3rd Annual Southern California Genitourinary Cancer Research Forum

Key Updates in Prostate Cancer

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Disclosures

- Consultant/Advisor for BeOne, Incycte, Pfizer, Bayer, Seagen, Agenus, Genentech, AstraZeneca, Eisai, and Taiho.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

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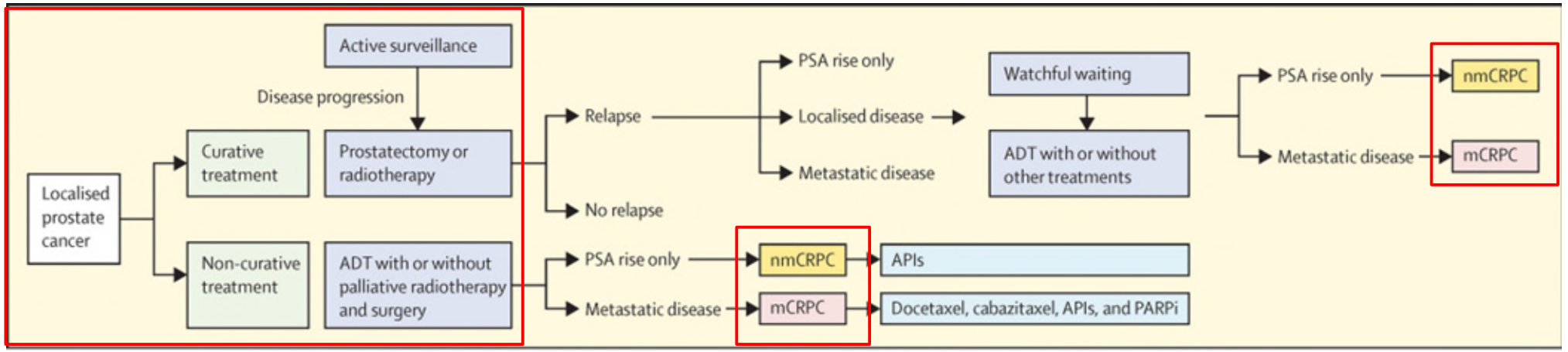
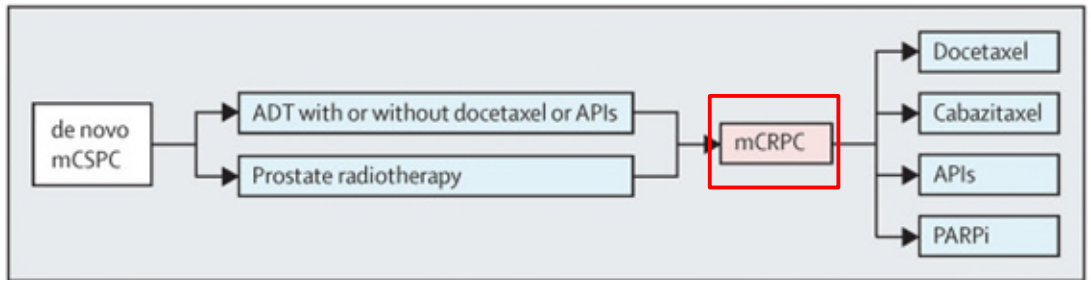
Defining disease states



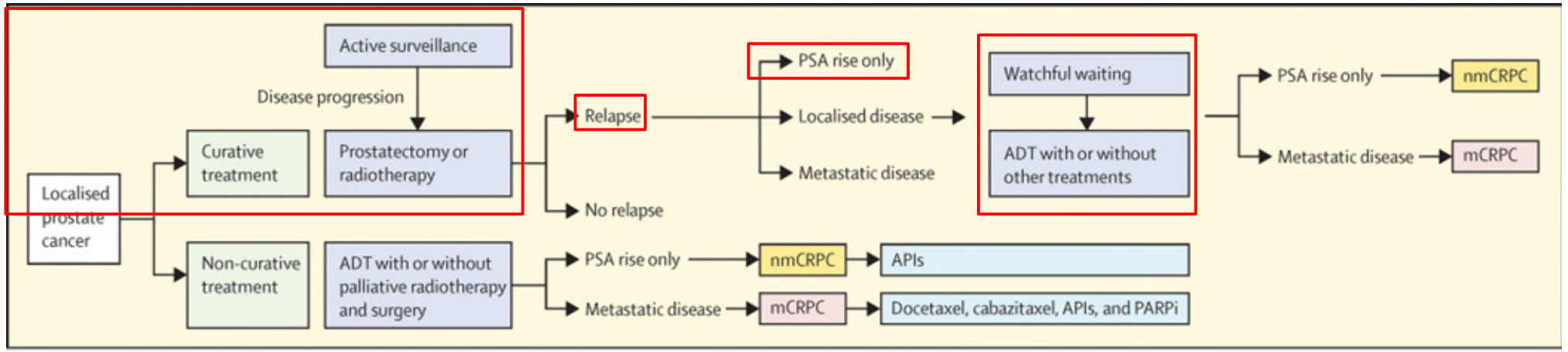


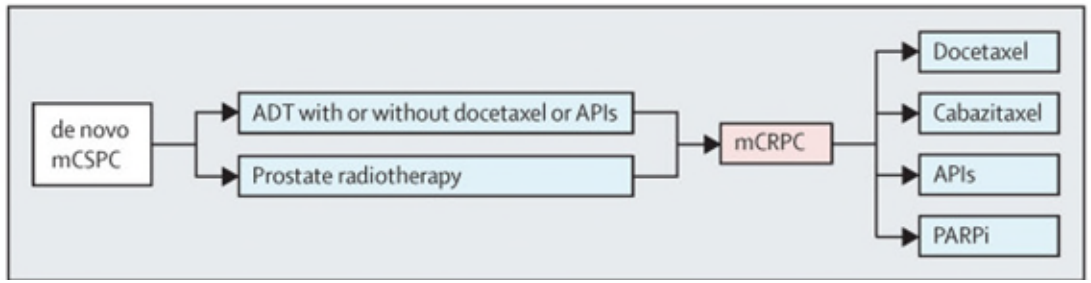
- Localized disease can have a varied course from indolent, slow growing to higher risk where disease relapse is expected following definitive treatment

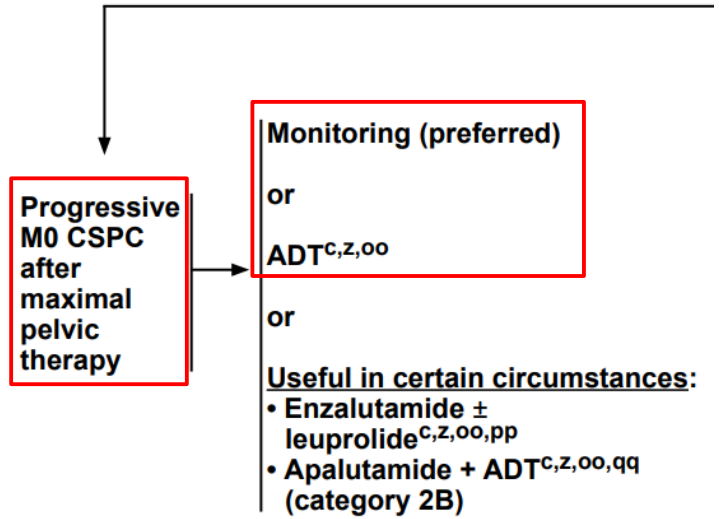
Whether localized disease or de novo metastatic disease → evolution to more aggressive disease states is characterized by castration-sensitive to castration-resistant prostate cancer

Sandhu S, et al. Lancet. 2021;398(10305):1075-1090

Biochemically recurrent prostate cancer

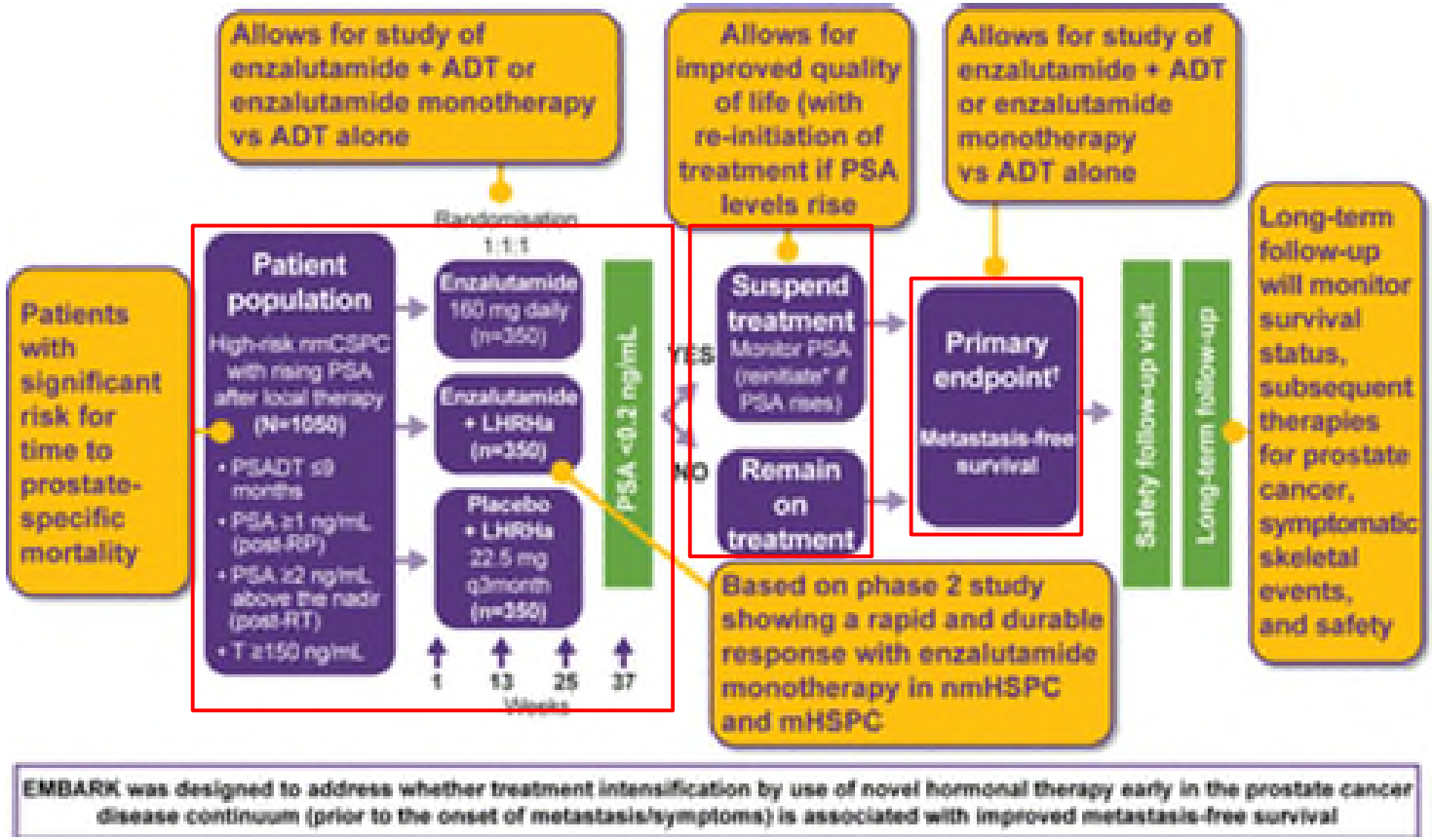






NCCN Guidelines. Prostate Cancer. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
Sandhu S, et al. Lancet. 2021;398(10305):1075-1090

EMBARK



EMBARK was designed to address whether treatment intensification by use of novel hormonal therapy early in the prostate cancer disease continuum (prior to the onset of metastasis/symptoms) is associated with improved metastasis-free survival

Phase III RCT

- Excluded pts after RP if considered candidates for salvage radiation therapy
- Allowed prior hormonal therapy for neoadjuvant or adjuvant therapy + definitive radiation therapy if <36 months and at least 9 months before randomization or a single dose or short course (≤6 months) for rising PSA levels at least 9 months before randomization

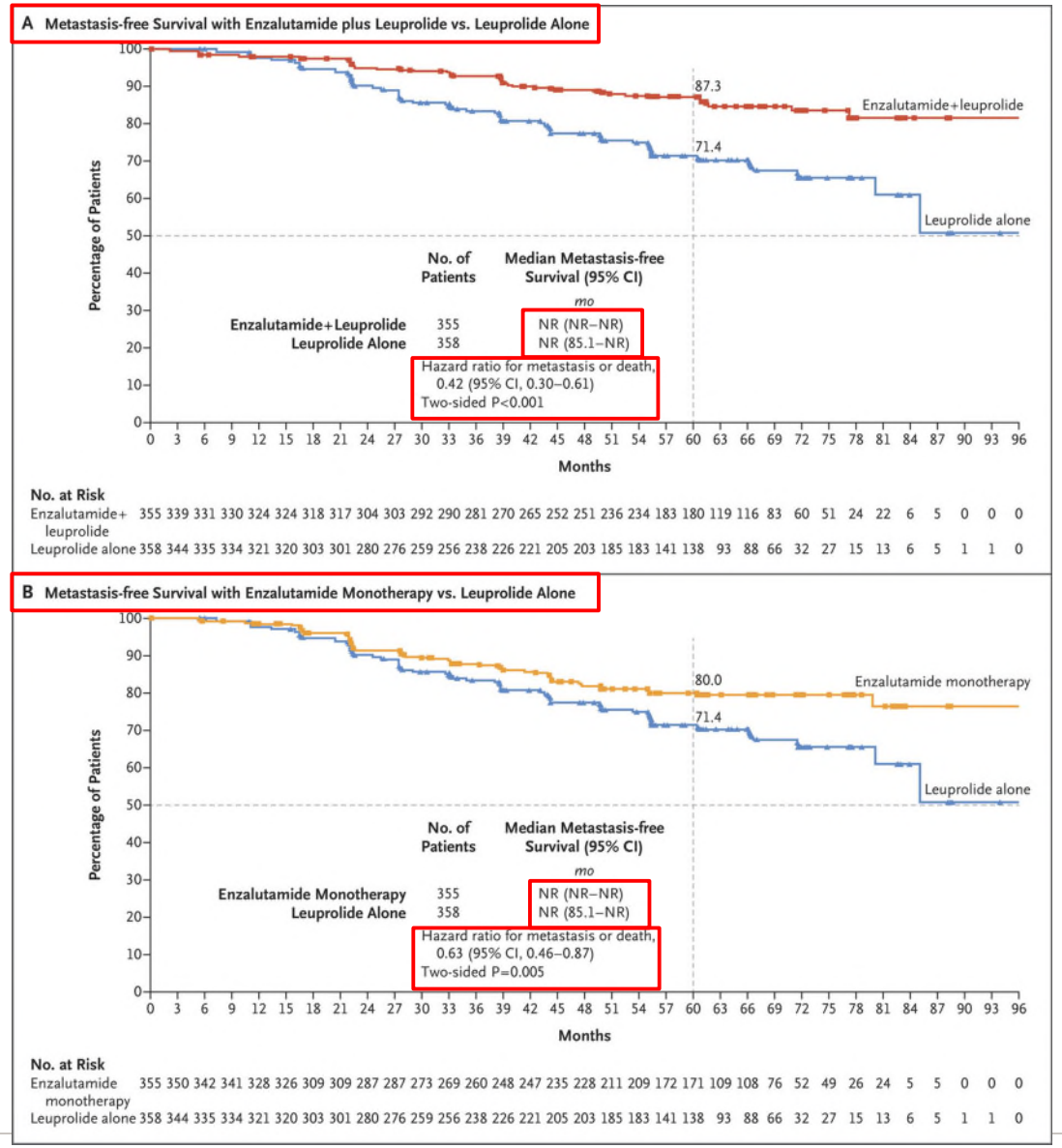
Treatment suspended at week 37 if the PSA level was <0.2; restarted when PSA ≥5.0 (if no prior RP) or ≥ 2.0 (if prior RP)

Freedland SJ, et al. BMJ Open. 2021;11:e0465885
Freedland SJ, et al. NEJM. 2023;389:1453-1465

EMBARK

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Enzalutamide + Leuprolide (N=355)	Leuprolide Alone (N=358)	Enzalutamide Monotherapy (N=355)
Median age (range) — yr	69 (51–87)	70 (50–92)	69 (49–93)
Age group — no. (%)			
<65 yr	81 (22.8)	91 (25.4)	91 (25.6)
65 to <75 yr	201 (56.6)	180 (50.3)	174 (49.0)
≥75 yr	73 (20.6)	87 (24.3)	90 (25.4)
Race or ethnic group — no. (%)†			
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)
American Indian or Alaska Native	4 (1.1)	1 (0.3)	0
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
Other	5 (1.4)	9 (2.5)	5 (1.4)
Not reported	10 (2.8)	5 (1.4)	14 (3.9)
Geographic region — no. (%)			
North America	144 (40.6)	137 (38.3)	133 (37.5)
Europe	130 (36.6)	128 (35.8)	146 (41.1)
Rest of the world	81 (22.8)	93 (26.0)	76 (21.4)
ECOG performance-status score — no. (%)‡			
0	328 (92.4)	336 (93.9)	321 (90.4)
1	26 (7.3)	21 (5.9)	34 (9.6)
>1	1 (0.3)	0	0
Missing data	0	1 (0.3)	0
PSA doubling time — no. (%)			
≤3 mo	69 (19.4)	80 (22.3)	76 (21.4)
>3 to 6 mo	187 (52.7)	142 (39.7)	164 (46.2)
>6 to 9 mo	98 (27.6)	135 (37.7)	114 (32.1)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)
Median PSA doubling time (range) — mo§	4.6 (0.9–9.6)	5.0 (1.1–10.8)	5.0 (1.0–18.9)
Median serum PSA level (range) — ng/ml	5.0 (1.0–308.3)	5.5 (1.1–163.3)	5.3 (1.1–37.0)
Previous hormonal therapy — no. (%)			
Yes	107 (30.1)	113 (31.6)	112 (31.5)
No	248 (69.9)	245 (68.4)	243 (68.5)
Primary definitive therapy — no. (%)			
Prostatectomy alone	90 (25.4)	75 (20.9)	99 (27.9)
Radiation therapy alone	86 (24.2)	104 (29.1)	90 (25.4)
Prostatectomy and radiation therapy	179 (50.4)	179 (50.0)	166 (46.8)

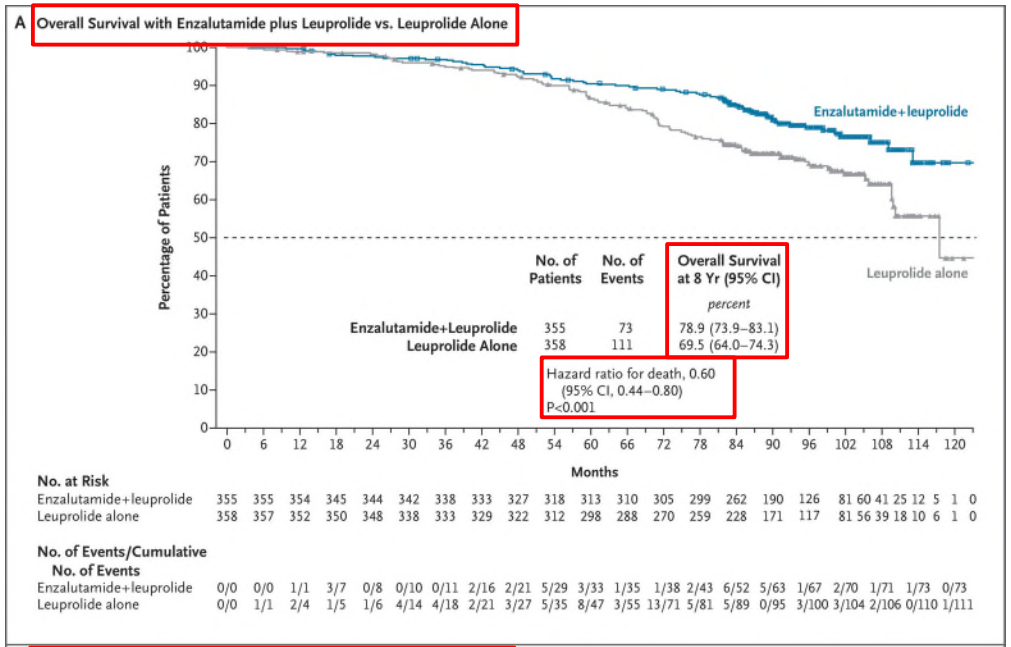


Freedland SJ, et al. NEJM. 2023;389:1453-1465

EMBARK

Median follow-up 94.2 mos in enza + ADT

OS benefit maintained for enza + ADT despite prolonged treatment suspension as mandated by the protocol for undetectable PSA at week 36



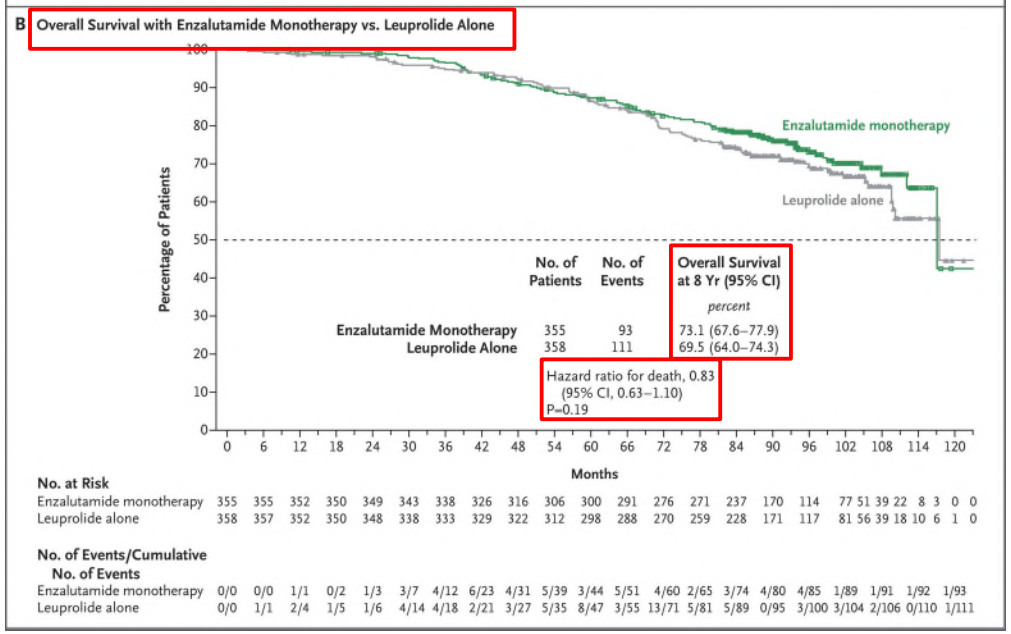


Table 1. Adverse Events (Safety Population).*

Event	Enzalutamide and Leuprolide (N=353)	Leuprolide Alone (N=354)	Enzalutamide Monotherapy (N=354)
	number of patients (percent)		
Adverse event that emerged during treatment	346 (98.0)	347 (98.0)	348 (98.3)
Adverse event that was the primary reason for discontinuation of treatment†	97 (27.5)	45 (12.7)	73 (20.6)
Adverse event that emerged during treatment and led to death‡	10 (2.8)	5 (1.4)	12 (3.4)
Any grade 3 or higher adverse event that emerged during treatment	185 (52.4)	175 (49.4)	203 (57.3)
Adverse event that emerged during treatment and was related to the trial drug§	307 (87.0)	286 (80.8)	316 (89.3)
Any grade 3 or higher adverse event that emerged during treatment and was related to the trial drug§	68 (19.3)	34 (9.6)	72 (20.3)
Serious adverse event that emerged during treatment	143 (40.5)	133 (37.6)	154 (43.5)
Serious adverse event that emerged during treatment and was related to the trial drug§	30 (8.5)	9 (2.5)	27 (7.6)
Adverse events that emerged during treatment and occurred in at least 10% of the patients in any group¶			
Hot flash	246 (69.7)‖	206 (58.2)‖	80 (22.6)
Fatigue	154 (43.6)‖	119 (33.6)‖	170 (48.0)‖
Arthralgia	104 (29.5)	75 (21.2)	89 (25.1)
Fall	104 (29.5)	60 (16.9)	71 (20.1)
Hypertension	92 (26.1)	75 (21.2)	76 (21.5)
Back pain	62 (17.6)	56 (15.8)	67 (18.9)
Diarrhea	55 (15.6)	31 (8.8)	47 (13.3)
Constipation	53 (15.0)	35 (9.9)	38 (10.7)
Hematuria	50 (14.2)	57 (16.1)	53 (15.0)
Dizziness	46 (13.0)	44 (12.4)	47 (13.3)
Headache	46 (13.0)	36 (10.2)	47 (13.3)
Insomnia	45 (12.7)	40 (11.3)	26 (7.3)
Nausea	43 (12.2)	31 (8.8)	57 (16.1)
Asthenia	42 (11.9)	21 (5.9)	41 (11.6)
Pain in arm or leg	42 (11.9)	37 (10.5)	44 (12.4)
Coronavirus disease 2019	38 (10.8)	51 (14.4)	50 (14.1)
Urinary incontinence	38 (10.8)	35 (9.9)	40 (11.3)
Urinary tract infection	33 (9.3)	28 (7.9)	46 (13.0)
Peripheral edema	32 (9.1)	40 (11.3)	37 (10.5)
Gynecomastia	31 (8.8)	32 (9.0)	163 (46.0)‖
Nasopharyngitis	31 (8.8)	26 (7.3)	40 (11.3)
Weight decreased	25 (7.1)	14 (4.0)	42 (11.9)
Nipple pain	13 (3.7)	4 (1.1)	54 (15.3)
Breast tenderness	4 (1.1)	4 (1.1)	51 (14.4)

* Patients in the safety population were evaluated according to the treatment that they received. Adverse events that occurred from the time of the first dose of the trial regimen through 30 days after permanent discontinuation of treatment are included. The data-cutoff date was May 27, 2025. The median duration of treatment, excluding treatment suspension, was 44.3 months (range, 0.1 to 111.3) among patients who received enzalutamide plus leuprolide, 40.7 months (range, 0.7 to 111.1) among patients who received leuprolide alone, and 59.3 months (range, 0.4 to 112.2) among patients who received enzalutamide monotherapy. Adverse events are defined according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 28.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Percentages may not total 100 because of rounding.

† Adverse events were identified as the primary reason for the discontinuation of treatment on the basis of information provided by the patient on the treatment discontinuation case report form.

‡ Adverse events that led to death were grade 5 adverse events; none were considered by the investigator to be related to treatment.

§ Adverse events that were considered by the investigator to be related to the trial drug were related to enzalutamide monotherapy, leuprolide, or both enzalutamide and leuprolide.

¶ Numbers include patients who had at least one adverse event that emerged during treatment. Patients who had multiple adverse events that met the definition for a given preferred term were counted only once for the preferred term. Events are sorted according to decreasing incidence of the type of event in the enzalutamide–leuprolide combination group.

‖ These events were among the most common adverse events that emerged during treatment (occurring in ≥30% of the patients in any group).

Shore ND, et al. NEJM. 2025; DOI: 10.1056/NEJMoa2510310

Biochemically recurrent prostate cancer

FDA approves enzalutamide for non-metastatic castration-sensitive prostate cancer with biochemical recurrence

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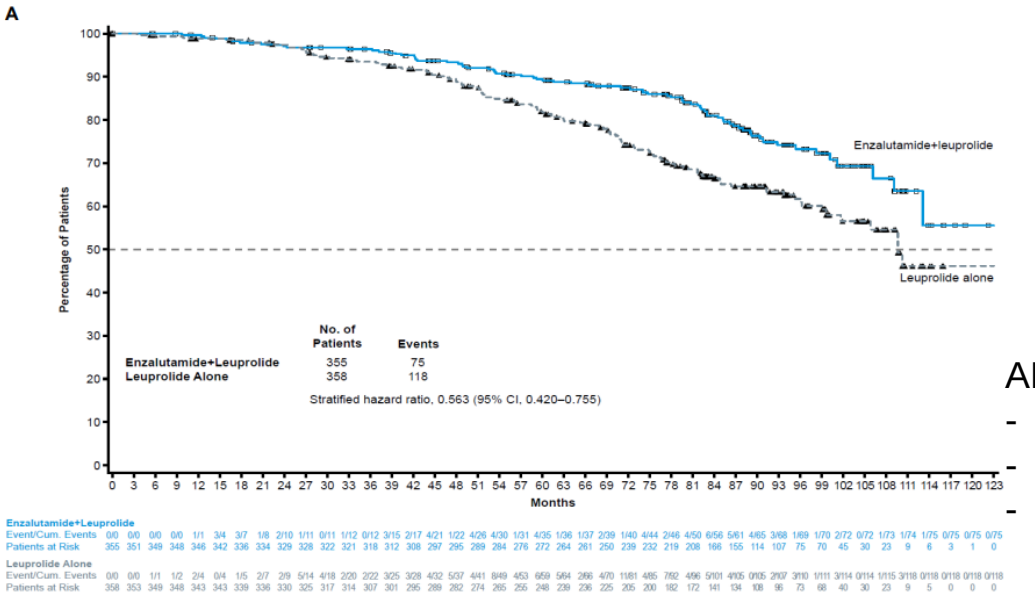
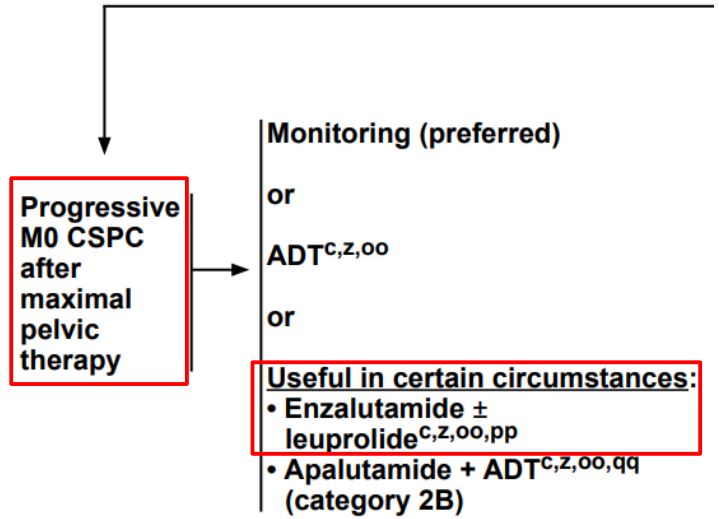
FDA approves enzalutamide for non-metastatic castration-sensitive prostate cancer with biochemical recurrence

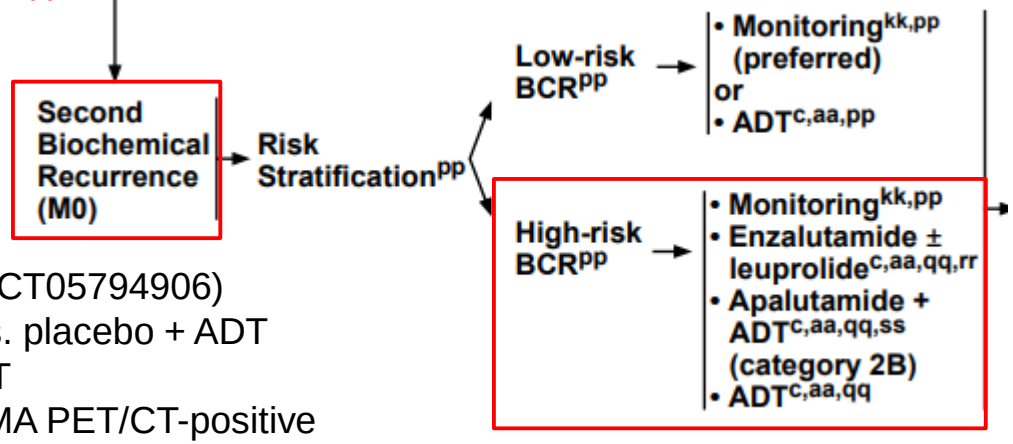
On November 16, 2023, the Food and Drug Administration approved enzalutamide (Xtandi, Astellas Pharma US, Inc.) for non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR).

Figure S3. Progression-Free Survival on First Subsequent Therapy (Intention-to-Treat Population) for (A) Enzalutamide plus Leuprolide vs Leuprolide Alone and (B) Enzalutamide Monotherapy vs Leuprolide Alone.





First Biochemical Recurrence = "salvage therapy"

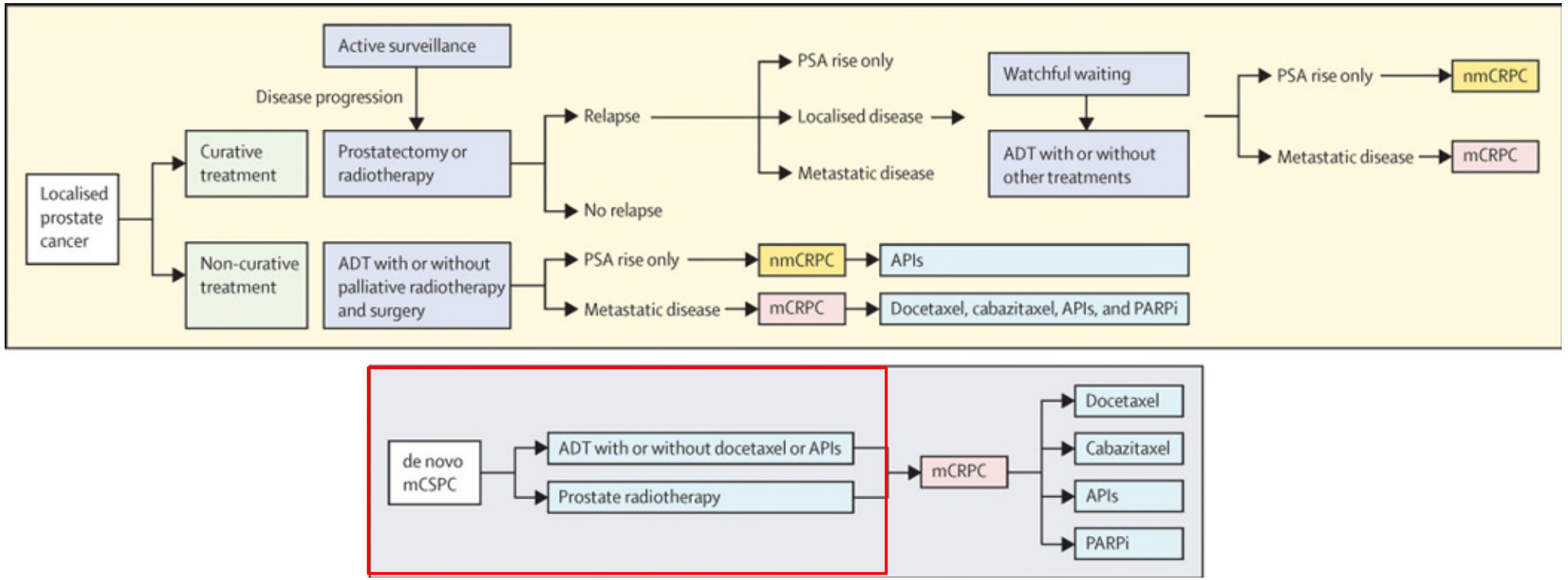


ARASTEP phase 3 trial (NCT05794906)

- Darolutamide + ADT vs. placebo + ADT
- rPFS by PSMA PET/CT
- high-risk BCR and PSMA PET/CT-positive lesions following primary therapy

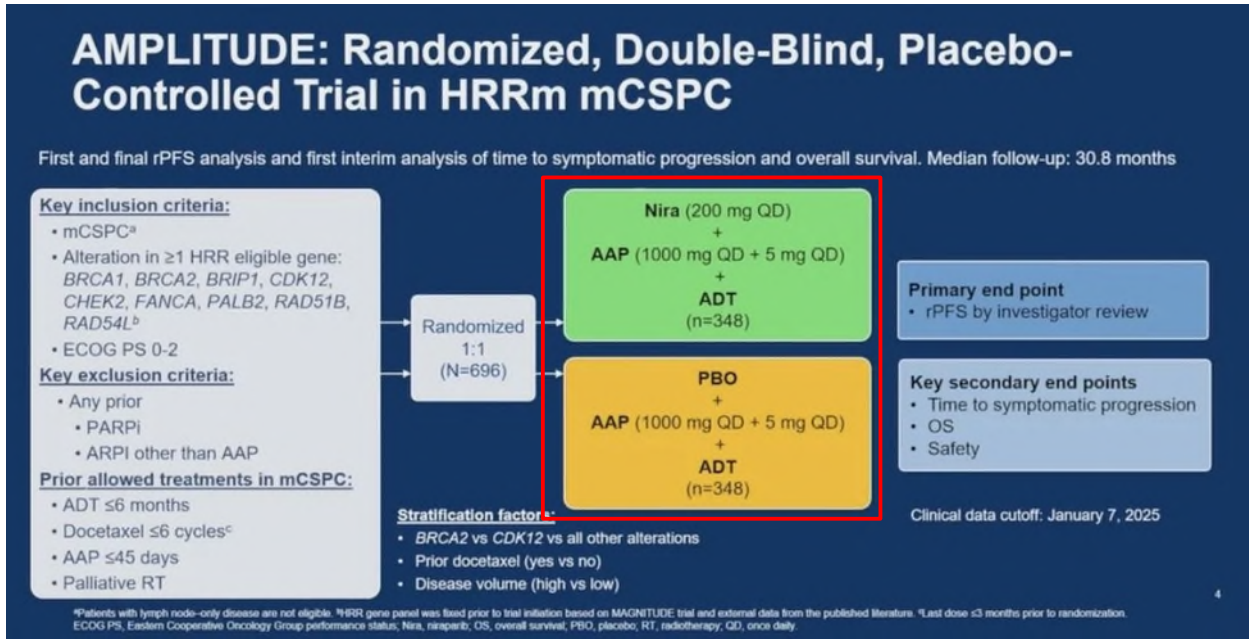
Aggarwal R, et al. PRESTO. J Clin Oncol. 2024;42:1114-1123
Shore ND, et al. NEJM. 2025; DOI: 10.1056/NEJMoa2510310
NCCN Guidelines. Prostate Cancer. Version 5.2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

mCSPC update



Sandhu S, et al. Lancet. 2021;398(10305):1075-1090

AMPLITUDE



- Central testing of tumor tissue (FoundationOne CDx; Foundation Medicine), plasma (FoundationOne Liquid CDx; Foundation Medicine) or germline (Invitae Multi-Cancer Panel; Invitae)

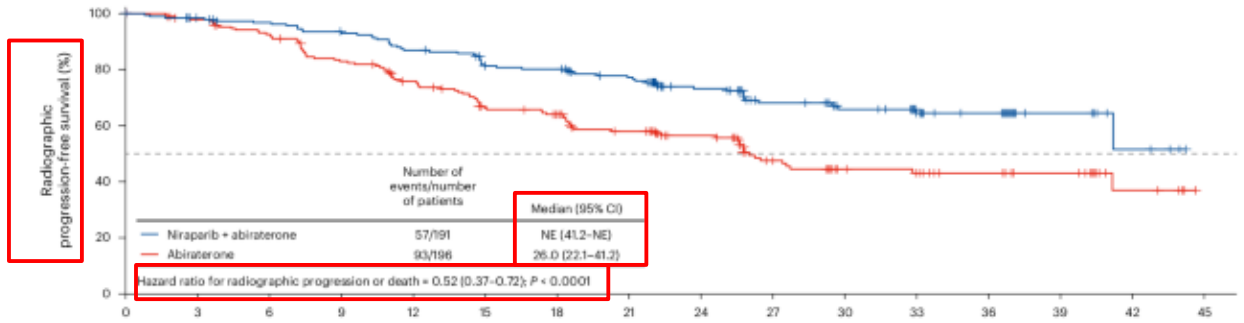
	Niraparib plus abiraterone (n = 348)	Abiraterone (n = 348)
	Intention-to-treat	
Median age (range), years	68 (40–88)	67 (40–92)
Race		
White	246 (70.7)	257 (73.9)
Asian	77 (22.1)	67 (19.3)
Black or African American	18 (5.2)	10 (2.9)
Other	3 (0.9)	6 (1.7)
Not reported/Unknown	4 (1.1)	8 (2.3)
Region		
Europe	168 (48.3)	177 (50.9)
Asia	72 (20.7)	63 (18.1)
North America	45 (12.9)	44 (12.6)
Rest of world	63 (18.1)	64 (18.4)
ECOG performance status[b]		
0	242 (69.5)	218 (62.6)
1	97 (27.9)	124 (35.6)
2	9 (2.6)	6 (1.7)
Gleason score at initial diagnosis[c]		
≤7	60 (17.2)	68 (19.5)
>7	276 (79.3)	262 (75.3)
Unknown	12 (3.4)	18 (5.2)
Metastatic stage at initial diagnosis		
M0	32 (9.2)	36 (10.3)
M1	301 (86.5)	302 (86.8)
Unknown	15 (4.3)	10 (2.9)
Disease volume		
High	269 (77.3)	271 (77.9)
Low	79 (22.7)	77 (22.1)
Median time from start of androgen deprivation therapy for M1 disease (range), months	2.46 (0.2–6.2)	2.30 (0.1–6.2)
Single gene alterations		
BRCA2	148 (42.5)	144 (41.4)
CHEK2	72 (20.7)	76 (21.8)
CDK12	28 (8.0)	28 (8.0)
BRCA1	25 (7.2)	25 (7.2)
FANCA	15 (4.3)	15 (4.3)
RAD54L	12 (3.4)	6 (1.7)
PALB2	9 (2.6)	13 (3.7)
BRIP1	9 (2.6)	6 (1.7)
RAD51B	4 (1.1)	5 (1.4)
Co-occurring *BRCA* alterations[d]	18 (5.2)	27 (7.8)
BRCA2/CHEK2	5 (1.4)	13 (3.7)
Co-occurring non-*BRCA* alterations[d]	8 (2.3)	5 (1.4)

Attard G, et al. Nat Med. 2025;31(12):4109-4118

AMPLITUDE

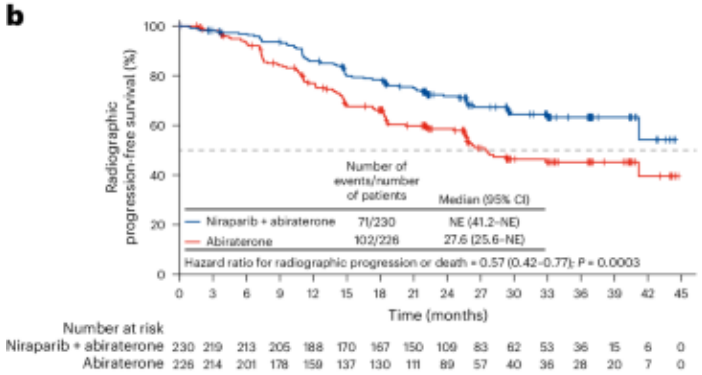
BRCA subgroup

a



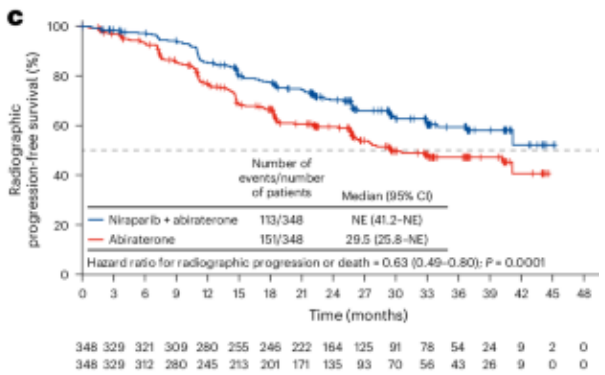
HRR effector subgroup

b



ITT

c

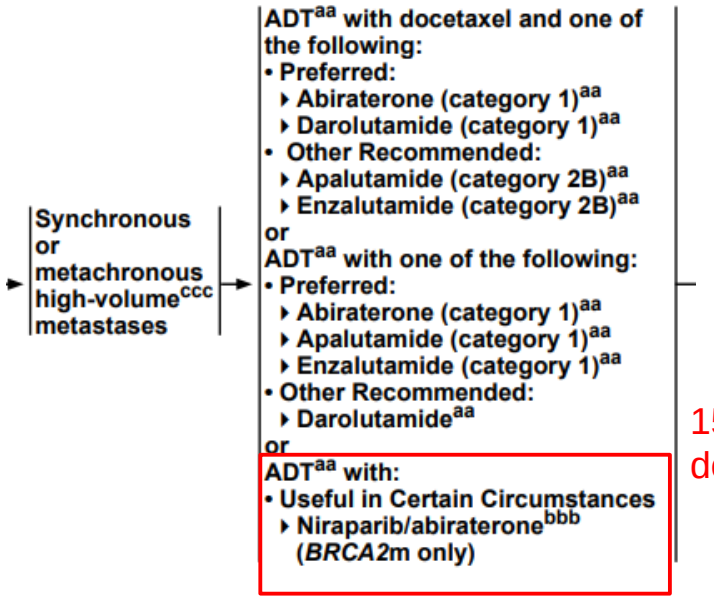


Endpoint	Niraparib plus abiraterone (n = 191)	Abiraterone (n = 196)	Hazard ratio (95% CI)	P value
	BRCA			
Secondary endpoints, median (months)				
Time to symptomatic progression[a]	NE	NE	0.44 (0.29–0.68)	0.0001
Overall survival[a]	NE	NE	0.75 (0.51–1.11)	0.15[b]
Time to subsequent therapy	44.6	30.0	0.47 (0.33–0.66)	< 0.0001[e]
Other endpoints				
Second progression-free survival, median (months)	NE	44.0	0.59 (0.41–0.83)	0.0026[e]
Objective response, n/N (%)	48/63 (76.2)	53/72 (73.6)	1.04 (0.85–1.26)[c]	0.73
Time to PSA progression, median (months)	NE	25.5	0.41 (0.29–0.59)	< 0.0001[e]
Confirmed PSA response, %[d]	88.5	85.7	1.03 (0.96–1.12)[c]	0.42
	HRR effector			
	Niraparib plus abiraterone (n = 230)	**Abiraterone (n = 226)**	**Hazard ratio (95% CI)**	***P* value**
Secondary endpoints, median (months)				
Time to symptomatic progression[a]	NE	NE	0.49 (0.33–0.74)	0.0004
Overall survival[a]	NE	NE	0.81 (0.57–1.16)	0.25[f]
Time to subsequent therapy	44.6	33.6	0.50 (0.36–0.69)	< 0.0001[e]
Other endpoints				
Second progression-free survival, median (months)	NE	44.0	0.63 (0.45–0.87)	0.0049[e]
Objective response, n/N (%)	58/76 (76.3)	58/79 (73.4)	1.04 (0.87–1.25)[c]	0.68
Time to PSA progression, months	NE	29.0	0.48 (0.35–0.66)	< 0.0001[e]
Confirmed PSA response, %[d]	87.0	85.8	1.01 (0.94–1.09)[c]	0.73

Attard G, et al. Nat Med. 2025;31(12):4109-4118

FDA approves niraparib and abiraterone acetate plus prednisone for BRCA2-mutated metastatic castration-sensitive prostate cancer

On December 12, 2025, the Food and Drug Administration approved niraparib and abiraterone acetate (Akeega, Janssen Biotech, Inc.) with prednisone for adults with deleterious or suspected deleterious BRCA2-mutated (BRCA2m) metastatic castration-sensitive prostate cancer (mCSPC), as determined by an FDA-approved test.



25.1% ≥ transfusion for anemia (median 2, range: 1–5)

15% received prior docetaxel <6 cycles

[bbb] Niraparib/abiraterone can be used following the completion of docetaxel in patients receiving triplet therapy or following EBRT to the primary tumor. The use of this combination in patients with low-volume disease is controversial because 78% of the patients in the trial had high-volume disease and there were very few patients with low-volume metachronous disease in particular. This regimen adds considerable toxicity, and patients with low-volume disease should be informed that the benefit in this setting is not clear.

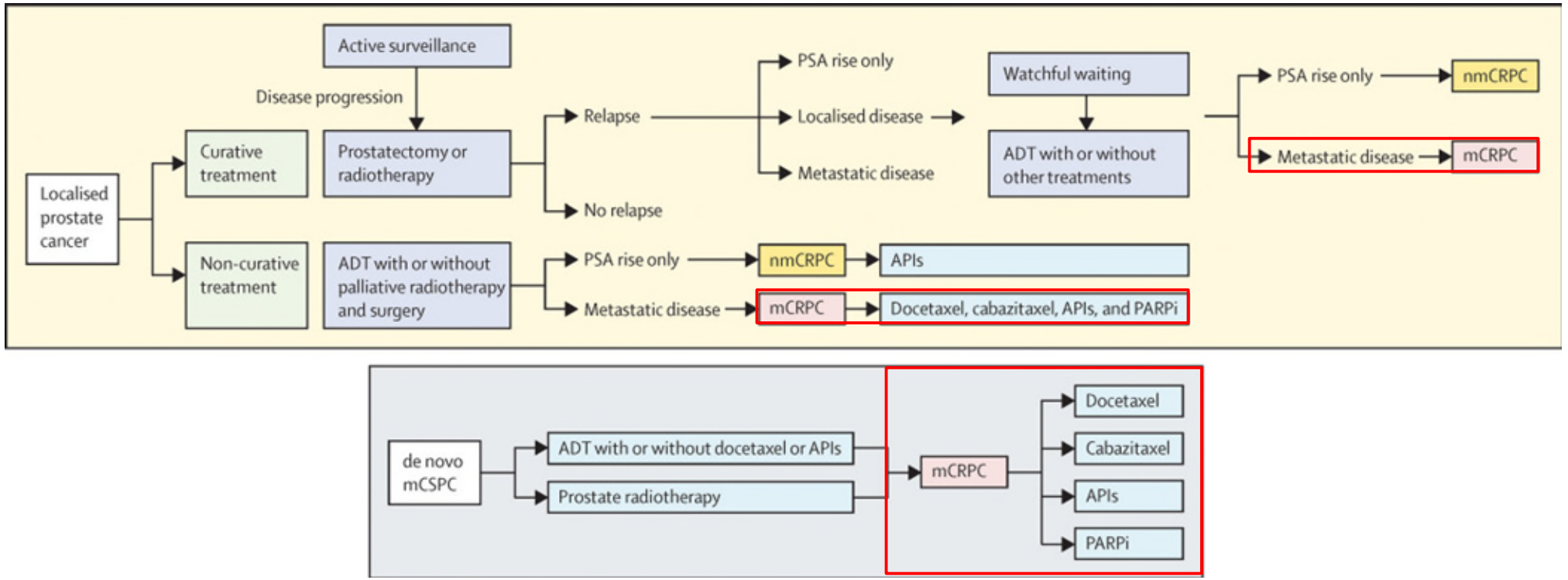
AMPLITUDE

	Niraparib plus abiraterone (*n* = 347)		Abiraterone (*n* = 348)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events reported in ≥15% of patients in either group, *n* (%)				
Anemia[b]	179 (51.6)	101 (29.1)	83 (23.9)	16 (4.6)
Hypertension[b]	152 (43.8)	92 (26.5)	113 (32.5)	64 (18.4)
Constipation	122 (35.2)	0	57 (16.4)	1 (0.3)
Nausea	107 (30.8)	0	50 (14.4)	0
Fatigue	91 (26.2)	7 (2.0)	64 (18.4)	4 (1.1)
Hypokalemia[b]	90 (25.9)	40 (11.5)	70 (20.1)	38 (10.9)
Neutropenia[b]	76 (21.9)	33 (9.5)	28 (8.0)	7 (2.0)
Arthralgia	73 (21.0)	2 (0.6)	74 (21.3)	6 (1.7)
Back pain	68 (19.6)	12 (3.5)	77 (22.1)	5 (1.4)
Thrombocytopenia[b]	66 (19.0)	24 (6.9)	20 (5.7)	1 (0.3)
COVID-19	65 (18.7)	3 (0.9)	71 (20.4)	4 (1.1)
Hot flush	63 (18.2)	0	48 (13.8)	0
Leukopenia	58 (16.7)	16 (4.6)	18 (5.2)	1 (0.3)
Vomiting	56 (16.1)	3 (0.9)	30 (8.6)	0
Peripheral edema[b]	55 (15.9)	1 (0.3)	42 (12.1)	0
Weight decreased	53 (15.3)	4 (1.2)	18 (5.2)	0
Alanine aminotransferase increased[b]	22 (6.3)	6 (1.7)	54 (15.5)	17 (4.9)

Attard G, et al. Nat Med. 2025;31(12):4109-4118

NCCN Guidelines. Prostate Cancer. Version 5.2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

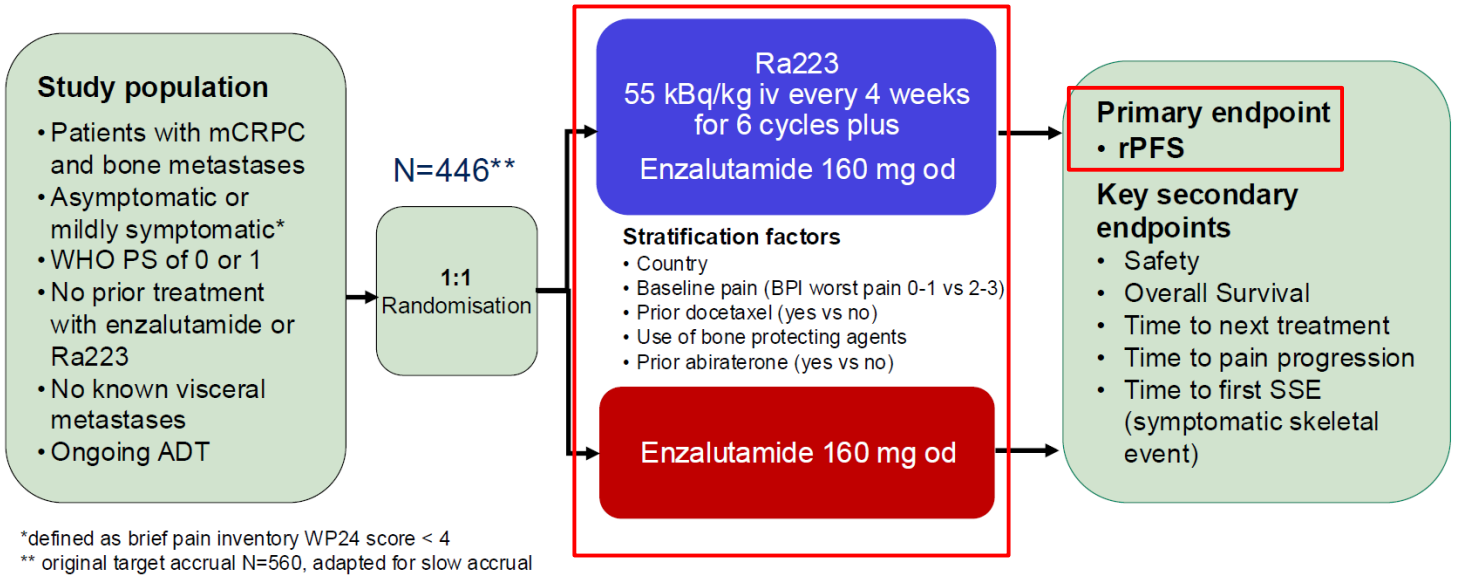
First-line mCRPC updates



Sandhu S, et al. Lancet. 2021;398(10305):1075-1090

PEACE-3

Open-label phase III RCT

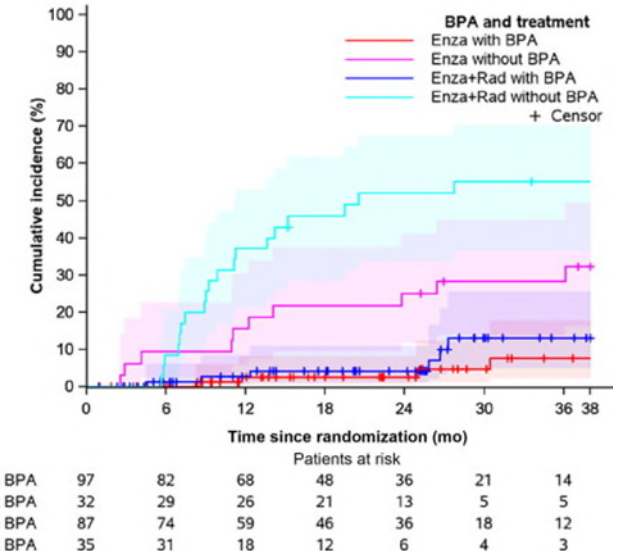


*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

- Following ERA-223 (abi + Ra223), PEACE3 amended in 2018 after 119 pts enrolled for mandatory monthly bone-protecting agent (BPA)
- Must receive at least 2 doses BPA before first Ra223 dose

Time point	Fine-Gray cumulative Incidence of fracture (95% CI)			
	BPA exposure		No BPA exposure	
	ENZA + ^{223}Ra	ENZA	ENZA + ^{223}Ra	ENZA
	(*n* = 87)	(*n* = 97)	(*n* = 35)	(*n* = 32)
3 mo	0	0	0	6.3 (1.1–18.4)
6 mo	1.3 (0.1–6.1)	0	8.6 (2.1–20.8)	9.4 (2.3–22.5)
9 mo	2.7 (0.5–8.5)	1.3 (0.1–6.1)	25.7 (12.6–41.0)	9.4 (2.3–22.5)
12 mo	**2.7 (0.5–8.5)**	**2.6 (0.5–8.3)**	**37.1 (21.3–53.0)**	**15.6 (5.6–30.3)**
15 mo	4.3 (1.1–10.9)	2.6 (0.5–8.3)	42.9 (26.1–58.6)	21.9 (9.5–37.5)
18 mo	**4.3 (1.1–10.9)**	**2.6 (0.5–8.3)**	**45.9 (28.6–61.6)**	**21.9 (9.5–37.5)**
21 mo	4.3 (1.1–10.9)	2.6 (0.5–8.3)	52.0 (33.8–67.5)	21.9 (9.5–37.5)

ENZA = enzalutamide; BPA = bone-protecting agent; CI = confidence interval.



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Gillessen S, et al. Ann Oncol. 2024;35(Suppl 2):S1254
Gillessen S, et al. Eur Urol. 2025; S0302-2838(24)02747-7

PEACE-3

446 patients enrolled in 12 countries, 11/2015 to 03/2023, median follow-up: 42.2 months

	Enza+Ra223 (N=222)	Enza (N=224)
	N (%)	N (%)
Age, Median (range) years	70.0 (43.0 - 90.0)	70.0 (47.0 - 90.0)
PSA, Median (Q25-Q75) ng/mL	25.3 (6.5 - 68.8)	23.0 (8.5 - 54.9)
WHO Performance status 0	152 (69)	154 (69)
Prior docetaxel(1)	67 (30.2)	66 (30)
Prior abiraterone(1)	4 (2)	7 (3)
Bone lesions(2)		
<10	109 (49)	105 (47)
≥10	93 (42)	99 (44)
Missing or diffuse lesions	20 (9)	20 (9)
Alkaline phosphatase		
≤ULN	127 (57)	107 (48)
>ULN	82 (37)	110 (49)
Missing	13 (6)	7 (3)
Extra-skeletal disease at baseline	77 (35)	73 (33)

(1) Prior docetaxel or abiraterone was allowed for mHSPC

(2) Per imaging guidelines, the type of bone lesions is reported by a radiologist and classified into focal, diffuse or equivocal. Only focal bone lesions can be counted.

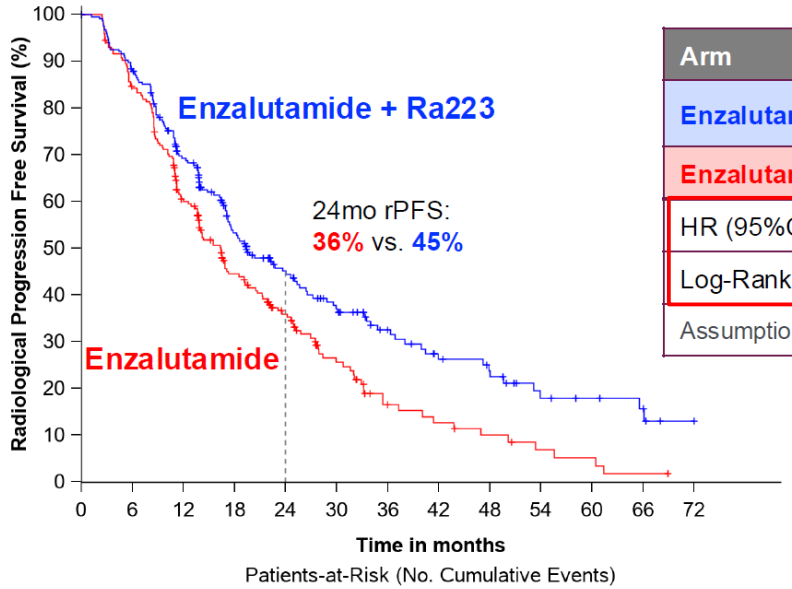
	Enza+Ra223	Enza
Enzalutamide treatment duration (months)		
	N=218	N=224
Median	17.3	14.0
Q25 – Q75	9.7 - 27.6	8.3 - 23.3
Radium, number of cycles		
	N=215	
< 6 cycles	25 (11.6%)	
6 cycles	189 (87.9%)	
Missing	1 (0.5%)	

Patients	Enza+Ra223 (N=218)	Enza (N=224)
	N (%)	N (%)
Adverse events (AEs)	218 (100)	216 (96)
Drug-related AEs	183 (84)	158 (71)
Serious AEs	93 (43)	66 (30)
Serious drug-related AEs	18 (8)	3 (1)
Grade 3-5 AEs	143 (66)	125 (56)
Grade 3-5 drug-related AEs	61 (28)	42 (19)
Death due to AE	7 (3)	4 (2)
Death due to a drug-related AE	0	0
Treatment discontinuation due to toxicity		
Enzalutamide	13 (8)	12 (7)
RA223	7 (3)	

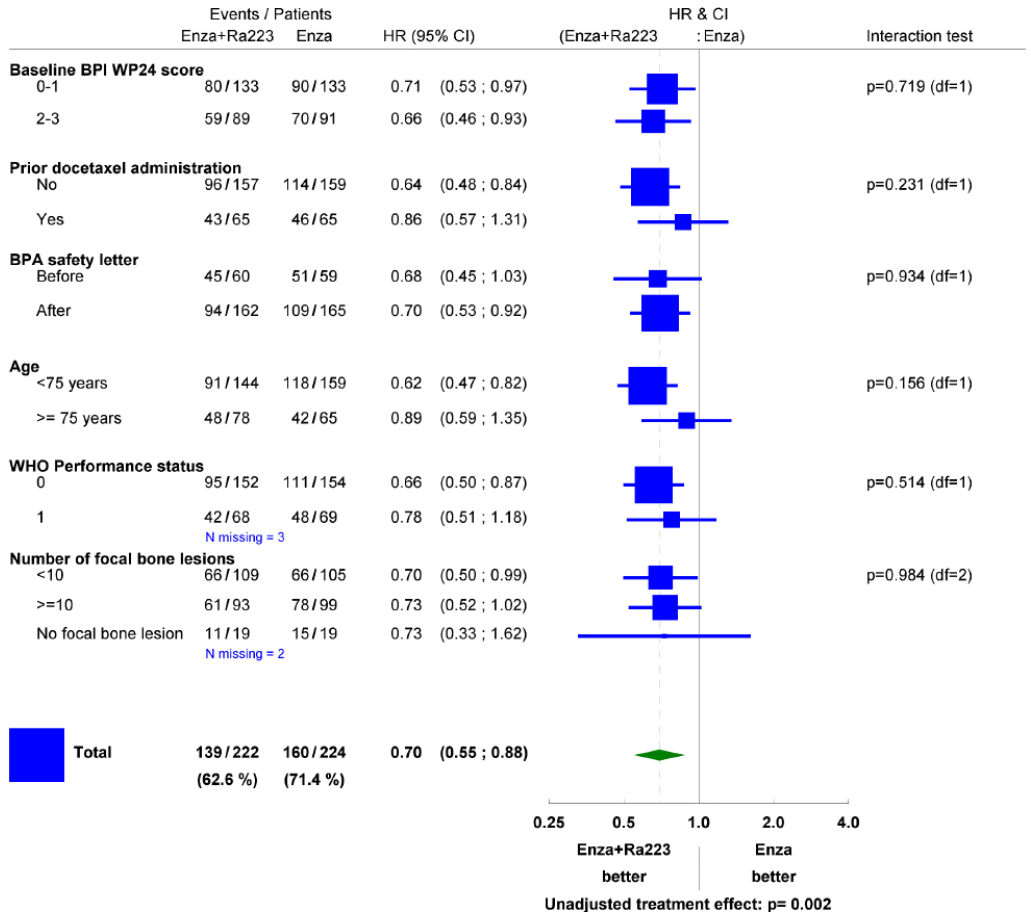
Gillessen S, et al. Ann Oncol. 2024;35(Suppl 2):S1254

Primary endpoint: rPFS

PEACE-3



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



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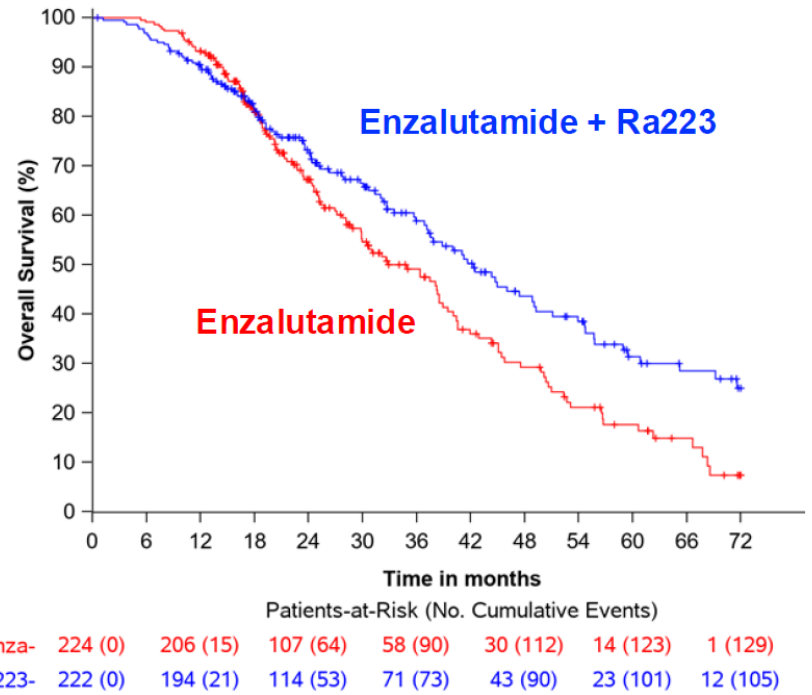
Gillessen S, et al. Ann Oncol. 2024;35(Suppl 2):S1254

PEACE-3

Overall Survival at interim analysis (80% of OS events)



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

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

SYSTEMIC THERAPY FOR M1 CRPC: ADENOC

Pre-ARPI[aa,lll]

Preferred:
- Abiraterone (category 1)
- Enzalutamide (category 1)

Other Recommended:
- Docetaxel[hhh] (category 1)

Useful in Certain Circumstances:
- Molecular Biomarker-Directed Therapy
  - *BRCA* mutation
    - ◊ Niraparib/abiraterone[mmm] (category 1)
    - ◊ Olaparib/abiraterone[mmm] (category 1)
    - ◊ Talazoparib/enzalutamide[mmm] (category 1)
  - *HRRm* (other than BRCA1/2)
    - ◊ Talazoparib/enzalutamide[mmm] (category 1)
- Disease State-Specific Therapy
  - Bone metastases
    - ◊ Radium-223[ooo]/enzalutamide

Potential new 1L mCRPC treatment with enza + Ra223 in pts who have not received a prior ARPI

EORTC Announces Final Overall Survival Results from the PEACE-3 Trial

19 Oct 2025

The European Organisation for Research and Treatment of Cancer (EORTC) is pleased to announce that the EORTC 1333/PEACE-3 trial has reached its final overall survival (OS) endpoint at the time of the final database lock on September 19, 2025.

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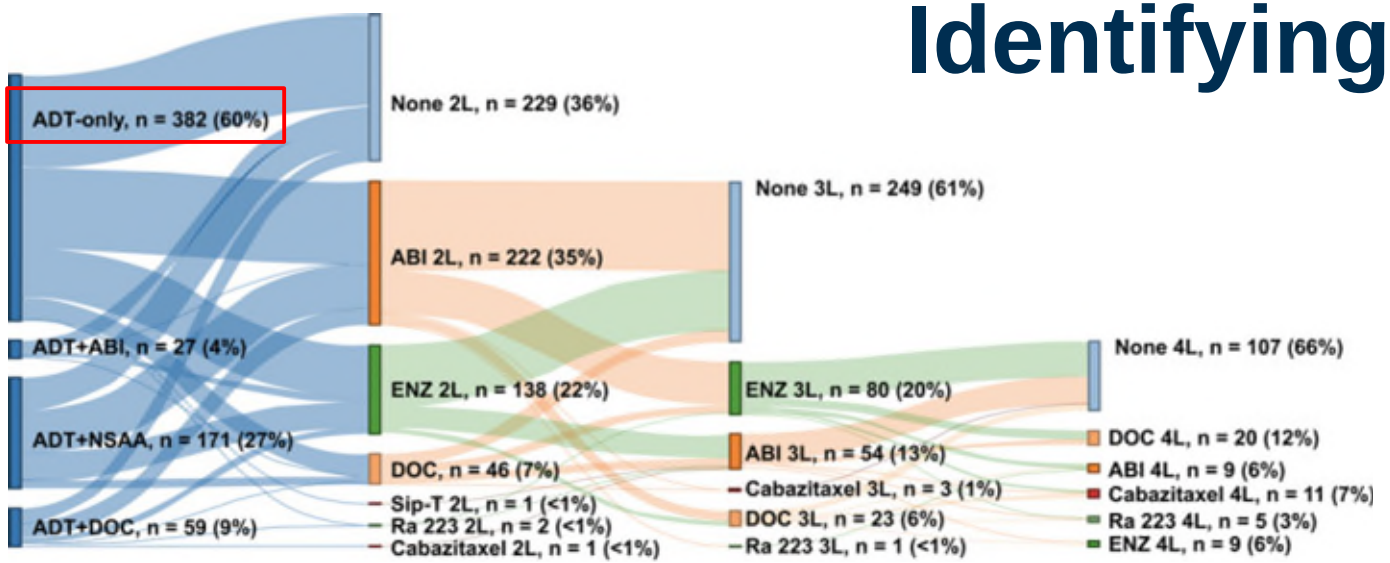
Tombal B, et al. Ann Oncol. 2025;36(9):1058-1067
Gillessen S, et al. Ann Oncol. 2024;35(Suppl 2):S1254
NCCN Guidelines. Prostate Cancer. Version 5.2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

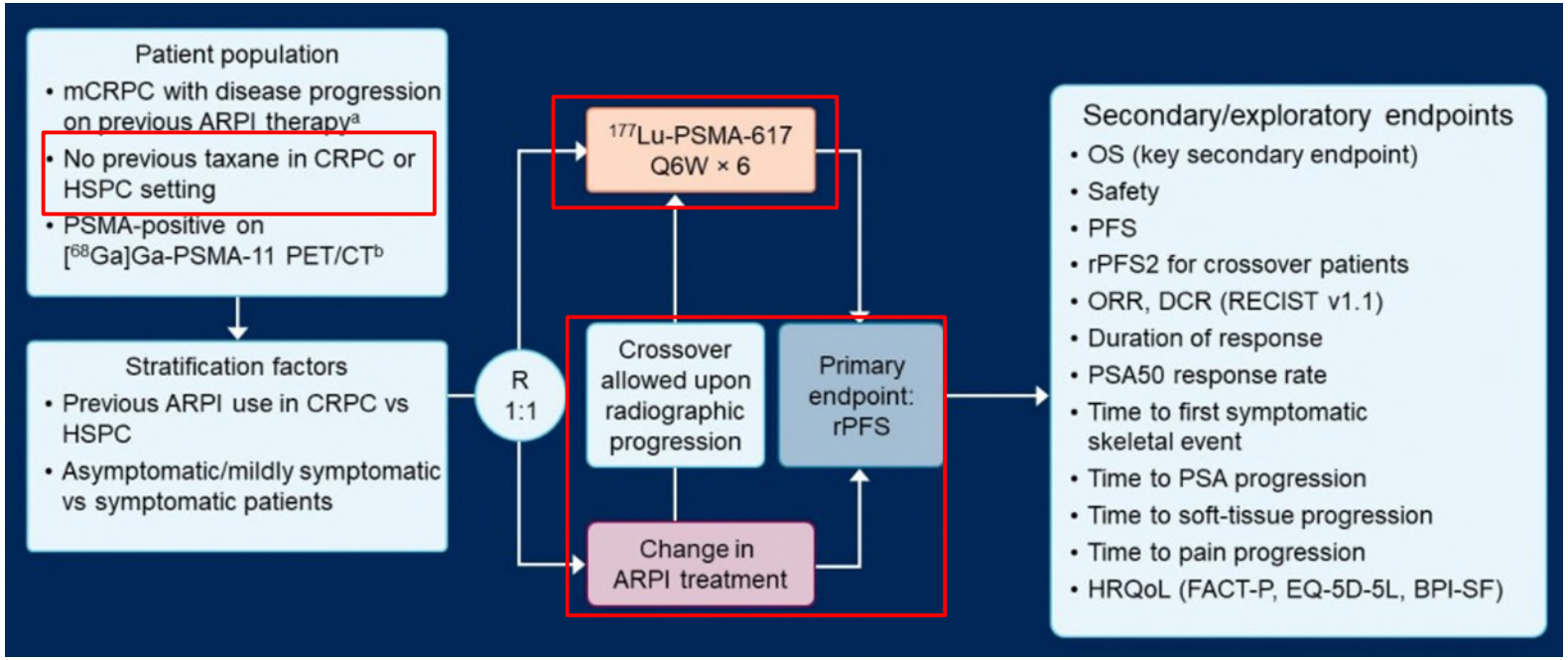
Identifying candidates for PEACE-3

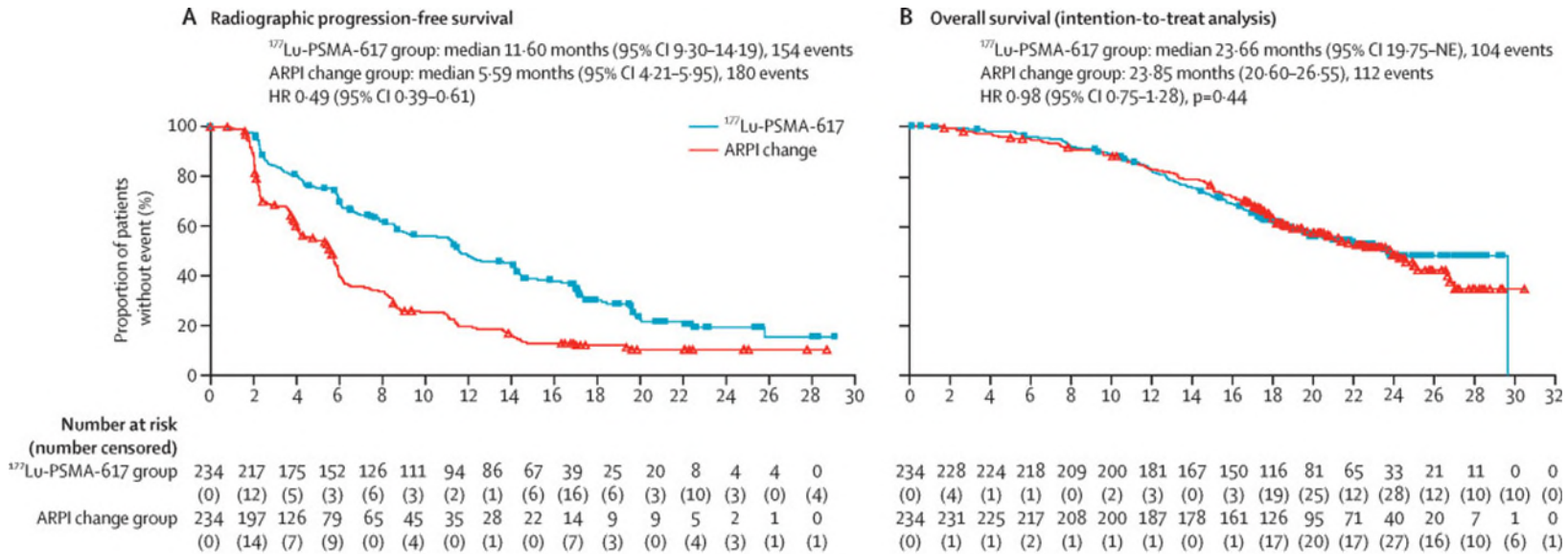


	All mHSPC patients		Diagnosed with mHSPC in 2015–2017		Diagnosed with mHSPC in 2018–2020	
	Not oligometastatic (*N* = 320)[a]	Oligometastatic (*N* = 79)	Not oligometastatic (*N* = 162)	Oligometastatic (*N* = 39)	Not oligometastatic (*N* = 320)[a]	oligometastatic (*N* = 79)
1L regimen, No. (%)						
ADT	163 (50.9)	51 (64.6)	95 (58.6)	26 (66.7)	68 (43.0)	25 (62.5)
ADT + abiraterone	55 (17.2)	11 (13.9)	11 (6.8)	2 (5.1)	44 (27.8)	9 (22.5)
ADT + apalutamide	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
ADT + chemotherapy	43 (13.4)	4 (5.1)	27 (16.7)	2 (5.1)	16 (10.1)	2 (5.0)
ADT + chemotherapy + abiraterone	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
ADT + enzalutamide	8 (2.5)	4 (5.1)	1 (0.6)	1 (2.6)	7 (4.4)	3 (7.5)
ADT + enzalutamide + abiraterone	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Died	49 (15.3)	8 (10.1)	28 (17.3)	8 (20.5)	21 (13.3)	0 (0.0)

Gong J, et al. Cancer. 2024;130(22):3815-3825
Freedland SJ, et al. Cancer Med. 2021;10:8570-8580

PSMAfore





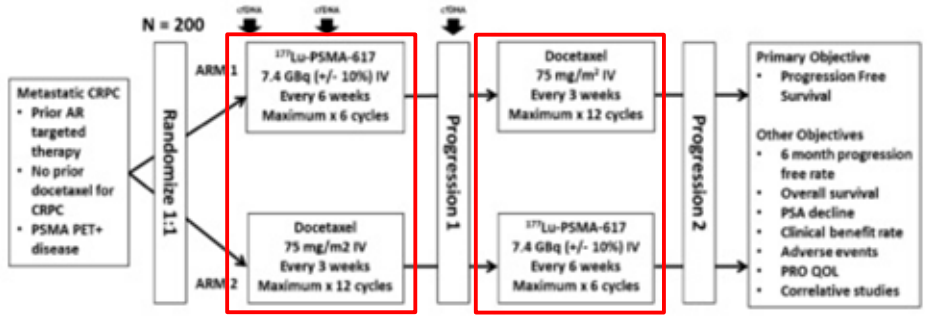
Morris M, et al. Lancet. 2024;404(10459):1227-1239

177-Lu-PSMA-617 pre-taxane mCRPC

FDA expands Pluvicto's metastatic castration-resistant prostate cancer indication

On March 28, 2025, the Food and Drug Administration expanded the indication for lutetium Lu 177 vipivotide tetraxetan (Pluvicto, Novartis Pharmaceuticals Corporation) to include adults with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay taxane-based chemotherapy.

CCTG.PR21 PLUDO (Prostate Lutetium/DOcetaxel): A Randomized Phase II Study of ^{177}Lu-PSMA-617 vs. Docetaxel in Patients with mCRPC and PSMA-Positive Disease



ClinicalTrials.gov Identifier: NCT04663997
PI's: Kim Chi, Fred Saad, Francois Benard
Funding: Prostate Cancer Canada/Movember

134/234 pts [57%] in ARPI change crossed over
?confounding OS analysis

PSMAfore did not examine a population with more aggressive disease for whom taxane-based chemotherapy more appropriate after ARPI progression

PSMAfore did not have a bidirectional crossover design
→ conclusions cannot be made about optimal sequencing of change of ARPI vs 2L 177Lu-PSMA-617

Outcome	LU-P (n=100) Median	DOC (n=99) Median	HR (LU-P/DOC)	p-value
rPFS(mo)	8.6 (90%CI 7.13 - 10.60)	10.7 (90%CI 7.82-11.10)	1.02 (90%CI 0.77-1.35)	0.54 (1 sided)
OS(mo)	14.3 (90%CI 10.8-16.6)	18.2 (90%CI 16.1-23.0)	1.64 (90%CI 1.14-2.35)	0.02 (2 sided)
ORR	16%	8%		
PSA ≥50%	53%	32%		

177Lu-PSMA-617 active/effective across mCRPC spectrum although optimal sequencing remains unclear

Chi KN, et al. Ann Oncol. 2025;36(2):S1630-S1631
Morris M, et al. Lancet. 2024;404(10459):1227-1239

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,jjj,kkk]

Pre-ARPI[aa,lll]	Post-ARPI[lll]/Pre-Docetaxel[aa]	Post-ARPI[lll]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[hhh] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[mmm] (category 1) ◊ Olaparib/abiraterone[mmm] (category 1) ◊ Talazoparib/enzalutamide[mmm] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[mmm] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[ooo]/enzalutamide	**Preferred:** • Docetaxel[hhh] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[mmm] (category 1, preferred) ◊ Rucaparib[mmm] (category 1, preferred) ◊ Niraparib/abiraterone[mmm] (category 2B) ◊ Talazoparib/enzalutamide[mmm] (category 2B) ▸ *HRRm* (other than BRCA1/2) ◊ Olaparib[mmm] ◊ Talazoparib/enzalutamide[mmm] (category 2B) • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[qqq] ▸ Aggressive variant[lll] ◊ Cabazitaxel/Carboplatin[hhh]	**Preferred:** • Cabazitaxel[hhh] (category 1) • Docetaxel rechallenge[hhh] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[mmm] (category 1) ◊ Rucaparib[mmm] ▸ *HRRm* (other than *BRCA1/2*) ◊ Olaparib[mmm] ▸ Other FDA-approved agents for tissue agnostic indications[hhh] • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177-PSMA-617[qqq] (category 1) ▸ Aggressive variant[lll] ◊ Cabazitaxel/carboplatin[hhh] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[hhh]

NCCN Guidelines. Prostate Cancer. Version 5.2026.
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Conclusions

- In high-risk biochemically recurrent prostate cancer, ADT + enza is an established standard option

- In mCSPC with BRCA2 mutation, ADT + nira/abiraterone/pred represents new precision medicine option in 1L setting
  - Triplet therapy should be considered for fit individuals with high-volume mHSPC (especially de novo mHSPC)
  - Greater uptake of ADT intensification in the real world is vital for improving outcomes

- In 1L mCRPC, PEACE-3 supports role of ADT + enza + Ra223 + BPA in those w/o prior ARPI

- In pre-taxane PSMA-positive mCRPC, 177Lu-PSMA-617 is an approved option and alternative in those considered for ARPI change
  - Risk/benefit discussion, select subgroups ?low tumor burden, not candidate for taxanes
  - Mature OS awaited for advancement into mCSPC setting (PSMAddition)