Management of mCRPC in 2025: New Data and Future Directions

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Sea Island, GA

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Partners for Advancing Clinical Education
Bio Ascend

Disclosures

Consultant:

Exelixis

Gilead

Research funding to Institution:

Bristol Myers-Squibb

Early Systemic Therapy Trials in mCRPC

Agent	Trial	Target Population	Arms	HR	Survival (months)	Reference
Docetaxel	TAX 327 N= 1006	mCRPC with or without symptoms	Docetaxel/prednisone vs mitoxantrone/prednisone	0.76	18.9 vs 16.5	Tannock, I. et al. N Engl J Med 351:1502-12, 2004
Sipuleucel-T	IMPACT N = 512	Few symptoms mCRPC	Sipuleucel – T vs Control	0.78	25.8 vs 21.7	Kantoff, P. et al. N Engl J Med 363:411-22, 2010
Cabazitaxel	TROPIC N = 755	Post-Docetaxel	Cabazitaxel/prednisone vs Mitoxantrone/prednisone	0.70	15.1 vs 12.7	de Bono, J. et al. Lancet 376:1147-54, 2010
Abiraterone	COU –AA-301 N = 1195	Post-Docetaxel	Abiraterone/prednisone vs Placebo/prednisone	0.65	14.8 vs 10.9	de Bono, J. et al. N Engl J Med 364:1995-2005, 2011
Radium -23	ALSYMPCA N = 921	Post-Docetaxel (or unsuitable)	Radium-223/BSC* vs placebo/BSC	0.70	14.9 vs 11.3	Parker, C. et al. ASCO 2012. J Clin Oncol 30, (suppl; abstr LBA4512), 2012.
Enzalutamide	AFFIRM N = 1199	Post-Docetaxel	MDV3100 vs Placebo	0.63	18.4 vs 13.6	Scher, H. et al. N Engl J Med 367:1187-1197, 2012.
Abiraterone	COU-AA-302	Pre-Docetaxel	Abiraterone/prednisone vs Placebo/prednisone	0.75	NR vs 27.2	Ryan C. et al. Clin Cancer Res 17:4854-61, 2011

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[f,fff,ggg,hhh,iii]

No prior docetaxel/no prior novel hormone therapy[jjj]	Progression on prior novel hormone therapy/no prior docetaxel[jjj]
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1 if no visceral metastases) ▸ Docetaxel[ddd] (category 1) ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Docetaxel (category 1)[ddd] ▸ Olaparib for *BRCA* mutation[lll] (category 1) ▸ Rucaparib for *BRCA* mutation[lll] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[ppp] ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[lll] ▸ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[z]
Progression on prior docetaxel/no prior novel hormone therapy[jjj]	**Progression on prior docetaxel and a novel hormone therapy[jjj]**
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1) ▸ Cabazitaxel[ddd] ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Niraparib/abiraterone[z, lll,mmm] for *BRCA* mutation ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Cabazitaxel[ddd] (category 1) ▸ Docetaxel rechallenge[ddd] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Lu-177–PSMA-617 for PSMA-positive metastases[ppp] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Olaparib for HRR mutation[lll] (category 1 for *BRCA* mutation) ▸ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb[ddd] ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]

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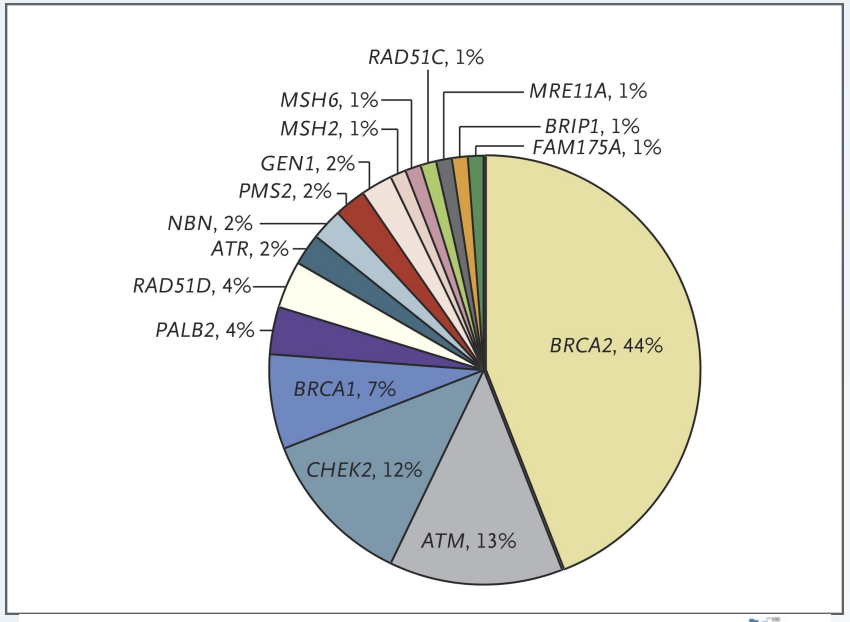
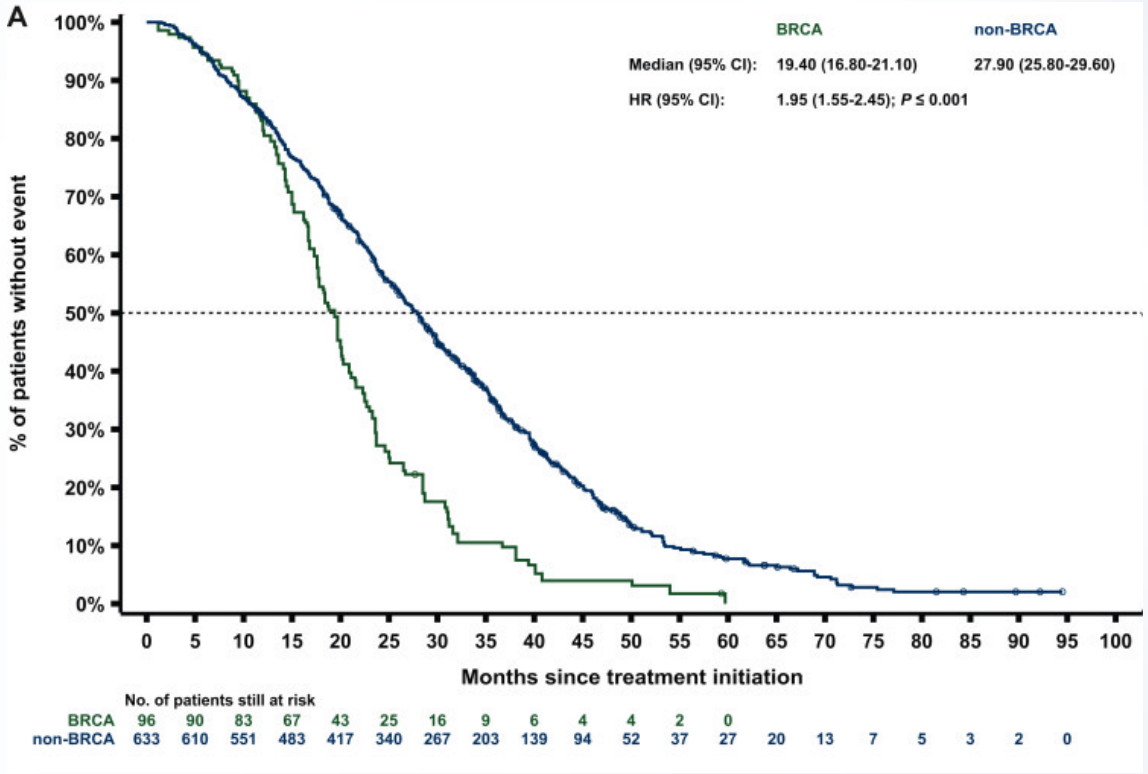
Common DNA Repair Mutations in Prostate Cancer often Associated with Worse Outcomes



12% Germline DDR alterations

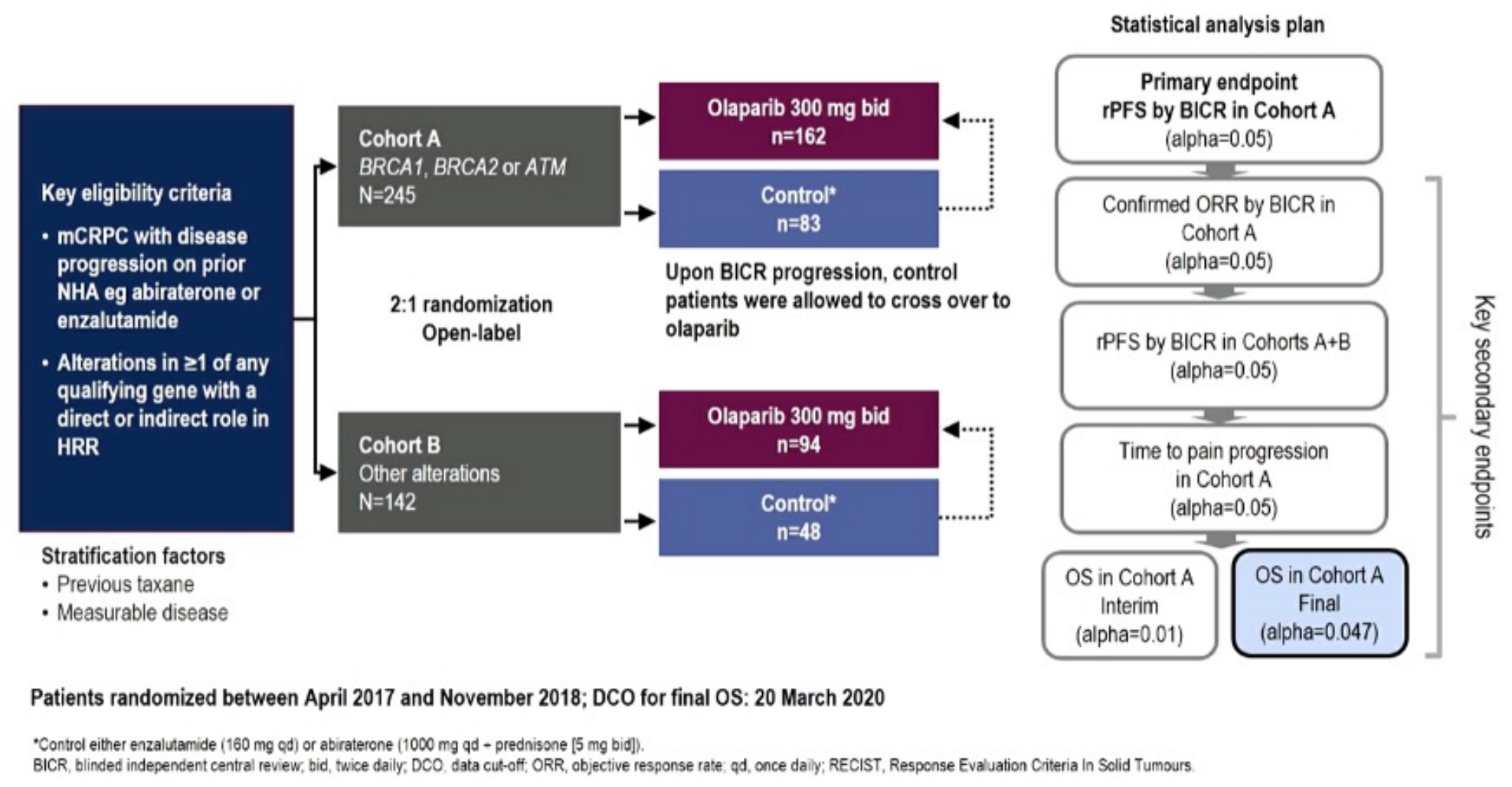
20-25% Somatic DDR alterations

Capture Study



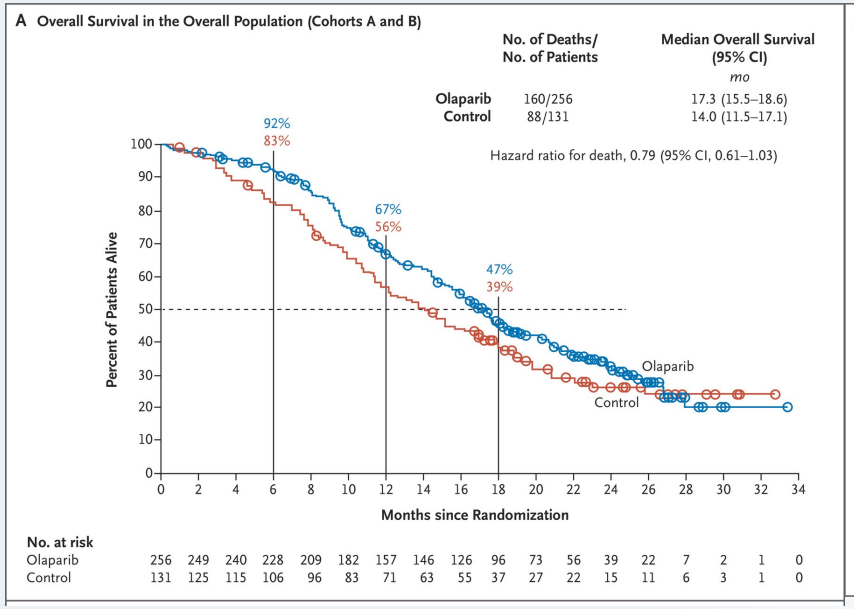
Pritchard, CC et al. N Eng J Med. 2016: 375: 443-445; Robinson, D, et al. Cell. 2015 May 21;161(5):1215-1228. Olmos D, et al. Ann Oncol. 2024 May;35(5):458-472.

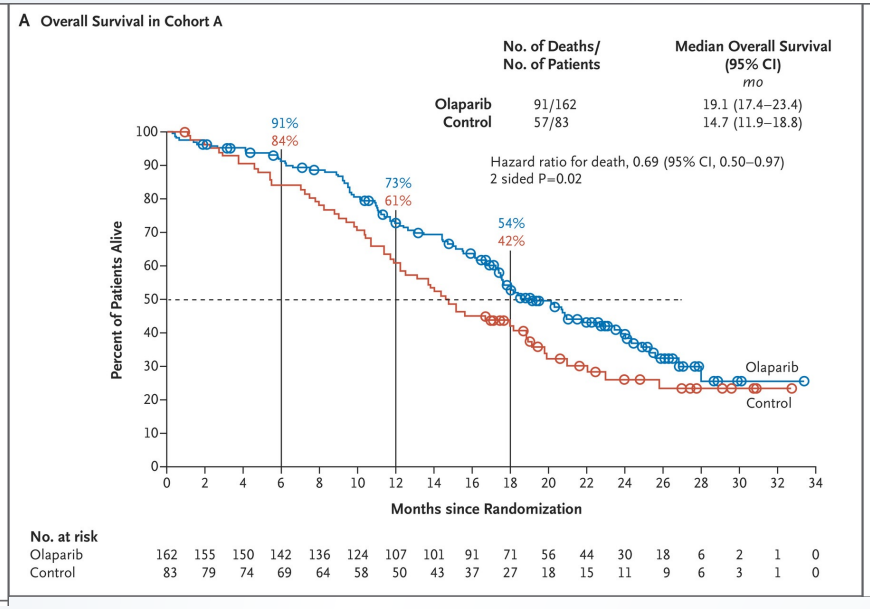
Profound Study: Phase III Trial of Olaparib in mCRPC

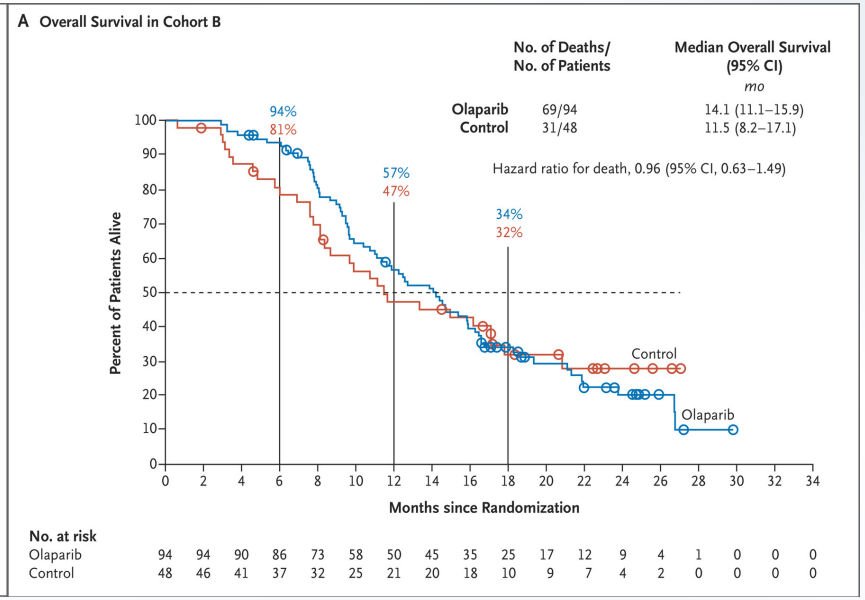


Hussain,M, et al. N Engl J Med 2020; 383:2345-2357. ESMO 2020, Mateo et al.

Profound Study: Phase III Trial of Olaparib in mCRPC







Alterations Overall

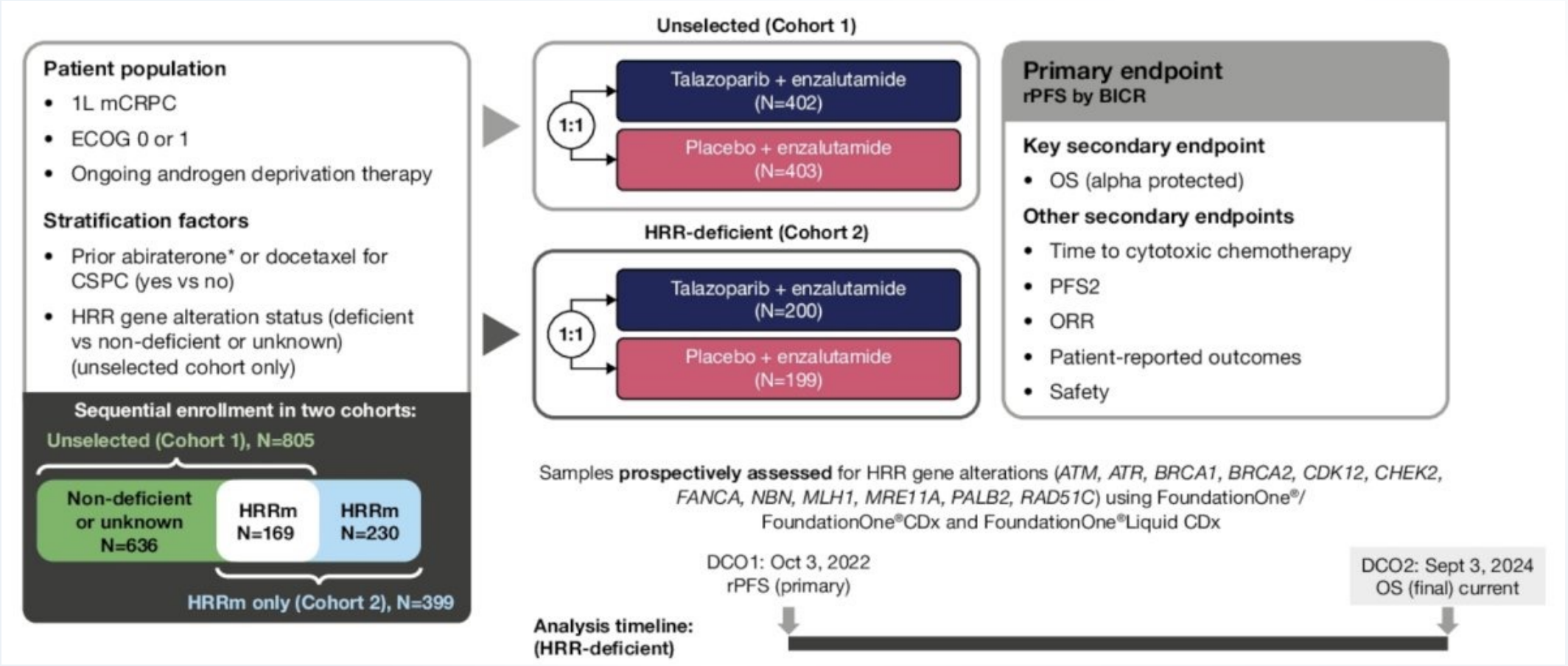
BRCA1, BRCA2, ATM

Other Alterations

Hussain, M, et al. N Engl J Med 2020; 383:2345-2357

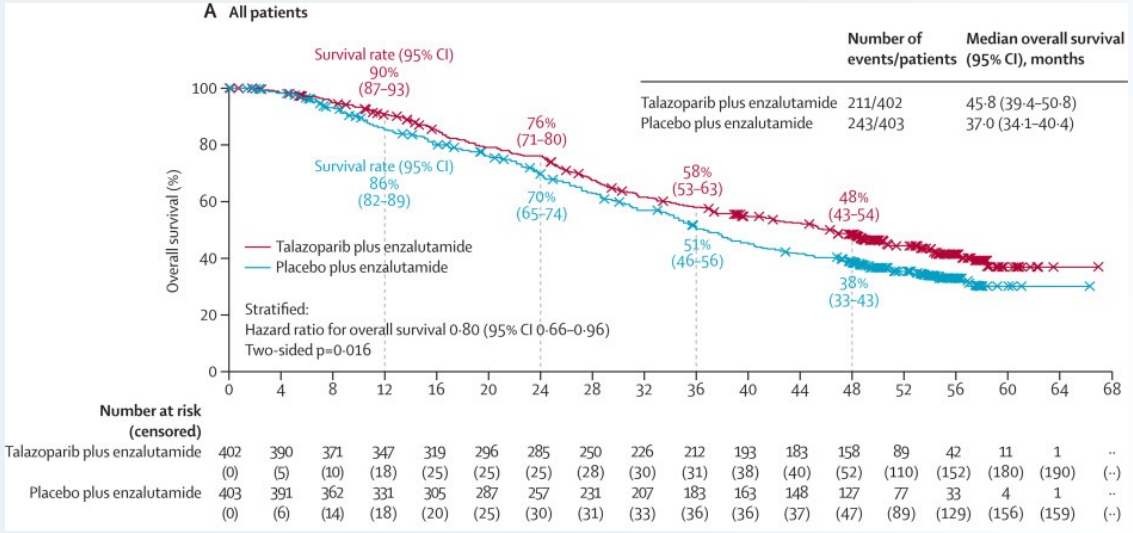
Talazoparib plus enzalutamide in men with first-line metastatic CRPC (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Updated Analysis

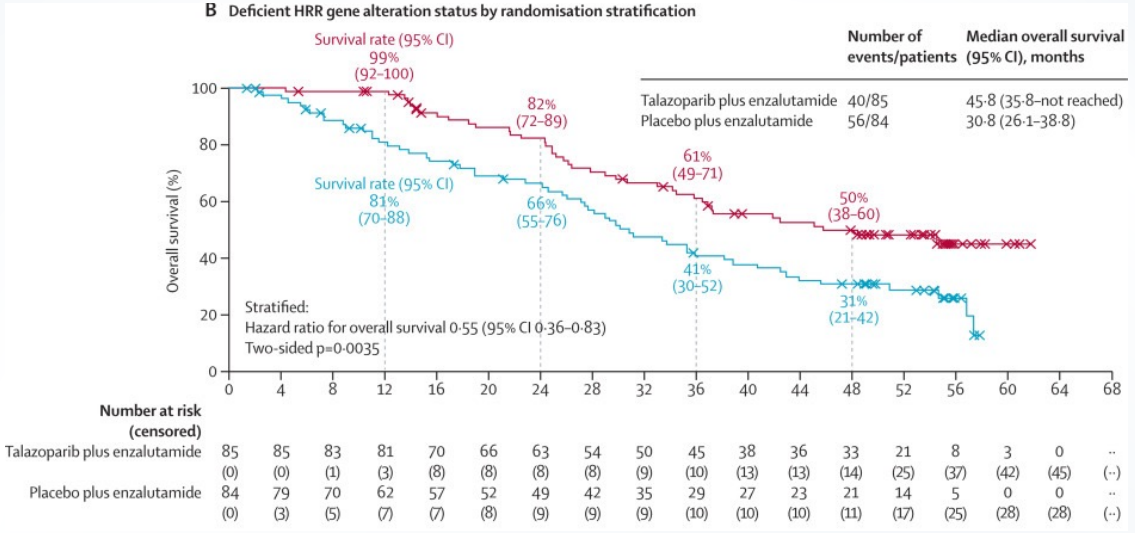
5% Prior NHA

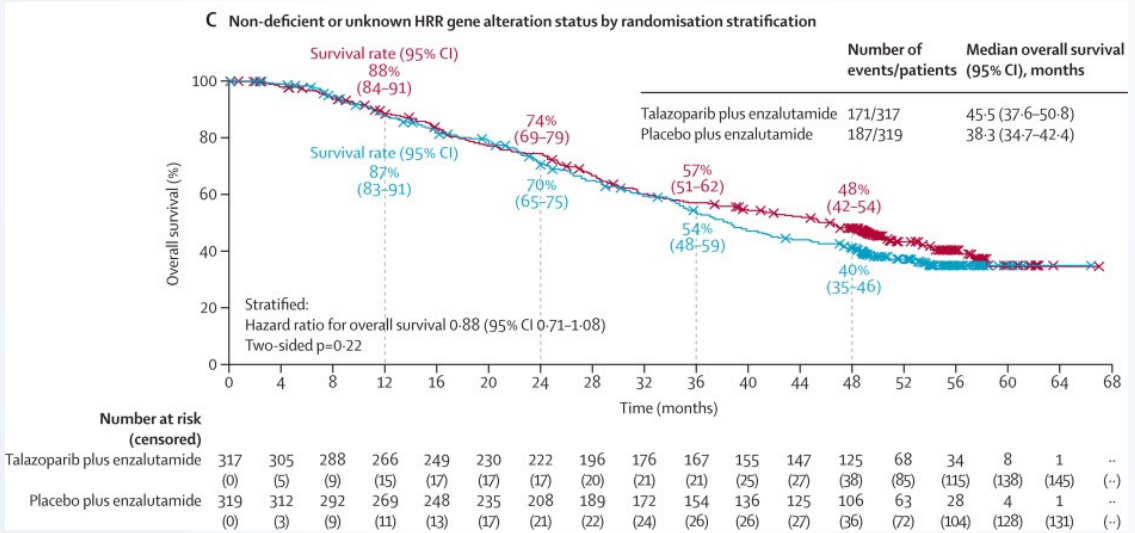


Fizazi, K, et al. GU ASCO, 2025; Agarwal N, et al. Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. Lancet. 2025 Jul 16:S0140-6736(25)00684-1.

Talazoparib plus enzalutamide in men with first-line metastatic CRPC (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Final OS Analysis

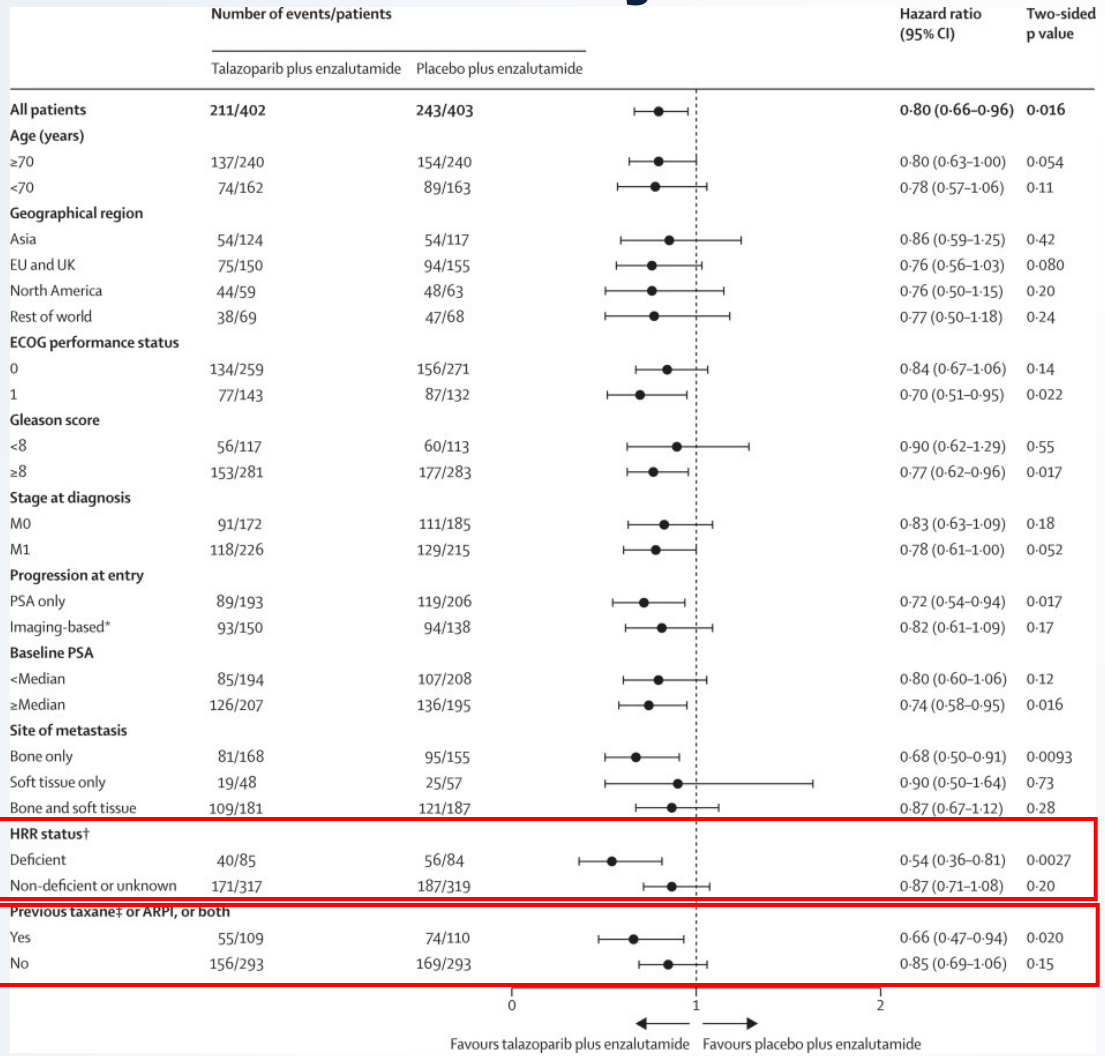






Agarwal N, et al. Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. Lancet. 2025 Jul 16:S0140-6736(25)00684-1.

Talazoparib plus enzalutamide in men with first-line metastatic CRPC (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Final OS Analysis.



	Number of events/patients		Hazard ratio (95% CI)	Two-sided p value
	Talazoparib plus enzalutamide	Placebo plus enzalutamide		
All patients	**211/402**	**243/403**	**0·80 (0·66–0·96)**	**0·016**
Age (years)				
≥70	137/240	154/240	0·80 (0·63–1·00)	0·054
<70	74/162	89/163	0·78 (0·57–1·06)	0·11
Geographical region				
Asia	54/124	54/117	0·86 (0·59–1·25)	0·42
EU and UK	75/150	94/155	0·76 (0·56–1·03)	0·080
North America	44/59	48/63	0·76 (0·50–1·15)	0·20
Rest of world	38/69	47/68	0·77 (0·50–1·18)	0·24
ECOG performance status				
0	134/259	156/271	0·84 (0·67–1·06)	0·14
1	77/143	87/132	0·70 (0·51–0·95)	0·022
Gleason score				
<8	56/117	60/113	0·90 (0·62–1·29)	0·55
≥8	153/281	177/283	0·77 (0·62–0·96)	0·017
Stage at diagnosis				
M0	91/172	111/185	0·83 (0·63–1·09)	0·18
M1	118/226	129/215	0·78 (0·61–1·00)	0·052
Progression at entry				
PSA only	89/193	119/206	0·72 (0·54–0·94)	0·017
Imaging-based*	93/150	94/138	0·82 (0·61–1·09)	0·17
Baseline PSA				
<Median	85/194	107/208	0·80 (0·60–1·06)	0·12
≥Median	126/207	136/195	0·74 (0·58–0·95)	0·016
Site of metastasis				
Bone only	81/168	95/155	0·68 (0·50–0·91)	0·0093
Soft tissue only	19/48	25/57	0·90 (0·50–1·64)	0·73
Bone and soft tissue	109/181	121/187	0·87 (0·67–1·12)	0·28
HRR status†				
Deficient	40/85	56/84	0·54 (0·36–0·81)	0·0027
Non-deficient or unknown	171/317	187/319	0·87 (0·71–1·08)	0·20
Previous taxane‡ or ARPI, or both				
Yes	55/109	74/110	0·66 (0·47–0·94)	0·020
No	156/293	169/293	0·85 (0·69–1·06)	0·15

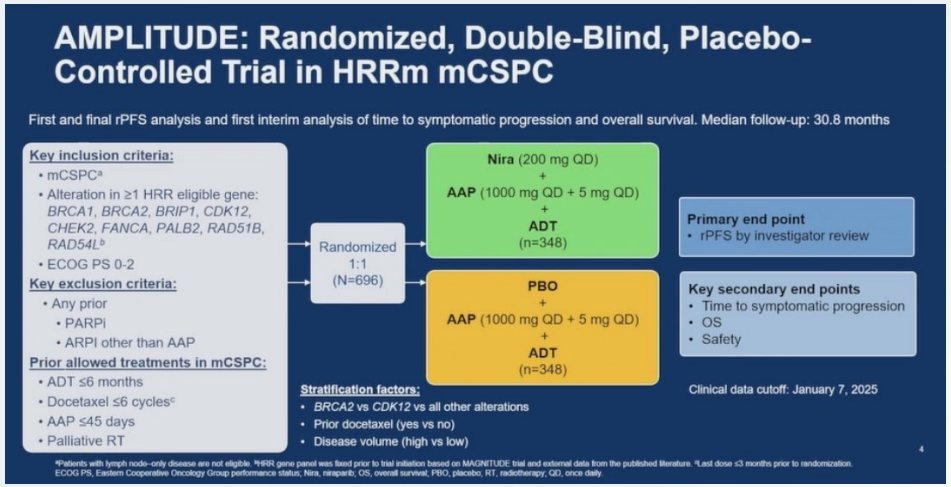
Previous ARPI for castration-sensitive prostate cancer (n=50), the HR for overall survival was 0·79 (0·40–1·55; two-sided p=0·49), and in patients who received previous docetaxel (n=180), the HR for overall survival was 0·63 (0·42–0·94; two-sided p=0·024).

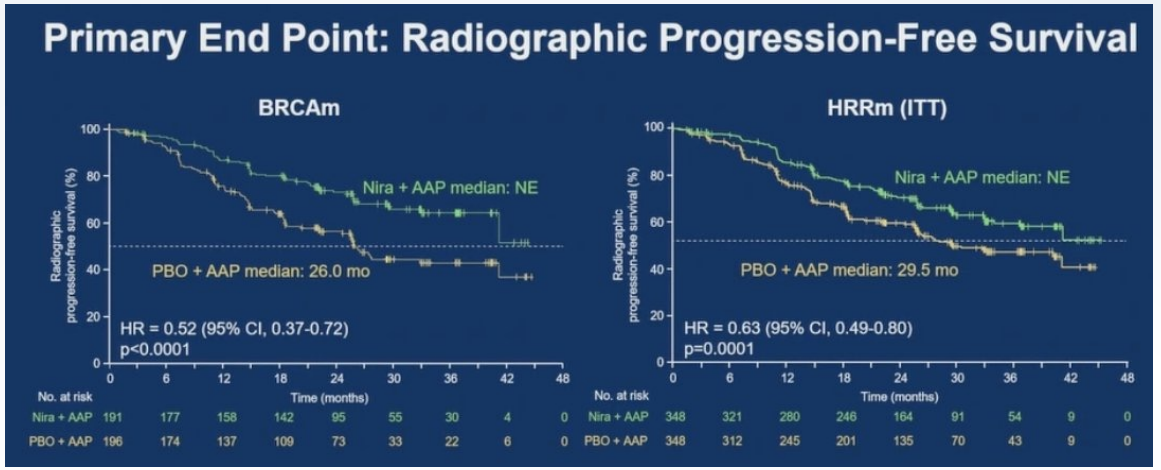
Agarwal N, et al. Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. Lancet. 2025 Jul 16:S0140-6736(25)00684-1.

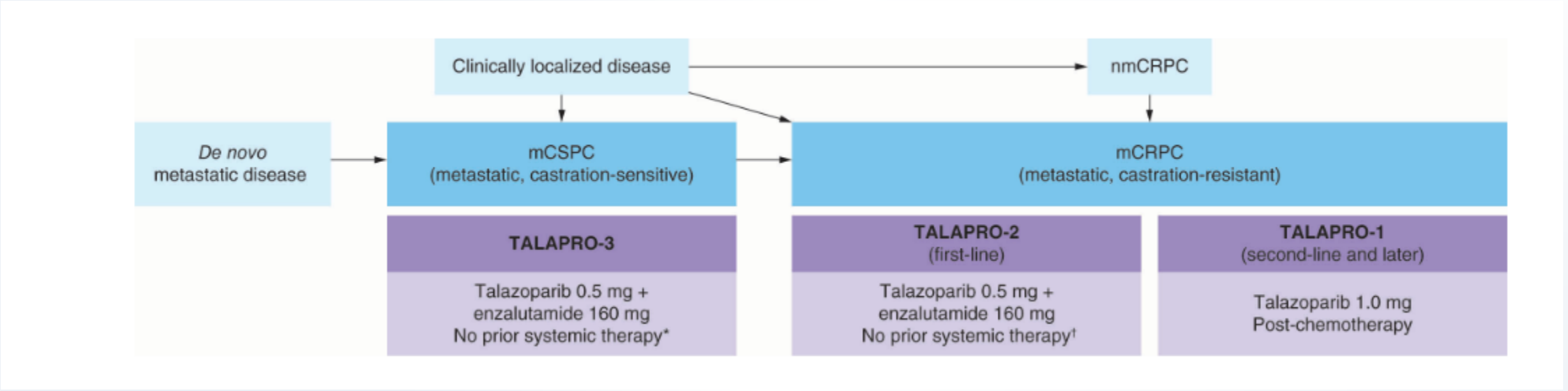
Recent PARP InhibitorTrials in CRPC

Trial N	Agents	Target Population	HR	Survival (months)	Reference
PROFOUND N = 805	Olaparib vs. 2nd novel hormonal agent	CRPC,HRR Mutant, Progressed on 1st line novel hormonal agent	0.79 HR Overall 0.69 HR Cohort A	17.3 v. 14.0 overall 19.1 vs. 14.7 cohort A	Hussain, M, et al. N Engl J Med 2020; 383:2345-2357
TRITON 2/3 N = 115 N = 405	Rucaparib, Ph II Rucaparib vs. MD Choice, Ph III	BRCA/ATM mutant, CRPC, Progression on NHA and Taxane,	0.50 HR BRCA PFS 0.61 HR Overall PFS	17.2 mos OS Ph II 10.2 mos vs. 6.4 mos PFS Ph III overall 11.2 mos vs. 6.4 mos PFS BRCA patients	Abida W, et al. *J Clin Oncol*. 2020;38:3763-3772 Fizazi, K, et al. N Engl J Med 2023;388:719-73
PROPEL N = 796	Abiraterone +/-Olaparib	1st Line CRPC, no prior Abi, Docetaxel Allowed HSPC	0.68 HR PFS 0.81 HR OS	42.1 mos vs. 34.8 mos	Saad F, et al. Lancet Oncol. 2023 Oct;24(10):1094-1108
TALAPRO 2 N = 805	Enzalutamide +/- Talazoparib	1st Line CRPC, 5% prior NHA	0.80 OS HR All comers 0.55 OS HR deficient 0.88 OS HR HRR Non Deficient 0.67 rPFS HR	mOS 45.8 mos vs. mOS 37 mos mPFS 33.1 mos Vs. mPFS19.5 mos *1st Line CRPC	Fizazi, K, et al. GU ASCO 2025 Agarwal N, et al. Lancet. 2025 Jul 16:S0140-6736(25)00684-1.
MAGNITUDE N = 1000	Abiraterone + /- Niraparib	1st line CRPC, < 4 mos Abi	0.73 HR PFS HRRm 0.53 HR PFS BRCA+ 0.785 HR OS HRRm (NS) 0.663 HR OS	16.5 vs. 13.7 mos mPFS (HRR+) 16.6 vs. 10.9 mos mPFS (BRCA1/2) 30.26 mos mOS vs. 28.55 mos	Chi KN, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351 Chi, KN et al. Eur Urol Oncol. 2025 May 5:S2588-9311(25)00107-5.

PARP Inhibitors in Castration –Sensitive Patients

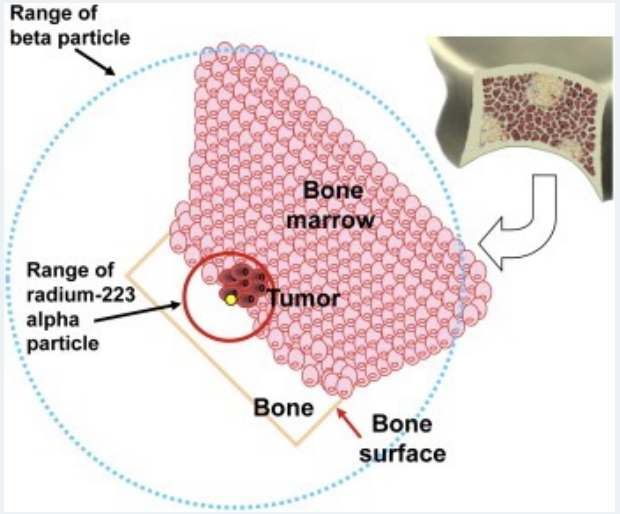






Attard, G, et al. ASCO Annual Meeting 2025; Agarwal N, et al. Future Oncol. 2024 Mar;20(9):493-505.

Radium-223 and Enzalutamide in Metastatic Castration-Resistant Prostate Cancer: EORTC-GUCG 1333/PEACE-3



Study population
- Patients with mCRPC and bone metastases
- Asymptomatic or mildly symptomatic*
- WHO PS of 0 or 1
- No prior treatment with enzalutamide or Ra223
- No known visceral metastases
- Ongoing ADT

N=446**

1:1 Randomisation

Ra223
55 kBq/kg iv every 4 weeks for 6 cycles plus
Enzalutamide 160 mg od

Stratification factors
- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone protecting agents
- Prior abiraterone (yes vs no)

Enzalutamide 160 mg od

Primary endpoint
- rPFS

Key secondary endpoints
- Safety
- Overall Survival
- Time to next treatment
- Time to pain progression
- Time to first SSE (symptomatic skeletal event)

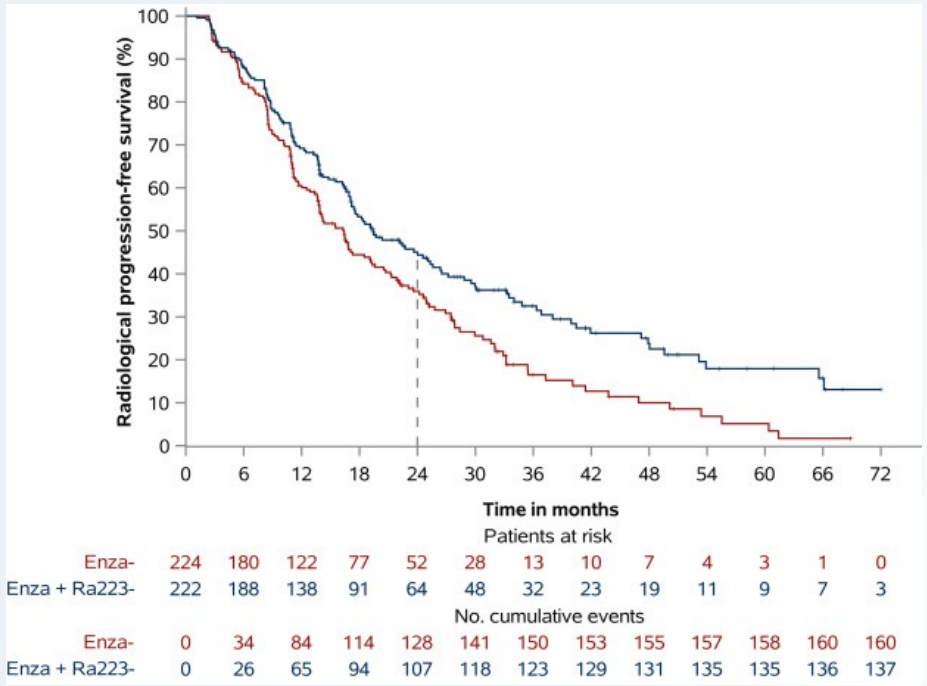
*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

BARCELONA 2024 ESMO congress

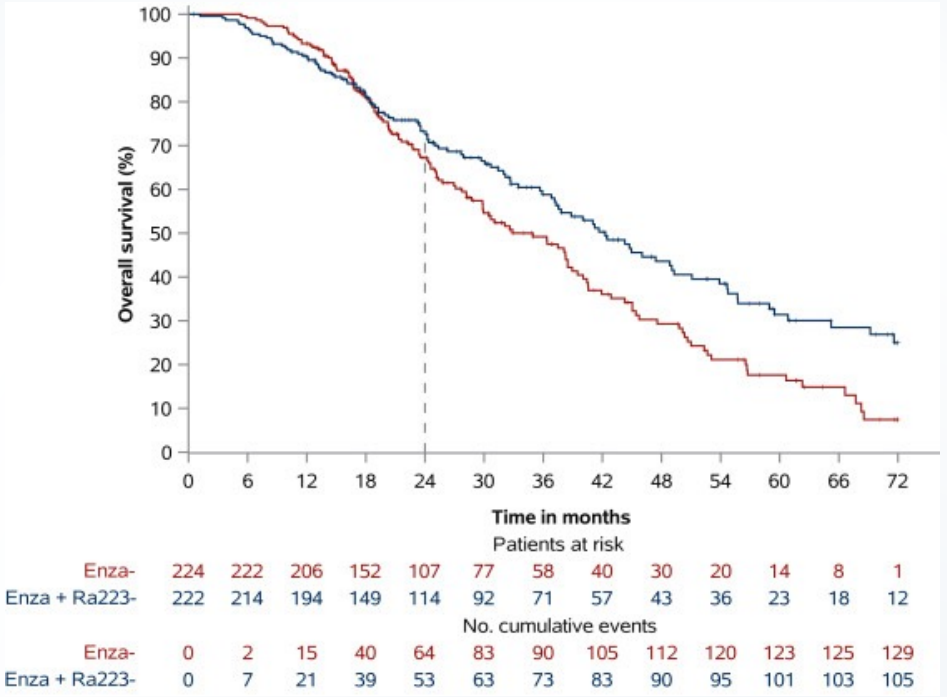
Use of bone protecting agents (BPA) made mandatory (after inclusion of 119 patients)

Shore, N. Urology. 2015 Apr;85(4):717-24.
Sommer, SG et al. ESMO 2024.

Increased PFS and OS with Radium 223 + Enzalutamide in EORTC-GUCG 1333/PEACE-3 Trial



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

*Fractures (regardless of their symptomatic or pathologic nature) were reported in 30 (13.4%) patients in the enzalutamide arm and 53 (24.3%) patients in the combination arm->obligatory Zoledronic Acid or Denosumaub amendment.
* (2.5%) patients had received an ARPI in the hormone-sensitive setting

Tombal B, et al. Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial. Ann Oncol. 2025 May 30:S0923-7534(25)00203-0; Sommer, SG et al. ESMO 2024;

COMRADE Study Design: Radium 223 +/- Olaparib in mCRPC

Eligibility

- -ECOG 0-1
- -Progressive metastatic CRPC
- -Presence ≥2 bone metastases
- -No visceral metastases
- -Adenopathy ≤ 4 cm
- -No prior radium-223
- -Prior docetaxel permitted*
- -Bone protecting agent use unless contraindicated

ctDNA collected at C1D1, on-treatment, and end of treatment

Phase 1

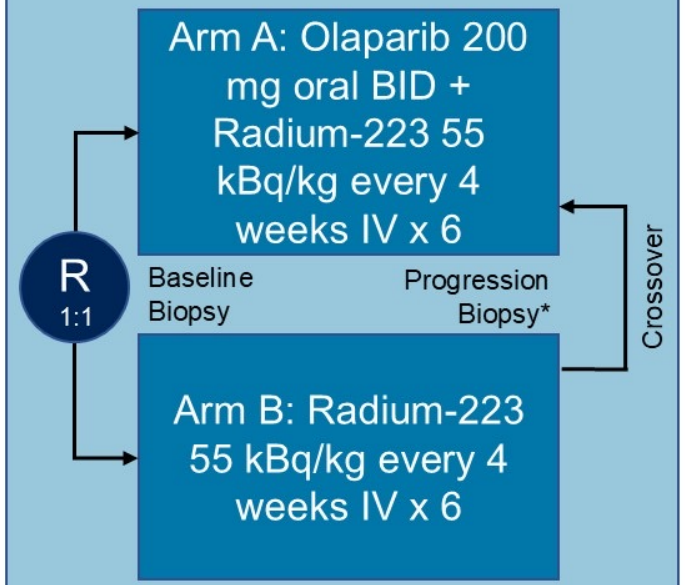
(3+3 dose escalation design)
1 cycle=28 days
DLT window first two cycles

Level	Ra-223	Olaparib
2	55 kBq/kg every 4 weeks IV x 6	300 mg BID
1		200 mg BID
-1		150 mg BID
-2		100 mg BID

Baseline Biopsy — Progression Biopsy**

Primary Endpoint: RP2D

Phase 2



Primary Endpoint: rPFS
(investigator assessed)

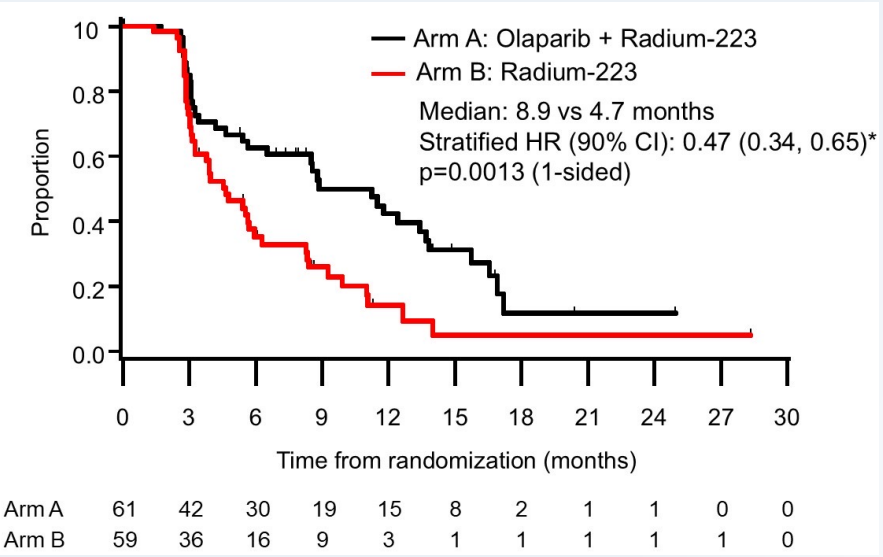
ECOG=Eastern Cooperative Oncology Group; CRPC=Castration resistant prostate cancer; DLT=Dose limiting toxicities; kBg/kg=Kilobecquerel/kilogram; IV=Intravenous; BID=Twice daily; RP2D=Randomized phase 2 dose; rPFS=Radiographic progression-free survival.
*Prior docetaxel permitted in any disease setting. **Optional.

Pan et al, Mol Cancer Ther, 2023

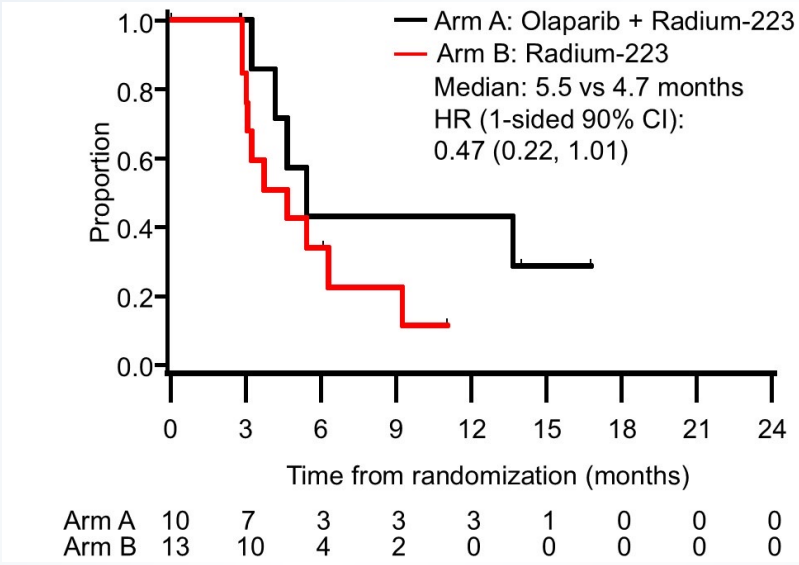
McKay, R et al, ASCO 2025; Pan et al. A Phase I Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Bone Metastases (COMRADE). Mol Cancer Ther. 2023 Apr 3;22(4):511-518.

Efficacy of Radium-223 +/- Olaparib in CRPC Patients

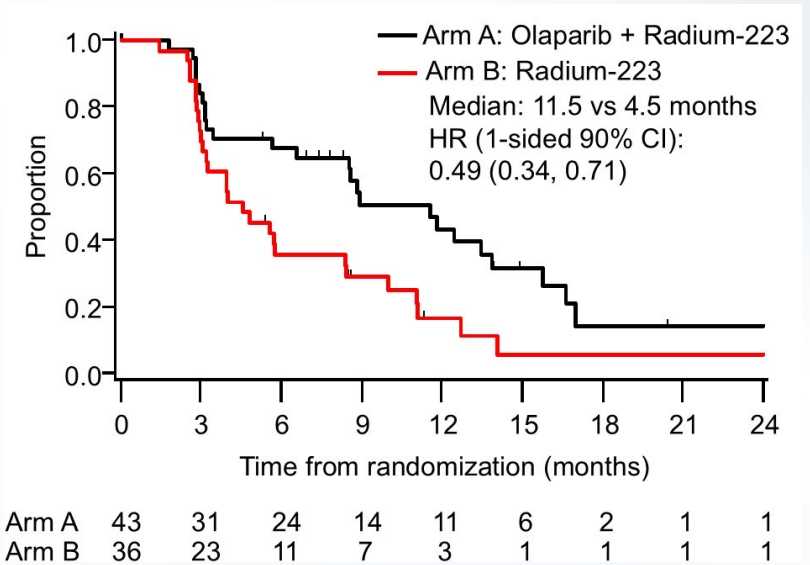
Overall Population



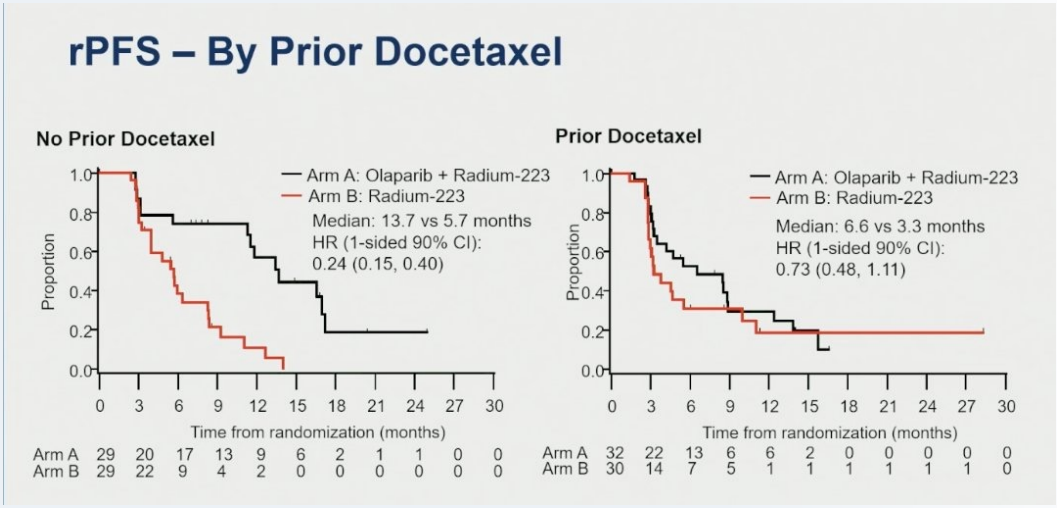
HRR Positive (23/102, 23%)



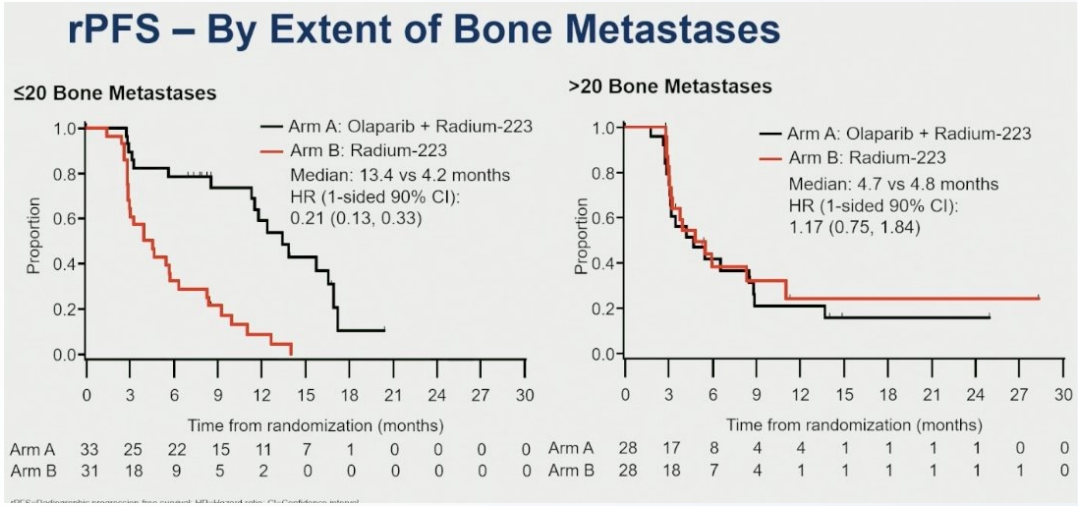
HRR Negative (79/102, 77%)



rPFS – By Prior Docetaxel

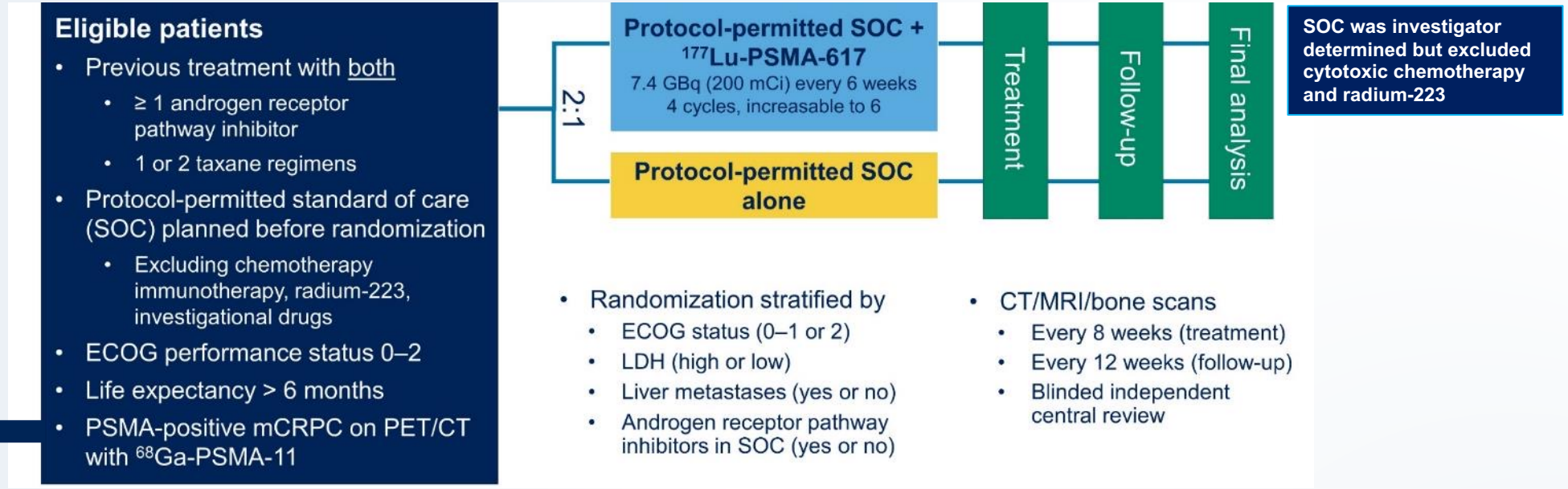


rPFS – By Extent of Bone Metastases



McKay, R et al, ASCO 2025

VISION: Phase 3, Open-Label Study of Protocol-Permitted SOC ± ^{177}Lu-PSMA-617 for PSMA-Positive mCRPC



Protocol Definitions:

- **PSMA(+) lesions:** ^{68}Ga-PSMA-11 uptake > liver parenchyma in ≥ 1 metastatic lesions of any size in any organ system
- **PSMA(-) lesions:** PSMA uptake ≤ liver parenchyma in any LN w/ short axis of ≥ 2.5 cm, in any metastatic solid-organ lesions w/ short axis ≥ 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of ≥ 1.0 cm in short axis. **Pts w/ any PSMA(-) metastatic lesion meeting these criteria were ineligible**.

Alternate primary endpoints

'Alternate' means the study would be positive if either or both primary endpoints were significant

Radiographic progression-free survival (rPFS) per PCWG3	• 84% power for HR of 0.67 at 364 events in 557 patients • Allocated one-sided α = 0.004 • Stratified log-rank test (plus Cox for HR)
Overall survival (OS)	• 90% power for HR of 0.7306 at 508 deaths in 814 patients • Allocated one-sided α = 0.021 (0.025 if rPFS positive) • Stratified log-rank test (plus Cox for HR)

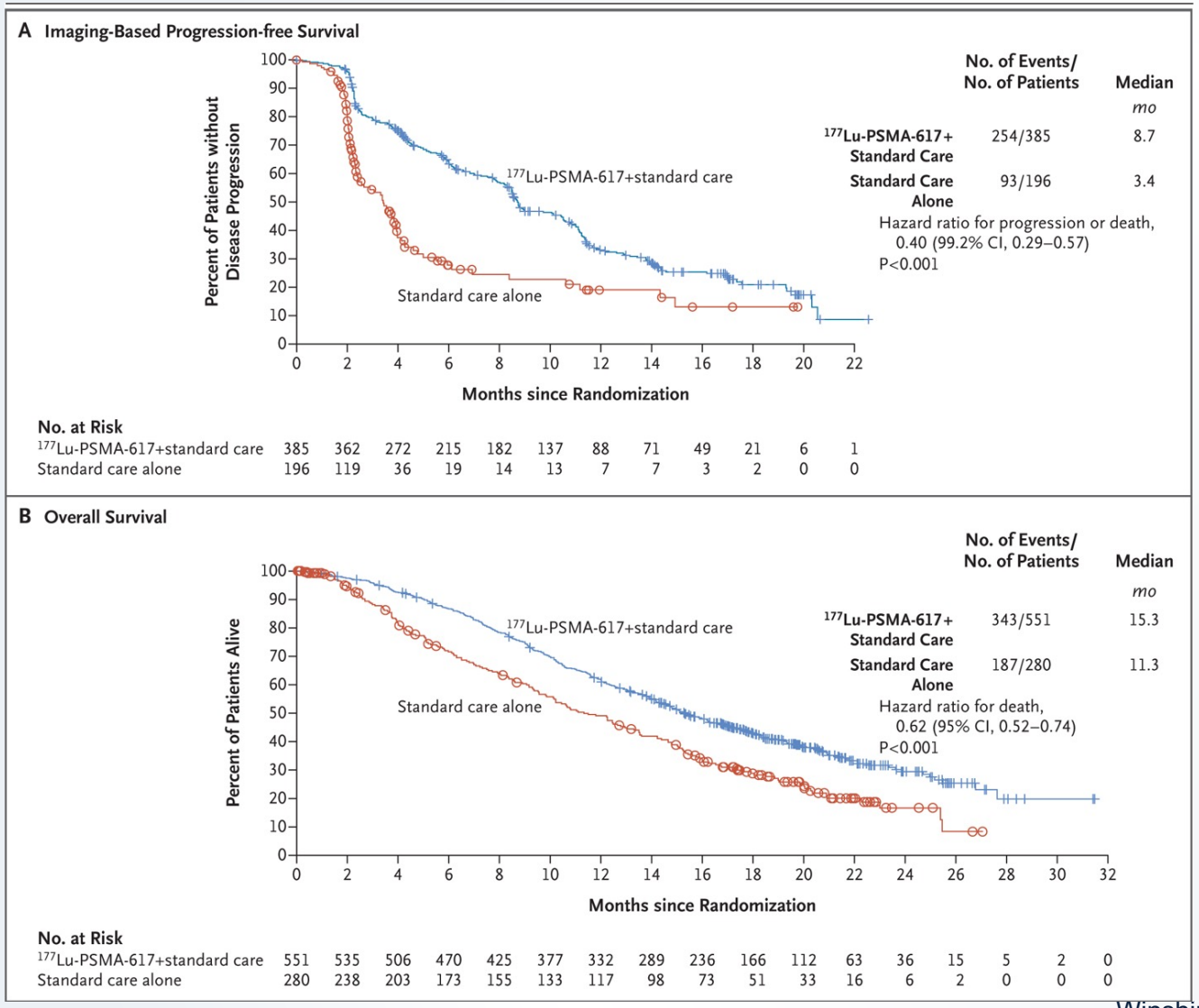
Key secondary endpoints

- Time to first symptomatic skeletal event (SSE)
- RECIST v1.1 overall response rate
- RECIST v1.1 disease control rate

Clinicaltrials.gov: NCT03511664

Sartor O, et al. *N Engl J Med*. 2021;385:1091-1103.
Morris M, et al. ASCO 2021. Abstract LBA4.

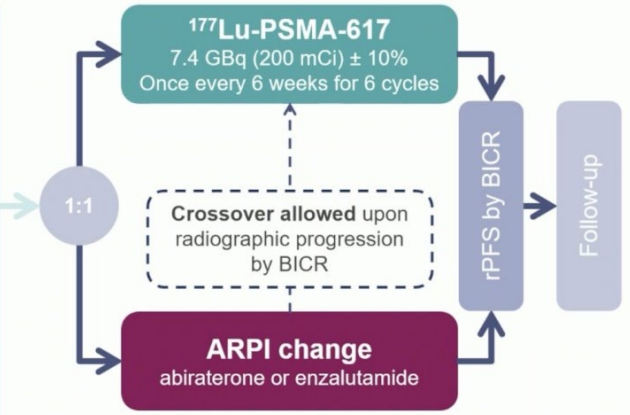
Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer



Sartor et al. N Engl J Med. 2021 Sep 16;385(12):1091-1103.

PSMAfore Phase 3 Trial of [177Lu]Lu-PSMA-617 in Taxane-Naive Patients with Metastatic CRPC

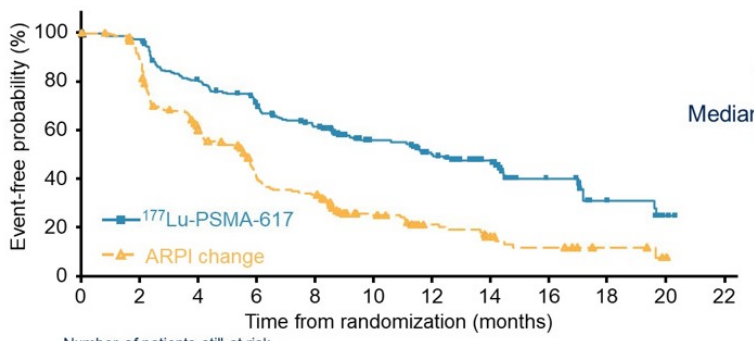
Eligible adults
- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [68Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



Stratification factors
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

Primary analysis[a] HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Second interim analysis[b] HR: 0.43 (95% CI: 0.33, 0.54)

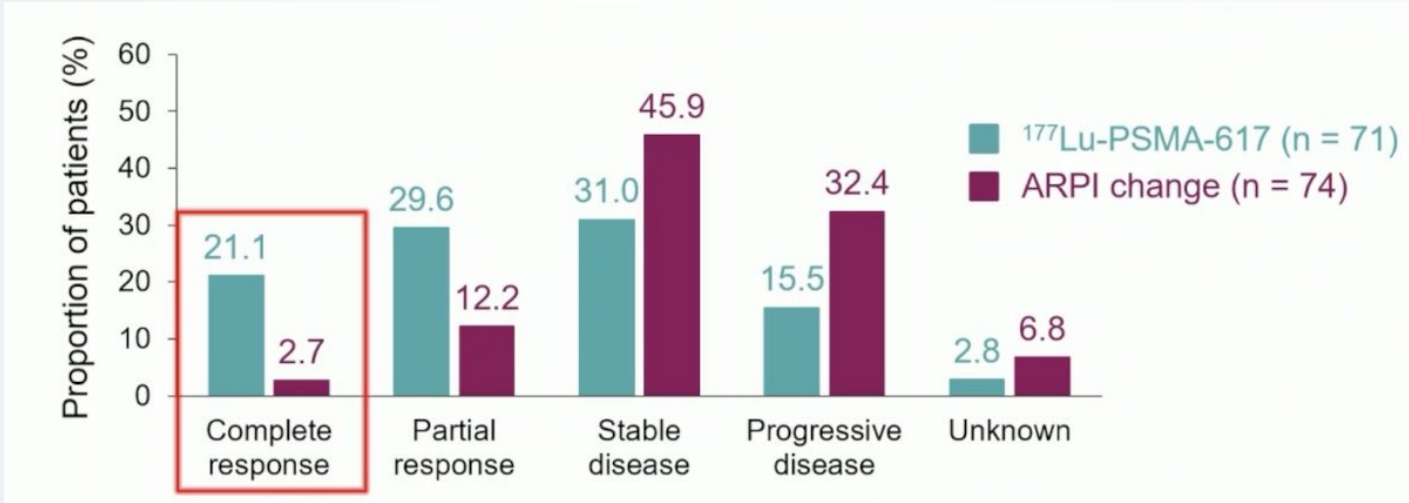


Number of patients still at risk

234	216	174	150	125	82	64	45	20	10	2	0
234	197	126	79	65	36	21	12	8	4	1	0

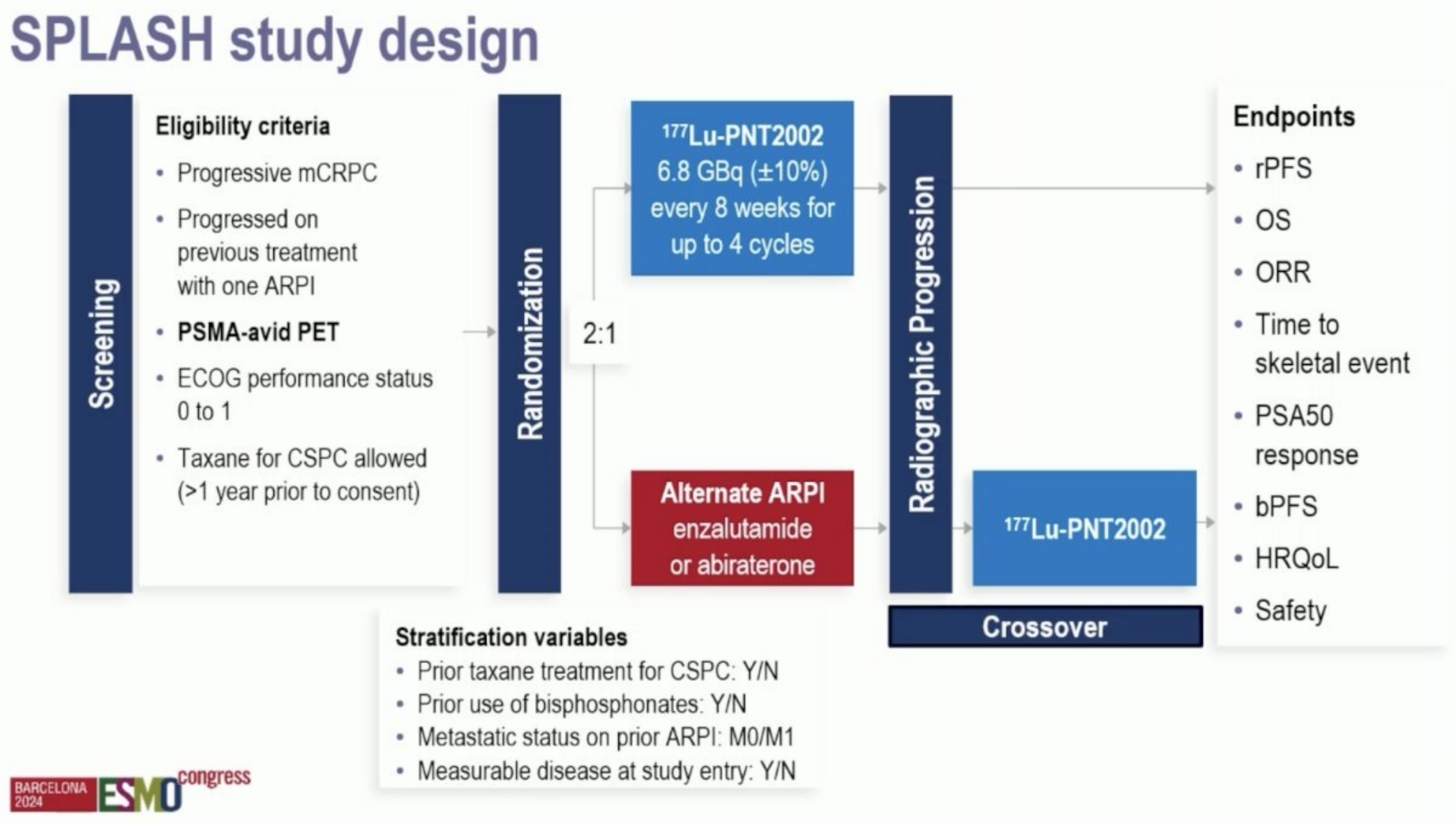
	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median, months (95% CI)	12.02 (9.30, 14.42)	5.59 (4.17, 5.95)

[a]Data cutoff October 2, 2022
[b]Data cutoff June 21, 2023
Previously presented at ESMO23
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival



Sartor, O et al, ESMO 2023;
Fizazi, K. et al. ASCO 2024;
Morris MJ, et al. Lancet. 2024 Sep 28;404(10459):1227-1239

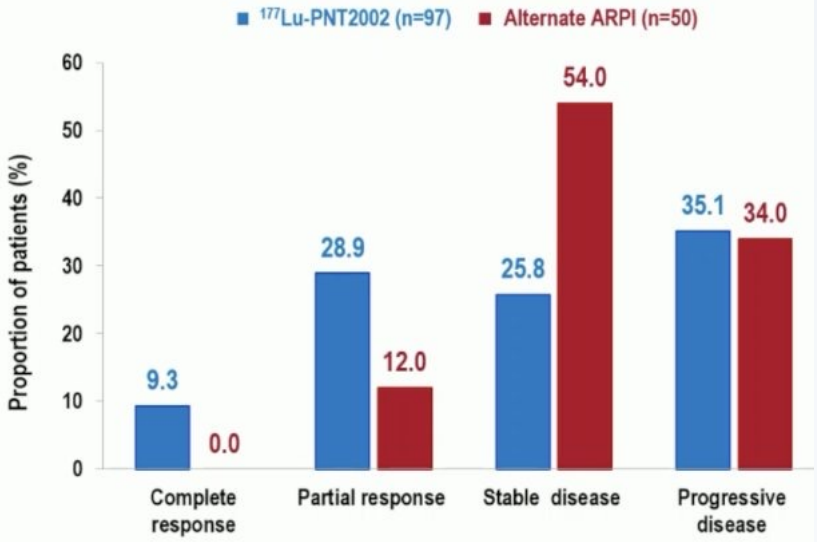
Efficacy of 177Lu-PNT2002 in PSMA-Positive mCRPC (SPLASH)



Sartor, O. et al. ESMO 2024

Efficacy of 177Lu-PNT2002 in PSMA-Positive mCRPC (SPLASH)

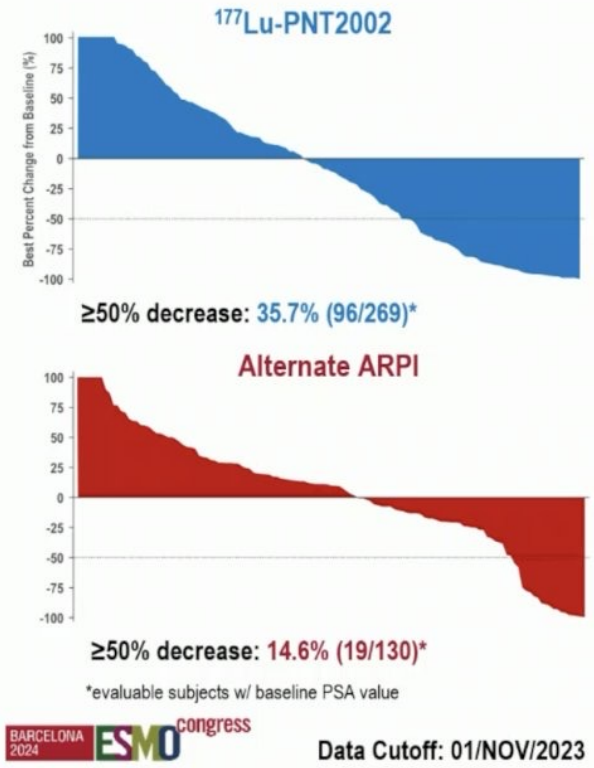
Overall Response Rate



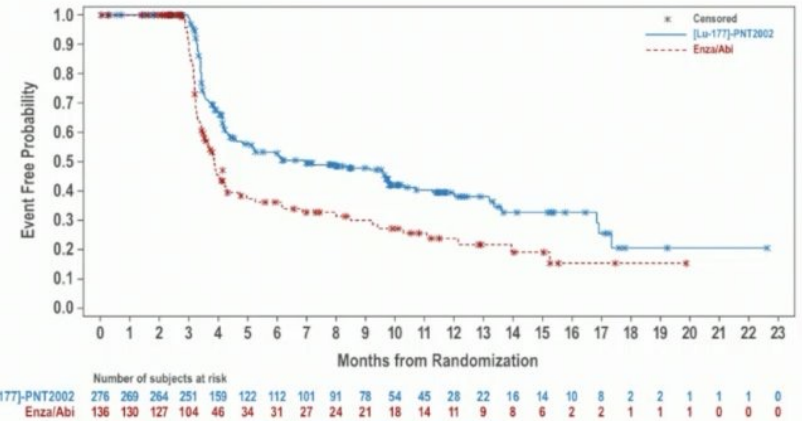
Best objective response in patients with measurable disease at baseline

	177Lu-PNT2002	Alternate ARPI	p-value
Best Overall Response (95% CI)	38.1% (37/97) (28.5, 48.6)	12% (6/50) (4.5, 24.3)	0.0021
Median DOR (95% CI)	9.4 months (5.9, 13.2)	7.3 months (1.6, NE)	

PSA50 Response



bPFS



	177Lu-PNT2002 (n = 276)	Alternate ARPI (n = 136)
Events, n	143 (51.8%)	82 (60.3%)
Median bPFS (95% CI)	7.0 months (4.8, 9.9)	3.9 months (3.5, 4.3)
Median follow-up (95% CI)	9.9 months (9.4, 10.8)	10.0 months (6.6, 11.6)
HR: 0.58 (95% CI: 0.44, 0.76) p <0.0001		

Sartor, O. et al. ESMO 2024; Hanen et al. Front Oncol. 2025 Jan 7;14:1483953.

Evolution Trial: 177-Lutetium with Ipi Nivo in mCRPC: A Phase II Trial

Key eligibility:
- mCRPC
- Prior ARPI
- ECOG 0-1
- PSMA SUVmax ≥15 at a site of disease, and SUVmax ≥10 at other sites of disease ≥10mm

Stratification:
Prior docetaxel

Randomize (2:1)

Experimental group (n=67)
^{177}Lu-PSMA-617, 7.5 Gbq q6w x 6 max
+
Induction
Ipilimumab 3 mg/kg q6w x 4
PLUS
Nivolumab 1 mg/kg q3w x 8
→ **Maintenance**
Nivolumab 480 mg q4w (up to 24 months)

Control group (n=33)
^{177}Lu-PSMA-617, 7.5 Gbq q6w x 6 max

Primary Endpoint
- 12 months PSA-PFS

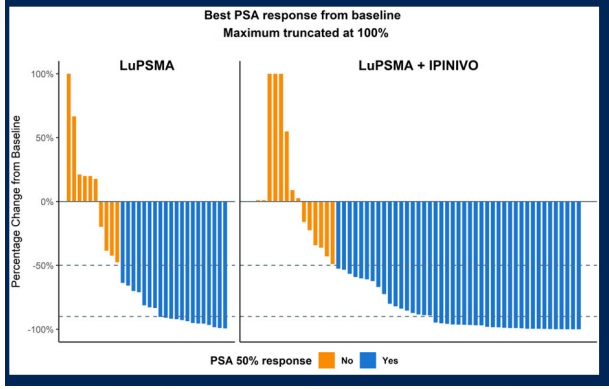
Secondary Endpoints
- RR-PSA
- Adverse Events
- rPFS
- OS
- ORR
- DOR
- HRQOL

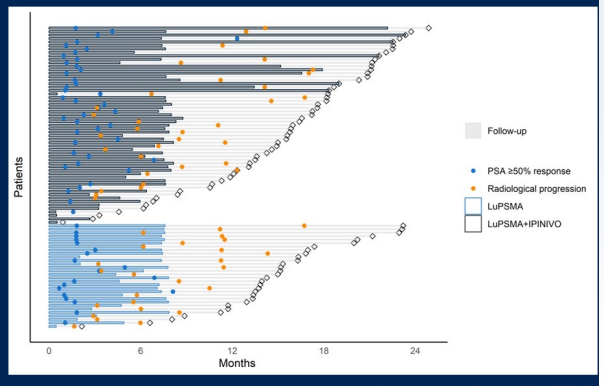
NHMRC Clinical Trials Centre

ANZUP Cancer Trials Group Limited

	^{177}Lu-PSMA-617 + ICI (n=57)	^{177}Lu-PSMA-617 (n=30)
PSA ≥ 50% response	43/57 (75%)	20/30 (67%)
PSA ≥ 90% response	26/57 (46%)	13/30 (43%)
PSA ≤ 0.2 rates	11/57 (19%)	2/30 (7%)

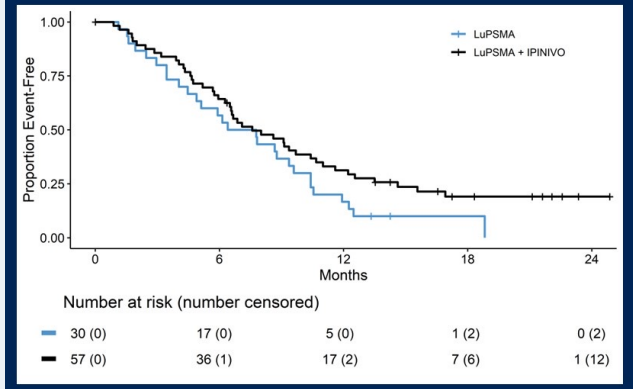
	^{177}Lu-PSMA-617 + ICI (n=21)	^{177}Lu-PSMA-617 (n=12)
ORR by RECIST 1.1	15/21 (71%)	6/12 (50%)
Suspension of ^{177}Lu-PSMA-617 for deep response	9/57 (16%)	0/30





PSA-PFS

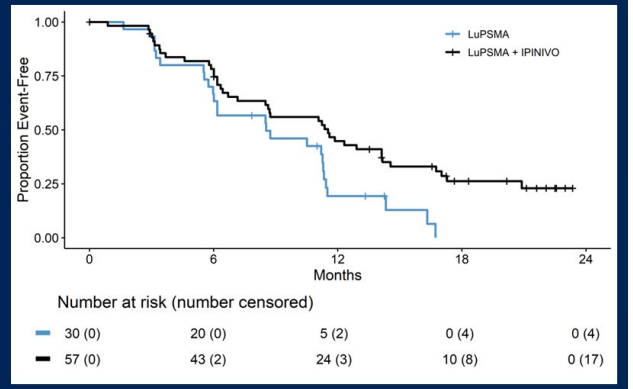
	^{177}Lu-PSMA-617 + ICI (n=57)	^{177}Lu-PSMA-617 (n=30)
PSA-PFS at 12 months	19/57 (33%)	5/30 (17%)
Median PSA-PFS, months (95% CI)	7.6 (6.5, 11)	7.1 (4.9, 10)



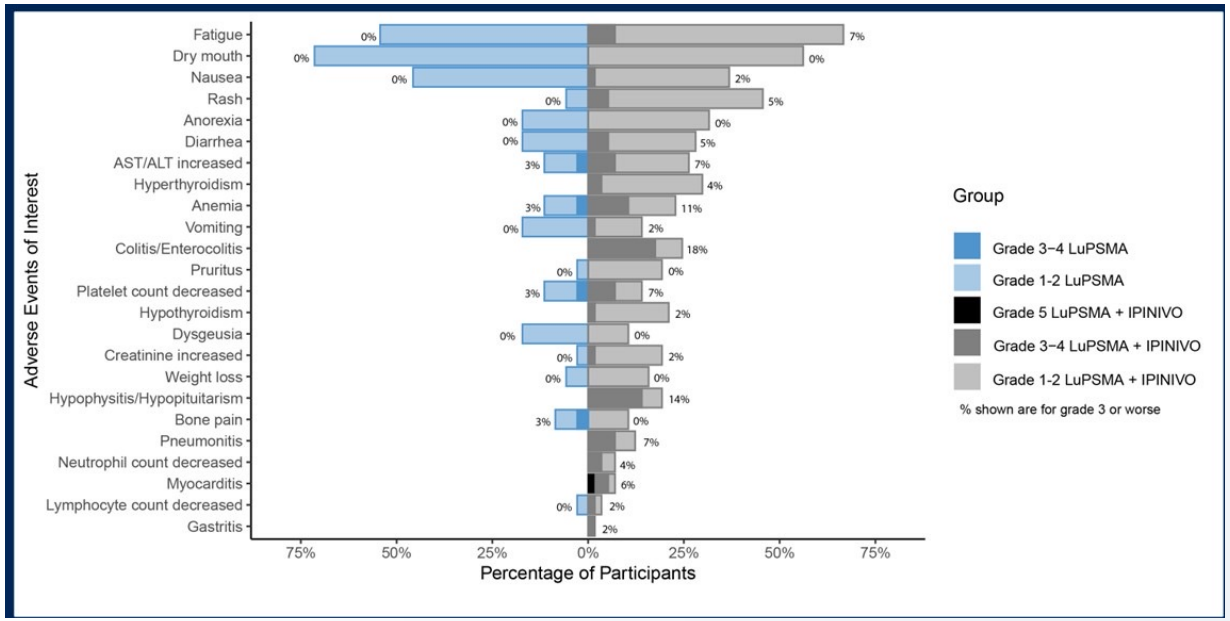
HR: 0.71 (95% CI:0.43,1.19)

rPFS

	^{177}Lu-PSMA-617 + ICI (n=57)	^{177}Lu-PSMA-617 (n=30)
rPFS at 12 months	27/57 (47%)	7/30 (23%)
Median rPFS, months (95% CI)	12 (8.5, 15)	8.5 (6.0, 11)

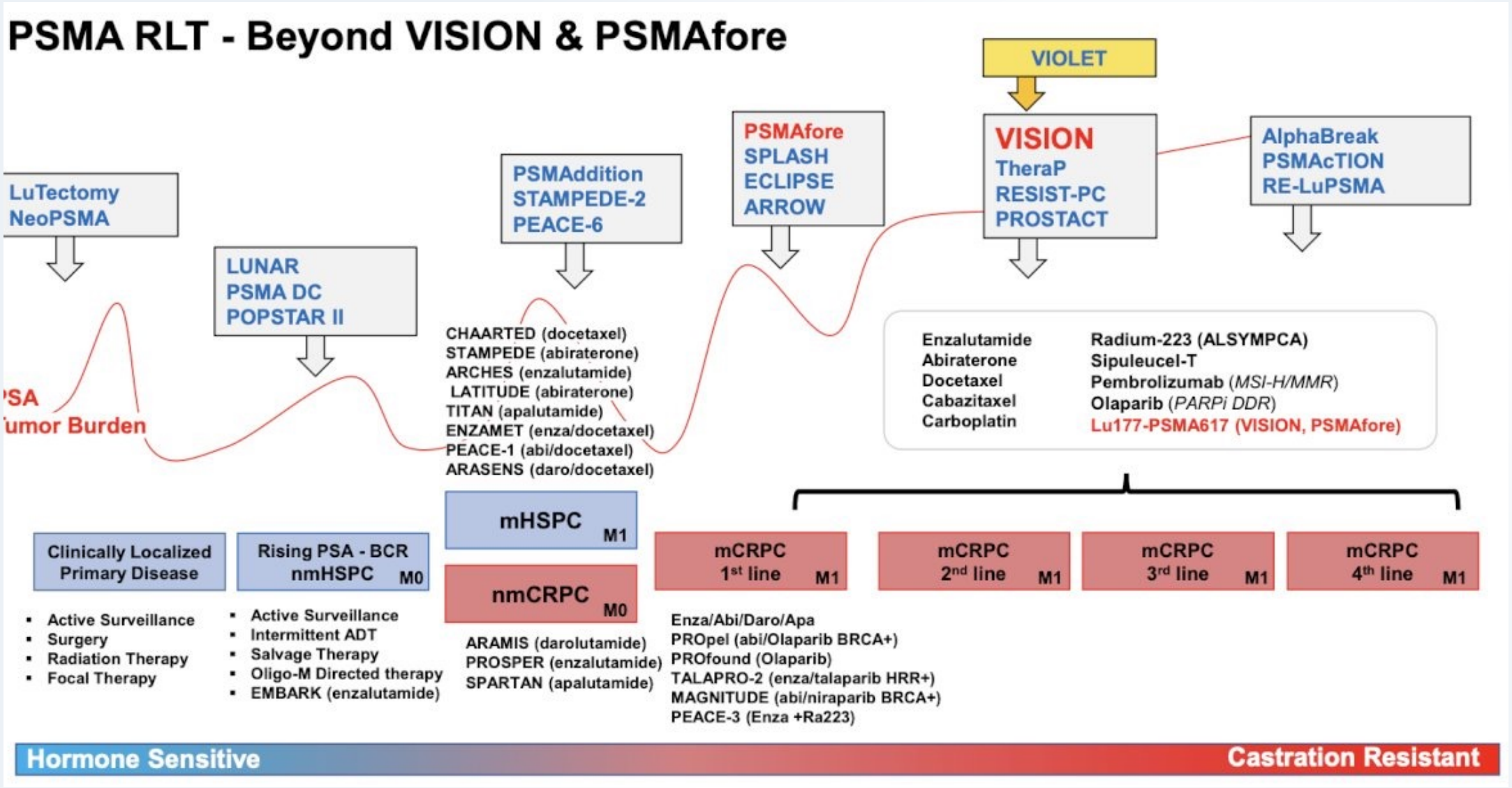


HR: 0.53 (95% CI:0.32,0.90)



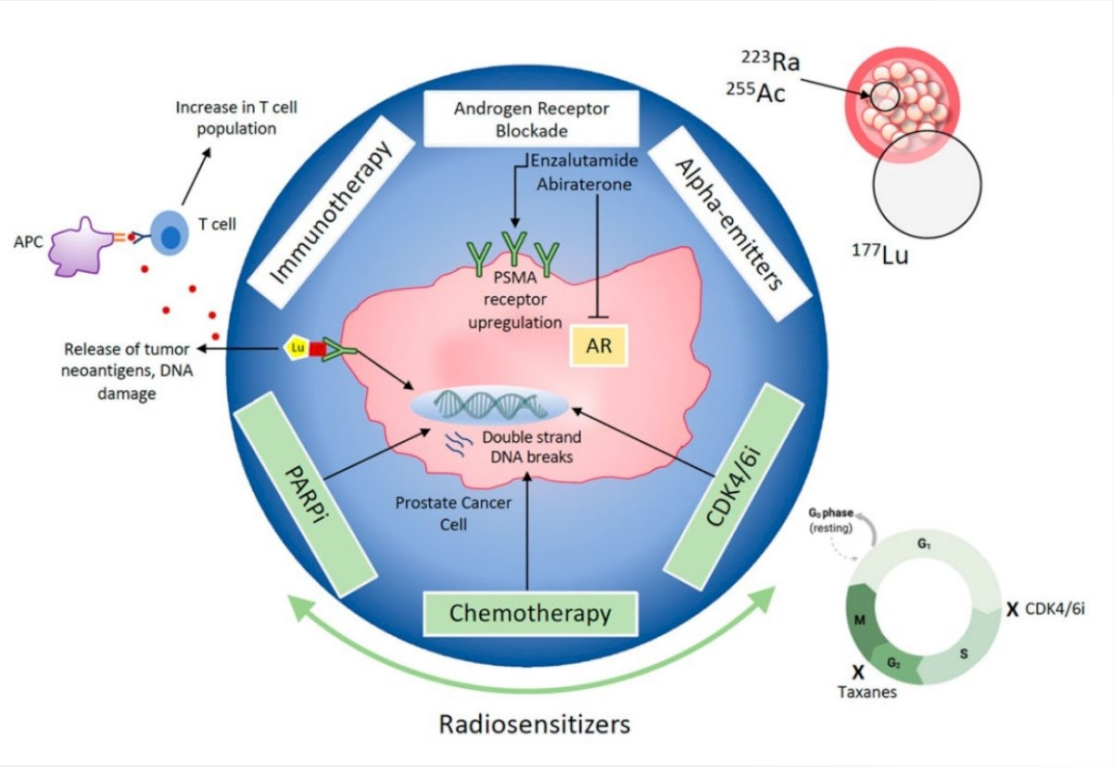
Sandhu, S et al. ASCO 2025

Current PSMA Radioligand Studies



Calais, J. ASCO 2025

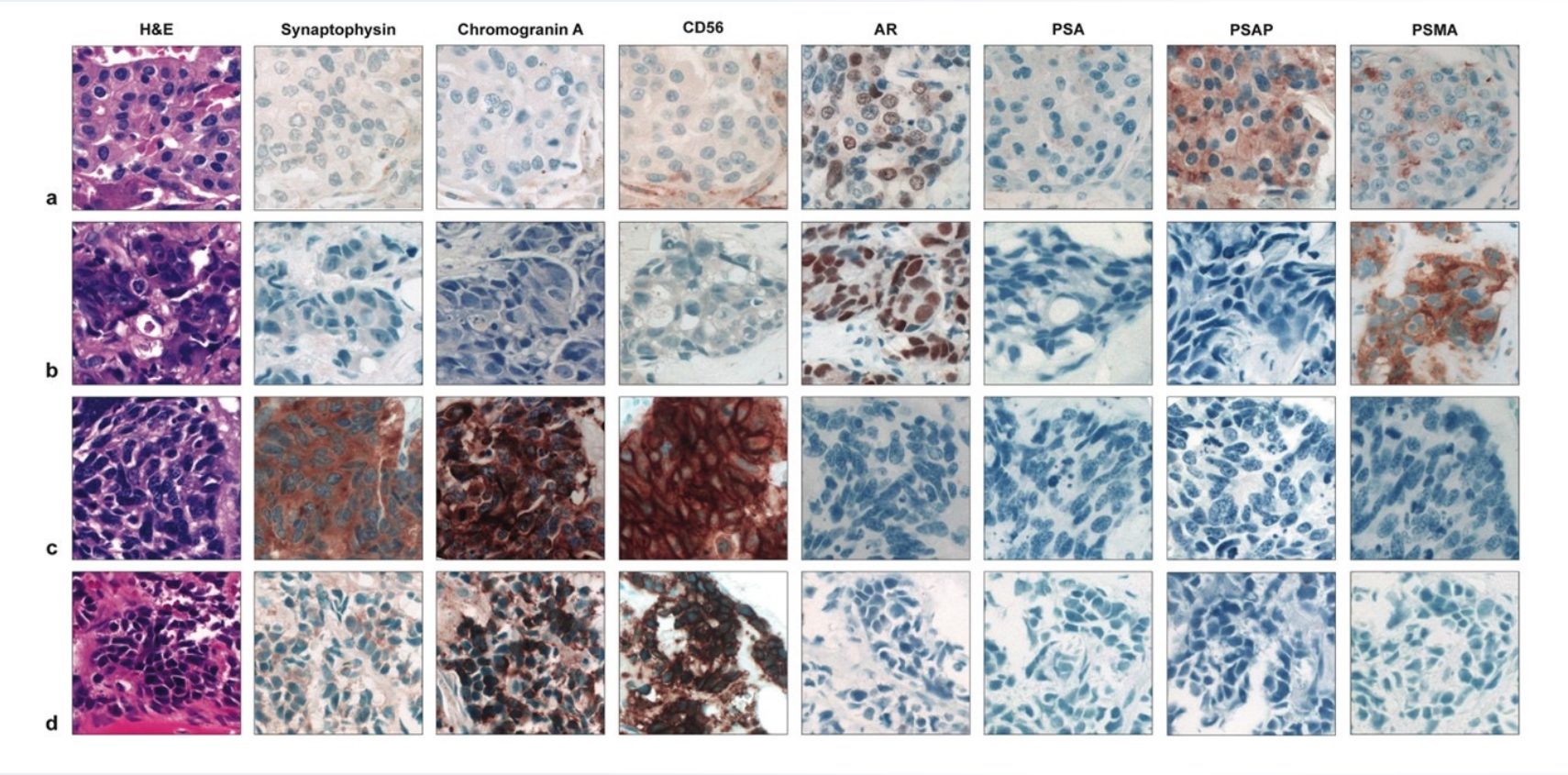
Current PSMA Radioligand Combinatorial Studies in CRPC



Trial		Setting	Phase	Combination Strategy	Treatment
Immunotherapy					
NCT03658447	PRINCE	mCRPC	I/II	RNT + immune checkpoint inhibitor	^{177}LuPSMA-617 + pembrolizumab
NCT03805594		mCRPC	I	RNT + immune checkpoint inhibitor	^{177}LuPSMA-617 + pembrolizumab
NCT05150236	EVOLUTION	mCRPC	II	RNT + immune checkpoint inhibitor	^{177}Lu-PSMA-617 + ipilimumab + nivolumab
NCT04946370		mCRPC	I/II	RNT + immune checkpoint inhibitor + antiandrogen therapy	^{225}Ac-J591 + pembrolizumab + AR pathway inhibitor (e.g., enzalutamide)
Radiosensitizers					
NCT03874884	LuPARP	mCRPC	I/II	RNT + PARP inhibitor	Olaparib + ^{177}Lu-PSMA-617
NCT05113537	UPLIFT	mCRPC	I/II	RNT + CDK-4/6 inhibitor	Abemaciclib + ^{177}Lu-PSMA-617
NCT05340374	LuCAB	mCRPC	I/II	RNT + chemotherapy	Cabazitaxel + ^{177}Lu-PSMA-617
NCT00916123		mCRPC	I	RNT + chemotherapy	Docetaxel + ^{177}Lu-J591
NCT04343885		mHSPC	II	RNT + chemotherapy	^{177}Lu-PSMA-617 followed by upfront docetaxel
PSMA Upregulation					
NCT04419402	ENZA-p	mCRPC	II	RNT + antiandrogen	Enzalutamide + ^{177}Lu-PSMA-617
Radionuclides					
NCT04886986		mCRPC	I/II	α- + β-RNT	^{225}Ac-J591 + ^{177}Lu-PSMA-I&T
NCT05383079	AlphaBet	mCRPC	I/II	α- + β-RNT	^{233}Ra + ^{177}Lu-PSMA-I&T

Calais, J. ASCO 2025

Treatment Related Tumor Heterogeneity and Loss of PSA Typical Expression Markers in CRPC



Adenocarcinoma[aaa] → PROS-16

Small cell/ neuroendocrine prostate cancer (NEPC)[aaa] →

First-line and subsequent treatment options[ccc]
- Chemotherapy[ddd]
  - Cisplatin/etoposide
  - Carboplatin/etoposide
  - Docetaxel/carboplatin
  - Cabazitaxel/carboplatin[eee]
  - For additional options, see NCCN Guidelines for Small Cell Lung Cancer
- Best supportive care

- Tarlatamab
- Lurbinectedin
- Topotecan
- Ipi/Nivo

Beltran et al, Nature Med 2016; NCCN Guidelines Prostate Cancer Version 2.2025.

Phase II Study: Anti PD-1 Therapy Improved PFS and OS of AVPC Patients on Niraparib Maintenance

Key Eligibility:
- ECOG 0-2
- mCRPC
- ≥ 1 AVPC criteria
- No prior carboplatin, cabazitaxel or PARP*i*
- Adequate organ function

NCT04592237

n=120 **CARBOPLATIN + CABAZITAXEL** q21 days on cycles 1-6

CETRELIMAB (αPD1) q21 days on cycles 2-6

1:1 prior chemotherapy

n=44 **NIRAPARIB** q28 days on cycles 7 → progression

n=44 **NIRAPARIB + CETRELIMAB** q28 days on cycles 7 → progression

TUMOR BIOPSY 1 | TUMOR BIOPSY 2 | TUMOR BIOPSY 3

PRIMARY OBJECTIVES:
- Progression free survival **from randomization**
- Change in intratumoral CD3+ cells with the addition of αPD1

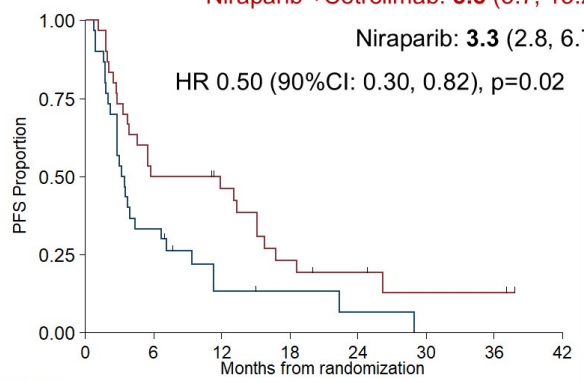
STATISTICAL DESIGN
HR of 0.53
1-sided 5% significance level, 80% power

mPFS (months) FROM RANDOMIZATION

Niraparib +Cetrelimab: **8.8** (3.7, 15.2)

Niraparib: **3.3** (2.8, 6.7)

HR 0.50 (90%CI: 0.30, 0.82), p=0.02

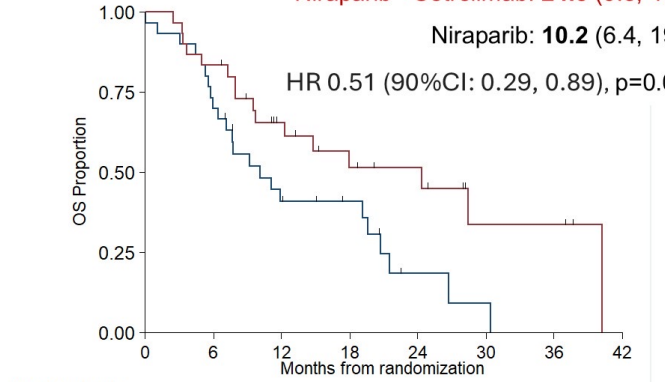


mOS (months) FROM RANDOMIZATION

Niraparib +Cetrelimab: **24.3** (9.5, 40.3)

Niraparib: **10.2** (6.4, 19.7)

HR 0.51 (90%CI: 0.29, 0.89), p=0.04



Adverse Events

Adverse event, n	Grade ≤2	
	N	N+C
Patients with highest grade ≤2 AEs	13	20
Platelet count decreased	11	18
Anemia	8	9
Neutrophil count decreased	6	7
Lymphocyte count decreased	6	5
Hyponatremia	4	9
White blood cell decreased	5	9
Arthralgia	5	9
Creatinine increased	6	7
Nausea	5	8
Constipation	6	6
Fatigue	5	6
AST increased	4	8

Adverse event, n	Grade ≥3	
	N	N+C
Patients with highest grade≥3 AEs	12	16
Anemia	3	5
Hypertension	2	0
Lymphocyte count decreased	1	3
Platelet count decreased	1	2
Neutrophil count decreased	0	3
Acute myelogenous leukemia	0	1

Aparacio et al, ASCO 2025

Factors in Choice of 1st Line CRPC Agents

Factor	Agent Choice
Rapid Pace, High Volume of Disease, Adverse Mutants (PTEN, Rb, p53)	Single Taxane or Combo Regimen (Cabazitaxel/Carboplatin)
HRR Mutant/Actionable Mutations	PARPi Monotherapy or Combo/Targeted Therapy (IO/AR)
PSMA expression	Lu-177 PSMA 617
High Grade or AVPC	Platinum Based Combination/Taxanes
Painful Bone Mets	Radium 223
Indolent - Moderate Pace of Disease, Chemo Averse, Modest PS	Lu-177 PSMA 617, NHA Swap
Metachronous Oligomets	SBRT +/- NHA

Metastatic Castration Resistant Prostate Cancer Highlights

- There has been rapid shift in agents to earlier usage and combinations
- Initial genomic testing important in maximizing therapeutic exposure
- DNA Repair agents & combinations provide notable efficacy in HRR+
- PSMA based combination radioligand therapies presents a novel approach for CRPC Patients
- Aggressive Variant Prostate Cancer/Neuroendocrine Prostate Cancer Reflect Need for Novel Therapeutics
- CRPC 1L choice depends on rapidity of disease, actionable targets, prior therapies and PS.