Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Making Sense of Many Options & Keeping the Patient at the Center: Newly Diagnosed Metastatic Prostate Cancer

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Disclosures

- Consultant for Abbvie, Astellas, AstraZeneca, Bayer, Dendreon, Janssen, Novartis & Pfizer. Grant/Research support from Abbvie, Amgen. AstraZeneca, Dendreon & Novartis.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Socioeconomic considerations and the lack of data on gender identity and orientation.*
- *Ways to overcome barriers with proactive identification to avoid differential treatment such as income, geography, and socioeconomic status.*

Scenario: patient with mHSPC at diagnosis

- 61 yo treated w/ testosterone by PCP, then noted to have elevated PSA to 60
  - Biopsy of prostate Gleason 4+5 adenocarcinoma
  - CT and bone scan with pelvic & RP LN, R iliac and R scapula mets
  - Germline testing negative (only VUS in MDM2 and CTC1)
- Started on **ADT + abiraterone 12/2016**
  - PSA dropped to undetectable by October
  - Received RT to prostate primary and pelvic LN
- Seen **in clinic 2/20/26 with undetectable PSA** and surveillance imaging with possible new bone met in sacral ala (2/2025 scans stable)

In this time he has been babysitting grandchildren, traveling… living a good life!

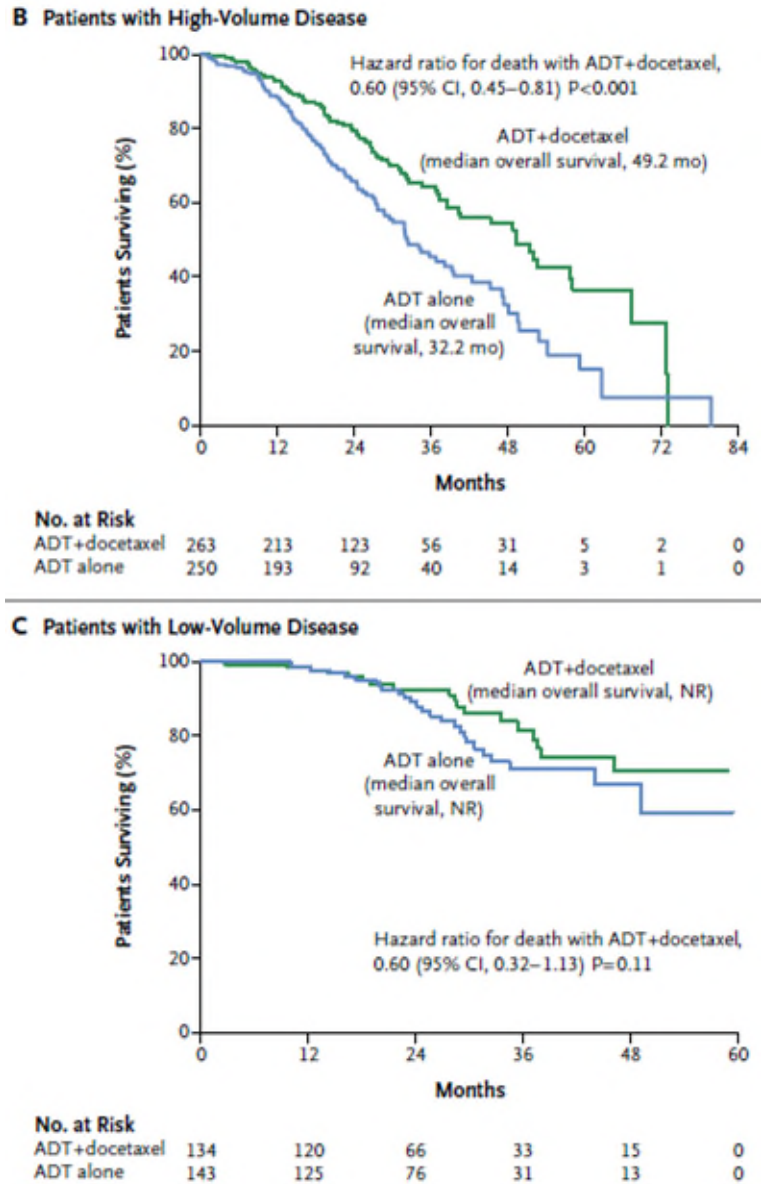
Summary of Doublets

Agent	Trial(s)	n	Primary endpoint	Considerations
Abiraterone	LATITUDE[1] STAMPEDE[2]	1199 957	OS HR 0.62 OS HR 0.62 (metastatic)	Cost effective Cardiovascular risks Prednisone 5 mg daily
Apalutamide	TITAN[3]	1052	OS HR 0.67	
Darolutamide	**ARANOTE[4]**	669	OS HR, 0.81 [95% CI, 0.59 to 1.12	Mostly ex-US; 10% black, 30% asian
Docetaxel	CHAARTED[5]	820	OS HR 0.6 (signif only for hi vol)	No longer NCCN rec as doublet b/c of triplet trials
Enzalutamide	ENZAMET[6]	1125	OS HR 0.67	**Control arm got bicalutamide** Some got docetaxel

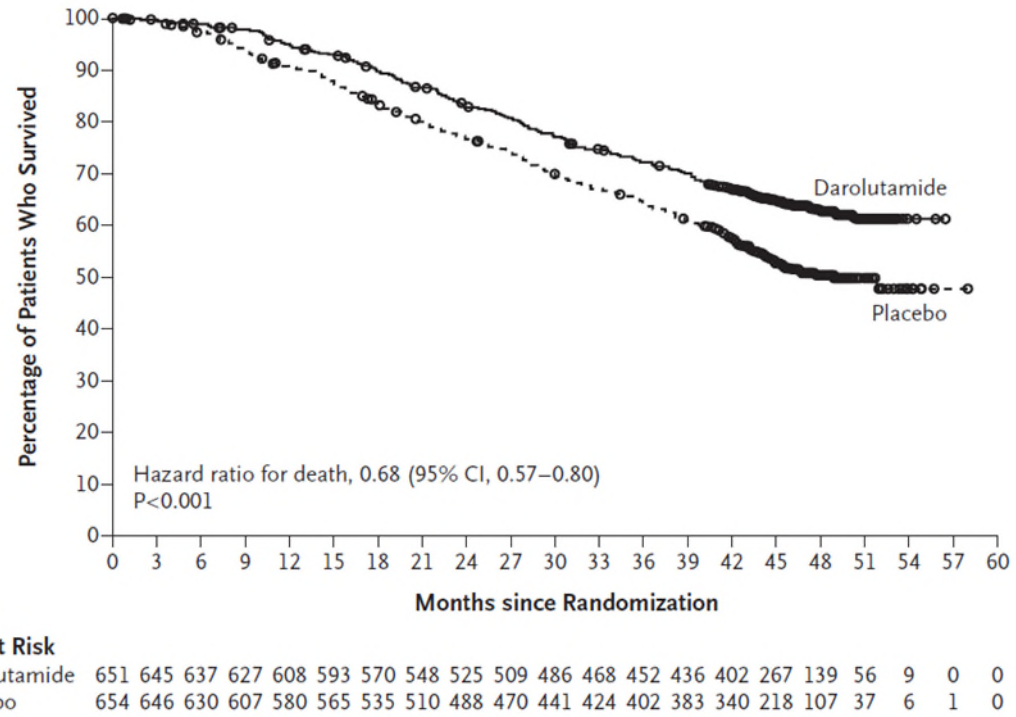
For low volume, radiation to prostate primary for synchronous improved rPFS independent of abiraterone (PEACE-1: Fizazi K et al, Lancet 2022)

1. Fizazi K et al. NEJM 2017
2. James ND et al. Lancet 2016; 387:1163
3. Chi KN et al. NEJM 2019; 381:13-24
4. **Saad F et al. JCO 2024; 42:4271**
5. Sweeney C et al, NEJM 2015; 373:737
6. Davis ID et al. NEJM 2019; 381:121-31

Early chemotherapy improved survival in metastatic APMN



CHAARTED (Sweeney CJ et al. NEJM 2015; 373:737-46)

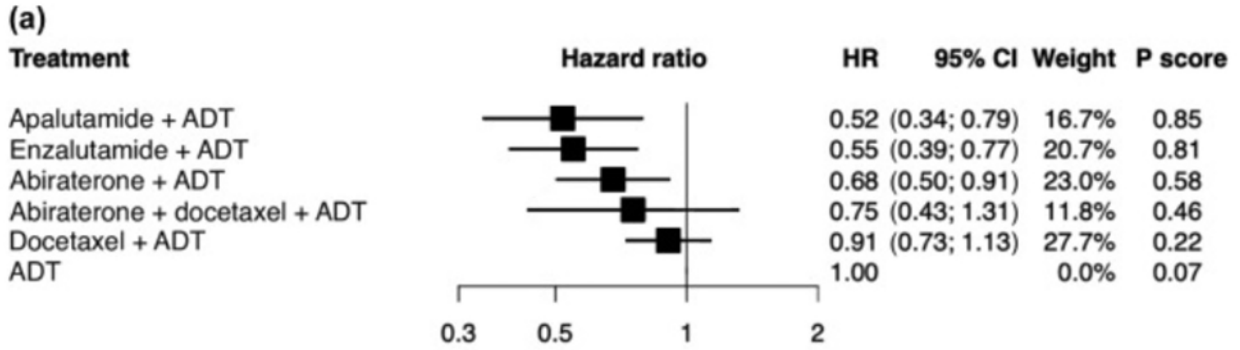


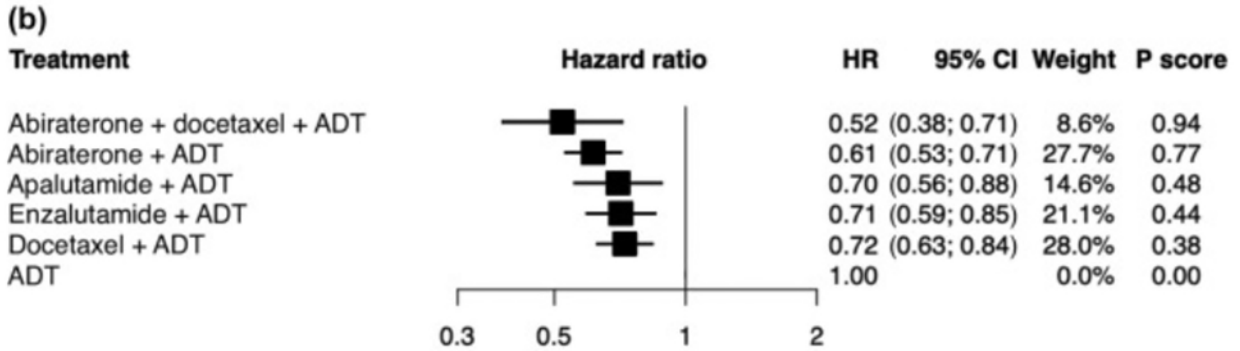
ARASENS shows you still need ARPI even wtth docetaxel

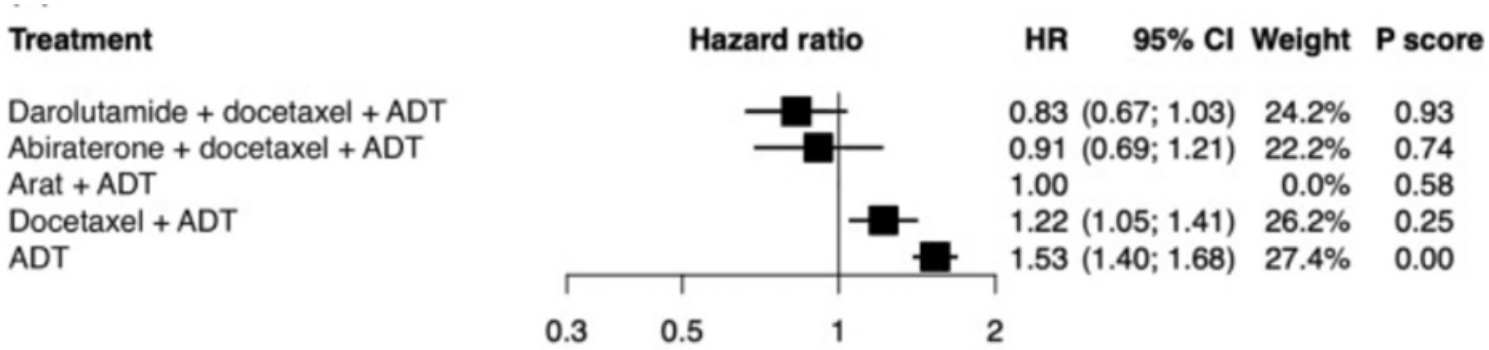
Smith MR et al NEJM 2022

Systematic meta-analysis finds triplets associated with greatest benefit

- Mandel P et al. Eur Urol Focus 2023; 9:96-105
- **Benefit primarily in high volume** (b) vs low volume (a)
- Overall HR for OS (bottom)







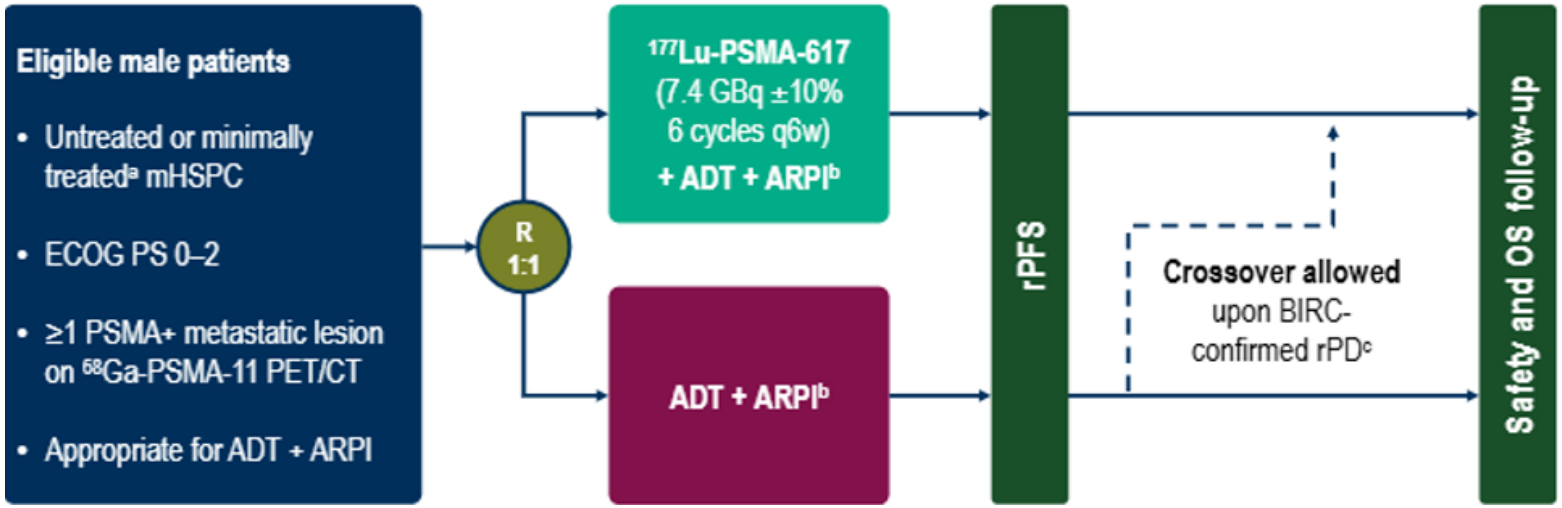
PSMAddition: ^{177}LU-PSMA-617 in mAPMN

PSMAFore found benefit for RLT prior to docetaxel

- But CCTG PR21 showed better OS with docetaxel head-to-head because of differential use of subsequent treatment

Concerns for met APMN

- Criteria for PSMA PET selection are not stringent
- Dosing is same as in **APMR** but PSMA+ lesions are disappearing on ADT + ARPI



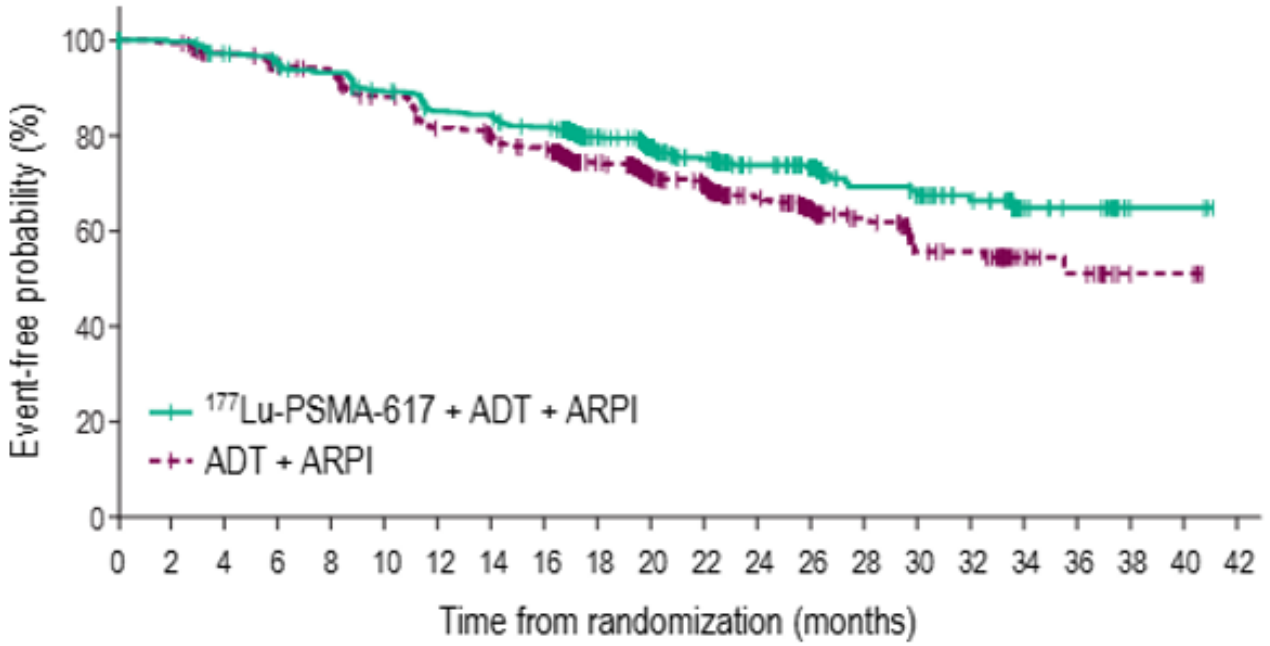
Presented at ESMO 2025 by S. Tagawa

FDA Approved July 2026

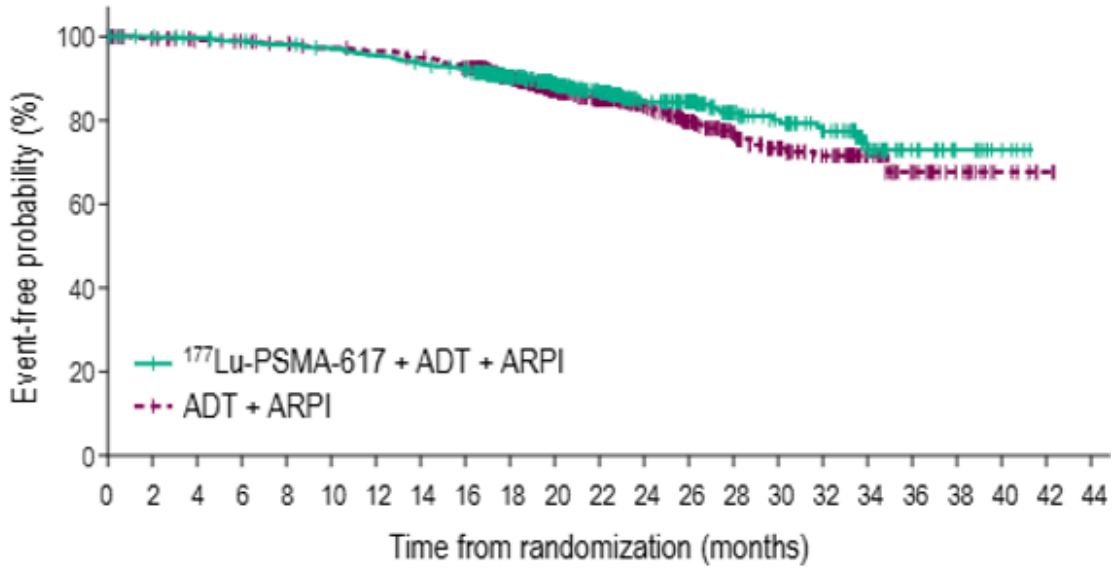
PSMAddtion: 177LU-PSMA-617 in mAPMN

FDA Approved July 2026

- rPFS HR 0.72 (0.6 – 0.9)
- ORR 85% vs 80%, CR 57% vs 42%



OS trending favorable



FDA Approved July 2026

PSMAddtion: 177LU-PSMA-617 in mAPMN: toxicity

Patients with on-treatment AE – n (%)[a]	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	555 (98.4)	286 (50.7)	546 (96.6)	243 (43.0)
Related to any study treatment	504 (89.4)	128 (22.7)	394 (69.7)	69 (12.2)
^{177}Lu-PSMA-617-related	441 (78.2)	78 (13.8)	–	–
ADT and/or ARPI-related	418 (74.1)	81 (14.4)	394 (69.7)	69 (12.2)
Serious	180 (31.9)	150 (26.6)	162 (28.7)	129 (22.8)
Related to any study treatment	39 (6.9)	31 (5.5)	14 (2.5)	12 (2.1)
^{177}Lu-PSMA-617-related	17 (3.0)	13 (2.3)	–	–
ADT and/or ARPI-related	27 (4.8)	22 (3.9)	14 (2.5)	12 (2.1)
Leading to death	15 (2.7)	15 (2.7)	14 (2.5)	14 (2.5)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16.1)	46 (8.2)	51 (9.0)	23 (4.1)
Leading to ^{177}Lu-PSMA -617...				
Discontinuation	45 (8.0)	28 (5.0)	–	–
Dose reduction	22 (3.9)	13 (2.3)	–	–
Dose delay	68 (12.1)	27 (4.8)	–	–

- More data needed about late toxicity (2nd malignancy, CKD)

Key considerations for triplet with docetaxel or 177Lu-PSMA-617

- Can we identify those who will do well with doublet?
  - Ex: SPOP mutation
- Consider overall comorbidity burden, life expectancy
  - Triplet does add toxicity, potential late/ long-term toxicity
  - First shot on goal = best shot, but preserve marrow, function for long-term
- More to learn about optimal patient selection and optimal treatment intensity/ duration particularly with 177Lu-PSMA-617

Relevance of NGS in prostate cancer: moving from APMR to APMN

Up to 20% may harbor BRCA or other HRR alteration

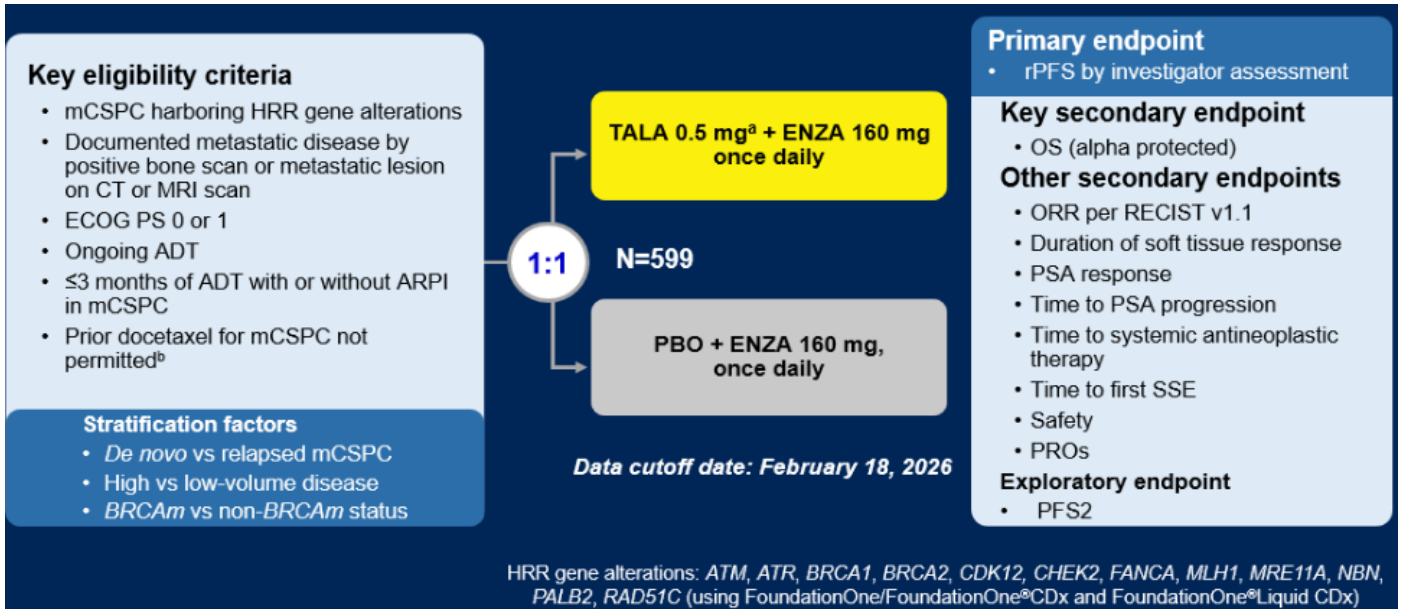
PARP inhibitor APMR (moving to met APMN)

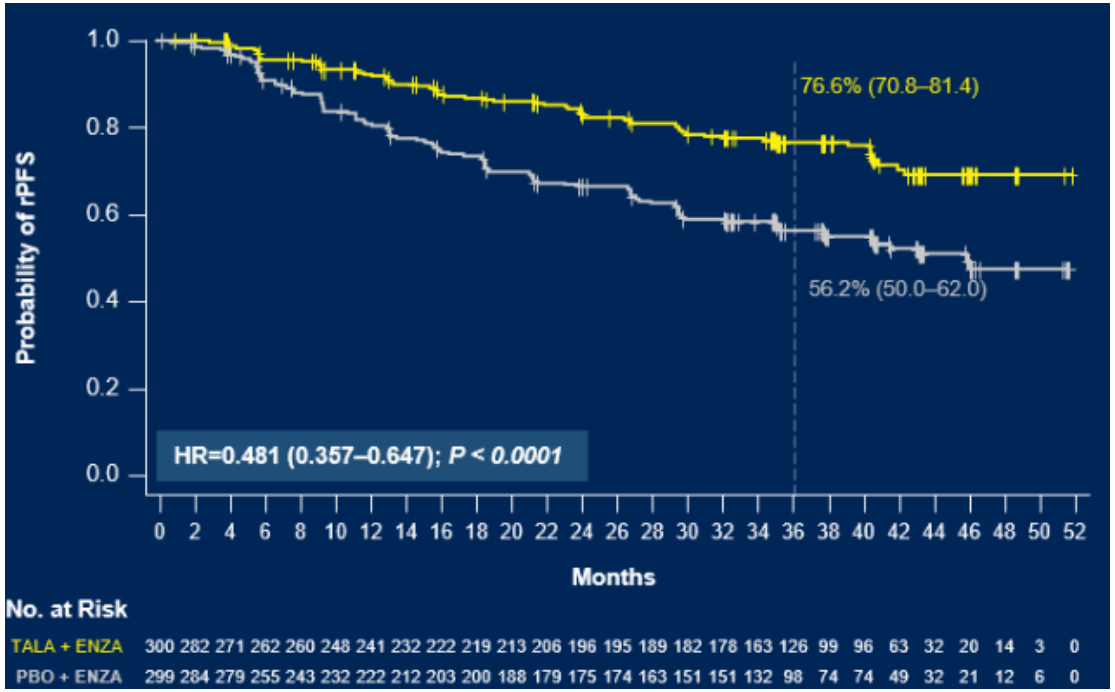
- Olaparib or rucaparib mono
- Tala + Enza or Nirap + Abi or Olap + Abi

PTEN loss (by IHC) identifies patients who may benefit from capivasertib

Future roles possibly for AVPC (2/3 RB1, PTEN, TP53)

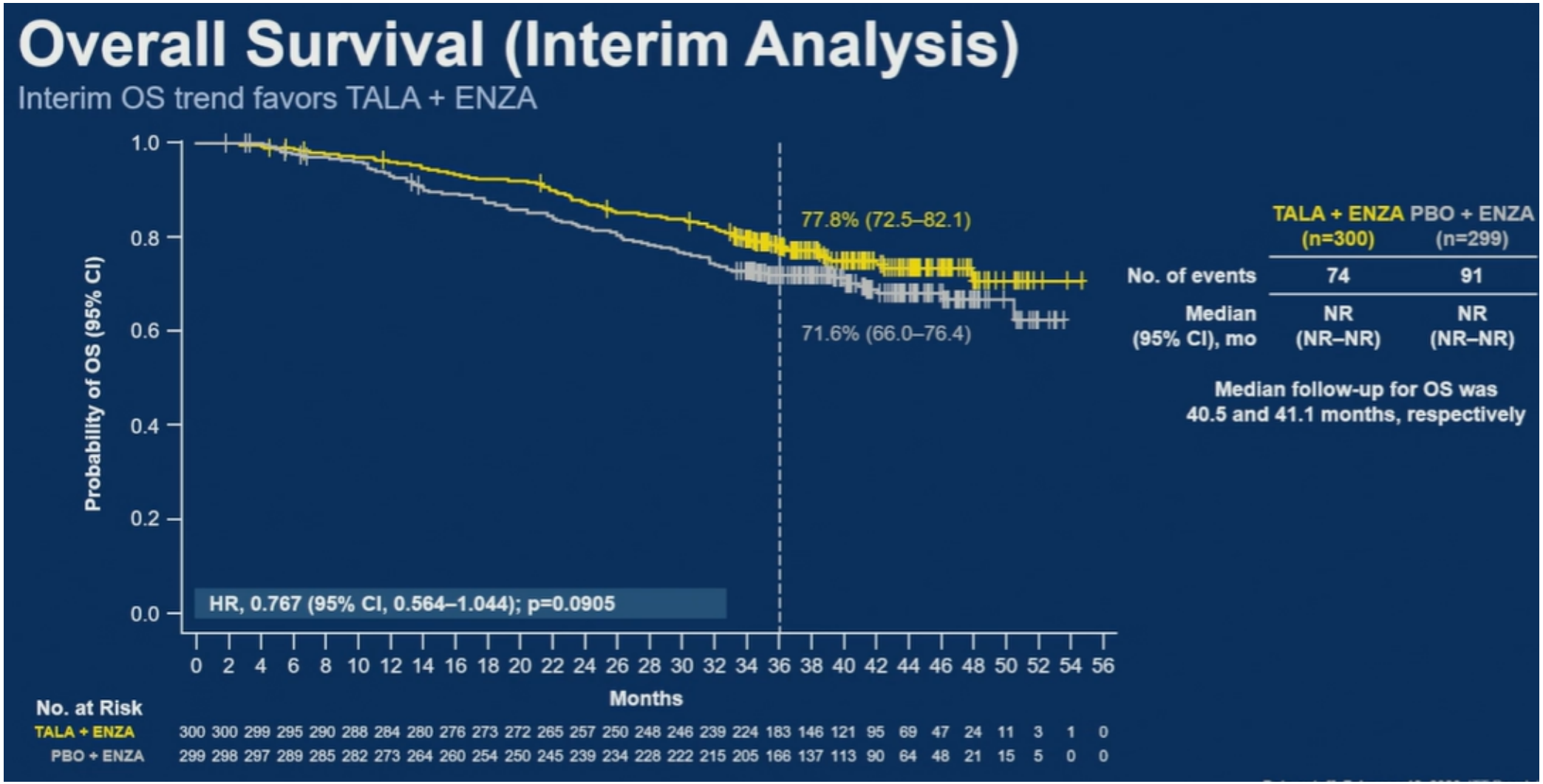
TALAPRO-3





- 35% BRCA 1 or 2
- 28% ATM, 19% CDK12, 15% CHEK2
- **rPFS 0.37 in BRCA subset**

TALAPRO-3: PARPi in pts w/ met APMN *and* HRR alteration



TALAPRO-3: Side effects

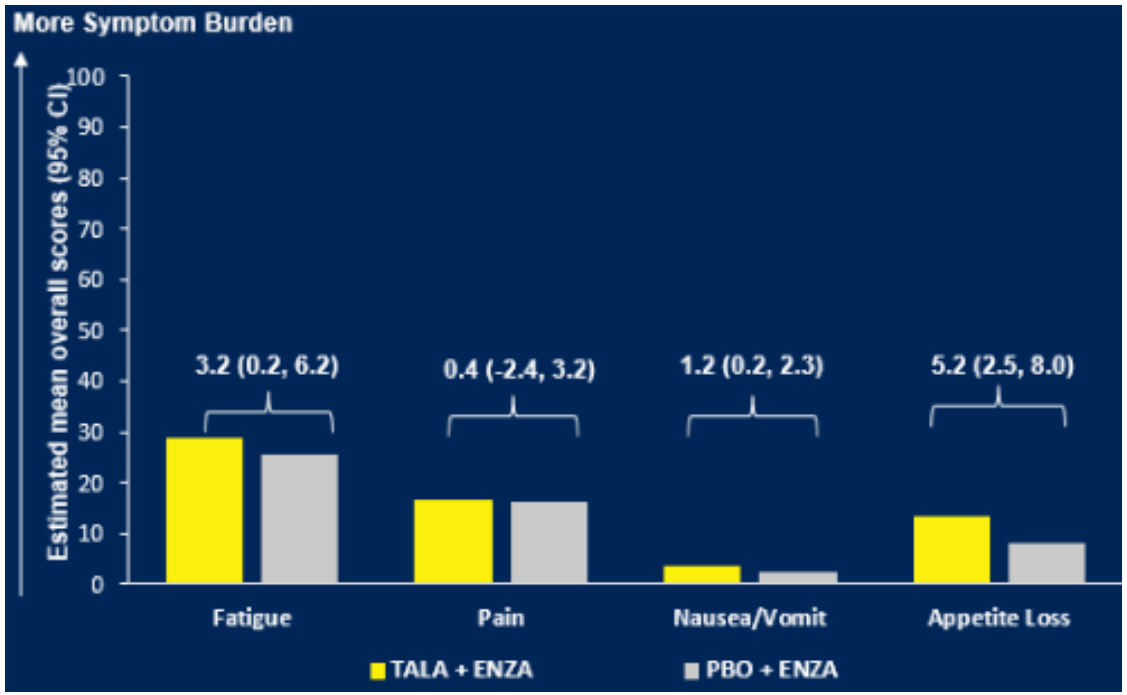
PARPi requires more management of AE (including 40% blood transfusion and 60% dose reduction)

19% discontinued due to AE

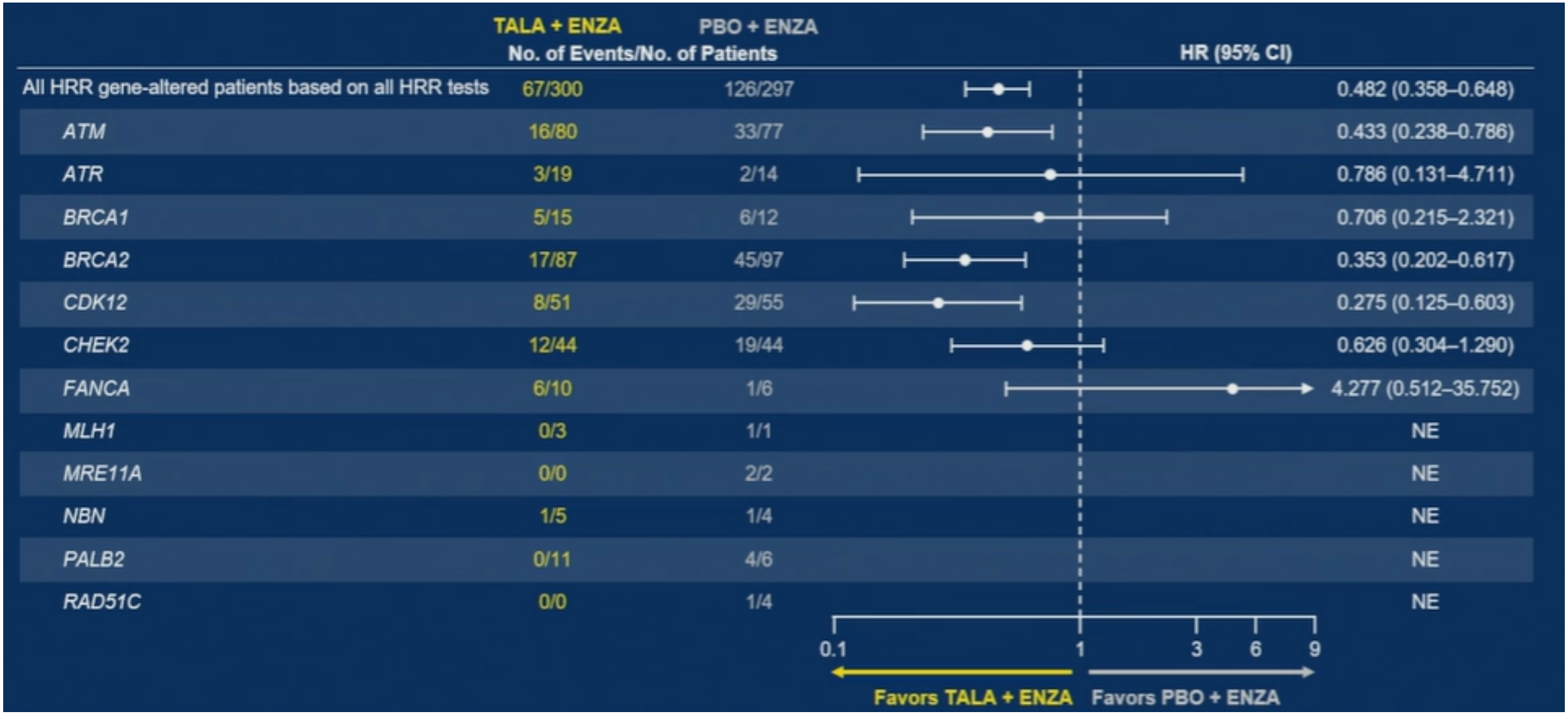
QOL similar, with more anorexia

MDS (3), AML (1) – on TALA (may be predisposing factors)

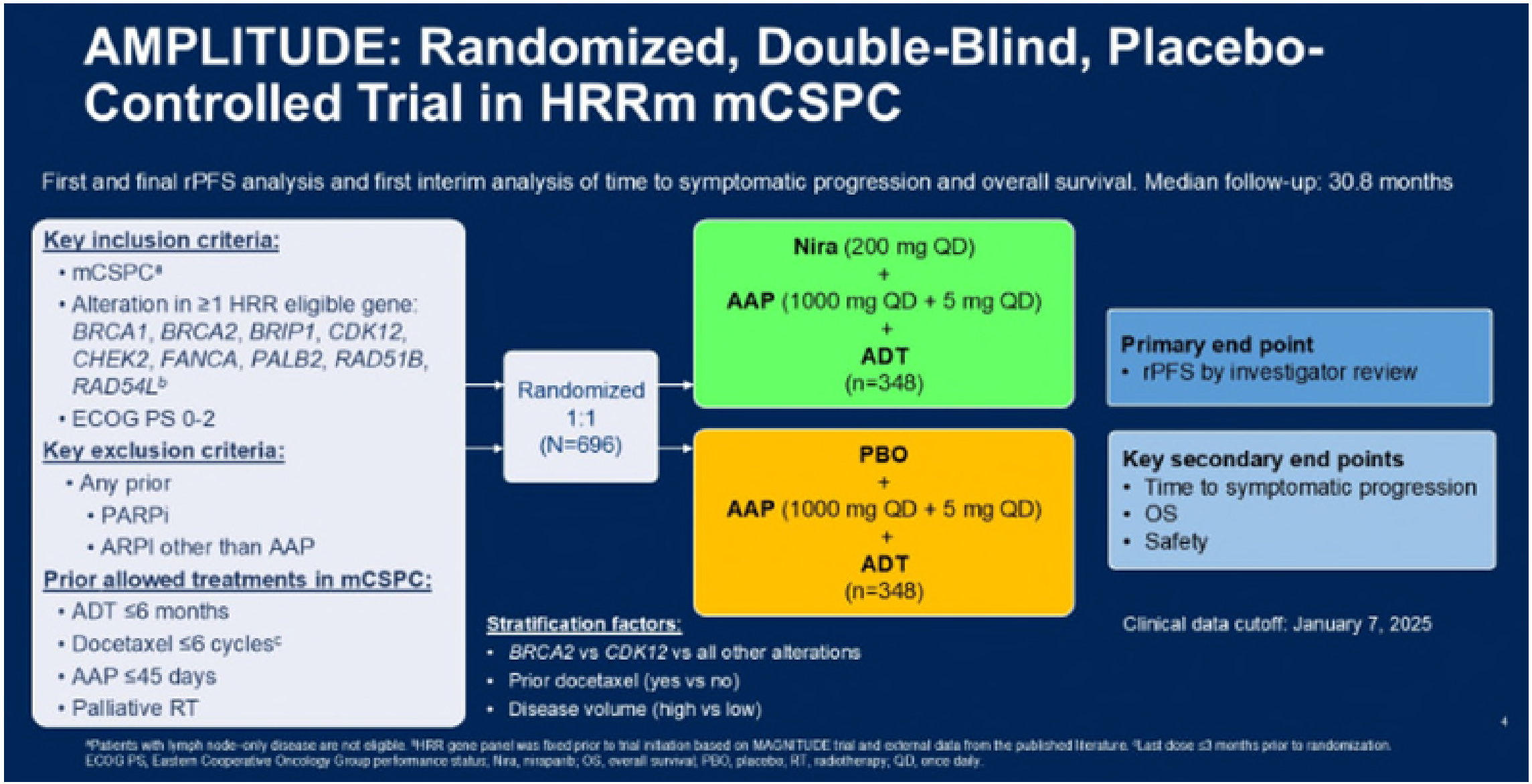
TEAEs, n (%)	TALA + ENZA (N=299)	PBO + ENZA (N=295)
Any TEAE	297 (99)	286 (97)
Treatment-related	277 (93)	213 (72)
SAEs	126 (42)	93 (32)
Treatment-related	66 (22)	18 (6)
Grade 3–5 TEAEs[a]	243 (81)	130 (44)
Treatment-related[b]	216 (72)	42 (14)
AE resulting in dose interruption of:		
TALA or PBO[c]	207 (69)	90 (31)
ENZA[d]	140 (47)	87 (29)
AE resulting in dose reduction of:		
TALA or PBO[c]	178 (60)	22 (7)
ENZA[d]	53 (18)	25 (8)



TALAPRO-3: outcomes in non-BRCA HRR



AMPLITUDE: study design

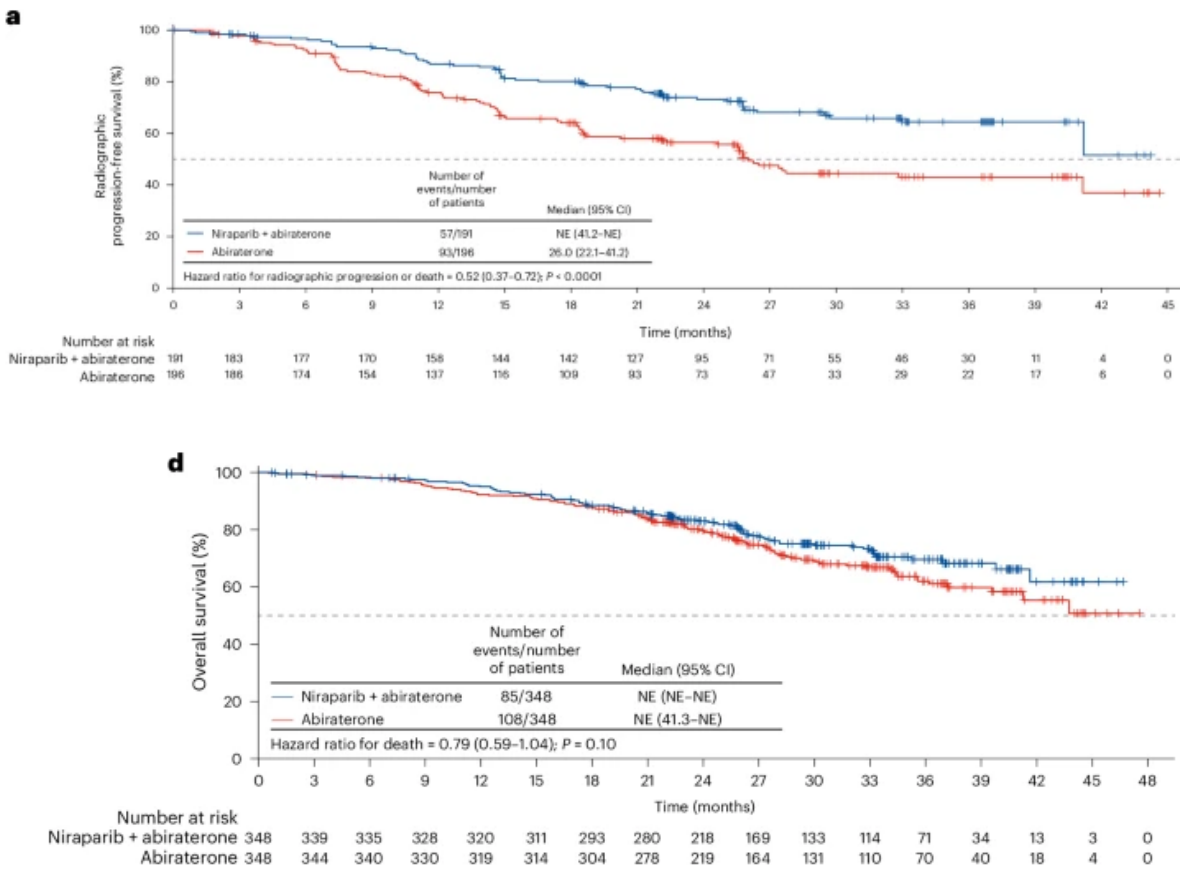


AMPLITUDE: ADT + abi +/- niraparib in met APMN

HRR altered

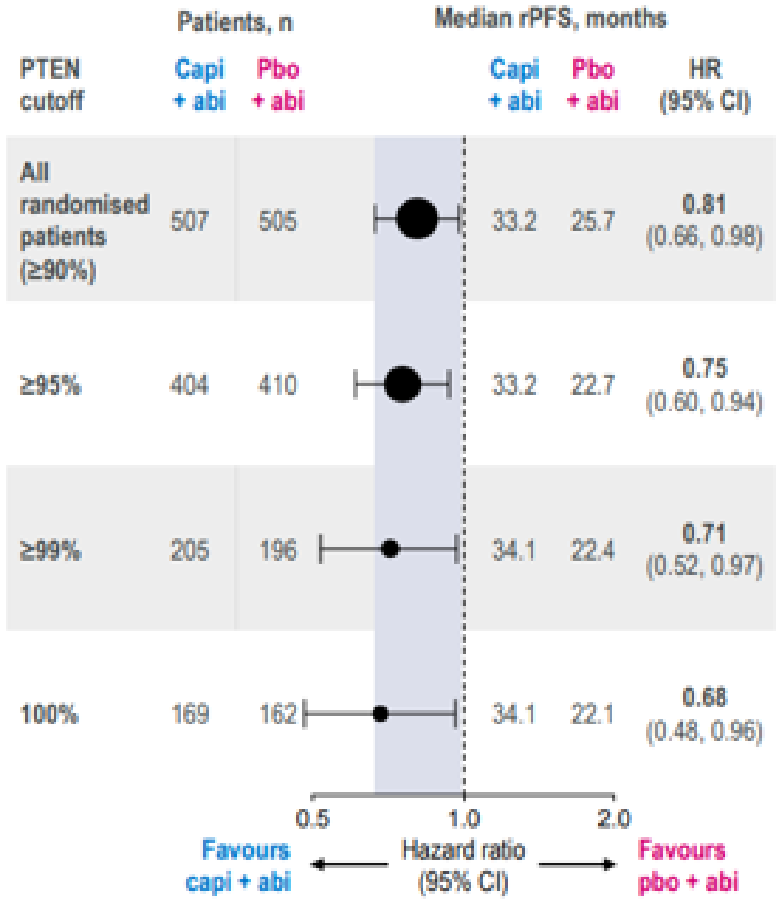
- rPFS (a) HR 0.57 (0.42-0.77) NR vs 27.6 mo
- OS est 0.75 (0.51 – 1.11) only BRCA subgroup
- 1 case MDS

FDA approval BRCA2+



Attard G et al. Nat Med 2025; 31:4109-18

Capivasertib in met APMN: Capitello-281



Patients with PTEN deficient *de novo* mHSPC

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

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

1,012 patients (R 1:1)

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

Primary endpoint

- **Investigator assessed rPFS**

Secondary endpoints

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

Exploratory *post-hoc* PTEN deficiency subgroups

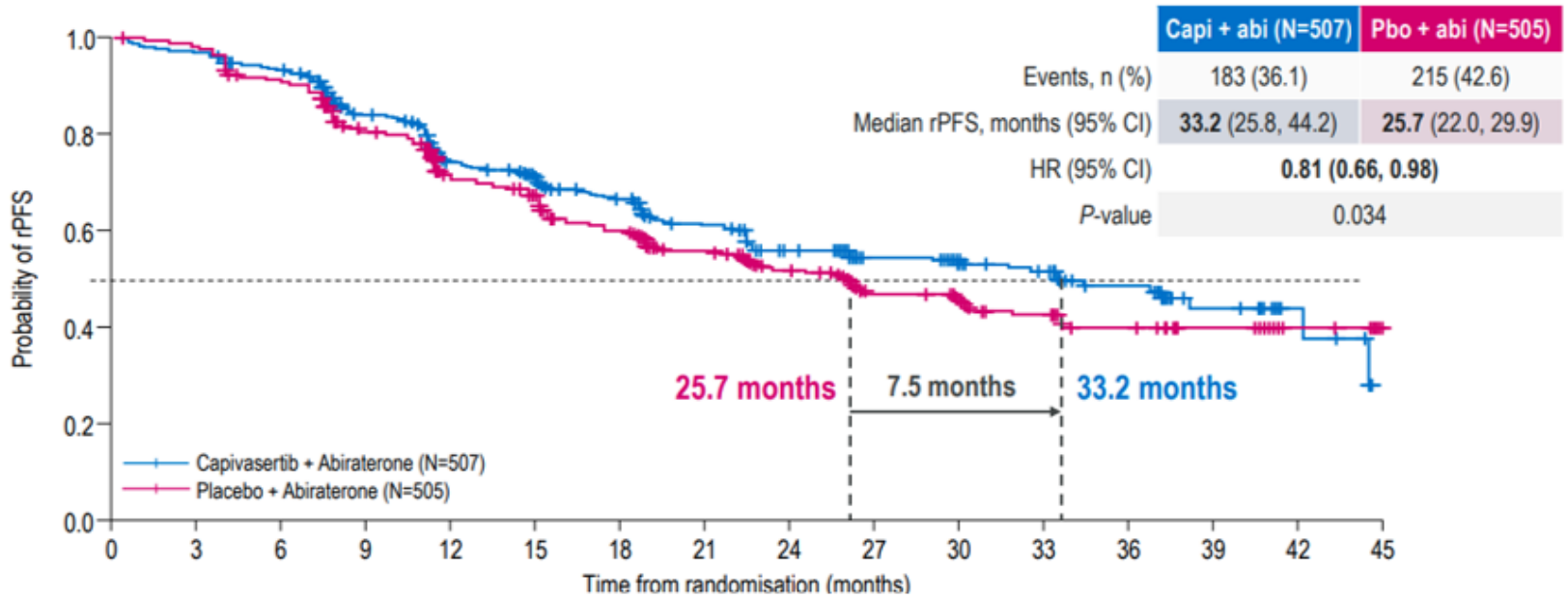
Stratification factors:†

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

Study timeline

Current analysis

Enrolment period	Primary rPFS DCO	Final OS DCO
13 July 2020–5 Feb 2024	7 Oct 2024 Median rPFS follow-up:‡ ~18 mo	Planned for 522 deaths (52.2% maturity)

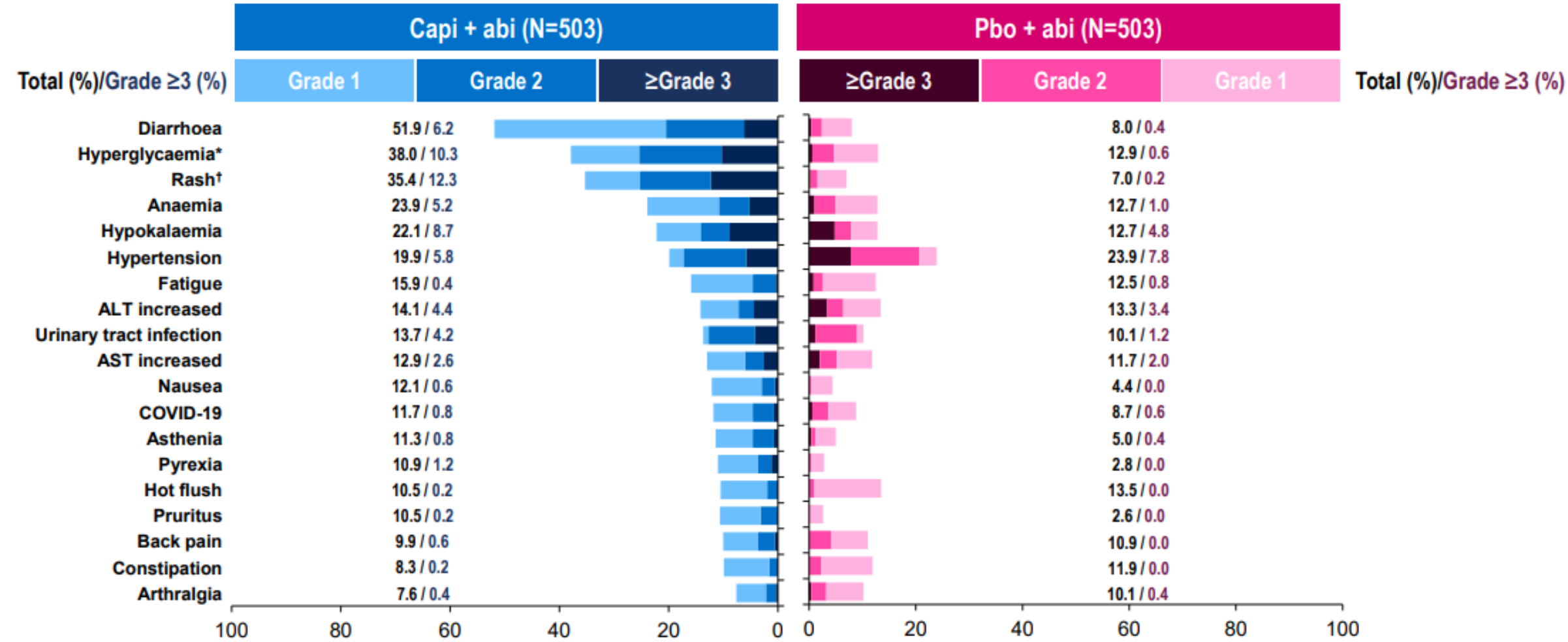


Fizazi K et al ESMO 2025; Abstr 2383O

CAPItello-281
AEs in ≥ 10% of Patients

FDA Approved July 2026

- **The most common Grade ≥3 AEs of rash and hyperglycemia are expected with AKT inhibition**



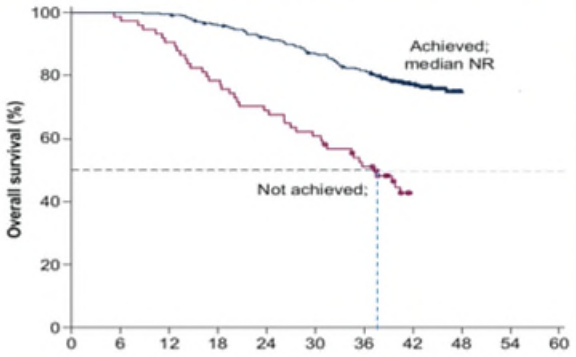
- Fizazi K, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. Abstract 2383O

Key Considerations for PARPi and Capivasertib

- Capivasertib best fit for strong PTEN loss, high volume
  - On NGS if PTEN del, reflex to IHC
  - No opportunity for capivasertib in APMR (CRPC)
  - Avoid in those with poorly controlled diabetes or significant weight loss
- PARPi best fit for BRCA2
  - Other mutations same risk with less benefit (though ATM looked strong in TALAPRO3)
  - Uncertain whether risk of MDS/leukemia is duration related
  - Docetaxel can be used first (based on AMPLITUDE)

Unmet need: those with PSA nadir at 7 months >0.2

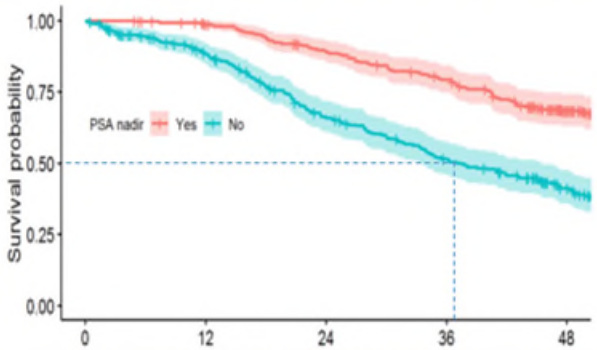
TITAN (apalutamide)



Chowdhury *et al Ann Oncol* 2023

Median OS = 37.2 mo

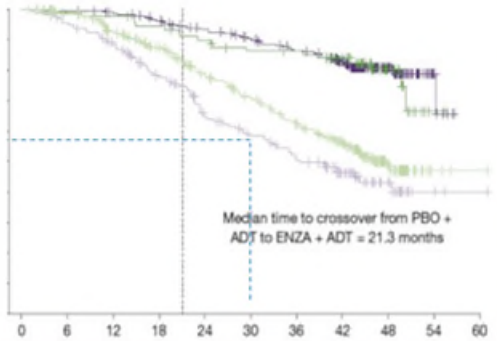
LATITUDE (abiraterone)



Roy and Ong 2024, *unpublished*
Matsubara *et al*, *Eur Urol*, 2019

Median OS = 37.5 mo

ARCHES (enzalutamide)



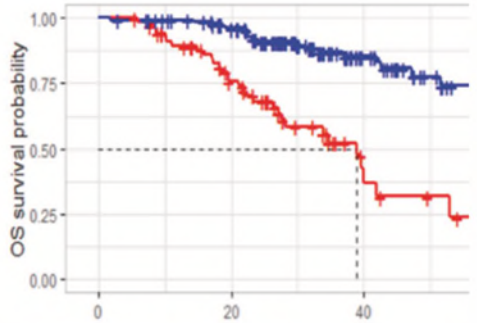
Szmulewitz *et al SESAUA* 2023

Median OS = 36.4 mo

anadien
Trials Group des essais sur le cancer

PSA nadir >0.2 at 7 months identifies those with shorter OS

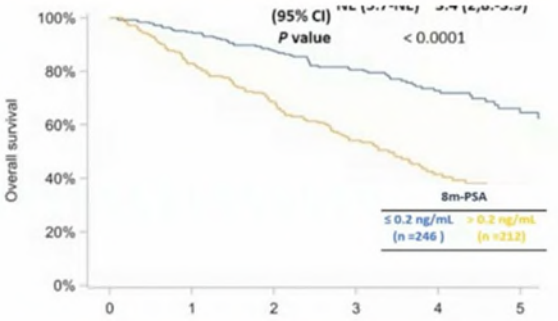
Real-World



Median OS = 38.9 mo

Gebrael *et al* Prostate Cancer and Prostatic Diseases 2023

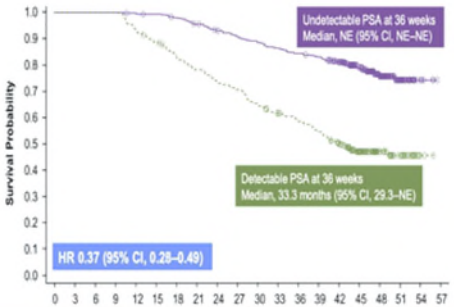
PEACE-1 (abiraterone, RT)



Median OS = 40.8 mo

Gravis Mescam *et al ESMO* 2022

ARASENS (darolutamide)

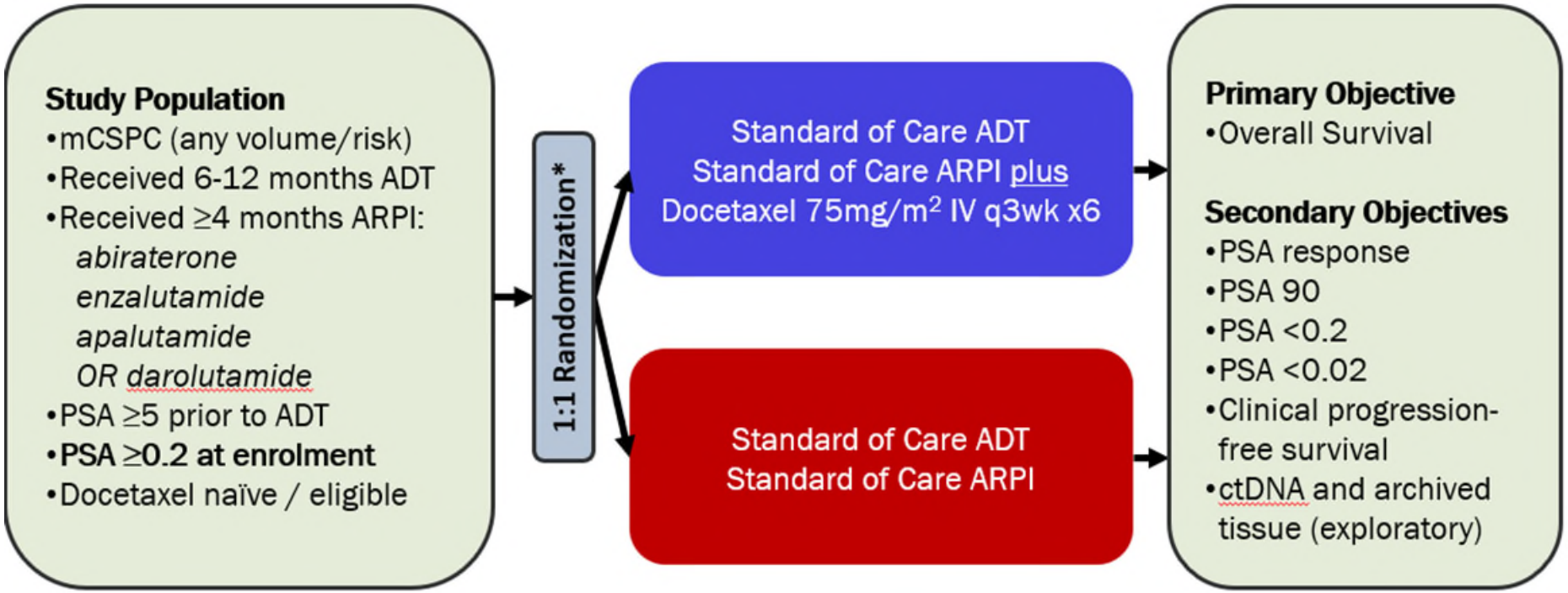


Median OS = 40.3 mo

Saad *et al AUA* 2023

Adapted from A. Sokolova

Coop Groups will try to fill knowledge gaps in metastatic APMN: Triple Switch- using inadequate PSA nadir to selectively use triplet



Triple Switch (PR26): *Actively enrolling*

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

SWOG CANCER RESEARCH NETWORK

PSMA PET detects occult metastatic disease in "localized" PC and sees much more disease to conventional imaging: what is "metastatic"?

- Nothing on conventional imaging = tx as hi risk localized/oligomet
- In my practice only conventional metastatic gets lifelong doublet +/- triplet

Imaging Modality	Pretreatment Scan	On-Treatment Scan 1 (≥week 8)	On-Treatment Scan 2	All Subsequent Scans
Bone scintigraphy				
	Comparator for on-treatment scan 1	Comparator for all subsequent scans POD only if ≥2 new lesions confirmed on the subsequent scan (2 + 2)[a]	POD: ≤5 new lesions: PCWG3 criteria 2 new lesions that are confirmed on a subsequent scan (2 + 0)[a] Or ≥6 new lesions	Same as on-treatment scan 2
CT/MRI				
Any measurable disease	Comparator	PCWG3/RECIST	PCWG3/RECIST	PCWG3/RECIST
PSMA-PET				
Bones and lymph nodes and lung metastases (non-RECIST qualifying by + on PET only)	Comparator	POD: ≤5 new lesions: 2 new lesions that are confirmed on a subsequent scan ≥6 new lesions	Same as on-treatment scan 1	Same as on-treatment scan 1
Liver parenchyma and nonpulmonary viscera	Comparator	POD: Any single new lesion that represents disease	Same as on-treatment scan 1	Same as on-treatment scan 1

Armstrong AJ et al. PCWG4. JCO 2026

Supporting our Patients on long term ADT

- Diet and Exercise
  - More plant based
  - Muscle building + cardio exercise
- Managing lipids, BP, insulin resistance is key

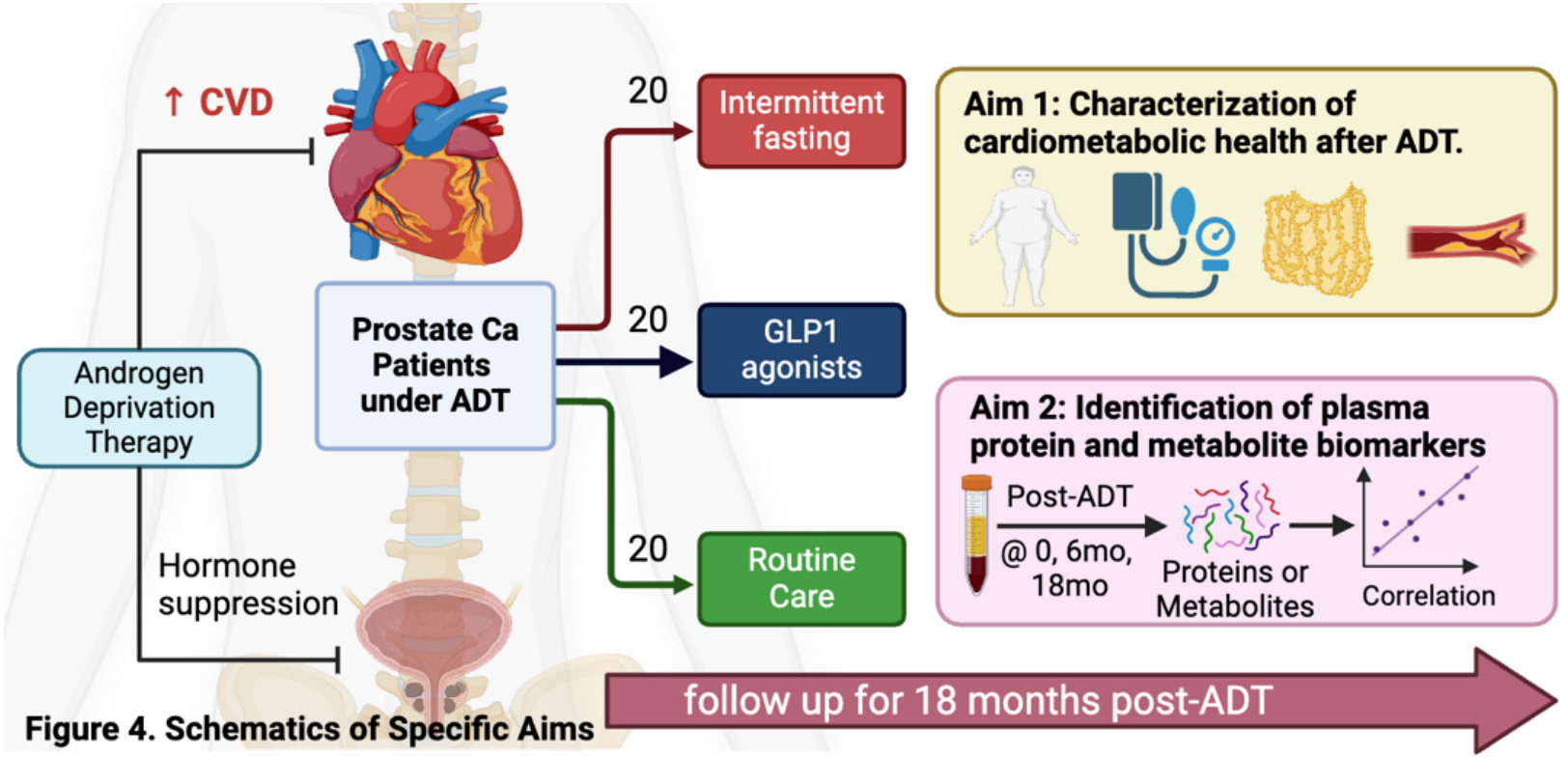


Figure 4. Schematics of Specific Aims

AHA funded clinical trial at COH (Duarte)
J. Rhee (Cardiology), Y. Li (Rad Onc), T. Dorff (Med Onc)

- Can managing the metabolic dysregulation impact cancer control?
  - FASTPRO study looking at both metabolic and cancer control outcomes

mHSPC: current and future status

- Current: Doublet w/ ARPi is minimum
  - Few are not candidates for ARPI
- Triplet for high volume, molecularly selected
  - PARPi prioritized for BRCA2
  - Capivasertib should be considered for PTEN loss >90%
  - 177Lu-PSMA-617 can be considered but maybe not 6 doses?!

- Future: Personalization, adaptive dosing
- De-intensification remains a goal
- Designing trials will need biomarkers, short term endpoints
  - Refine choices as LONG TERM SAFETY data evolve

Our work isn't done until we get to cure