Updates in metastatic prostate cancer

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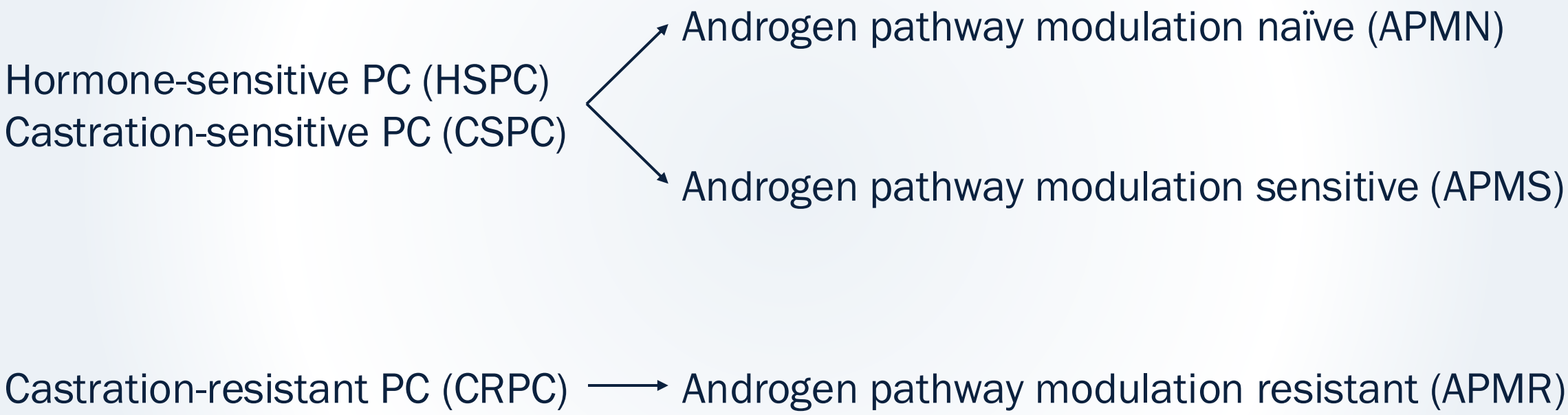
Disclosures

- **Speaker Honoraria:** Guardant Health, Natera
- **Consulting / Advisory Role:** Guardant Health, Precede Biosciences, Natera, Tracer Biotechnologies, Harbinger Health, Genome Medical, Oncotect, Musculo, Johnson & Johnson
- **Equity:** Precede Biosciences, Genome Medical, Oncotect, Tracer Biotechnologies, Musculo, Cityblock Health
- **Research Funding:** Guardant Health, Precede Biosciences

Updated terminology for metastatic disease states from the Prostate Cancer Working Group (PCWG) 4

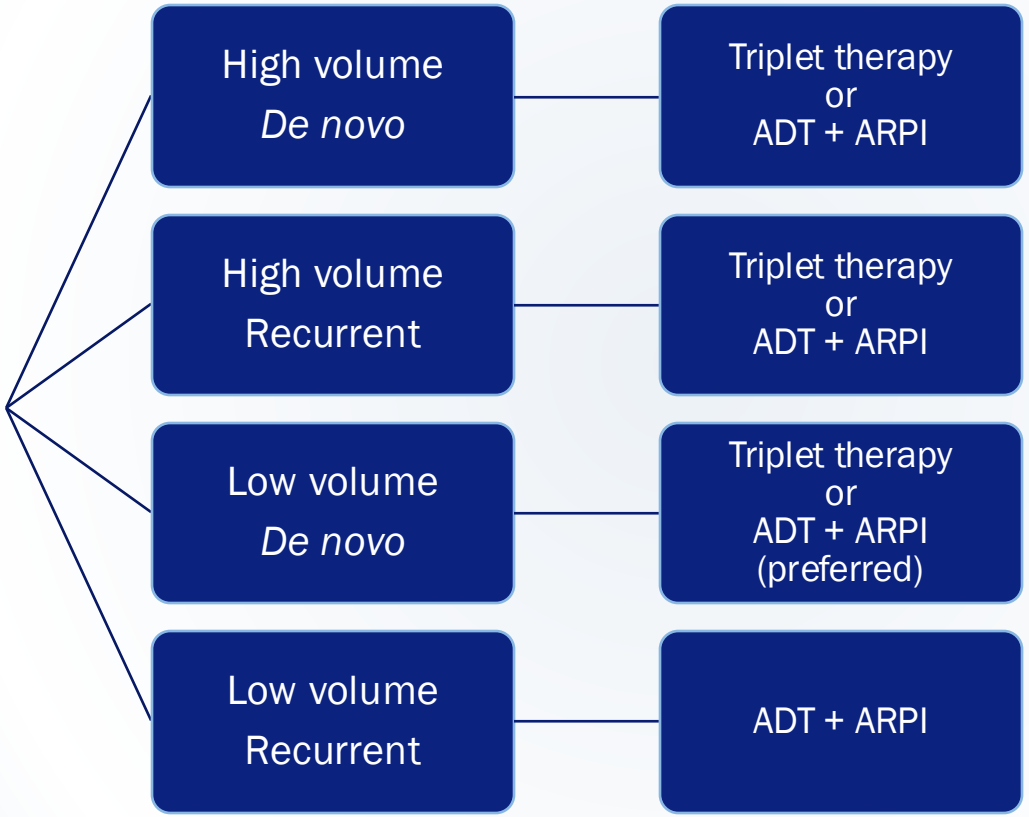


Armstrong A et al, JCO 2026

mHSPC or mAPMN/S

First-line treatment options for mHSPC in 2025

Newly diagnosed mHSPC in **2025**



Additional Considerations

Favor triplet therapy (ADT + ARPI + Docetaxel) if:

- Able to tolerate chemotherapy
- High-volume
- *De novo* metastatic
- Liver metastases
- Lytic bone metastases
- Symptomatic disease

Consider ADT alone if:

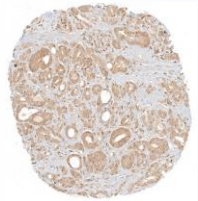
- Not able to tolerate ARPI (very small minority)
- Competing risks with life expectancy < 5 years

First-line treatment options for mHSPC in 2026-2027

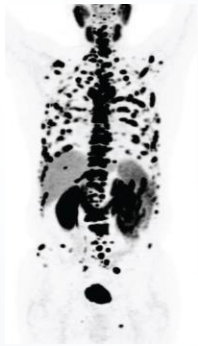
Newly diagnosed mHSPC in **2027**

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

Darolutamide causes significantly less cognitive decline than enzalutamide

- ARACOG: Randomized phase 2 trial of 111 patients with nmCRPC, mHPSC, mCRPC stratified by age
- Primary endpoint met – significantly greater decline in objectively assessed cognitive function for patients treated with enzalutamide when compared with darolutamide over 24 weeks
- Although a similar number of patients were eligible for crossover by 24 weeks, only patients treated with enzalutamide crossed to the other treatment

Primary Outcome: MCCD by 24 weeks

	Darolutamide (N=48)	Enzalutamide (N=47)	P-value
CANTAB test	PALFAM Visual Memory/ Executive Function	SWM Working Memory/ Executive Function	
Median Change	-15.8	-36.1	P=0.009

Secondary Endpoint: Crossover

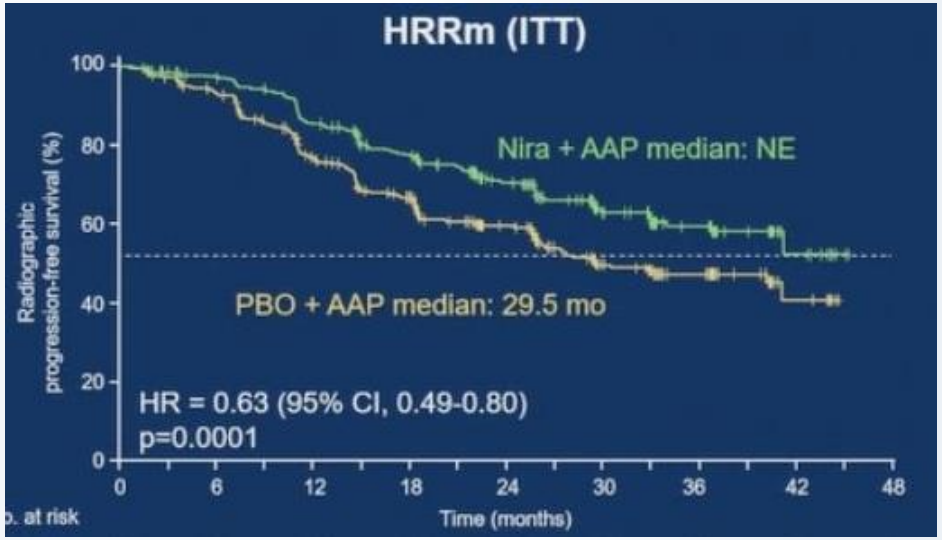
Crossover Enzalutamide to Darolutamide	Between Baseline & 12 Weeks	At 12 Weeks	Between 12 & 24 Weeks	At 24 Weeks	Total
Observed crossovers	2	16	0	12	30
Unique patients eligible for crossover	2	31	0	17 (14 previously met criteria at 12 wks)	36

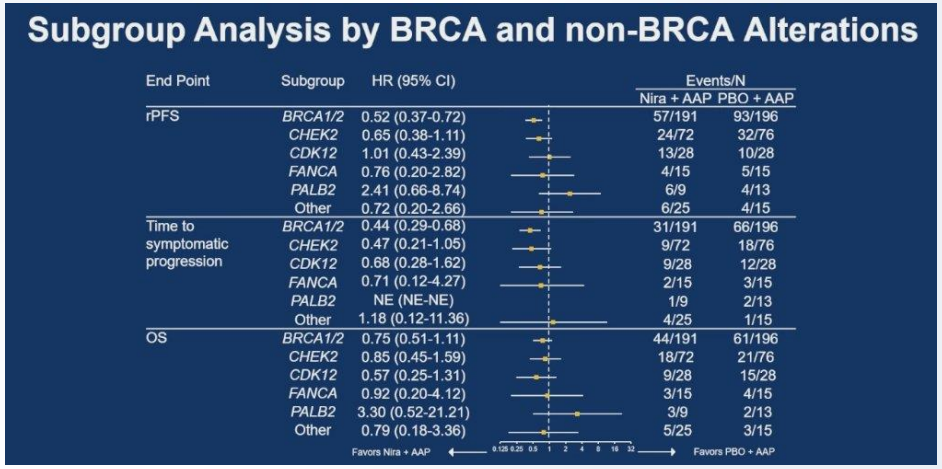
Crossover Darolutamide to Enzalutamide	Between Baseline & 12 Weeks	At 12 Weeks	Between 12 & 24 Weeks	At 24 Weeks	Total
Observed crossovers	0	0	0	0	0
Unique patients eligible for crossover	0	24	0	24 (14 previously met criteria at 12 wks)	34

Morgans A, ASCO 2026

First PARPi FDA approved for mHSPC: ADT + abiraterone + niraparib in BRCA2 mutant mHSPC

- **AMPLITUDE:** Patients with HRR mutant mHSPC treated with ADT + abiraterone were randomized to niraparib vs placebo
- Primary endpoint met – improvement in rPFS in the ITT population
- Benefit driven by BRCA2 mutant patients
- OS is immature, but favors niraparib (HR: 0.79 in ITT, 0.75 in BRCAm)
- 29% G3/4 anemia
- **ADT + Abiraterone + Niraparib FDA approved in Dec 2025 for patients with BRCA2m mHSPC**
- **Ideal patient in 2026:** BRCA2m low-volume OR high-volume but not fit for docetaxel

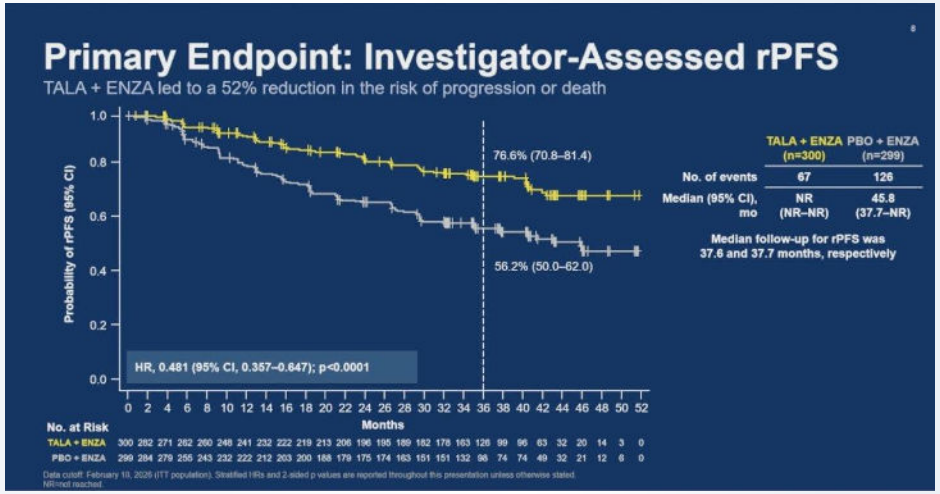


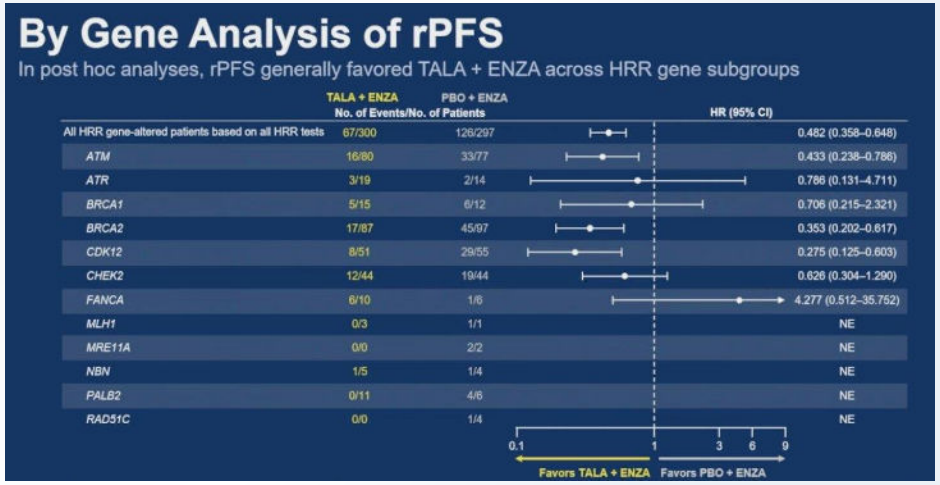


Attard G, ASCO 2025; Attard G, Nat Med 2025

TALAPRO-3: Talazoparib + Enzalutamide in HRR Gene-Altered mHSPC

- Patients with HRR mutant mHSPC treated with ADT + enzalutamide were randomized to talazoparib vs placebo
- Primary endpoint met – improvement in rPFS in the ITT population
- Benefit driven by BRCA2, but seen across multiple genes
- OS is immature, but favors talazoparib (HR: 0.77 in ITT)
- 51% G3/4 anemia
- PROs maintained
- FDA submission planned

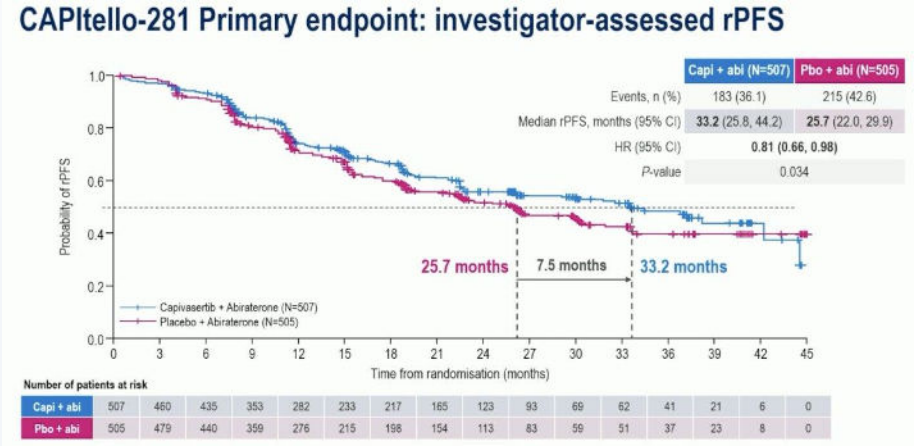


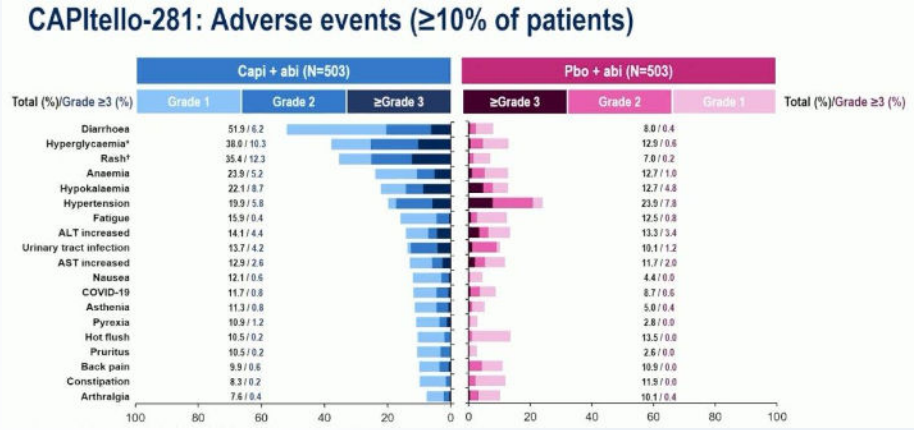


Agarwal N, ASCO 2026; Agarwal N, NEJM 2026

CAPItello-281: Capivasertib + abiraterone in PTEN-deficient mHSPC

- PTEN deficiency (~25% of mHSPC) activates PI3K/AKT independent of AR – these patients have poor outcomes on ADT + ARPI
- Patients with PTEN-deficient mHSPC (<10%+ by IHC) treated with ADT + abiraterone were randomized to capivasertib vs placebo
- Primary endpoint met
- OS is immature (26%), but favors capivasertib (HR: 0.90; 95%CI 0.71-1.15)
- **ADT + Abiraterone + Capivasertib FDA approved in June 2026 for patients with PTEN-deficient mHSPC**
- Toxicity is real: 52% diarrhea, 38% hyperglycemia, 35% rash; time to physical well-being decline favored control arm

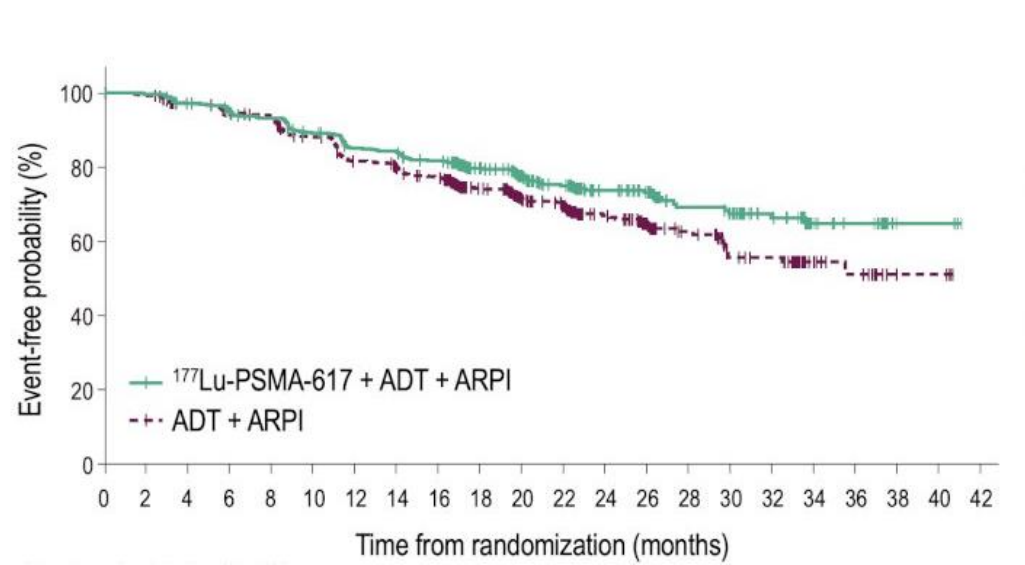




Fizazi K, ESMO 2025; Fizazi K, Annals of Oncology 2025

PSMAddition: ADT + ARPI + ^{177}Lu-PSMA-617 in PSMA-positive mHSPC

- Lutetium-177currently FDA approved for mCRPC pre- and post-docetaxel
- Patients with PMSA PET-positive mHSPC treated with ADT + ARPI were randomized to Lutetium-177 vs placebo
- rPFS benefit consistent across all prespecified subgroups: HV (0.72), LV (0.73), de novo (0.74), recurrent (0.74)
- OS is immature, but favors Lutetium-177 (HR: 0.84) – note 60% crossover
- NDA filed late 2025, expect FDA ruling this year



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

Tagawa S, ESMO 2025

Summary of new data for mHSPC

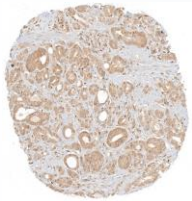
Trial	Agent	Biomarker	FDA Status	rPFS HR	OS HR	OS Verdict
AMPLITUDE	Niraparib + abiraterone	BRCA2 mutation	✅ Approved Dec 2025	0.52	0.75	🟡 Immature — not significant
TALAPRO-3	Talazoparib + enzalutamide	HRR alteration	➡️ SOON Submission imminent	0.48	0.77	🟡 Immature — not significant
CAPItello-281	Capivasertib + abiraterone	PTEN loss (IHC)	✅ Approved June 2026	0.81	0.90	🟡 Immature — not significant
PSMAddition	Lutetium-177 + ARPI	PSMA+ (PET)	⏳ NDA filed – H2 2026	0.72	0.84	🟡 Immature – not significant

First-line treatment options for mHSPC in 2026-2027

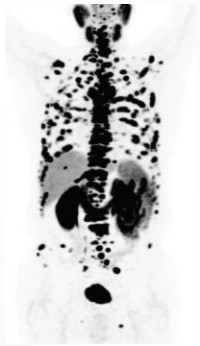
Newly diagnosed mHSPC in **2027**

Biomarker testing

Germline genetic testing and tumor genomic profiling



PTEN IHC



PSMA PET scan

BRCA2 alteration HRR alteration	Abi + Niraparib Enza + Talazoparib
PTEN loss on IHC	Abi + Capivasertib
PSMA PET positive	ARPI + Lutetium-177
None of the above	ADT + ARPI +/- Docetaxel

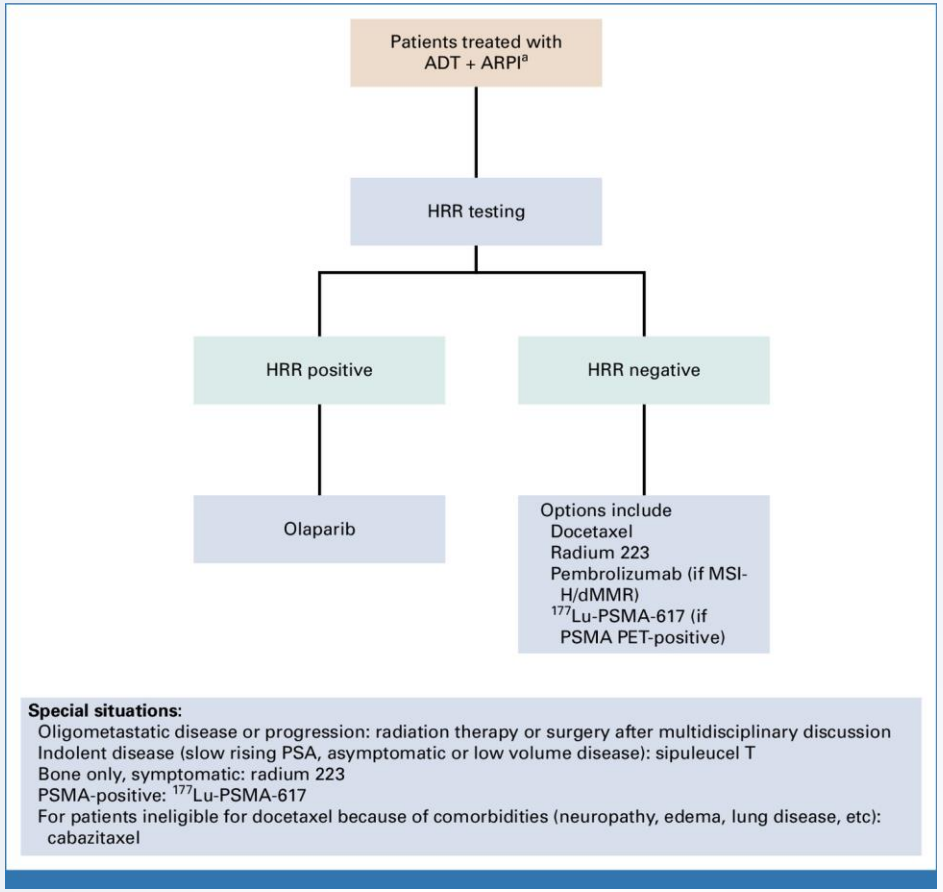
Outstanding questions that will inform the mHSPC treatment paradigm

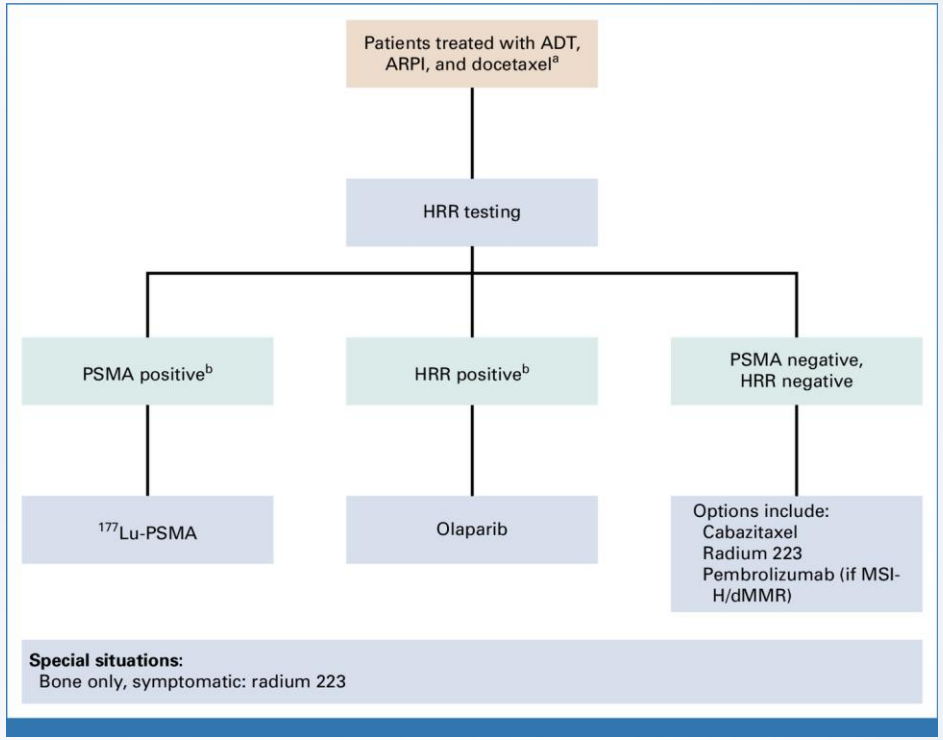
- **Does adding a targeted agent replace docetaxel for high-volume patients?**
  - For high-volume BRCA2-altered, PTEN-deficient, or PSMA-positive mHSPC — is ADT + ARPI + targeted agent sufficient, or do we still need docetaxel? None of these trials randomized against a triplet control arm.
- **What do you do when biomarkers overlap?**
  - A meaningful proportion of patients are BRCA2-altered AND PTEN-deficient AND PSMA-positive. No trial addresses combination or sequential use of targeted agents.
- **Which of these agents will show an overall survival benefit?**
  - Every new agent shows a favorable OS trend (HR 0.75-0.90). None has crossed the line. All are immature. OS is the standard we should hold these drugs to, and we owe patients honesty about what we know and what we're still waiting for.

mCRPC or mAPMR

First-line mCRPC treatment depends on mHSPC treatment

Recommendations from the ASCO mCRPC Living Guidelines 2026.1





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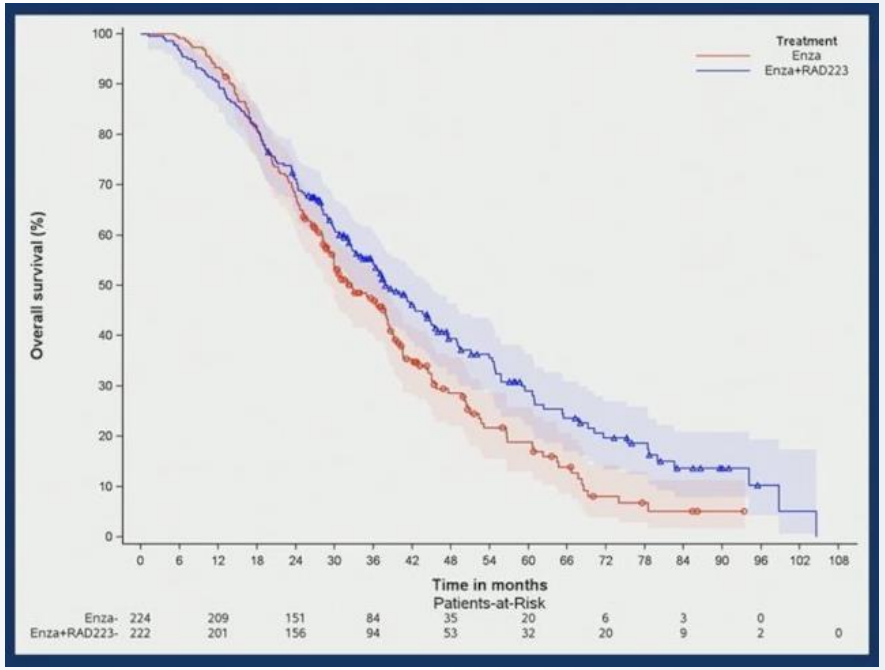
Combinations
Sequence
New strategies

Taplin ME, JCO 2026

PEACE-3: Enzalutamide + Radium-223 in mCRPC

- Patients with asymptomatic or mildly symptomatic bone-only mCRPC treated with ADT were randomized to enza vs enza + radium
- Notes: patients were only allowed to receive ADT +/- docetaxel, so were ARPI naïve; bone protecting agents mandatory
- Primary endpoint met – final OS HR 0.76 (p = 0.0096) Median OS 38.2 vs. 32.6 months (+5.6 months); rPFS also improved
- **Who is this patient in 2026?** ARPI-naïve, bone-dominant, PSMA-low; real, but rare



	Event/ Total	Median (95%CI) (months)[1]	Hazard Ratio (95% CI)[2]	1-sided P-value
Treatment				Logrank: 0.0096[3] Permutation:0 .0105
Enza	165/224	32.62 (29.31-38.24)	0.76 (0.60-0.96)	
Enza+Ra223	152/222	38.21 (33.08-44.75)		

Gallardo E, ASCO GU 2026; Gillessen S, Annals of Oncology 2026

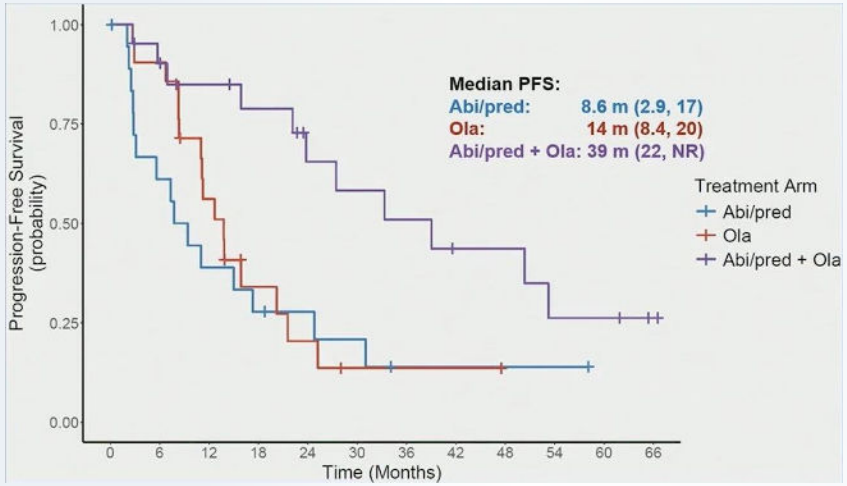
The current landscape of molecularly guided therapies for mCRPC in 2026

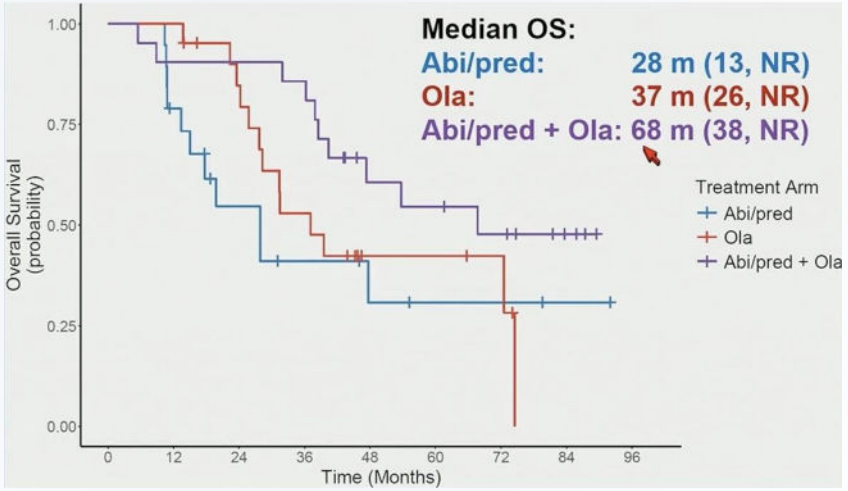
- Pembrolizumab approved for MMRd/MSI-high mCRPC (~3%)
- Several PARP inhibitor regimens approved for HRR-altered mCRPC (~20%)

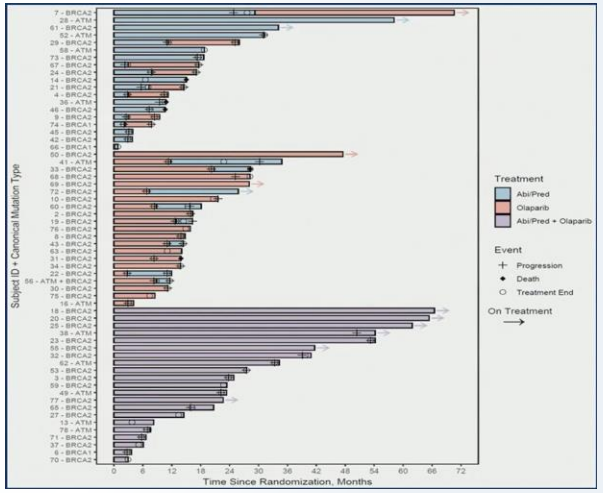
	ATM	*ATR*	*BARD1*	***BRCA1***	***BRCA2***	*BRIP1*	*CDK12*	*CHEK1*	*CHEK2*	*FANCA*	*FANCL*	*MLH1*	*MRE11A*	*NBN*	*PALB2*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD54L*
Olaparib	X		X	X	X	X	X	X	X		X				X	X	X	X	X
Rucaparib				X	X														
Olaparib + Abiraterone				X	X														
Niraparib + Abiraterone				X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

Do patients with BRCA-altered mCRPC need a PARPi + ARPI combo?

Patients with ARPI-naïve mCRPC with ATM/BRCA1/BRCA2 alterations were randomized to 1) abiraterone, 2) olaparib, 3) abiraterone + olaparib – crossover allowed



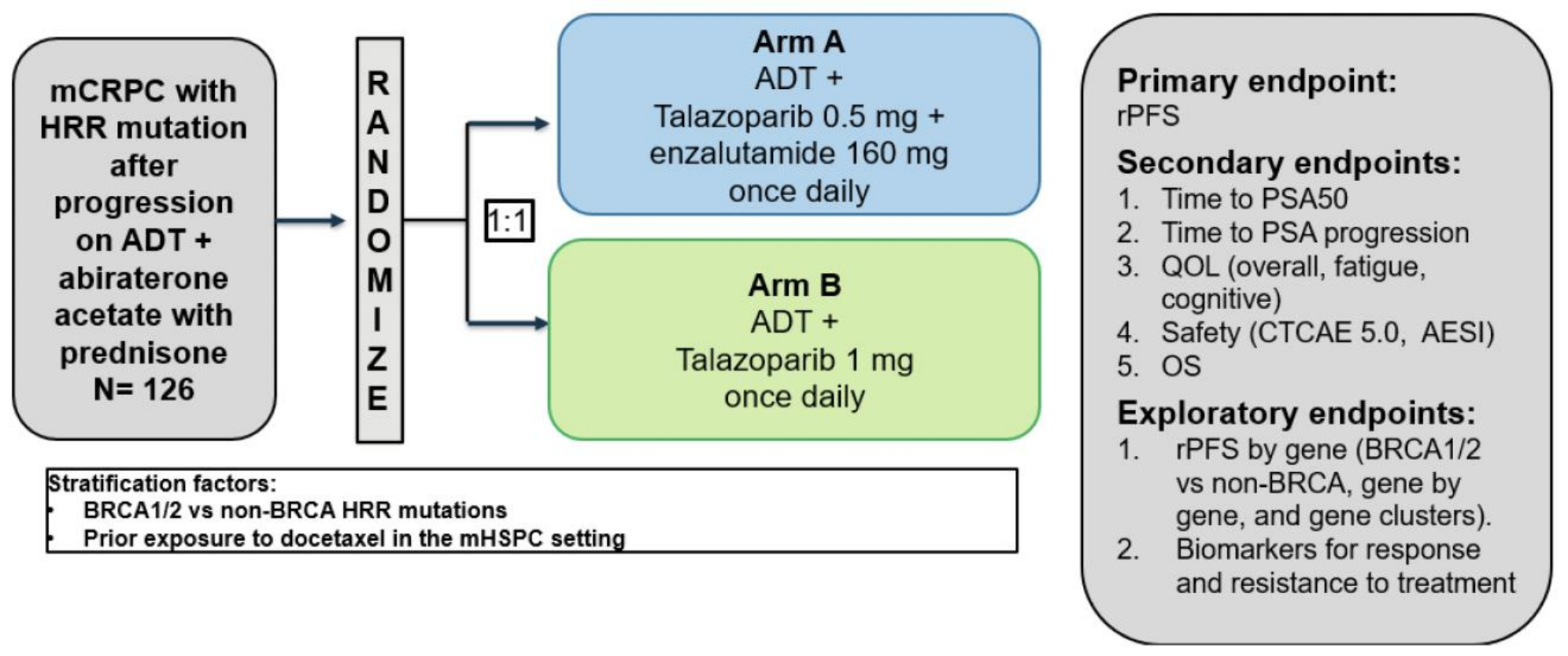




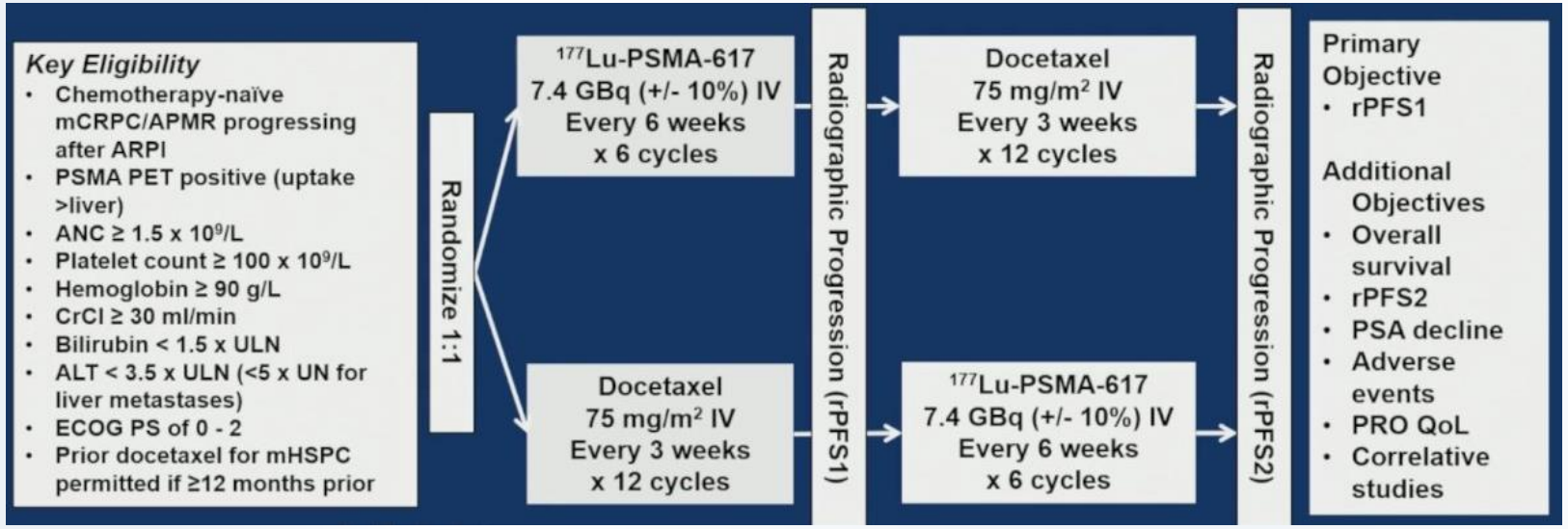
Is this data relevant in 2026? Only for ARPI-naïve mCRPC, which is rare. But informs practice for those patients.

Hussain M, ASCO GU 2026

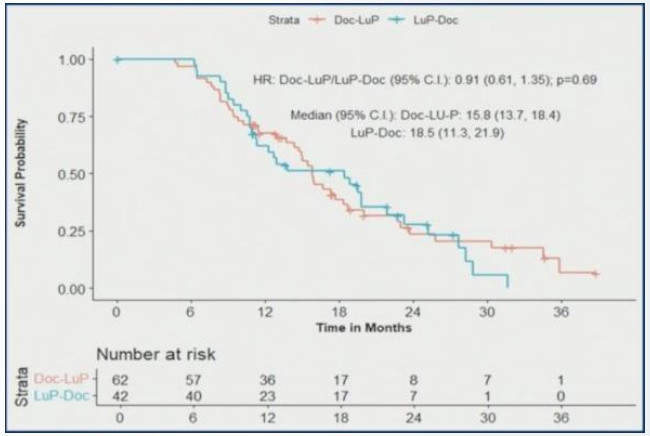
TALENT: A randomized open-label phase 2 study of talazoparib +/- enzalutamide in patients with HRR-altered mCRPC after progression on abiraterone



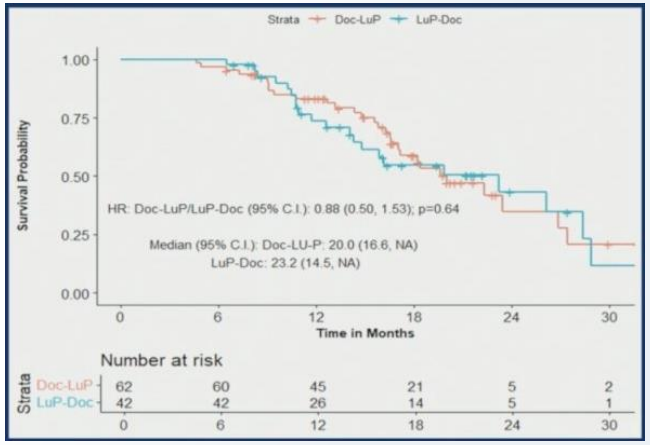
PLUDO: Lutetium-177 vs docetaxel in post-ARPI mCRPC – order matters less than ensuring patients receive both agents



rPFS2 from randomization



OS from randomization



Among patients who received both Lutetium-177 and docetaxel, there were no significant differences in rPFS or OS between the sequencing strategies

Chi K, ASCO 2026

The pipeline for mCRPC is promising

Drug	Company	Class	Target	Trial Name	NCT	Control Arm
BMS-986365	Bristol Myers Squibb	AR degrader (PROTAC)	AR + LBD mutations	rechARge	NCT06764485	Docetaxel / ARPI switch
Opevesostat	Merck/Orion	CYP11A1 inhibitor	All steroid biosynthesis	OMAHA-003	NCT06136624	ARPI switch
Mevrometostat	Pfizer	EZH2 inhibitor	Epigenetic / NE plasticity	MEVPRO-1	NCT06551324	Physician's choice
TLX591-Tx	Telix	RLT	PSMA	ProstACT Global	NCT06520345	SOC
Ac-225 PSMA-617	Novartis	RLT (alpha-emitting)	PSMA	PSMAcTION	NCT06780670	SOC
Ifinatamab deruxtecan	Merck / Daiichi Sankyo	ADC	B7-H3	IDeate-Prostate01	NCT06925737	Docetaxel
BNT324/DB-1311	BioNTech / DualityBio	ADC	B7-H3	BNT324-03	NCT07365995	Docetaxel
Pasritamig	J&J	BiTE	KLK2	KLK2-PASenger	NCT07225946	Docetaxel
Xaluritamig	Amgen	BiTE	STEAP1	XALute	NCT06691984	Cabazitaxel / ARPI

Key takeaways

- mHSPC
  - All patients should get germline & somatic testing for HRR and PTEN IHC at diagnosis today
    - Patients with BRCA2 alterations should be considered for ADT + abiraterone + niraparib
    - Patients with PTEN loss should be considered for ADT + abiraterone + capivasertib
  - PSMA PET could be standard by end of 2026 pending FDA review of PSMAddition
  - Whether these should replace docetaxel for high-volume disease and how to handle overlapping biomarkers remain unanswered questions
- mCRPC
  - First-line treatment depends on what happened with mHSPC – follow the ASCO Living Guidelines
  - Use both Lutetium-177 and docetaxel – order matters less than ensuring patients receive both
  - PEACE-3 delivered the clearest new OS win of the past year for enzalutamide + radium-223 in bone-dominant mCRPC – caveat that this was in ARPI-naïve patients
  - Many distinct mechanism in active phase 3 trials: novel AR pathway modulations, EZH2 inhibitors, RLT, ADC, BiTEs

Q&A