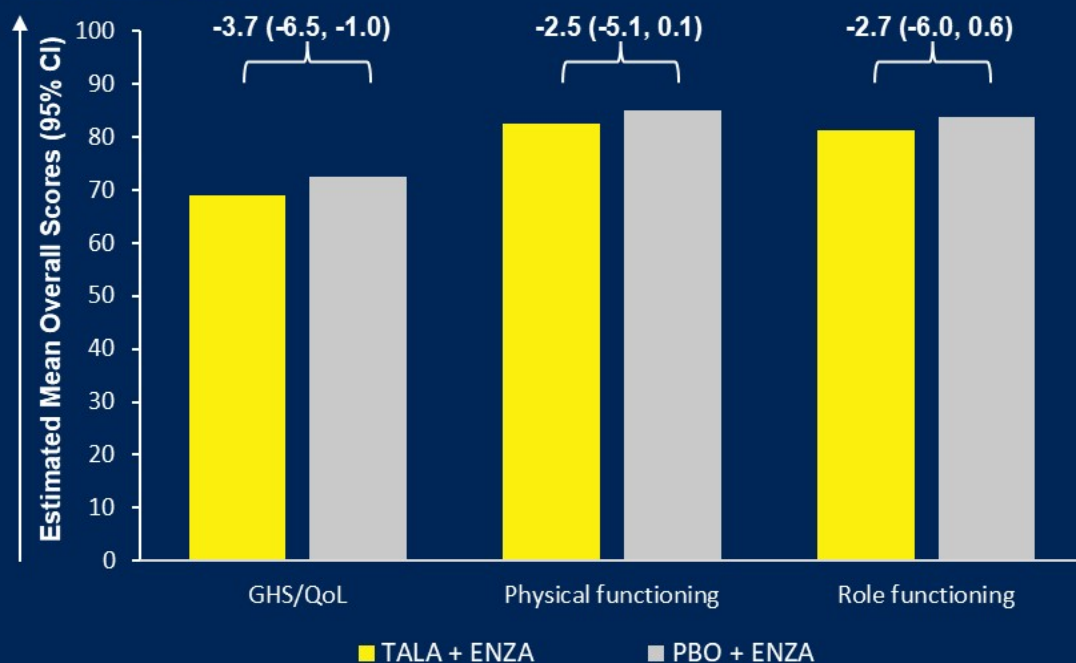
In the TALA arm:

- At baseline, 43% had Grade 1–2 anemia
- Median time to onset of Grade 3–4 anemia: 3.2 mo
- 40% received a packed RBC transfusion, with median of 2 transfusions over the entire duration of TALA treatment (among those transfused)
- The median duration of TALA treatment: 34.2 mo for patients with Grade 3–4 anemia and 35.9 mo for patients without Grade 3–4 anemia
- 14% had recurrent Grade 3–4 anemia after dose reduction of TALA
- 5% permanently discontinued TALA due to anemia

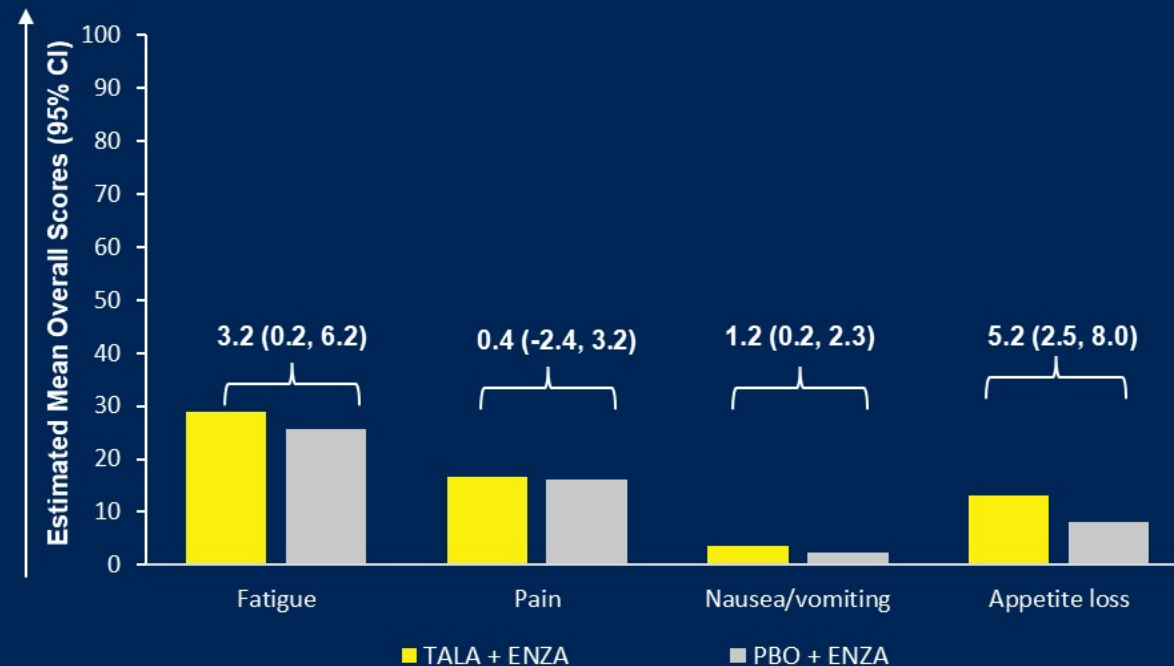
Patient-Reported Outcomes

No clinically meaningful differences in PROs were observed between the TALA + ENZA and PBO + ENZA arms (except appetite loss per EORTC QLQ-C30)

Better QoL/Function



More Symptom Burden



Data cutoff: February 18, 2026 (PRO-evaluable population with a baseline and ≥ 1 post-baseline PRO assessment before the end of the study). Comparison of least-squares means (95% CI) are shown above the bars. A minimum clinically meaningful difference was defined as a 5-point difference between arms.¹

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS=global health status; QoL=quality of life.

1. Gamper EM et al. *BMC Cancer*. 2021;21:1083.

Comparing Amplitude to Talapro 3

Docetaxel.

- **AMPLITUDE** enrolled patients receiving either doublet (ADT + ARPI) or triplet (plus docetaxel) therapy
- **Results support using niraparib/abiraterone after docetaxel; TALAPRO-3 excluded prior docetaxel, so it does not inform that sequence. [2][4]**

Gene panel.

- **TALAPRO-3's 12-gene panel notably included ATM (~28% of enrolled patients) and other genes (ATR, MLH1, MRE11A, NBN, RAD51C) absent from AMPLITUDE's 9-gene panel.**
- **TALAPRO-3 showed activity extending to ATM (HR 0.43) and CDK12, supporting sensitivity beyond BRCA,**
- **AMPLITUDE's non-BRCA benefit weaker and less certain (HR 0.81).**

Control-arm performance.

- **Placebo rPFS in TALAPRO-3 (45.8 mo with enzalutamide) AMPLITUDE (29.5 mo with abiraterone), despite both enrolling HRR-altered populations —**
- **Possible differences in populations, gene panels, ARPI backbone**

Pivotal questions

#1. Do we really need the combination of PARPI and ARPI?

#2. What constitutes appropriate selection for HRM?

#3. Does the PARPI matter?

#4 What is the best *management strategy* for these patients?

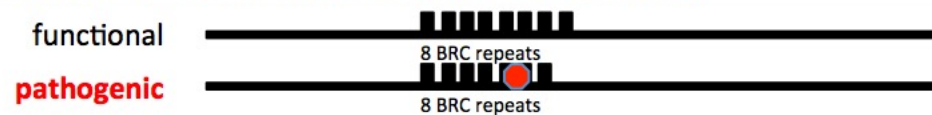
Could Intermittent Rx be better than continuous?

Reversion deletions in *BRCA2*

Patients with BRCA-mutated tumors develop resistance to PARP inhibitors thru reversion deletions:

Normal cells:

Germline: *BRCA2* heterozygous mutation



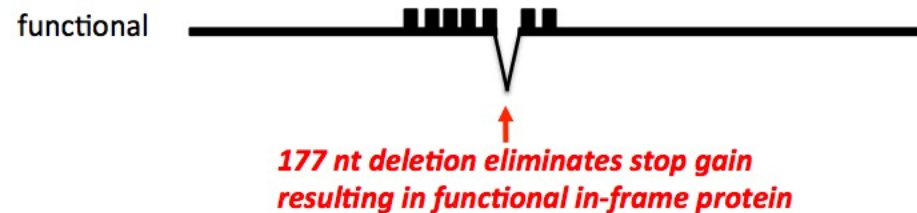
Metastasis (prior to PARPi):

BMN-naïve tumor: Loss of WT allele



Metastasis (after resistance to PARPi):

BMN-resistant tumor: 177bp deletion restores *BRCA2* function

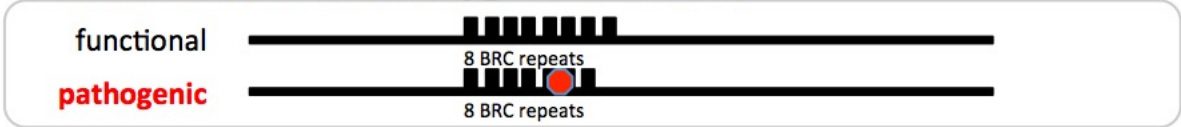


Reversion deletions in *BRCA2*

Patients with BRCA-mutated tumors develop resistance to PARP inhibitors thru reversion deletions:

Normal cells:

Germline: *BRCA2* heterozygous mutation



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BMN-naïve tumor: Loss of WT allele



Metastasis (after resistance to PARPi):

BMN-resistant tumor: 177bp deletion restores *BRCA2* function

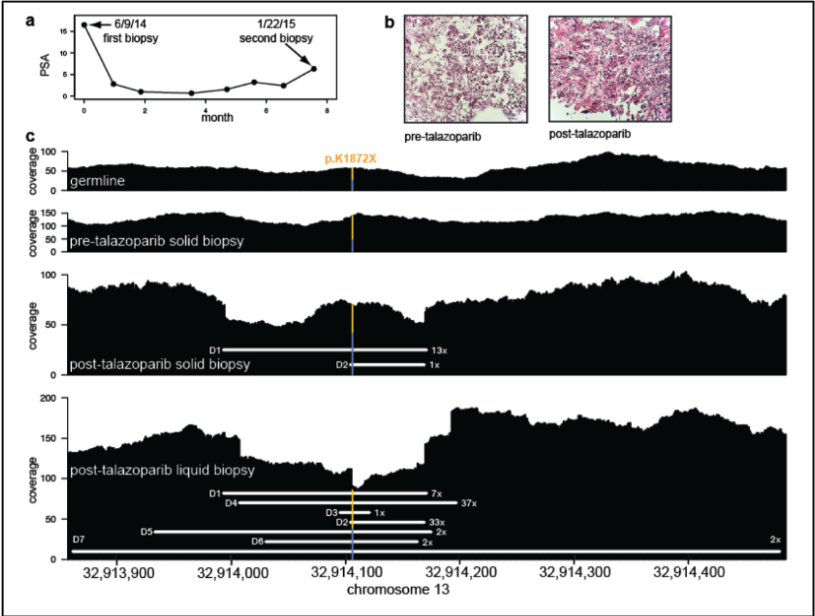
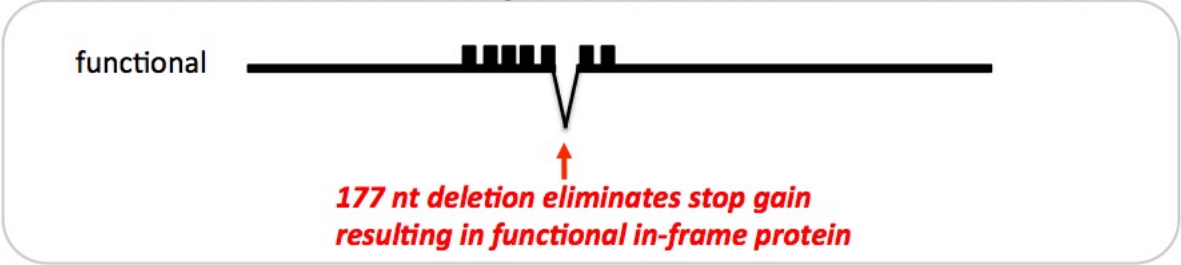


Figure 2: PARPi resistance by multiple large reversion deletions. 2a: Timeline of patient's serum PSA level before and during treatment with talazoparib. 2b: H&E stains of the solid tumor biopsy pre- and post-talazoparib were consistent with approximately 60% tumor purity. 2c: DNA read coverage of patient's germline, pre- and post-talazoparib solid tumor, and post-talazoparib liquid biopsy. Horizontal white lines indicate the span of reversion deletions, numbered D1 through D7, with deletion frequency indicated at the right side. The location and frequency of the p.K1872X/wild type allele is noted in gold/blue.

Reversion Mutations are now reported on cf-DNA clinical reports

74 yo patient with APMR

Known BRCA2 positive.

2022-2023 Rx with Olaparib

2024 Lu 177 → No response

2024 Docetaxel



Sample Information

Report Date: Jul 6th, 2026
Receipt Date: Jun 26th, 2026
Collection Date: Jun 24th, 2026
Specimen: Blood
Status: FINAL

Order Information

Physician Name: Charles Ryan
Account: Memorial Sloan Kettering Sidney Kimmel
Center for Prostate and Urologic Cancers
Address: 353 E 68th St., New York, NY, 10065,
United States
Ph: (646) 422-4468 | Fax: (646) 227-2417
Additional Recipient: N/A



Complete Tumor Response Map on page 3

BIOMARKERS ASSOCIATED WITH FDA-APPROVED TREATMENT OPTIONS

Clinical Trial Information
on page 5.



Approved in Indication



Approved in Other Indication



Lack Of Response

Biomarker(s)	Level	Associated FDA-Approved Therapies
AR Amplification	High (+++)	Abiraterone, Apalutamide, Enzalutamide, Niraparib+abiraterone, Olaparib+abiraterone, Talazoparib+enzalutamide
BRCA2 S1982Rfs*22	46.0%	Olaparib, Rucaparib
BRCA2 Deletion, exon 11	5.7%	Olaparib, Rucaparib
BRCA2 Biallelic Loss (Single Copy Deletion + Co-Occurring LOF Variant)	DETECTED	Olaparib, Rucaparib

Sample Summary

Tumor Fraction : 61.5% - Based on 2696 patient-specific epigenomic biomarkers.

Comments

Multiple alterations in BRCA2 were detected in close proximity to one another in this sample. In some cases, this may indicate BRCA2 reversion, which is associated with resistance to PARP inhibitors and platinum agents. Clinical correlation is suggested.

Microsatellite status: MSI-High NOT DETECTED. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue.
Reported by: VL

Clinical trials to clear Reversion mutations?

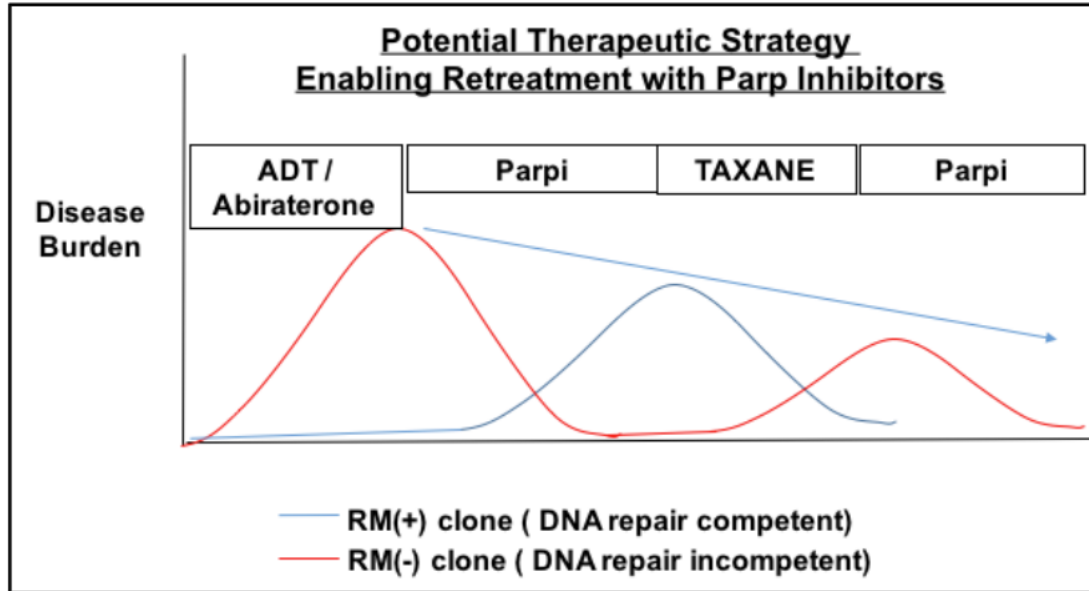


Figure 5: Model for the application of dose density chemotherapy in the setting of PARPi reversion mutations. Y-axis: disease burden; X-axis: time. In this model, ADT, PARPi, and taxane produce distinct selective pressures and effectively clear disease by virtue of their increased efficacy when applied to smaller tumor cell populations..

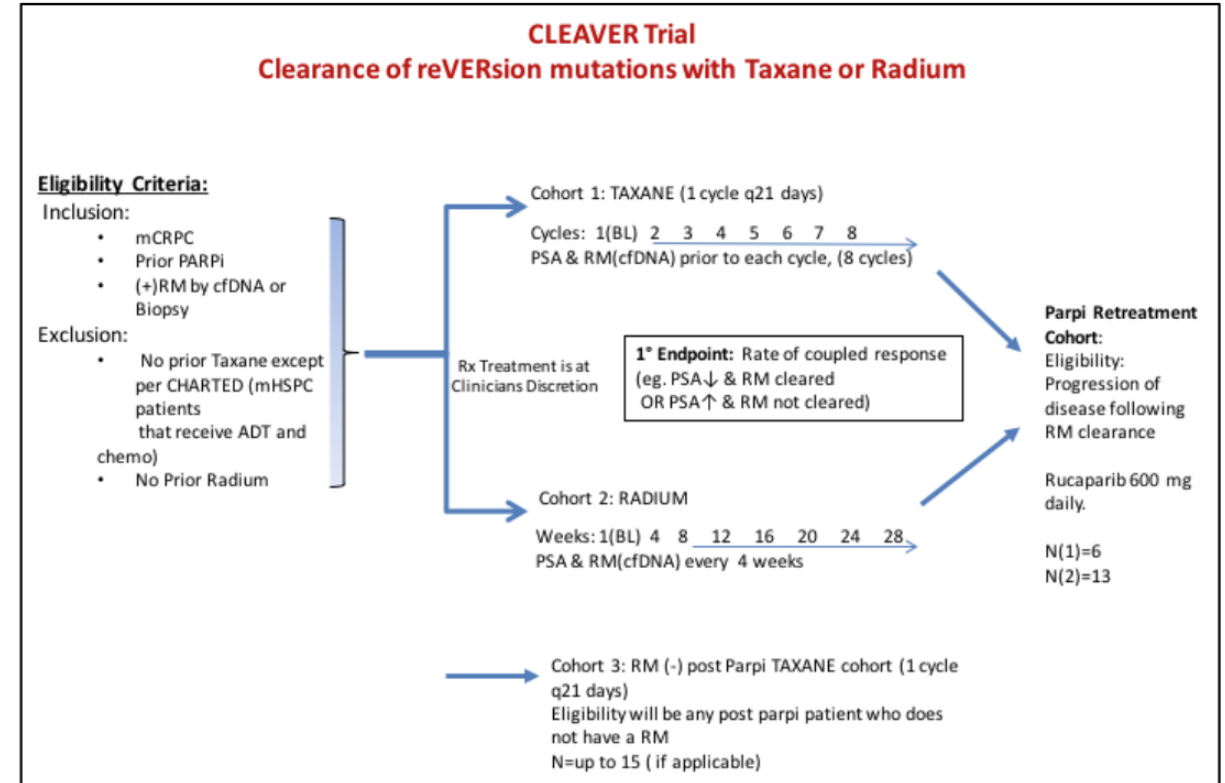
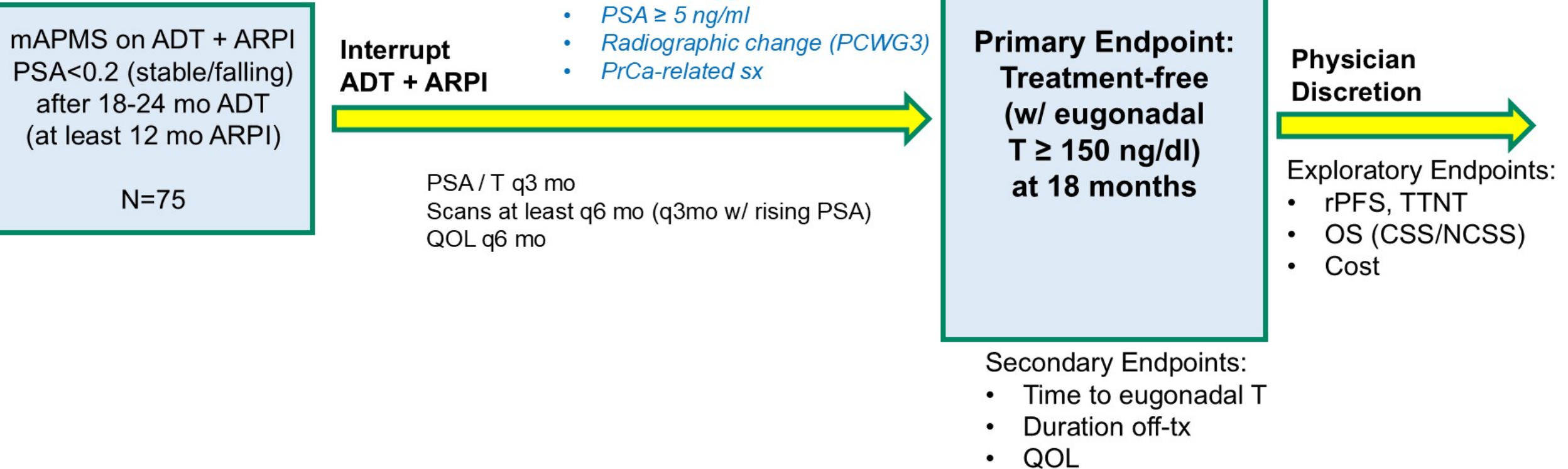


Figure 6: CLEAVER Trial Schema

For How Long?

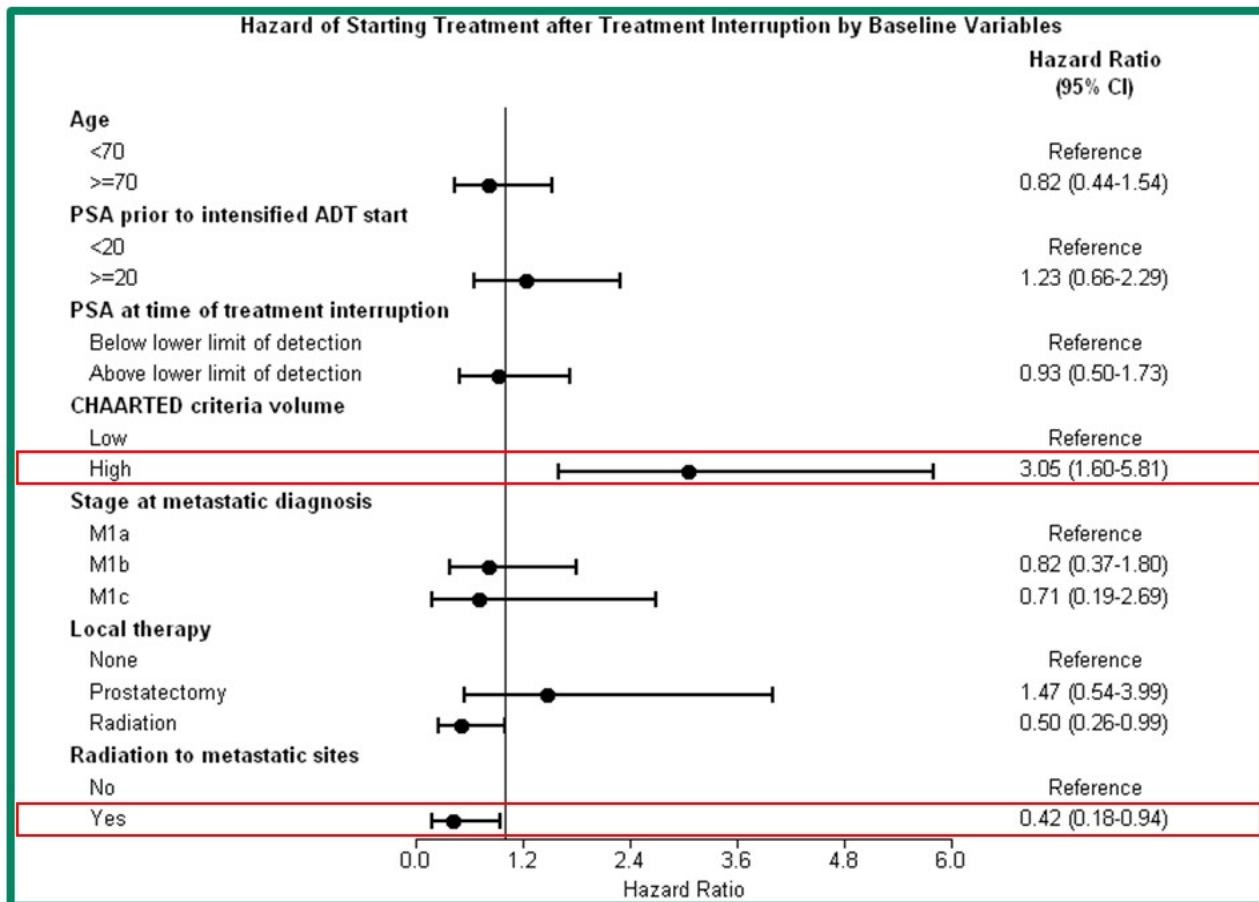
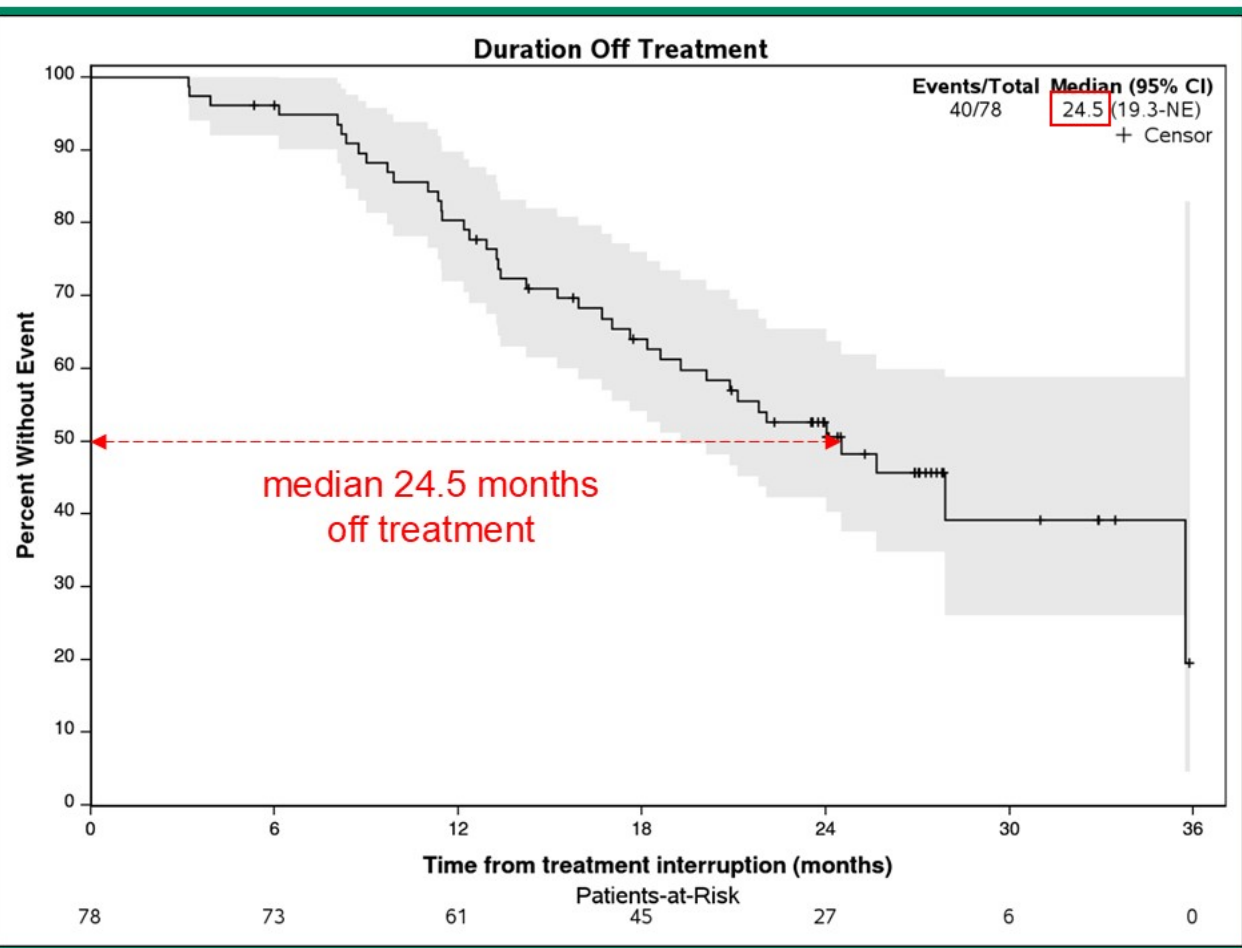
Study Design

The “A DREAM STUDY”



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

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

WHAT ABOUT MDS/LEUKEMIA?

REVIEW



Hematological toxicity of parp inhibitors in solid tumors: a systematic review and safety meta-analysis

Brigida Anna Maiorano¹ · Martina Catalano² · Mauro Francesco Pio Maiorano³ · Alessio Signori⁴ · Vera Loizzi³ · Gennaro Cormio³ · Michele Reni^{1,5} · Giandomenico Roviello² · Andrea Necchi^{1,5}

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Abstract

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) are effective agents in different tumor types. A typical class of adverse events (AEs) associated with these agents, often leading to treatment modifications and discontinuations of treatment, is hematological toxicity. In our systematic review and safety meta-analysis, we investigated the incidence and risk of all grades and $\geq$ grade (G) 3 hematological AEs, including anemia, neutropenia, thrombocytopenia, and acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) due to PARPis, used alone or in combination, in patients diagnosed with solid tumors. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. We systematically searched the PubMed, EMBASE, and Cochrane databases, the American Society of Clinical Oncology, and the European Society of Medical Oncology meeting abstracts for randomized clinical trials (RCTs) concerning the use of PARPis in patients with solid tumors. The search deadline was April 30, 2024. We calculated risk ratios (RRs) for all-grade and $\geq$ G3 AEs of PARPis versus non-PARPis. 31 phase II/III RCTs were included. Anemia was the most common all-grade (49.2%) and $\geq$ G3 AE (25.0%). The administration of PARPis significantly increased the risk of developing all grades of anemia (RR = 2.15, $p < 0.00001$), neutropenia (RR = 1.50, $p = 0.0002$), and thrombocytopenia (RR = 2.59, $p < 0.00001$) compared to non-PARPis. Similarly, a significant increase in the risk of $\geq$ G3 anemia (RR = 5.43, $p < 0.00001$), neutropenia (RR = 1.70, $p = 0.002$), and thrombocytopenia (RR = 5.42, $p < 0.00001$) was detected. PARPis did not increase the risk of AML/MDS ($p = 0.86$). PARPis increase the risk of hematologic toxicity compared to other treatments in solid tumors. Clinicians should be aware of this risk, especially given the expected increase in PARPis use in the next year in different tumor types.

Keywords PARP inhibitors · Hematological toxicity · Solid tumors · Anemia · Neutropenia · Thrombocytopenia · MCRPC · Ovarian cancer · Breast cancer · Prostate cancer

Outcomes	N ₂ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-PARPis	Risk difference with PARPis
Anemia	10155 (29 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 2.15 (1.68-2.76)	234 per 1.000	269 more per 1.000 (159 more to 412 more)
Neutropenia	8482 (25 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 1.50 (1.21-1.85)	243 per 1.000	121 more per 1.000 (51 more to 206 more)
Thrombocytopenia	8063 (23 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 2.59 (1.88-3.58)	133 per 1.000	211 more per 1.000 (117 more to 342 more)
$\geq$ G3 Anemia	10472 (29 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 5.43 (3.45-8.56)	54 per 1.000	237 more per 1.000 (131 more to 405 more)
$\geq$ G3 Neutropenia	8732 (24 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 1.58 (1.16-2.15)	134 per 1.000	77 more per 1.000 (21 more to 154 more)
$\geq$ G3 Thrombocytopenia	7752 (21 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 5.42 (2.83-10.39)	20 per 1.000	86 more per 1.000 (36 more to 183 more)
AML/MDS	4873 (12 RCTs)	$\oplus\oplus\oplus\oplus$ $\oplus$ High	RR 1.05 (0.60-1.85)	11 per 1.000	1 more per 1.000 (4 fewer to 9 more)

Fig. 5 Summary of Findings of the systematic review and meta-analysis. AML/MDS: acute myeloid leukemia/myelodysplastic syndrome; CI: confidence interval; RCT: randomized controlled trial; RR: relative risk; $\geq$ G3: equal to over grade 3

One additional leukemia per 1,000 patients treated.
But could this worsen with additional duration of therapy?

Data Gaps in mCSPC/APMR

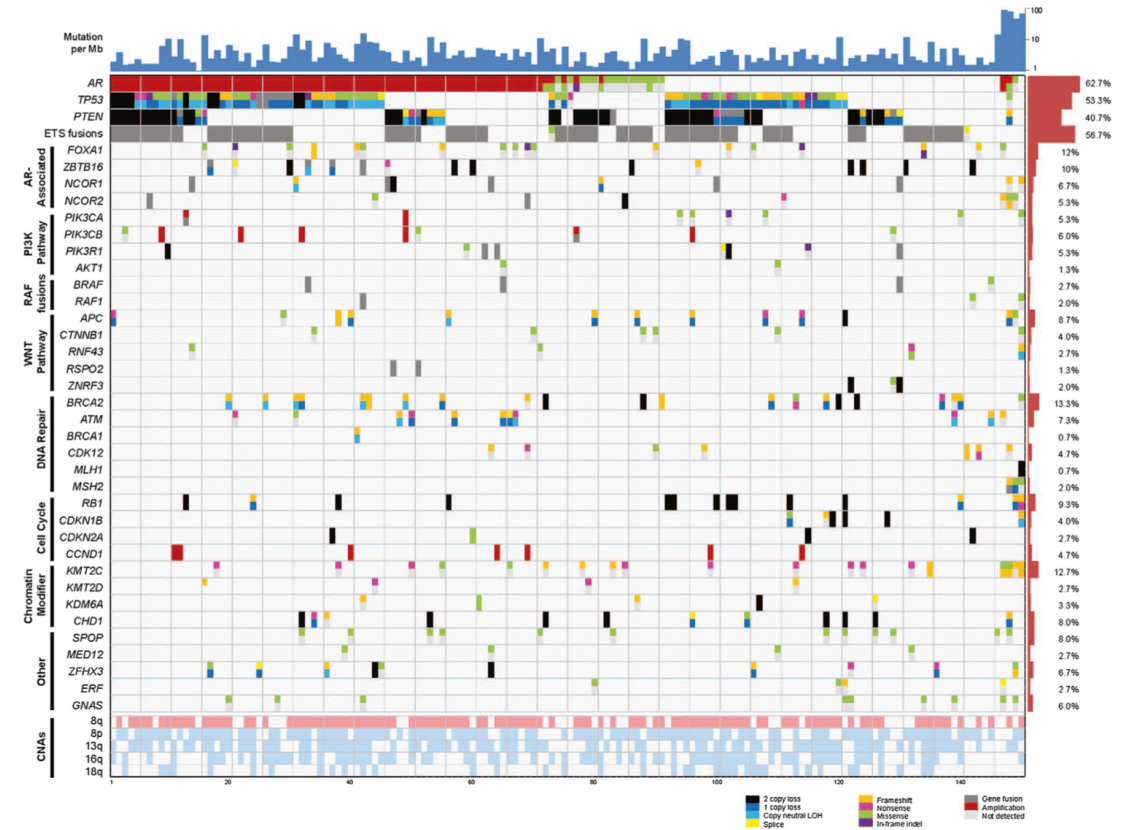
#1 Lu177 / PSMAAddition – Should we NOT offer Lu177 to HRRm Patients with APMS?

#2 Capivasertib - Does PTEN loss in the face of HRRm dominate the choice? Wide ranging data.

- In the GENIE dataset, homozygous PTEN deletion occurred in 12.4% of metastatic BRCA2-deficient prostate tumors (vs 1.5% in primary BRCA2-deficient tumors), neg w FDR correction. [5]
- TRITON2 cohort, patients with BRCA2 mutations had PTEN co-alterations in 29% (and TP53 in 42%). [1]
- BRCA2-mutated metastatic prostate cancers carry higher rates of PTEN (and TP53/RB1) alterations than ATM-mutated tumors, consistent with BRCA2's more aggressive, biallelic-HRD phenotype
- Direct BRCA2-PTEN co-occurrence is uncommon: among 147 patients BRCA2m in 10% and PTEN in 18%, but only 2 patients harbored both (Arduini ASCO Gu'26)

#3. In HRRm Population – what is the hierarchy of treatment choice?

e.g BRCA2 (m) plus High Volume---> **Docetaxel?**



¡Gràcias!

Título diapositiva

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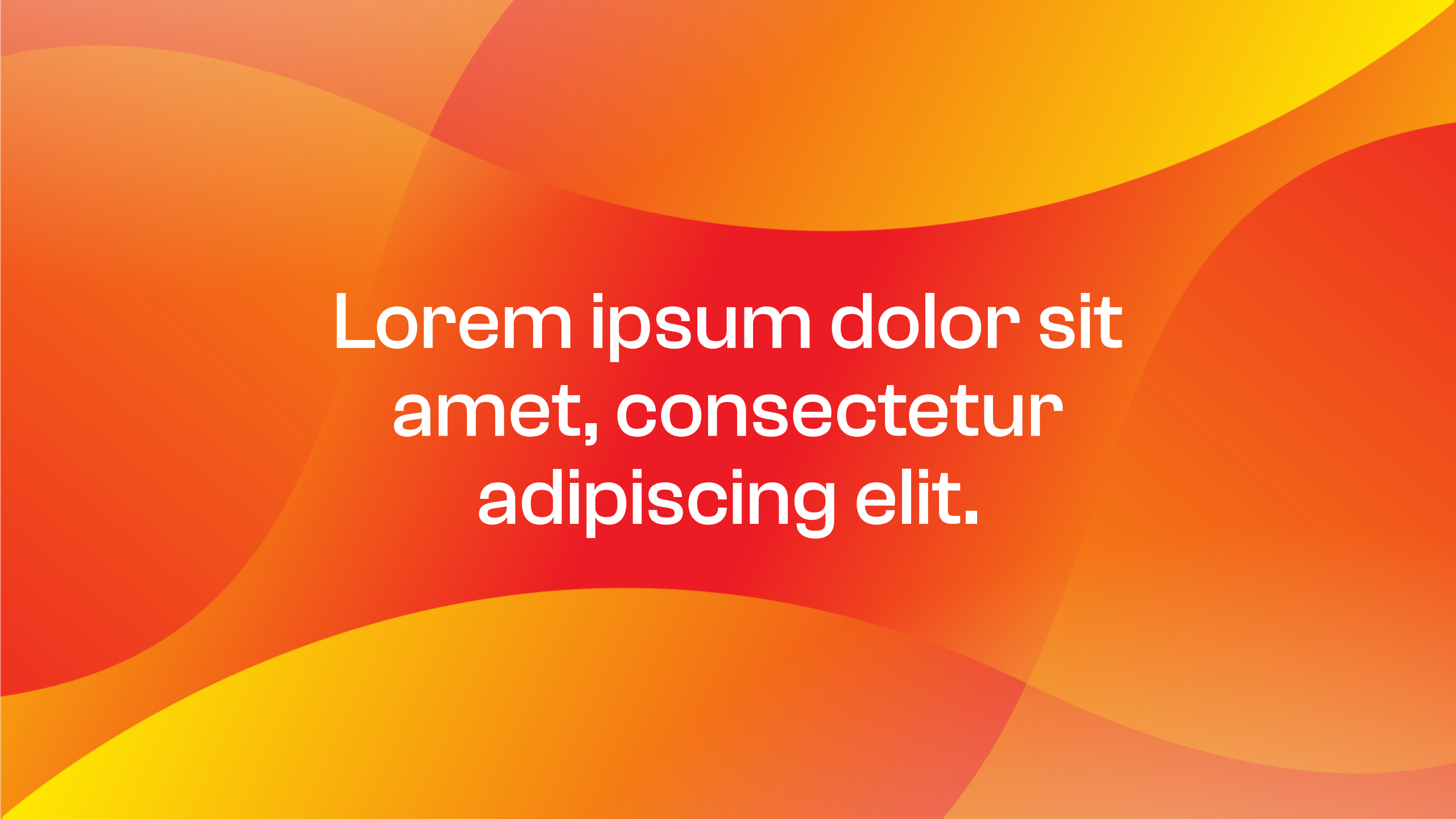
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