Second Opinion: Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2026 American Urological Association Annual Meeting (AUA2026)

Sunday, May 17, 2026

5:30 PM – 7:30 PM ET

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Moderator

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No relevant financial relationships to disclose.

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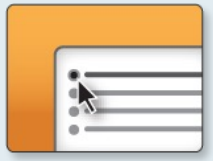

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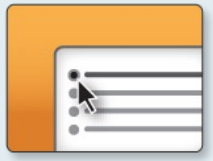

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Moderator

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Second Opinion

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Agenda

Module 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Shore

Module 2: Current Hormonal Treatment for Metastatic HSPC (mHSPC) — Dr Petrylak

Module 3: Current and Future Role of PARP Inhibitors for Metastatic Prostate Cancer (mPC) — Dr Agarwal

Module 4: Emerging Role of AKT Inhibition for Patients with mHSPC — Dr Heath

Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

Agenda

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Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

Advancing Options in BCR: Interprofessional Intensification Strategies Reshaping Care

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Biochemical Recurrence After Local Therapy

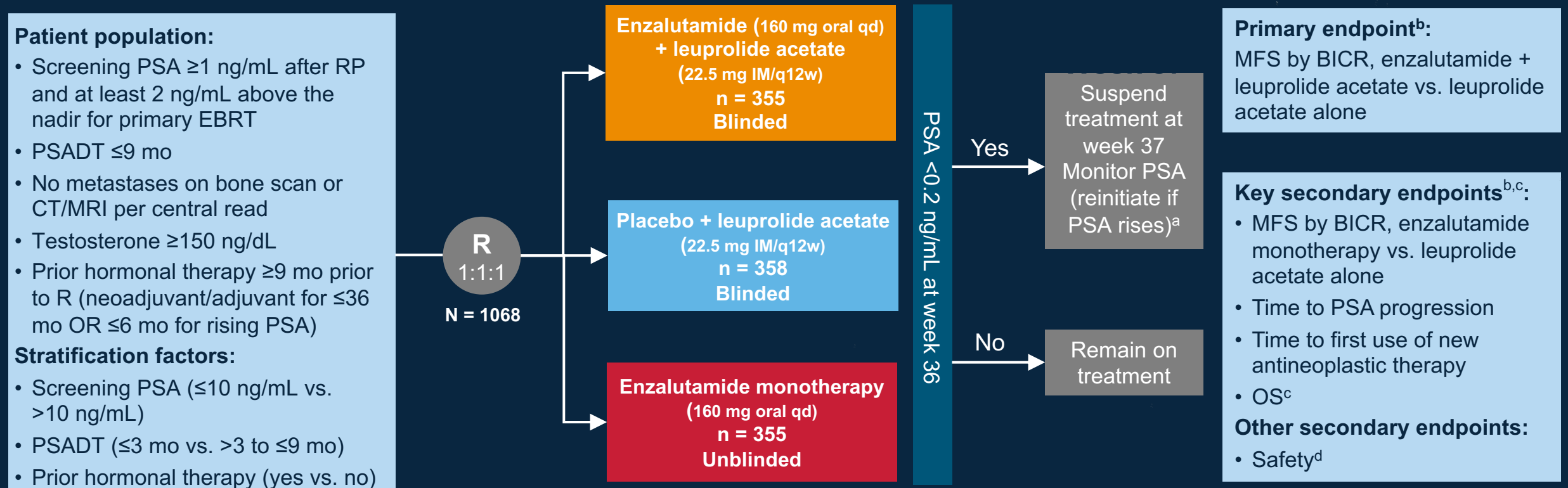
Prostatectomy

- Definition of recurrence: PSA >0.2
- Staging: conventional imaging vs PSMA-PET
- Treatment
  - Salvage RT ± ADT
  - Intermittent ADT?
  - Enzalutamide ± ADT

Primary Radiation +/- ADT

- Definition of recurrence: PSA >2.0 from nadir with eugonadal testosterone
- Staging: conventional imaging vs PSMA-PET
- Some consideration of salvage RP or salvage RT (HDR brachytherapy)
- Treatment
  - Intermittent ADT?
  - Enzalutamide ± ADT

EMBARK study design



[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; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Freedland SJ, et al. *New Engl J Med*. 2023;389(16):1453–1465.

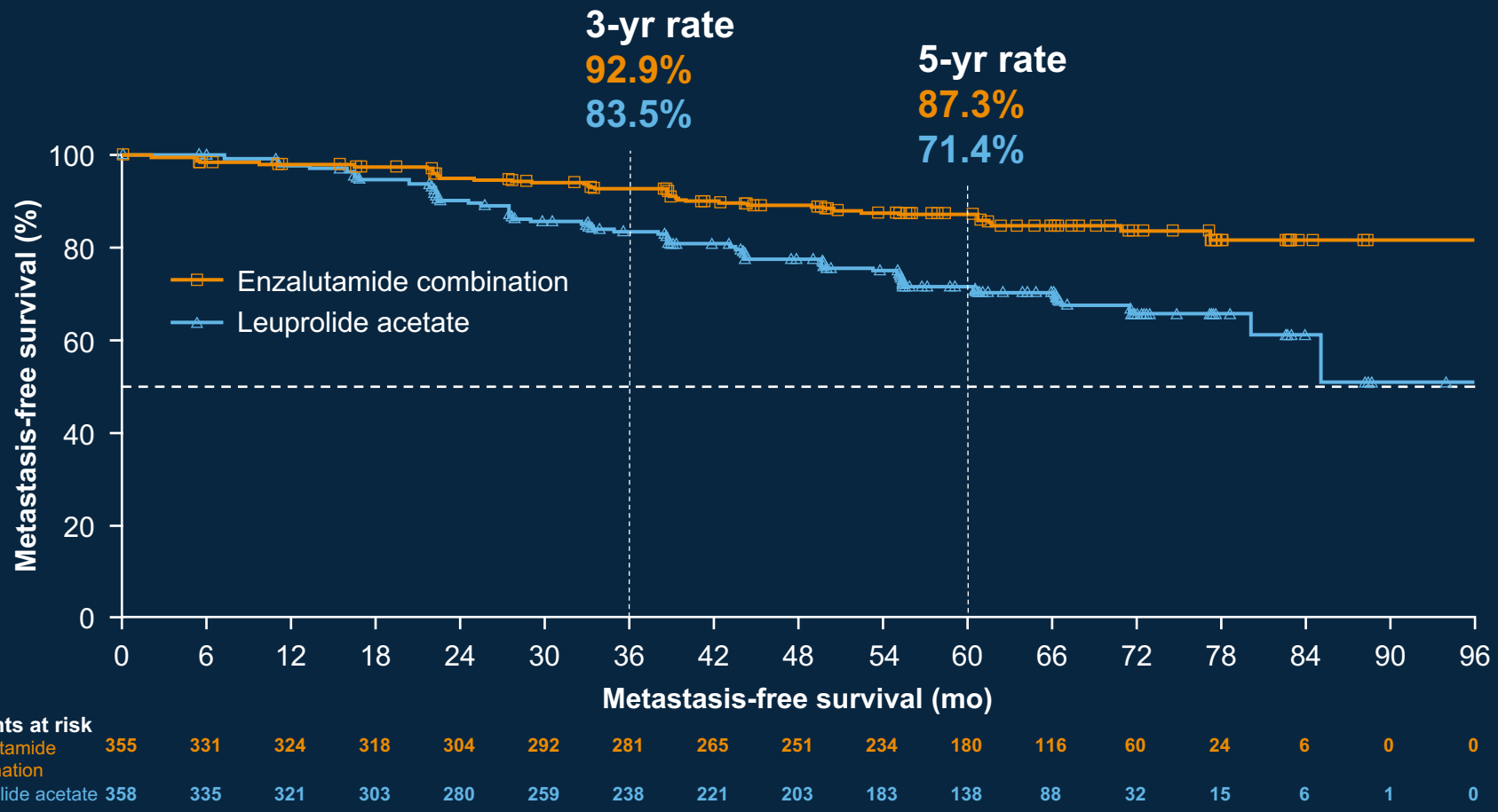
Demographics

Characteristic	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)	Enzalutamide monotherapy (n = 355)
Age, median (range), yr	69 (51–87)	70 (50–92)	69 (49–93)
Race, n (%)[a]			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
Other[b]	10 (2.8)	10 (2.8)	5 (1.4)
PSADT, n (%)[c]			
≤3 mo	69 (19.4)	80 (22.3)	76 (21.4)
>3 to ≤9 mo	285 (80.3)	277 (77.4)	278 (78.3)
PSADT, median, mo	4.6	5.0	5.0
Serum PSA, median, n (%), ng/mL[d]	5.0	5.5	5.3
≤10	278 (78.3)	273 (76.3)	272 (76.6)
>10	77 (21.7)	83 (23.2)	82 (23.1)
Prior hormonal therapy, n (%)	107 (30.1)	113 (31.6)	112 (31.5)
RP alone, n (%)	90 (25.4)	75 (20.9)	99 (27.9)
RT alone, n (%)	86 (24.2)	104 (29.1)	90 (25.4)
RP and RT, n (%)	179 (50.4)	179 (50.0)	166 (46.8)

[a]Not reported included: enzalutamide combination, n = 10 (2.8%); leuprolide acetate, n = 5 (1.4%); enzalutamide monotherapy, n = 14 (3.9%). [b]Includes patients who identified as multiple races (enzalutamide combination, n = 5; leuprolide acetate, n = 9; enzalutamide monotherapy, n = 5), American Indian or Alaskan Native (enzalutamide combination, n = 4; leuprolide acetate, n = 1; enzalutamide monotherapy, n = 0), Native Hawaiian or other Pacific Islander (enzalutamide combination, n = 1; leuprolide acetate and enzalutamide monotherapy, n = 0). [c]Missing included n = 1 (0.3%) for each treatment group. [d]Missing included: leuprolide acetate, n = 2; enzalutamide monotherapy, n = 1. RT, radiation therapy; yr, year.

Freedland SJ, et al. *New Engl J Med*. 2023;389(16):1453–1465.

Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.42 (0.31–0.61); *P*<0.0001[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); *P*<0.0001

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value was based on a stratified log-rank. CI, confidence interval; HR, hazard ratio; IWRS, interactive web response system; NR, not reached.

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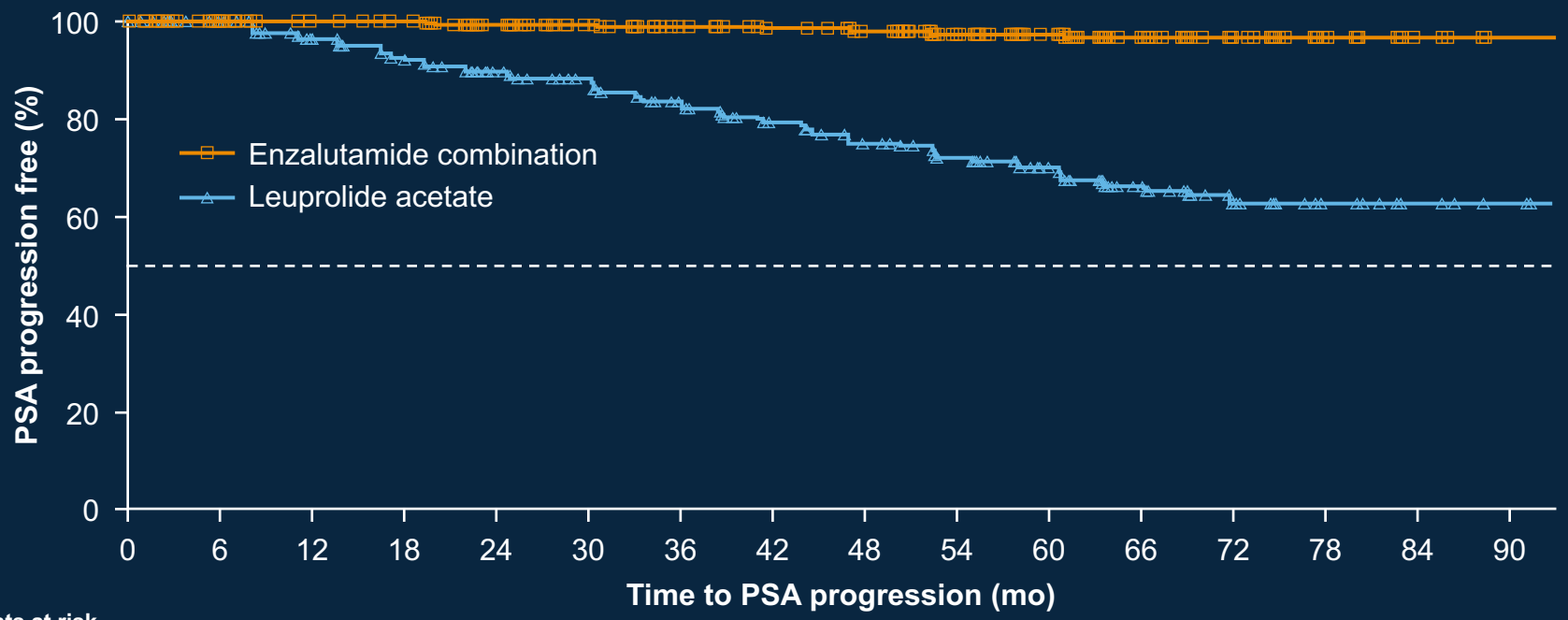
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

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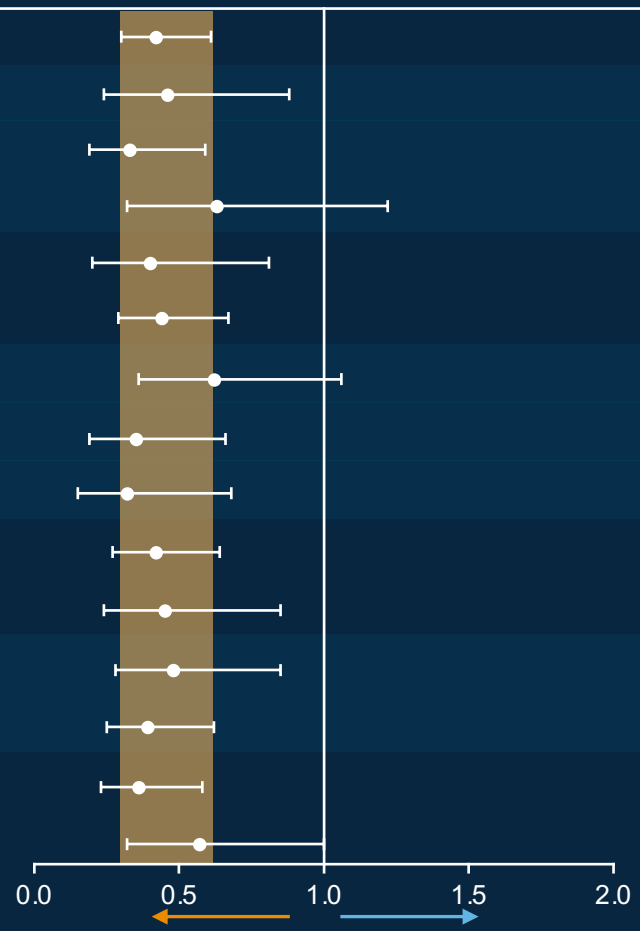
Subgroup analysis of MFS for enzalutamide combination vs. leuprolide acetate

Subgroup		Enzalutamide combination	Leuprolide acetate	MFS HR (95% CI)
		Events, n /patients, n		
All patients		45/355	92/358	0.42 (0.30–0.61)
PSADT	≤3 mo	14/69	30/80	0.46 (0.24–0.88)
	>3 to ≤6 mo	18/187	35/142	0.33 (0.19–0.59)
	>6 to ≤9 mo	13/98	27/135	0.63 (0.32–1.22)
Baseline age	≤65 years	11/81	28/91	0.40 (0.20–0.81)
	≥65 years	34/274	64/267	0.44 (0.29–0.67)
Geographic region	North America	22/144	32/137	0.62 (0.36–1.06)
	Europe	14/130	33/128	0.35 (0.19–0.66)
	ROW	9/81	27/93	0.32 (0.15–0.68)
Baseline PSA	≤10 ng/mL	31/278	64/273	0.42 (0.27–0.64)
	>10 ng/mL	14/77	28/83	0.45 (0.24–0.85)
Prior hormonal therapy	Yes	19/107	34/113	0.48 (0.28–0.85)
	No	26/248	58/245	0.39 (0.25–0.62)
Prior RP	Yes	26/269	61/254	0.36 (0.23–0.58)
	No	19/86	31/104	0.57 (0.32–1.00)



Data cutoff: January 31, 2023. For all patients, HR and 95% CI are based on stratified Cox regression model stratified by randomization stratification factors; for subgroups, HR and 95% CI are based on unstratified Cox regression model.

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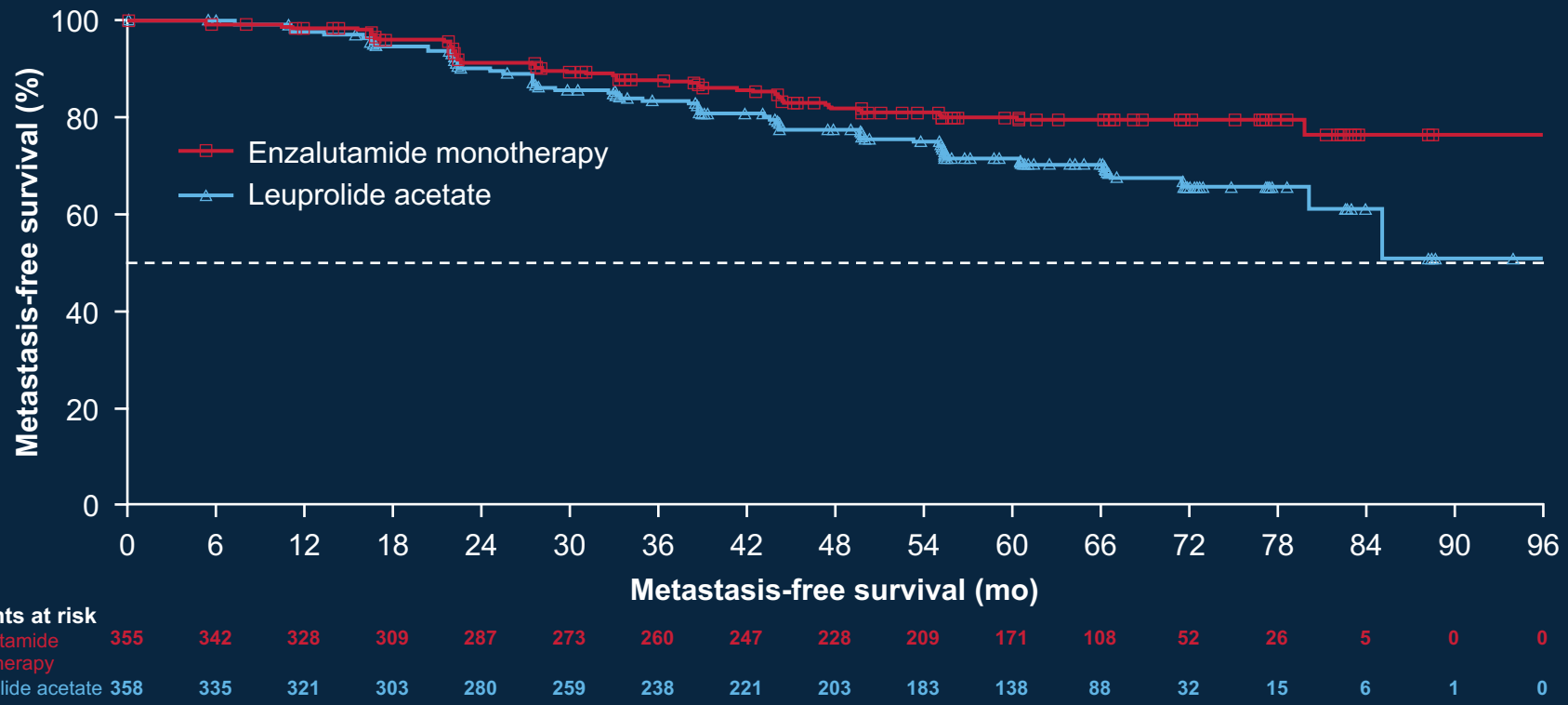
Key secondary endpoint — MFS for enzalutamide monotherapy vs. leuprolide acetate



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.56 (0.40–0.78); *P*=0.0006

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy; the two-sided *P*-value was based on a stratified log-rank test.

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Most common TEAEs

Most common TEAEs (>15% of patients), n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
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)
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)	3 (0.8)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0

- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AEs that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. TEAE, treatment-emergent AE.

Freedland SJ, et al. *New Engl J Med*. 2023;389(16):1453–1465.

Background and objective

- In the phase 3 EMBARK trial (NCT02319837), enza combo (enza + leuprolide) and enza mono significantly improved MFS vs leuprolide alone in patients with hrBCR prostate cancer who were conventional imaging-negative for metastases
  - MFS for enza combo vs leuprolide alone (primary endpoint): HR 0.42; 95% CI: 0.30, 0.61; *P*<0.001
  - MFS for enza mono vs leuprolide alone (key secondary endpoint): HR 0.63; 95% CI: 0.46, 0.87; *P*=0.005
- Enza combo and enza mono also improved time to PSA progression, first use of new antineoplastic therapy, distant metastasis, and symptomatic progression
- Overall survival is a key alpha-protected secondary endpoint of EMBARK
- At the time of the original analysis and publication, survival data were immature

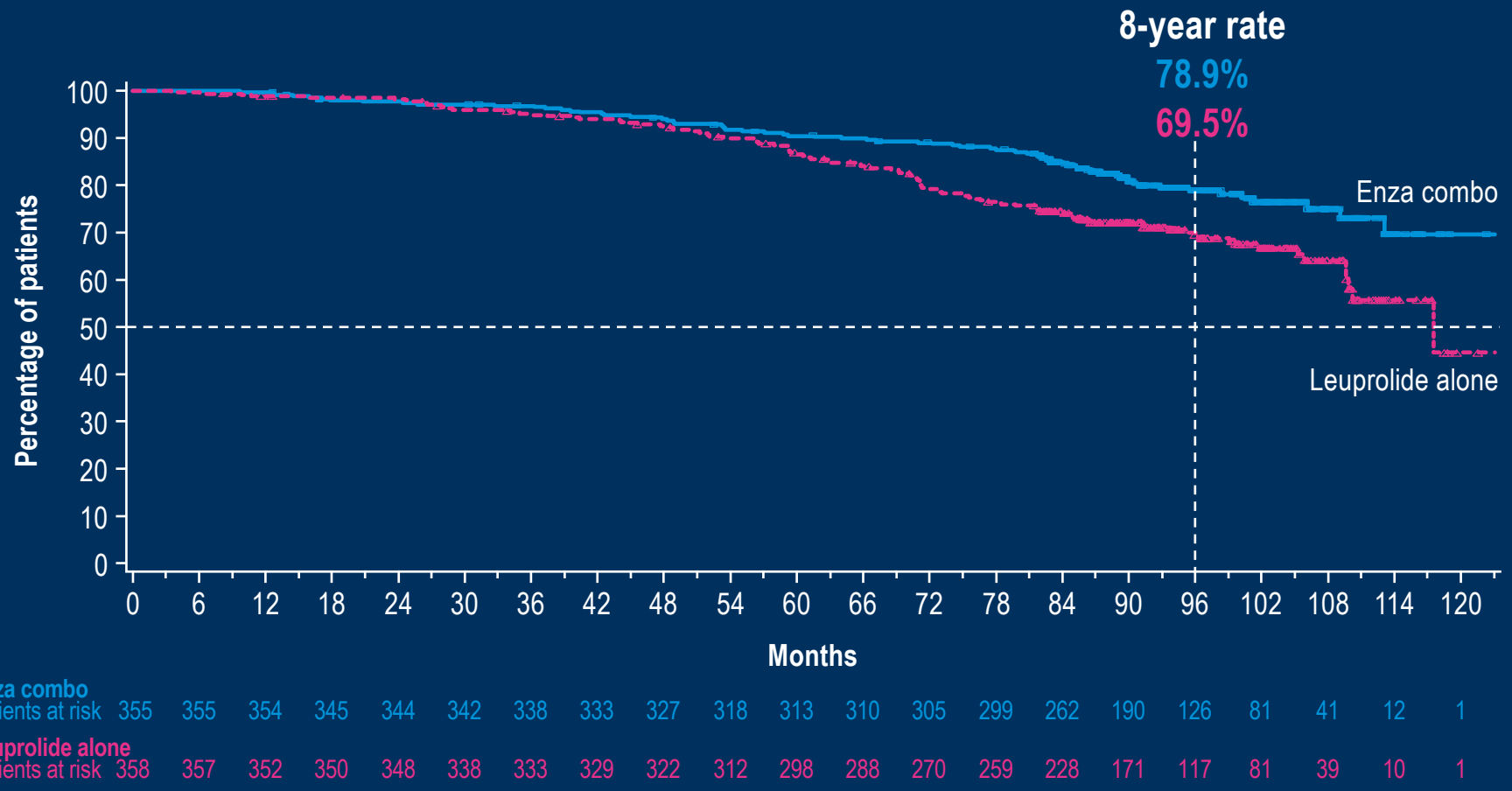
Objective

To present the final overall survival, updated secondary endpoints, and long-term safety data for EMBARK patients treated with enza combo, enza mono, or leuprolide alone

CI, confidence interval; enza combo, enzalutamide plus leuprolide; enza mono, enzalutamide monotherapy; hrBCR, high-risk biochemically recurrent, HR, hazard ratio; MFS, metastasis-free survival; PSA, prostate-specific antigen.

Freedland SJ, et al. *New Engl J Med*. 2023;389(16):1453–1465.

Overall survival: Enza combo



	Enza combo (n=355)	Leuprolide alone (n=358)
Events	73	111
8-year OS (95% CI), %	78.9 (73.9, 83.1)	69.5 (64.0, 74.3)

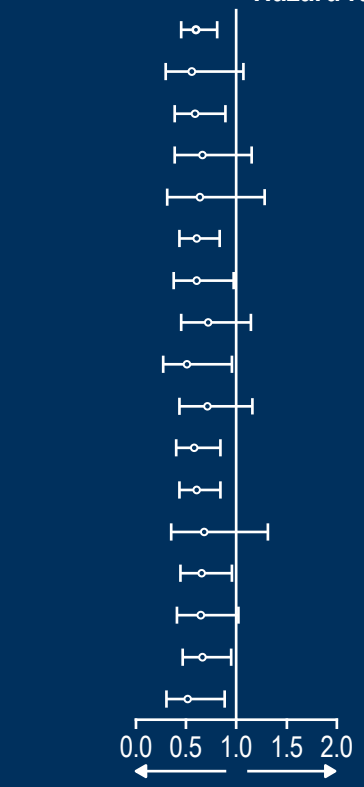
HR (95% CI): 0.597 (0.444, 0.804); *P*=0.0006

The risk of death was 40.3% lower for enza combo compared with leuprolide alone

Intent-to-treat population. The median follow-up was 94.2 months in the enza combo group and 94.0 months in the leuprolide-alone group. OS was defined as the time between randomization and death due to any cause. HRs were calculated using a Cox regression model with treatment as the only covariate, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza combo, enzalutamide plus leuprolide; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Prespecified subgroup analysis of OS: Enza combo

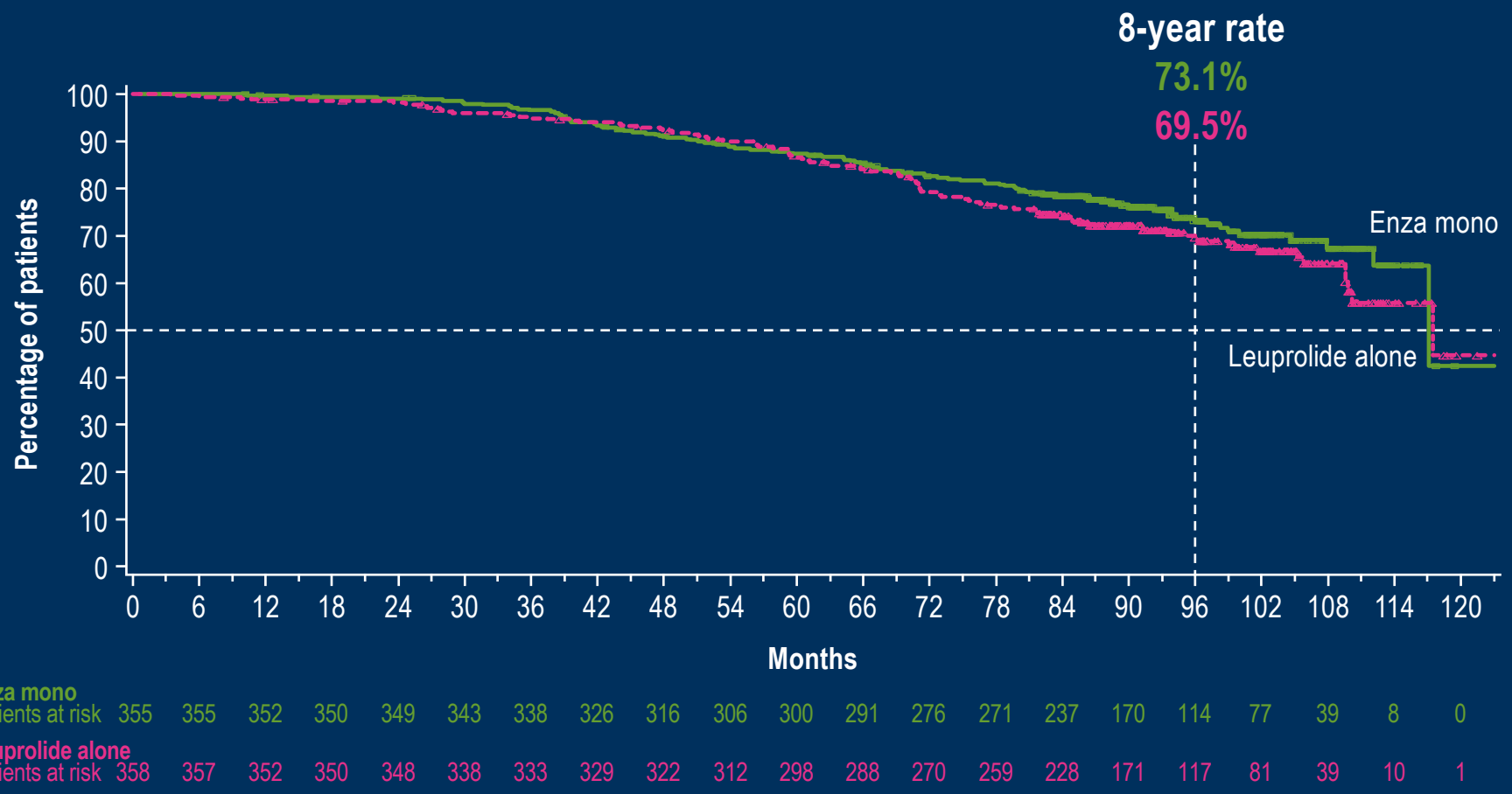
Subgroup	Enza combo	Leuprolide alone	Hazard ratio (95% CI)
	No. of patients (No. of events)		
All patients	355 (73)	358 (111)	0.597 (0.444, 0.804)
PSA doubling time (≤3 months)	69 (14)	80 (25)	0.552 (0.287, 1.064)
PSA doubling time (>3 to ≤6 months)	187 (39)	142 (47)	0.583 (0.381, 0.891)
PSA doubling time (>6 to ≤9 months)	98 (19)	135 (39)	0.661 (0.381, 1.148)
Baseline age category (<65 years)	81 (12)	91 (21)	0.631 (0.310, 1.282)
Baseline age category (≥65 years)	274 (61)	267 (90)	0.599 (0.433, 0.829)
Geographic region (North America)	144 (28)	137 (42)	0.599 (0.371, 0.966)
Geographic region (Europe)	130 (31)	128 (40)	0.715 (0.447, 1.142)
Geographic region (Rest of the world)	81 (14)	93 (29)	0.502 (0.265, 0.952)
Prior hormonal therapy (Yes)	107 (27)	114 (38)	0.704 (0.429, 1.157)
Prior hormonal therapy (No)	248 (46)	244 (73)	0.578 (0.399, 0.836)
Prior radiation therapy (Yes)	265 (57)	283 (92)	0.602 (0.432, 0.838)
Prior radiation therapy (No)	90 (16)	75 (19)	0.674 (0.346, 1.311)
Prior prostatectomy (Yes)	269 (44)	254 (60)	0.646 (0.438, 0.953)
Prior prostatectomy (No)	86 (29)	104 (51)	0.642 (0.407, 1.013)
PSA value at baseline (≤10 ng/mL)	278 (53)	273 (74)	0.663 (0.466, 0.944)
PSA value at baseline (>10 ng/mL)	77 (20)	83 (37)	0.512 (0.297, 0.883)



A consistent OS benefit was observed across all prespecified subgroups with enza combo compared with leuprolide alone

Intent-to-treat population. The hazard ratios and their 95% CIs for all patients are based on a stratified Cox regression model stratified by randomization stratification factors. The hazard ratios and their 95% CIs for each subgroup are based on an unstratified Cox regression model. A hazard ratio of less than 1 indicated superiority to leuprolide alone. Subgroups with >10 events had sufficient size for analysis. The widths of the CIs for subgroups have not been adjusted for multiplicity and cannot be used to infer treatment effects. The data cutoff date was May 27, 2025.
CI, confidence interval; enza combo, enzalutamide plus leuprolide; OS, overall survival; PSA, prostate-specific antigen.

Overall survival: Enza mono



	Enza mono (n=355)	Leuprolide alone (n=358)
Events	93	111
8-year OS (95% CI), %	73.1 (67.6, 77.9)	69.5 (64.0, 74.3)

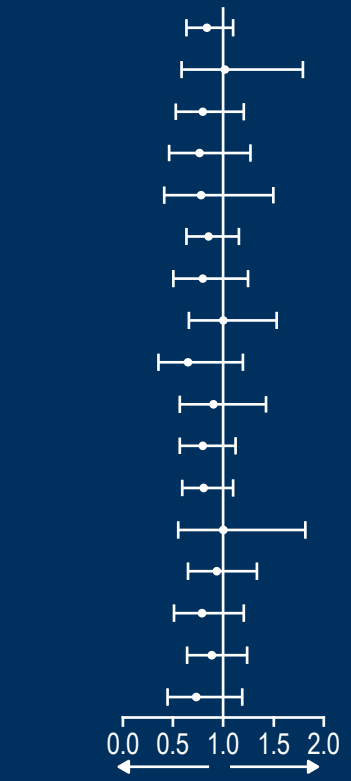
HR (95% CI): 0.830 (0.630, 1.095); *P*=0.1867

The risk of death was 17.0% lower for enza mono compared with leuprolide alone, which did not reach statistical significance

Intent-to-treat population. The median follow-up was 93.8 months in the enza mono group and 94.0 months in the leuprolide-alone group. OS was defined as the time between randomization and death due to any cause. HRs were calculated using a Cox regression model with treatment as the only covariate, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza mono; enzalutamide monotherapy; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Prespecified subgroup analysis of OS: Enza mono

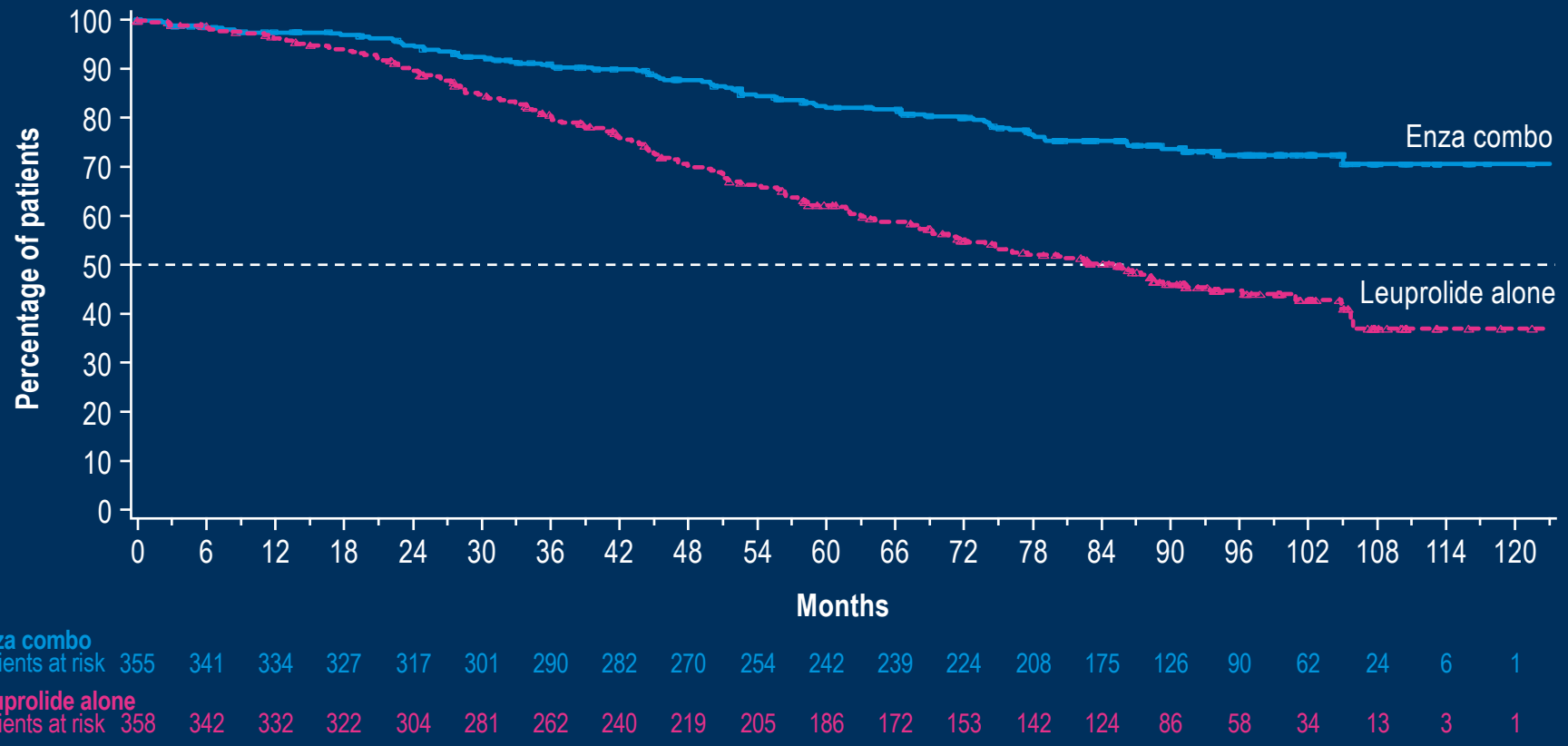
Subgroup	Enza mono	Leuprolide alone	Hazard ratio (95% CI)
	No. of patients (No. of events)		
All patients	355 (93)	358 (111)	0.830 (0.630, 1.095)
PSA doubling time (≤3 months)	76 (23)	80 (25)	1.016 (0.577, 1.790)
PSA doubling time (>3 to ≤6 months)	164 (45)	142 (47)	0.796 (0.529, 1.198)
PSA doubling time (>6 to ≤9 months)	114 (25)	135 (39)	0.763 (0.460, 1.266)
Baseline age category (<65 years)	91 (16)	91 (21)	0.779 (0.407, 1.493)
Baseline age category (≥65 years)	264 (77)	267 (90)	0.851 (0.627, 1.153)
Geographic region (North America)	133 (33)	137 (42)	0.788 (0.499, 1.244)
Geographic region (Europe)	146 (44)	128 (40)	0.999 (0.651, 1.533)
Geographic region (Rest of the world)	76 (16)	93 (29)	0.648 (0.352, 1.194)
Prior hormonal therapy (Yes)	112 (35)	114 (38)	0.898 (0.567, 1.421)
Prior hormonal therapy (No)	243 (58)	244 (73)	0.795 (0.563, 1.123)
Prior radiation therapy (Yes)	256 (69)	283 (92)	0.802 (0.587, 1.097)
Prior radiation therapy (No)	99 (24)	75 (19)	0.996 (0.545, 1.819)
Prior prostatectomy (Yes)	265 (58)	254 (60)	0.931 (0.648, 1.336)
Prior prostatectomy (No)	90 (35)	104 (51)	0.781 (0.507, 1.201)
PSA value at baseline (≤10 ng/mL)	272 (65)	273 (74)	0.884 (0.634, 1.234)
PSA value at baseline (>10 ng/mL)	82 (28)	83 (37)	0.727 (0.444, 1.188)



Directionally consistent OS benefits were observed in several prespecified subgroups for enza mono compared with leuprolide alone

Intent-to-treat population. The hazard ratios and their 95% CIs for all patients are based on a stratified Cox regression model stratified by randomization stratification factors. The hazard ratios and their 95% CIs for each subgroup are based on an unstratified Cox regression model. A hazard ratio of less than 1 indicated superiority to leuprolide alone. Subgroups with >10 events had sufficient size for analysis. The widths of the CIs for subgroups have not been adjusted for multiplicity and cannot be used to infer treatment effects. The data cutoff date was May 27, 2025.
CI, confidence interval; enza mono, enzalutamide monotherapy; OS, overall survival; PSA, prostate-specific antigen.

Time to first use of new antineoplastic therapy: Enza combo



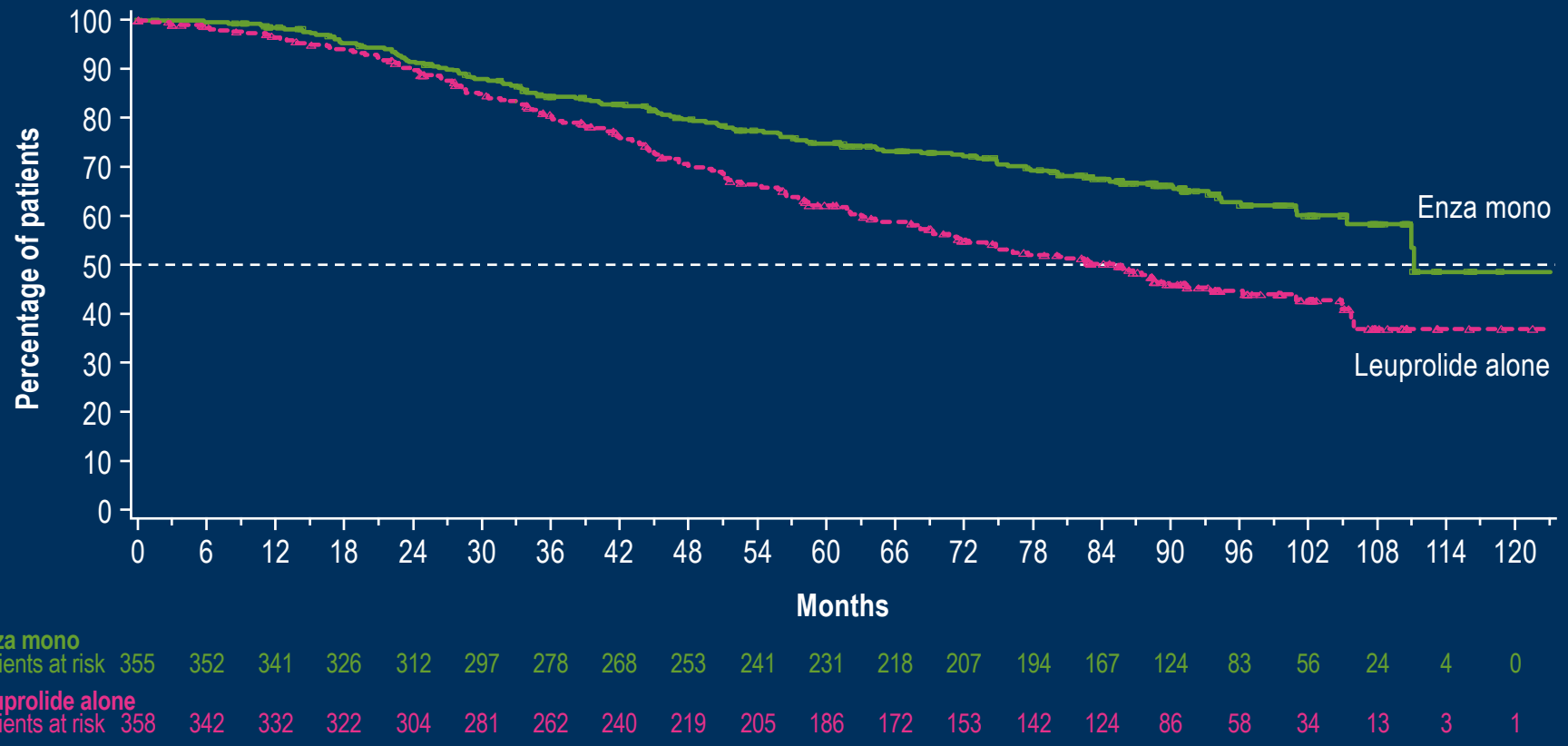
	Enza combo (n=355)	Leuprolide alone (n=358)
Events	82	173

HR (95% CI): 0.374 (0.287, 0.489)
Nominal *P*<0.0001

Significant improvement was observed after an additional 2.3 years of follow-up for time to first use of antineoplastic therapy for enza combo vs leuprolide alone

Intent-to-treat population. To calculate the HRs, a Cox regression model with treatment as the only covariate was used, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects.
The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza combo, enzalutamide plus leuprolide; HR, hazard ratio; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Time to first use of new antineoplastic therapy: Enza mono



	Enza mono (n=355)	Leuprolide alone (n=358)
Events	118	173

HR (95% CI): 0.570 (0.450, 0.721)
Nominal *P*<0.0001

Enza mono Patients at risk	355	352	341	326	312	297	278	268	253	241	231	218	207	194	167	124	83	56	24	4	0
Leuprolide alone Patients at risk	358	342	332	322	304	281	262	240	219	205	186	172	153	142	124	86	58	34	13	3	1

Significant improvement was observed after an additional 2.3 years of follow-up for time to first use of antineoplastic therapy for enza mono vs leuprolide alone

Intent-to-treat population. To calculate the HRs, a Cox regression model with treatment as the only covariate was used, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects.
The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza mono, enzalutamide monotherapy; HR, hazard ratio; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Conclusions

- Enza combo reduced the risk of death by more than 40% vs leuprolide alone in patients with hrBCR prostate cancer
- Enza mono led to a numerically lower risk of death vs leuprolide alone, although the difference did not reach statistical significance
- Significant improvements in time to first use of new antineoplastic therapy, time to symptomatic skeletal events, and PFS2 further highlight the benefit of both enza combo and enza mono
- No new safety signals were observed in the long-term safety analysis

These findings support the previously reported improved MFS and further confirm enzalutamide plus androgen deprivation as the standard of care for hrBCR prostate cancer

Enza combo, enzalutamide plus leuprolide; enza mono, enzalutamide monotherapy; hrBCR, high-risk biochemically recurrent; MFS, metastasis-free survival; OS, overall survival.; PFS2, progression-free survival on first subsequent therapy

Phase 3 PRESTO Trial: Study Design

- PSA recurrence after RP
- PSADT <10 months
- PSA >0.5 (RP)
- Testosterone >150 ng/dL
- No metastases on conventional imaging

N = 160 → ADT alone

N = 163 → ADT + apalutamide

N = 161 → ADT + apalutamide + abiraterone + prednisone

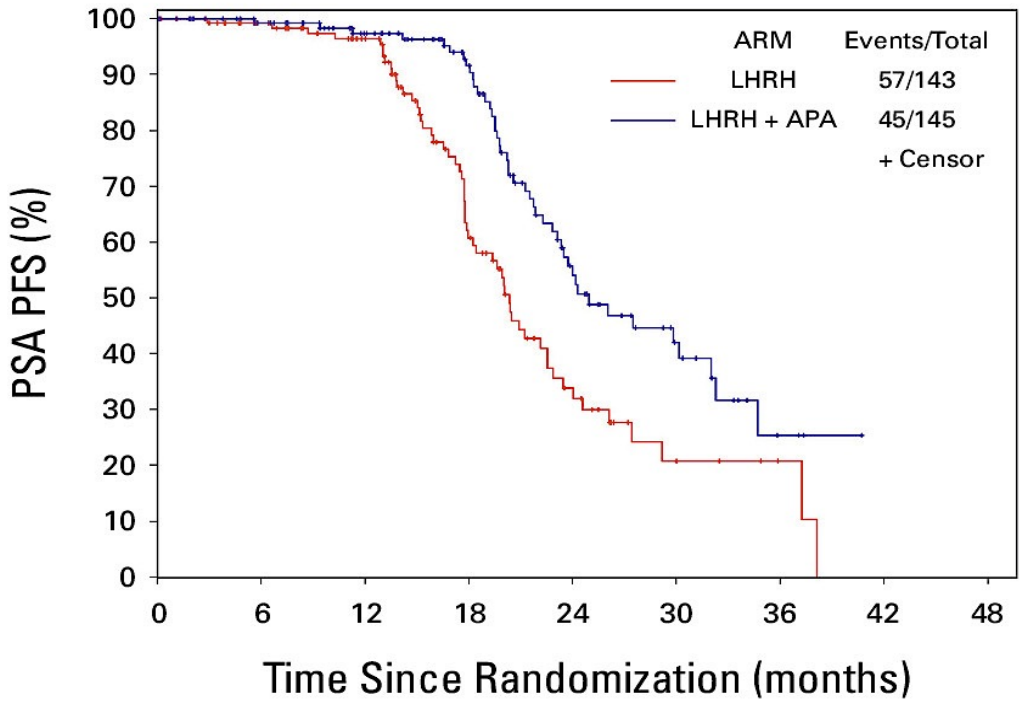
52 weeks RX

Primary endpoint: PSA-PFS defined as PSA rise of at least 25% and 2 ng/mL above nadir, confirmed on repeat
ADT compared separately to each experimental arm

Aggarwal R, et al. *J Clin Oncol*. 2024;42(10):1114-1123.

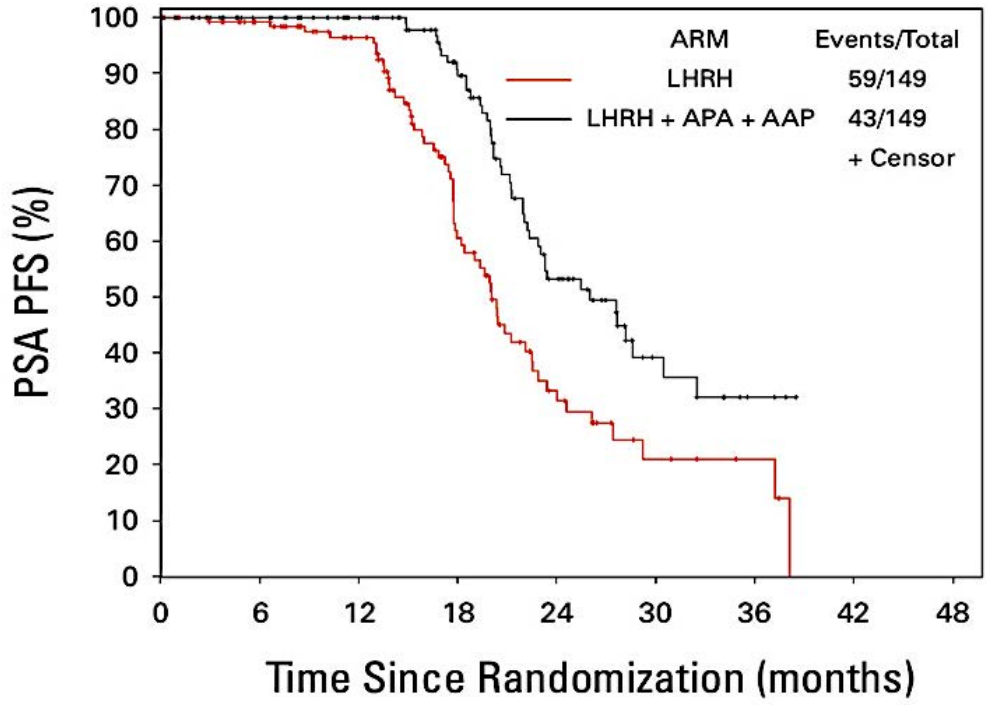
PRESTO: PSA-PFS

ADT + apalutamide vs ADT alone



No. at risk:					
LHRH	143	94	18	2	0
LHRH + APA	145	101	32	3	0

ADT + apalutamide + abiraterone acetate + prednisone versus ADT alone

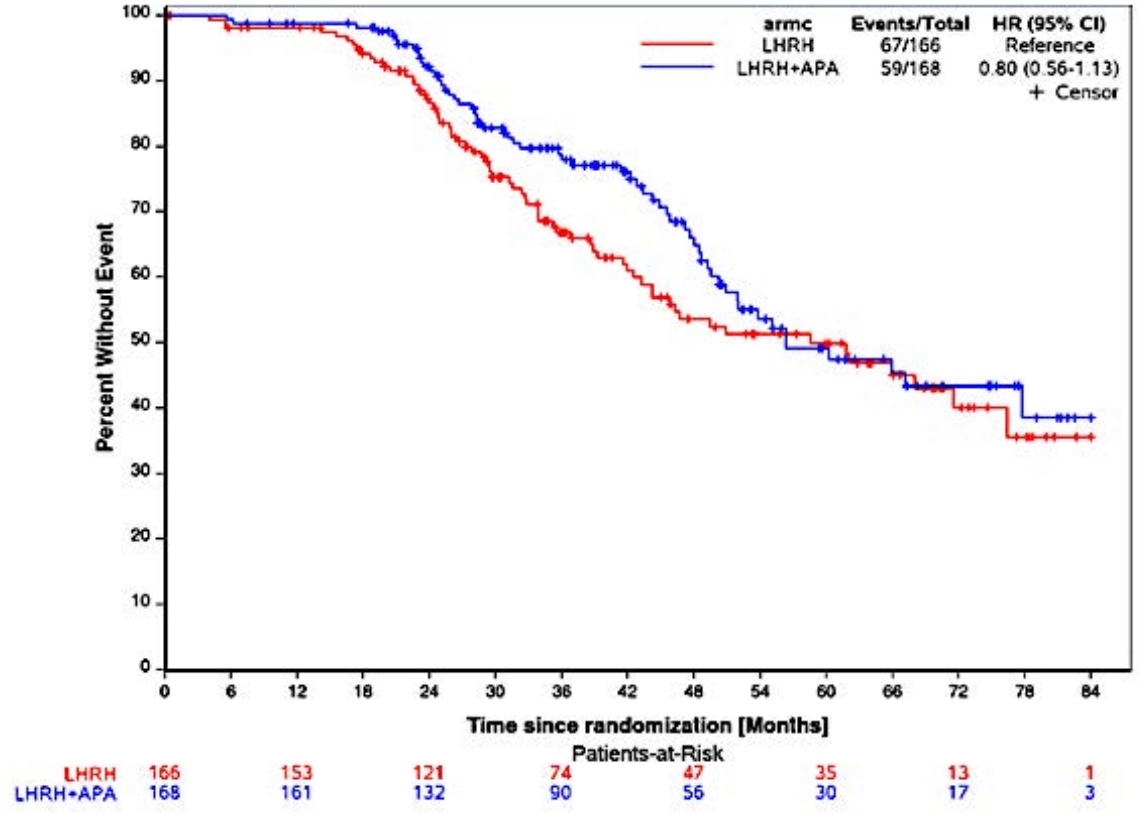


No. at risk:					
LHRH	149	97	18	3	0
LHRH + APA + AAP	149	103	35	3	0

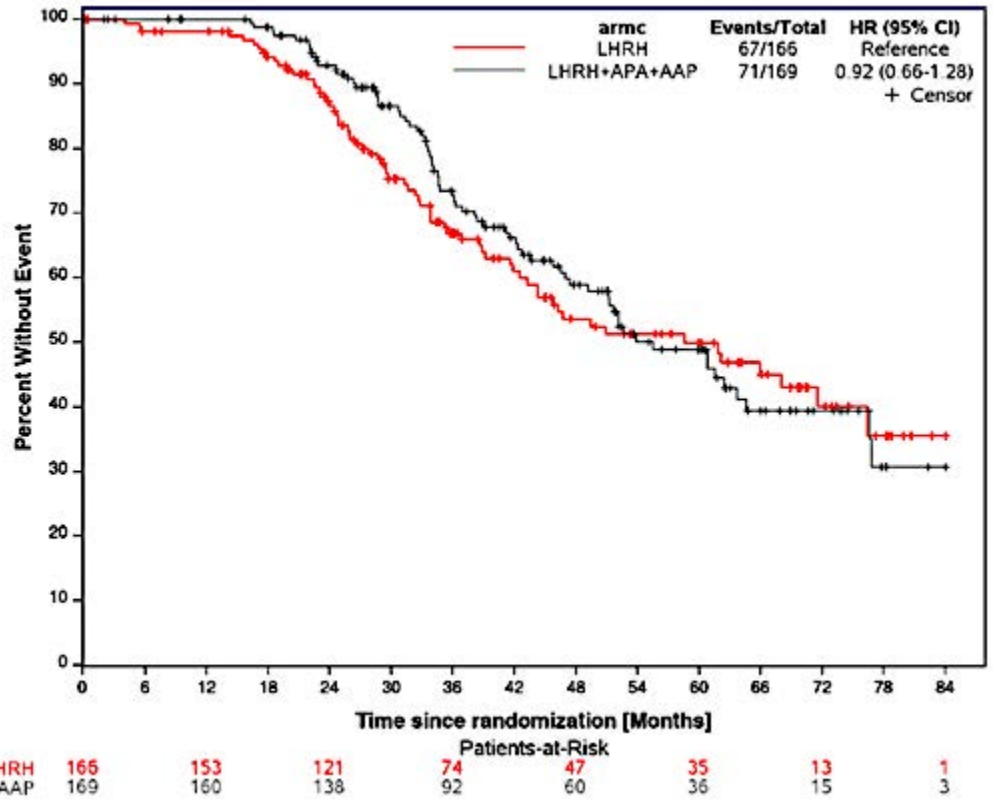
Aggarwal R, et al. *J Clin Oncol*. 2024;42(10):1114-1123.

PRESTO: MFS

ADT + apalutamide vs ADT alone

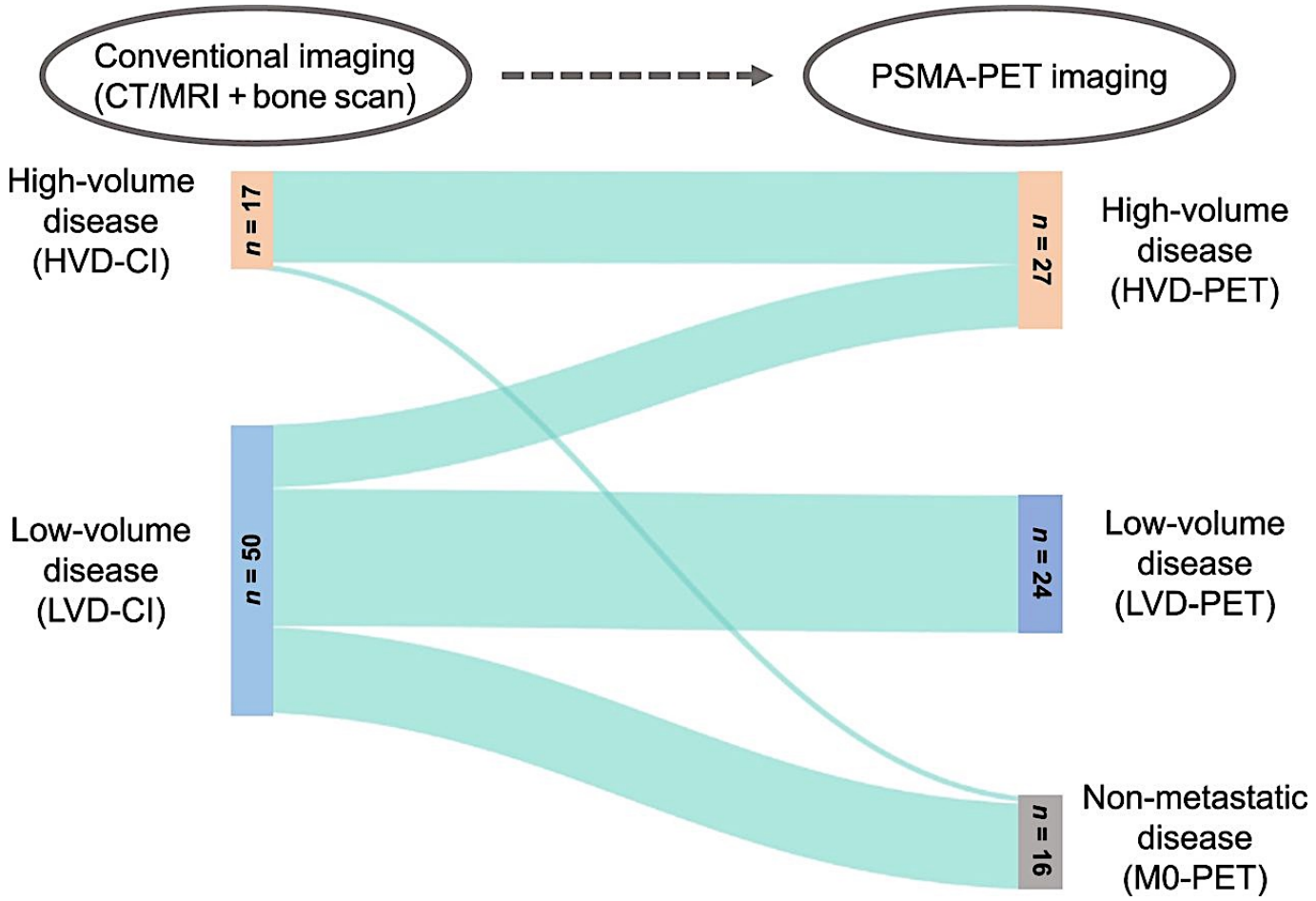


ADT + apalutamide + abiraterone acetate + prednisone versus ADT alone



Aggarwal R, et al. ESMO 2025. Abstract LBA88.

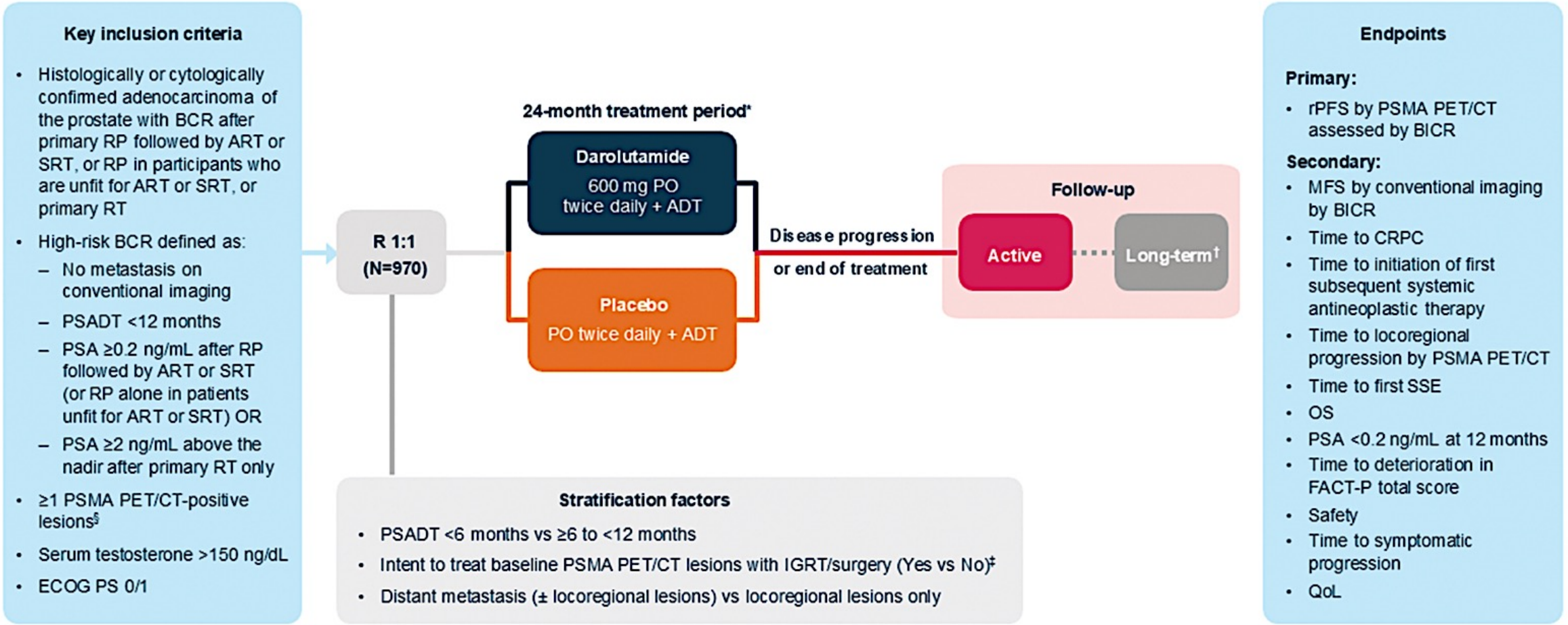
Conventional Imaging vs PSMA-PET Imaging



- Compared with conventional imaging, addition of PSMA-PET leads to downstaging to M0 in every third patient and LVD to HVD upstaging in every fifth patient
- Future HVD and LVD definitions based on PSMA-PET/CT should be adjusted based on patient outcome

Unterrainer LM, et al. *J Nucl Med*. 2025;66(1):54-60.

Phase 3 ARASTEP Trial: Study Design



Morgan AK, et al. *Future Oncol*. 2025;21(27):3491-3498.

Key Takeaways

- ADT intensification **improves outcomes** in biochemically recurrent disease
- **Risk stratification tools** are important for identifying patients with BCR who are most likely to benefit from ADT +ARPI vs ARPI monotherapy
- ADT intensification needs to be **individualized** based on patient preferences…shared decision making matters
- Mitigating strategies to affect adverse events(fatigue, hot flashes, sexual dysfn,etc) are essential
- **Multidisciplinary team** coordination and alignment can promote patient safety and adherence to treatment
- **Biomarkers** are in development to further enhance outcomes in BCR

Second Opinion

Andrew J Armstrong, MD, ScM

Rana R McKay, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

For which patients with M0 biochemical recurrence are you recommending an EMBARK approach, and are you using intermittent therapy? Do you usually discuss the option of enzalutamide monotherapy? How do you prevent and manage gynecomastia?

QUESTIONS FOR THE FACULTY

What is the design of the Phase III PROTEUS study evaluating perioperative (neoadjuvant and adjuvant) apalutamide + ADT? What do you think the upcoming ASCO presentation is going to show, and how do you think this will affect clinical practice?

Are there other ongoing neoadjuvant, adjuvant or perioperative trials you find interesting and exciting?

Second Opinion

Sandy Srinivas, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What do you think about the PATCH study evaluating the benefit of transdermal estradiol? In what clinical situations do you believe this would be a good option?

Are there any other novel endocrine-based treatments that are being evaluated in prostate cancer? PROTACs?

Agenda

Module 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Shore

Module 2: Current Hormonal Treatment for Metastatic HSPC (mHSPC) — Dr Petrylak

Module 3: Current and Future Role of PARP Inhibitors for Metastatic Prostate Cancer (mPC) — Dr Agarwal

Module 4: Emerging Role of AKT Inhibition for Patients with mHSPC — Dr Heath

Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

Current Hormonal Treatments for Metastatic HSPC

Daniel P. Petrylak, MD

Professor of Medicine and Urology

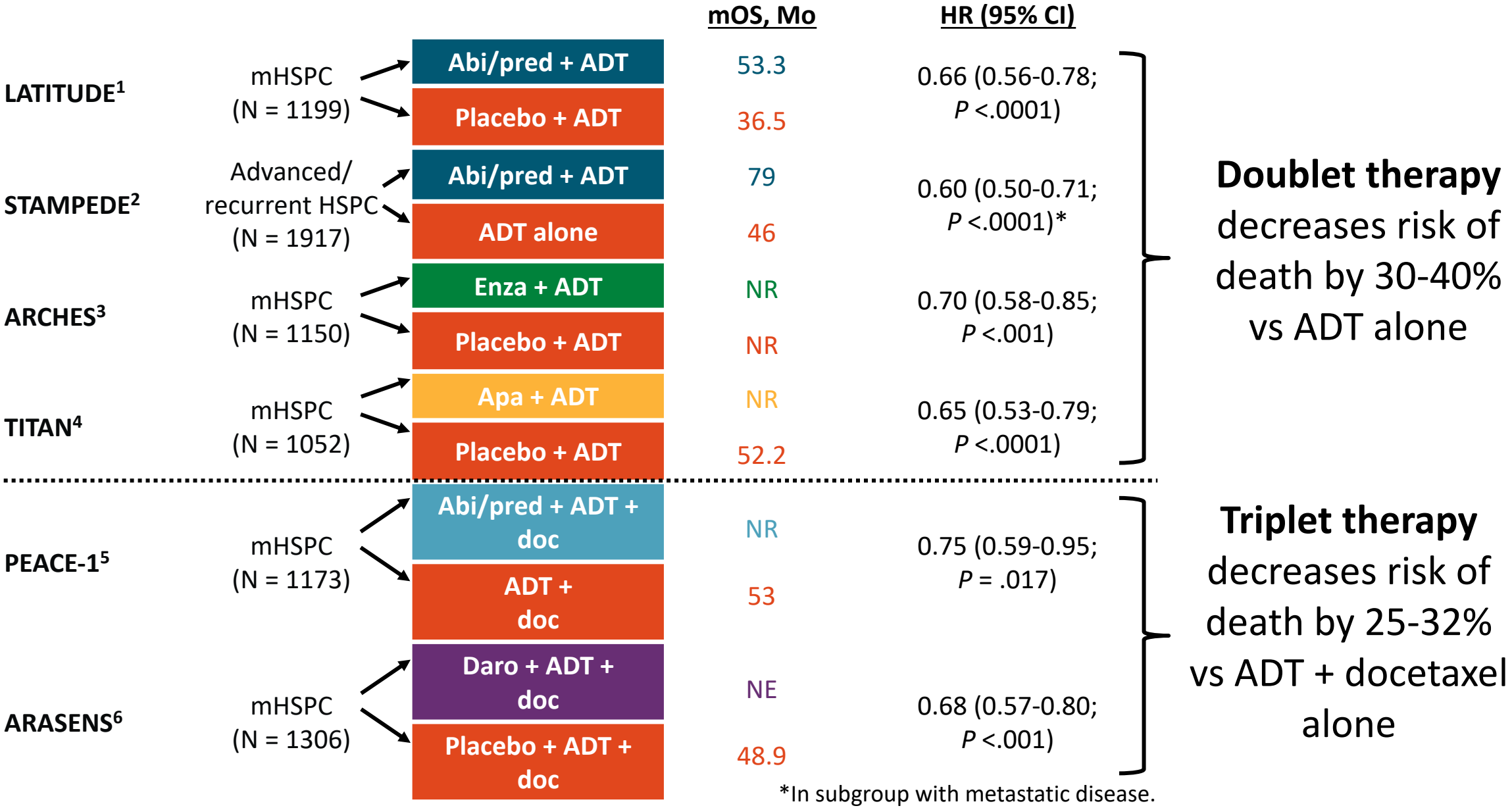
Division Chief, Genitourinary Cancer

Smilow Cancer Center

Yale University School of Medicine

New Haven, CT

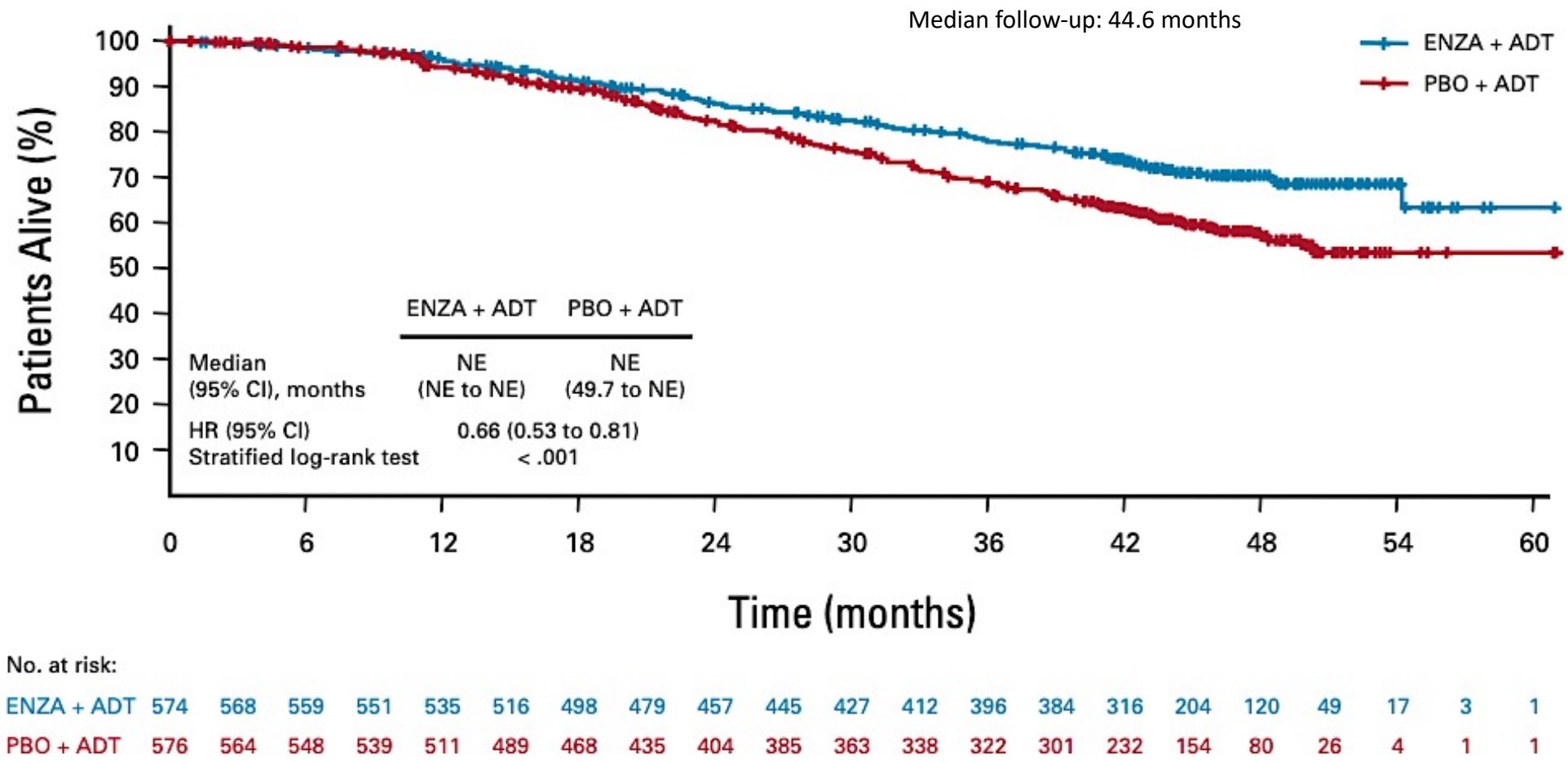
OS With Doublet and Triplet Therapy in mHSPC



*In subgroup with metastatic disease.

1. Fizazi. Lancet Oncol. 2019;20:686. 2. James. Int J Cancer. 2022;151:422. 3. Armstrong. Eur Urol. 2026;89:396-403.
4. Chi. JCO. 2021;39:2294. 5. Fizazi. Lancet. 2022;399:1695. 6. Smith. NEJM. 2022;386:1132.

ARCHES: Final Analysis OS



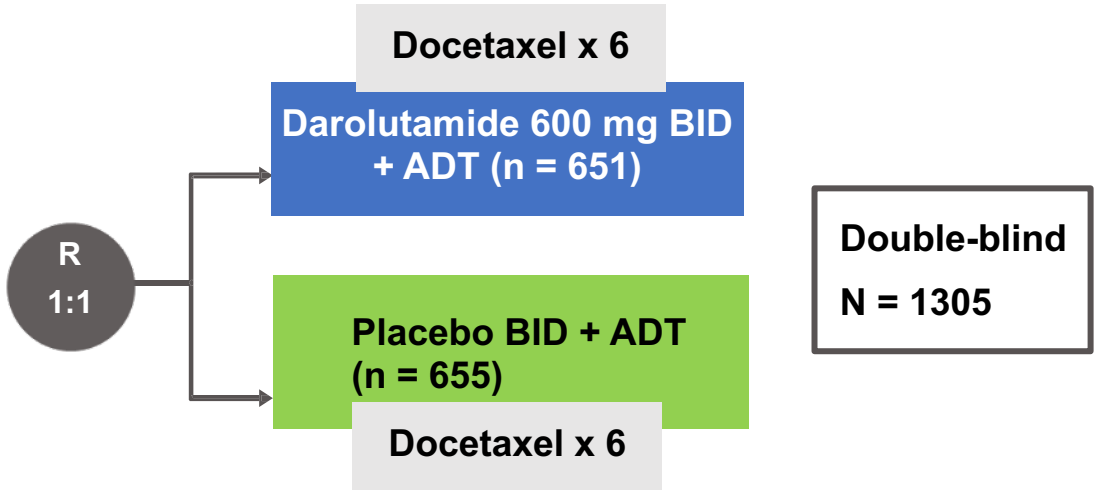
Armstrong AJ, Azad AA, Iguchi T, et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol*. 2022;40(15):1616-1622. doi:10.1200/JCO.22.00193

ARASENS Trial Design: Darolutamide + ADT + Docetaxel in mHSPC

Key eligibility criteria

- mCSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratified by extent of disease (M1a vs M1b vs M1c) and ALP < vs ≥ ULN



Primary endpoint:

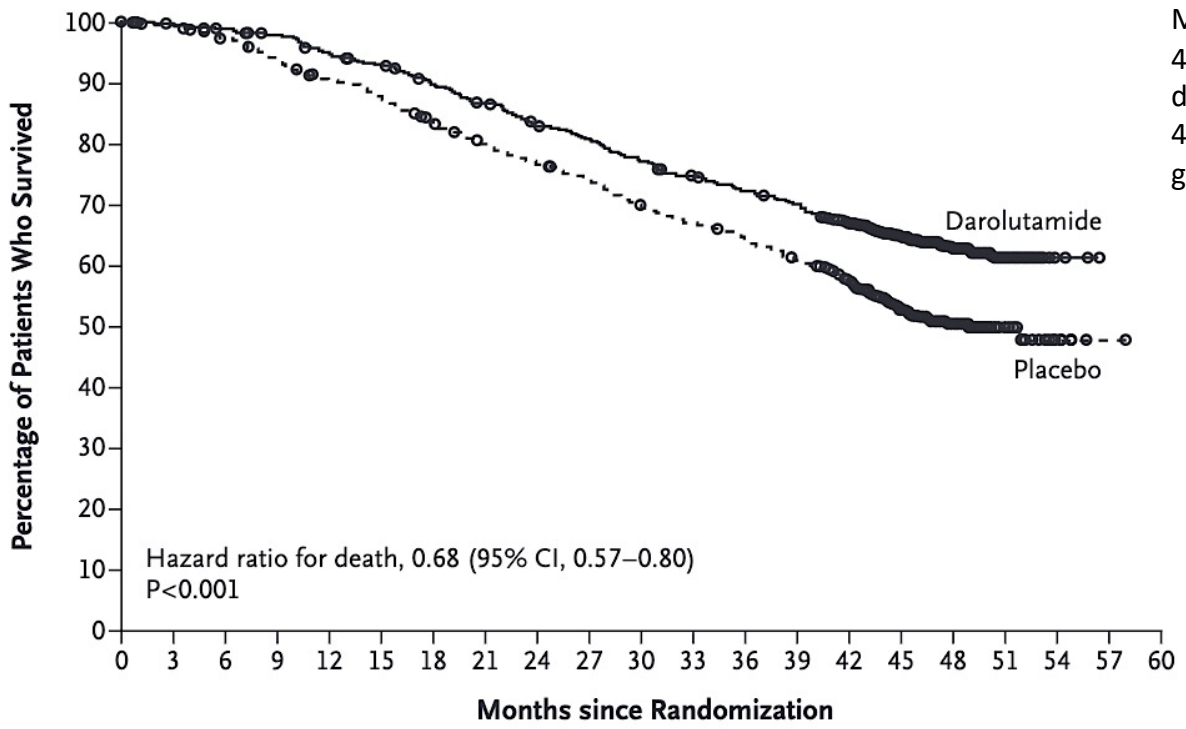
- **OS**

Secondary endpoints:

- **Time to CRPC**
- **Time to initiation of subsequent anti-cancer therapy**
- **SSE-free survival**
- **Time to first SSE**
- **Time to worsening of disease-related physical symptoms**
- **Time to pain progression**
- **Time to initiation of opioid use of ≥ 7 consecutive days**
- **Safety**

Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med*. 2022;386(12):1132-1142. doi:10.1056/NEJMoa2119115; NCT04736199

ARASENS: OS



Median follow-up:
43.7 months in the darolutamide group
42.4 months in the placebo group

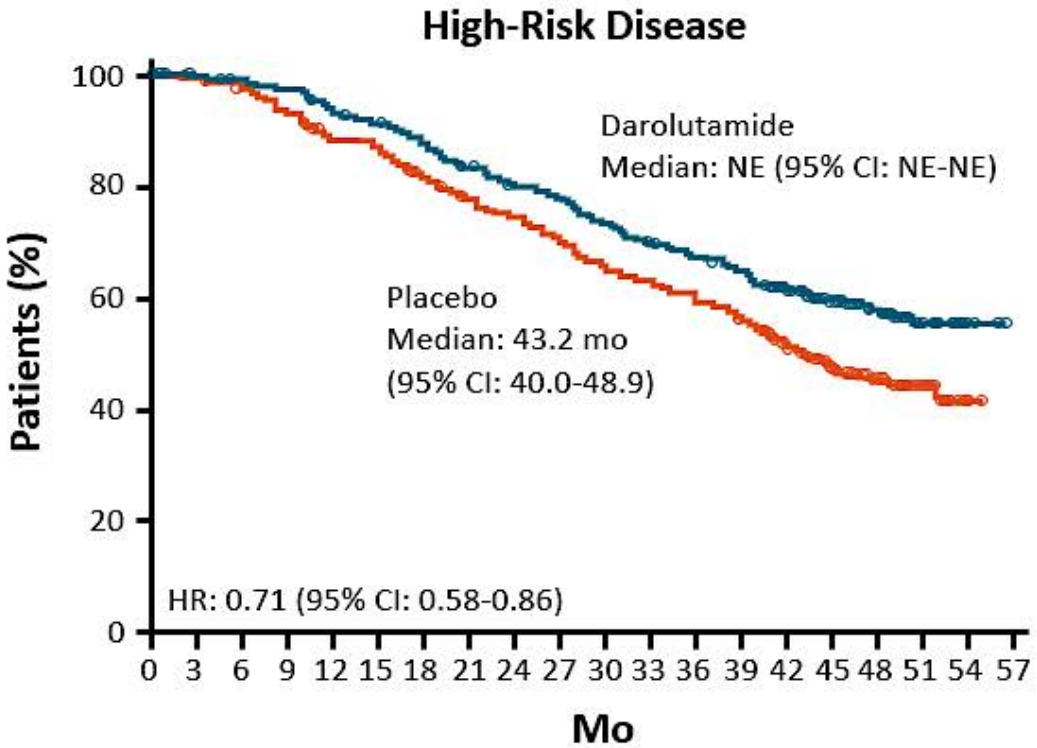
	Median Survival (95% CI)
	mo
Darolutamide	NE
Placebo	48.9 (44.4–NE)

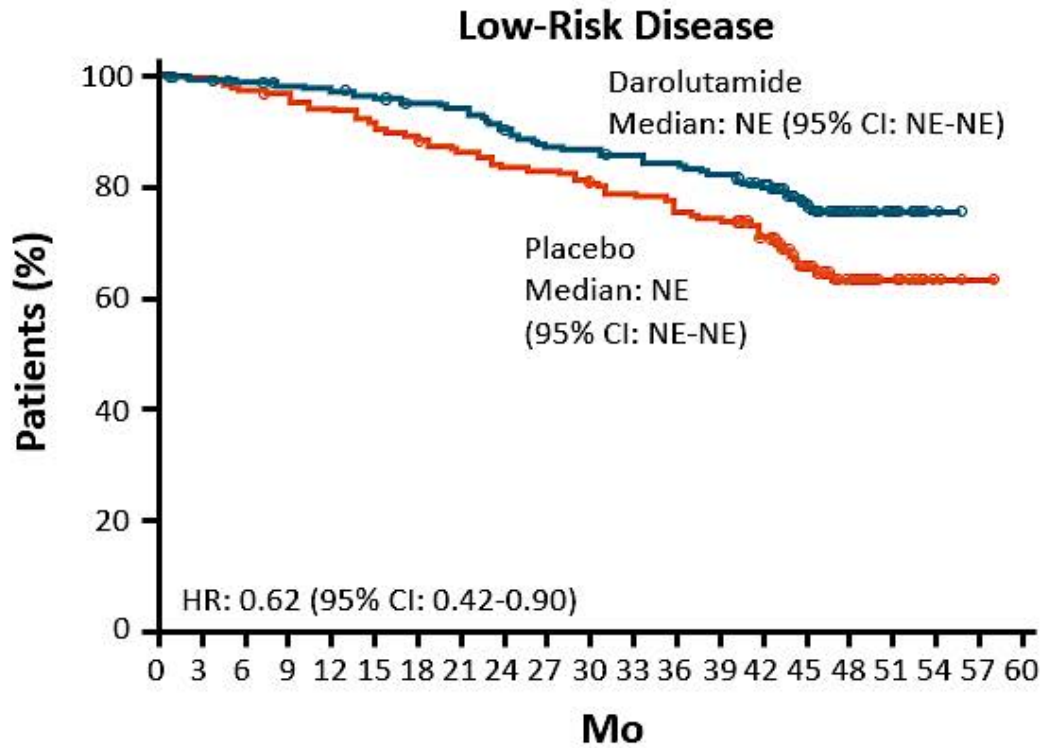
Figure 1. Overall Survival (Full Analysis Set).

Kaplan–Meier estimates of overall survival are shown. For the analysis of overall survival, data were censored as of the last known date the patients were alive. One patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set. CI denotes confidence interval, and NE not estimable.

Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med*. 2022;386(12):1132-1142. doi:10.1056/NEJMoa2119115NCT04736199

ARASENS: OS by Disease Risk





Patients at Risk, n

Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Patients at Risk, n

Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

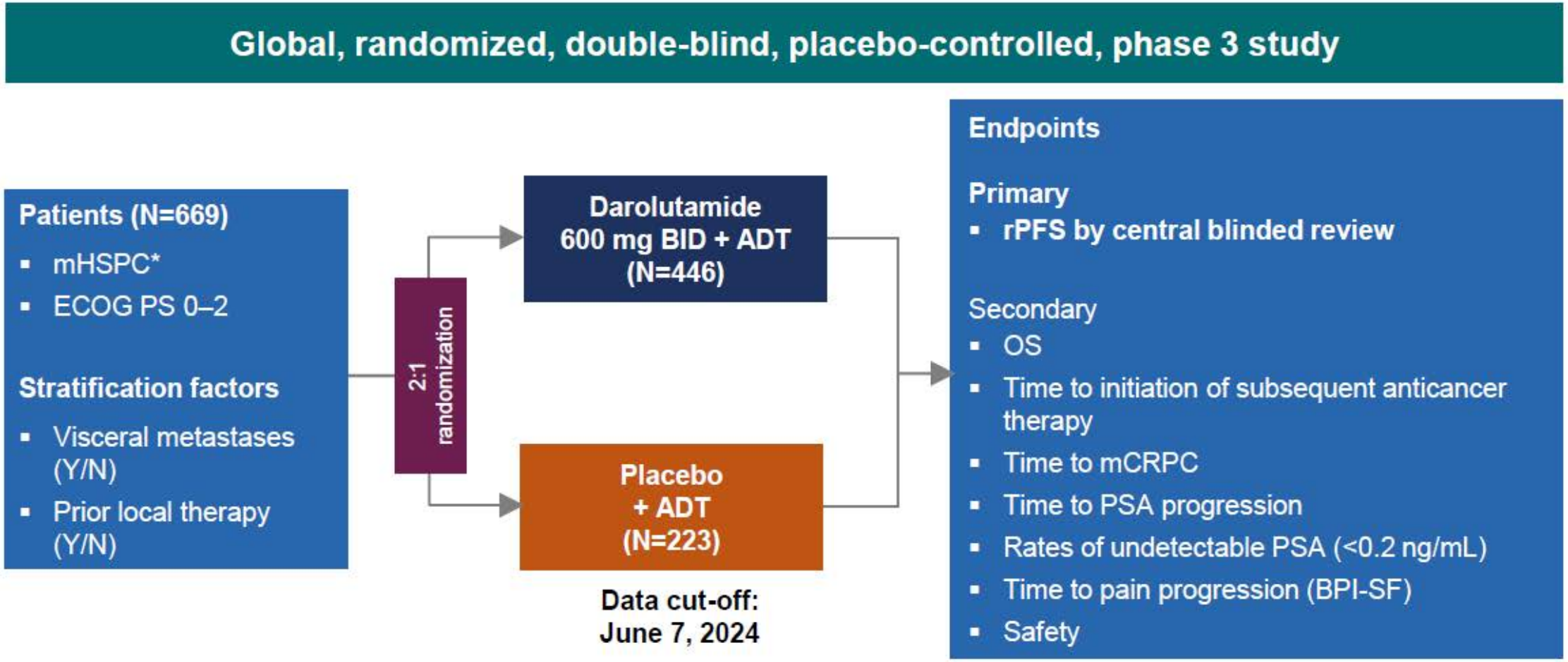
Hussain. JCO. 2023;[Epub]. Hussain. ASCO GU 2023. Abstr 15.

ARASENS: Safety

Event	Darolutamide–ADT–Docetaxel (N = 652)†	Placebo–ADT–Docetaxel (N = 650)†
	number of patients (percent)	
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
Neutropenia§	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

Smith MR_*N Engl J Med*_2022

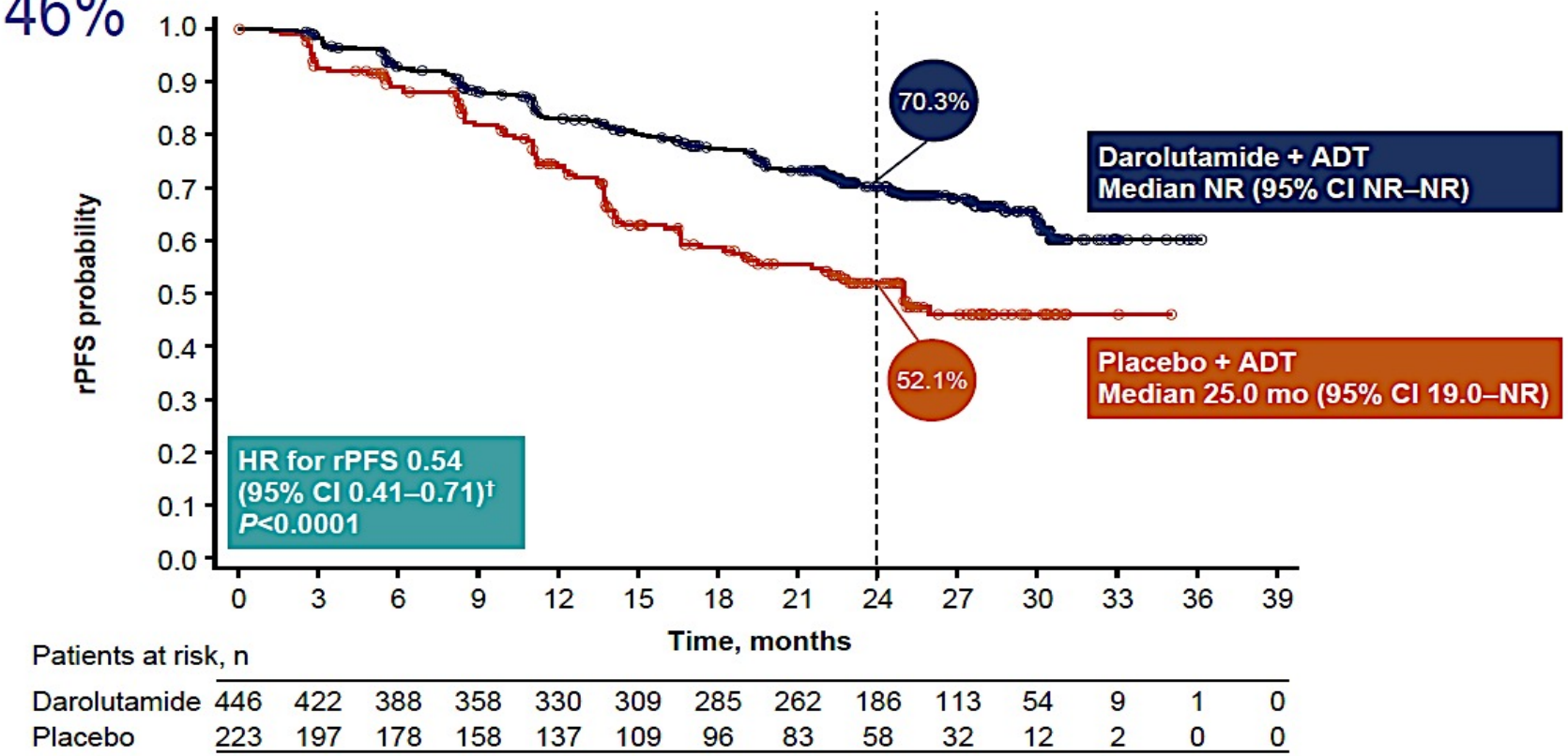
ARANOTE Trial Design: Darolutamide + ADT in mHSPC



Saad F, ESMO 2024 LBA68; Clinical Trial Registration Number NCT04736199

ESMO 2024: ARANOTE Primary Endpoint rPFS

Darolutamide significantly reduced the risk of radiological progression or death by 46%



Patients at risk, n

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

BARCELONA 2024 ESMO congress

Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

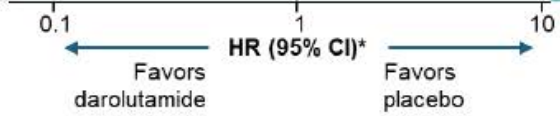
*Primary analysis occurred after 222 events (darolutamide 128; placebo 94).

†HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

Saad F, ESMO 2024 LBA68

ARANOTE rPFS: Subgroup Analysis

rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



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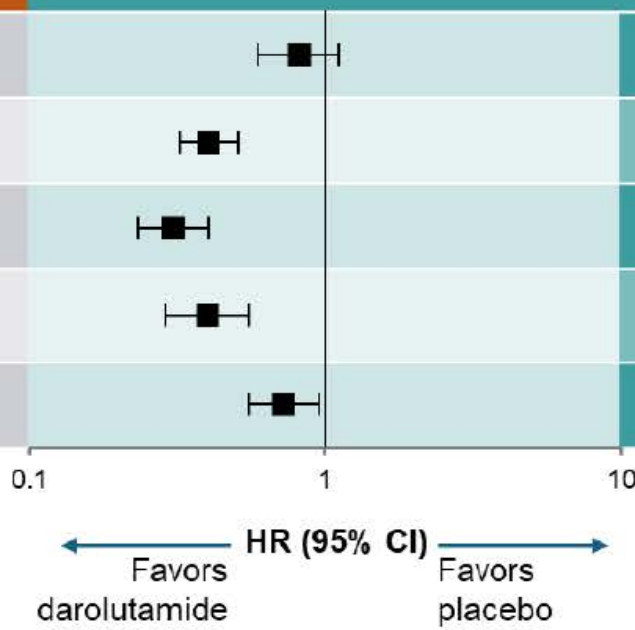
*HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.

Saad F, ESMO 2024 LBA68

ARANOTE Secondary Endpoints

Endpoint	Darolutamide (n=446)		Placebo (n=223)		Stratified HR (95% CI)
	n (%)	Median, months	n (%)	Median, months	
OS*	103 (23.1)	NR	60 (26.9)	NR	0.81 (0.59–1.12)
Time to mCRPC	154 (34.5)	NR	143 (64.1)	13.8	0.40 (0.32–0.51)
Time to PSA progression	93 (20.9)	NR	108 (48.4)	16.8	0.31 (0.23–0.41)
Time to initiation of subsequent systemic therapy for prostate cancer	68 (15.2)	NR	74 (33.2)	NR	0.40 (0.29–0.56)
Time to pain progression	124 (27.8)	NR	79 (35.4)	29.9	0.72 (0.54–0.96)



*At the time of primary analysis, OS data are immature.

ARANOTE Safety

TEAEs, %	Darolutamide + ADT (n=445*)	Placebo + ADT (n=221*)
Any	91.0	90.0
Worst grade		
Grade 3 or 4	30.8	30.3
Grade 5	4.7	5.4
Serious	23.6	23.5
TEAEs leading to permanent discontinuation of study drug	6.1	9.0

Median treatment duration: darolutamide group 24.2 months; placebo group 17.3 months

Saad F, ESMO 2024 LBA68

ARANOTE Safety

TEAEs	Darolutamide + ADT (n=445)		Placebo + ADT (n=221)	
	Incidence, %	EAIR/100 PY	Incidence, %	EAIR/100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment disorder	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilatation and flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

Saad F, ESMO 2024 LBA68

Treatment Selection for mHSPC

- Choice of agent depends on cost, safety profile, patient comorbidities

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
▪ Generic ▪ Requires K+/LFT/BP monitoring ▪ Concern for long-term HTN and prednisone ▪ Less fatigue than AR antagonists ▪ **Can intensify to triplet therapy**	▪ Less monitoring ▪ Concern for neurocognitive issues	▪ Less monitoring ▪ Concern for rash and neurocognitive issues	▪ Less monitoring ▪ **Can intensify to triplet therapy**	▪ Least expensive ▪ Completed after 6 cycles ▪ Offer while chemo fit ▪ Potential for new/worsened neuropathy ▪ Can consider stopping early if exceptional responder/not tolerating chemo

- **Triplet therapy** often used in fit patients with aggressive disease or features suggesting less dependence on AR (high volume of metastatic disease, low PSA given volume of disease, high grade/poorly differentiated)

Abiraterone PI. Shpilsky. Expert Opin Pharmacother. 2021;22:1227. Fizazi. Lancet. 2022;399:1695. Enzalutamide PI. Ryan. Prostate Cancer Prostatic Dis. 2020;23:207. Apalutamide PI. Schulte. Am Soc Clin Oncol Educ Book. 2020;40:1. Darolutamide PI. Smith. NEJM. 2022;386:1132. Docetaxel PI. Thomas. Cancers. 2022;14:8. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. v.1.2023. Maluf. JCO Glob Oncol. 2021;7:559.

Managing Key AEs With Second-Generation AR Inhibitors

Key AEs With All Approved AR Inhibitors

Hypertension	Falls and Fractures	Fatigue	Rash	Gastrointestinal
▪ Monitor BP, signs/symptoms ▪ Optimize current antihypertensive meds ▪ Treat risk factors	▪ Assess fall risk at each visit ▪ "Get up and go" test ▪ Counsel to remove rugs, use night lights	▪ Take before bed ▪ Encourage physical activity	▪ Emollients ▪ Topical corticosteroids	▪ *Nausea:* antiemetics ▪ *Diarrhea:* antidiarrheals ▪ *Constipation:* bulk-forming laxatives

Key AEs With Specific AR Inhibitors

Seizures (Apalutamide, Darolutamide, Enzalutamide)	Headache* and Dizziness (Enzalutamide)	Cognitive Impairment (Apalutamide)	Hypothyroidism (Apalutamide)
▪ Counsel on potential sudden loss of consciousness ▪ Unknown if can use antiepileptic prophylaxis	▪ Manage HA with OTC analgesics ▪ Ask about other meds causing dizziness	▪ Ask about cognition ▪ 3-min Mini-Cog	▪ Check TSH at baseline and then every 4 mo ▪ Monitor T3, T4

- *High-grade/intolerable AEs:* Withhold, modify dose
- *If taking abiraterone/prednisone:* Ensure adherent to prednisone

*Very bad headache may be symptom of PRES (rare).

Abiraterone PI. Alkhudair. Saudi Pharm J. 2019;27:368. Apalutamide PI. Armstrong. JCO. 2022;40:1616. Auchus. Oncologist. 2014;19:1231. cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/headaches. Chi. NEJM. 2019;381:13. Smith. NEJM. 2022;386:1132. Darolutamide PI. Enzalutamide PI. medlineplus.gov/lab-tests/fall-risk-assessment/. mskcc.org/cancer-care/patient-education/medications/enzalutamide. Olivier. Int J Urol Nurs. 2021;15:47. van Dorst. Circ Res. 2021;128:1040. Rama. Clin J Oncol Nurs. 2015;19:723. Wefel. CNS Drugs. 2022;36:419. Wickham. J Adv Pract Oncol. 2017;8:149.

STOPCAP

- Meta analysis of 7 of 11 HSPC clinical trials comparing ADT +ARPI to ADT alone (Total 7778 patients, or 70% of all ARPI trial patients)
- Performed an intent to treat, two-stage common effect meta-analysis of hazard ratios using a core set of covariates (age, PSA, performance status, Gleason, timing of diagnosis) and use of concomitant docetaxel.
- The main effects were based on overall survival. Interaction effects were based on progression-free survival to maximize power, then overall survival whenever progression-free survival interactions were found ($p < 0.10$).

Fisher et al Proc ASCO GU 2025

STOPCAP Patient Characteristics

Trial	Synchronous	High Volume	Docetaxel SOC
STAMPEDE (Abiraterone)	94%	56%	0%
LATITUDE (Abiraterone	100%	54%	0%
PEACE-1 (Abiraterone)	100%	57%	61%
ENZAMET (Enzalutamide)	68%	54%	45%
TITAN (Apalutamide)	86%	63%	11%
STAMPEDE (Abi + Enza)	93%	53%	9%
SWOG 1216 (TAK-700)	Unknown	Unknown	0%

Fisher et al Proc ASCO GU 2025

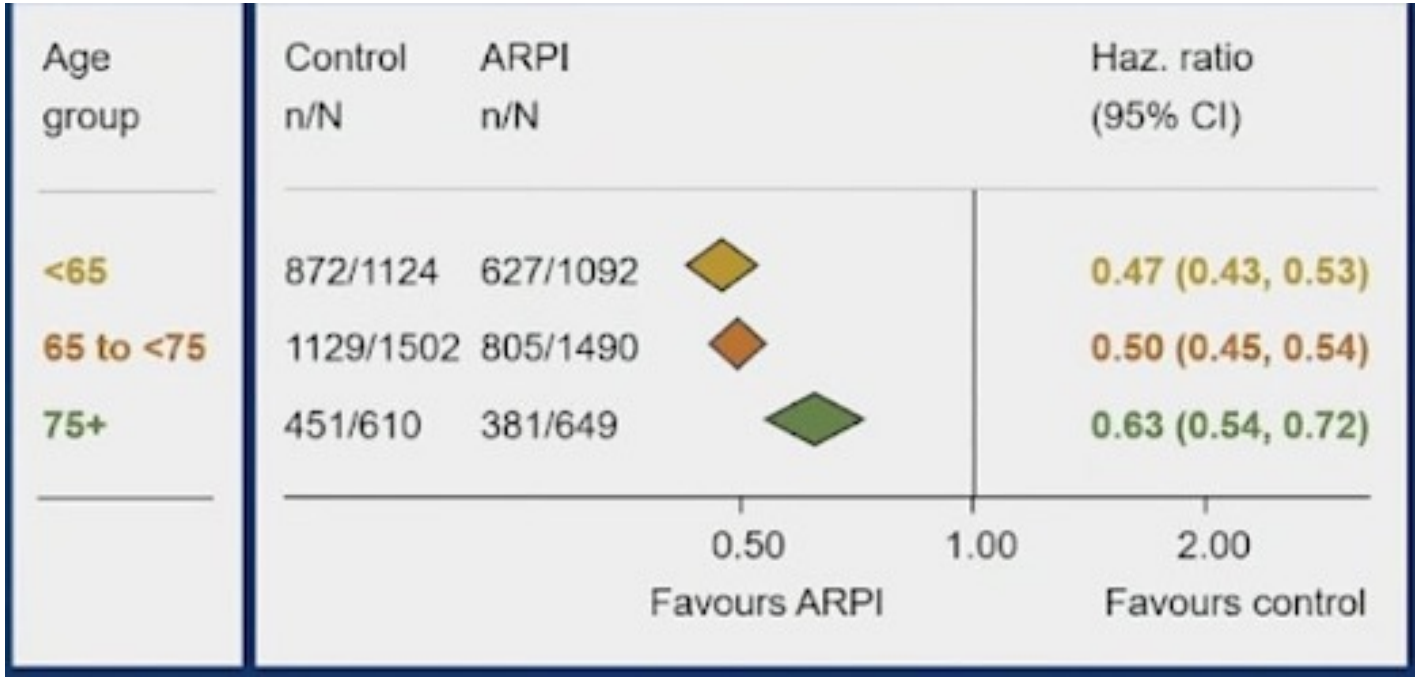
STOPCAP: Addition of ARPI

- ARPIs improved progression free and overall survival by 21 and 13% at 5 years follow-up, respectively.
- There was no clear difference when accounting for volume or location of metastases, timing of metastatic diagnosis, performance status, Gleason score, and timing of metastatic diagnosis

Fisher et al Proc ASCO GU 2025

Effects of ARPIs By Age Group

PFS

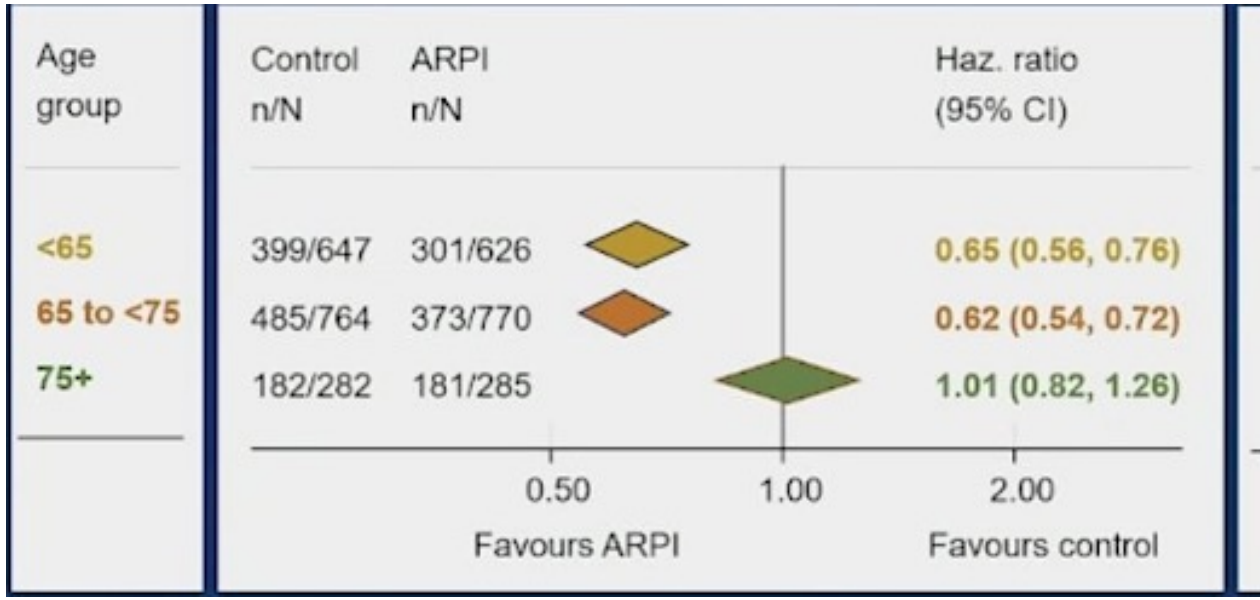


OS

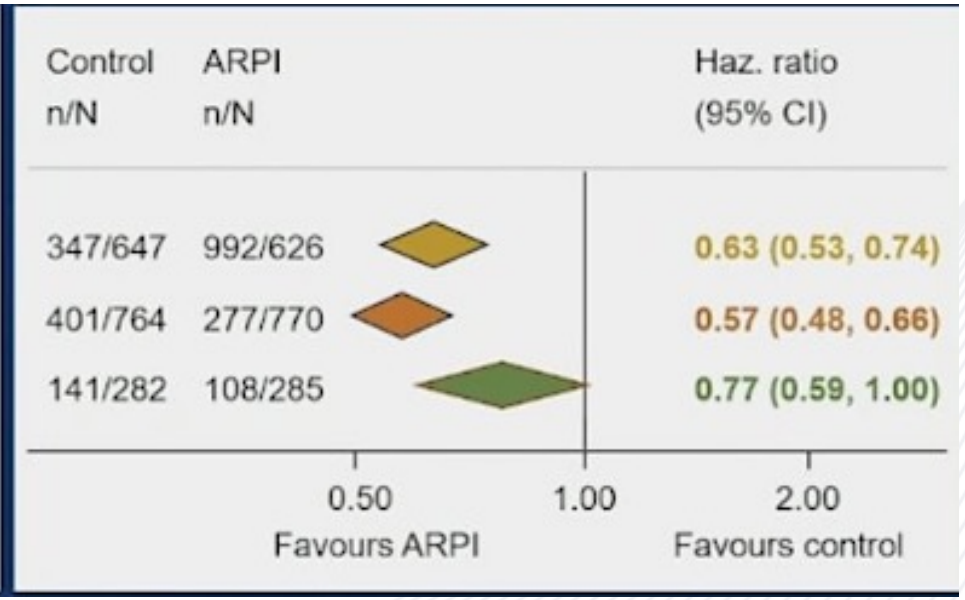
Fisher et al Proc ASCO GU 2025

Effects of ARPIs by Age Group: Abiraterone Trials

OS



PCSS



Fisher et al Proc ASCO GU 2025

Effects of ARPIS by Age Group: Amide Trials

PFS

Age group	Control n/N	ARPI n/N	Haz. ratio (95% CI)
<65	339/477	233/466	0.46 (0.39, 0.55)
65 to <75	512/738	341/720	0.48 (0.42, 0.55)
75+	229/328	172/364	0.47 (0.38, 0.58)

0.50 1.00 2.00
Favours ARPI Favours control

OS

Control n/N	ARPI n/N	Haz. ratio (95% CI)
246/477	179/466	0.61 (0.50, 0.75)
362/738	285/720	0.69 (0.59, 0.81)
187/328	142/364	0.57 (0.45, 0.71)

0.50 1.00 2.00
Favours ARPI Favours control

Fisher et al Proc ASCO GU 2025

5-year absolute effects of ARPIs, by age group

		PFS	OS	PCSS*
Younger age groups (<75)	Abiraterone trial data	~25%	~16%	~17%
	Amide (± abi) trial data	~27%	~18%	?
Oldest age group (75+)	Abiraterone trial data	~8%	~0%	~9%
	Amide (± abi) trial data	~27%	~19%	?

Fisher et al Proc ASCO GU 2025

Conclusions

- There is a clear benefit of androgen receptor pathway inhibitors on overall survival and progression free survival for the majority of mHSPC patients
- Side effect profile should be considered in selecting an ARPI
- For young patients, there is a clear benefit from all androgen receptor pathway inhibitors
- For older patients, there should be a consideration of the benefits and risks of abiraterone and “amides”

Second Opinion

Rana R McKay, MD, FASCO

Sandy Srinivas, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How are you currently approaching the selection of endocrine therapy for patients with androgen pathway modulator-sensitive (APMS) metastatic disease?

In what situations, if any, do you use ADT alone? Do you have a preferred ARPI + ADT doublet? Do you use intermittent therapy in this setting, and if so, how?

Second Opinion

Andrew J Armstrong, MD, ScM

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your usual approach to biomarker evaluation for patients with APMS mPC, including somatic and genetic testing?

Is archival tissue adequate? What about tissue from the bone? What about liquid biopsy? Which assays, if any, are worth repeating upon disease progression?

Agenda

Module 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Shore

Module 2: Current Hormonal Treatment for Metastatic HSPC (mHSPC) — Dr Petrylak

Module 3: Current and Future Role of PARP Inhibitors for Metastatic Prostate Cancer (mPC) — Dr Agarwal

Module 4: Emerging Role of AKT Inhibition for Patients with mHSPC — Dr Heath

Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

RTP RESEARCH TO PRACTICE

Current and Future Role of PARP Inhibitors in Metastatic Prostate Cancer

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research, Huntsman Cancer Institute (HCI)
HCI Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Huntsman Cancer Institute, University of Utah (NCI-CCC)

May 17, 2026, AUA 2026 — Symposium on PARP Inhibitors in Metastatic Prostate Cancer

Current and Future Role of PARPi in mPC: Talk Overview

- Incidence of BRCA1/2 and HRR abnormalities in mPC; optimal genetic testing
- Long-term efficacy and safety: olaparib + abiraterone, niraparib + abiraterone, talazoparib + enzalutamide in 1L mCRPC
- Phase III AMPLITUDE: niraparib + abiraterone/prednisone in HRR-mutated mHSPC
- Phase III TALAPRO-3: talazoparib + enzalutamide in HRR-mutated mHSPC
- Saruparib: mechanistic differences and ongoing Phase III evaluation (EvoPAR-Prostate01)

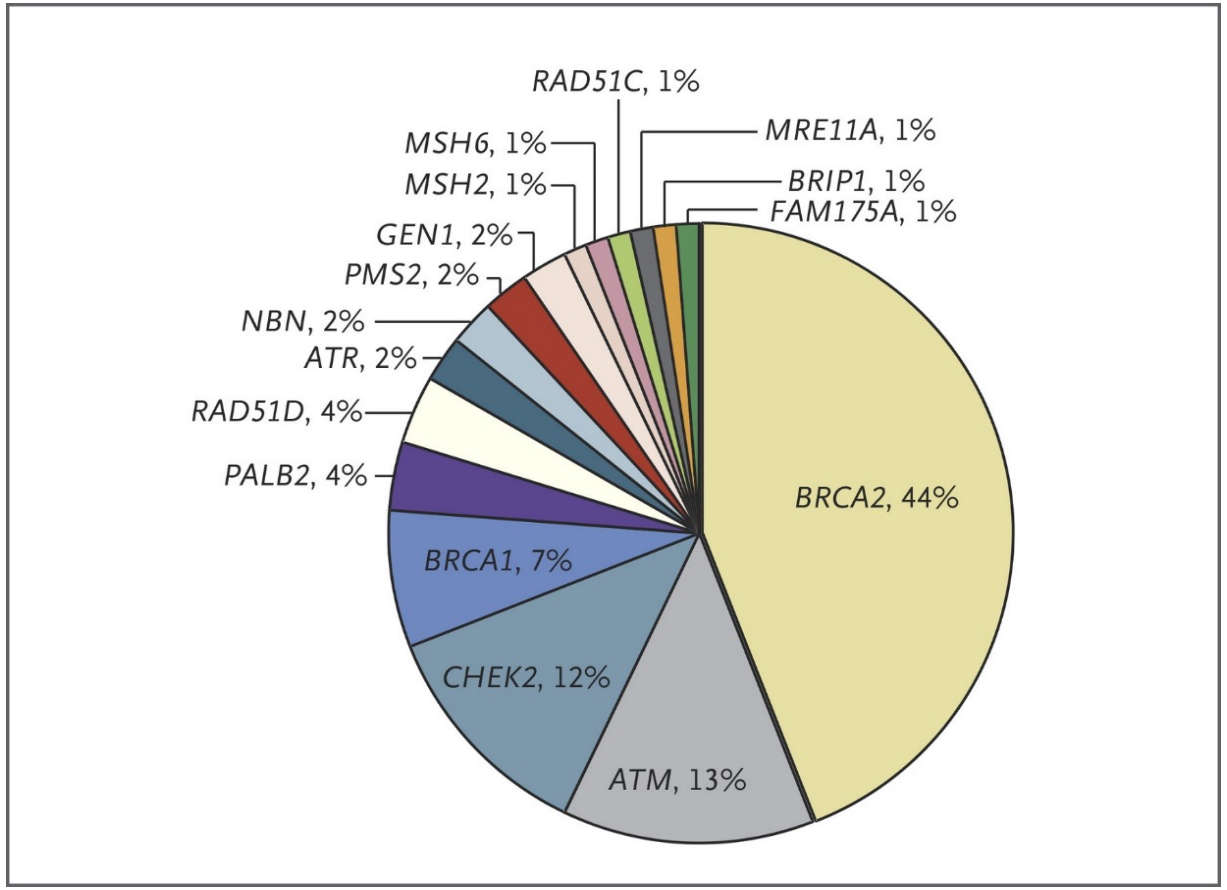
Germline HRR mutations in metastatic prostate cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson



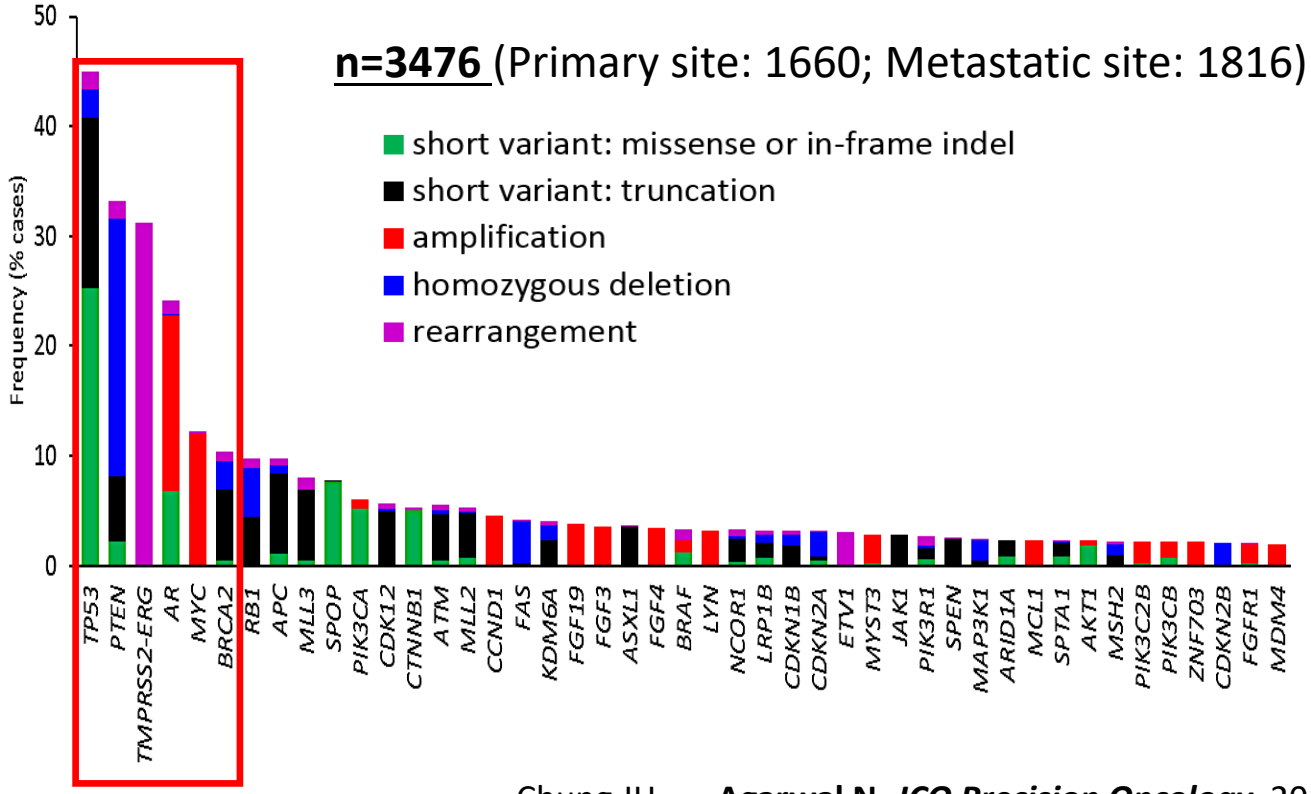
Pritchard et al. NEJM 2016

Genomic Landscape in Advanced Prostate Cancer (Tissue DNA)

JCO® Precision Oncology
An American Society of Clinical Oncology Journal

Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumors

Jon H. Chung, PhD[1]; Ninad Dewal, PhD[1]; Ethan Sokol, PhD[1]; Paul Mathew, MD[2]; Robert Whitehead, MD[3]; Sherri Z. Millis, PhD[1]; Garrett M. Frampton, PhD[1]; Gennady Bratslavsky, MD[4]; Sumanta K. Pal, MD[5]; Richard J. Lee, MD, PhD[6]; Andrea Necchi, MD[7]; Jeffrey P. Gregg, MD[8]; Primo Lara Jr, MD[8]; Emmanuel S. Antonarakis, MD[9]; Vincent A. Miller, MD[1]; Jeffrey S. Ross, MD[1,4]; Siraj M. Ali, MD, PhD[1]; and Neeraj Agarwal, MD[10]



Chung JH, …, **Agarwal N.** ***JCO Precision Oncology*** 2019

Optimal Methods for Genetic Testing in mPC

Germline Testing

- Recommended for **all patients** at time of metastatic diagnosis
- Identifies inherited mutations — important for family counseling and cascade testing
- **Key genes:** BRCA1, BRCA2, ATM, CDK12, CHEK2

Somatic Tumor Testing

- **NGS of tumor tissue (preferred)** or ctDNA
- Tumor-only testing may detect additional somatic HRR alterations not in germline
- ctDNA useful when tissue unavailable; sensitivity may be lower
- **Prospective tissue testing** detects more HRR+ patients than retrospective ctDNA

All patients with mPC should undergo BOTH germline and somatic tumor testing for HRR gene mutations

NCCN Guidelines 2025; ASCO Guidelines*, 2025*

The rationale for combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

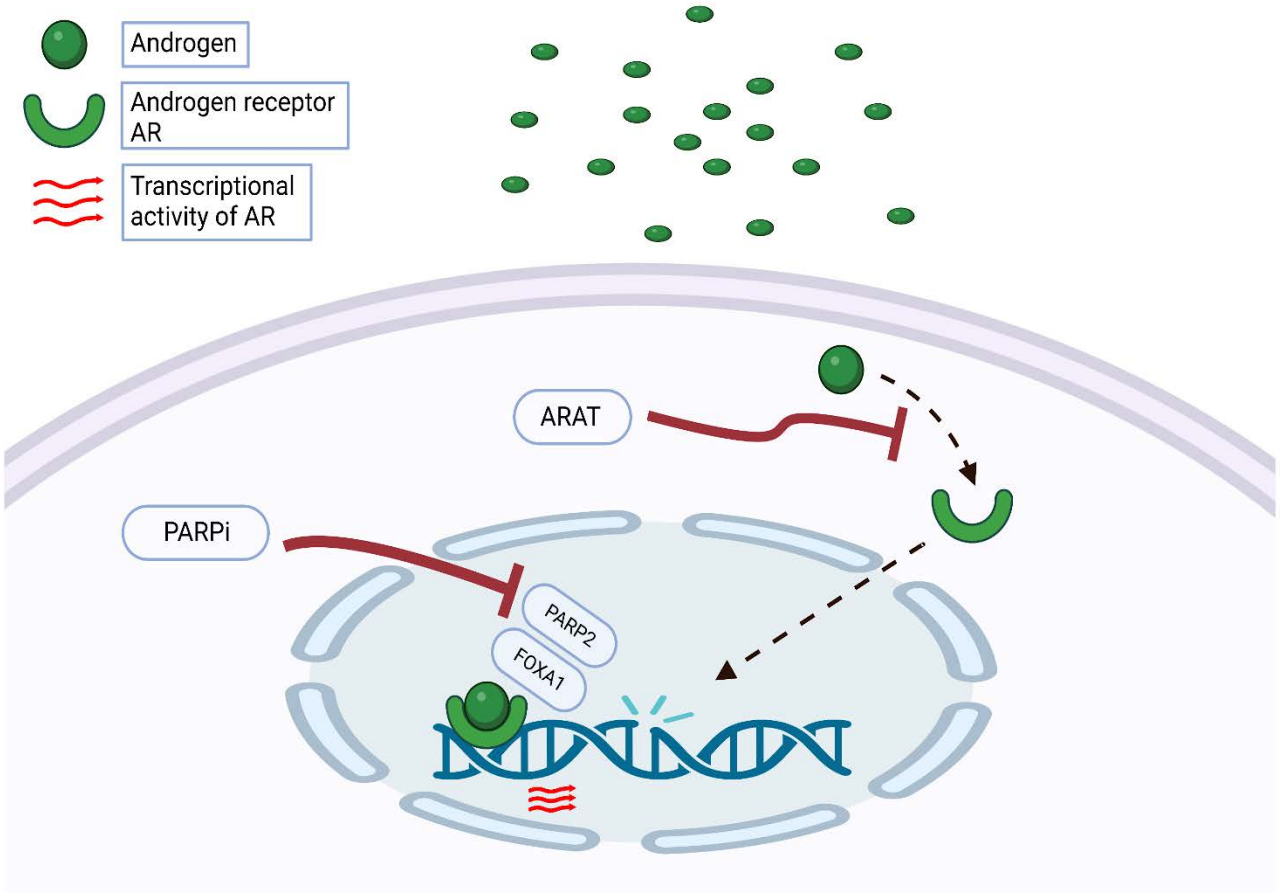
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

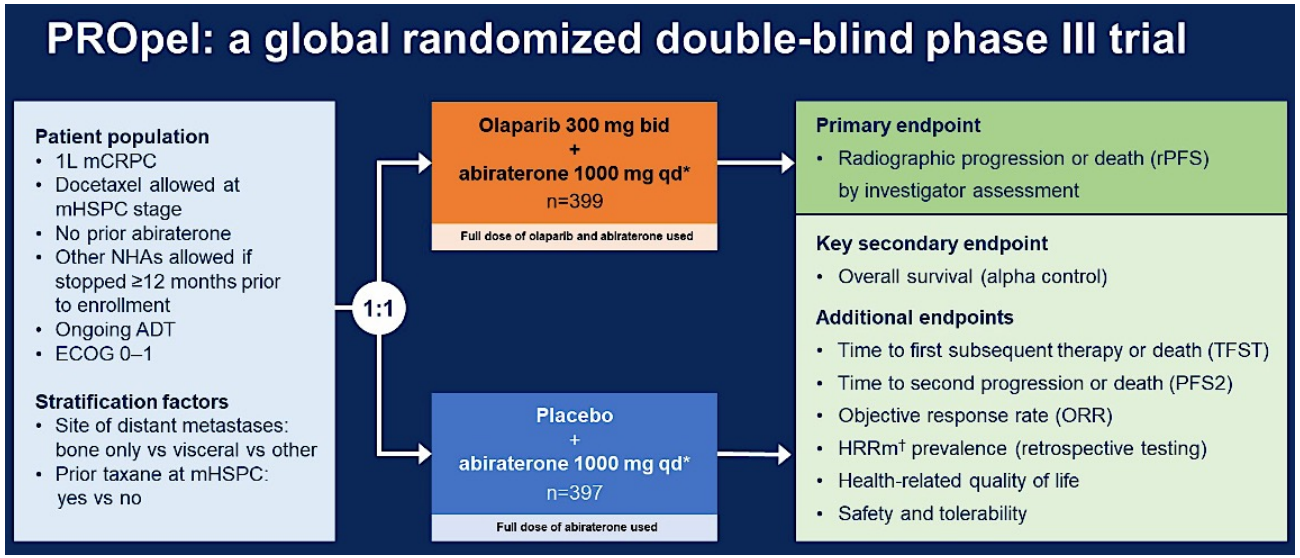
PARP inhibitors may attenuate resistance to ARPIs

PARP inhibitors extend the benefits of ARPIs

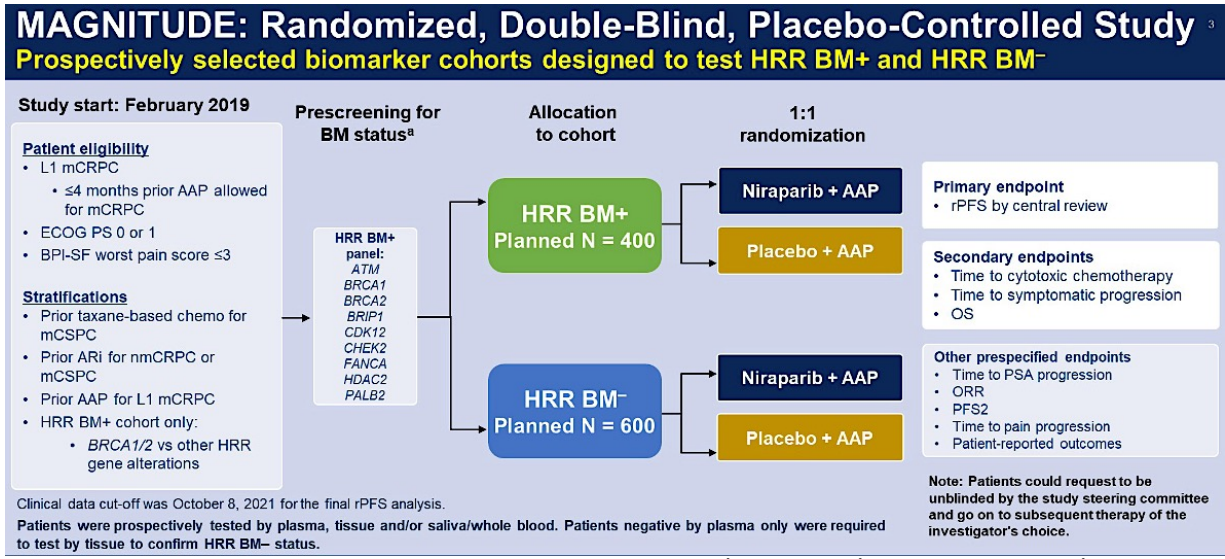


1. Adapted from Bin Gui et al., *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. **Agarwal N**, et al European Journal of Cancer, 2023.

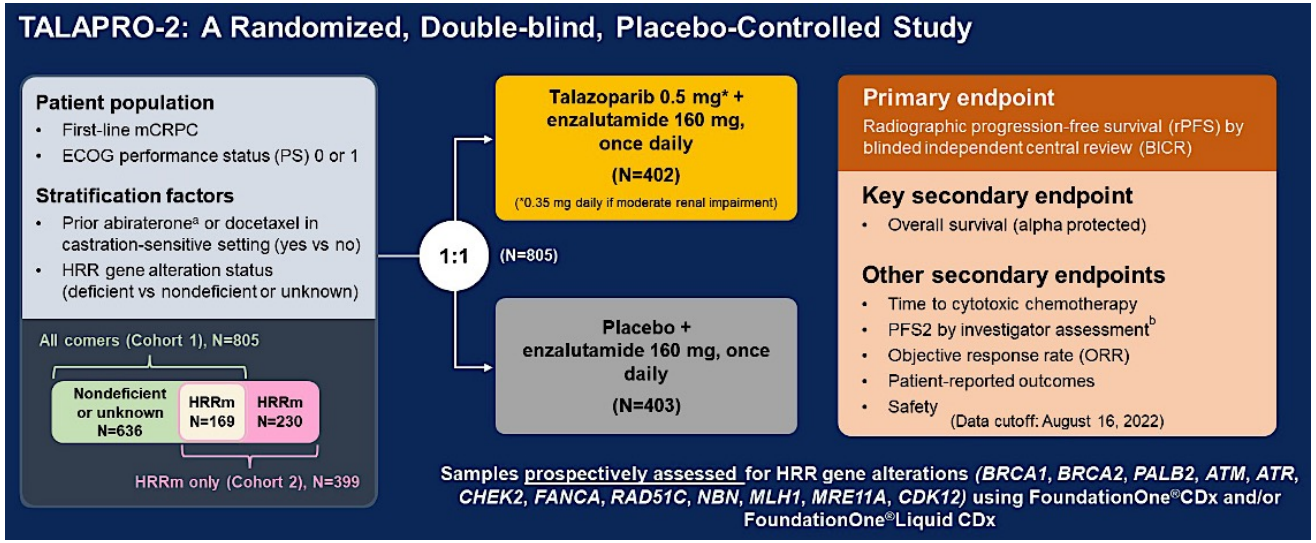
Phase 3 PARPi + ARPI Trials Design



Clarke, NW. *et al.* ***NEJM Evidence,*** 2022



Chi, KN. *et al.* ***ASCO GU 2022;****Abstract 12*



Agarwal, N. *et al.* ***Lancet,*** 2023.

Phase 3 Combination trials of PARP inhibitors with an APRI

	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomisation Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomisation abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomisation Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomisation Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	HR 0.50 (0.34-0.73)	HR 0.73 (0.56-0.96)	HR 0.46 (0.30-0.70)	HR 0.45 (0.33-0.61)
BRCA+	HR 0.23 (0.12-0.43)	HR 0.53 (0.36-0.79)	HR 0.23 (0.10-0.53)	HR 0.20 (0.11-0.36)
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.66 (0.46-0.95) (only for BRCA 1/2)	**45.8 vs 37 months** **HR 0.80 (0.66–0.96)**	**45.1 vs 31.1 months** **HR 0.62 (0.48–0.81)**
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N….Saad F. ***NEJM Evidence***, 2022	Chi K….Sandhu S. ***JCO***, 2023	**Agarwal N**….Fizazi K. ***The Lancet***, 2025	Fizazi K….**Agarwal N.** ***The Lancet***, 2025

PROpel Trial: Long-Term Efficacy and Safety

PROpel: Olaparib 300mg bid + Abiraterone 1000mg qd vs Placebo + Abiraterone — 1L mCRPC (N=796)

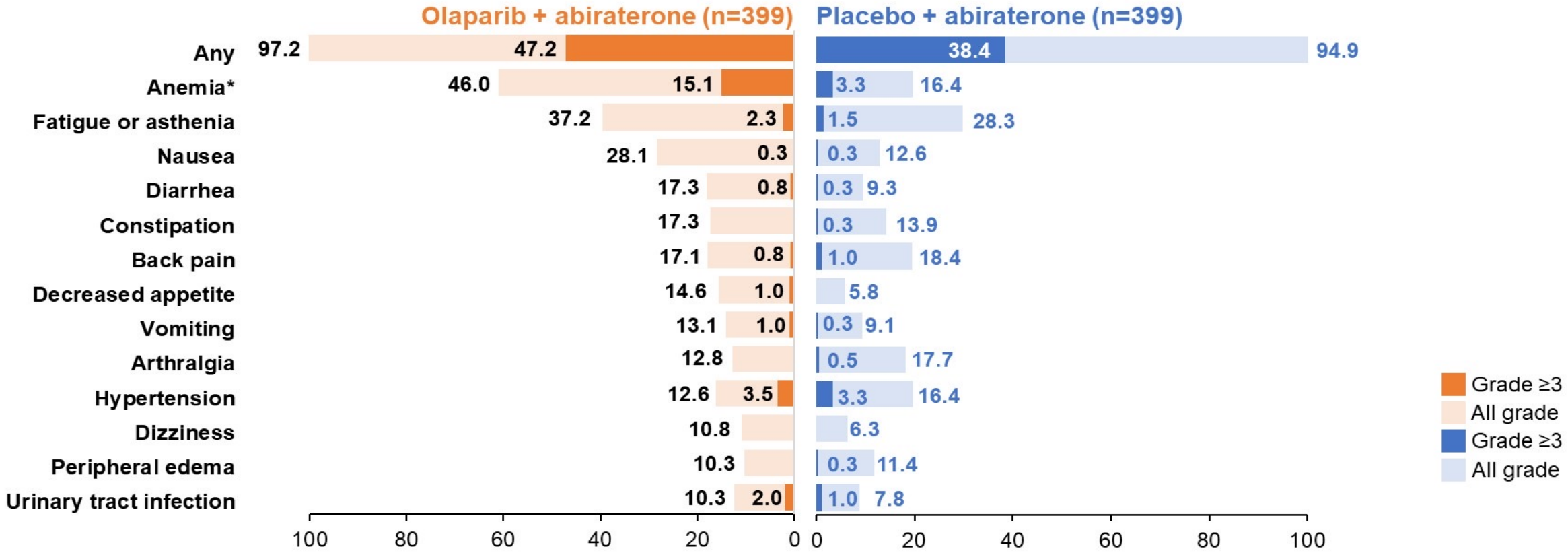
rPFS — All Comers	rPFS — HRR+ Subgroup	rPFS — BRCA+	OS — All Comers
HR 0.66	**HR 0.50**	**HR 0.23**	**HR 0.81**
95% CI 0.54–0.81 ✓	95% CI 0.34–0.73 ✓	95% CI 0.12–0.43 ✓	95% CI 0.67–1.0 (trend)

- **FDA/EMA Approval:** mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy not indicated
- **ORR (all comers):** 58% vs 48%; safety profile consistent with individual drug profiles

Clarke N…Saad F. NEJM Evidence 2022; Saad F…Clarke N. Lancet Oncology 2023

PROpel: most common adverse events

AE profile was consistent with the known toxicity profiles for the individual drugs



Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments.
*Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.

MAGNITUDE Trial: Long-Term Efficacy and Safety

MAGNITUDE: Niraparib 200mg qd + Abiraterone 1000mg qd vs Placebo + Abiraterone — 1L mCRPC (N=423 HRR cohort)

rPFS — All HRR+	rPFS — BRCA1/2	OS — BRCA1/2	ORR — HRR+
HR 0.73	**HR 0.53**	**HR 0.66**	**60%**
95% CI 0.56–0.96 ✓	95% CI 0.36–0.79 ✓	95% CI 0.46–0.95 ✓	vs 28% (placebo)

- **Non-HRR cohort:** Closed early due to futility; 100% prospective tissue-based HRR testing
- **FDA/EMA Approval:** mCRPC with BRCA1/2 mutations

Chi K…Sandhu S. JCO 2023; Fizazi K…Chi K. NEJM Evidence 2022; Chi K…Olmos D. Eur Urol Oncol 2025

MAGNITUDE HRR BM+: TEAEs Consistent With the Known Safety Profile for Each Therapy

Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n = 212		PBO + AAP, n = 211	
		All grades	Grade ≥3	All grades	Grade ≥3
Hematologic	Anemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropenia	29 (13.7)	14 (6.6)	12 (5.7)	3 (1.4)
	Acute myeloid leukemia/ Myelodysplastic syndrome	0	0	1 (0.5)	1 (0.5)
Cardiovascular	Hypertension	67 (31.6)	33 (15.6)	47 (22.3)	30 (14.2)
	Arrhythmia	27 (12.7)	6 (2.8)[a]	12 (5.7)	3 (1.4)
	Cardiac failure	4 (1.9)	3 (1.4)[a]	4 (1.9)	1 (0.5)
	Ischemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)[b]
General disorders	Fatigue	56 (26.4)	7 (3.3)	35 (16.6)	9 (4.3)
Gastrointestinal	Constipation	65 (30.7)	–	29 (13.7)	–
	Nausea	50 (23.6)	1 (0.5)	29 (13.7)	0
Hepatotoxicity		25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders		6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)[a]

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo.
[a]Includes 1 grade 5 event.
[b]Includes 3 grade 5 events.

TALAPRO-2 Trial: Long-Term OS Data (The Lancet, 2025)

TALAPRO-2: Talazoparib 0.5mg qd + Enzalutamide 160mg qd vs Placebo + Enzalutamide — 1L mCRPC

COHORT 1 — All Comers (N=805)		COHORT 2 — HRR Mutated (N=399)	
Median OS	OS Hazard Ratio	Median OS	OS Hazard Ratio
45.8 mo	**HR 0.80**	**45.1 mo**	**HR 0.62**
vs 37.0 mo (placebo)	0.66–0.96 ✓	vs 31.1 mo (placebo)	0.48–0.81 ✓

★ **BRCA+ (Cohort 2): rPFS HR 0.20 (0.11–0.36) — Dramatic, highly significant benefit**

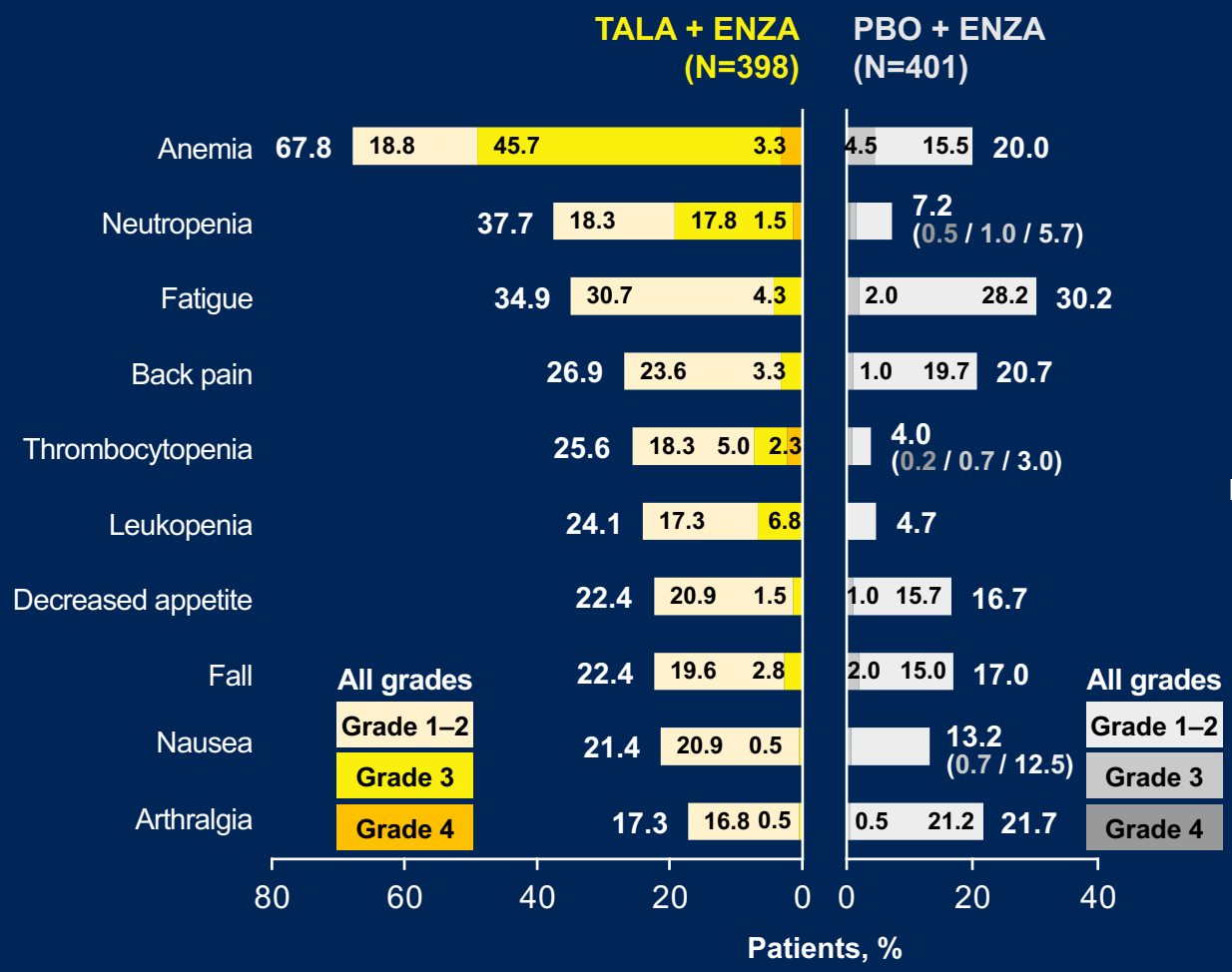
- **FDA/EMA Approval:** mCRPC with any HRR mutations; mCRPC when chemotherapy not clinically indicated

Agarwal N…Fizazi K. *The Lancet* 2025; Fizazi K…Agarwal N. *The Lancet* 2025

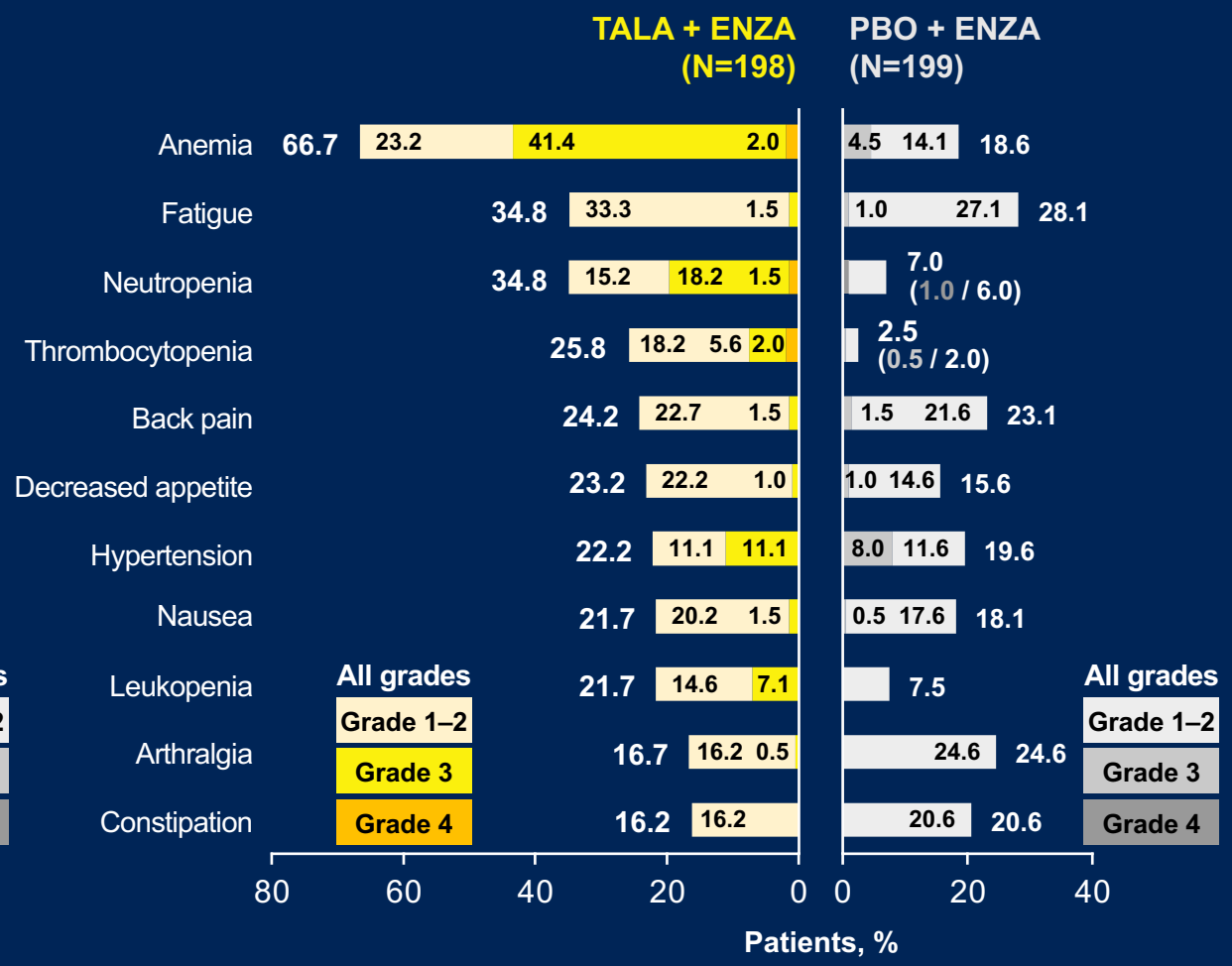
TALAPRO-2 Unselected
TALAPRO-2 HRRm

Most Common All-Cause TEAEs

Unselected population



HRR-deficient population



Figures include TEAEs reported in ≥20% of patients in either arm.

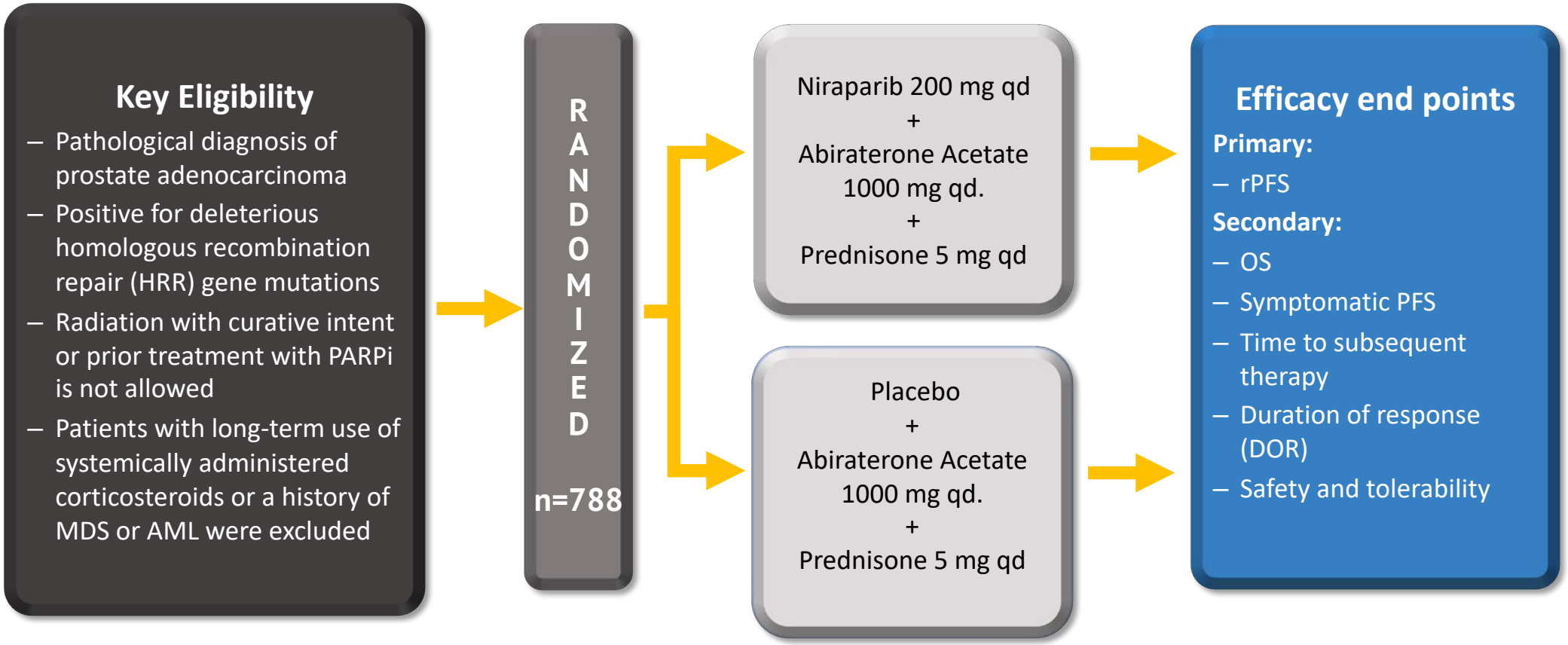
FDA-Approved PARPi Combinations for mCRPC: Summary

Combination (Trial)	FDA/EMA Population	rPFS HR (BRCA+)	OS Benefit
Olaparib + Abiraterone (PROpel)	mCRPC BRCA1/2; or chemotherapy not indicated	**HR 0.23** (0.12–0.43)	HR 0.81 (trend favoring olaparib)
Niraparib + Abiraterone (MAGNITUDE)	mCRPC with BRCA1/2 mutations	**HR 0.53** (0.36–0.79)	HR 0.66 BRCA1/2 (significant OS)
Talazoparib + Enzalutamide (TALAPRO-2)	mCRPC any HRR mutations; or chemo not indicated	**HR 0.20** (0.11–0.36) ★	OS HR 0.80 all-comers; 0.62 HRR+ (significant)

⚠ Key Clinical Messages

HRR testing at mCRPC diagnosis is essential to identify PARPi candidates
Greatest benefit in BRCA1/2 patients (rPFS HR range: 0.20–0.53)
OS benefit demonstrated for talazoparib + enzalutamide in all-comers (FDA labels 2023)

AMPLITUDE Phase 3 Trial: PARPi in mHSPC

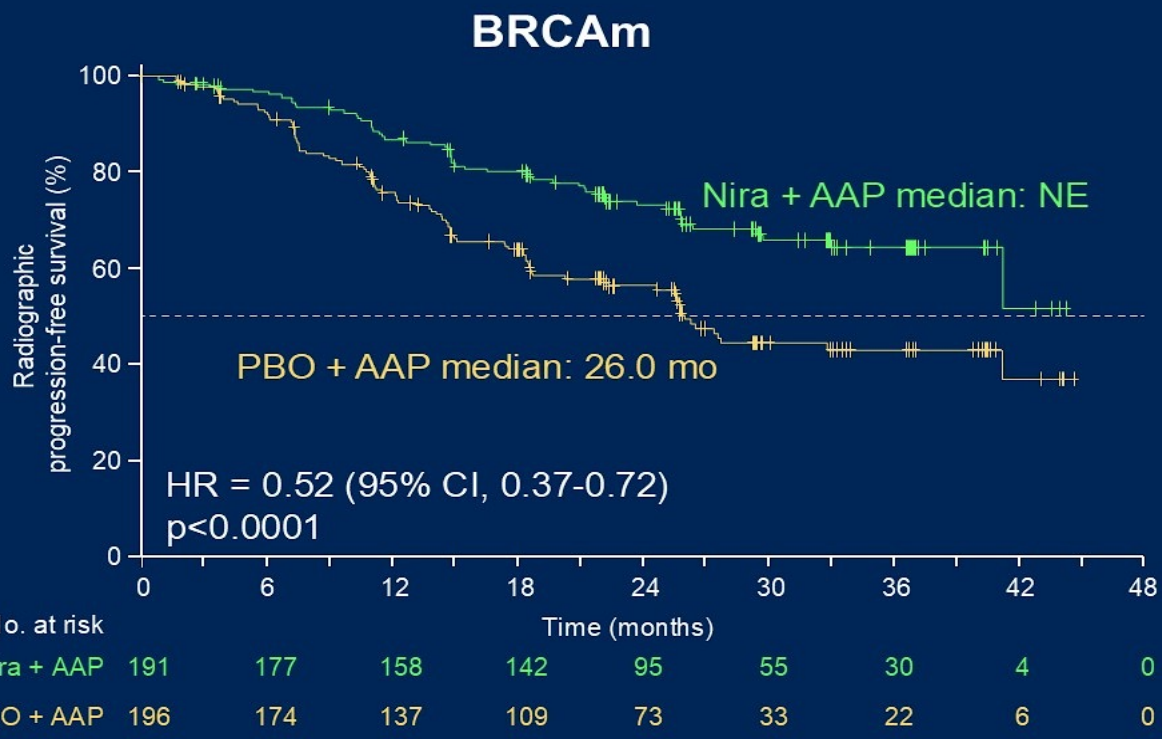


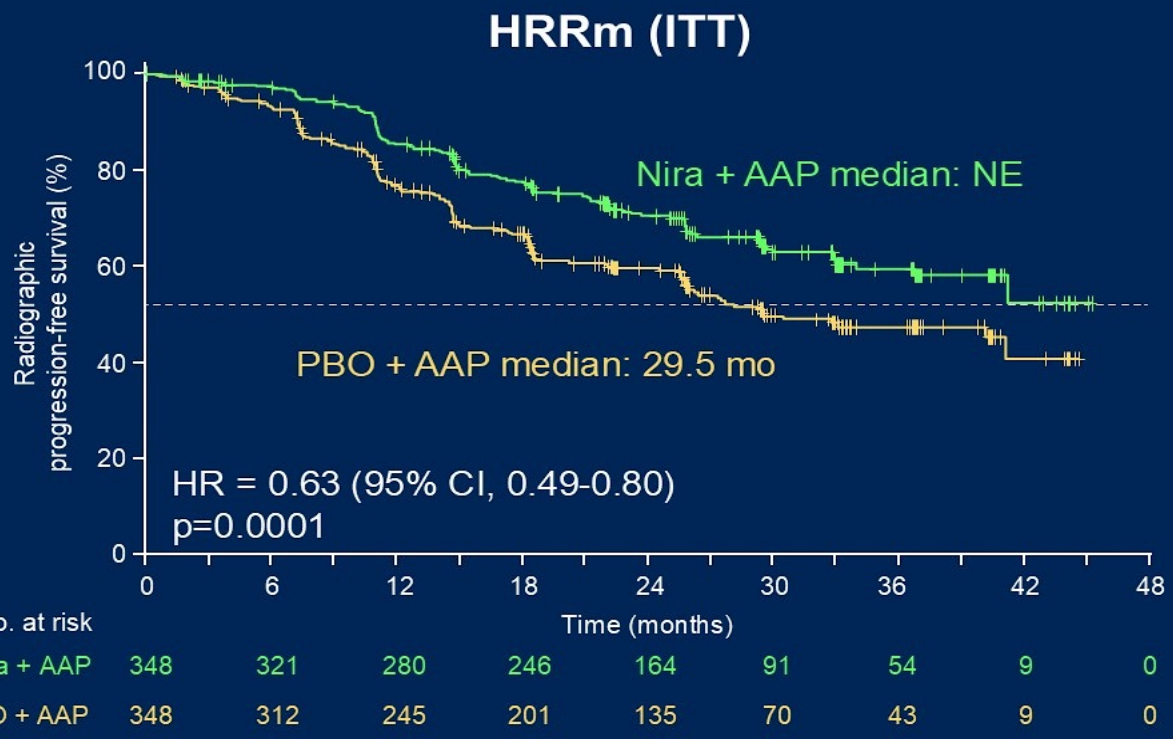
www.clinicaltrials.gov: (NCT04497844)

Eligible HRR genes were:
BRCA1, *BRCA2*, *BRIP1*, *PALB2*, *RAD51B*, *RAD54L*, *CDK12*, *CHEK2* and *FANCA*.

Attard, **Agarwal**…Rathkopf. *Nature Medicine*, 2025

Primary End Point: Radiographic Progression-Free Survival





AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

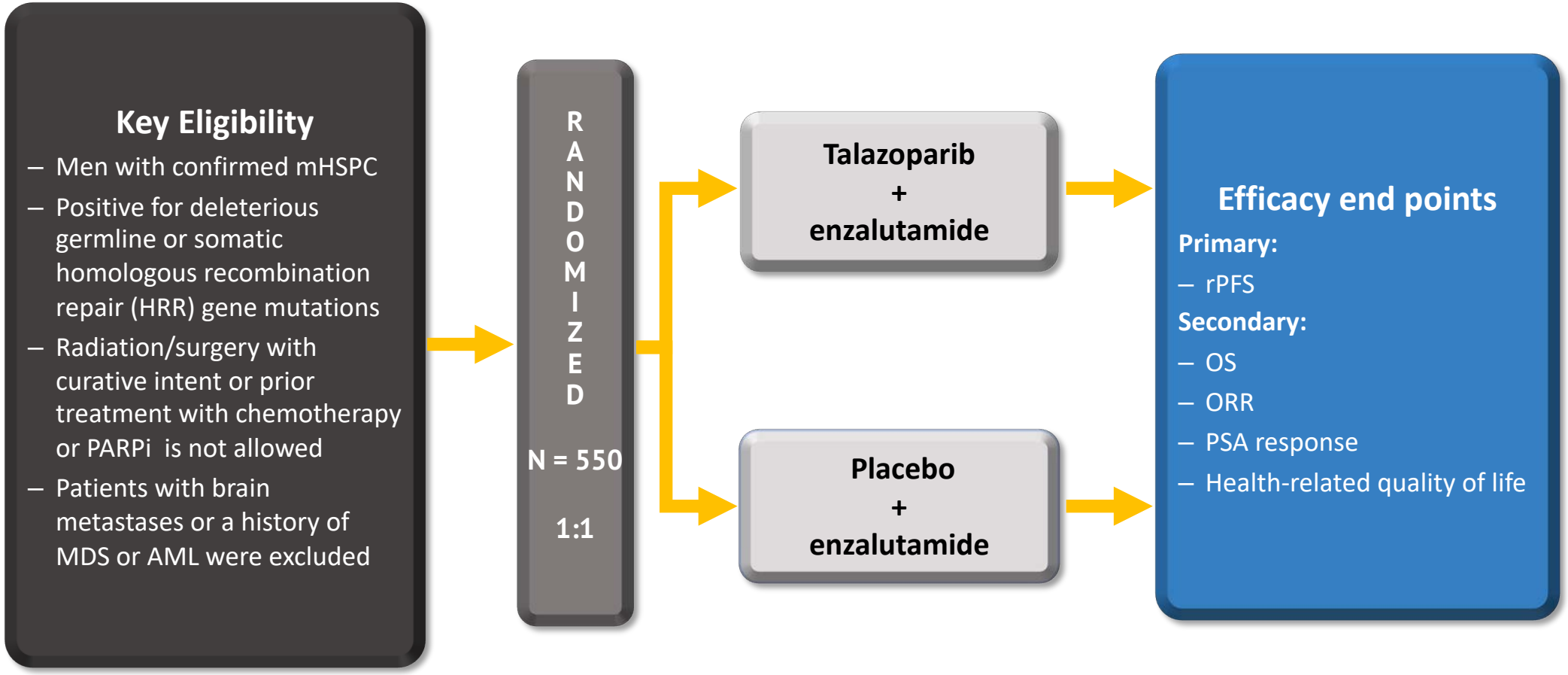
[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm group.
NE, not estimable.

AMPLITUDE Trial: PARPi in mHSPC

Endpoint		Niraparib + Abiraterone	Placebo + Abiraterone	Hazard Ratio (HR) (95% CI)	P-value
rPFS (median, mo)	All	Not reached	29.5	**0.63** (0.49–0.80)	0.0001
	BRCA1/2	Not reached	26	**0.52** (0.37-0.72)	<0.0001
Time to pain progression (median, mo)	All	Not reached	Not reached	**0.50** (0.36–0.69)	<0.0001
	BRCA1/2	Not reached	Not reached	**0.44** (0.29-0.68)	0.0001
OS (median, mo)	All	Not reached	Not reached	0.79 (0.59–1.04)	0.10
	BRCA1/2	Not reached	Not reached	0.75 (0.51-1.11)	0.15

Attard G, Agarwal N…. Rathkopf. Nature Medicine 2025

Phase 3 TALAPRO-3 Trial



www.clinicaltrials.gov: (NCT04821622)

Agarwal… Fizazi. *Future Oncology*, 2024

Phase 3 TALAPRO-3 Trial Press Release

Talazoparib Plus Enzalutamide Significantly Improves Radiographic Progression-Free Survival in Metastatic Prostate Cancer

Thursday, March 19, 2026 - 06:45am | 17 min read

- *Primary endpoint met in Phase 3 TALAPRO-3 study demonstrating **a statistically significant and clinically meaningful reduction in risk of disease progression or death** in HRR gene-mutated metastatic hormone sensitive prostate cancer*
- *Consistent rPFS efficacy benefit was observed in patients whose tumors harbored BRCA and non-BRCA HRR gene alterations*
- *Interim analysis showed a strong trend toward improvement in overall survival*
- *These results will be discussed with global health authorities to potentially expand Talazoparib indication in this earlier stage disease*

Saruparib (AZD5305): Selective PARP1 Inhibitor — Mechanism

Next-generation PARP1-selective inhibitor — a key mechanistic advance

PARP1 Selectivity Profile

- **460-fold** selectivity for PARP1 vs PARP2 (biochemical)
- **435-fold** selectivity (cellular assay)
- **PARP1 IC50: 3 nmol/L** vs PARP2 IC50: 1,400 nmol/L
- Mechanism: **Traps PARP1 on DNA** — PARP2 neither inhibited nor trapped

Clinical Significance

- **Reduced hematologic toxicity:** PARP2 inhibition implicated in anemia and thrombocytopenia seen with older PARPi
- **Better tolerability** while maintaining anti-tumor efficacy
- **Higher-dose combinations** with ARPI without dose reductions from hematologic toxicity

460-fold PARP1 selectivity — the defining mechanistic advantage of saruparib

Illuzzi G et al. Clin Cancer Res 2022; Johannes JW et al. 2021

Saruparib vs Current PARPi: Mechanistic Differences

Feature	Current PARPi (Olaparib, Niraparib, Talazoparib)	Saruparib (AZD5305) Next Generation
PARP Selectivity	PARP1 + PARP2 (dual)	**PARP1 only (460-fold selective)**
Hematologic Toxicity	Higher (anemia, thrombocytopenia)	**Lower (PARP2 sparing)**
PARP1 Trapping	PARP1 + PARP2 both trapped	**PARP1 only (maintained efficacy)**
Activity After Prior PARPi	Shared resistance mechanisms	**Distinct resistance profile — potential activity**
Patient Eligibility	Excludes patients with cytopenias	**May include patients unfit for current PARPi**

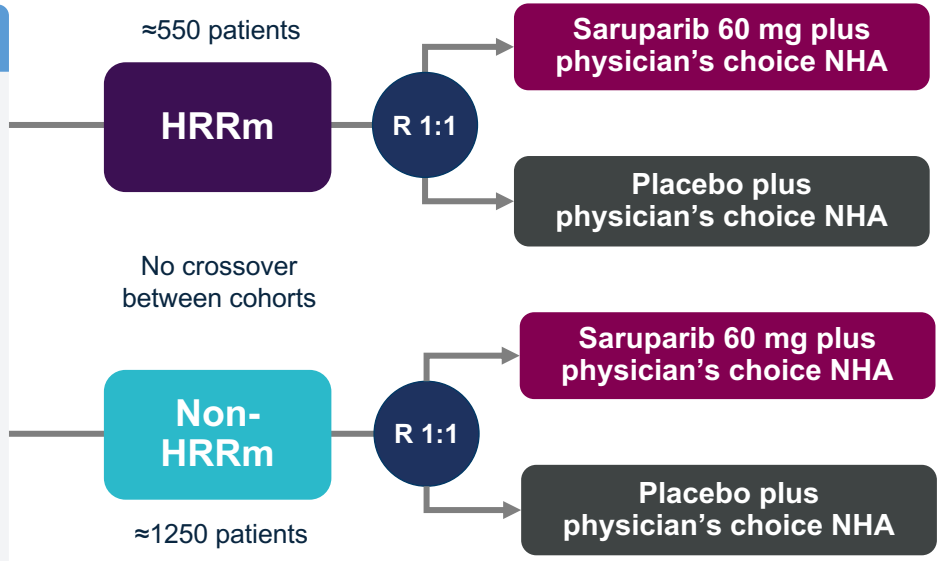
Illuzzi G et al. Clin Cancer Res 2022

EvoPAR-Prostate01 : Phase 3 Trial Design (mHSPC)

A Phase III, 2-cohort, 2-arm, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of saruparib plus physician's choice of NHA (abiraterone, darolutamide, or enzalutamide) versus placebo plus physician's choice of NHA in participants with mCSPC

Eligibility criteria

- Aged ≥18 years
- Histologically confirmed mCSPC (*de novo* or recurrent low- or high-volume disease)
- ECOG PS 0–1
- Prospectively defined HRRm status*
- Must be receiving ADT throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with NHAs
- No prior treatment with PARP inhibitors, CT, or NHAs in the metastatic setting†
- No suspected or prior history of myelodysplastic syndrome/acute myeloid leukemia



Treatment will continue until disease progression, unacceptable toxicity, or participant-initiated withdrawal

Select endpoints

HRRm cohort
- rPFS
- OS

Non-HRRm cohort
- rPFS
- OS

Statistical analyses

rPFS and OS will be tested for each cohort separately using a stratified log-rank test

www.clinicaltrials.gov: (NCT06120491)

Agarwal N. *et al*, **AUA** 2024;
Azad A et al, ASCO GU 2025

Unmet Needs and Future Directions in PARPi Therapy

- **Despite PARPi advances, significant unmet needs remain:**
- **Sequencing challenges:**
  - Optimal sequence of PARPi + ARPI in mCRPC vs mHSPC remains undefined
  - PARPi efficacy after prior PARPi in earlier line: largely unknown
- **Resistance mechanisms:**
  - BRCA reversion mutations; RAD51 overexpression; CCND1 amplification
  - Secondary BRCA mutations restored HRR function — primary resistance mechanism
- **Expanding eligibility:**
  - Non-HRR patients: modest benefit in all-comers; understanding which patients benefit is critical
  - Saruparib (EvoPAR-Prostate01): testing selective PARP1 inhibition in both HRR+ and non-HRR mCSPC cohorts

Lord CJ, Ashworth A. Science 2017; Agarwal N et al. AUA 2024

Key Takeaways: PARPi in Metastatic Prostate Cancer

- HRR mutations present in ~20–25% of mCRPC; BRCA1/2 in ~10%; comprehensive germline + somatic testing essential at time of metastatic diagnosis
- Three PARPi+ARPI combinations now FDA-approved in 1L mCRPC; talazoparib+enzalutamide shows first OS benefit in all-comers (Lancet 2025)
- AMPLITUDE: niraparib+abiraterone demonstrates significant rPFS benefit in HRR-mutated mHSPC (Nature Medicine 2025)
- TALAPRO-3: talazoparib+enzalutamide meets primary rPFS endpoint in HRR-mutated mHSPC (Press release, March 2026) — Full data release in ASCO 2026
- Saruparib (AZD5305), a selective PARP1 inhibitor, may offer improved tolerability; EvoPAR-Prostate01 Phase 3 underway in mCSPC (both HRR+ and non-HRR)

Second Opinion

Andrew J Armstrong, MD, ScM

Sandy Srinivas, MD

Rana R McKay, MD, FASCO

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Currently, what is the optimal approach to therapy for a patient with APMS mPC and a BRCA2 mutation? Do you think your response will likely change after ASCO? Do you think you will be looking to use PARP inhibitors for a large portion of patients with HRR pathway abnormalities?

Does combination therapy with an ARPI and a PARP inhibitor offer meaningful advantages over sequential single-agent treatment? How did the BRCAAway study seek to answer this question, and what did it find?

QUESTIONS FOR THE FACULTY

How do you approach the prevention and management of acute GI toxicities with PARP inhibitors? What is your experience with cytopenias, including anemia, related to these agents?

What do you think about the ongoing EvoPAR-Prostate02 trial? Do you believe saruparib offers any advantages over currently available PARP inhibitors in terms of efficacy or tolerability?

Do you think PARP inhibitors will have a future role in earlier-stage disease, including the localized setting?

Agenda

Module 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Shore

Module 2: Current Hormonal Treatment for Metastatic HSPC (mHSPC) — Dr Petrylak

Module 3: Current and Future Role of PARP Inhibitors for Metastatic Prostate Cancer (mPC) — Dr Agarwal

Module 4: Emerging Role of AKT Inhibition for Patients with mHSPC — Dr Heath

Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

MAYO CLINIC

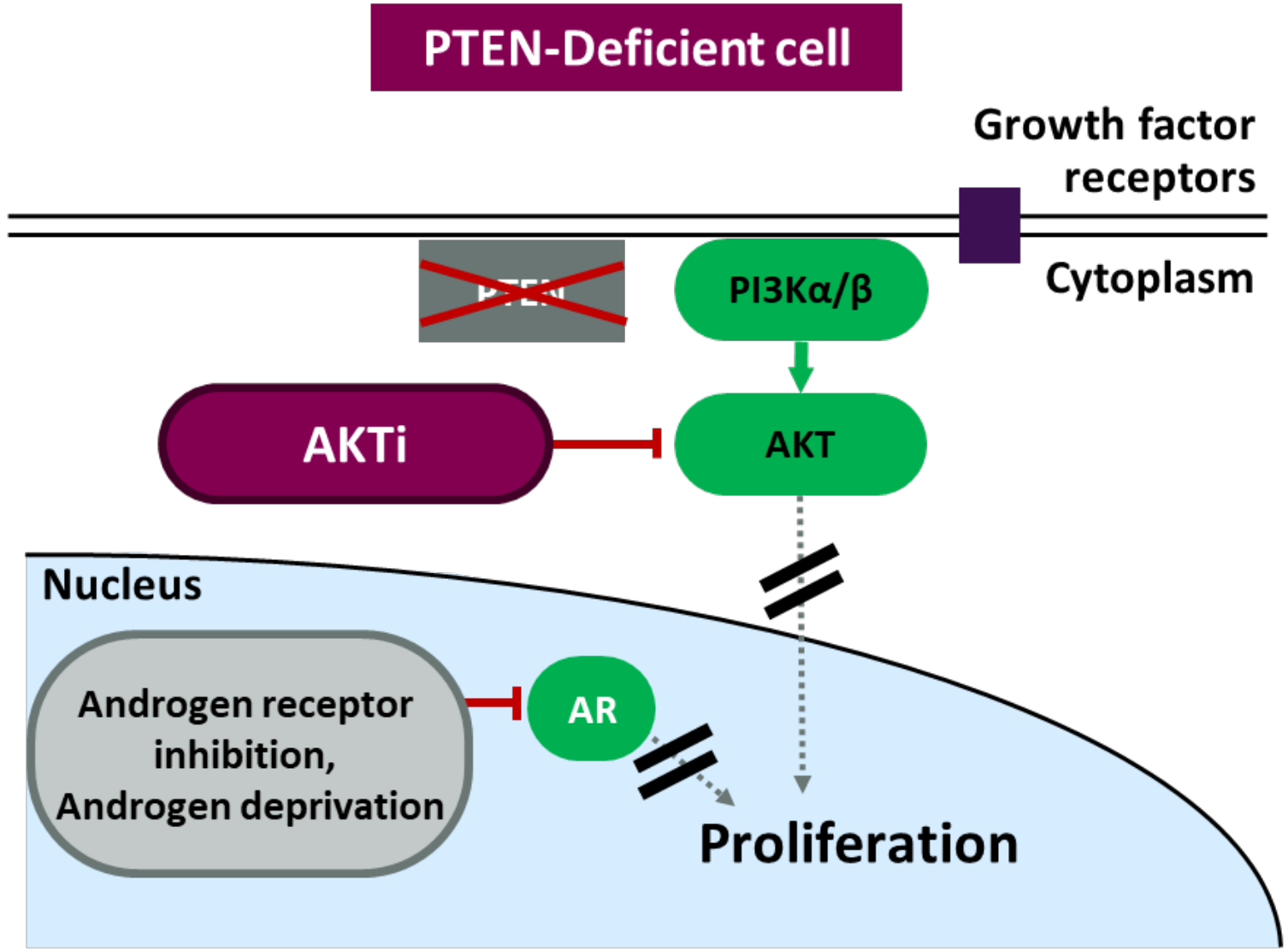
EMERGING ROLE OF AKT INHIBITION IN PATIENTS WITH mHSPC

Elisabeth Heath, MD, FACP

Professor of Oncology
Chair, Department of Oncology
Rochester, MN

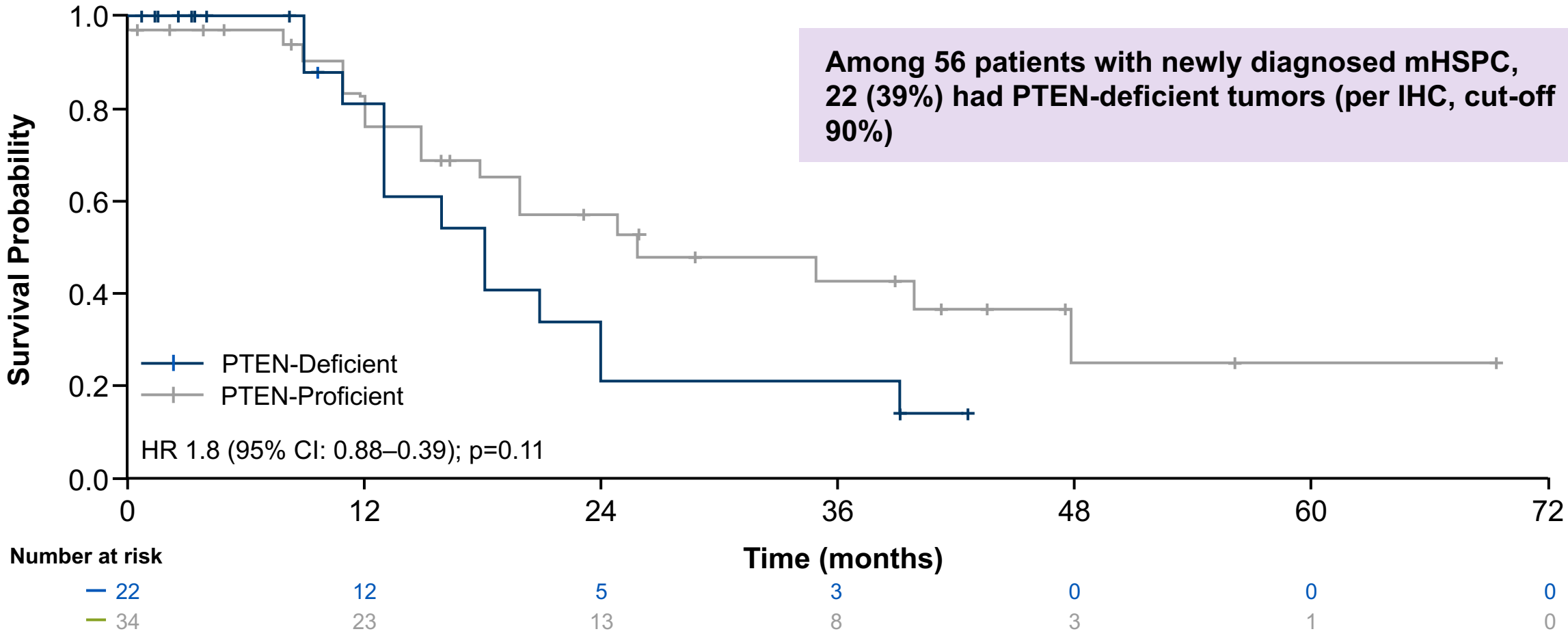
PTEN-DEFICIENCY IN mHSPC PROVIDES ADDITIONAL DRIVER OF PROLIFERATION: *BIOLOGIC RATIONALE FOR DUAL PATHWAY TARGETING*

- PTEN-deficiency leads to activation of the PI3K-AKT pathway
- PI3K-AKT signaling provides a complimentary driver of proliferation



AR, androgen receptor; AKT, protein kinase B; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog. Carver st et al. Cancer Cell 2011;575-586. Crumbaker M et al. Cancers;2017:34. Kaarbo M et al. Cell Oncol 2010;21:11-27. Li L et al. Br J Cancer 2011;104:19-23. Marques RB et al. Eur Urol 2015;1177-1185.

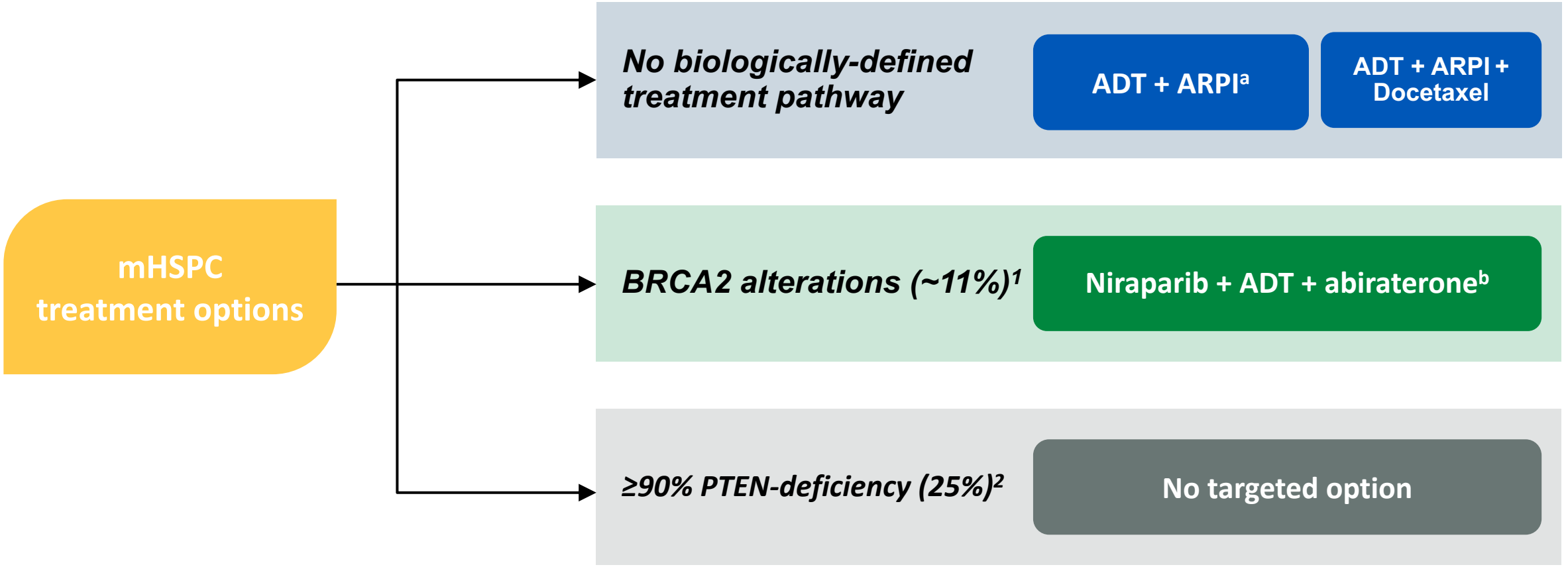
PTEN DEFICIENCY IN mHSPC IS ASSOCIATED WITH SHORTER TIME TO CASTRATION RESISTANCE



Among 56 patients with newly diagnosed mHSPC, 22 (39%) had PTEN-deficient tumors (per IHC, cut-off 90%)

Thouvenin J, et al. Poster presented at the 2021 European Society for Medical Oncology Congress; September 16-21, 2021 [virtual]; Poster 624P

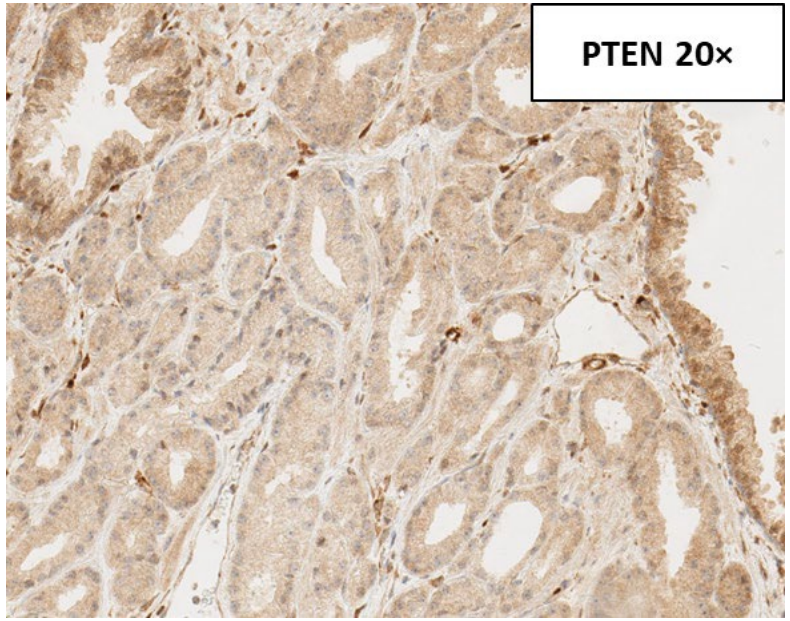
EVOLVING TREATMENT PARADIGM MOVING TOWARD BIOLOGICALLY-DEFINED SUBPOPULATIONS



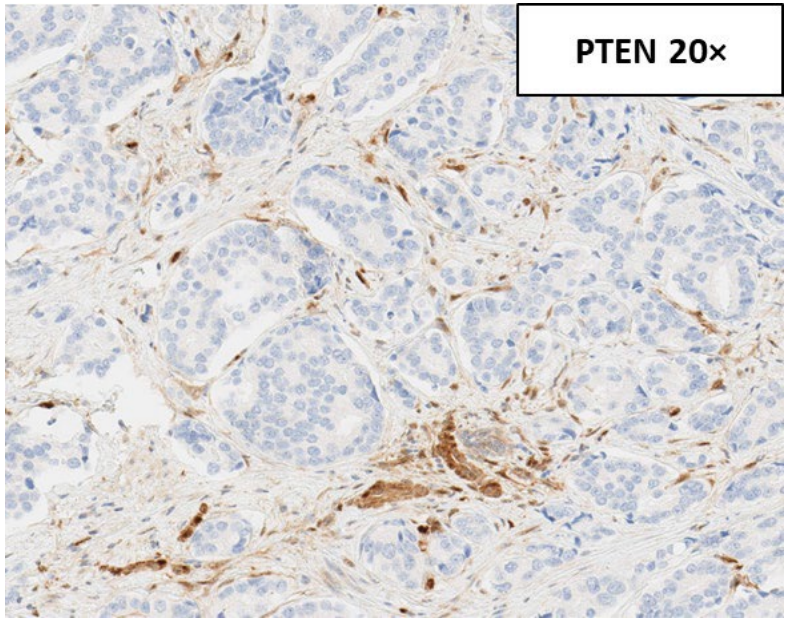
[a] ARPIs include: abiraterone, darolutamide, enzalutamide, and apalutamide; [b] For BRCA2-mutated tumors;
[1] Olmos D, et al. Ann Oncol. 2025;36(10):1190-1202; [2] Lenis A, et al. Clin Cancer Res. 2024;30(17):3894-3903.

DETECTING PTEN DEFICIENCY IN CLINICAL PRACTICE: ROLE OF IMMUNOHISTOCHEMISTRY (IHC)

PTEN-Proficient
(>10% of viable malignant cells with any cytoplasmic staining)



PTEN-Deficient
(≥90% of viable malignant cells with no cytoplasmic staining)



VENTANA PTEN (SP218) RxDx Assay Interpretation Guide for Prostate Adenocarcinoma.

IHC offers the most reliable method to identify patients with PTEN-deficient tumors suitable for treatment with AKT inhibitors

IHC

Laboratory technique that uses antibodies to detect antigens (markers) in a sample of tissue[1]

- ✓ Less expensive and less time-consuming than NGS[2]
- ✓ 2.5× less biopsy sample/tissue required than NGS[3,4]
- ✓ Can detect PTEN protein levels compromised by mutations in the gene or miRNA or epigenetic-regulated mechanisms, undetectable by NGS[5,6]
- ✓ Low testing failure rates of ~5%[7]
- ✓ High concordance with NGS for detecting PTEN deficiency (85.5%)[8]
- x Dysfunctional PTEN protein as a result of genetic point mutations, is still detected by IHC at the protein level[9]

NGS

Technology used for cfDNA and RNA sequencing and variant/mutation detection[10,11]

- ✓ Can analyse multiple mutation targets at the same time[10]
- x Longer turnaround time and higher associated costs than IHC[2]
- x High *PTEN* testing failure rates (~30%)[2]
- x May underestimate the frequency of PTEN deficiency[6]
- x Requires more tumor tissue than IHC[2]
- x Full sequencing of the gene is required to reliably detect *PTEN* alterations due to gene deletions or rearrangements[12]

cfDNA, cell-free DNA; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; miRNA, microRNA; mPC, metastatic prostate cancer; NGS, next-generation sequencing; PTEN, phosphatase and tensin homologue.

1. NIH. Immunohistochemistry. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunohistochemistry (accessed October 2024); 2. Tsao MS, Yatabe Y. *J Thorac Oncol* 2019;14:2035–2038; 3. Foundation Medicine. Specimen Instructions. https://www.foundationmedicine.com/sites/default/files/media/documents/2024-04/F1CDx_Specimen_Instructions.pdf (accessed November 2024); 4. Foundation Medicine. IHC Specimen Instructions. https://www.foundationmedicine.com/media/459/fmi-view (accessed November 2024); 5. Wise HM, et al. *Clin Sci* 2017;131:197–210; 6. de Bono JS, et al. *Clin Cancer Res* 2019;25:928–936; 7. Jamaspishvili T et al. *Nat Rev Urol.* 2018;15:222–234; 8. de Bono J, et al. Presented at ASCO Genitourinary Cancers Symposium 2021; 9. Wang L, et al. *Int J Gynecol Pathol* 2022;41:12–19; 10. Qin D. *Cancer Biol Med* 2019;16:4–10; 11. Al-Toubat M, et al. *Urol Oncol* 2023;41:455.e7–455.e15; 12. Li X, et al. Poster presented at: San Antonio Breast Cancer Symposium®; December 10–13, 2024; San Antonio, TX.

CAPItello-281 Study Design

A global, multicentre, randomized, double-blind, Phase 3 study

Patients with PTEN deficient *de novo* mHSPC

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

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

1,012 patients (R 1:1)

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

Primary endpoint

- **Investigator assessed rPFS**

Secondary endpoints

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

Exploratory *post-hoc* PTEN deficiency subgroups

Stratification factors:†

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

Study timeline

Enrolment period
13 July 2020–5 Feb 2024

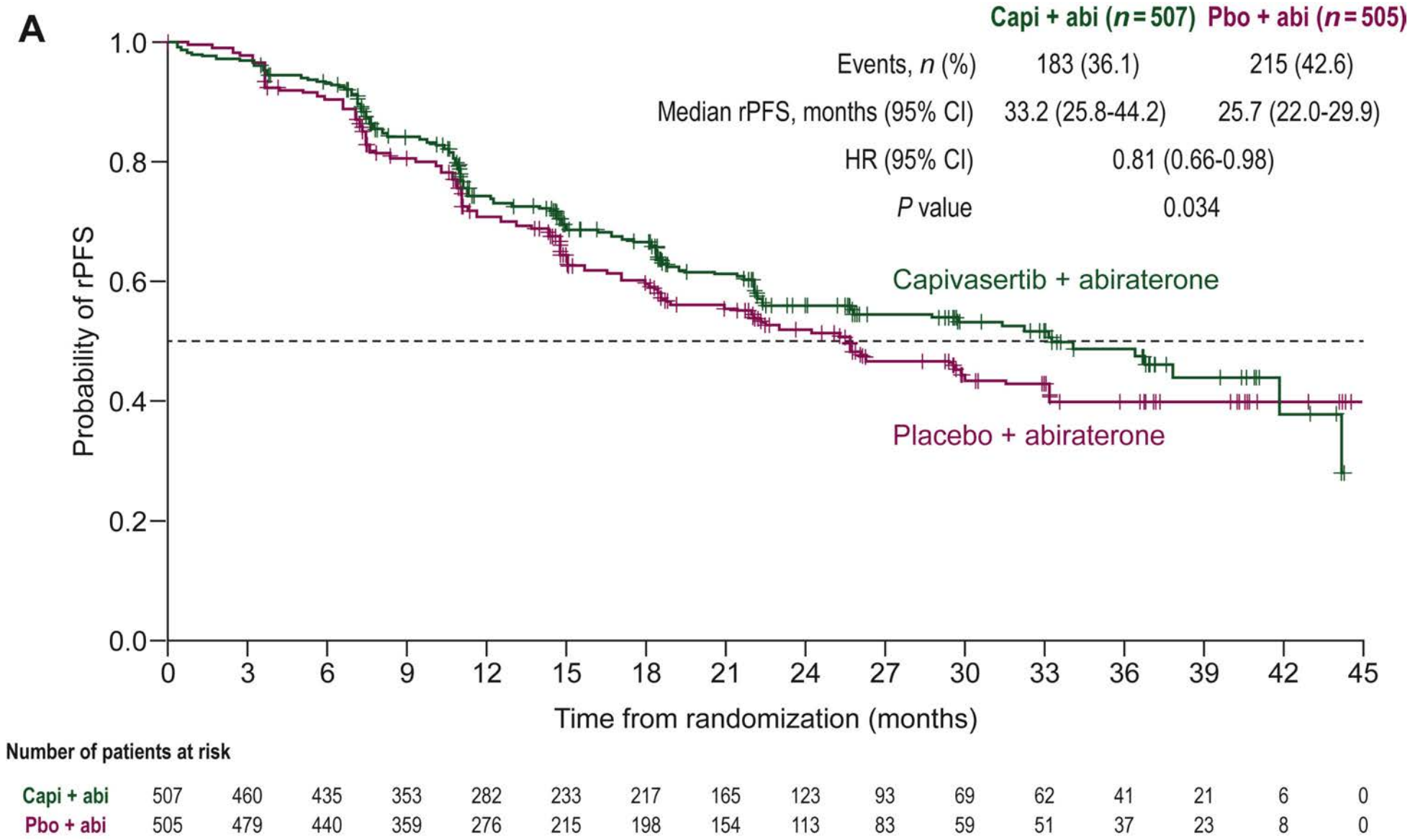
Current analysis

Primary rPFS DCO
7 Oct 2024
Median rPFS follow-up:‡ ~18 mo

Final OS DCO
Planned for 522 deaths
(52.2% maturity)

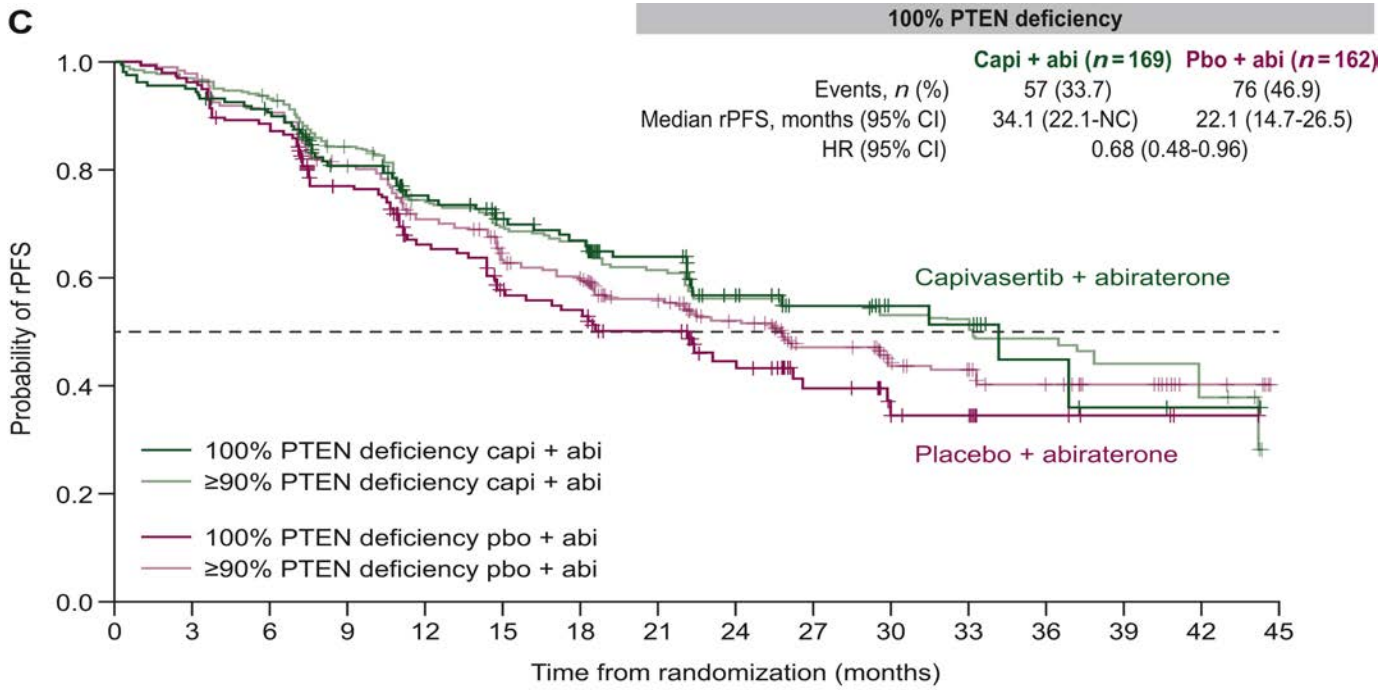
Fizazi K et al. ESMO 2025;Abstract 2383O

INCREASED RADIOGRAPHIC PROGRESSION FREE SURVIVAL



Fizazi K et al. 2026. Annals of Oncology;37:53-68.

rPFS FOR PTEN CUTOFFS >90%

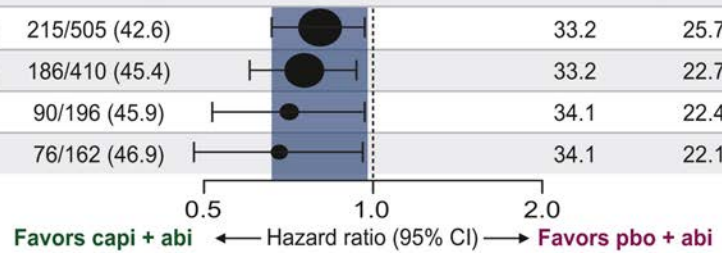


Number of patients at risk (100% PTEN deficiency)

Capi + abi	169	152	142	105	90	76	68	51	34	25	16	15	7	2	1	0
Pbo + abi	162	151	137	104	79	64	59	45	30	21	12	10	7	3	1	0

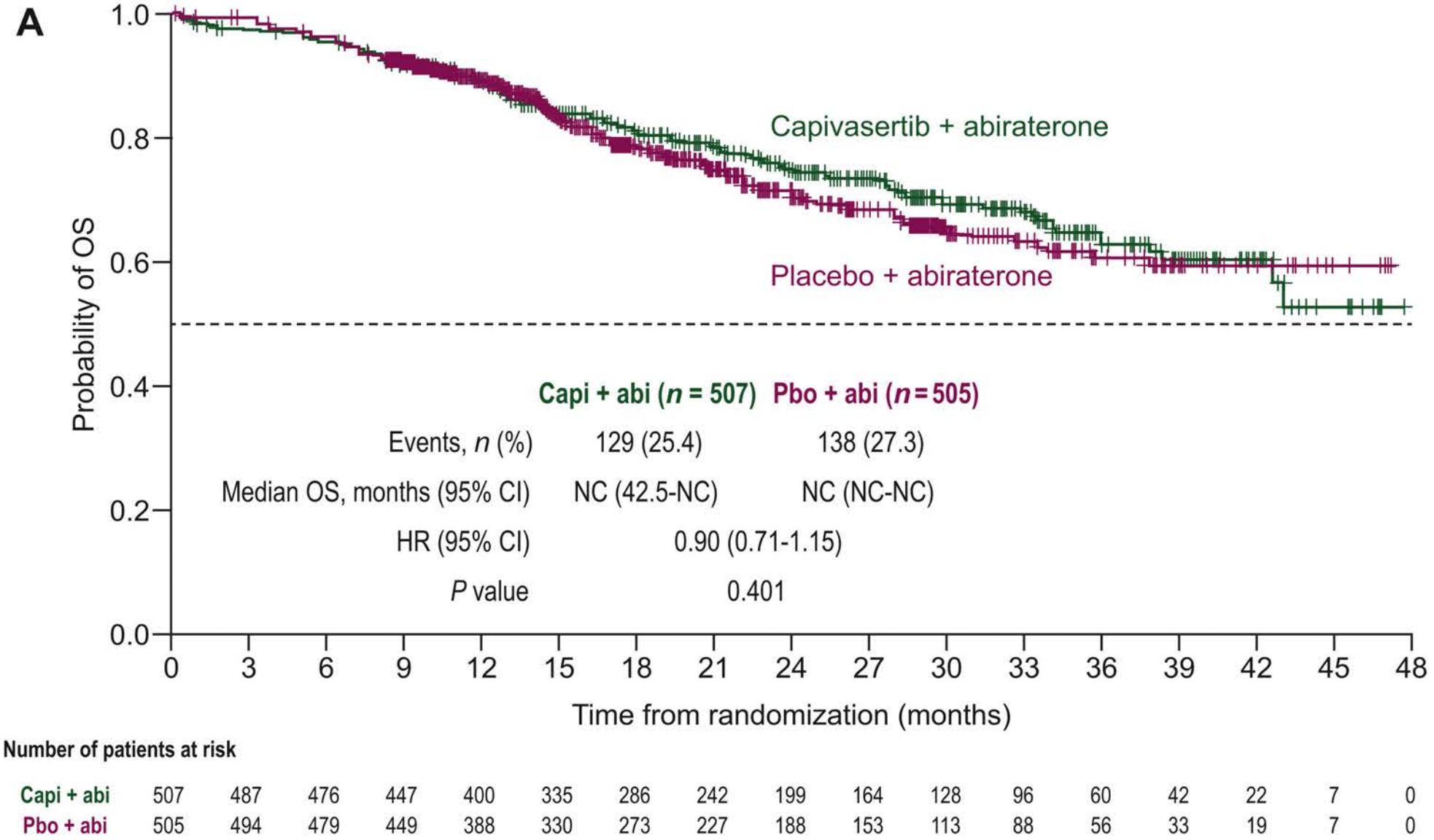
D

	Number of events/number of patients (%)		Median, months		
	Capi + abi	Pbo + abi	Capi + abi	Pbo + abi	HR (95% CI)
***Post hoc* analysis**					
All randomized patients	183/507 (36.1)	215/505 (42.6)	33.2	25.7	0.81 (0.66-0.98)
PTEN score ≥95%	146/404 (36.1)	186/410 (45.4)	33.2	22.7	0.75 (0.60-0.94)
PTEN score ≥99%	69/205 (33.7)	90/196 (45.9)	34.1	22.4	0.71 (0.52-0.97)
PTEN score 100%	57/169 (33.7)	76/162 (46.9)	34.1	22.1	0.68 (0.48-0.96)



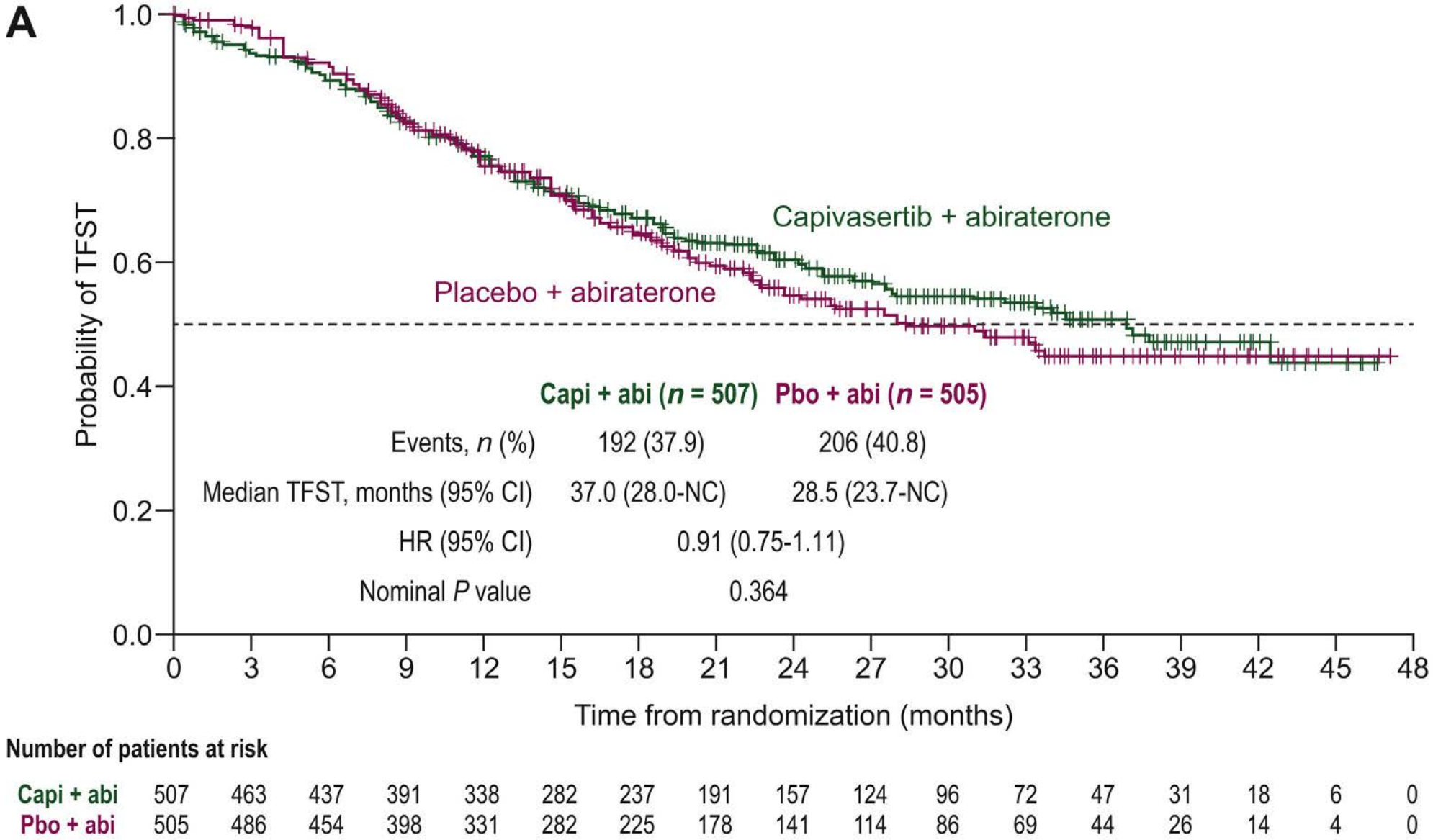
Fizazi K et al. 2026. Annals of Oncology;37:53-68.

OVERALL SURVIVAL



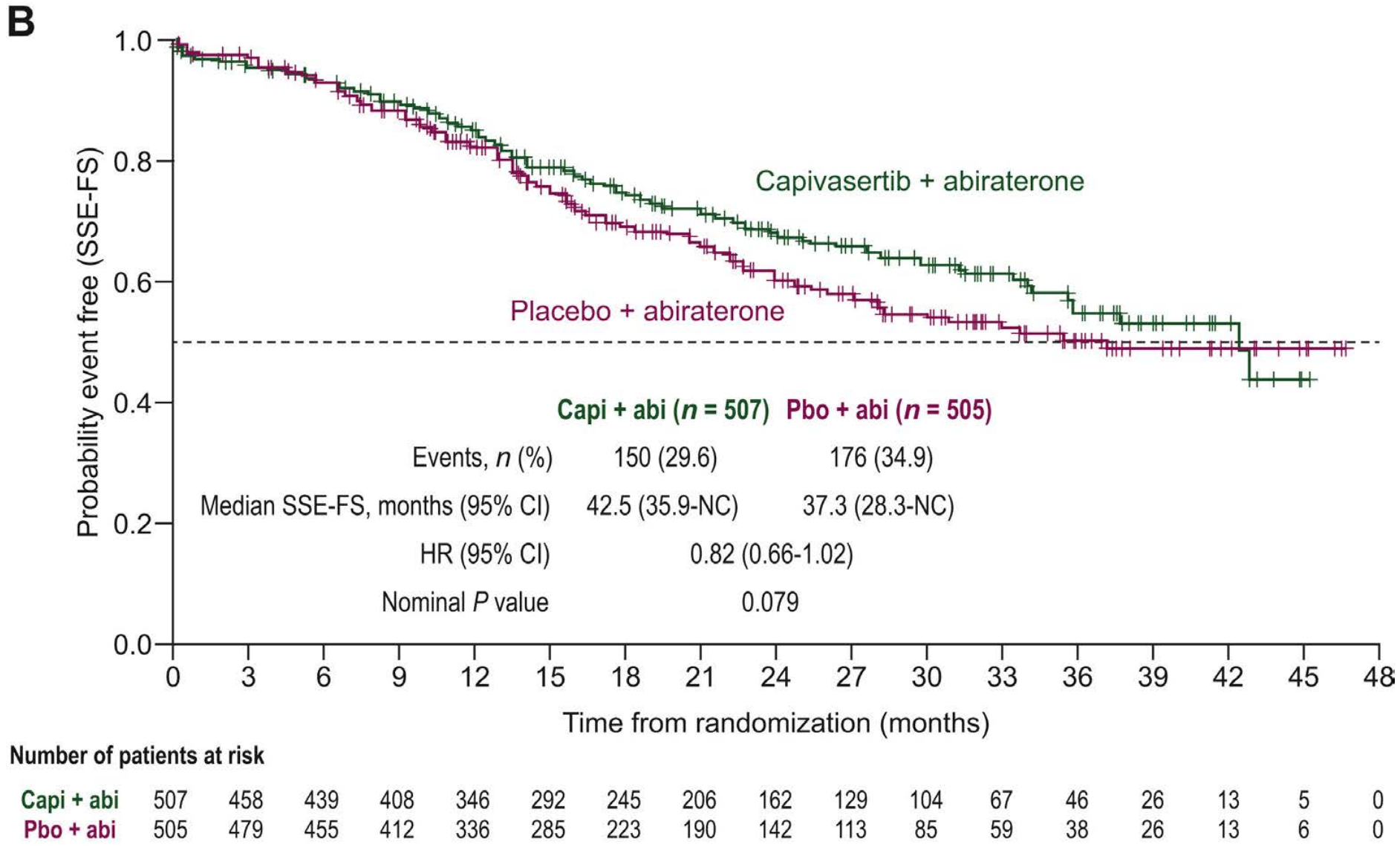
Fizazi K et al. 2026. Annals of Oncology;37:53-68.

INCREASED TIME TO FIRST SUBSEQUENT THERAPY



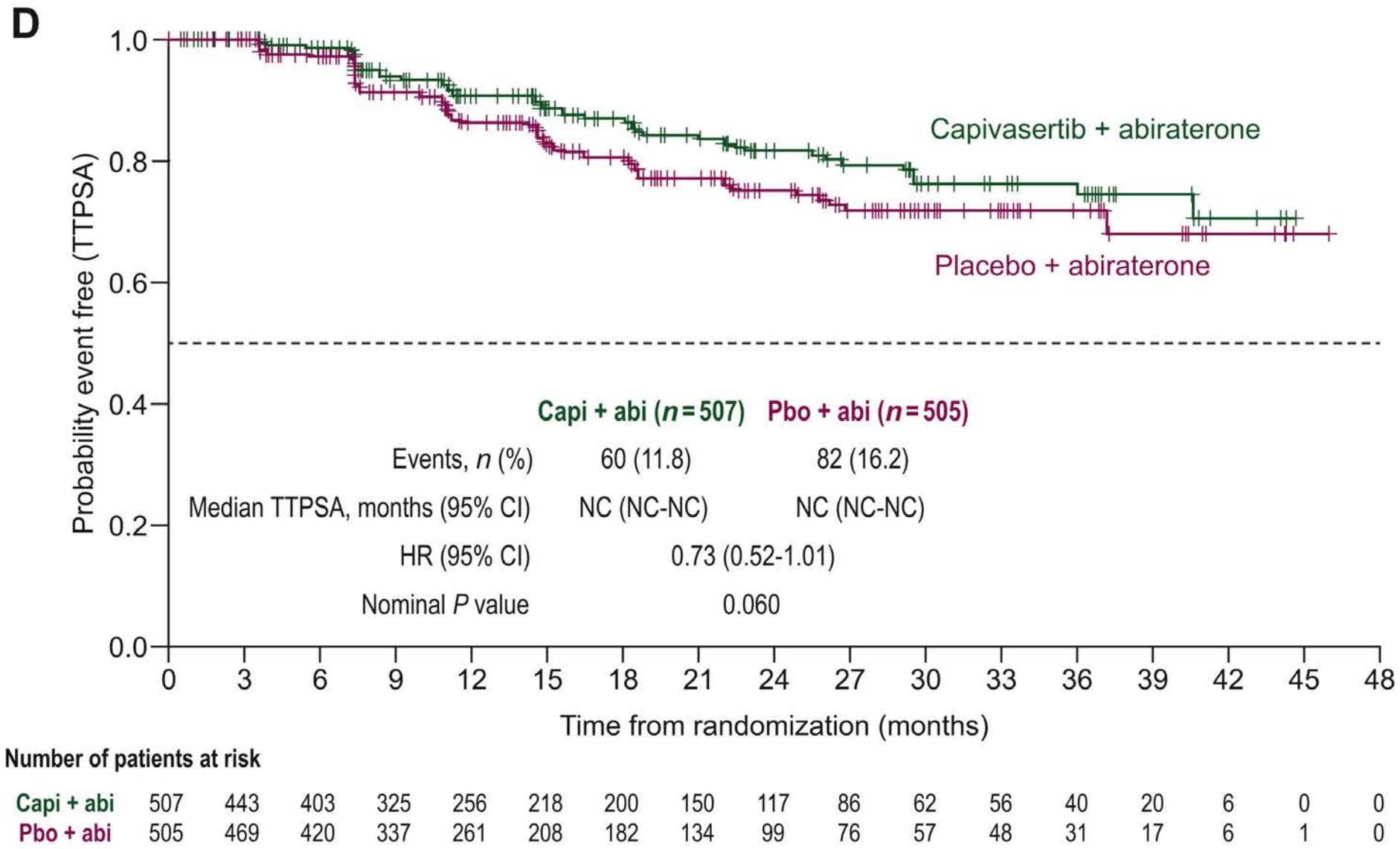
Fizazi K et al. 2026. Annals of Oncology;37:53-68.

INCREASED TIME TO FIRST SYMPTOMATIC SKELETAL EVENT



Fizazi K et al. 2026. Annals of Oncology;37:53-68.

TIME TO PSA PROGRESSION

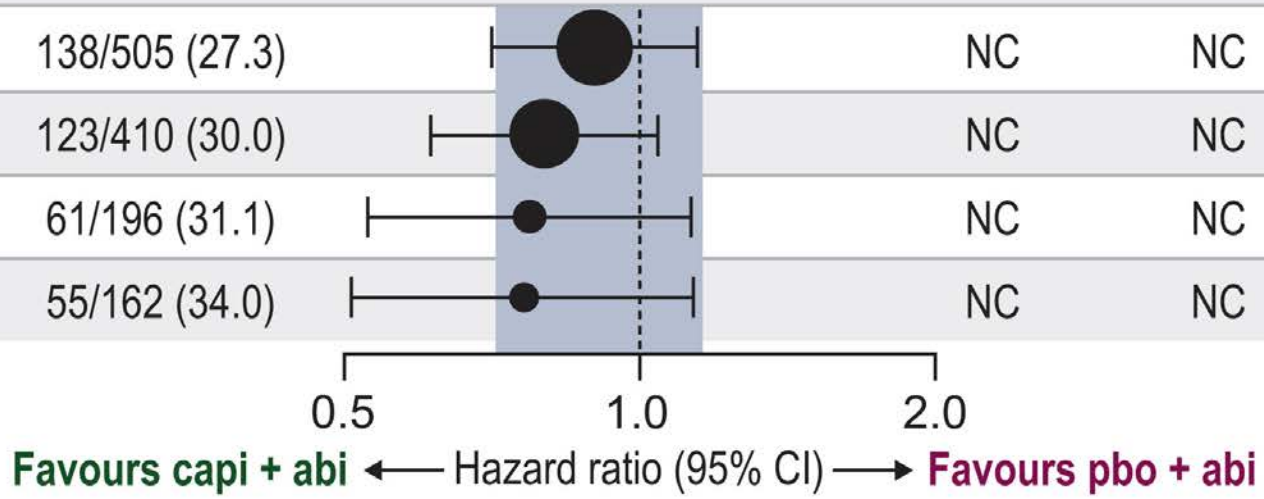


Fizazi K et al. 2026. Annals of Oncology;37:53-68.

POST HOC ANALYSIS FOR LOSS OF PTEN CUT-OFFS

C

	Number of events/number of patients (%)		Median, months		
	Capi + abi	Pbo + abi	Capi + abi	Pbo + abi	HR (95% CI)
***Post hoc* analysis**					
All randomized patients	129/507 (25.4)	138/505 (27.3)	NC	NC	0.90 (0.71, 1.15)
PTEN score ≥95%	101/404 (25.0)	123/410 (30.0)	NC	NC	0.80 (0.62, 1.04)
PTEN score ≥99%	50/205 (24.4)	61/196 (31.1)	NC	NC	0.77 (0.53, 1.12)
PTEN score 100%	43/169 (25.4)	55/162 (34.0)	NC	NC	0.77 (0.51, 1.14)



Fizazi K et al. 2026. Annals of Oncology;37:53-68.

SAFETY SUMMARY

n (%)	Capi + abi (n=503)	Pbo + abi (n=503)
Any AE	497 (98.8)	463 (92.0)
Any AE Grade ≥3	337 (67.0)	203 (40.4)
Any SAE	214 (42.5)	131 (26.0)
Any AE leading to death*	36 (7.2)	26 (5.2)
Any AE leading to discontinuation of capivasertib/placebo	92 (18.3)	24 (4.8)
Any AE leading to discontinuation of abiraterone	48 (9.5)	27 (5.4)
Any AE leading to dose interruption of capivasertib/placebo	316 (62.8)	135 (26.8)
Any AE leading to dose interruption of abiraterone	238 (47.3)	127 (25.2)
Any AE leading to dose reduction of capivasertib/placebo	146 (29.0)	18 (3.6)
Any AE leading to dose reduction of abiraterone	49 (9.7)	27 (5.4)

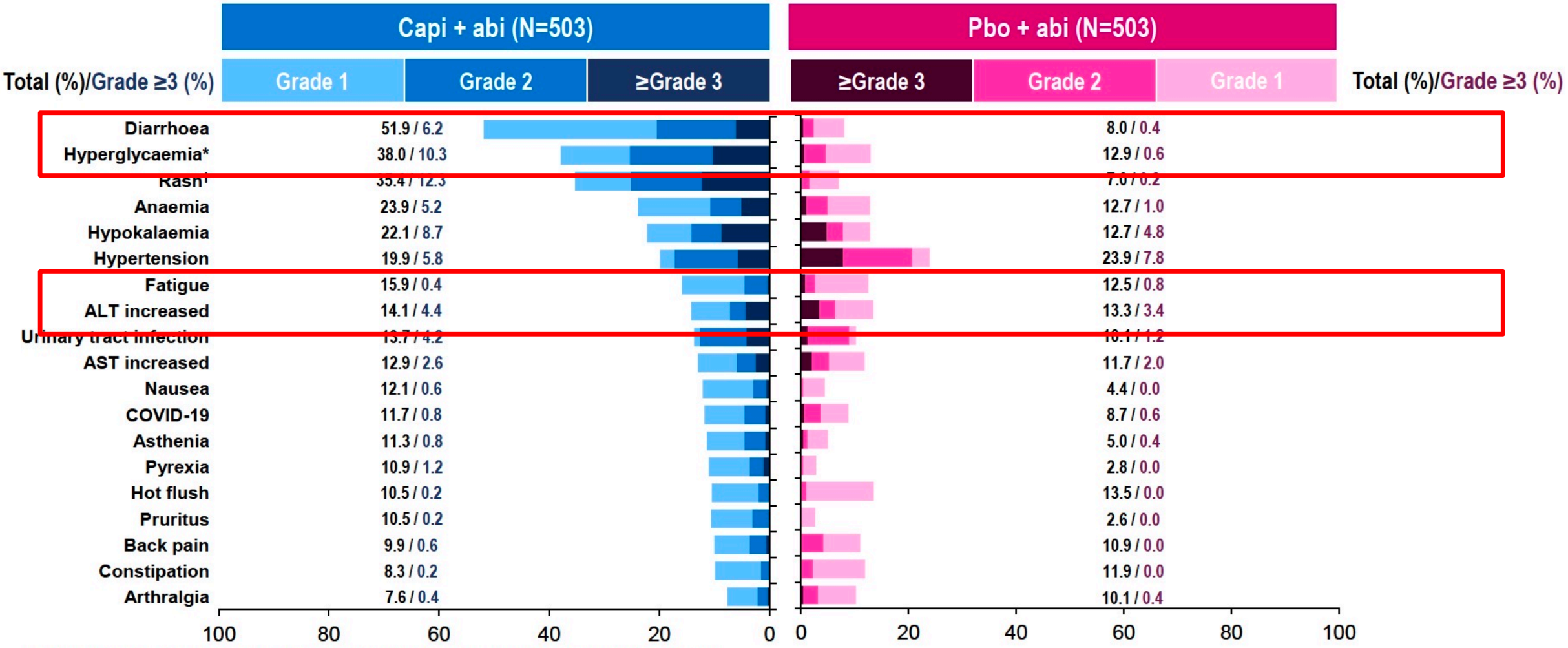
The adverse event profile of capivasertib plus abiraterone was consistent irrespective of PTEN deficiency cutoff

Median (range) total duration of treatment with capivasertib/placebo was **13.6 (0.1, 46.6) months** in the capi + abi arm, compared with **14.9 (0.1, 47.1) months** with pbo in the pbo + abi arm

*AEs leading to death, considered by the investigator to be related to capi/pbo were reported in 6 (1.2%) and 1 (0.2%) patient(s), respectively.
abi, abiraterone; AE, adverse event; capi, capivasertib; pbo, placebo; SAE, serious adverse event

Fizazi K et al. ESMO 2025;Abstract 2383O

CAPITELLO-281: ADVERSE EVENTS (≥ 10% OF PATIENTS)



Diabetic ketoacidosis was reported in 6 patients (1.2%) in the capi + abi arm, and 0 patients in the pbo + abi arm.

*Grouped term (includes the preferred terms of blood glucose increased, hyperglycaemia). †Grouped term (includes the preferred terms of erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic).

abi, abiraterone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; capi, capivasertib; pbo, placebo

Fizazi K et al. ESMO 2025;Abstract 2383O

CUTANEOUS ADVERSE EVENT MANAGEMENT

GRADE 1	< 10% MACULE/PAPULE WITH OR WITHOUT SYMPTOMS	• CONTINUE CAPIVASERTIB
GRADE 2	10-30% MACULE/PAPULE, WITH OR WITHOUT SYMPTOMS	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • RESUME CAPIVASERTIB AT THE SAME DOSE • PERSISTENT OR RECURRENT: REDUCE CAPIVASERTIB BY ONE LOWER DOSE
GRADE 3	> 30% MACULE/PAPULE, WITH MODERATE/SEVERE SYMPTOMS	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE • IF RECOVERY IN > 28 DAYS, RESUME CAPIVASERTIB AT ONE LOWER DOSE • FOR RECURRENT GRADE 3, PERMANENTLY DISCONTINUE CAPIVASERTIB
GRADE 4	NOT DEFINED	• PERMANENTLY DISCONTINUE CAPIVASERTIB

GASTROINTESTINAL ADVERSE EVENT MANAGEMENT

GRADE 1	< 4 STOOLS PER DAY	• CONTINUE CAPIVASERTIB
GRADE 2	4-6 STOOLS PER DAY	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE OR ONE DOSE LOWER AS CLINICALLY INDICATED • IF RECOVERY IN > 28 DAYS, RESUME AT ONE LOWER DOSE AS CLINICALLY INDICATED • FOR RECURRENCE, REDUCE CAPIVASERTIB BY ONE LOWER DOSE
GRADE 3	≥ 7 STOOLS PER DAY	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE OR ONE DOSE LOWER AS CLINICALLY INDICATED • IF RECOVERY IN > 28 DAYS, PERMANENTLY DISCONTINUE CAPIVASERTIB
GRADE 4	LIFE THREATENING	• PERMANENTLY DISCONTINUE CAPIVASERTIB

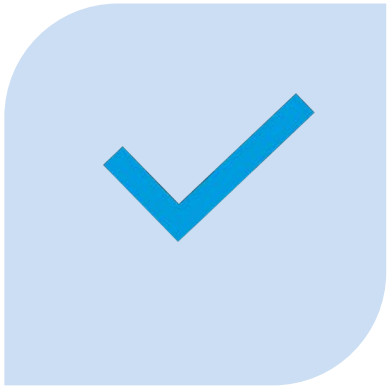
HYPERGLYCEMIA ADVERSE EVENT MANAGEMENT

FG > ULN-160 MG/DL OR HBA1C > 7%	• CONTINUE CAPIVASERTIB WITH NO DOSE ADJUSTMENT • CONSIDER INITIATION OR INTENSIFICATION OR ORAL ANTI-DIABETIC TREATMENT
FG > 500 OR LIFE THREATENING SEQUELAE OF HYPERGLYCEMIA AT ANY FG LEVEL	• FOR LIFE-THREATENING SEQUELAE OF HYPERGLYCEMIA OR FG PERSISTS AT ≥ 500 MG/DL AFTER 24 HOURS, PERMANENTLY DISCONTINUE CAPIVASERTIB • IF FG < 500 MG/DL WITHIN 24 HOURS, THEN FOLLOW GUIDANCE ABOVE

Clinically significant abnormalities of glucose metabolism as defined by any of the following:

- **Patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment ii. HbA1c ≥8.0% (63.9 mmol/mol)**

RECOMMENDED MONITORING FOR HYPERGLYCEMIA



BEFORE INITIATING TREATMENT WITH CAPIVASERTIB, TEST FG LEVELS, HBA1C, AND OPTIMIZE FG

AFTER INITIATING CAPIVASERTIB, MONITOR FG LEVELS ON DAY 3 OR 4 OF THE DOSING WEEK DURING WEEKS 1, 2, 4, 6, AND 8, THEN MONTHLY WHILE ON TREATMENT

MONITOR HBA1C Q 3 MONTHS

FATIGUE ADVERSE EVENT MANAGEMENT

GRADE 1	FATIGUE RELIEVED BY REST	• CONTINUE CAPIVASERTIB
GRADE 2	FATIGUE NOT RELIEVED BY REST, LIMITING INSTRUMENTAL ADL	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • RESUME CAPIVASERTIB AT THE SAME DOSE
GRADE 3	FATIGUE NOT RELIEVED BY REST, LIMITING SELF CARE ADL	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE • IF RECOVERY IN > 28 DAYS, RESUME CAPIVASERTIB AT ONE LOWER DOSE
GRADE 4	N/A	• PERMANENTLY DISCONTINUE CAPIVASERTIB

Second Opinion

Andrew J Armstrong, MD, ScM

Rana R McKay, MD, FASCO

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What type of testing do you use – or will you be using – to assess PTEN deficiency? Do you believe that quantitative IHC assays present an advantage (eg, 90% vs 99% staining)?

Given the adverse prognostic impact of PTEN deficiency and the possibility of clinical and imaging progression without PSA progression in these patients, how do you follow them?

QUESTIONS FOR THE FACULTY

If capivasertib is approved, will you offer it as an option to all eligible patients? Would you consider adding it for a patient with high-volume APMS mPC and PTEN deficiency who had a suboptimal response to darolutamide/ADT/docetaxel?

Second Opinion

Joyce O'Shaughnessy, MD

Neil Love, MD

QUESTIONS FOR THE FACULTY

How do the adverse events associated with capivasertib compare clinically to those of other commonly used prostate cancer therapies (eg, ADT, ARPI, PARPi, docetaxel, lutetium Lu 177 vipivotide tetraxetan)?

Which preemptive strategies, if any, would you employ for a patient receiving capivasertib/abiraterone/prednisone/ADT?

Do you believe capivasertib can be safely used by a community-based urologist?

QUESTIONS FOR THE FACULTY

How will you approach the use of capivasertib for patients with a history of diabetes? Is there a baseline HbA1c at which you would not be comfortable starting this drug? To which patients will you recommend a continuous on-body glucose monitor?

In which situations will you hold capivasertib treatment, and when and how will you approach dose reductions?

Agenda

Module 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Shore

Module 2: Current Hormonal Treatment for Metastatic HSPC (mHSPC) — Dr Petrylak

Module 3: Current and Future Role of PARP Inhibitors for Metastatic Prostate Cancer (mPC) — Dr Agarwal

Module 4: Emerging Role of AKT Inhibition for Patients with mHSPC — Dr Heath

Module 5: Current and Future Use of Radiopharmaceuticals in mPC — Dr Saad

RTP RESEARCH TO PRACTICE

Current and Future Use of Radiopharmaceuticals in Metastatic Prostate Cancer

Fred Saad CQ MD FRCS FCAHS
Professor and Chairman, Department of Surgery,
Raymond Garneau Chair in Prostate Cancer
University of Montreal
Director of GU Oncology and Prostate Cancer Research
University of Montreal Hospital Center

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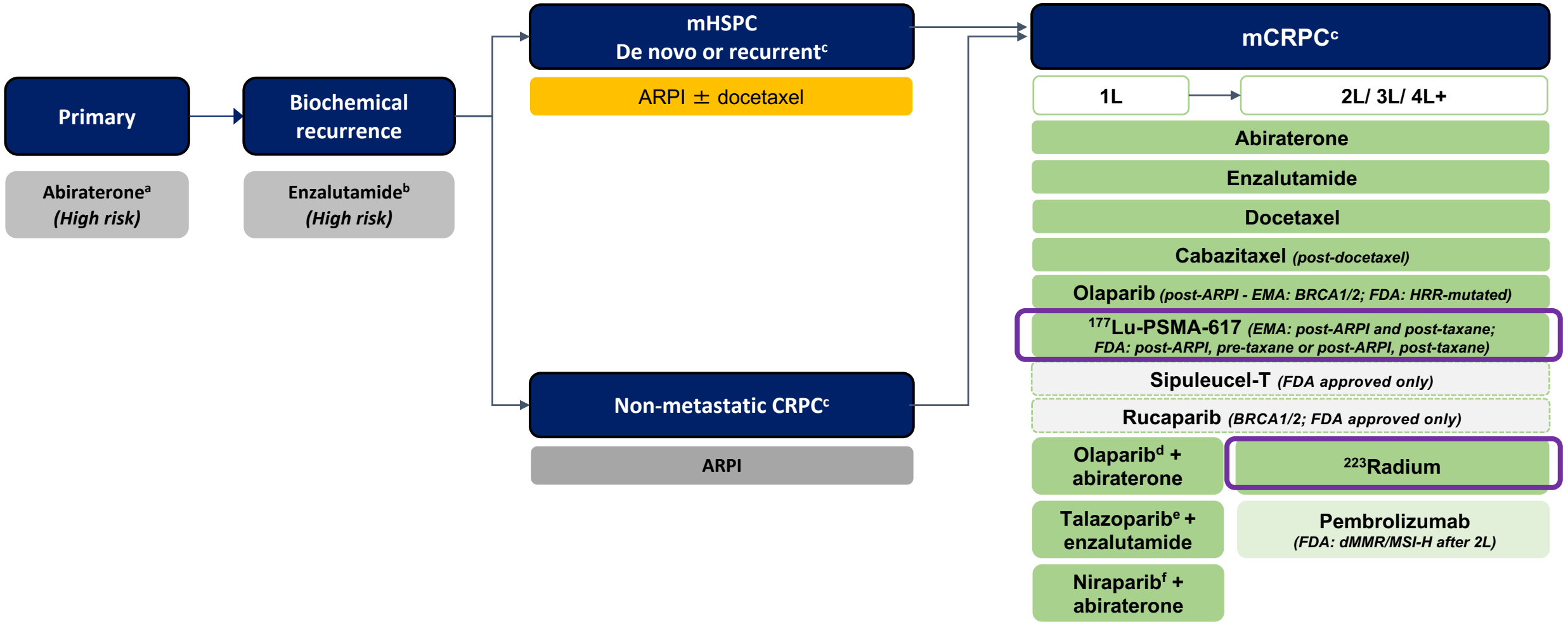
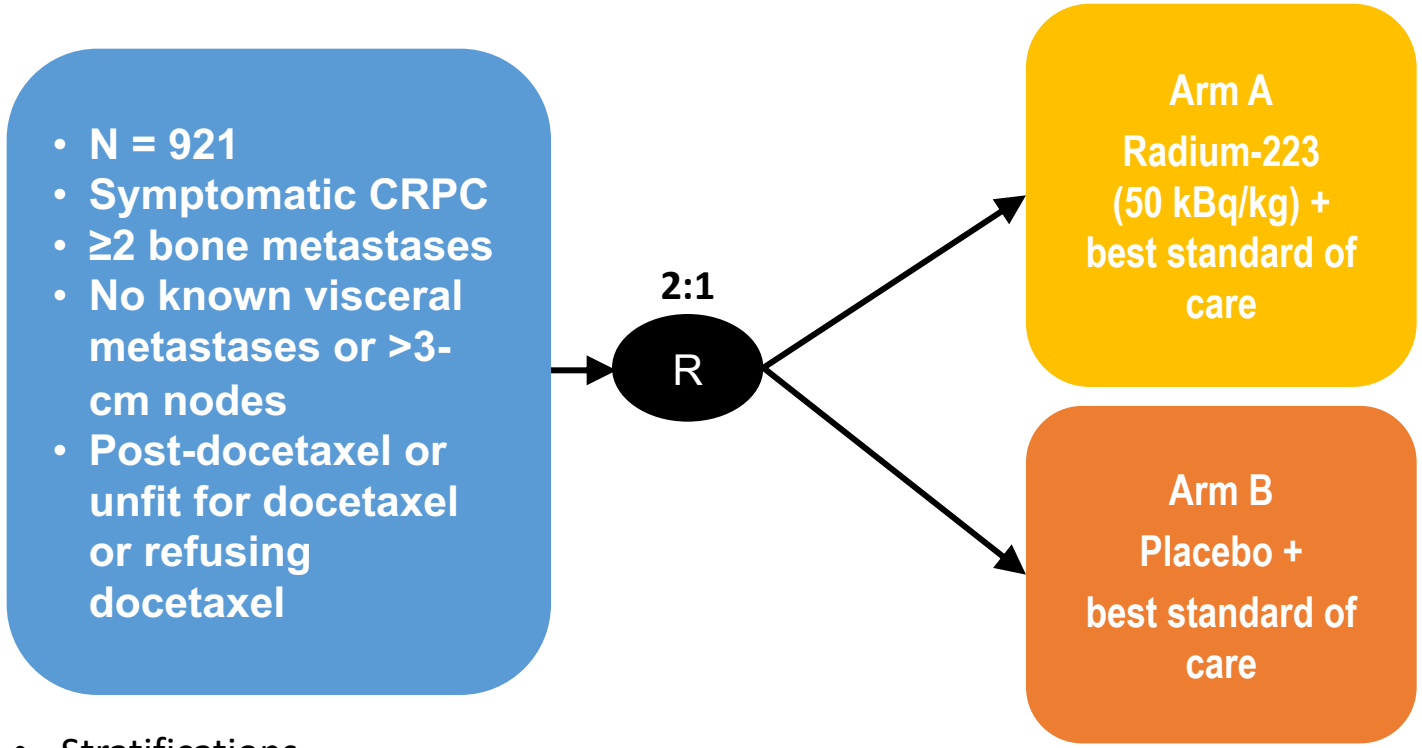
Systemic therapies for prostate cancer in 2026



Radium-223 in mCRPC: ALSYMPCA



Primary endpoint
Overall survival

- Stratifications
  - Total ALP <220 U/L vs ≥220 U/L
  - Bisphosphonates
  - Prior docetaxel

1. Parker C et al. *N Engl J Med*. 2013;369:213-223.

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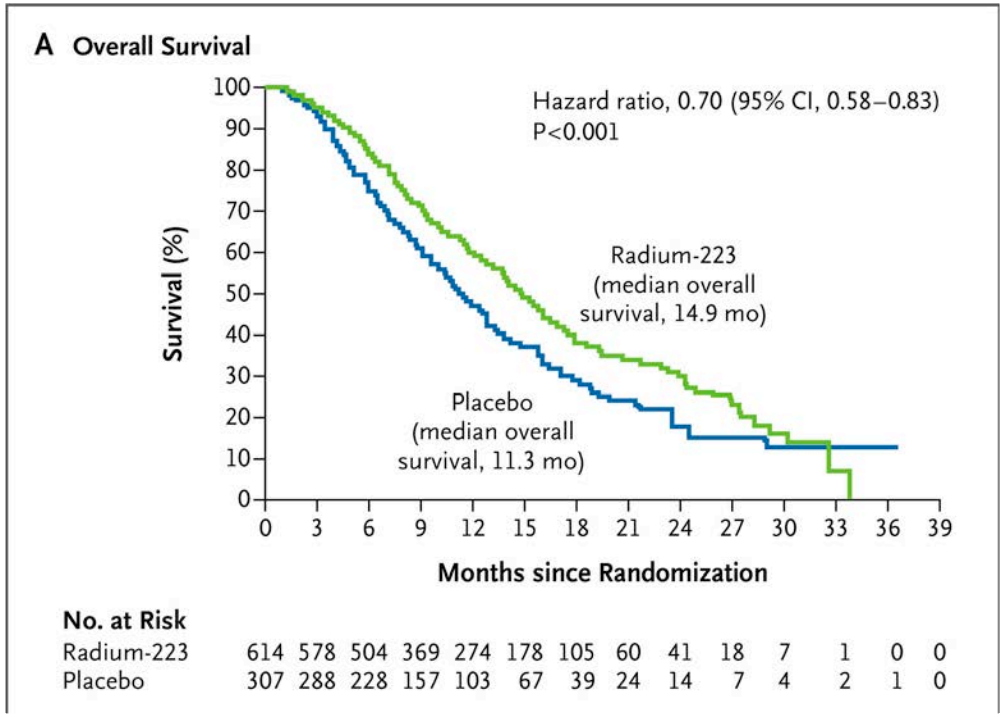
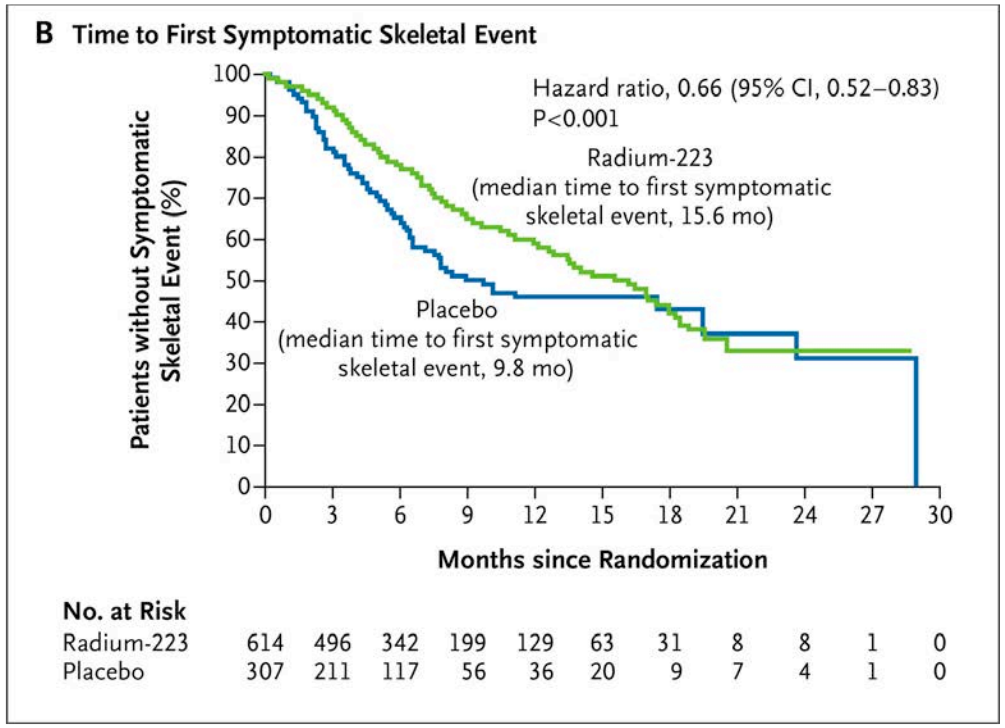
ALSYMPCA results

Overall Survival



Time to First SSE



Survival benefit seen in both pre and post docetaxel patients

Parker C et al. *N Engl J Med.* 2013;369:213-223 Hoskin et al. Lancet Oncol 2014;15:1397-406.

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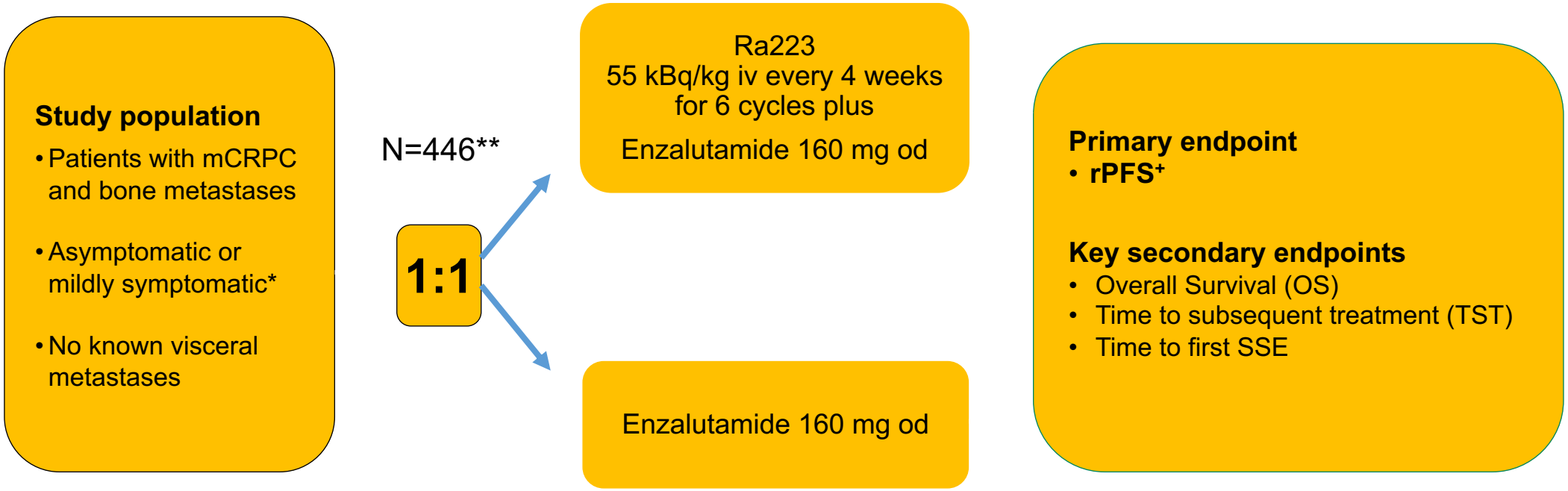
Does adding Radium to an ARPI improve outcome?

PEACE-3 STUDY DESIGN



Tombal B, et al. Ann Oncol. 2025 Sep;36(9):1058-1067.

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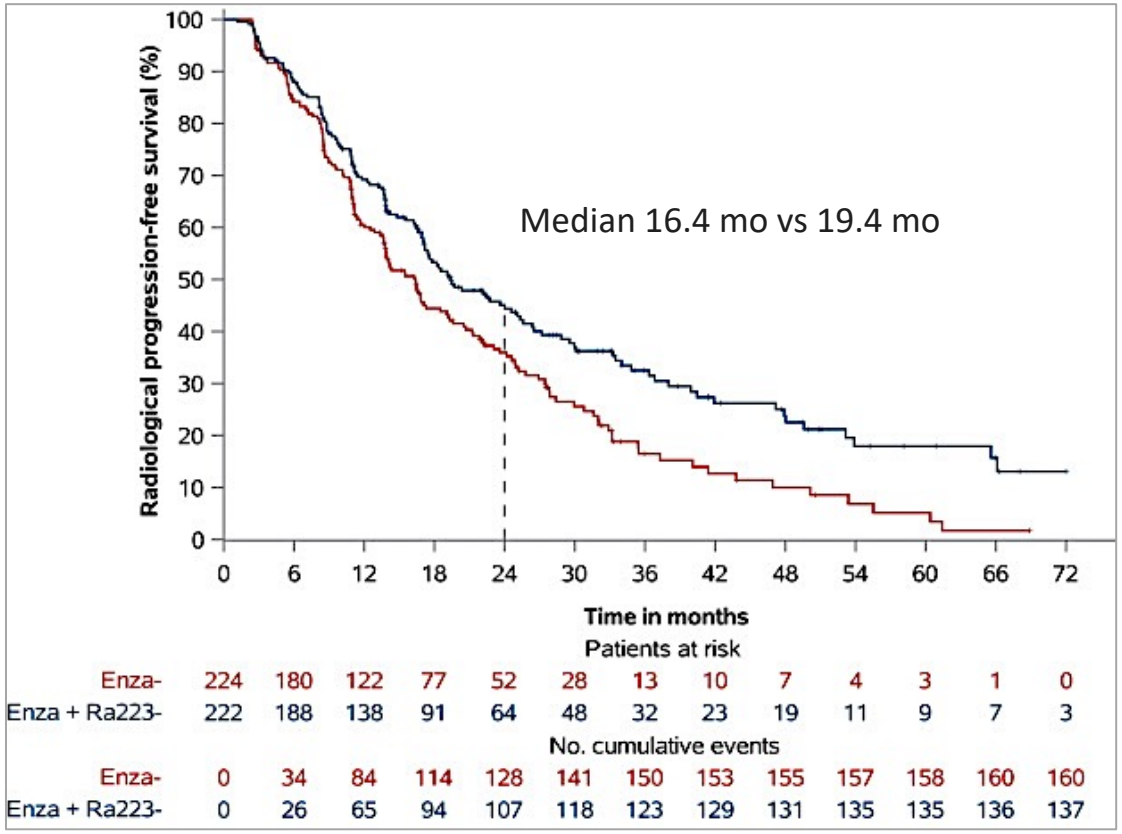
RESULTS

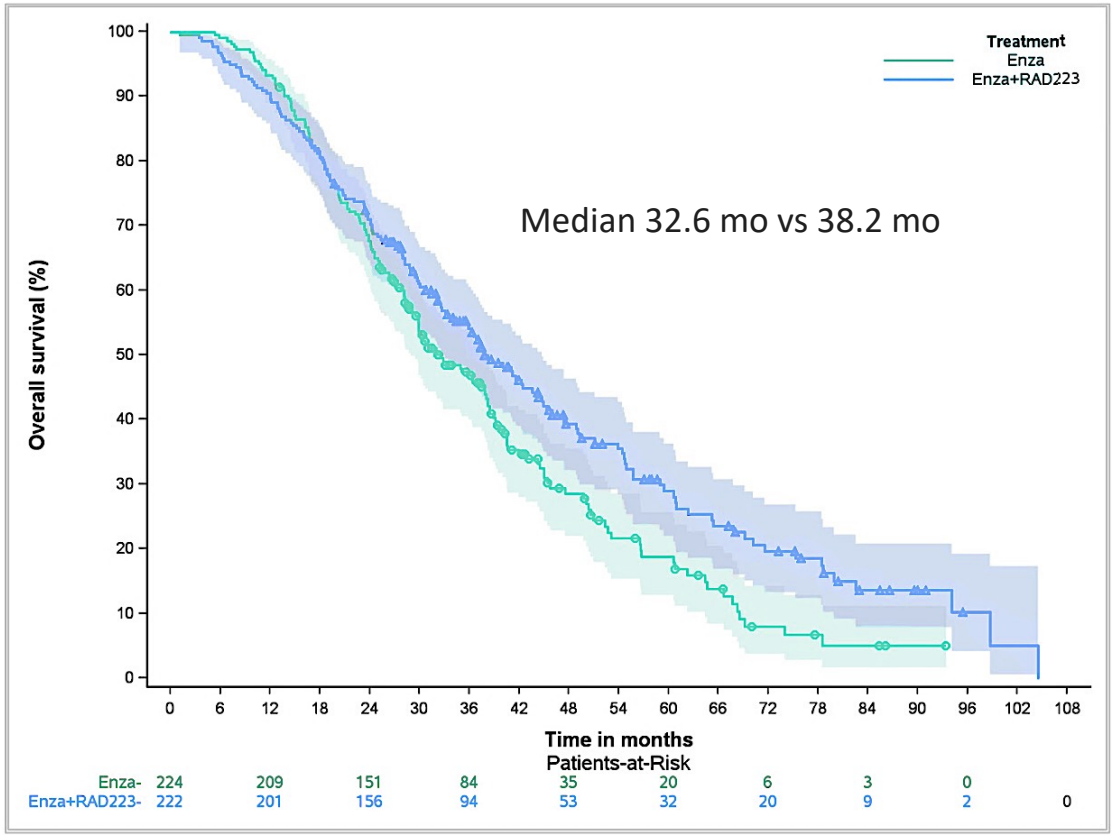
Primary endpoint: rPFS



HR 0.69 (95% CI 0.54-0.87, *P* = 0.0009),

Tombal B, et al. Ann Oncol. 2025 Sep;36(9):1058-1067.

Secondary endpoint: OS



HR 0.76 (95% CI 0.52-0.90, *P* = 0.01)

Gallardo E. et al. ASCO GU 2026

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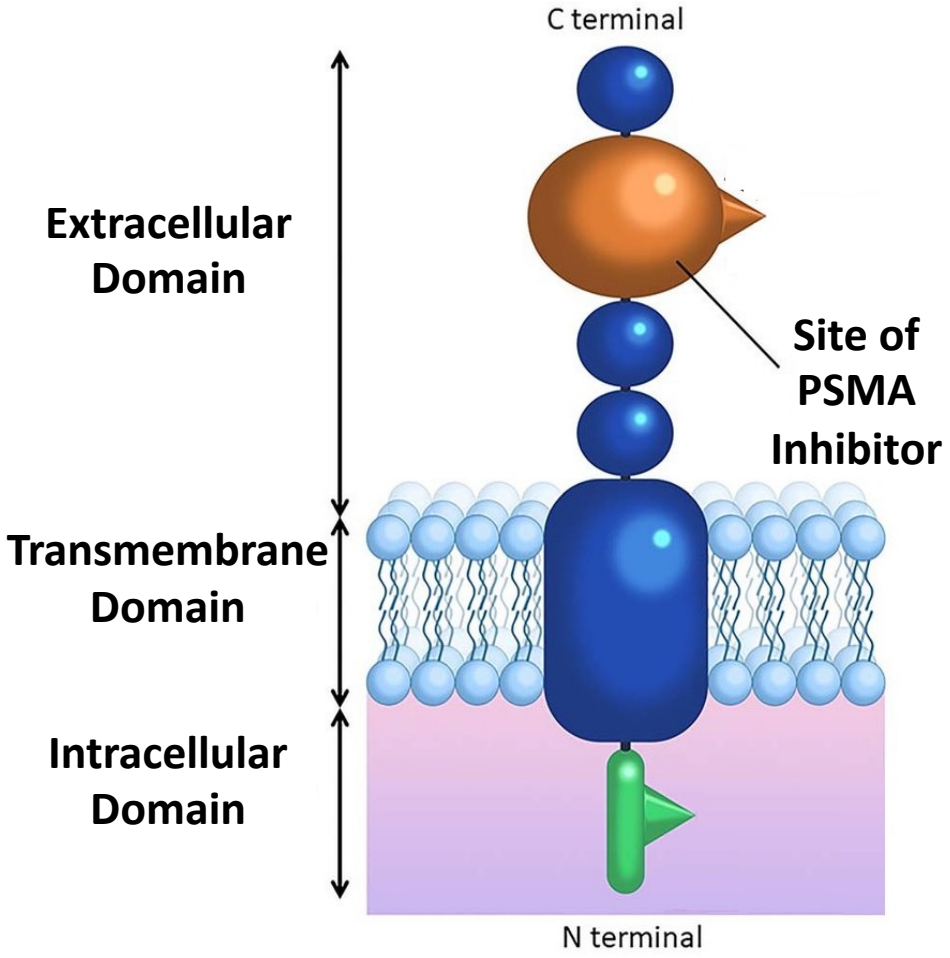
PSMA PET

- Overexpressed in prostate cancer
- Level of PSMA expression correlates with tumour stage and tumor grade
- Commonly used PSMA agents:
  - F-18 PyL, F-18 1007 and Ga-68 PSMA-11
- Excellent for precision therapeutics



Barrio, M., Expt Rev. Mol. Diagn. 2016; 16(11):1177-1188.
Tateishi, U., Jpn. J. Clin. Oncol. 2020; 50(4):349-356

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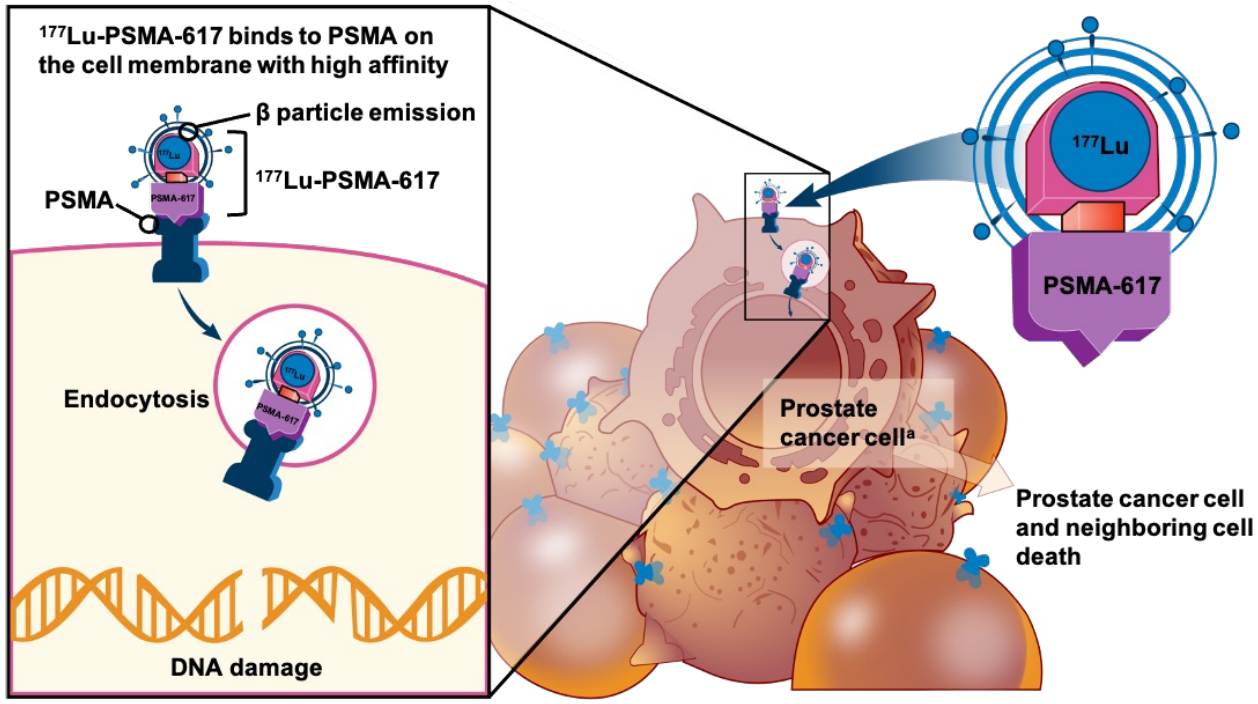
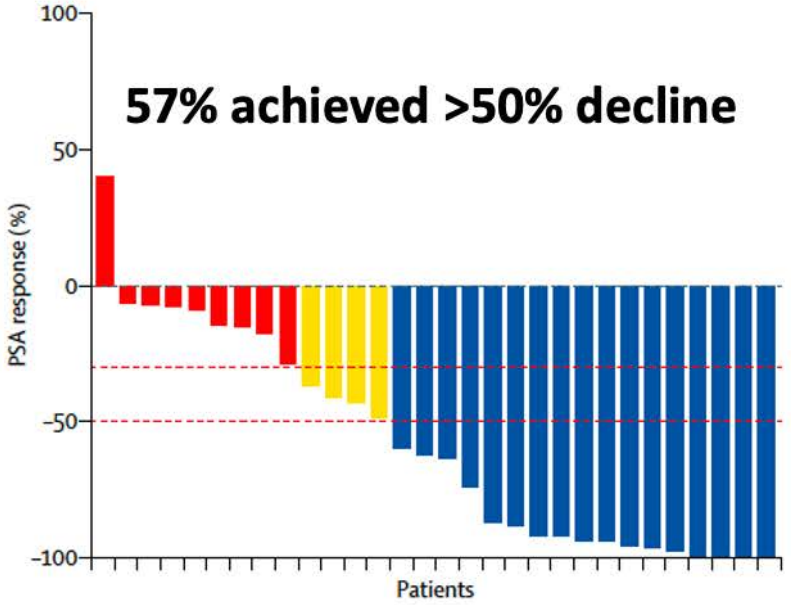
Lu-PSMA-617: A PSMA-targeted radioligand therapy



First single arm study: PSA endpoint

- N=30; mCRPC after taxane and ARPI
  - Eligible if one met had SUV > 1.5xLiver
  - Excluded if one met was FDG+/PSMA-
- 4 cycles of ^{177}Lu-PSMA-617
- Primary endpoint:
  - PSA response
  - Toxicity
- 82% had RECIST response



Hofman et al. Lancet Oncol Volume 19, Issue 6, June 2018, Pages 825-833

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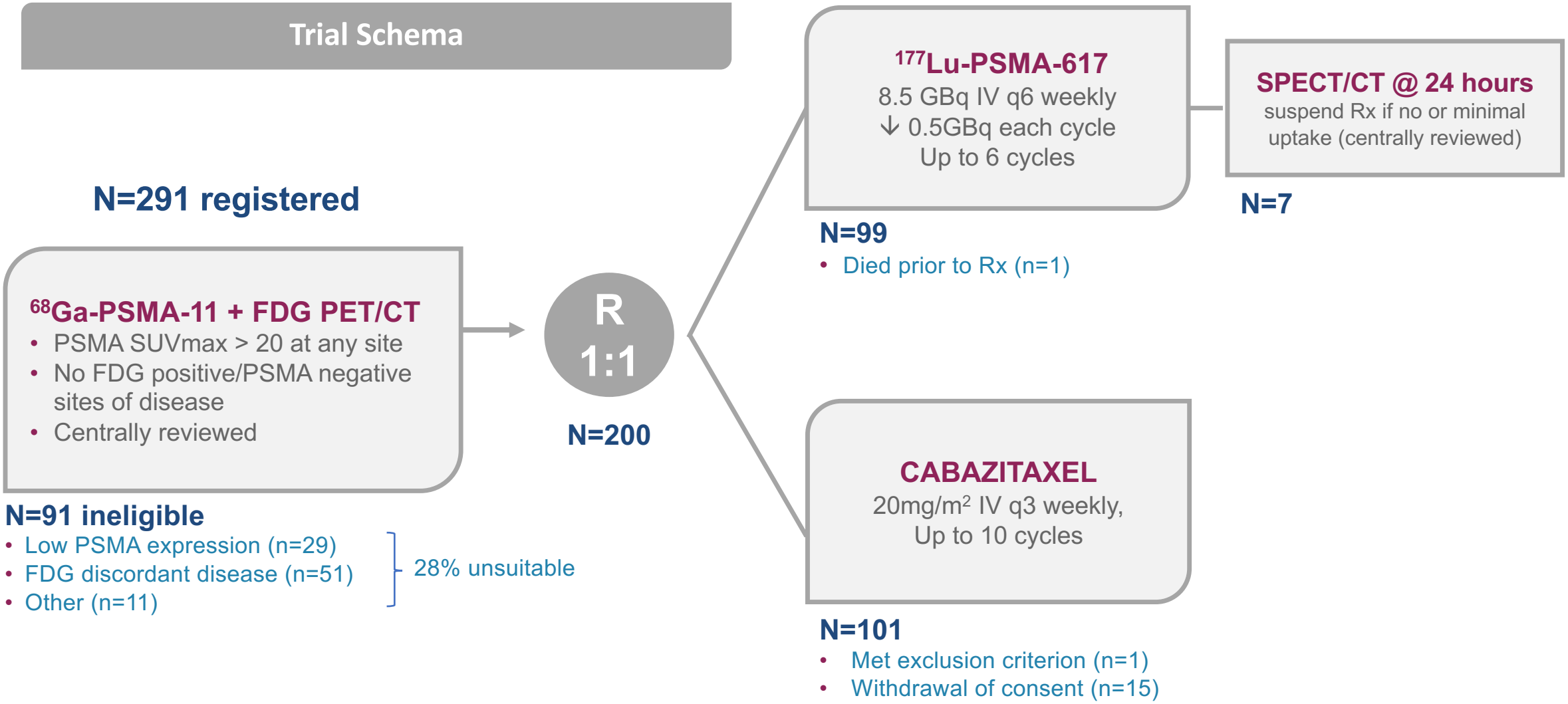
Phase 2 TheraP study: Lu-PSMA vs Cabazitaxel post Docetaxel



Hofman MS, et al. Lancet. 2021 Feb 27;397(10276):797-804

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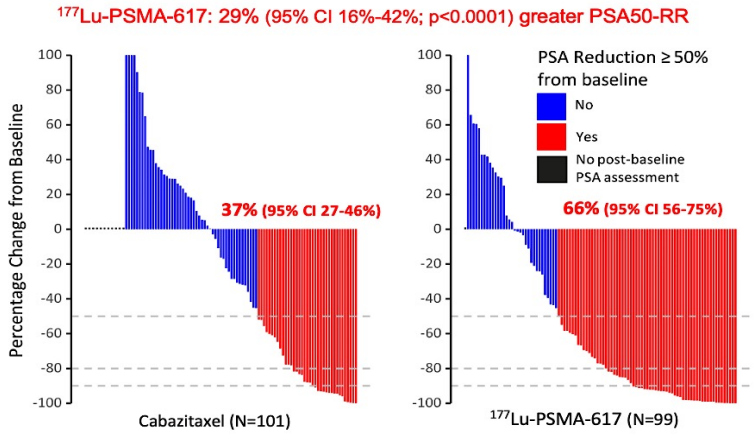
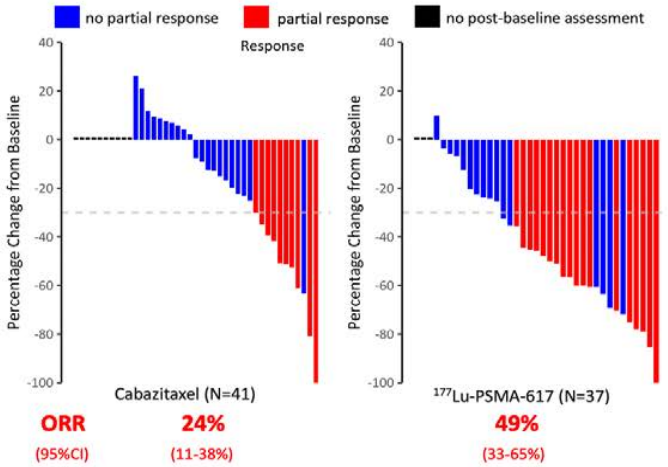
RESULTS: All favoured Lu-PSMA over Cabazitaxel

PSA 50 response



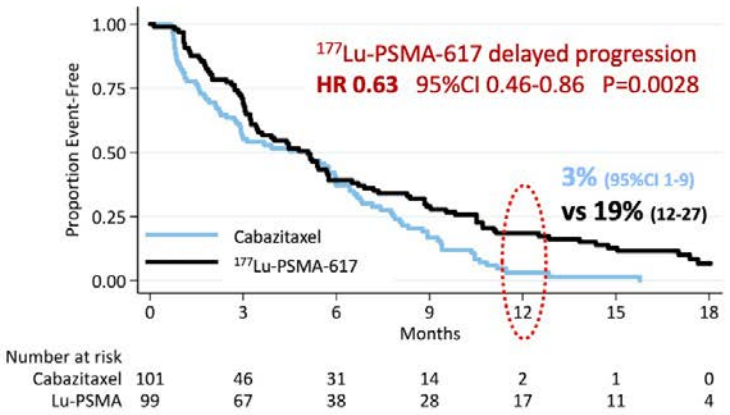
RECIST 1.1 objective response rate



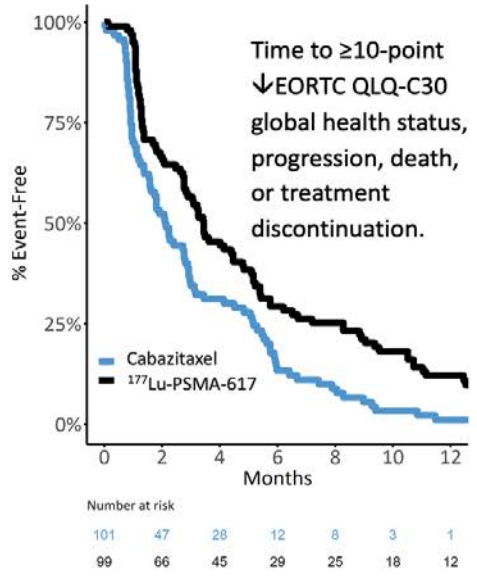
Adverse Events

	Cabazitaxel (N=85)		177Lu-PSMA-617 (N=98)	
	G1-2 (%)	G3-4 (%)	G1-2 (%)	G3-4 (%)
Neutropenia ± fever	5	**13**	7	4
Thrombocytopenia	5	0	**18**	**11**
Dry mouth	21	0	**60**	0
Diarrhea	**52**	**5**	18	1
Dry eye	4	0	**30**	0
Dysgeusia	**27**	0	12	0
Neuropathy (motor or sensory)	**26**	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	40	1
Anemia	13	8	19	8
Vomiting	12	2	12	1
TOTAL (all AEs)	**40**	**53**	**54**	**33**

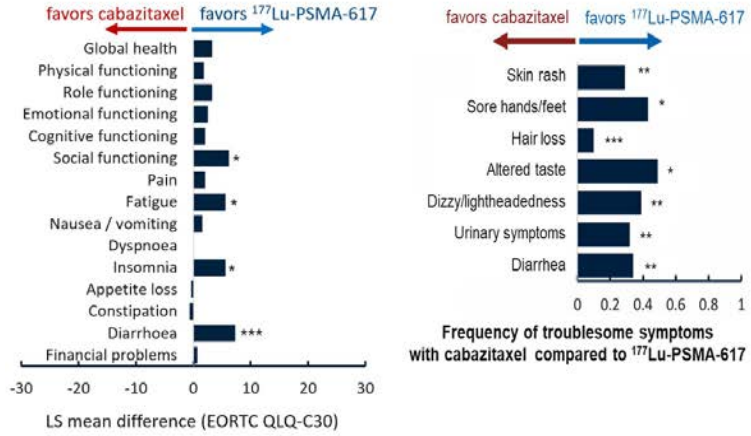
PFS (PSA or rPFS)



Deterioration Free Survival



Patient Reported Outcomes



Hofman MS, et al. Lancet. 2021 Feb 27;397(10276):797-804

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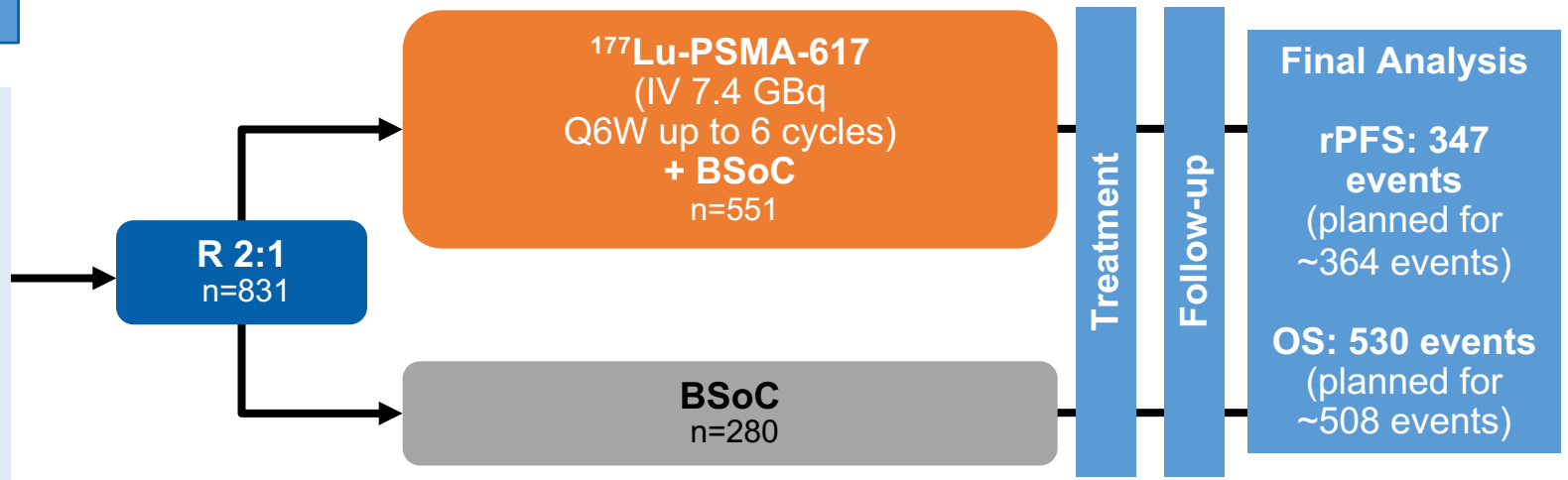
VISION Trial Design

Phase III trial of BSoC ± ^{177}Lu-PSMA-617 in PSMA-positive mCRPC[1–3]

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- ECOG performance status 0–2
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11



No FDG imaging required: 83% of patients eligible

Morris M, et al. Oral presentation at the 2021 ASCO Annual Meeting; June 6, 2021; Abstract LBA4. Sartor et al. NEJM 2021

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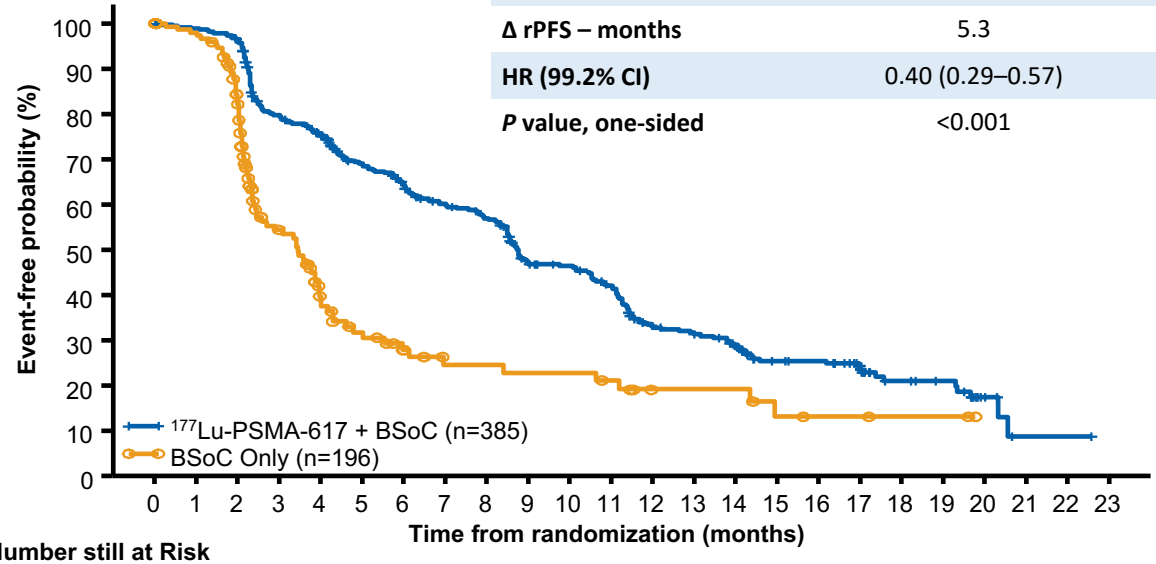
Results

rPFS

	^{177}Lu-PSMA-617	BSoC
Median rPFS – months	8.7	3.4
Δ rPFS – months	5.3	
HR (99.2% CI)	0.40 (0.29–0.57)	
***P* value, one-sided**	<0.001	

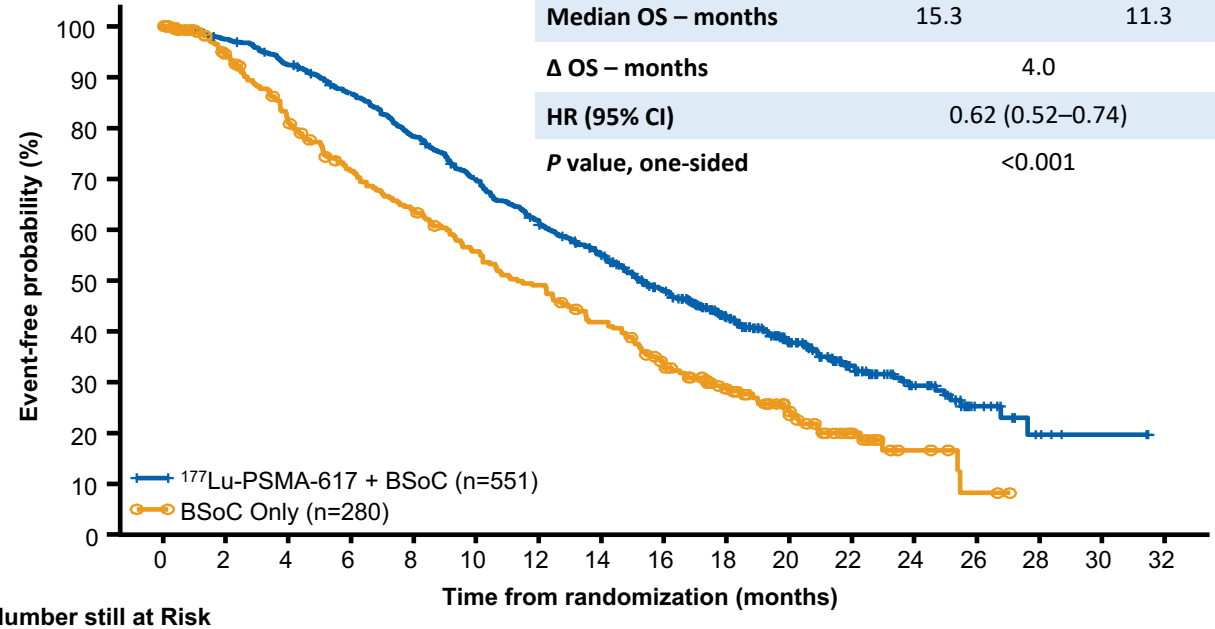


Number still at Risk

^{177}Lu-PSMA-617 + BSoC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
BSoC Only	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

Overall Survival

	^{177}Lu-PSMA-617	BSoC
Median OS – months	15.3	11.3
Δ OS – months	4.0	
HR (95% CI)	0.62 (0.52–0.74)	
***P* value, one-sided**	<0.001	



Number still at Risk

^{177}Lu-PSMA-617 + BSoC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
BSoC Only	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Sartor et al. NEJM 2021 Sep 16;385(12):1091-1103

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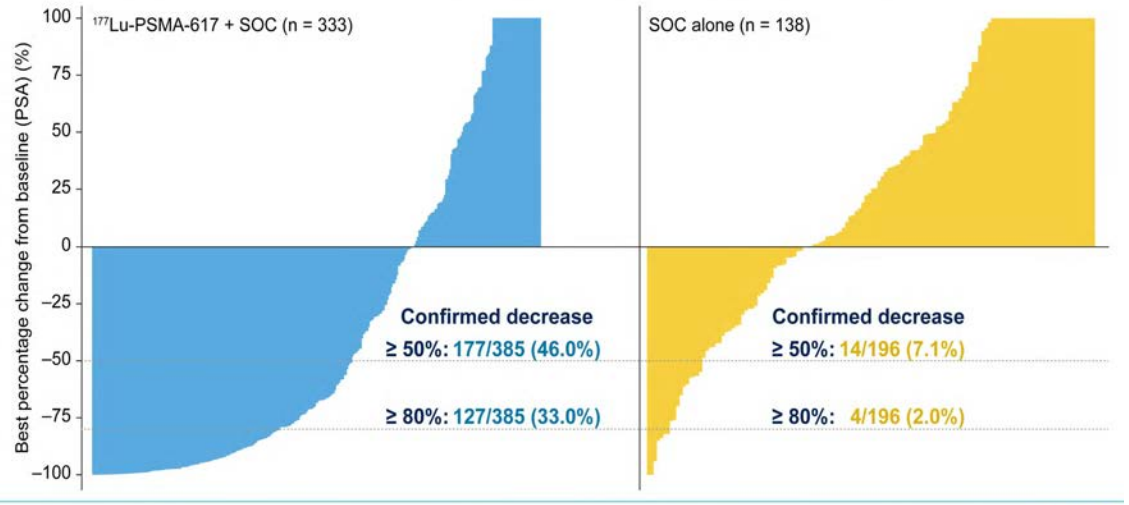
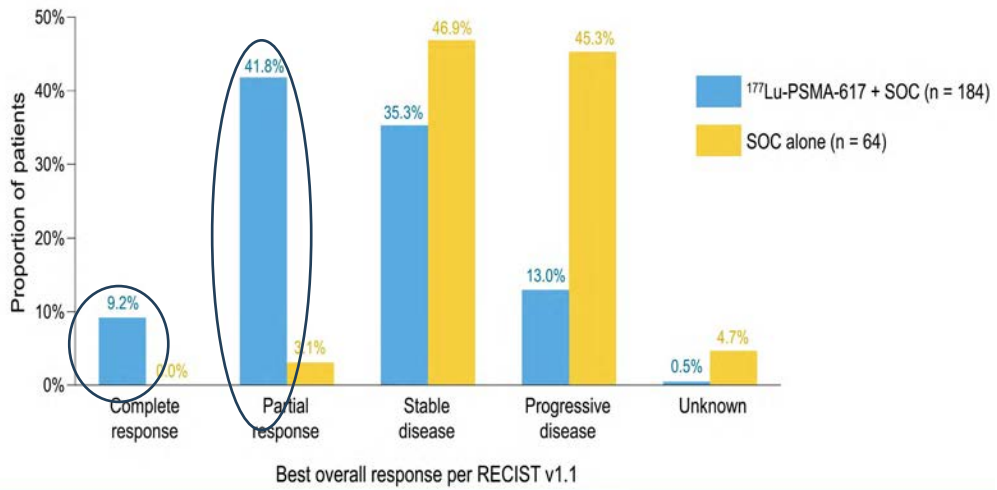
Results

PSA response



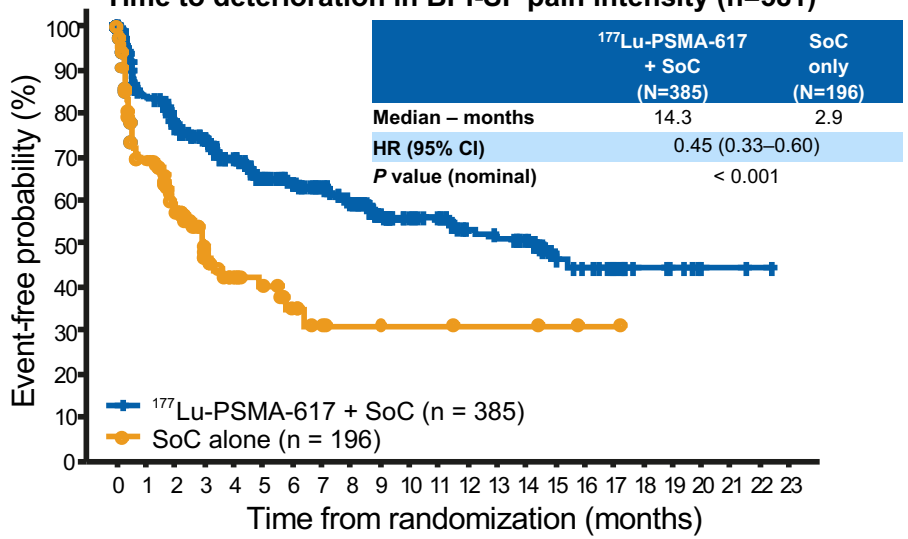
Measurable response



Morris M, et al. Oral presentation at the 2021 ASCO Annual Meeting; June 6, 2021; Abstract LBA4. Sartor et al. NEJM 2021

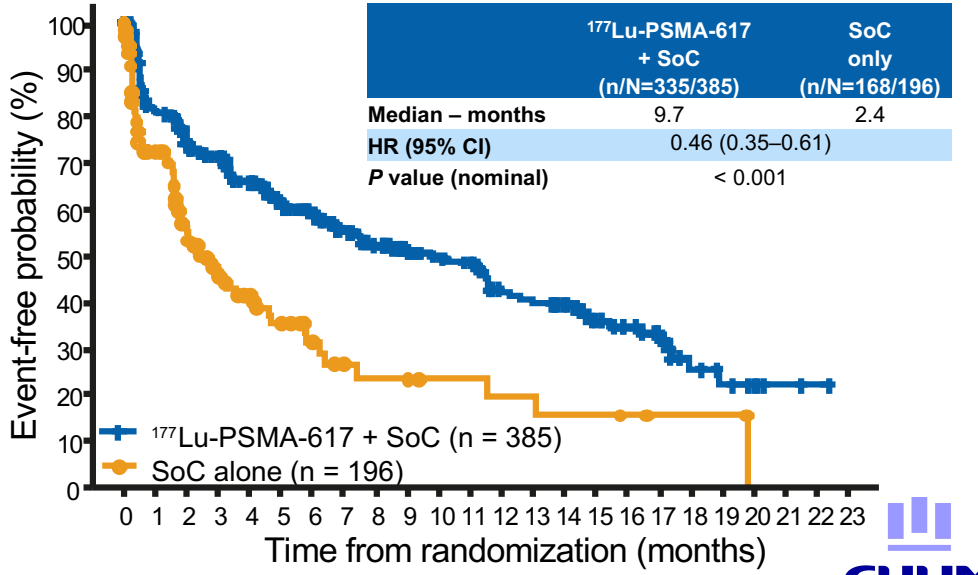
Quality of Life

Time to deterioration in BPI-SF pain intensity (n=581)[b]



	177Lu-PSMA-617 + SoC (N=385)	SoC only (N=196)
Median – months	14.3	2.9
HR (95% CI)	0.45 (0.33–0.60)	
P value (nominal)	< 0.001	

Time to deterioration in FACT-P total score (n=581)[a]



	177Lu-PSMA-617 + SoC (n/N=335/385)	SoC only (n/N=168/196)
Median – months	9.7	2.4
HR (95% CI)	0.46 (0.35–0.61)	
P value (nominal)	< 0.001	

Fizazi K, et al. Lancet Oncol 2023;24(6):597–610; 2

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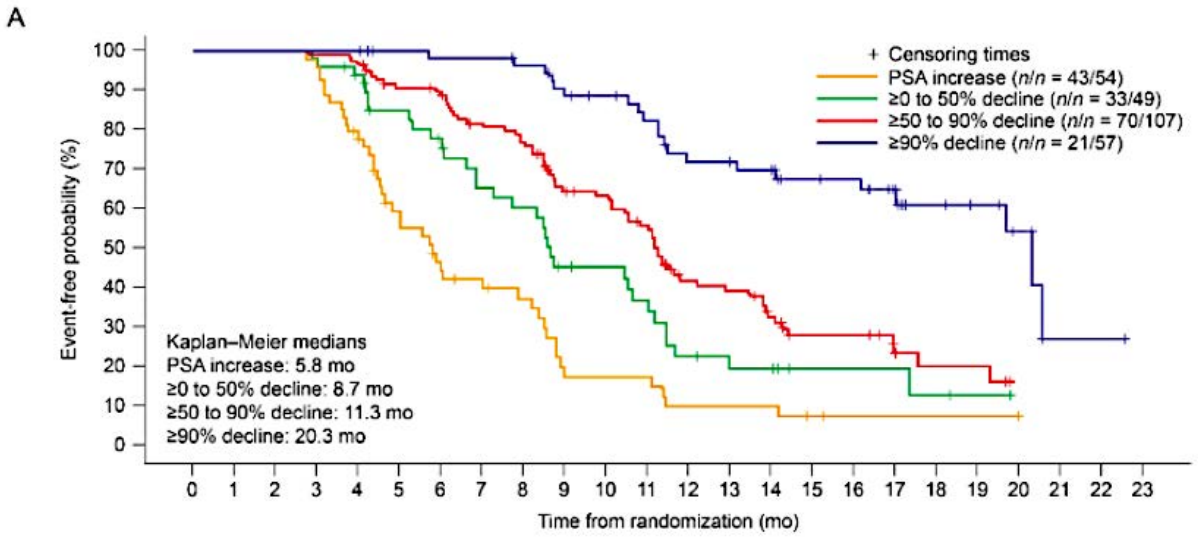
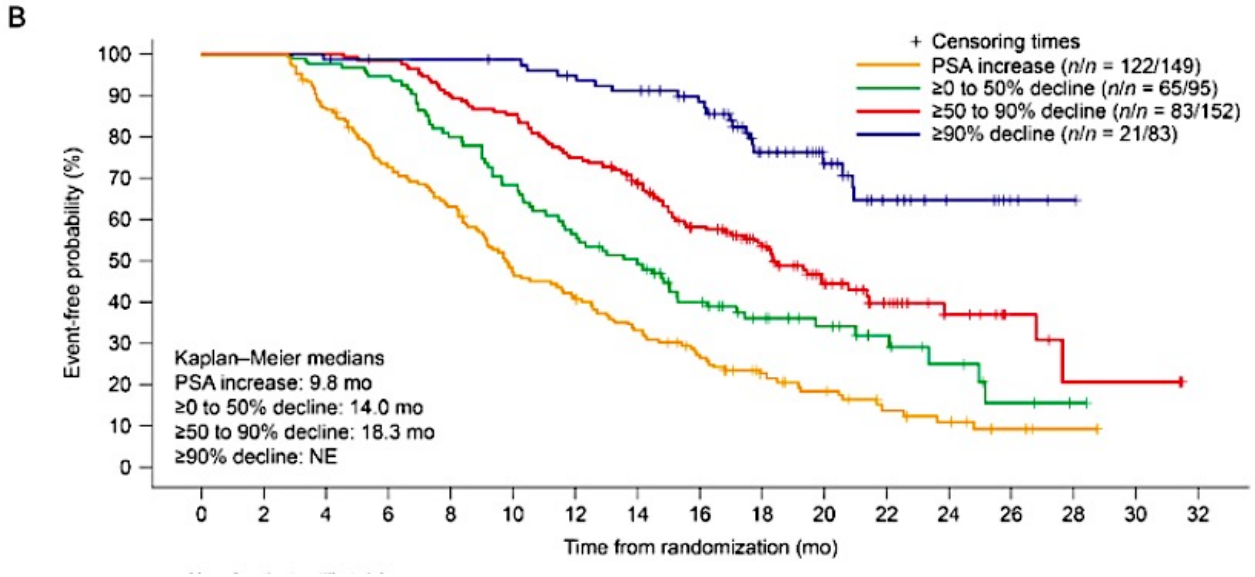
Who is more or less likely to benefit?

PSA response at 12 weeks and outcome

rPFS



Overall Survival



Saad et al. AUA 2023, Armstrong et al. Eur Urol 2024

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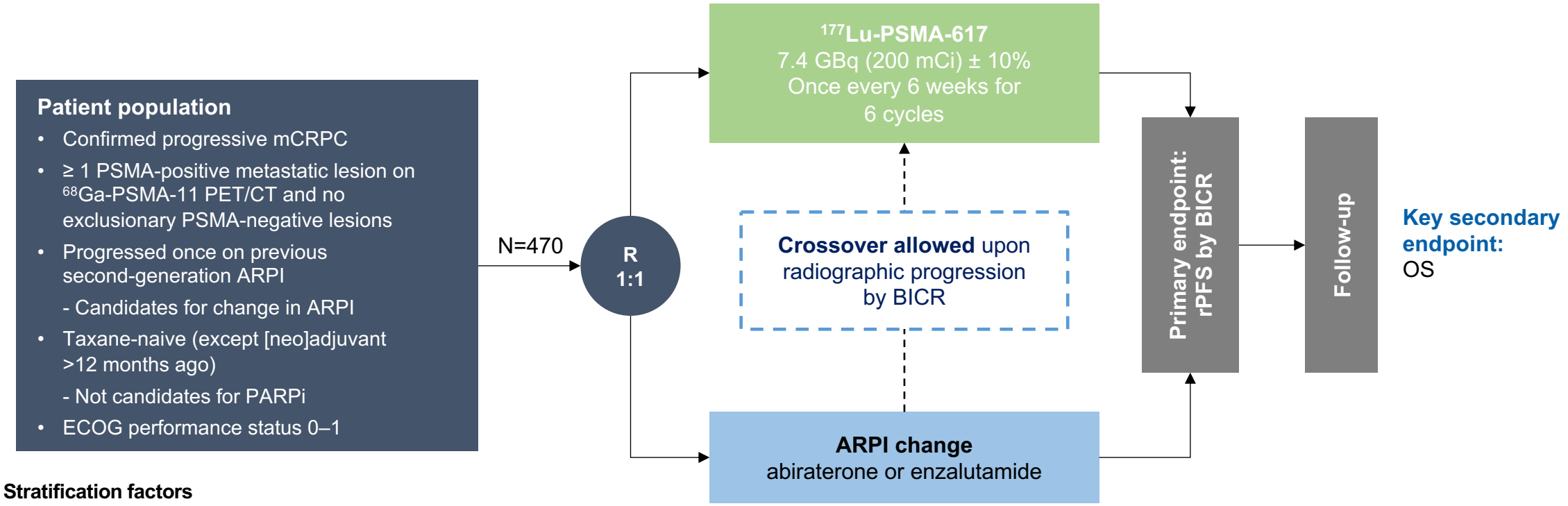
PSMAfore: Lu-PSMA-617 in taxane-naive mCRPC

Phase 3 study of ^{177}Lu-PSMA-617 vs ARPI change in taxane-naive mCRPC patients who had progressed once on a previous ARPI[1]



Stratification factors

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

1. Morris MJ, et al. Lancet. 2024;404(10459):1227-1239.

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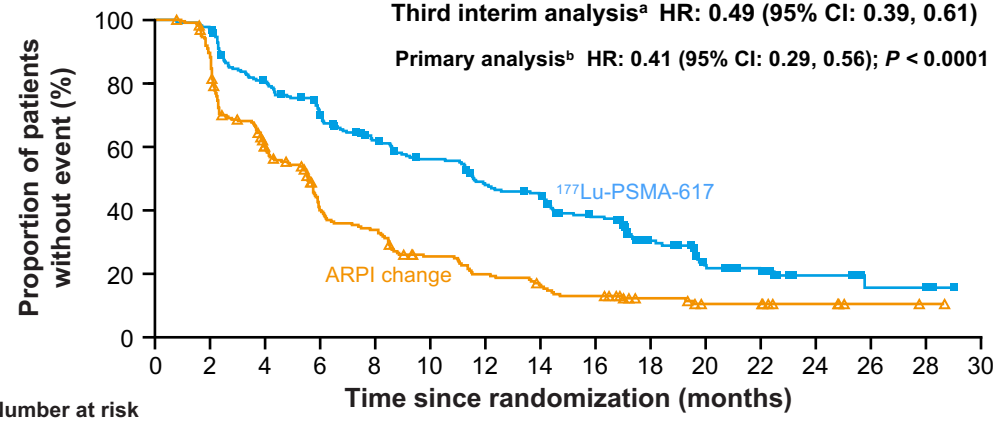
PSMAfore: RESULTS

rPFS[1]

rPFS	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	154	180
Median, months (95% CI)	11.60 (9.30, 14.19)	5.59 (4.21, 5.95)

Third interim analysis[a] HR: 0.49 (95% CI: 0.39, 0.61)

Primary analysis[b] HR: 0.41 (95% CI: 0.29, 0.56); *P* < 0.0001



Number at risk

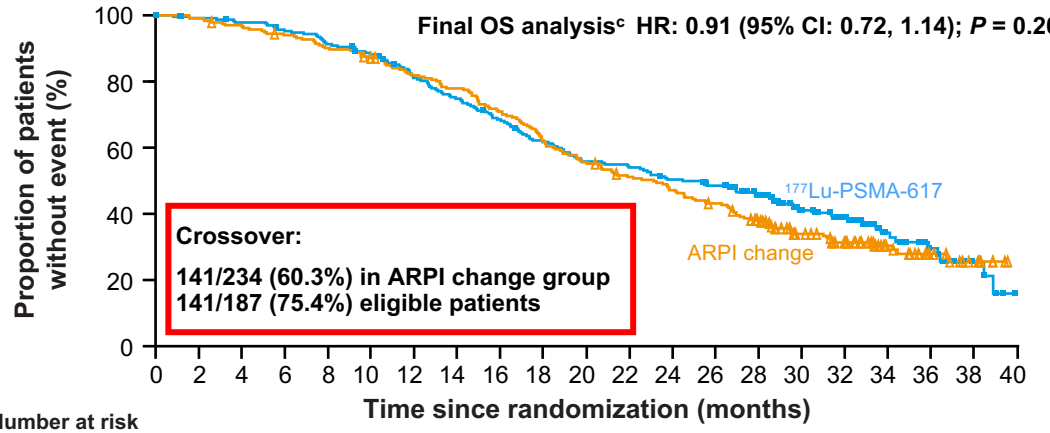
^{177}Lu-PSMA-617	234	217	175	152	126	111	94	86	67	39	25	20	8	4	4	0
ARPI change	234	197	126	79	65	45	35	28	22	14	9	9	5	2	1	0

^{177}Lu-PSMA-617 prolonged rPFS vs ARPI change, with a manageable safety profile in taxane-naive mCRPC patients who had progressed once on a previous ARPI[1]

OS (ITT analysis)[2]

OS	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	142	157
Median, months (95% CI)	24.48 (19.55, 28.94)	23.13 (19.61, 25.53)

Final OS analysis[c] HR: 0.91 (95% CI: 0.72, 1.14); *P* = 0.20



Number at risk

^{177}Lu-PSMA-617	234	229	225	218	209	200	181	167	152	136	123	119	110	103	85	57	45	24	15	6	0
ARPI change	234	232	226	218	209	200	187	178	162	142	127	115	106	96	79	56	44	25	14	7	0

No difference vs the ITT analysis; crossover confounded the OS analysis[2]

IPCW crossover-adjusted OS analysis[2]: HR: 0.59 (95% CI, 0.38–0.91)

1. Morris M, et al. Lancet 2024;404(10459):1227-1239. 2. Fizazi K, et al. Ann Oncol. 2025. DOI: 10.1016/j.annonc.2025.07.003.

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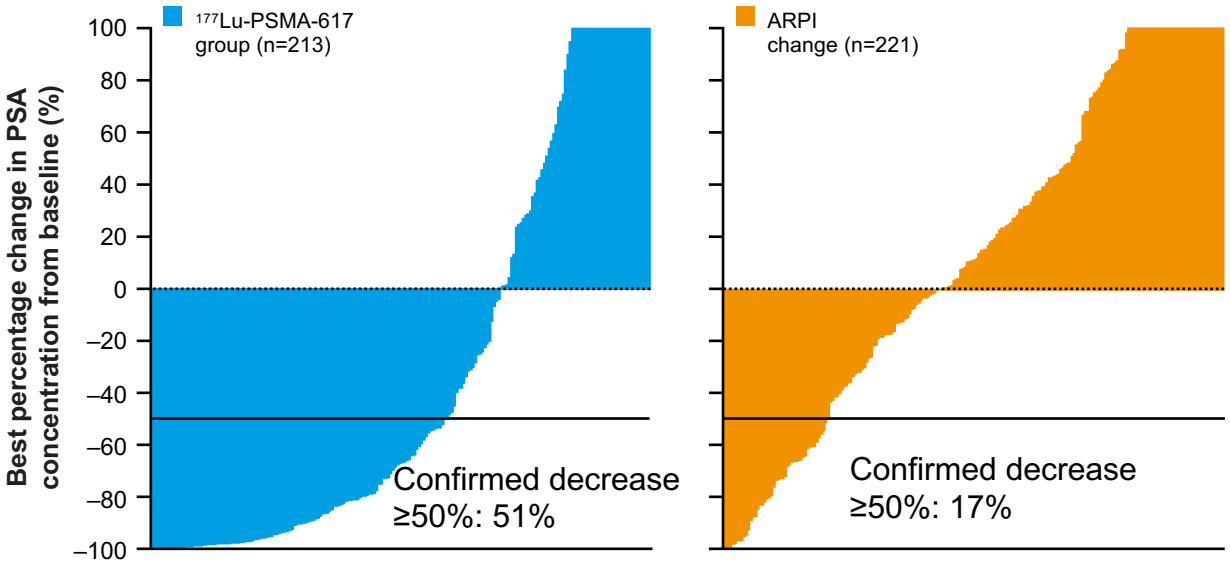
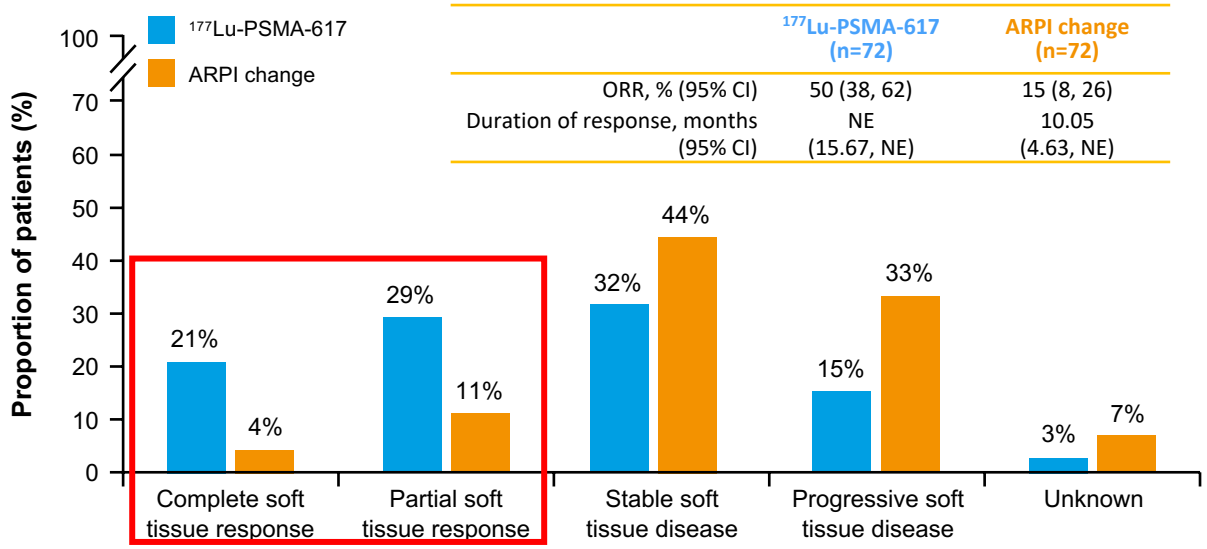
PSMAfore: RESULTS

PSA response



Increases greater than 100% are truncated to 100%. Assessments were at 3, 6, and 12 months after randomization.

ORR



	177Lu-PSMA-617 (n=72)	ARPI change (n=72)
ORR, % (95% CI)	50 (38, 62)	15 (8, 26)
Duration of response, months (95% CI)	NE (15.67, NE)	10.05 (4.63, NE)

Best response in soft tissue as per RECIST v1.1 in patients with measurable disease at baseline

50% PR or CR

Morris et al. Lancet 2024 Sep 28;404(10459):1227-1239.

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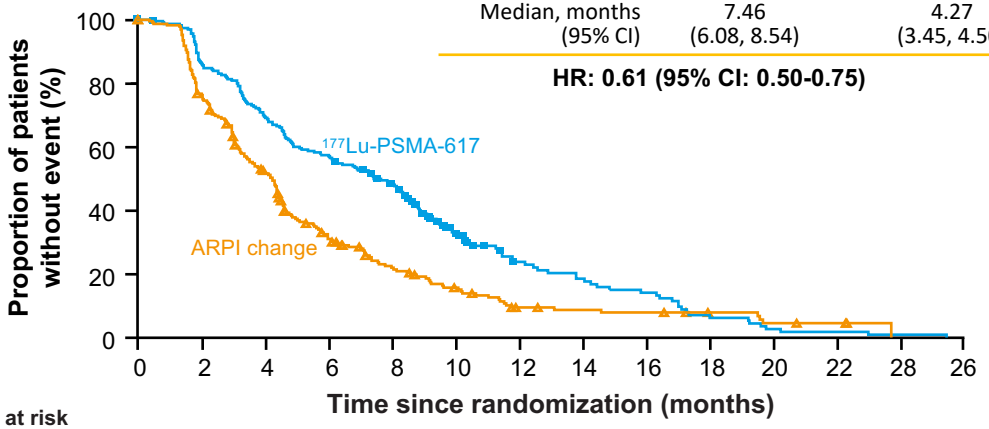
PSMAfore: Quality Of Life

FACT-P total score[a]

	^{177}Lu-PSMA-617 (n=234)	ARPI change (n=234)
Events, n	187	199
Median, months (95% CI)	7.46 (6.08, 8.54)	4.27 (3.45, 4.50)

HR: 0.61 (95% CI: 0.50-0.75)

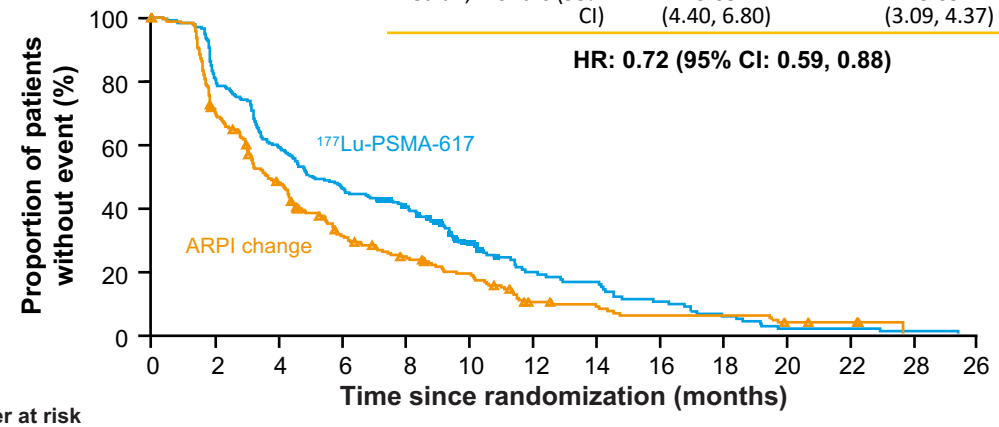


Number at risk														
^{177}Lu-PSMA-617	234	200	161	132	105	52	27	21	16	8	3	2	1	0
ARPI change	234	177	116	66	41	26	13	11	10	7	4	3	0	0

BPI-SF pain intensity scale[a]

	^{177}Lu-PSMA-617 (n=234)	ARPI change (n=234)
Events, n	198	205
Median, months (95% CI)	5.03 (4.40, 6.80)	3.65 (3.09, 4.37)

HR: 0.72 (95% CI: 0.59, 0.88)



Number at risk														
^{177}Lu-PSMA-617	234	190	138	108	88	49	25	21	13	8	2	2	1	0
ARPI change	234	163	107	64	47	35	15	13	8	8	5	3	0	0

Time to worsening in FACT-P total score and BPI-SF pain intensity favored ^{177}Lu-PSMA-617 vs ARPI change

Morris et al. Lancet 2024 Sep 28;404(10459):1227-1239.

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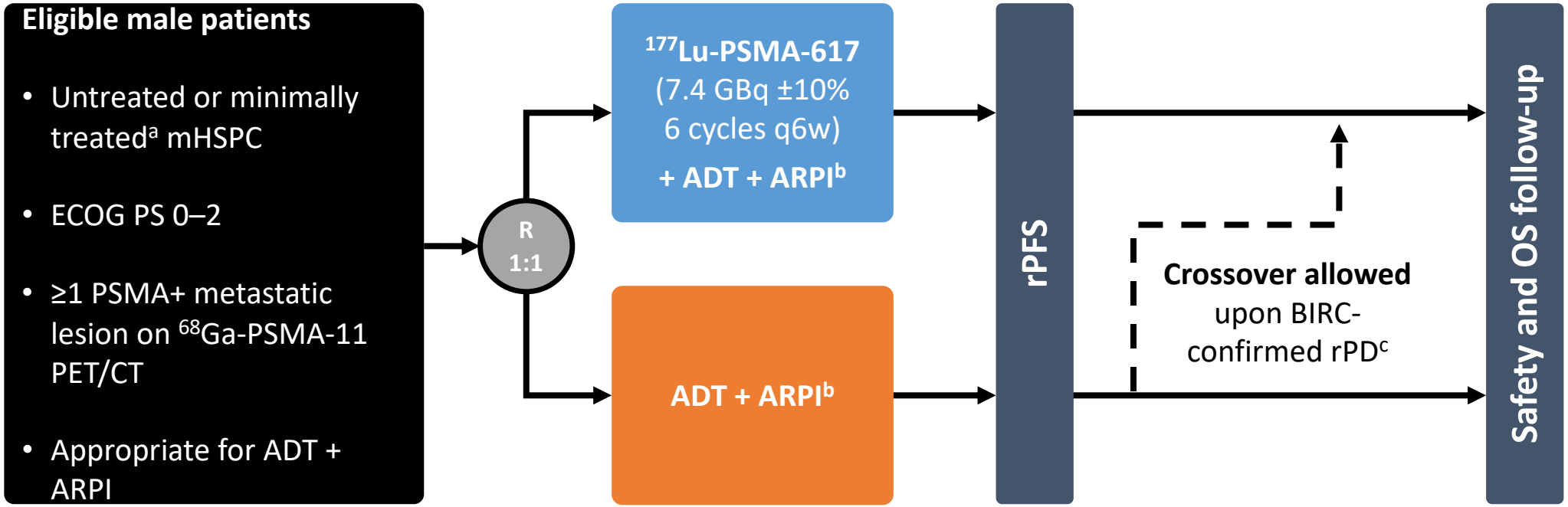
PSMAddition: phase 3 trial of ^{177}Lu-PSMA-617 in mHSPC



Stratification factors
- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

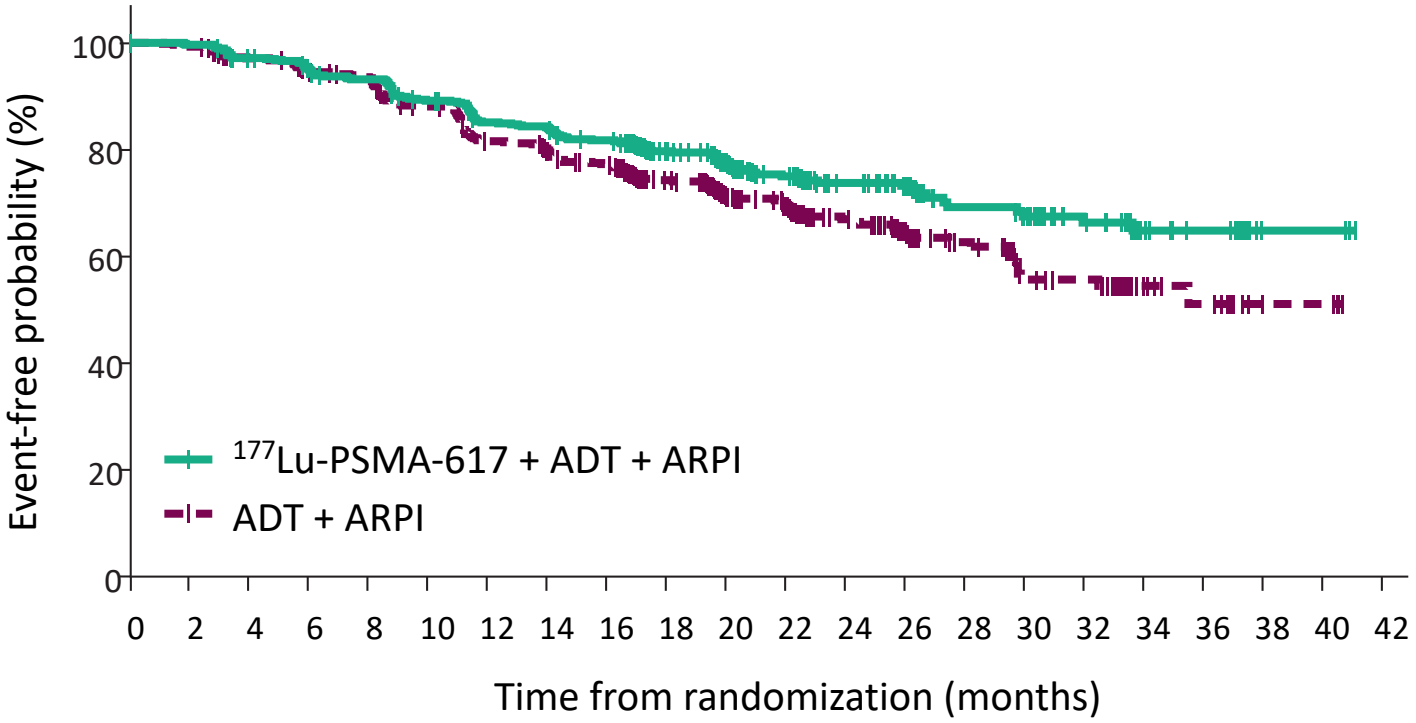
Follow-up periods
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

[a] ADT in the neo-/adjuvant setting and/or up to 45 days of ADT/ARPI for metastatic disease was allowed before study entry | [b] Any ARPI with one switch allowed | [c] ADT/ARPI not mandatory after crossover

ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PET/CT, positron-emission tomography/computed tomography; q6w, every 6 weeks; rPD, radiographic disease progression; rPFS, radiographic progression-free survival

1. Sweeney CT *et al. N Engl J Med* 2015;373:737–46

rPFS by BIRC – the primary endpoint was met



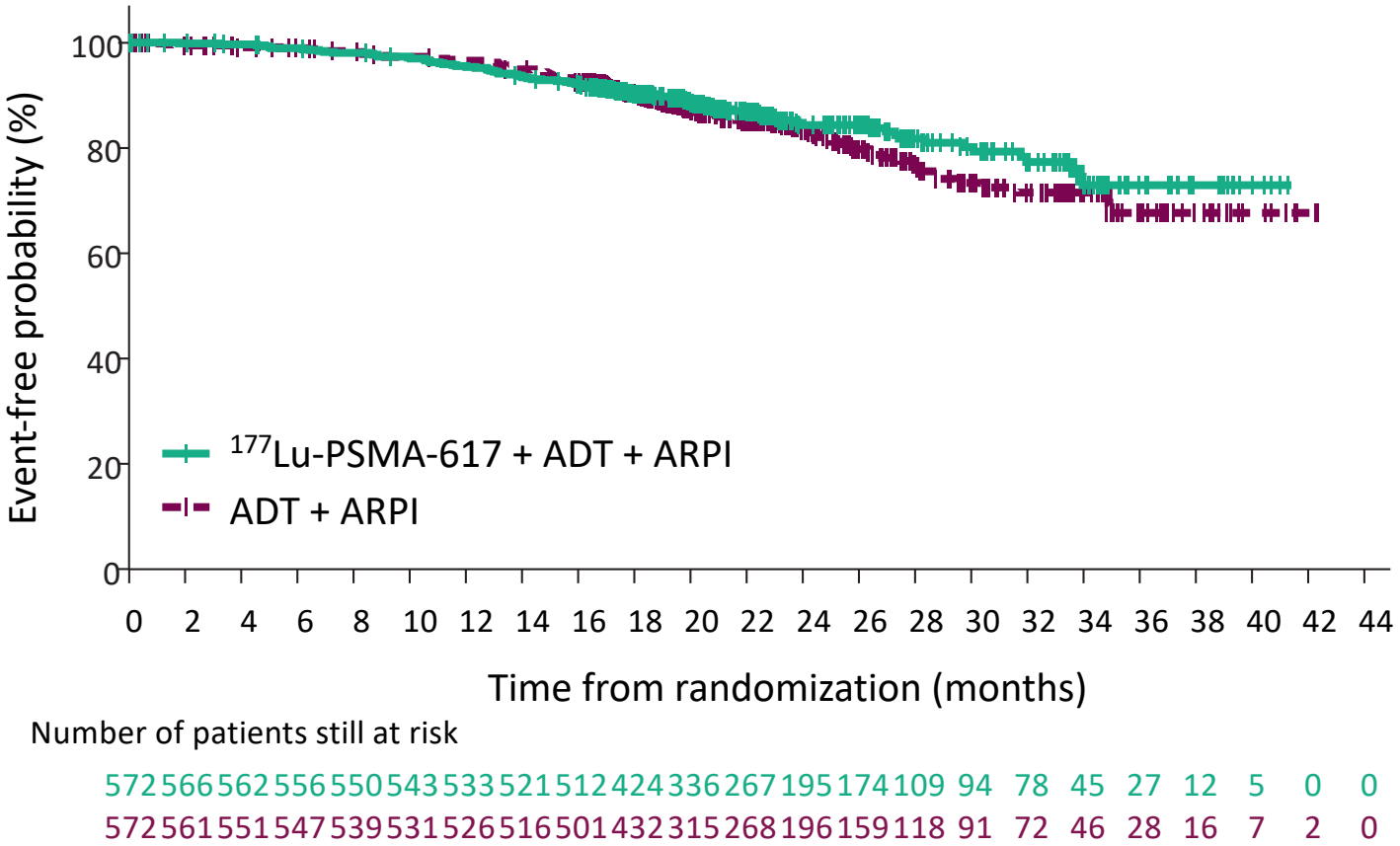
Number of patients still at risk

^{177}Lu-PSMA-617 + ADT + ARPI	572	558	539	524	512	485	458	452	436	337	252	212	153	134	79	73	59	23	18	3	3	0
ADT + ARPI	572	550	527	507	495	461	424	408	391	304	225	195	134	99	74	50	47	19	15	4	4	0

	^{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)

[a] Significance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%
CI, confidence interval; IA, interim analysis; NE, not estimable; NR, not reached

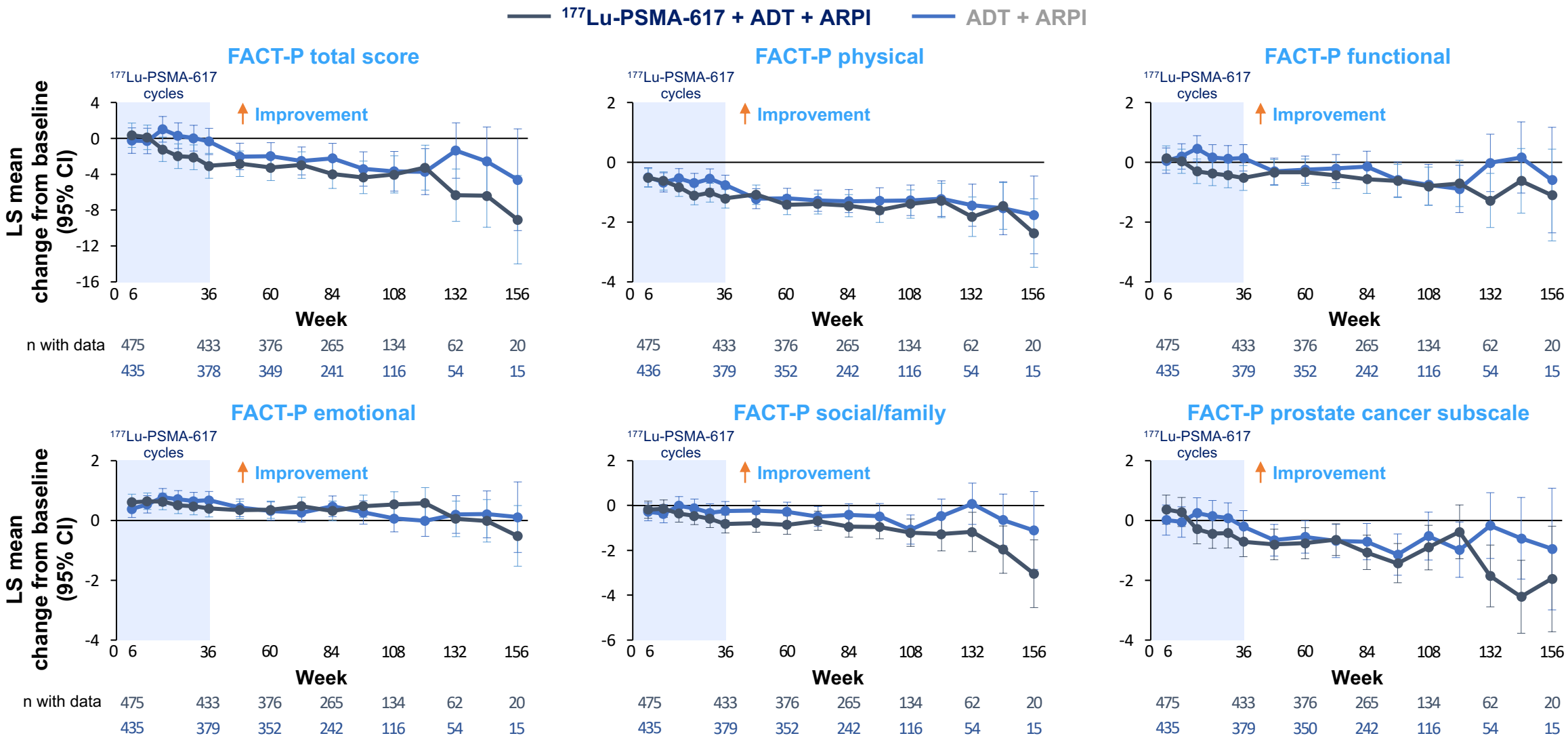
Interim Overall Survival (follow-up continues)



	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	85 (14.9)	99 (17.3)
Censored – n (%)	487 (85.1)	473 (82.7)
HR (95% CI)	0.84 (0.63, 1.13)	
p value	0.125[a]	
Median OS (95% CI) – months	NR (NE, NE)	NR (NE, NE)

[a] Significance threshold at OS IA1: 0.0011 (one-sided; stratified log-rank test); information fraction, 47.3%

QOL: Longitudinal assessment of change from baseline



LS means from linear mixed-effect model for change from baseline in score.

Morris et al. ASCO GU 2026

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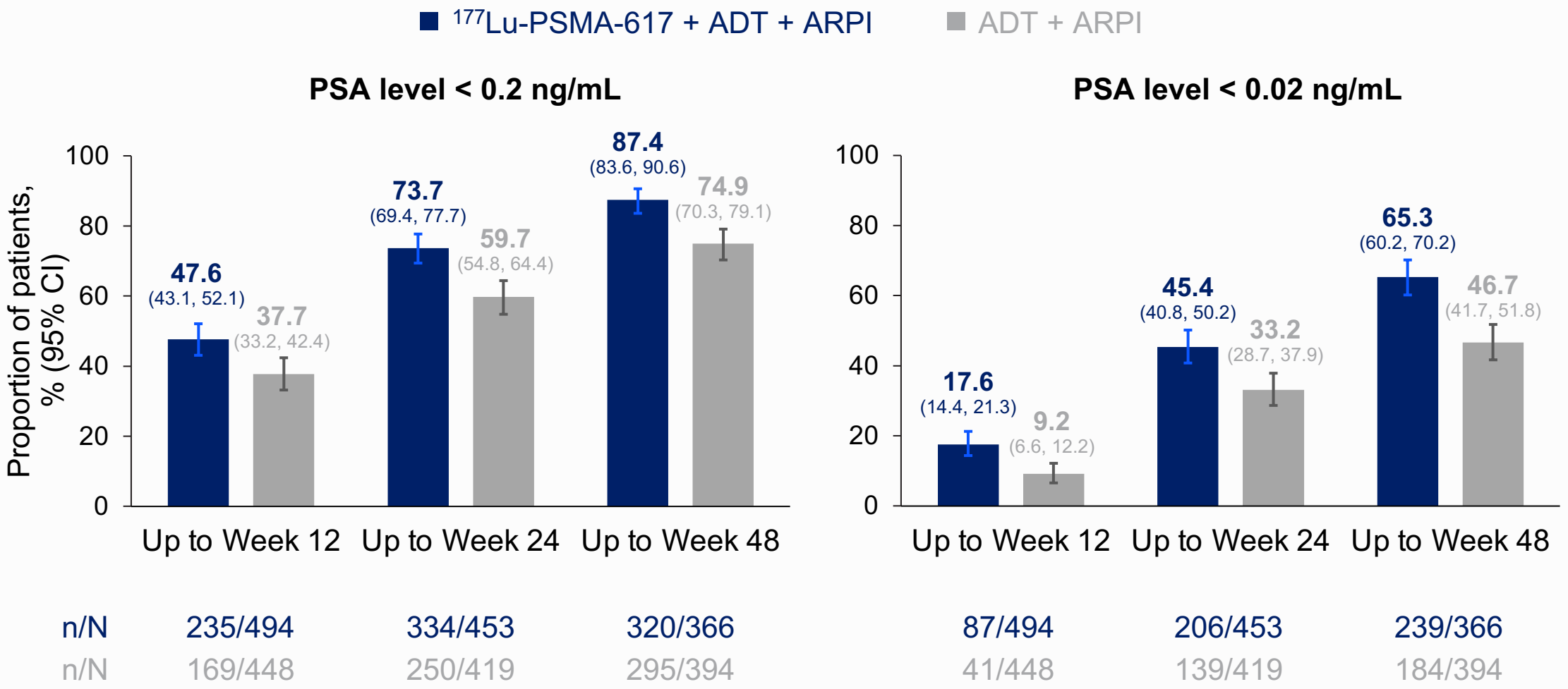
Rates of PSA levels < 0.2 and < 0.02 ng/mL were higher in the ^{177}Lu-PSMA-617 arm than in the control arm

Data cut-off: January 13, 2025



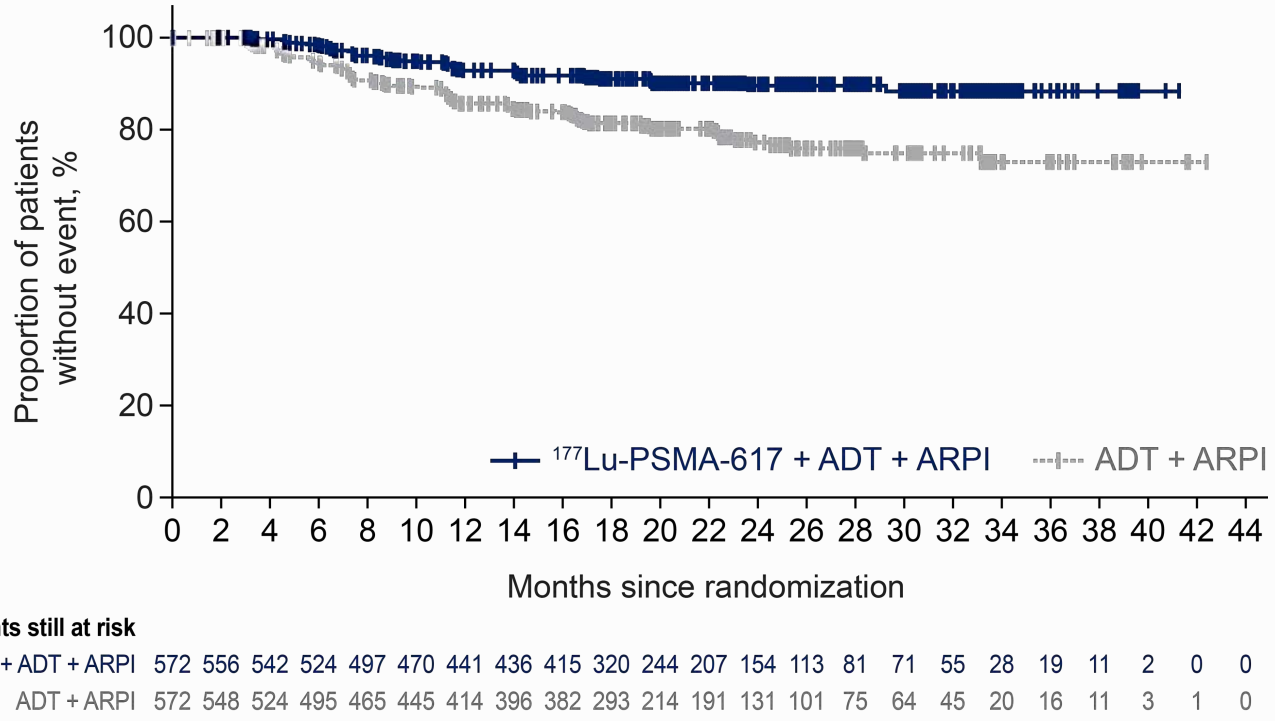
	PSA level < 0.2 ng/mL			PSA level < 0.02 ng/mL		
	Up to Week 12	Up to Week 24	Up to Week 48	Up to Week 12	Up to Week 24	Up to Week 48
n/N	235/494	334/453	320/366	87/494	206/453	239/366
n/N	169/448	250/419	295/394	41/448	139/419	184/394

Saad F et al. AUA 2026

58% risk reduction in PSA progression in the ^{177}Lu-PSMA-617 arm

Data cut-off: January 13, 2025

Time to PSA progression



No. of patients still at risk

^{177}Lu-PSMA-617 + ADT + ARPI	572	556	542	524	497	470	441	436	415	320	244	207	154	113	81	71	55	28	19	11	2	0	0
ADT + ARPI	572	548	524	495	465	445	414	396	382	293	214	191	131	101	75	64	45	20	16	11	3	1	0

	^{177}Lu-PSMA-617 + ADT + ARPI n = 572	ADT + ARPI n = 572
Events, n (%)	50 (8.7)	107 (18.7)
Censored, n (%)	522 (91.3)	465 (81.3)
Median time to PSA progression, months	NR (NE, NE)	NR (NE, NE)
HR (95% CI)[a]	**0.42 (0.30, 0.59)**	

Saad F et al. AUA 2026

RLT beyond VISION and PSMAfore: Expanding across prostate cancer continuum

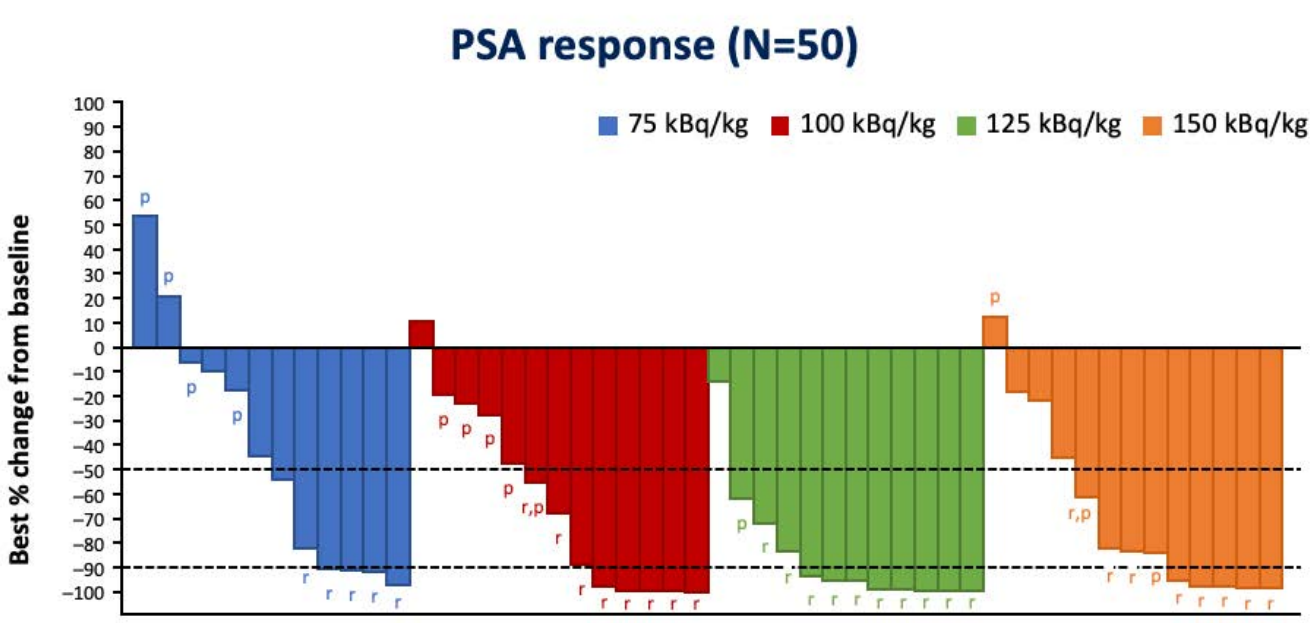
Lines of therapy	^{177}Lu-PSMA RLT in earlier lines of therapy	Alpha-emitting RLT and other isotopes	Key RLT combination strategies	
Post-taxane mCRPC	**Post-ARPI, pre-taxane & post-taxane** **ProstACT GLOBAL Ph3[1] -** ^{177}Lu-TLX591+SoC	**Post-ARPI, post-taxane** **SatisfACtion Ph1/2[9] -** ^{225}Ac-PSMA-R2 **AlphaBreak Ph2/3[10] -** ^{225}Ac-PSMA-I&T **PAnTHA Ph1[11] -** ^{225}Ac-PSMA-Trillium **NCT06052306 Ph1[12] -** ^{225}Ac-BAY3546828 **NCT06492122 Ph1[13] -** ^{225}Ac-FL-020 **CONVERGE-01 Ph2[14] -** ^{225}Ac-J591 **NCT04506567 Ph1/2[15] -** ^{225}Ac-J591 **PSMAcTION Ph2/3[16] -** ^{225}Ac-PSMA-617 **TheraPb Ph1/2[18] -** ^{212}Pb-ADVC001	**Post-ARPI, post-taxane** **RLT + PARP inhibitors** **LuPARP Ph1[23] -** ^{177}Lu-PSMA-617 + olaparib **RLT + Chemotherapy** **LuCarbo Ph1[24] -** ^{177}Lu-PSMA-617 + carboplatin **RLT + Alpha emitters** **NCT04886986 Ph 1/2[26] –** ^{177}Lu-PSMA-I&T + ^{225}Ac-J591	**Post-ARPI, pre-taxane & post-taxane** **RLT + Immunotherapy** **PRINCE Ph1/2[27] –** ^{177}Lu-PSMA-617 + pembro **EVOLUTION Ph2[28] –** ^{177}Lu-PSMA-617 ± (ipilimumab + nivolumab) **RLT + Alpha emitters** **AlphaBet Ph1/2[25] –** ^{223}Ra + ^{177}Lu-PSMA-I&T
Pre-taxane mCRPC	**Post-ARPI, pre-taxane** **PSMAfore Ph3[2] -** ^{177}Lu-PSMA-617 **SPLASH Ph3[3] -** ^{177}Lu-PNT2002 **ECLIPSE Ph3[4] -** ^{177}Lu-PSMA-I&T **PR21/PLUDO Ph2a[5] -** ^{177}Lu-PSMA-617	**Post-ARPI, pre-taxane** **TATCIST Ph2[19] -** ^{225}Ac-PSMA-I&T **SECuRE Ph1/2[20] -** ^{67}Cu-SAR-bisPSMA **Post-ARPI, pre-taxane and post-taxane** **AcTION Ph1[21] -** ^{225}Ac-PSMA-617* **ACCEL Ph1/2[22] -** ^{225}Ac-PSMA-62 **Pre-ARPI, pre-taxane** **NCT05725070 Ph0/1[17] -** ^{212}Pb-NG001 **AcTFirst Ph3[31] -** ^{225}Ac-PSMA-617 ± ARPI	**Post-ARPI, pre-taxane** **RLT + ARPI** **ARROW Ph2[30] -** ^{131}I-1095 + enza **RLT + PARP inhibitors** **NCT06909825 Ph2[32] –** ^{225}Ac-PSMA-I&T + olaparib	**Pre-taxane** **RLT + ARPI** **NCT04946370 Ph1/2[29] –** ^{225}Ac-J591 ± pembro + ARPI **AcTFirst Ph3[31] –** ^{225}Ac-PSMA-617 + ARPI **ENZA-p Ph2[33] –** ^{177}Lu-PSMA-617 ± enza **PSMAndARPI Ph2[34] –** ^{177}Lu-PSMA-617 ± ARPI
mHSPC	**PSMAddition Ph3[6] -** ^{177}Lu-PSMA-617+SoC **UpFrontPSMA Ph2[35] -** ^{177}Lu-PSMA-617 + docetaxel (*sequential use*)	**SatisfACtion Ph1/2[9] -** ^{225}Ac-PSMA-R2		
Oligo/CRPC	**PSMA-DC Ph3[7] -** ^{177}Lu-PSMA-617 **PSMACare Ph2[8] -** ^{177}Lu-PSMA-617 ± ARPI	**ACCEL Ph1[22] -** ^{225}Ac-PSMA-62	**RLT + ARPI** **PSMACare Ph2[8] -** ^{177}Lu-PSMA-617 ± ARPI	

References: Clinicaltrials.gov Accessed July 2025. 1. NCT04876651; 2. NCT04689828, 3. NCT04647526; 4. NCT05204927; 5. NCT04663997; 6. NCT04720157; 7. NCT05939414, 8. NCT05849298; 9. NCT05983198; 10. NCT06402331; 11. NCT06217822; 12. NCT06052306; 13. NCT06492122; 14. NCT06549465; 15. NCT04506567; 16. NCT06780670; 17. NCT05725070; 18. NCT05720130; 19. NCT05219500; 20. NCT04868604; 21. NCT04597411; 22. NCT06229366; 23. NCT03874884; 24. NCT06303713; 25. NCT05383079; 26. NCT04886986; 27. NCT03658447; 28. NCT05150236; 29. NCT04946370; 30. NCT03939689; 31. NCT06855277; 32. NCT06909825; 33. NCT04419402; 34. NCT06894511; 35. NCT04343885.

CHUM

One example

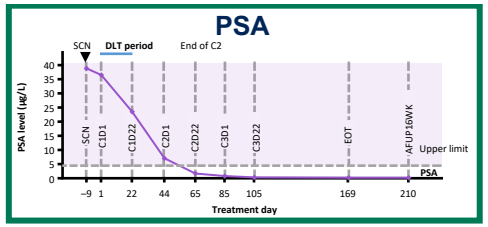
^{225}Ac-PSMA-Trillium Phase 1 dose escalationPost ARPI/TAXANE



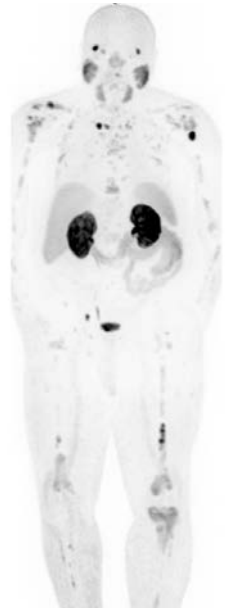
	All patients (N=50)	125 kBq/kg dose (N=12)
PSA50 response rate, %	62	83
PSA90 response rate, %	40	67
Overall response rate[a,c], %	50	71
Disease control rate[a,c], %	79	71

PSMA PET

Screening



Post 2 Cycles



TTV: 471.3mL **(–83.2%)**
SUVmean: 4.7

Saad F, et al. ASCO-GU 2026

CHUM

Conclusion

- Radium-223 (with a BPA) is a therapeutic option in the pre and post docetaxel in mCRPC
- ARPI + Radium may provide added benefit over either alone in first line mCRPC
- Radioligand PSMA based therapy is safe and effective
  - Earlier treatment with RLT may improve outcome
    - Less heterogeneity and less PSMA negative/undifferentiated lesions
  - Very welcome addition to our treatment options and may soon be available for mHSPC
- Ongoing research with new RLT's and in combination with other therapies

Optimal sequencing/combinations + lines of therapy leads to longer survival

CHUM

Second Opinion

Andrew J Armstrong, MD, ScM

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Regulatory and reimbursement issues aside, in which situations, if any, would you utilize lutetium-177 vipivotide tetraxetan for a patient with APMS mPC? How many doses would you use?

How much of an issue is xerostomia with this therapy, and how do you prevent and manage it? What about cytopenias?

Second Opinion

Andrew J Armstrong, MD, ScM

Sandy Srinivas, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What are your thoughts about opevesostat? Do you find initial efficacy and tolerability data with this agent encouraging?

Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

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RTP RESEARCH TO PRACTICE