2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

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Advancing care in metastatic hormone-sensitive prostate cancer

Jacob Berchuck, MD

Assistant Professor, Emory University School of Medicine
Medical Oncologist, Winship Cancer Institute

Disclosures

Consultant/Advisor/Speaker: Guardant Health, Precede Biosciences, Tracer Biotechnologies, Genome Medical

Researcher: Precede Biosciences

Royalties or Patent Beneficiary: Precede Biosciences

Remarkable progress in the last decade

2015

Newly diagnosed mHSPC

↓

ADT

↓

Median OS
3-4 years

Five new drugs and seven new regimens FDA approved for mHSPC

2025

Newly diagnosed mHSPC

↓

ADT plus
1) Abiraterone or
2) Enzalutamide or
3) Apalutamide or
4) Darolutamide or
5) Abiraterone plus Docetaxel or
6) Darolutamide plus Docetaxel

↓

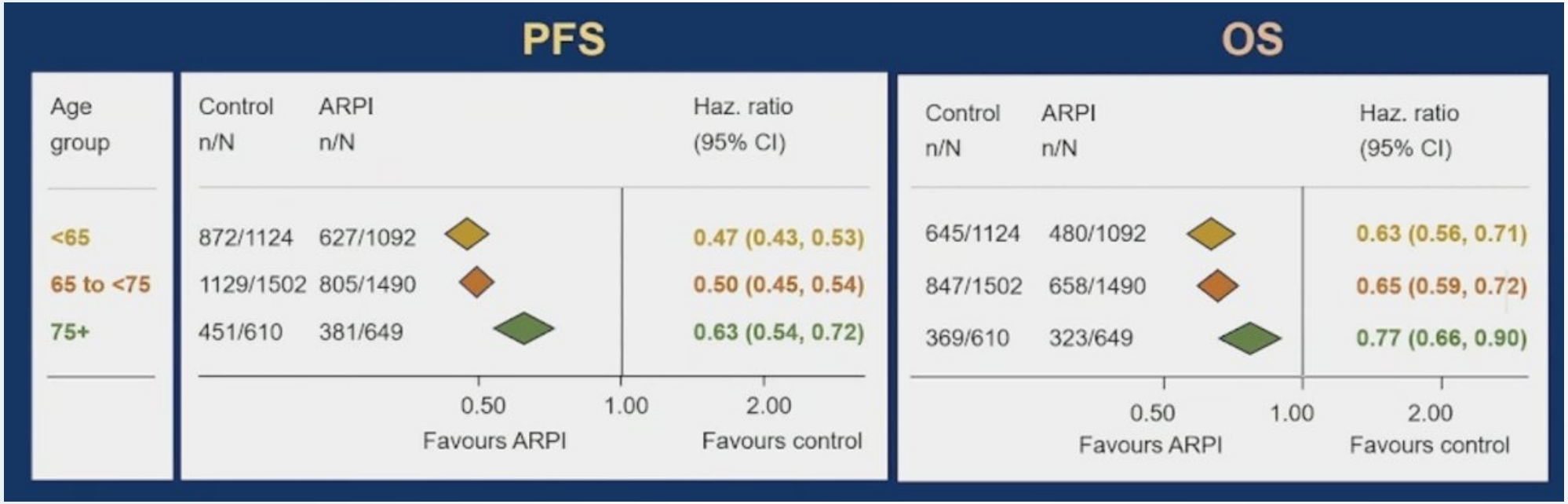
Median OS
> 5 years

How do we treat mHSPC in 2025?

All patients with mHSPC should get ADT plus an ARPI !!! (with a few exceptions)

Across studies all subgroups of patients benefit from addition of ARPI to ADT

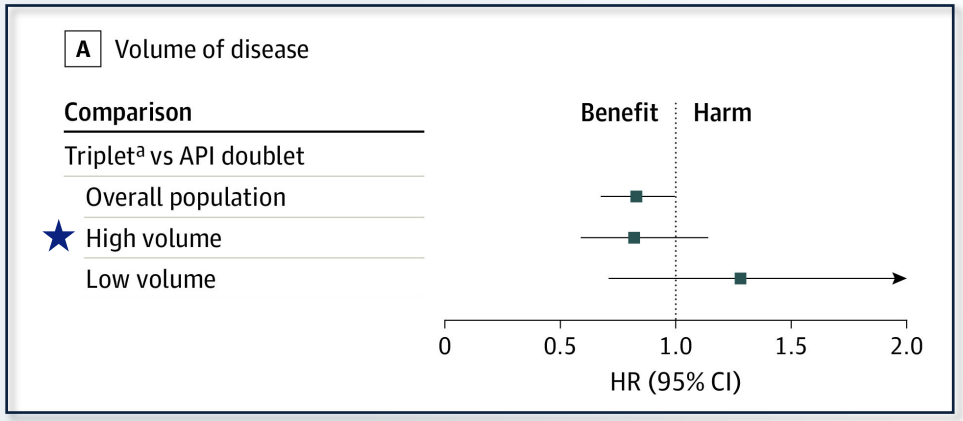
Don’t discriminate by age!

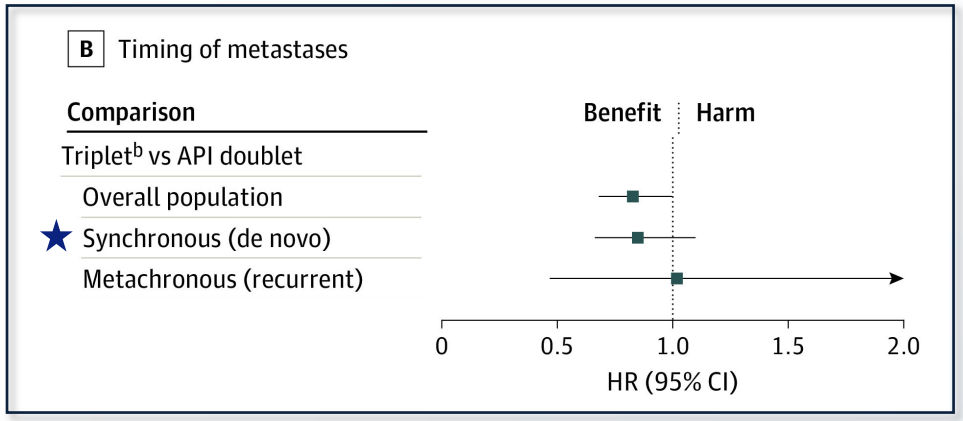


Fischer D et al, ASCO GU 2025

The biggest question in mHSPC today – who benefits from the addition of docetaxel to ADT + ARPI?

Meta-analysis of mHSPC trials suggests that **high-volume disease*** and ***de novo* metastatic disease**** predict benefit for docetaxel



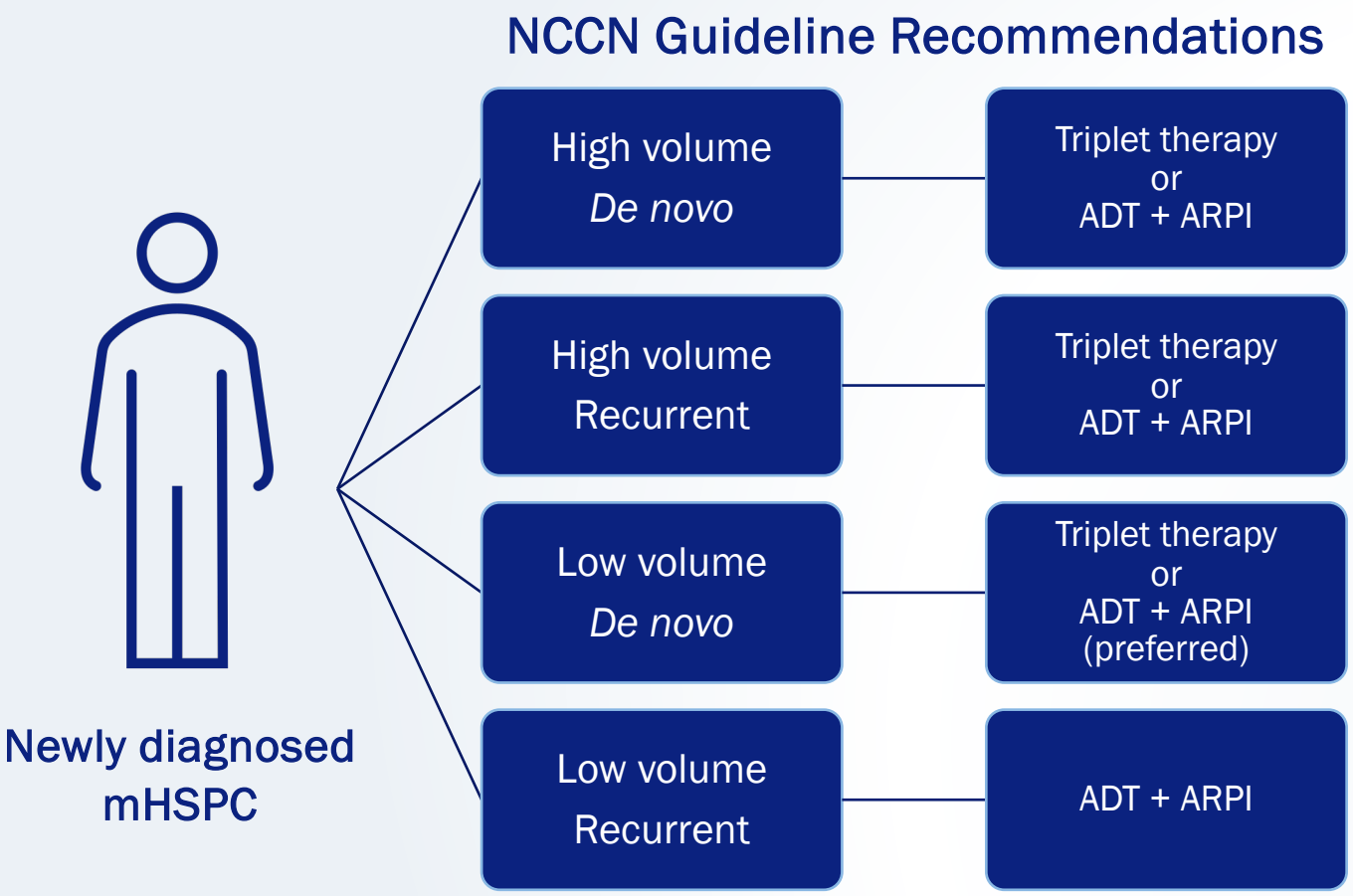


* High volume defined by the CHAARTED criteria as presence of visceral disease or ≥ 4 bone lesions with ≥ 1 outside the pelvis or vertebrae on **conventional imaging** (CT and bone scan)

** *De novo* (or synchronous) metastatic disease means metastatic disease is present at the time of prostate cancer diagnosis

Riaz IB et al, *JAMA Oncology* 2023

The treatment-paradigm for mHSPC in July 2025



Additional Considerations

Favor triplet therapy if:

- Able to tolerate chemotherapy
- Younger patients
- Liver metastases
- Lytic bone metastases
- Symptomatic disease

Consider ADT alone if:

- Not able to tolerate ARPI (very small minority)
- Competing risks with life expectancy < 5 years

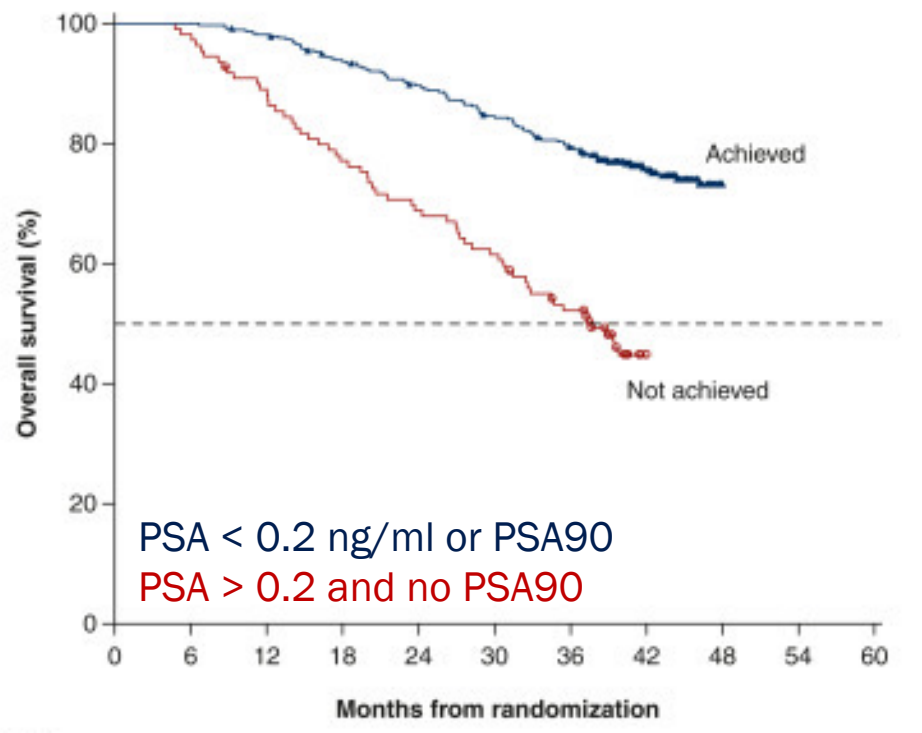
NCCN Guidelines Version 2.2025: Prostate Cancer

How can we improve outcomes for men with mHSPC?

1. Treatment intensification in poor responders
2. Treatment de-intensification in exceptional responders
3. Leveraging our understanding of tumor biology to develop more effective therapies
4. Developing better clinical biomarkers to personalize therapeutic decision-marking

PSA response strongly associates with long-term outcomes

OS by PSA response at 3 months in patients treated with ADT +/- apalutamide (TITAN)

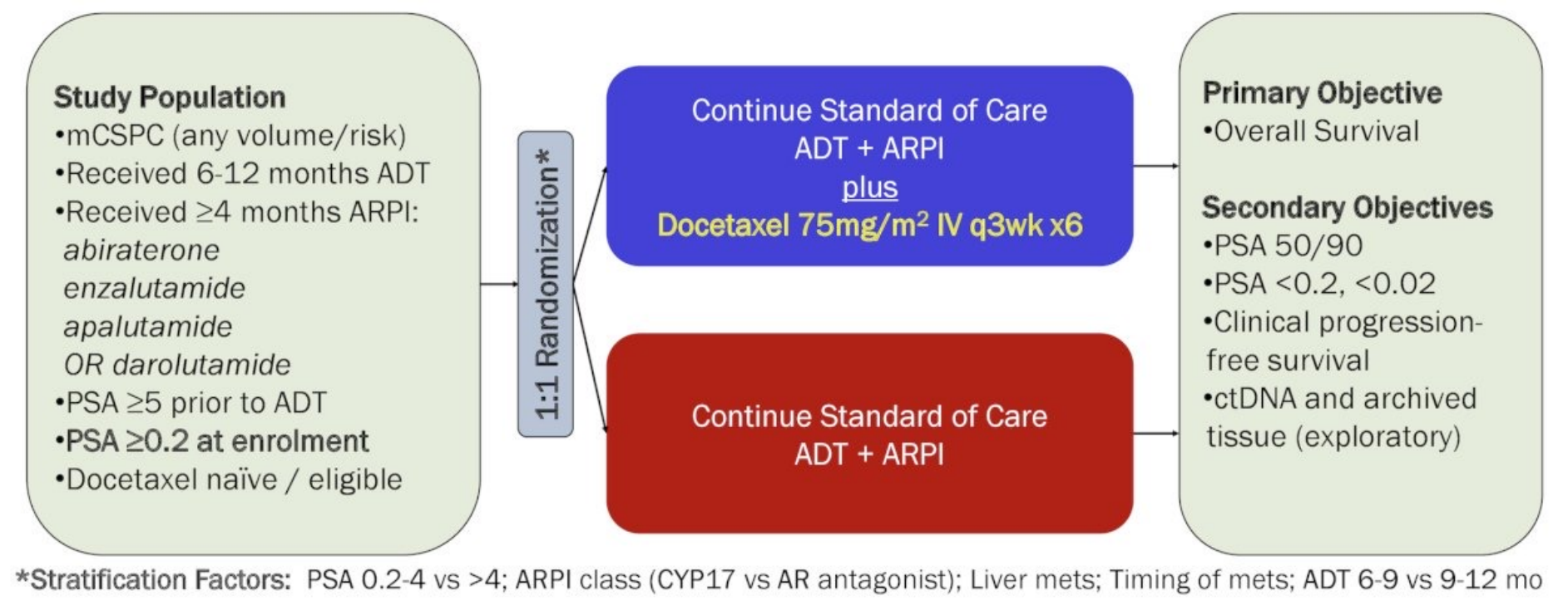


Can we use PSA response in patients treated with ADT plus ARPI to identify those who will benefit from treatment intensification or de-intensification?

Chowdhury S et al, *Annals of Oncology* 2023

Treatment **intensification** in patients with sub-optimal PSA response to ADT plus ARPI

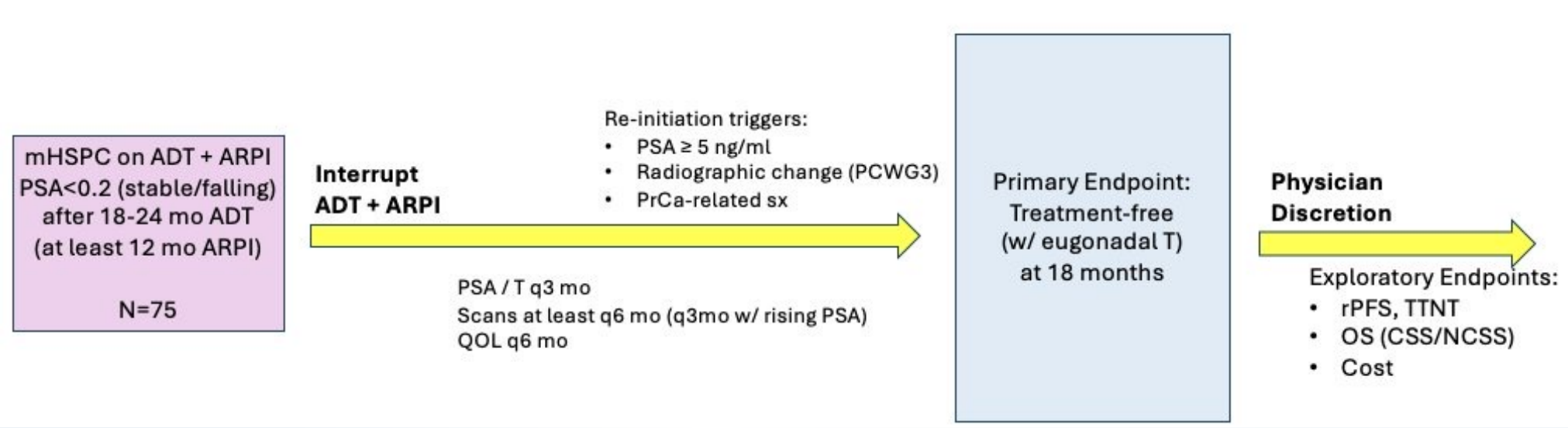
TRIPLE-SWITCH (SWOG/CCTG-PR26): A Randomized Phase III Clinical Trial for the Addition of Docetaxel to Androgen Receptor Pathway Inhibitors in Patients with mCSPC and Suboptimal PSA Response



Ong M et al, ASCO 2025

Treatment **de-intensification** in patients with excellent long-term PSA response to ADT plus ARPI

A-DREAM (Alliance A032101): A Phase 2 Trial of ADT Interruption in Patients Responding Exceptionally to AR-Pathway Inhibitor in Metastatic Hormone-Sensitive Prostate Cancer



Choudhury A et al, ASCO 2024

The current landscape of molecularly guided therapies for mCRPC in 2025

Germline and somatic testing recommended for all patients with metastatic prostate cancer

- Pembrolizumab approved for MMRd/MSI-high mCRPC (~3%)
- Several PARP inhibitor regimens approved for HRR-altered mCRPC (~20%)

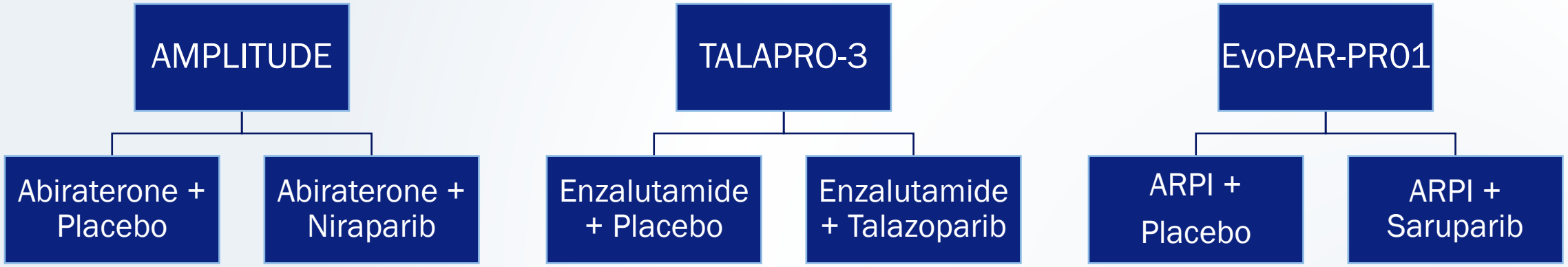
	ATM	*ATR*	*BARD1*	***BRCA1***	***BRCA2***	*BRIP1*	*CDK12*	*CHEK1*	*CHEK2*	*FANCA*	*FANCL*	*MLH1*	*MRE11A*	*NBN*	*PALB2*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD54L*
Olaparib	X		X	X	X	X	X	X	X		X				X	X	X	X	X
Rucaparib				X	X														
Olaparib + Abiraterone				X	X														
Niraparib + Abiraterone				X	X														
Talazoparib + Enzalutamide	X	X		X	X		X		X	X		X	X	X	X		X		

Unanswered questions for PARPi in metastatic prostate cancer

- Which gene alterations predict benefit from PARP inhibitors?
  - BRCA1/2 >>> other HRR >>> non-HRR
- Does combining PARPi with an ARPI improve upon PARPi monotherapy?
  - We don’t know
  - TALENT trial is investigating PARPi +/- ARPI in mCRPC (NCT06844383)
- At what point in the disease course should we use a PARPi?
  - Currently first or second line mCRPC – what about mHSPC???

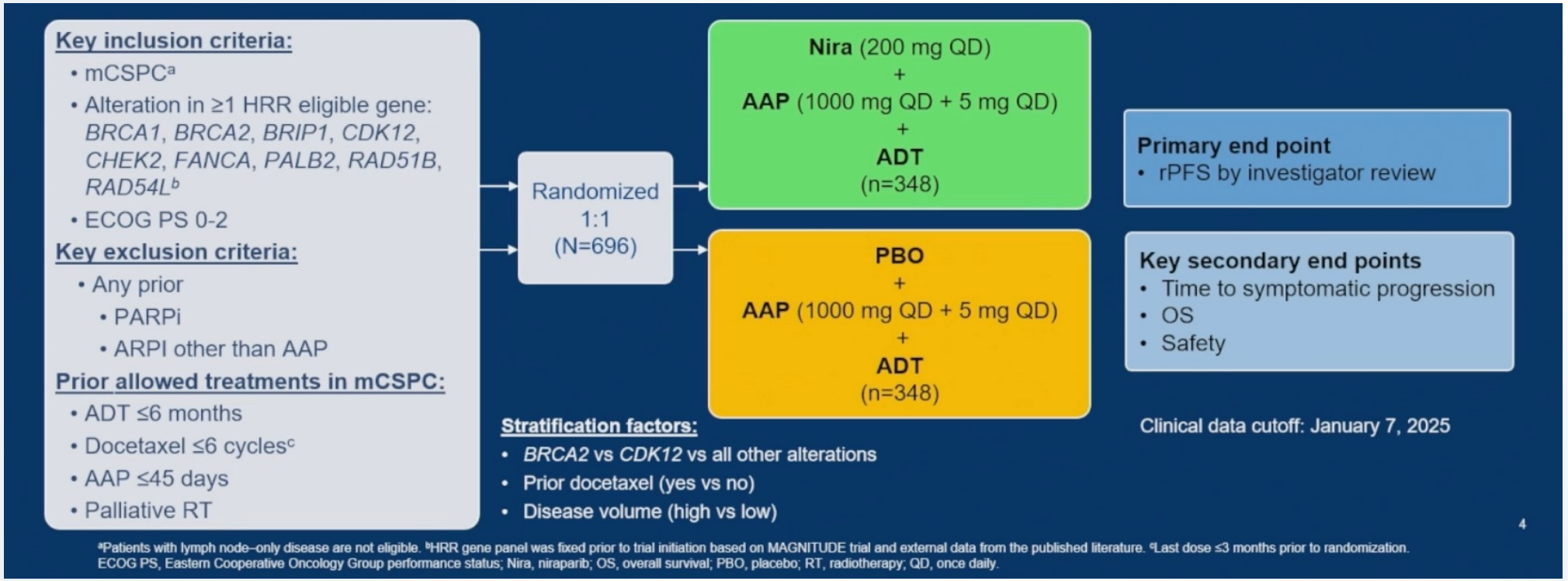
What is the role of PARPi in HRR-altered mHSPC?

Ongoing trials evaluating PARPi in mHSPC



HOT OFF THE PRESS

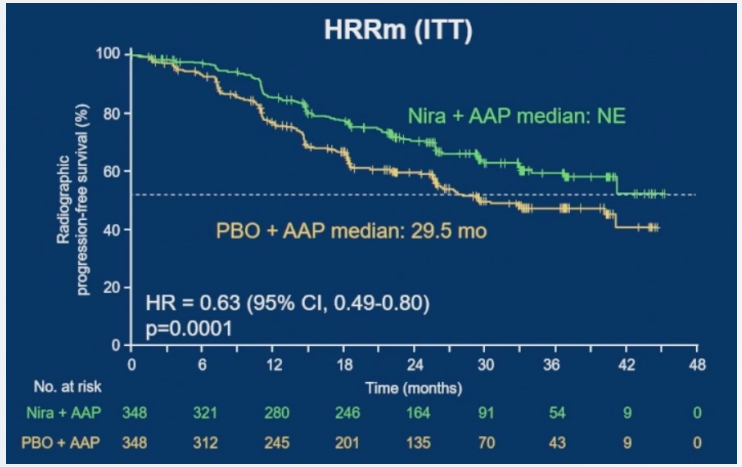
AMPLITUDE Trial: Niraparib and Abiraterone for mCSPC Patients with Alterations in HRR Genes



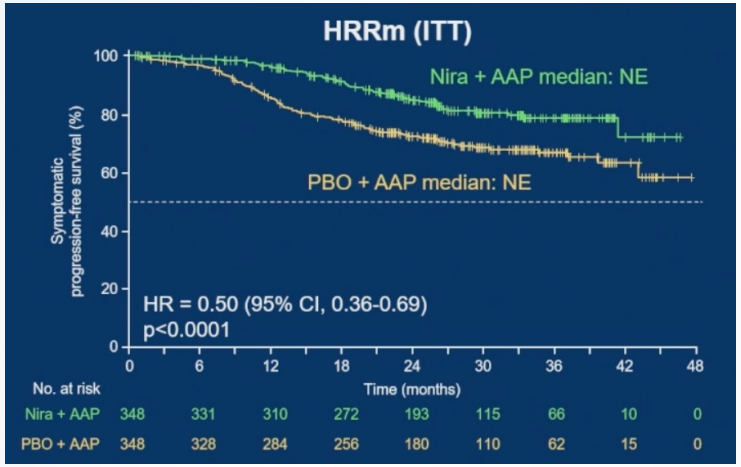
Attard G et al, ASCO 2025

Addition of niraparib to abiraterone improves outcomes in HRR-altered mHSPC

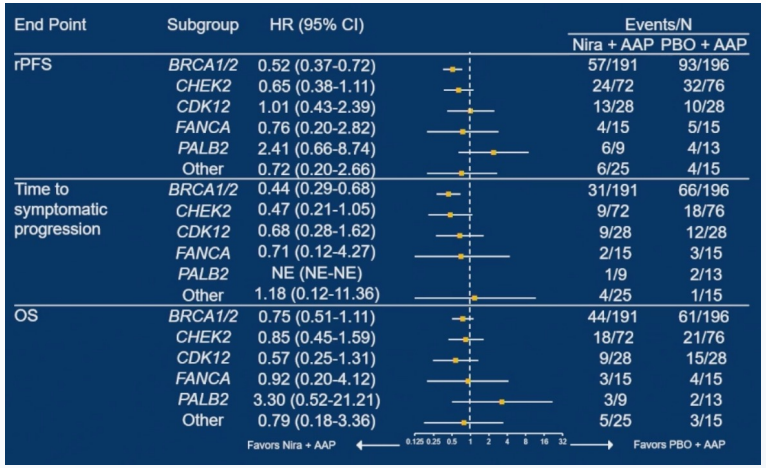
rPFS (primary endpoint)



Time to symptomatic progression



rPFS subgroup analysis by gene



End Point	Subgroup	HR (95% CI)	Events/N Nira + AAP	Events/N 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

In patients with HRR-altered mHSPC, the addition of niraparib to abiraterone improved rPFS by 37% and time to symptomatic progression by 50%

Benefit of adding niraparib greatest in patients with *BRCA1/2* alterations

Attard G et al, ASCO 2025

The current state and future questions for PARPi in mHSPC

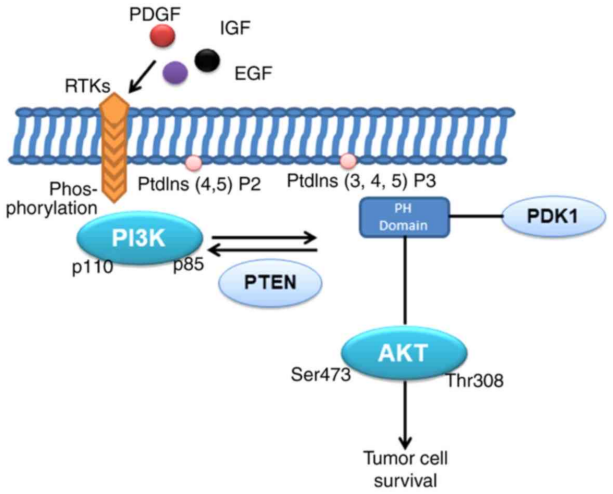
- AMPLIITUDe showed that the addition of niraparib to abiraterone improves rPFS and time to symptomatic progression in patients with HRR-altered mHSPC

- Lots of questions remain:
  - Does the addition of PARPi improve OS?
    - Trend towards yes, but data is immature.
  - Do patients with non-*BRCA1/2* HRR alterations benefit?
  - Do we need to give it in the mHSPC setting for patients to receive benefit?
    - Only 36% of patients received subsequent PARPi – without crossover we don't know whether benefit is specific to giving in mHSPC setting or patients would derive similar benefit if given in the mCRPC setting

- AMPLITUDE data will mature, and we'll get readout on other PARPi mHSPC trials in the next year

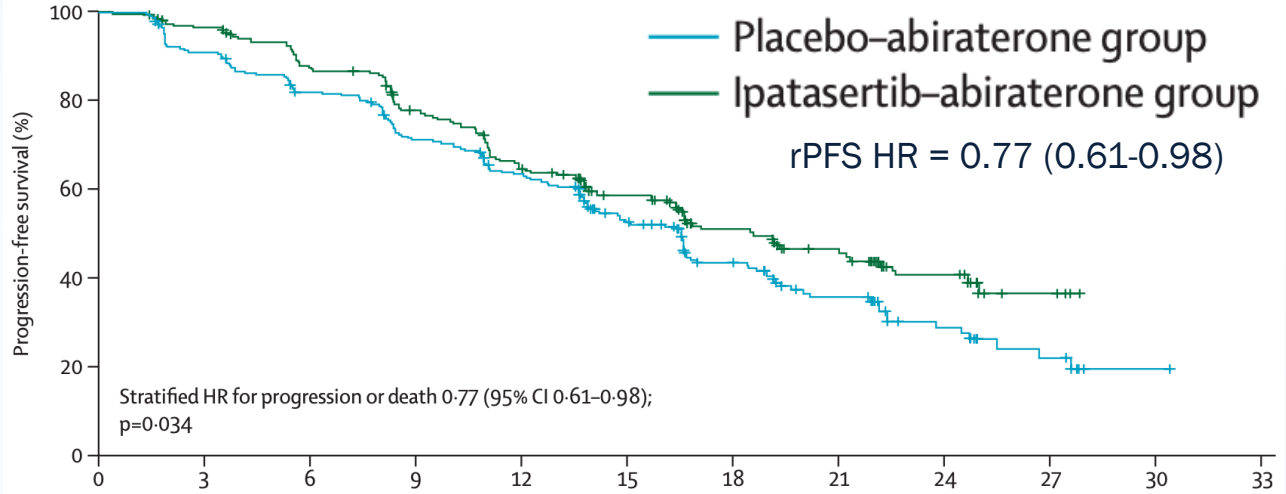
AKT inhibition in PTEN-deficient metastatic prostate cancer

Deleterious *PTEN* genomic alterations are present in ~40% of metastatic prostate tumors



IPATential150 evaluated the addition Ipatisertib (AKT inhibitor) to abiraterone in PTEN-deficient mCRPC

Subset with PTEN loss by IHC



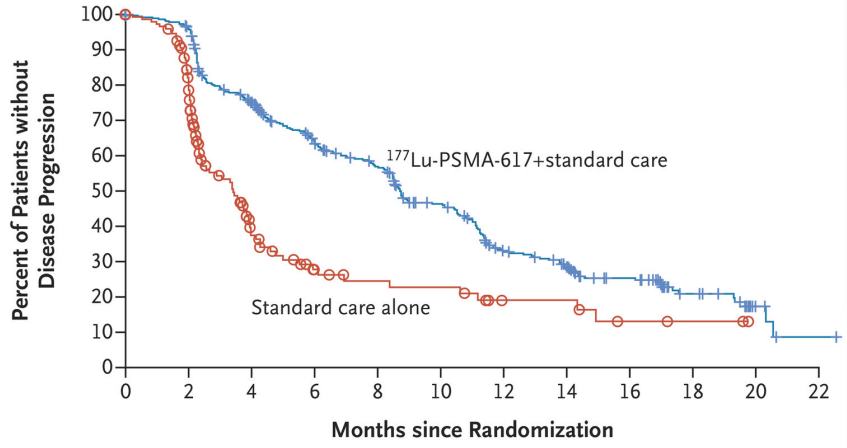
Robinson D et al, *Cell* 2015; Sweeney CJ et al, *Lancet* 2021

CAPItello-281 (NCT04493853) is studying the AKT inhibitor Capivasertib in PTEN deficient mHSPC

Press release from Nov 2024 that the addition of Capivasertib to ADT and abiraterone in PTEN-deficient mHSPC “demonstrated statistically significant and clinically meaningful improvement in rPFS.”

Lutetium-PSMA is an FDA approved radioligand therapy for PSMA-positive mCRPC

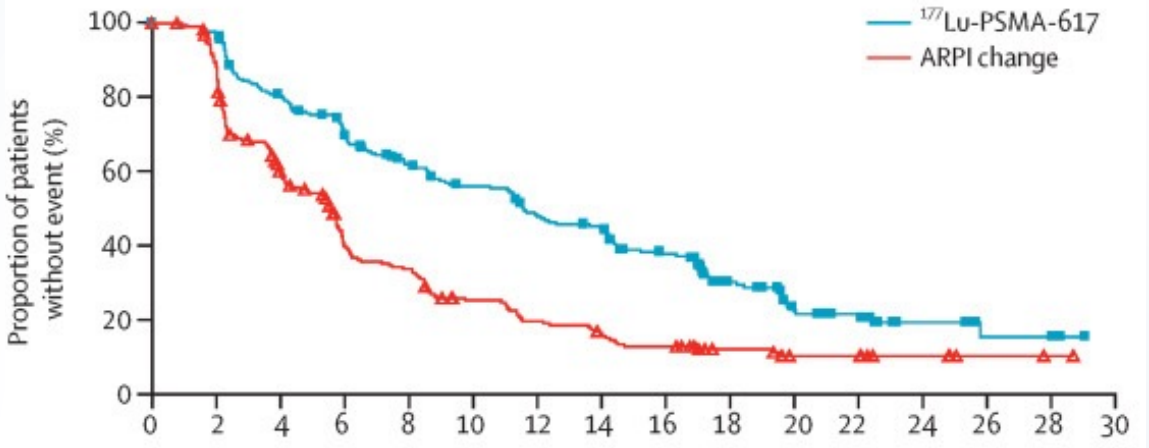
VISION trial (post-taxane)



HR = 0.40 (0.29-0.57)

FDA approved in 2021

PSMAfore trial (pre-taxane)

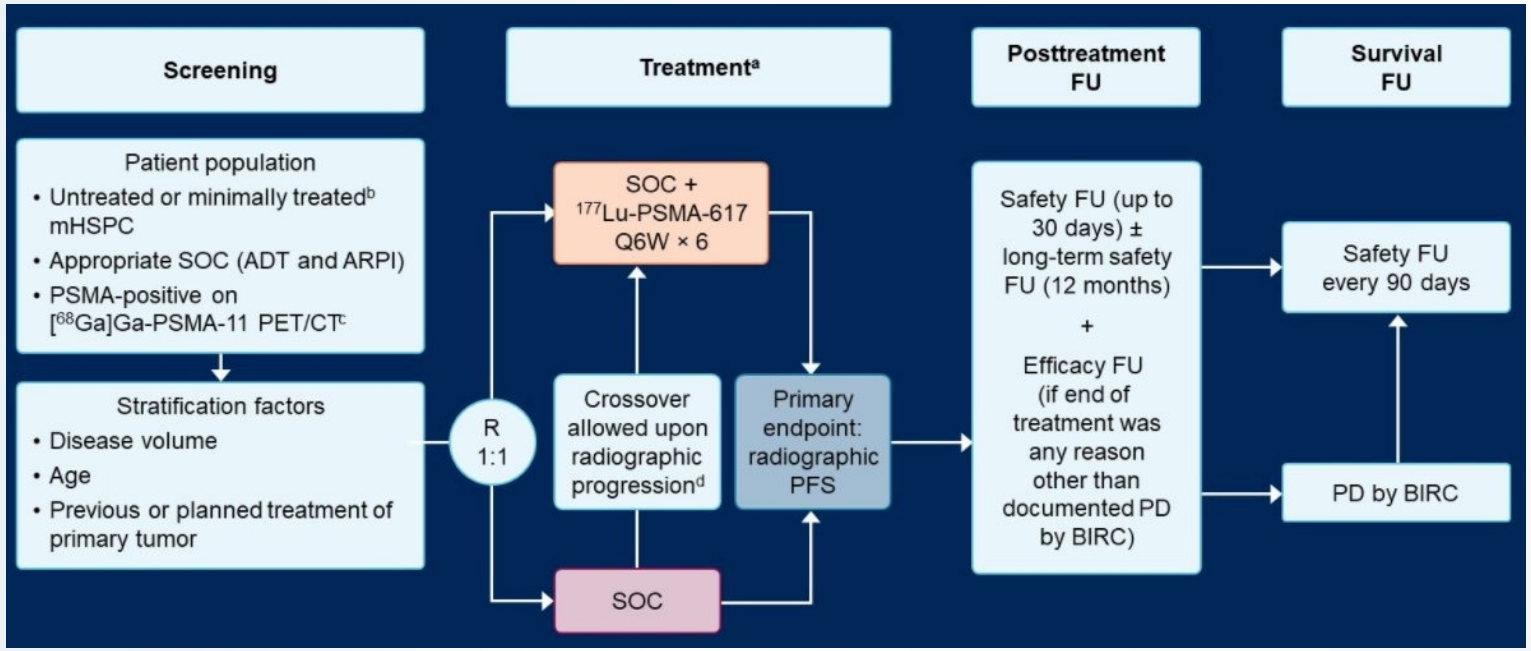


HR = 0.49 (0.39-0.61)

FDA label expanded in March 2025

Sartor O et al, *NEJM* 2021; Morris M et al, *Lancet* 2024

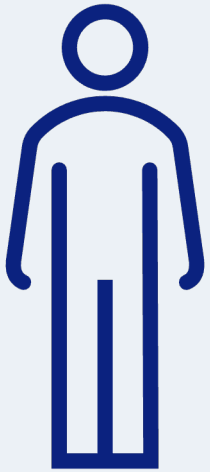
PSMAddition (NCT04720157) is studying Lutetium-PSMA in PSMA PET-positive mHSPC



Press release from June 2025 that the addition of Lutetium-PSMA to SOC treatment “demonstrates significant and clinically meaningful rPFS benefit in patients with PSMA-positive mHSPC.”

Sartor O et al, ASCO GU 2022

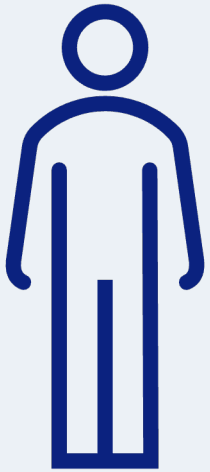
Evolution of the treatment paradigm for mHSPC in the coming years



Newly diagnosed mHSPC in **2025**

High volume *De novo*	Triplet therapy or ADT + ARPI
High volume Recurrent	Triplet therapy or ADT + ARPI
Low volume *De novo*	Triplet therapy or ADT + ARPI (preferred)
Low volume Recurrent	ADT + ARPI

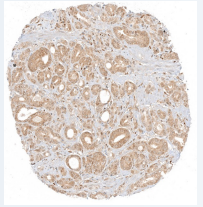
Evolution of the treatment paradigm for mHSPC in the coming years



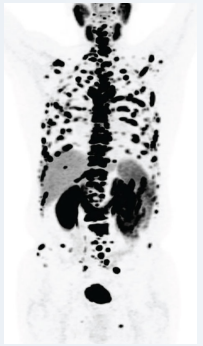
Newly diagnosed mHSPC in **2027**

Biomarker testing

Germline genetic testing and tumor genomic profiling



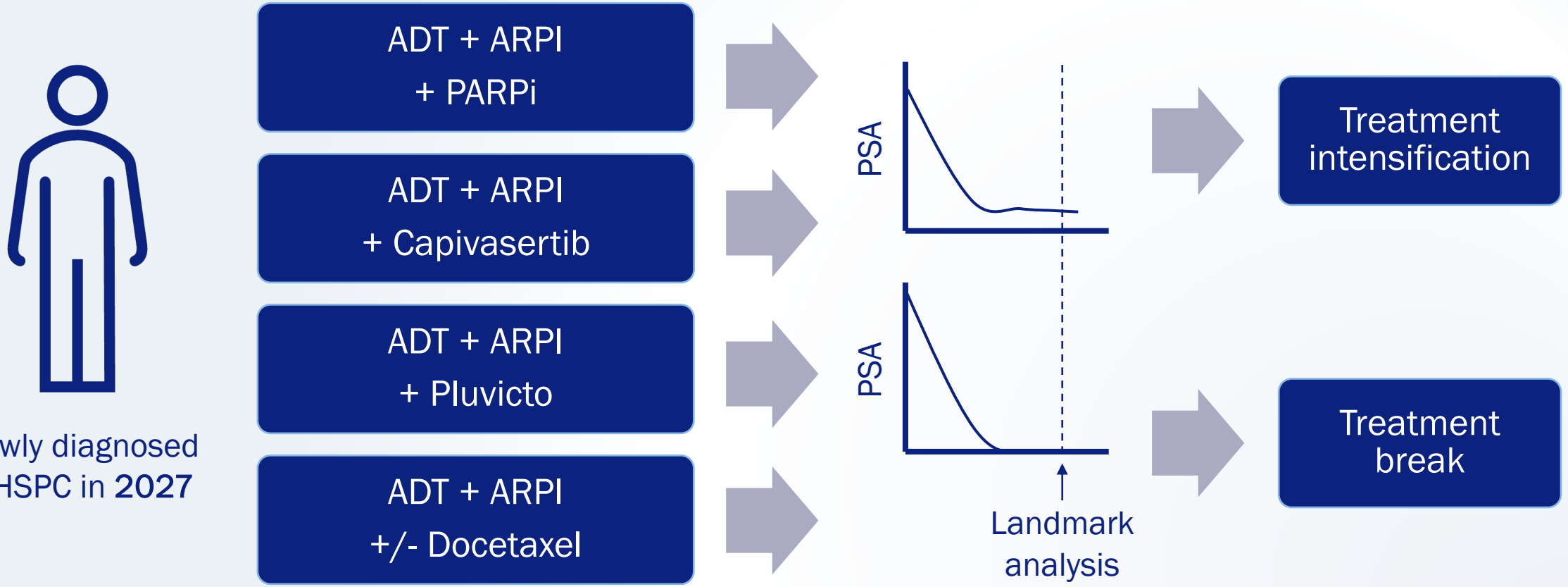
PTEN IHC



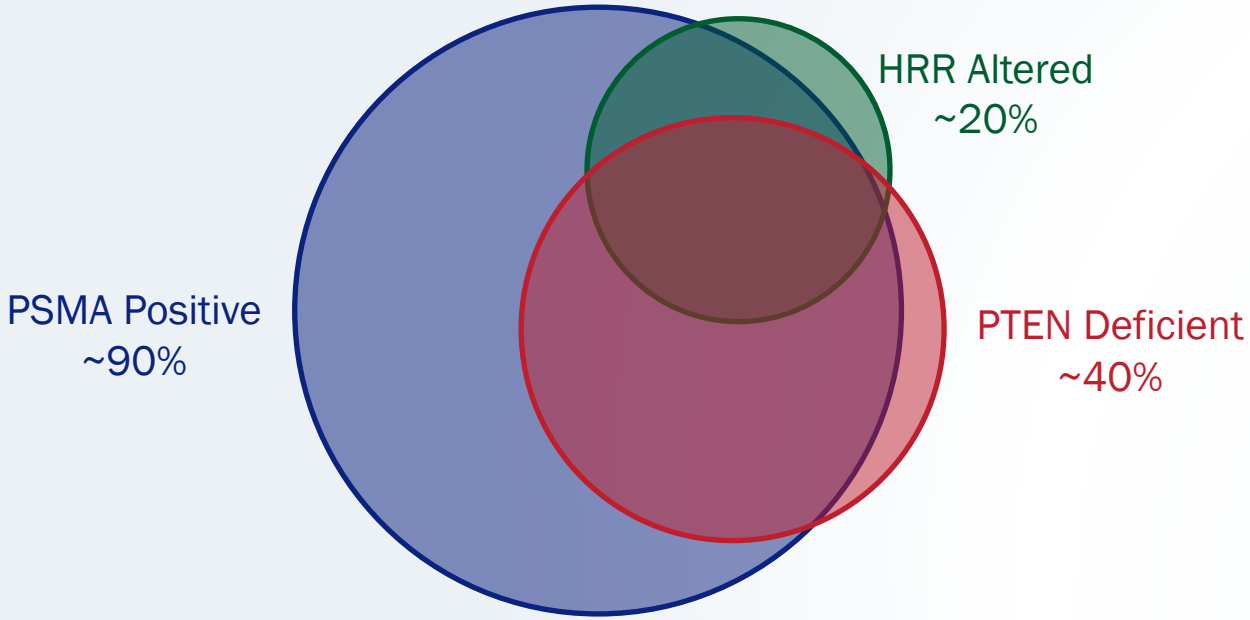
PSMA PET scan

HRR alteration	ADT + ARPI + PARPi
PTEN loss on IHC	ADT + ARPI + Capivasertib
High SUV on PSMA PET	ADT + ARPI + Lutetium-PSMA
None of the above	ADT + ARPI +/- Docetaxel

Evolution of the treatment paradigm for mHSPC in the coming years



Lots of progress … and lots of questions left to solve



Group	PSMA	HRR	PTEN
1	Positive	Altered	Deficient
2	Positive	Altered	Proficient
3	Positive	WT	Deficient
4	Positive	WT	Proficient
5	Negative	Altered	Deficient
6	Negative	Altered	Proficient
7	Negative	WT	Deficient
8	Negative	WT	Proficient

Summary

- ADT + ARPI is the standard of care for (almost) all patients with mHSPC with some patients (high volume) benefiting from the addition of docetaxel
- Strategies to intensify or de-intensify treatment based on PSA response may help optimize both long-term cancer outcomes and patient QOL
- Targeted treatments in molecular subgroups (HRR altered, PTEN deficient, PSMA positive) are coming to mHSPC
- We're going to need better biomarkers to determine which treatment strategy to choose for which patient to optimize outcomes in mHSPC

Q&A