Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Breast Cancer: *Drs Burstein, Goetz, McArthur and Nanda*

Module 2 — Prostate Cancer: *Drs Antonarakis and M Smith*

Module 3 — Colorectal Cancer: *Drs Lieu and Strickler*

Module 4 — Diffuse Large B-Cell Lymphoma and Follicular Lymphoma: *Drs Lunning and S Smith*

Prostate Cancer Faculty

Emmanuel S Antonarakis, MD
Clark Endowed Professor of Medicine
Division of Hematology, Oncology and Transplantation
University of Minnesota
Minneapolis, Minnesota

Matthew R Smith, MD, PhD
Claire and John Bertucci Endowed Chair in Genitourinary Cancers
Professor of Medicine
Harvard Medical School
Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

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RESEARCH TO PRACTICE

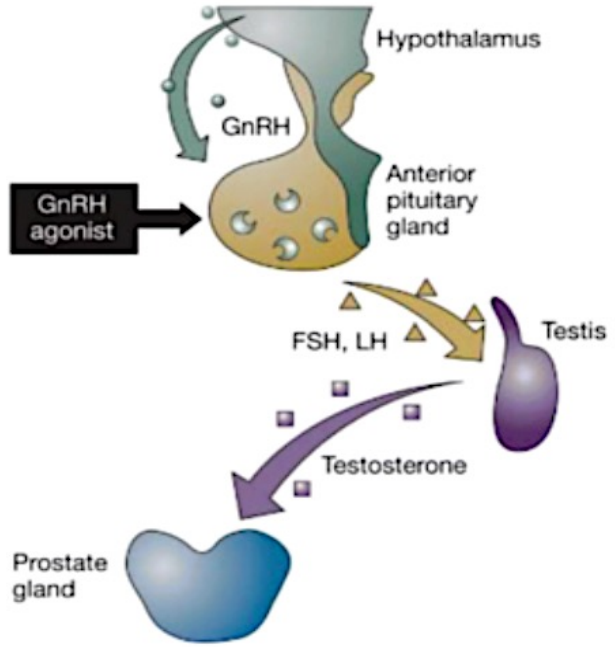
Optimizing the Role of Hormonal Therapy in in the Care of Patients with Prostate Cancer

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

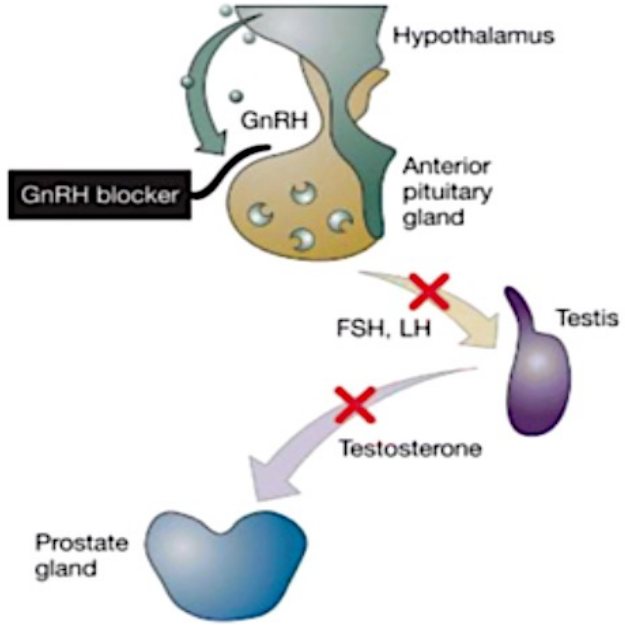
Matthew R. Smith, M.D.,Ph.D.
Professor of Medicine, Harvard Medical School
Director, MGH Genitourinary Malignancies Program

GnRH agonists



- Surge in FSH, LH and testosterone before suppression
- Microsurges in LH and testosterone on repeat injection
- FSH suppression, but not maintained long term

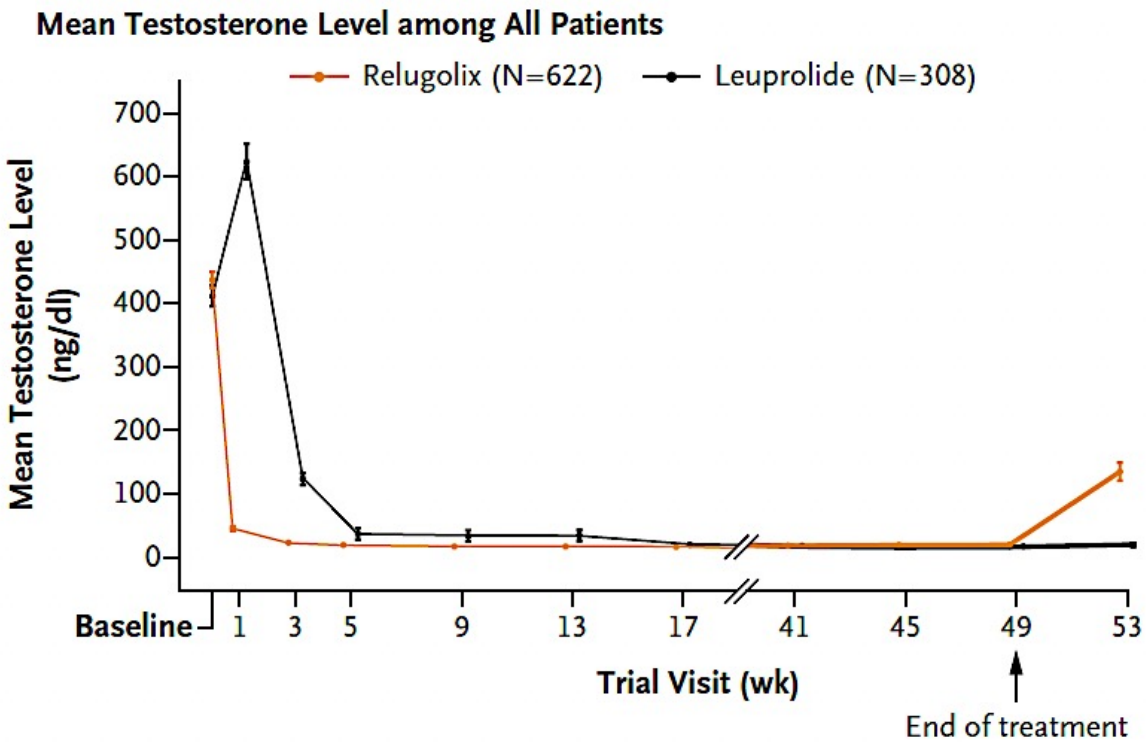
GnRH antagonists

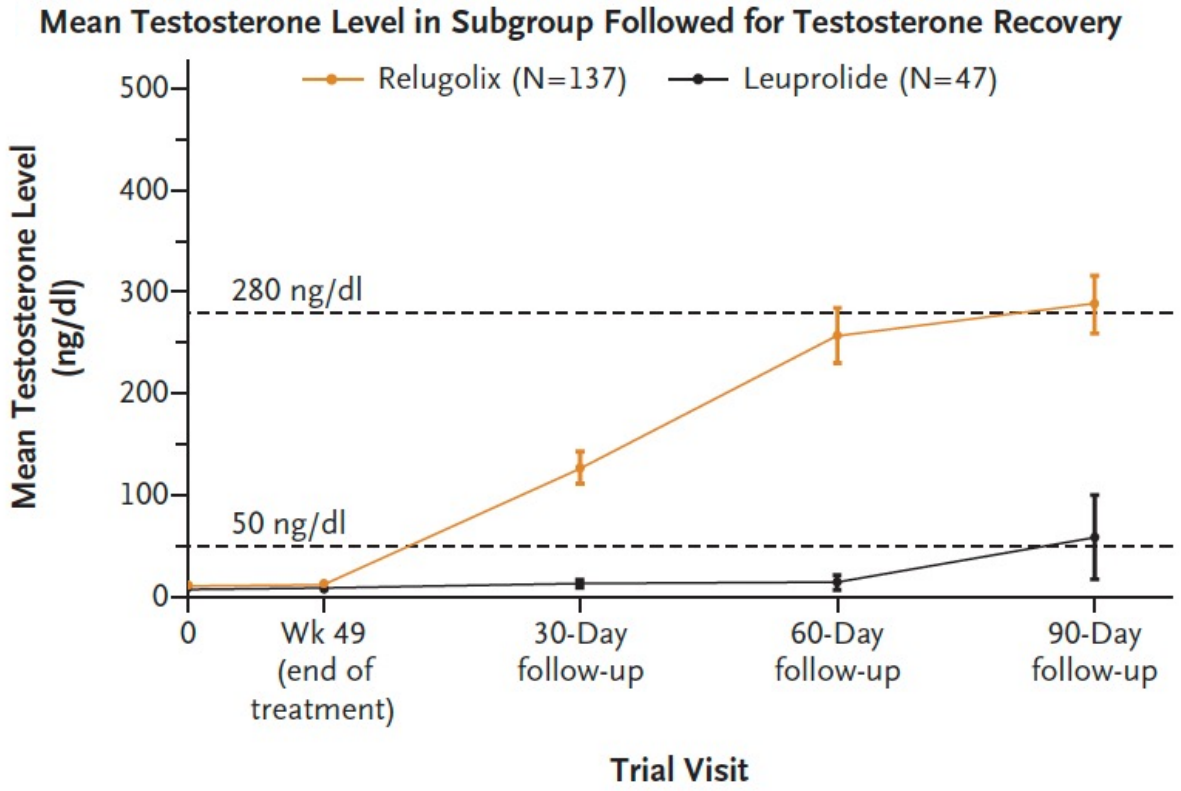


- Immediate suppression of FSH, LH and testosterone
- No microsurges
- Prolonged suppression of FSH, LH and testosterone

Melloni and Nelson (2020) Journal of Cardiovascular Translational Research 13(1):1-12.

HERO: Randomized Controlled Trial of Leuprolide vs. Relugolix





Shore N et al. *N Engl J Med* 2020;382:2187-96.

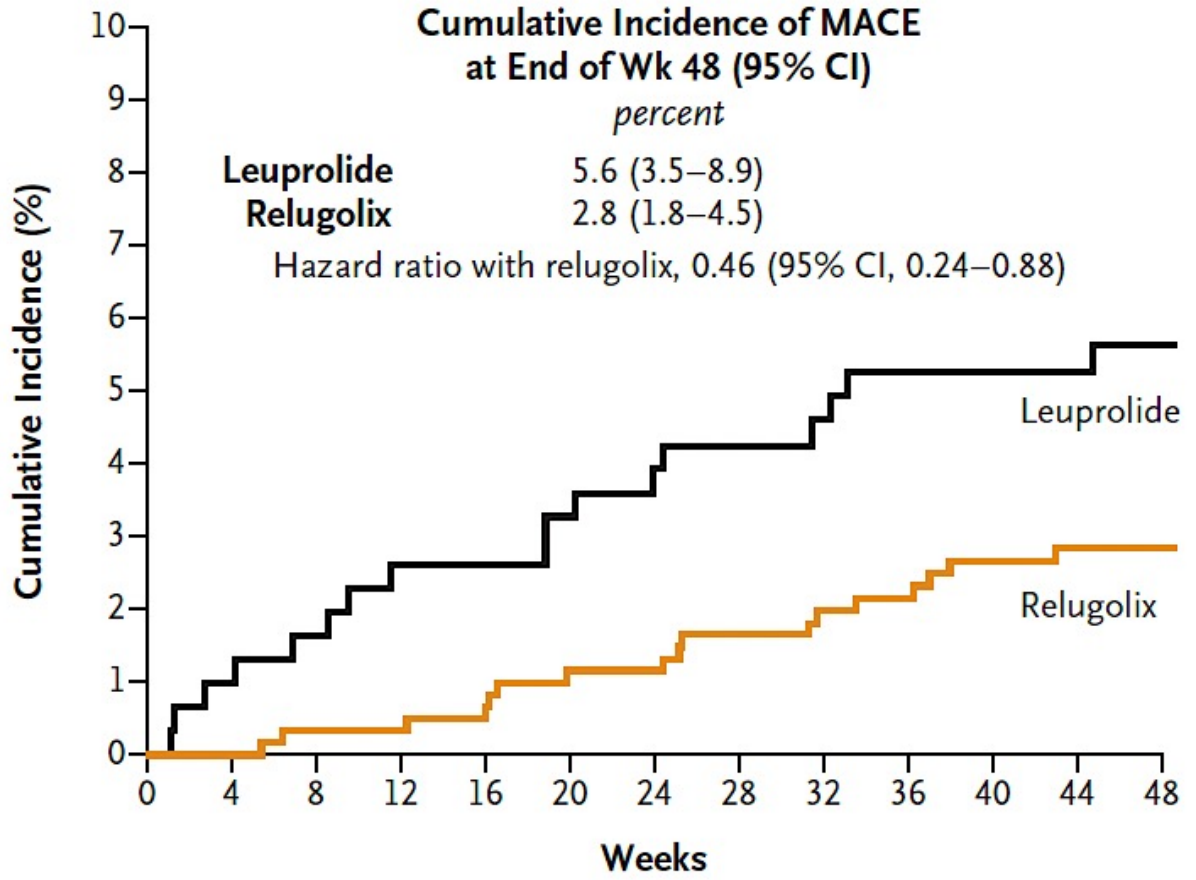
HERO: Randomized Controlled Trial of Leuprolide vs. Relugolix

Table 3. Adverse Events.*

Event	Relugolix (N = 622)		Leuprolide (N = 308)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event — no. (%)	578 (92.9)	112 (18.0)	288 (93.5)	63 (20.5)
Serious adverse event — no. (%)	76 (12.2)	61 (9.8)	47 (15.3)	35 (11.4)
Fatal adverse event — no. (%)	7 (1.1)	—	9 (2.9)	—
MACE — no. (%)†	18 (2.9)	8 (1.3)	19 (6.2)	4 (1.3)
Without a history of MACE — no./total no. (%)	15/538 (2.8)	—	11/263 (4.2)	—
With a history of MACE — no./total no. (%)	3/84 (3.6)	—	8/45 (17.8)	—
Adverse events that occurred in >10% of patients in either group — no. (%)				
Hot flash	338 (54.3)	4 (0.6)	159 (51.6)	0
Fatigue	134 (21.5)	2 (0.3)	57 (18.5)	0
Constipation	76 (12.2)	0	30 (9.7)	0
Diarrhea	76 (12.2)	0	21 (6.8)	0
Arthralgia	75 (12.1)	2 (0.3)	28 (9.1)	0
Hypertension	49 (7.9)	10 (1.6)	36 (11.7)	2 (0.6)

Shore N et al. *N Engl J Med* 2020;382:2187-96.

HERO: Randomized Controlled Trial of Leuprolide vs. Relugolix



No. at Risk

Leuprolide	308	305	303	298	298	293	292	288	281	279	278	269	259
Relugolix	622	621	616	610	605	596	595	588	582	575	563	559	538

Shore N et al. *N Engl J Med* 2020;382:2187-96.

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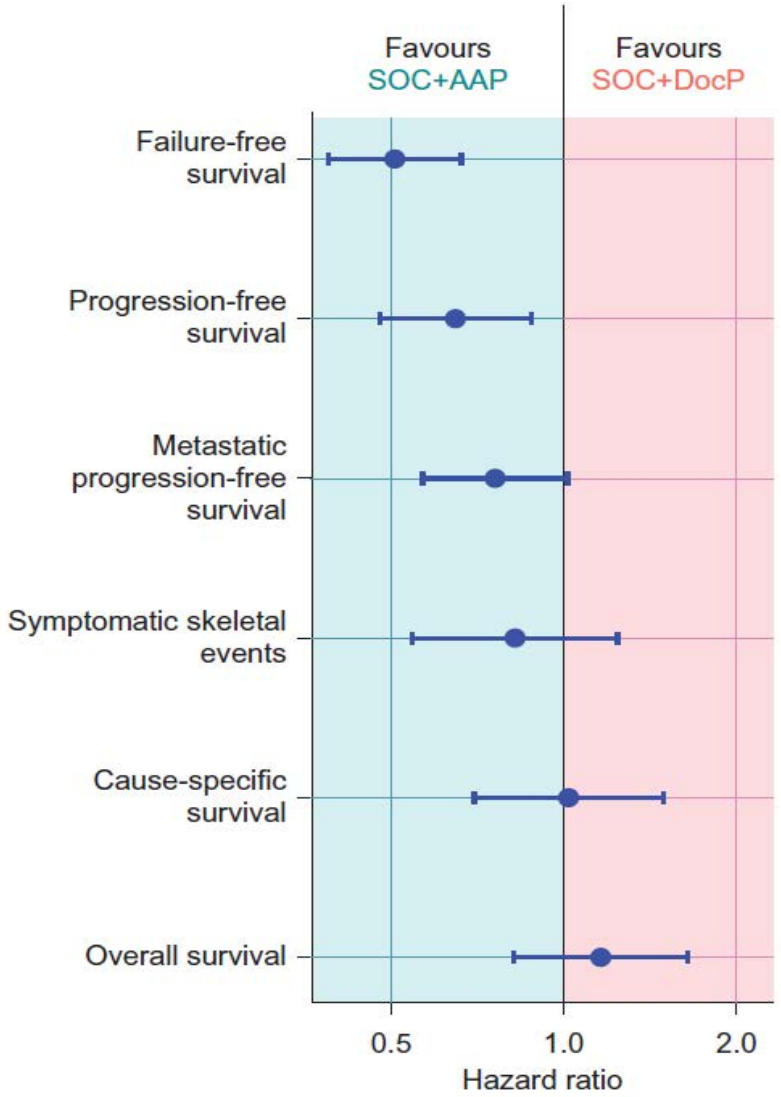
Level 1 Evidence for Improved Overall Survival in mCSPC

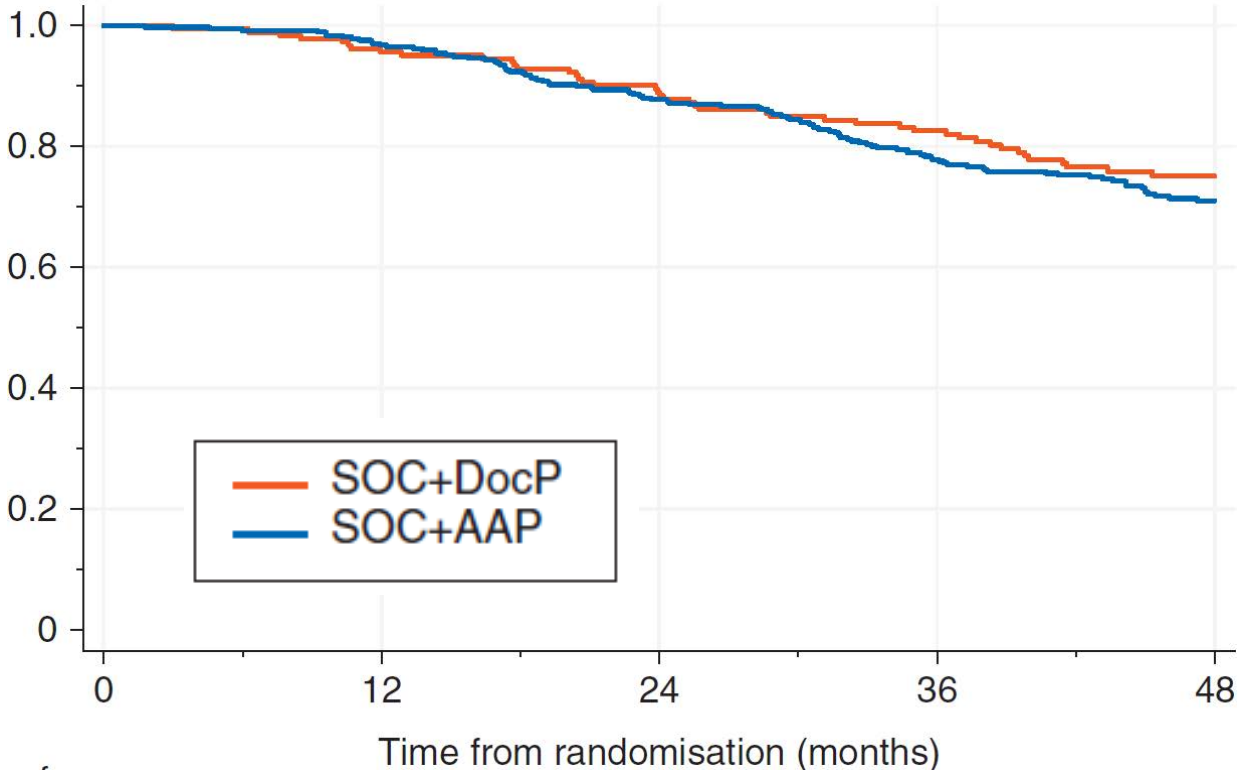
Studies	Intervention	Control	Comments
GETUG-15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

Parker et al Lancet 2018; Armstrong et al JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

STAMPEDE: Docetaxel vs Abiraterone Comparison



Overall Survival



Sydes et al (2018) *Annals of Oncology* 29:1235-1248

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

Docetaxel × 6

Darolutamide 600 mg twice daily + ADT

Placebo twice daily + ADT

Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Data cut-off
Oct 25, 2021

Endpoints

Primary: OS

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

***One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.**

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

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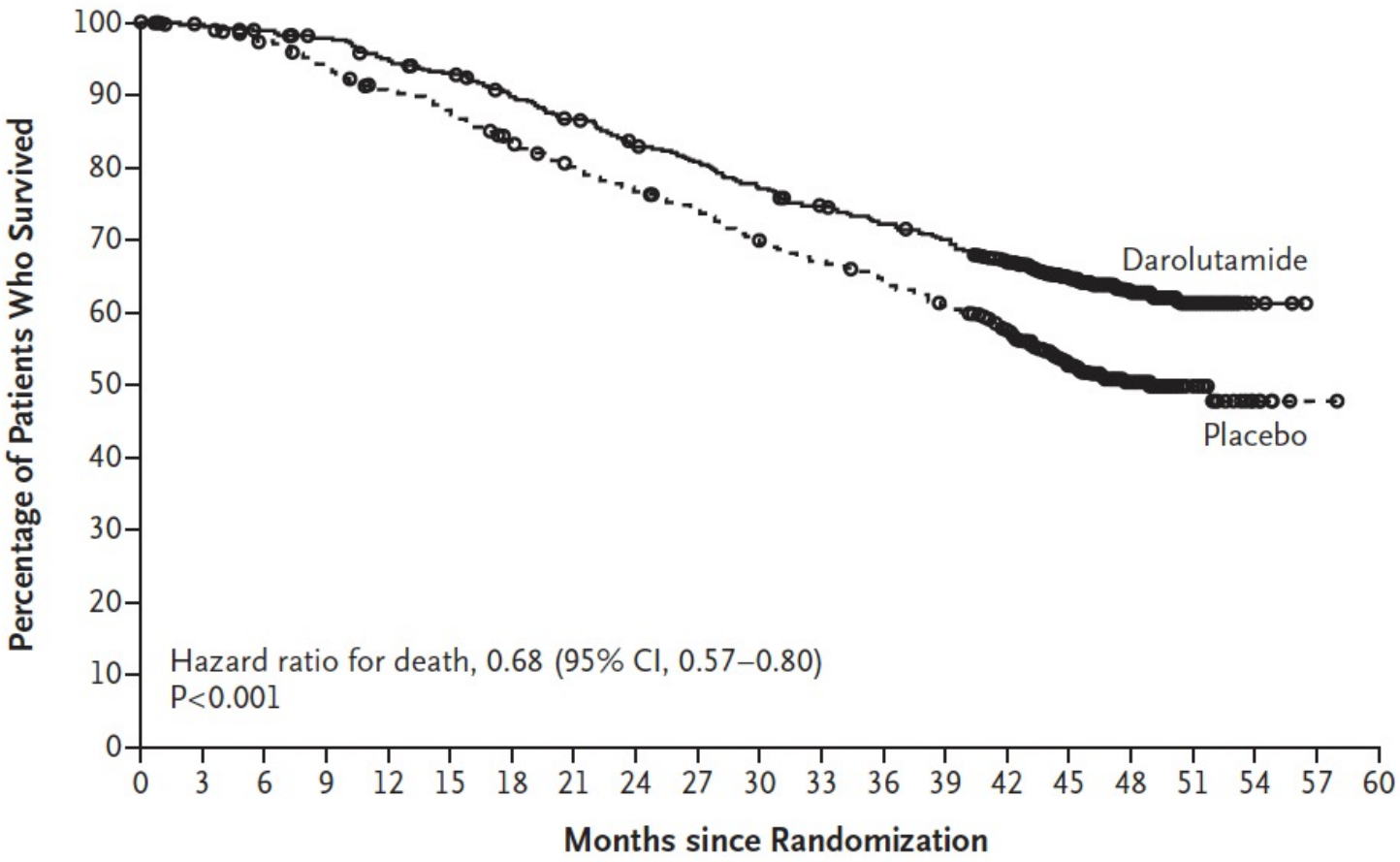
ARASENS Primary Endpoint: Overall Survival



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

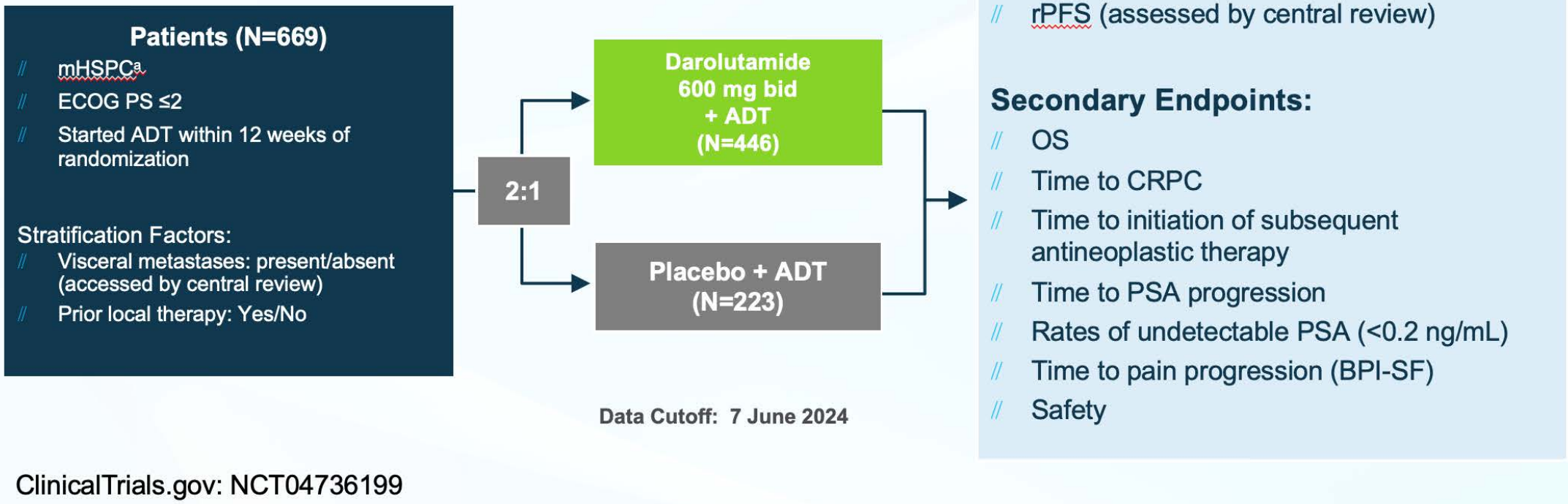
No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

ARANOTE Study Design

A randomized, double-blind, placebo-controlled phase 3 study



ClinicalTrials.gov: NCT04736199

[a]Metastatic disease confirmed by conventional imaging method either by a positive ^{99}mTc-phosphonate bone scan, or soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by central review.
ADT, androgen deprivation therapy; bid, twice a day; AE, adverse event; BPI-SF, Brief Pain Inventory-Short Form; CRPC, castration-resistant prostate cancer; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate specific antigen; rPFS, radiological progression-free survival.
1. Clinicaltrials.gov identifier: NCT04736199. Accessed September 2024. https://clinicaltrials.gov/ct2/show/NCT04736199. 2. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

Saad *et al* (2024) J Clin Oncol 42(36): 4271-4275

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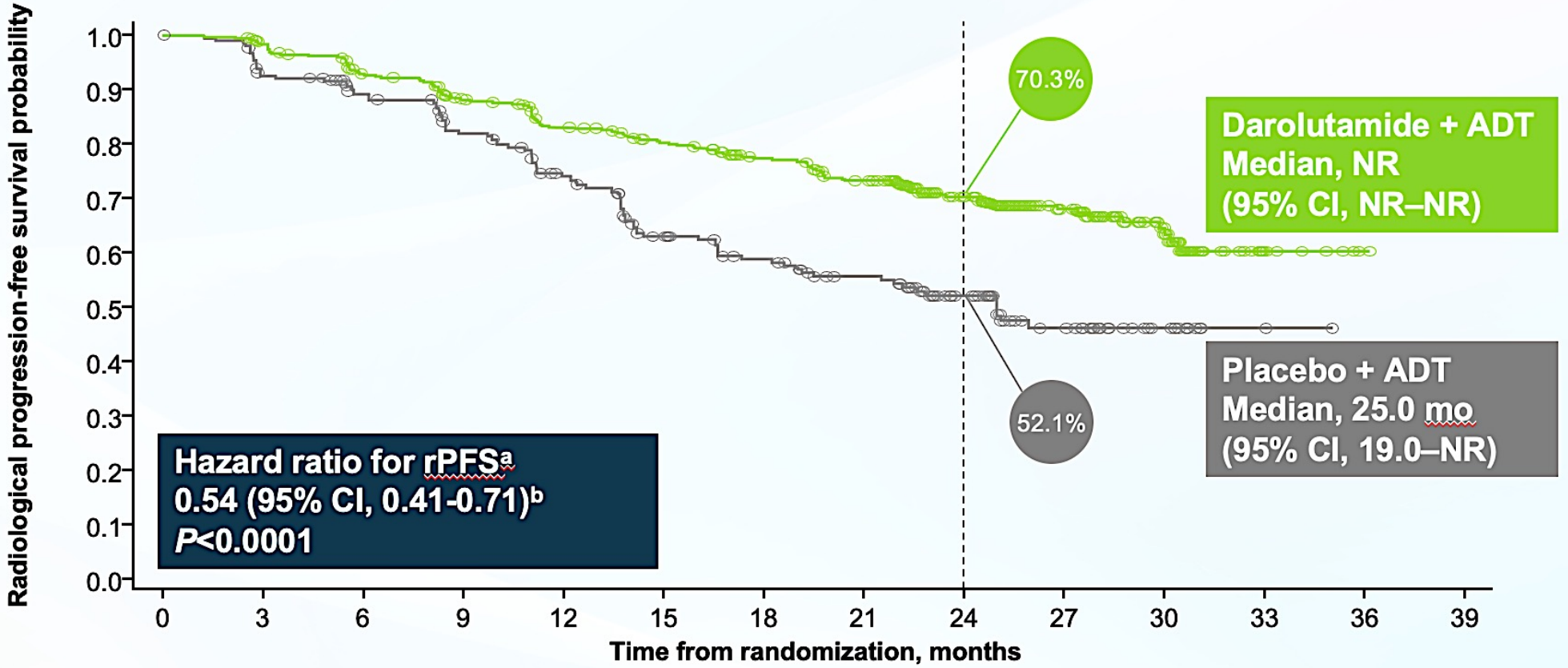
ARANOTE Primary Endpoint: rPFS



No. of patients at risk														
Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

Saad *et al* (2024) J Clin Oncol 42(36): 4271-4275

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ARANOTE: Safety

Adverse Event, No. of Patients (%)	Darolutamide + ADT (n = 445[a])	Placebo + ADT (n = 221[a])
Any adverse event	405 (91.0)	199 (90.0)
Serious adverse event	105 (23.6)	52 (23.5)
Grade 3 or 4 adverse event	137 (30.8)	67 (30.3)
Grade 5 adverse event	21 (4.7)	12 (5.4)
Adverse event leading to permanent discontinuation of study drug	27 (6.1)	20 (9.0)

Saad *et al* (2024) J Clin Oncol 42(36): 4271-4275

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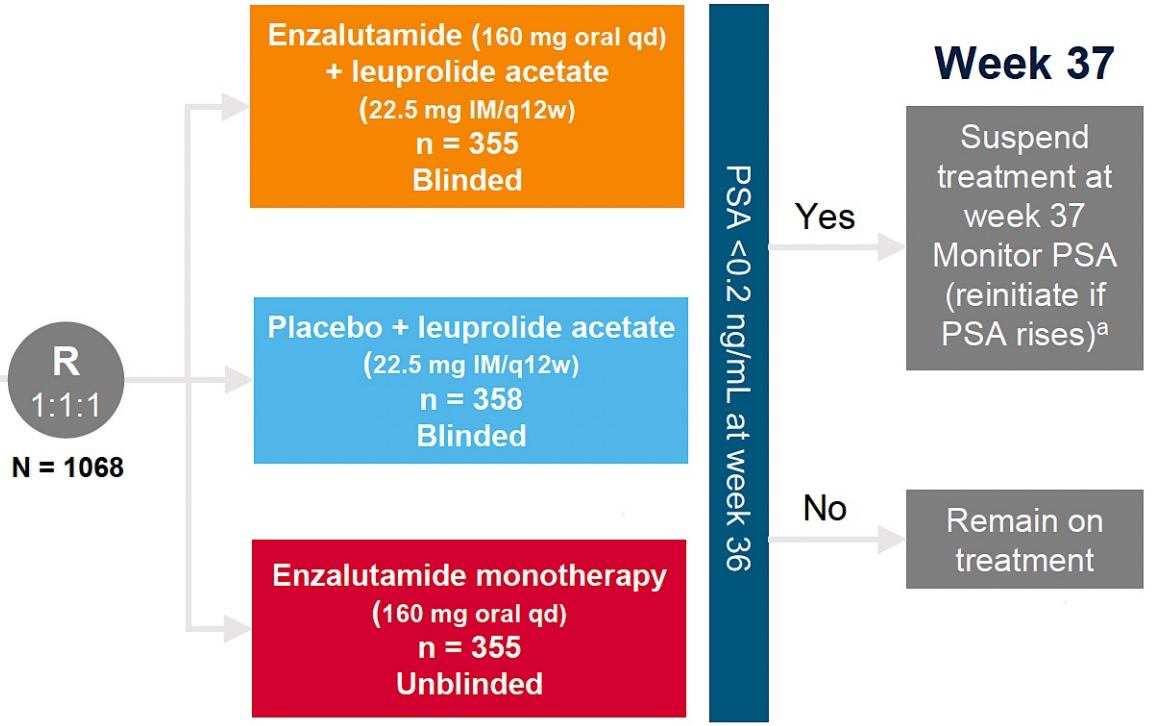
EMBARK Study Design

Patient population:
- Screening PSA ≥1 ng/mL after RP and at least 2 ng/mL above the nadir for primary EBRT
- PSADT ≤9 mo
- No metastases on bone scan or CT/MRI per central read
- Testosterone ≥150 ng/dL
- Prior hormonal therapy ≥9 mo prior to R (neoadjuvant/adjuvant for ≤36 mo OR ≤6 mo for rising PSA)

Stratification factors:
- Screening PSA (≤10 ng/mL vs. >10 ng/mL)
- PSADT (≤3 mo vs. >3 to ≤9 mo)
- Prior hormonal therapy (yes vs. no)



Primary endpoint:[b]
MFS by BICR, enzalutamide + leuprolide acetate vs. leuprolide acetate alone

Key secondary endpoints:[b,c]
- MFS by BICR, enzalutamide monotherapy vs. leuprolide acetate alone
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- OS[c]

Other secondary endpoints:
- PROs
- Safety[d]

[a]Study treatment was suspended once at week 37 if PSA was <0.2 ng/mL and restarted when PSA was ≥5.0 ng/mL (without prior RP) and ≥2 ng/mL (prior RP). [b]Intent-to-treat population. [c]Primary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. *P*-value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. [d]Safety population. BICR, blinded independent central review; CT, computed tomography; d, day; EBRT, external beam radiotherapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PROs, patient-reported outcomes; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Freedland *et al* (2023) N Engl J Med 2023;389:1453-1465

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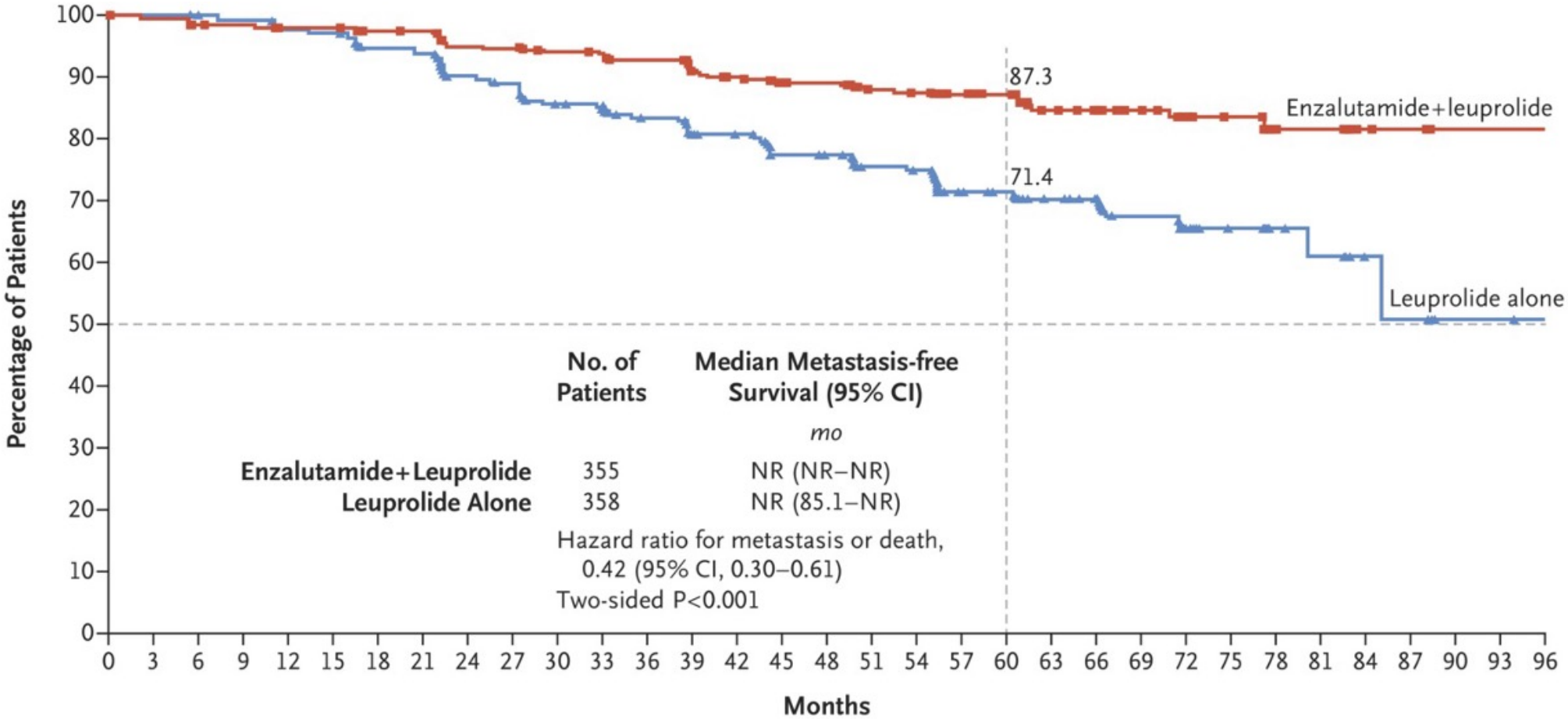
EMBARK Primary Endpoint:
MFS for Enzalutamide Combination vs. Leuprolide



No. at Risk

Enzalutamide+ leuprolide	355	339	331	330	324	324	318	317	304	303	292	290	281	270	265	252	251	236	234	183	180	119	116	83	60	51	24	22	6	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Freedland *et al* (2023) N Engl J Med 2023;389:1453-1465

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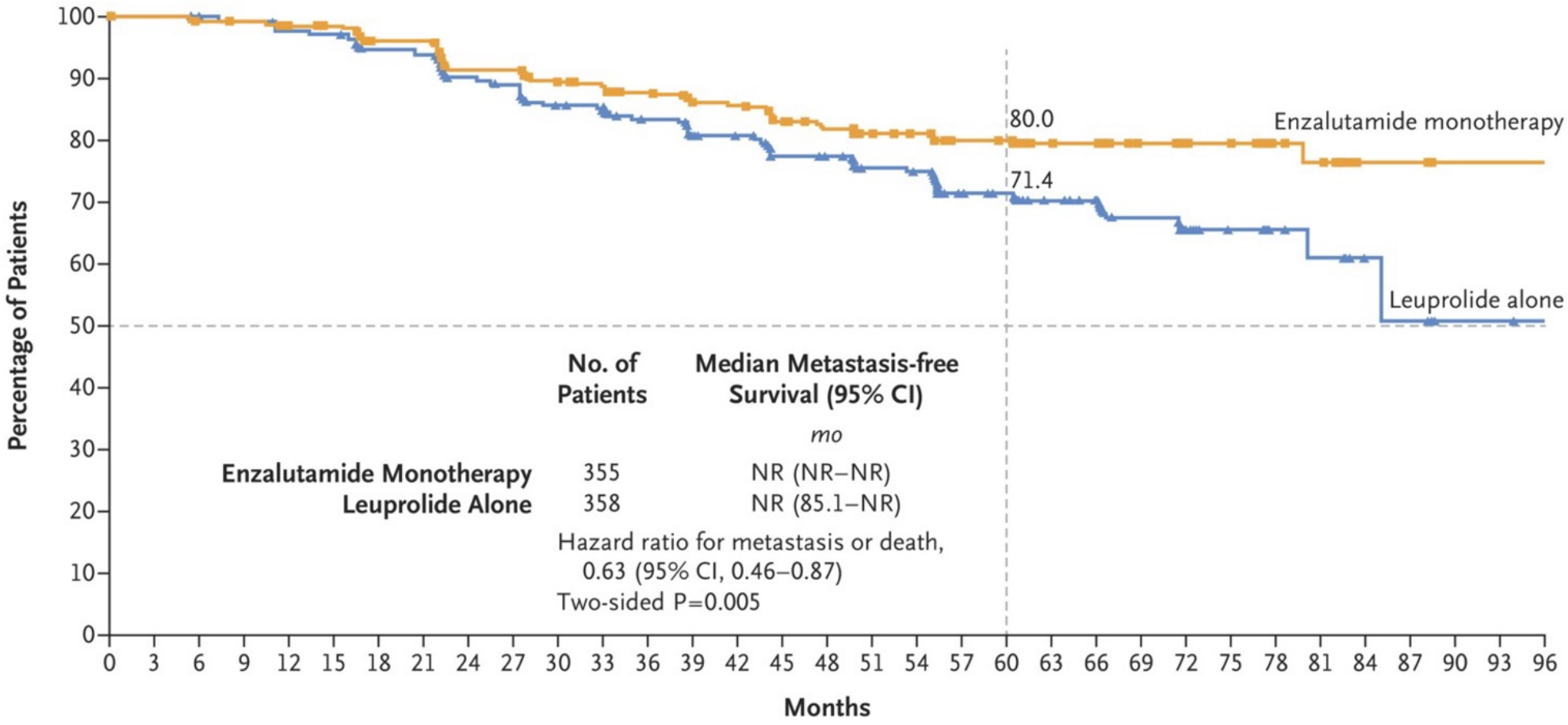
EMBARK Key Secondary Endpoint: MFS for Enzalutamide Monotherapy vs. Leuprolide



No. at Risk

Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Freedland *et al* (2023) N Engl J Med 2023;389:1453-1465

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EMBARK: Safety

Table 2. Adverse Events (Safety Population).*

Event	Enzalutamide + Leuprolide (N=353)		Leuprolide Alone (N=354)		Enzalutamide Monotherapy (N=354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
Hot flash	243 (68.8)§	2 (0.6)	203 (57.3)§	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	151 (42.8)§	12 (3.4)	116 (32.8)	5 (1.4)	165 (46.6)§	14 (4.0)
Arthralgia	97 (27.5)	7 (2.0)	75 (21.2)	1 (0.3)	81 (22.9)	2 (0.6)
Hypertension	82 (23.2)	24 (6.8)	69 (19.5)	18 (5.1)	67 (18.9)	19 (5.4)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Back pain	60 (17.0)	3 (0.8)	54 (15.3)	1 (0.3)	62 (17.5)	3 (0.8)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	1 (0.3)
Constipation	46 (13.0)	1 (0.3)	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	8 (2.3)	44 (12.4)	4 (1.1)	45 (12.7)	9 (2.5)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Pain in arm or leg	41 (11.6)	3 (0.8)	36 (10.2)	2 (0.6)	40 (11.3)	1 (0.3)
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	2 (0.6)	37 (10.5)	2 (0.6)	41 (11.6)	3 (0.8)
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	4 (1.1)	28 (7.9)	3 (0.8)	36 (10.2)	6 (1.7)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	3 (0.8)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	2 (0.6)
Peripheral edema	27 (7.6)	1 (0.3)	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	7 (2.0)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

Freedland *et al* (2023) N Engl J Med 2023;389:1453-1465

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EMBARK Phase 3 Study of Enzalutamide Plus Leuprolide in Non-Metastatic CSPC

July 10, 2025 Press Release:

For patients treated with enzalutamide plus leuprolide versus placebo plus leuprolide, EMBARK met the key secondary endpoint with a statistically significant and clinically meaningful improvement in OS. Results also showed a favorable trend towards improved OS for patients treated with enzalutamide monotherapy versus placebo plus leuprolide, however the difference did not reach statistical significance.

https://www.pfizer.com/news/press-release/press-release-detail/xtandir-plus-leuprolide-significantly-improves-survival

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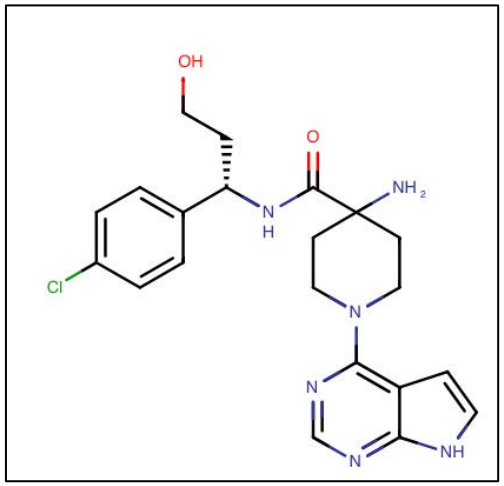
Capivasertib



- Oral AKT inhibitor
- Approved by the FDA in combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more alterations in PIK3CA/AKT1/PTEN gene(s).[1]
- This approval is based on favorable results obtained from the CAPItello-291 trial, in which the combination of capivasertib and fulvestrant reduced the risk of disease progression or death by 50% compared to fulvestrant alone.[2]

[1]www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer.
[2]Turner et al (2023) N Engl J Med 388: 2025-2070

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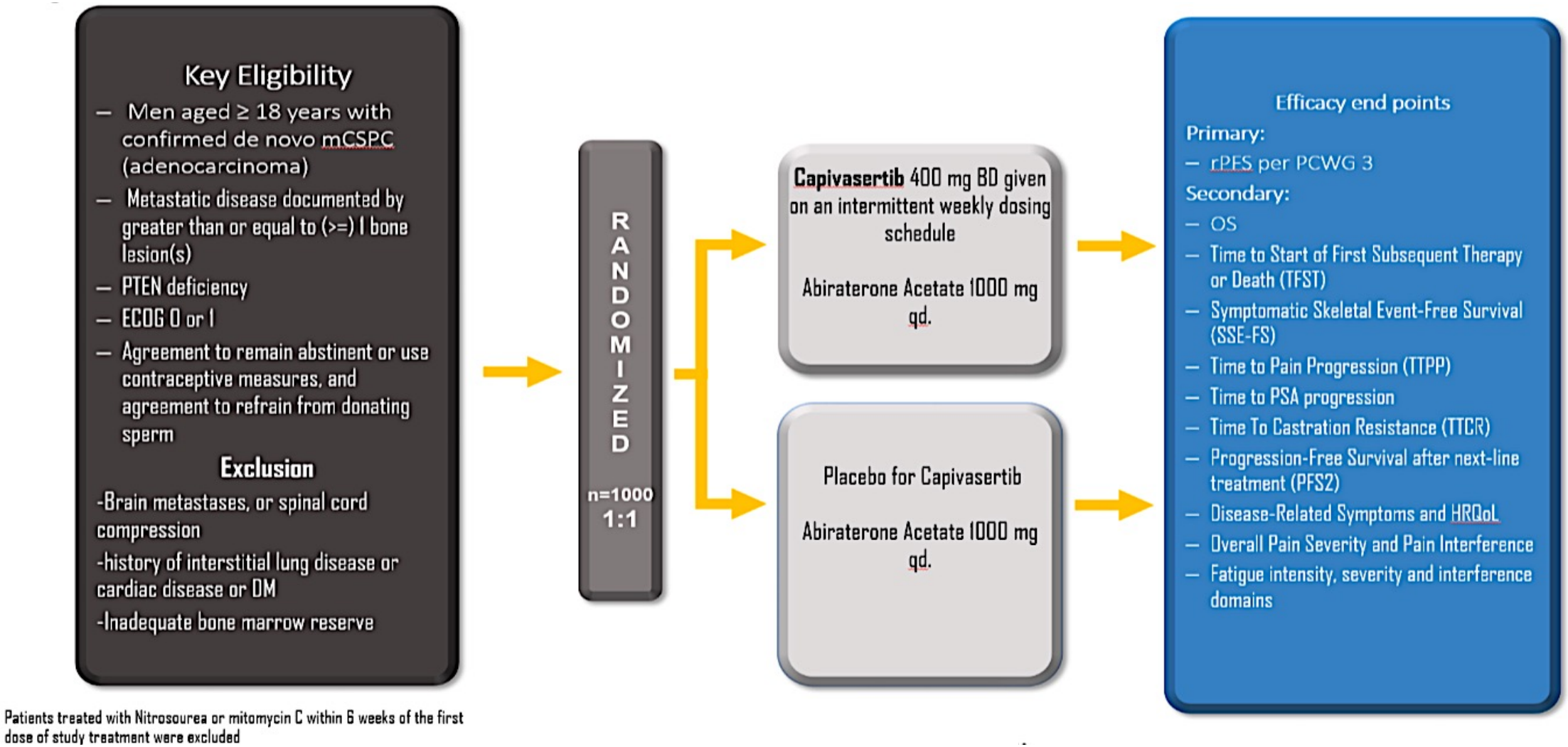
CAPItello-281 Phase 3 Study of Capivasertib in mCSPC



Patients treated with Nitrosourea or mitomycin C within 6 weeks of the first dose of study treatment were excluded

https://clinicaltrials.gov/study/NCT04493853

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CAPItello-281 Phase 3 Study of Capivasertib in mCSPC

<u>November 25, 2024 Press Release</u>:
"Capivasertib combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial.

The safety profile of capivasertib in combination with abiraterone and ADT in CAPItello-281 was broadly consistent with the known profile of each medicine."

https://www.astrazeneca.com/media-centre/press-releases/2024/truqap-improved-rpfs-in-advanced-prostate-cancer.html

Conclusions

AR pathway inhibitors (ARPIs) have an important role across a broad range of prostate cancer disease states:

- Abiraterone and enzalutamide improve rPFS and OS in mCRPC, either before or after chemotherapy
- Apalutamide, enzalutamide and darolutamide improve MFS and OS in nmCRPC
- Abiraterone, apalutamide, enzalutamide and darolutamide improve OS in mCSPC

- Abiraterone improves MFS and OS in high-risk primary and recurrent nmCSPC

- Enzalutamide improves MFS in recurrent nmCSPC

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

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RESEARCH
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EMBARK: Overall Survival with Enzalutamide in Biochemically Recurrent Prostate Cancer

Freedland S et al.

ESMO 2025;Abstract LBA47.

PROFFERED PAPER | SUNDAY, OCTOBER 19 | 10:52 CEST

A Phase III Study of Capivasertib (capi) + Abiraterone (abi) vs Placebo (pbo) + abi in Patients (pts) with PTEN Deficient *de novo* Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): CAPItello-281

Fizazi K et al.

ESMO 2025;Abstract 2383O.

PROFFERED PAPER | SUNDAY, OCTOBER 19 | 11:19 CEST

Questions from General Medical Oncologists

- **In what situations, if any, do you use intermittent endocrine treatment, and what is your protocol?**

Questions from General Medical Oncologists

- When do you use relugolix versus degarelix?
- Do you prefer relugolix for patients with cardiovascular risk factors?
- 72-year-old man with high-volume mHSPC, history of atrial fibrillation and prior NSTEMI: Would you use relugolix, and how do you weigh adherence with daily oral dosing?
- Can relugolix be used with enzalutamide in the nonmetastatic setting? What advantages might this provide?

Questions from General Medical Oncologists

- **In what situations, if any, do you use enzalutamide monotherapy? What preemptive breast protection strategies do you use, if any?**

Questions from General Medical Oncologists

- **How do you select which AR pathway inhibitor to combine with ADT for mHSPC?**

Questions from General Medical Oncologists

- **In what situations do you use docetaxel in addition to an AR pathway inhibitor for mHSPC?**
- **Can I start with a doublet and then add chemotherapy later if the patient fails to respond?**
- **When can I give a treatment holiday to patients who have mHSPC with good response and an undetectable PSA?**

Questions from General Medical Oncologists

- **A 63-year-old man with de novo mHSPC has PTEN loss on NGS. Where will capivasertib fit in, and do you see urologists prescribing it?**
- **What is the best way to assess PTEN status in prostate cancer? Should community-based oncologists be ordering PTEN testing at the current time? If so, when in the treatment sequence?**
- **Is the tolerability profile with capivasertib in prostate cancer any different than it is in breast cancer? Does it exacerbate any of the side effects associated with AR pathway inhibitors and/or ADT when these drugs are used in combination?**
- **How much of a concern is hyperglycemia when capivasertib is combined with abiraterone/ADT?**

Research To Practice
October 11, 2025

Available and Emerging Therapeutic Approaches for Metastatic CRPC

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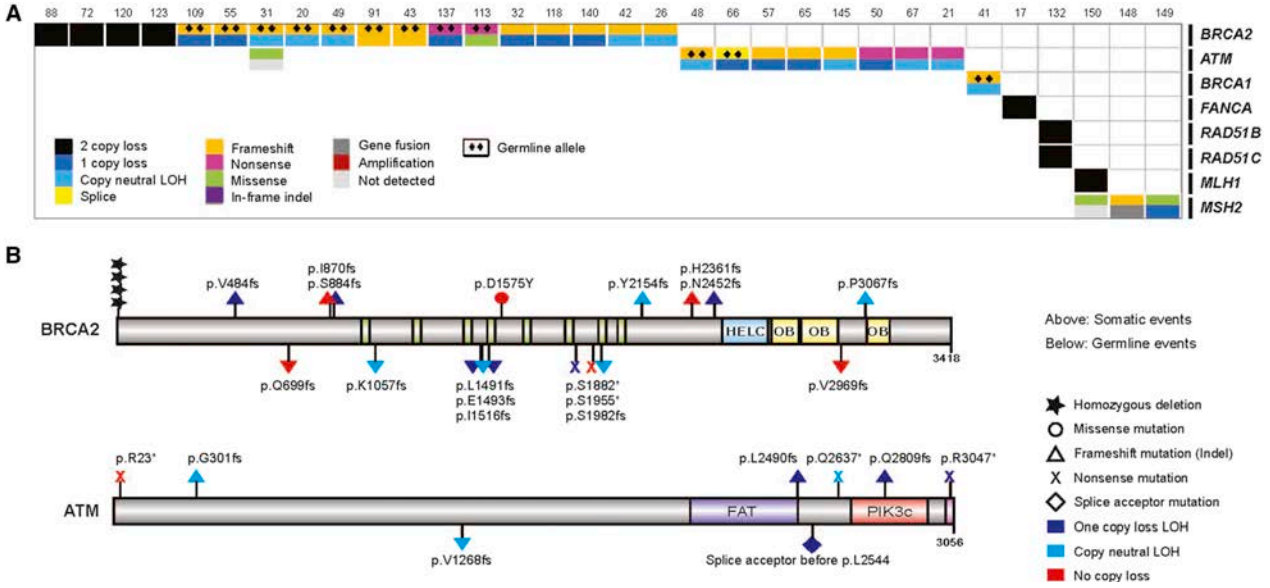
PARP inhibitors for HRR_m and *BRCA1/2*$_m$ advanced prostate cancer

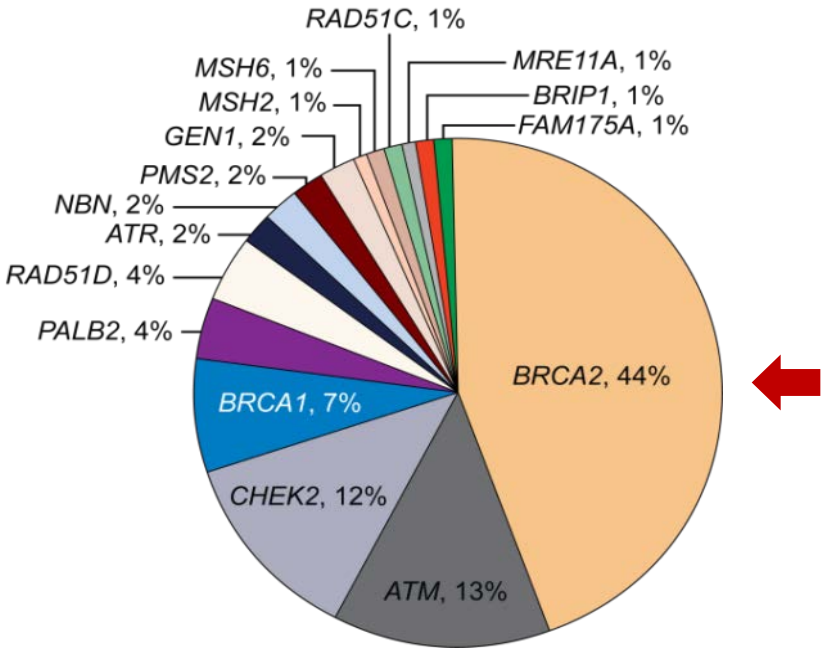
HRR Genes and Metastatic Prostate Cancer

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



Germline



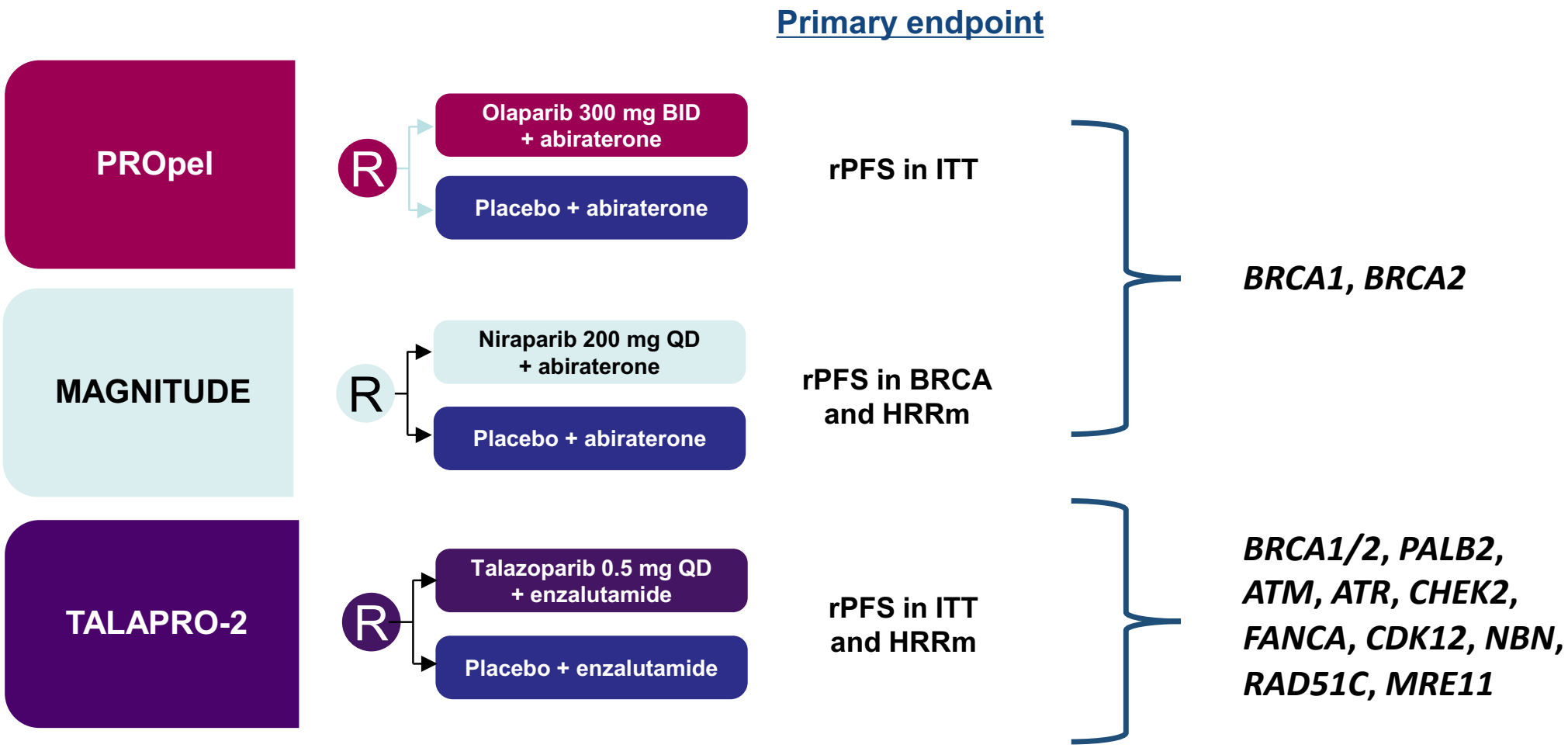
- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

1. Robinson D, et al. Cell. 2015;161:1215-28. **2.** Pritchard CC, et al. N Engl J Med. 2016;375:443-53.

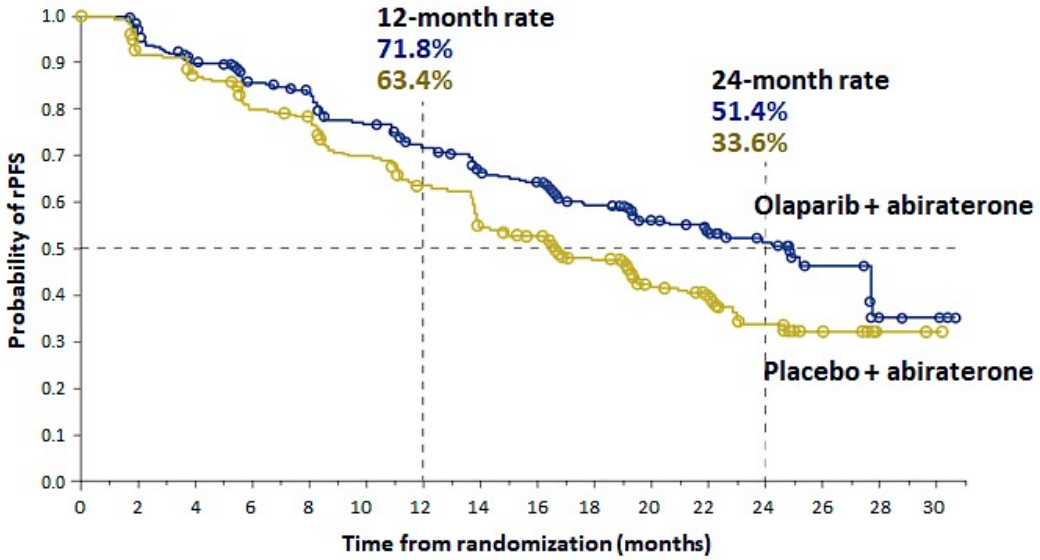
Most relevant HRR_m for PARPi efficacy?

"First Tier"	"Second Tier"	"Third Tier"
BRCA2 (6–8%)	***CDK12*** (5–7%)	***ATM*** (5–7%)
BRCA1 (1–2%)	***BARD1*** (1%)	***CHEK2*** (2–3%)
PALB2 (1–2%)	***BRIP1*** (1–2%)	***CHEK1*** (1%)
RAD51B (1%)	***RAD51C*** (1%)	***FANCL*** (1–2%)
RAD54L (1%)	***RAD51D*** (1%)	

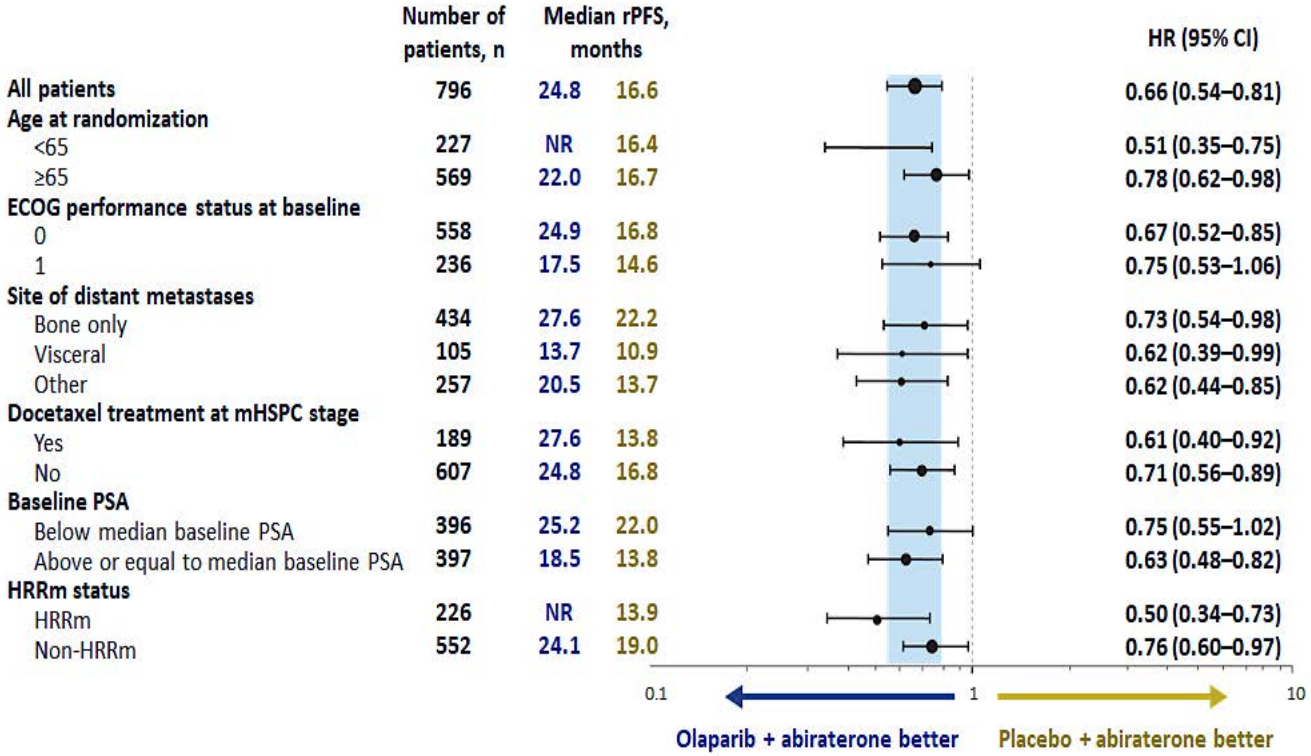
mCRPC ARPI + PARPi: PROpel, MAGNITUDE, TALAPRO-2



PROpel: Radiographic progression-free survival



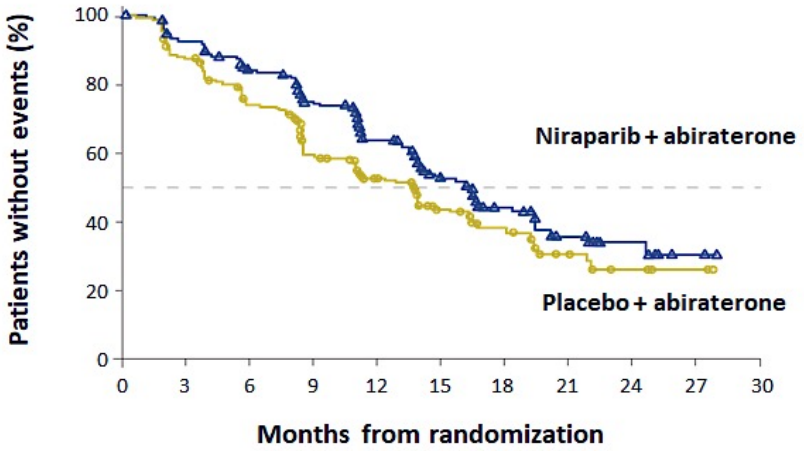
	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



Saad F et al. *NEJM Evidence*; 2022.

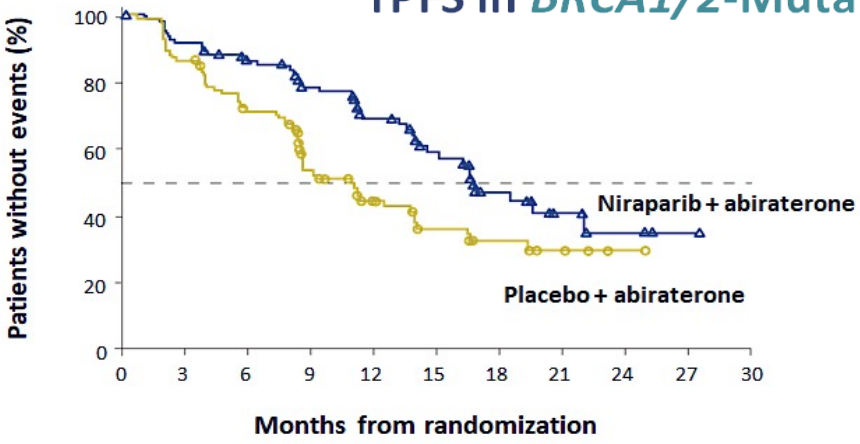
Magnitude: Radiographic progression-free survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

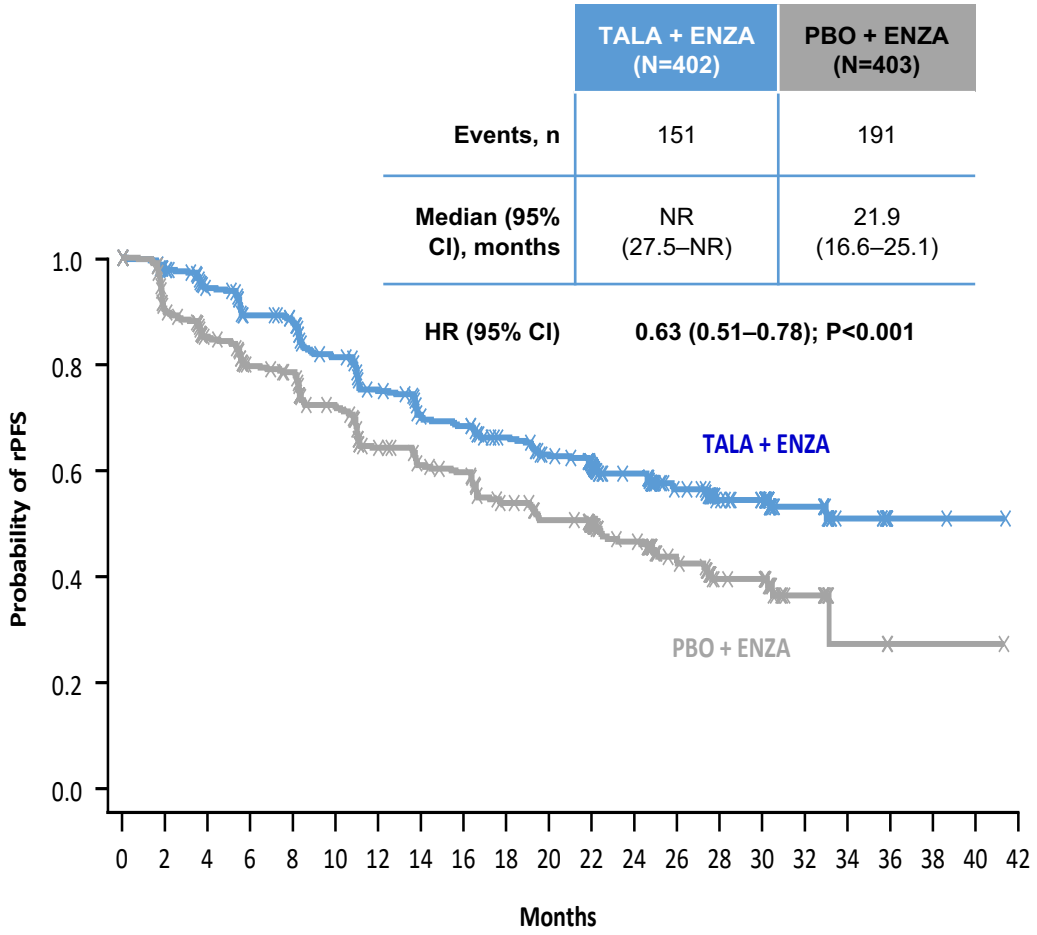
rPFS in *BRCA1/2*-Mutated Group



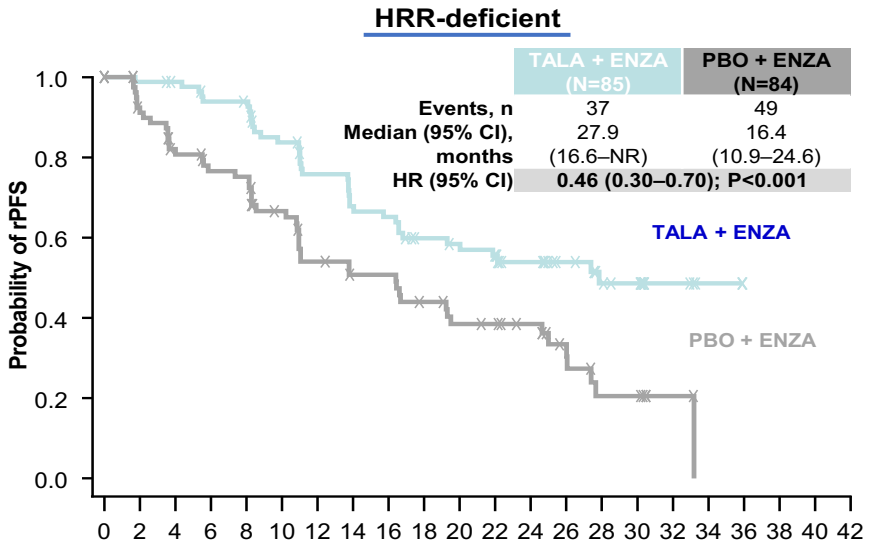
	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

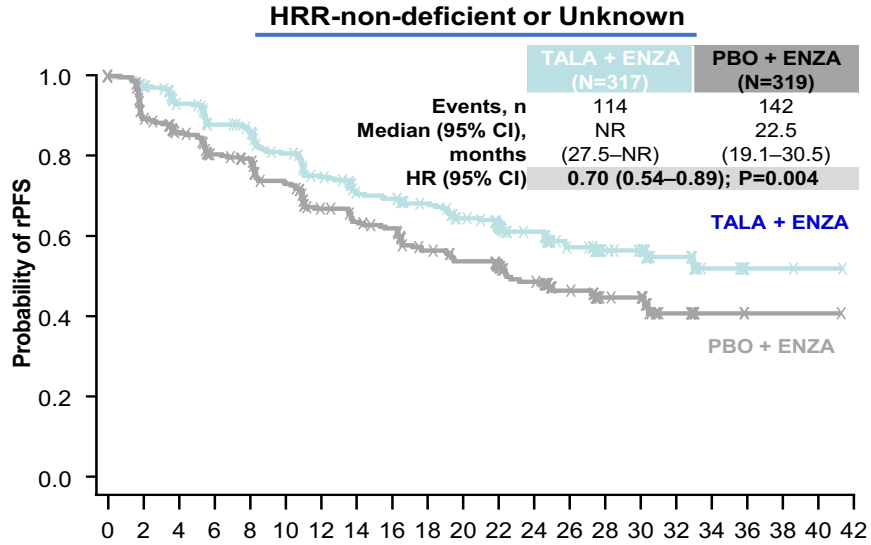
Chi KN et al. *J Clin Oncol 2023*.

Talapro-2: Phase III Trial of Enza +/– Talazoparib



Agarwal N et al. *Lancet 2023*; 402: 291-303.

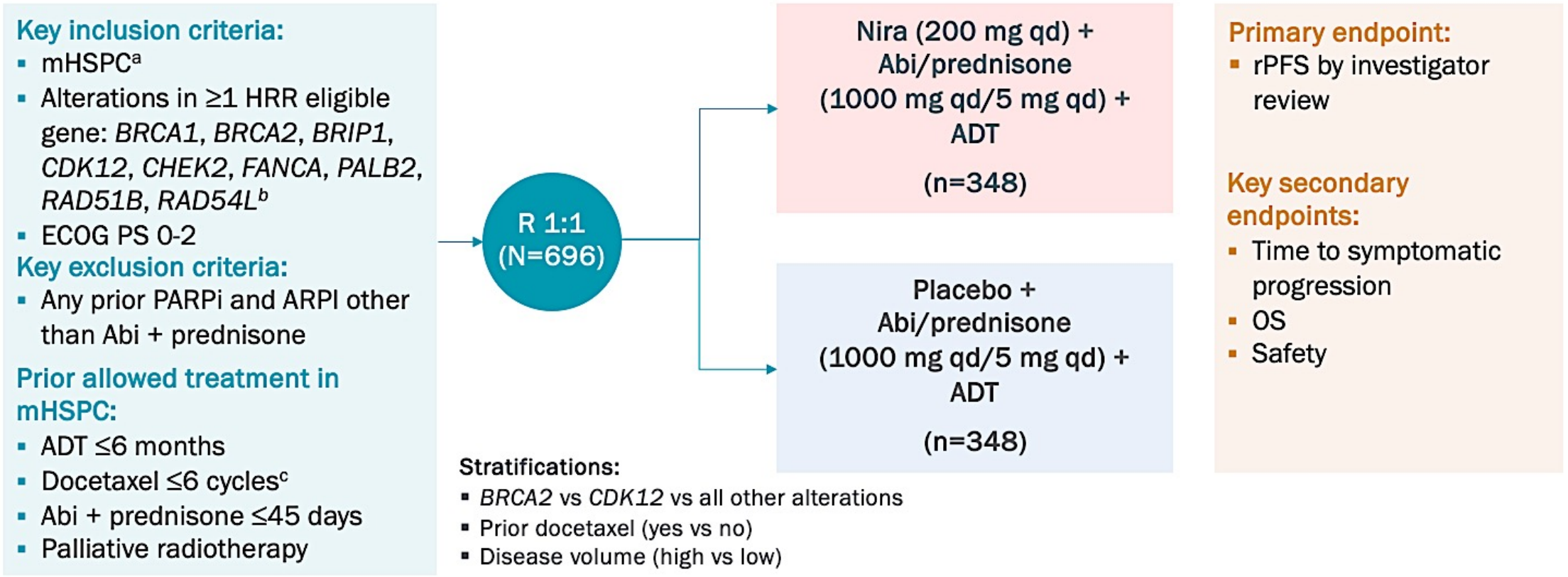




Adverse Events across the 3 studies

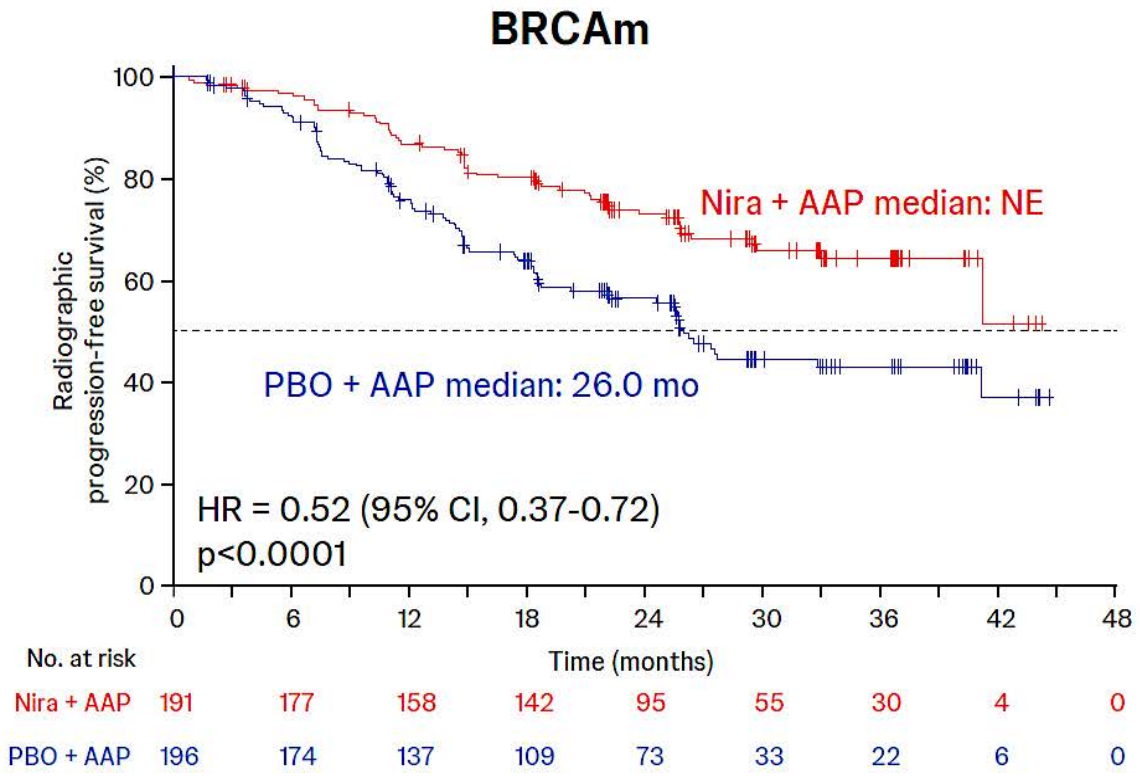
	MAGNITUDE N = 212 (HHRm Cohort)		PROPEL N = 398 (All Comers)		TALAPRO-2 N = 198 (HHRm Cohort)	
	All Grades (%)	Grade 3-4 (%)	All Grades	Grade 3-4	All Grades	Grade 3-4
Anemia	52	31	50	16	65	41
Fatigue	30	4	38	3	33	2
Nausea	24	1	30	1	21	2
Thrombocytopenia	24	8	7	1	25	7
Neutropenia	16	7	10	5	36	18
Pulmonary embolism	2		7		2	
Transfusion	27		18		36	
AML/MDS	N = 0		N = 2		N = 2	

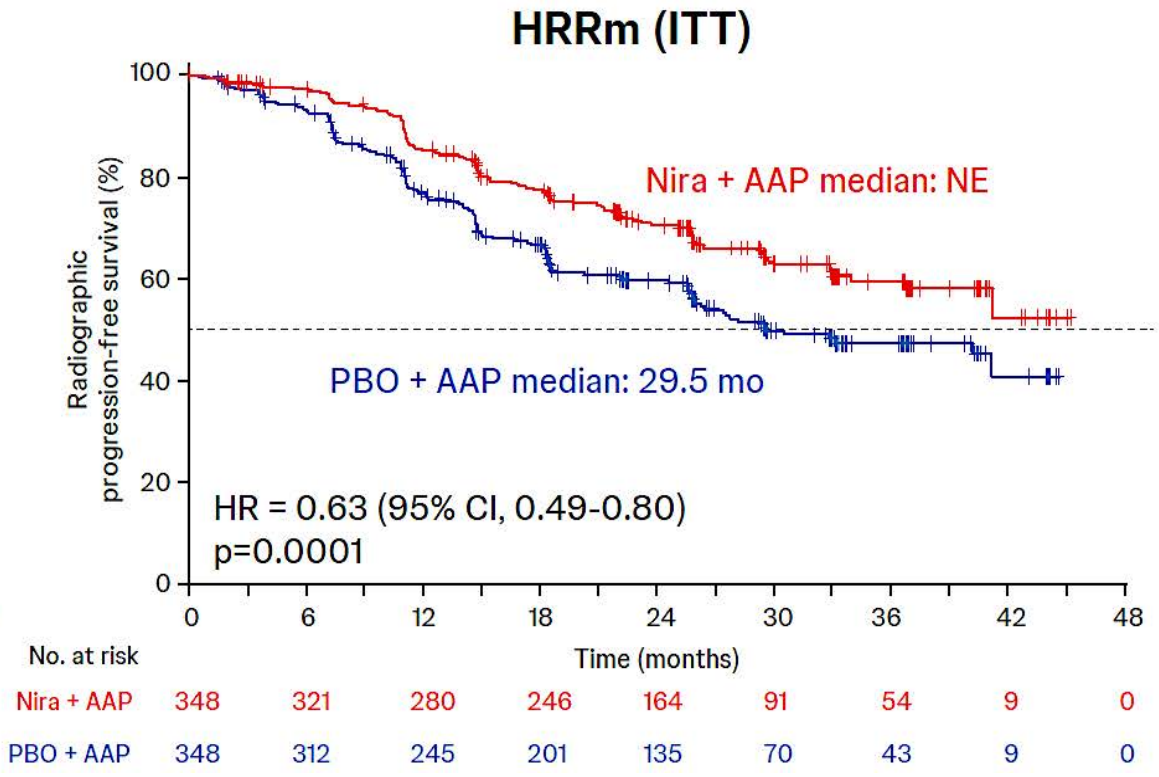
AMPLITUDE: ADT + Abi ± Nira in HRR_m mHSPC



Attard G., et al. *ASCO Annual 2025*, Abstract LBA5006.

rPFS Outcomes, by HRR_m or *BRCA1/2*$_m$ status

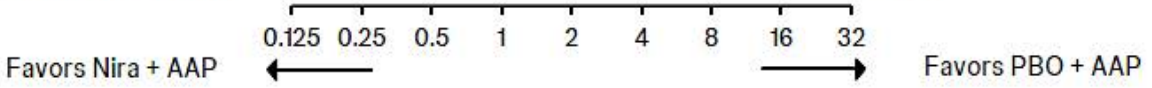




Attard G., et al. *ASCO Annual 2025*, Abstract LBA5006.

rPFS and OS outcomes, by key HRR genes

End Point	Subgroup	HR (95% CI)	Events/N	
			Nira + AAP	PBO + AAP
rPFS	*BRCA*	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
OS	*BRCA*	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



Attard G., et al. *ASCO Annual 2025*, Abstract LBA5006.

Select Ongoing Trials of PARP Inhibitors for mHSPC

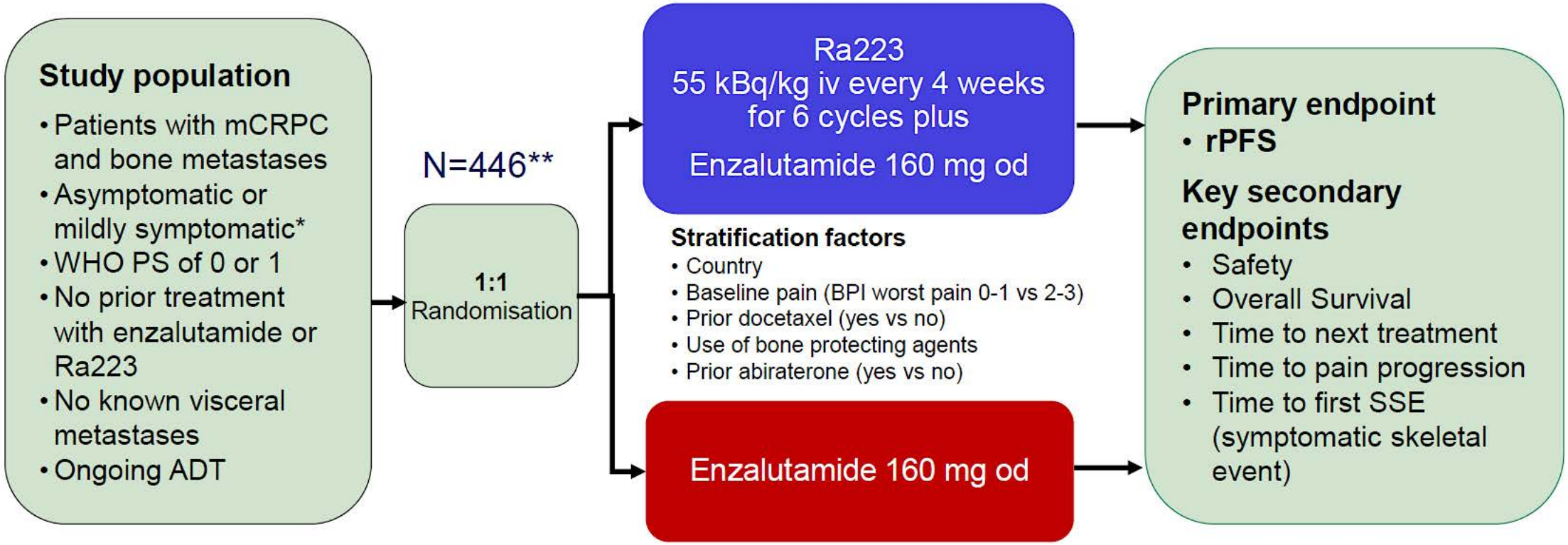
Trial Identifier	Phase	Study Population	Treatment Arms	Estimated Primary Completion Date
TALAPRO-3 (NCT04821622)	III	DDR gene mutation	• Talazoparib + enzalutamide • Placebo + enzalutamide	September 2025
EvoPAR-PR01 (NCT06120491)	III	de novo and recurrent, HRRm and non-HRRm	• Saruparib + physician's choice NHA • Placebo + physician's choice NHA	January 2028
NCT04734730	II	mHSPC	• Talazoparib + abiraterone/ prednisone + ADT	August 2027

NHA = new hormonal agent (abiraterone, darolutamide, enzalutamide)

www.clinicaltrials.gov. Accessed October, 2025.

Ra-223 plus Enzalutamide for first-line bone-metastatic mCRPC patients.

PEACE-3 trial: Enza +/- Radium^{223} in mCRPC

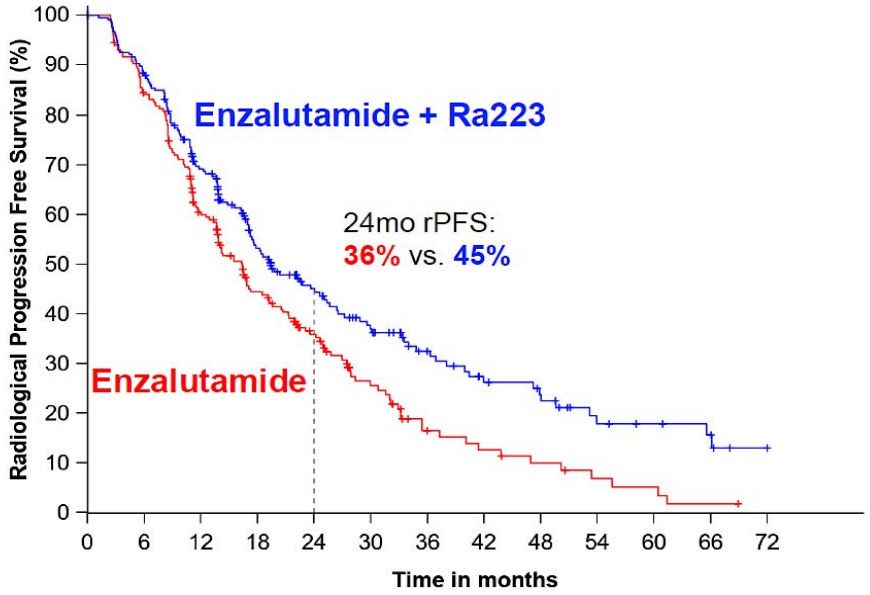


Gillessen S, et al. *ESMO* 2024; abstract LBA1.
Tombal B, et al. *Ann Oncol* 2025; 36: 1058-67.

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

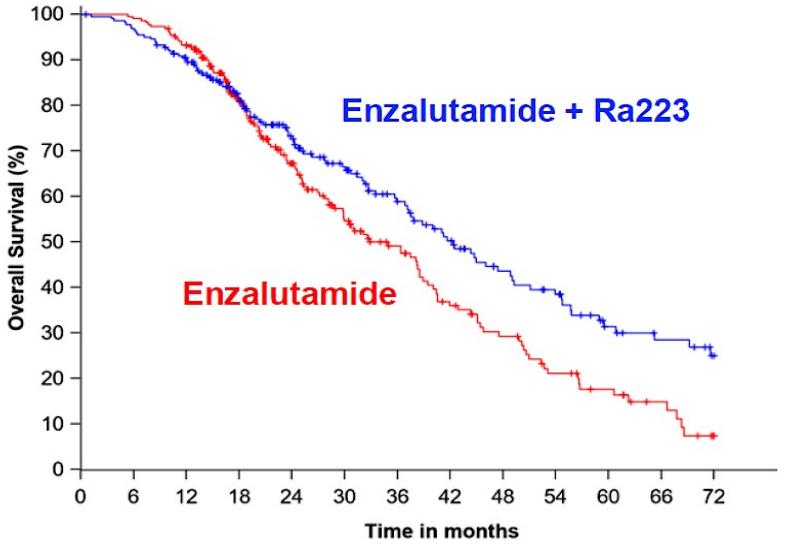
PEACE-3 trial: Enza +/- Radium^{223} in mCRPC

Primary endpoint: rPFS



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**	

Overall Survival at interim analysis



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

Gillessen S, et al. *ESMO* 2024; abstract LBA1. Tombal B, et al. *Ann Oncol* 2025; 36: 1058-67.

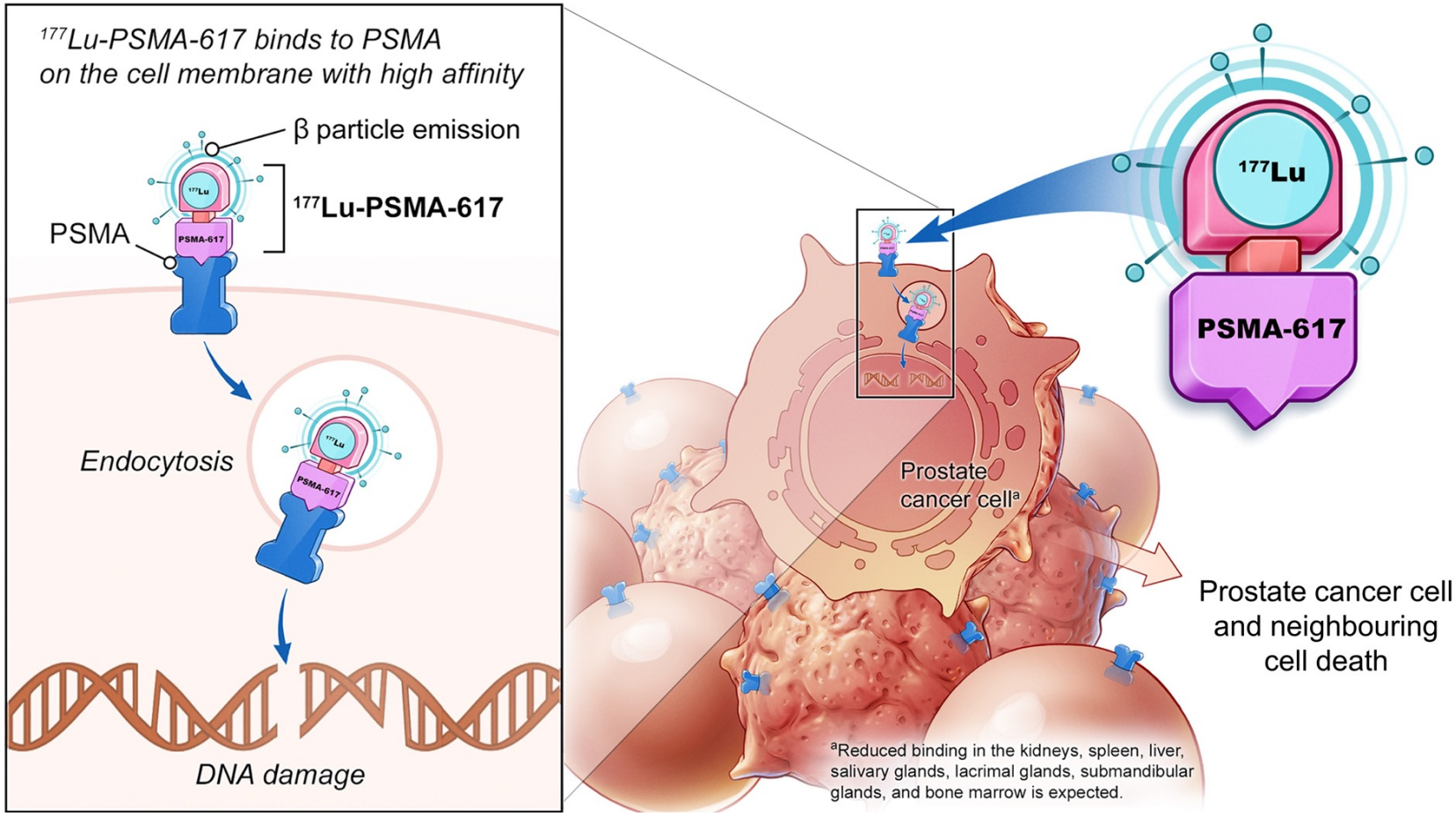
PEACE-3 trial: Adverse Events

Most common grade 3-5 treatment emergent AE (TEAE)	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
All		
Hypertension	73 (33.5)	77 (34.4)
Fatigue	12 (5.5)	4 (1.8)
Fracture	11 (5.1)	3 (1.3)
Anaemia	10 (4.6)	5 (2.2)
Neutropenia	10 (4.6)	0
Bone Pain	9 (4.1)	11 (4.9)
Weight Decreased	7 (3.2)	1 (0.4)
Spinal Cord Compression	6 (2.8)	8 (3.6)
Treatment related		
Hypertension	25 (11.5)	27 (12.1)
Fatigue	9 (4.1)	3 (1.3)
Anaemia	6 (2.8)	0
Neutropenia	7 (3.2)	0

Gillessen S, et al. *ESMO* 2024; Abstract LBA1. Tombal B, et al. *Ann Oncol* 2025; 36: 1058-67.

Lu-177 vipivotide tetraxetan “radioligand” therapy for advanced prostate cancer.

^{177}Lu-PSMA-617 Radioligand therapy



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4).

VISION trial for patients with PSMA+ mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

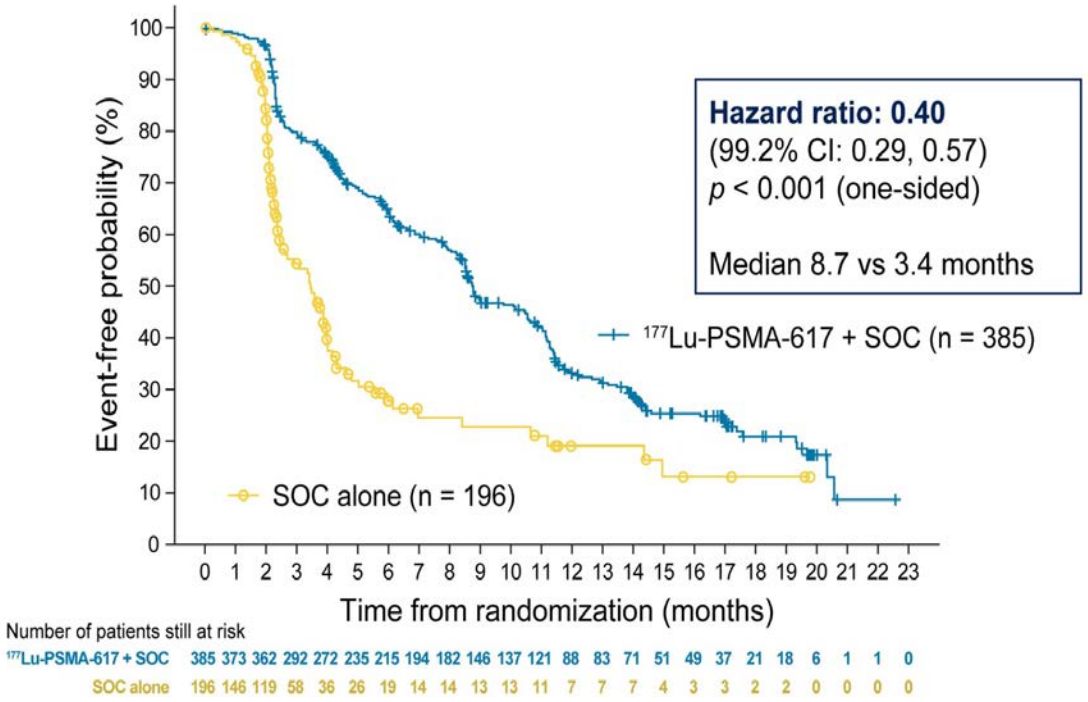
Treatment → Follow-up → Final analysis

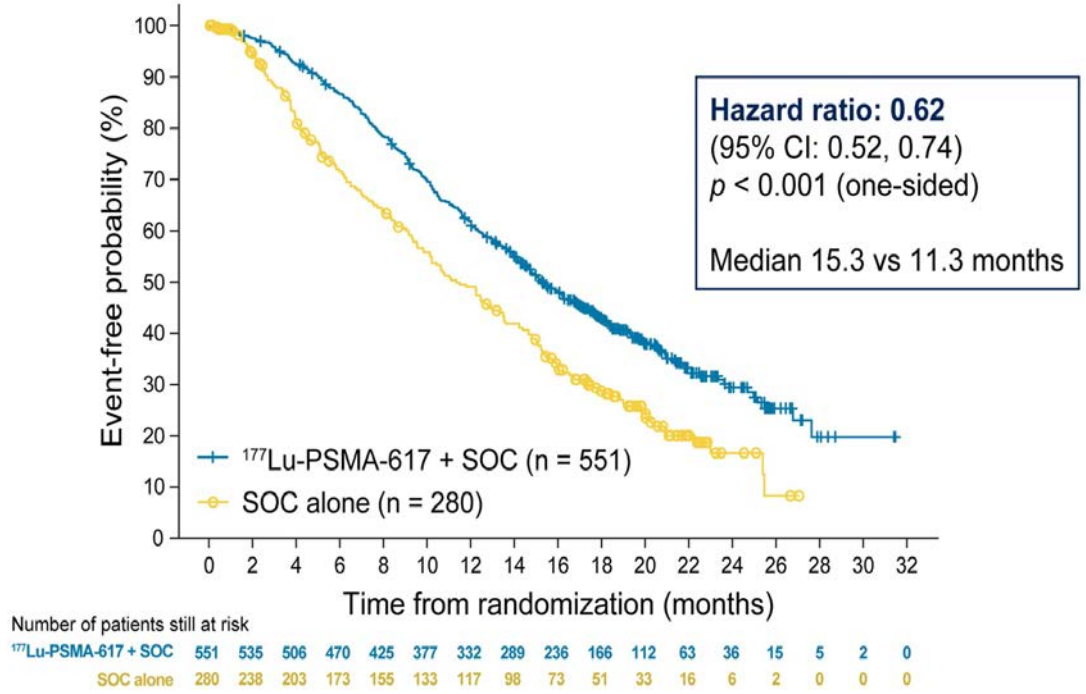
- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021; 385: 1091-1103.

VISION trial: rPFS and OS outcomes





Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021; 385: 1091-1103.

VISION trial: Adverse Events

Table 2. Adverse Events.*

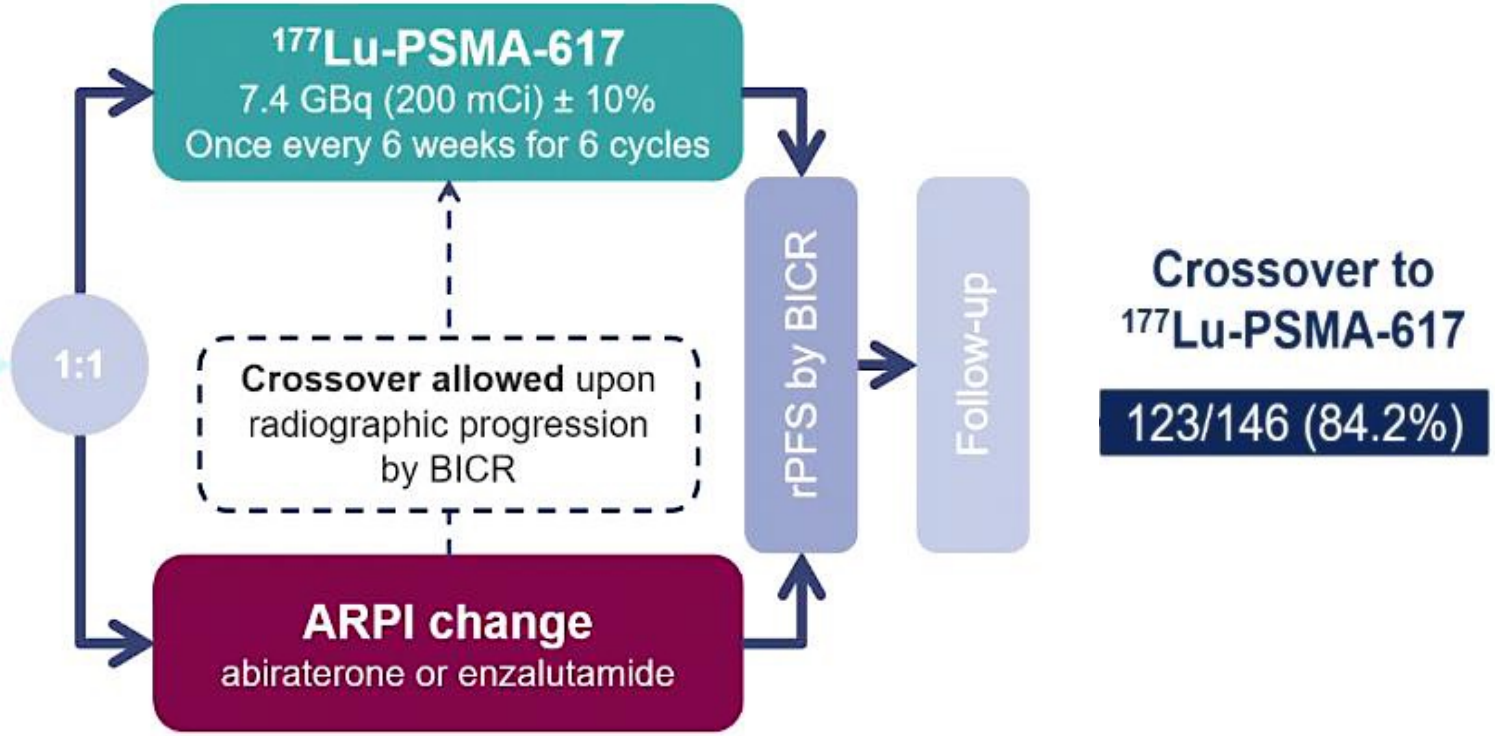
Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)

Sartor O, et al. *NEJM* 2021; 385: 1091-1103.

PSMAfore: ^{177}Lu-PSMA-617 in *pre-taxane* mCRPC

Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]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

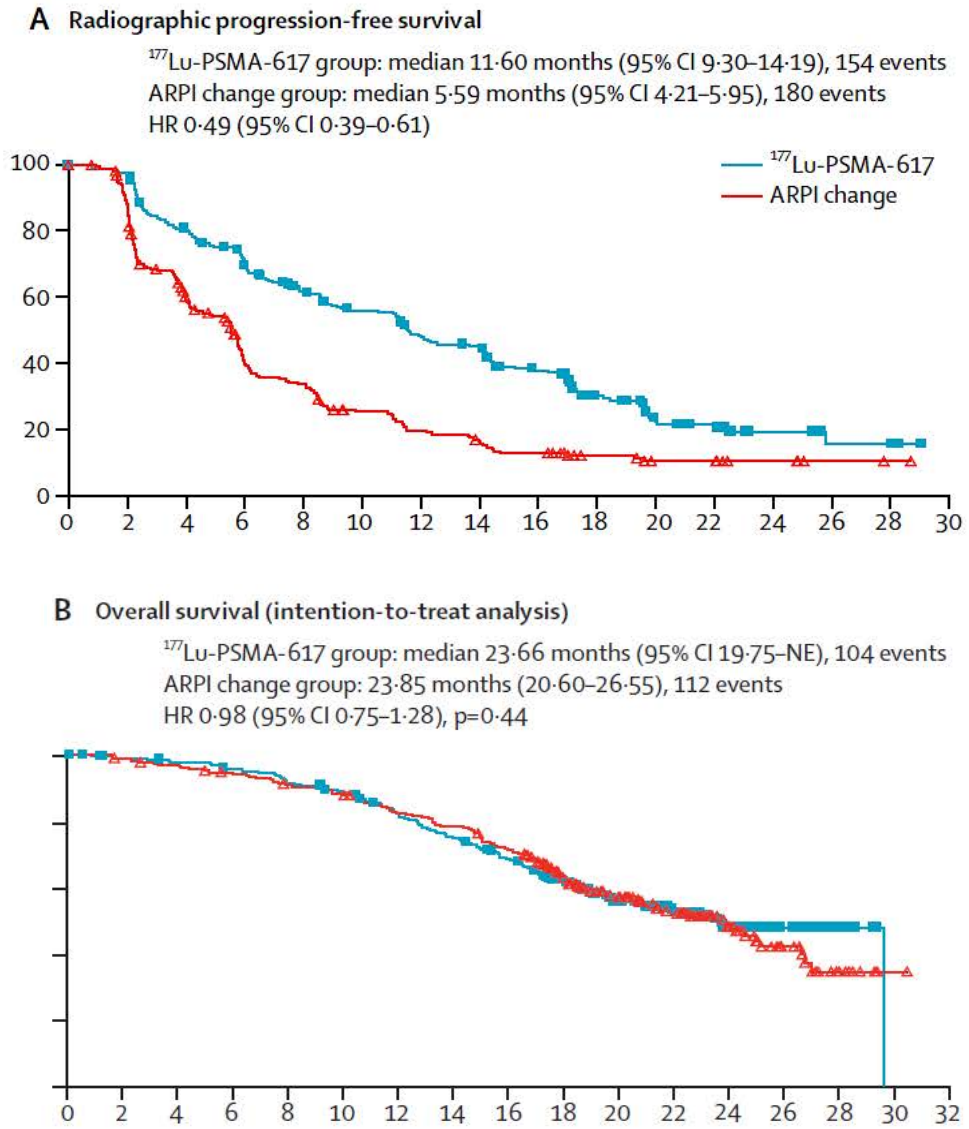


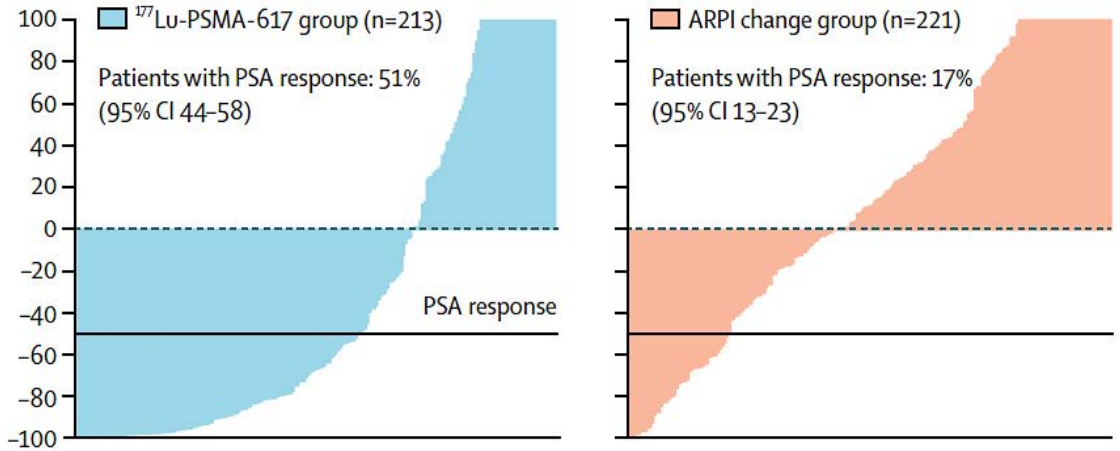
Stratification factors

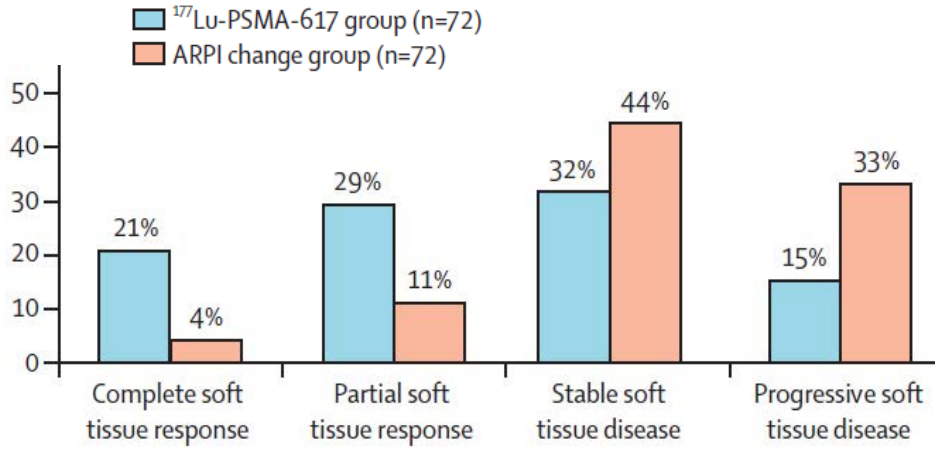
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

PSMAfore: ^{177}Lu-PSMA-617 vs. ARPI switch







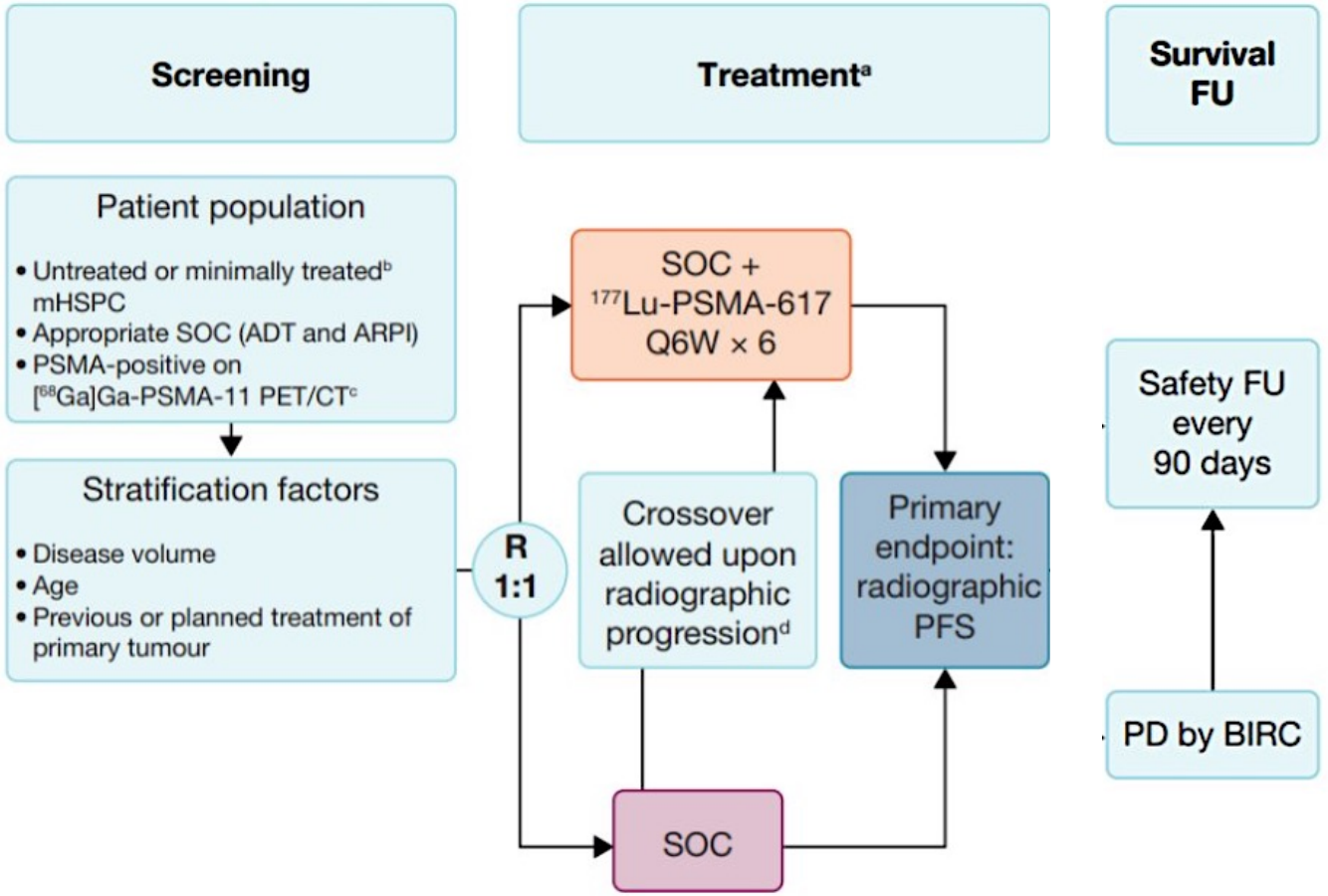
Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

PSMAfore: Adverse Events

	^{177}Lu-PSMA-617 group (n=227)		ARPI change group (n=232)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	224 (99%)	81 (36%)*	226 (97%)	112 (48%)*
Occurring in >10% of patients				
Dry mouth	131 (58%)†	2 (1%)	6 (3%)†	0
Asthenia	74 (33%)	2 (1%)	67 (29%)	8 (3%)
Nausea	72 (32%)	0	27 (12%)	1 (<1%)
Anaemia	61 (27%)	14 (6%)	44 (19%)	16 (7%)
Fatigue	53 (23%)	1 (<1%)	59 (25%)	4 (2%)
Constipation	50 (22%)	1 (<1%)	33 (14%)	0
Decreased appetite	49 (22%)	0	43 (19%)	1 (<1%)
Arthralgia	45 (20%)	0	54 (23%)	1 (<1%)
Diarrhoea	38 (17%)	0	21 (9%)	1 (<1%)
COVID-19	36 (16%)	1 (<1%)	27 (12%)	1 (<1%)
Back pain	31 (14%)	3 (1%)	46 (20%)	6 (3%)
Vomiting	26 (11%)	0	11 (5%)	0
Oedema peripheral	19 (8%)	0	28 (12%)	0
Pain in extremity	17 (7%)	1 (<1%)	25 (11%)	1 (<1%)
Weight loss	15 (7%)	1 (<1%)	32 (14%)	3 (1%)

Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

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



Tagawa ST, et al. *ASCO Annual 2023*; Abstract TPS5116. **NCT04720157**.

PSMAddition: *Press release* on 6/2/2025

Lutetium vipivotide tetraxetan demonstrates statistically significant and clinically meaningful rPFS benefit in patients with PSMA-positive metastatic hormone-sensitive prostate cancer

Jun 02, 2025

Ad hoc announcement pursuant to Art. 53 LR

- *At interim analysis, PSMAddition trial met its primary endpoint showing statistically significant and clinically meaningful benefit for ^{177}Lu plus hormone therapy versus hormone therapy alone, with positive trend in overall survival (OS)[1]*
- *^{177}Lu is already approved for metastatic castration-resistant prostate cancer (mCRPC) and now shows potential in patients in an earlier disease setting[1,2]*
- *Manufacturer to present results at an upcoming medical meeting and, based on FDA feedback, will submit for regulatory review in the second half of the year*

https://www.novartis.com/news/media-releases/novartis-pluvictotm-demonstrates-statistically-significant-and-clinically-meaningful-rpfs-benefit-patients-psma-positive-metastatic-hormone-sensitive-prostate-cancer

Promising novel agents and strategies for patients with advanced prostate cancer.

Other promising novel agents & strategies

- PI3K-AKT-mTOR pathway: Capivasertib
- CYP11 inhibition: Opevesostat
- AR-targeting PROTACs: Bavdegalutamide, ARV-766, BMS-986365
- EZH2 inhibitors: Mevrometostat
- B7-H3–targeting Antibody-drug conjugates (ADCs)
- Bispecific immune engagers: Xaluritamig, Pasritamig

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Phase 3 Trial of [177Lu]Lu-PSMA-617 Combined with ADT + ARPI in Patients with PSMA-Positive Metastatic Hormone-Sensitive Prostate Cancer (PSMAddition)

Tagawa ST et al.

ESMO 2025;Abstract LBA6.

PRESIDENTIAL SYMPOSIUM II | SUNDAY, OCTOBER 19 | 17:14 CEST

First Interim Efficacy Analysis of the Phase I/II PETRANHA Trial of Saruparib + Androgen Receptor Pathway Inhibitors (ARPI) in Patients (pts) with Metastatic Prostate Cancer (mPC)

Azad AA et al.

ESMO 2025;Abstract 2384MO.

MINI ORAL | FRIDAY, OCTOBER 17 | 14:35 CEST

Questions from General Medical Oncologists

- How do you rate the sensitivity to PARPi of the various HRR abnormalities from a practical perspective? BRCA1/2, PALB2, others? Somatic versus genetic?
- In Europe, PARPi are approved for all comers, do you foresee that in the US? Would you like to be able to use these agents for all patients?

Questions from General Medical Oncologists

- **How do you see integrating PARPi into the management of mHSPC? Which one and how? Are you attempting to do this now?**

Questions from General Medical Oncologists

- **A 71-year-old man with mCRPC and a somatic BRCA1 mutation has disease progression after enzalutamide. Should we switch to a PARPi alone or continue AR-targeted therapy and add a PARPi? Which PARPi?**

Questions from General Medical Oncologists

- **For men with prostate cancer receiving a PARPi, how much of an issue are cytopenias? GI issues? AML/MDS?**

Questions from General Medical Oncologists

- **How do you see integrating ^{177}Lu-PSMA-617 into the management of mHSPC?**
- **With the potential emergence of several new triplet approaches (PARP, AKT, PSMA) how do you envision selecting between these and currently available approaches for mHSPC?**

Questions from General Medical Oncologists

- **For a patient who is eligible for both radium-223 and ^{177}Lu-PSMA-617, how do you choose which to use first?**