

The evolving role of ARPIs in mHSPC

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Outline

- Adapting trial data to clinical practice
- Efficacy and toxicity data of ARPIs
- Treatment algorithm and recommendations in international guidelines
- Long term results of enzalutamide in mHSPC
- Supportive care for patients with mHSPC
- Future projections

Treatment choice should be based on the available evidence and current circumstances

- To limit disease burden, progression from mHSPC to mCRPC requires additional treatments¹
- **However**, there are **prognostic biomarkers** currently used for advanced prostate cancer...²
- **...but** we cannot yet reliably predict:¹



How each patient will **respond** to treatment



If patients will develop **intolerable** or **serious adverse events**



If patients will **be able to survive**, or

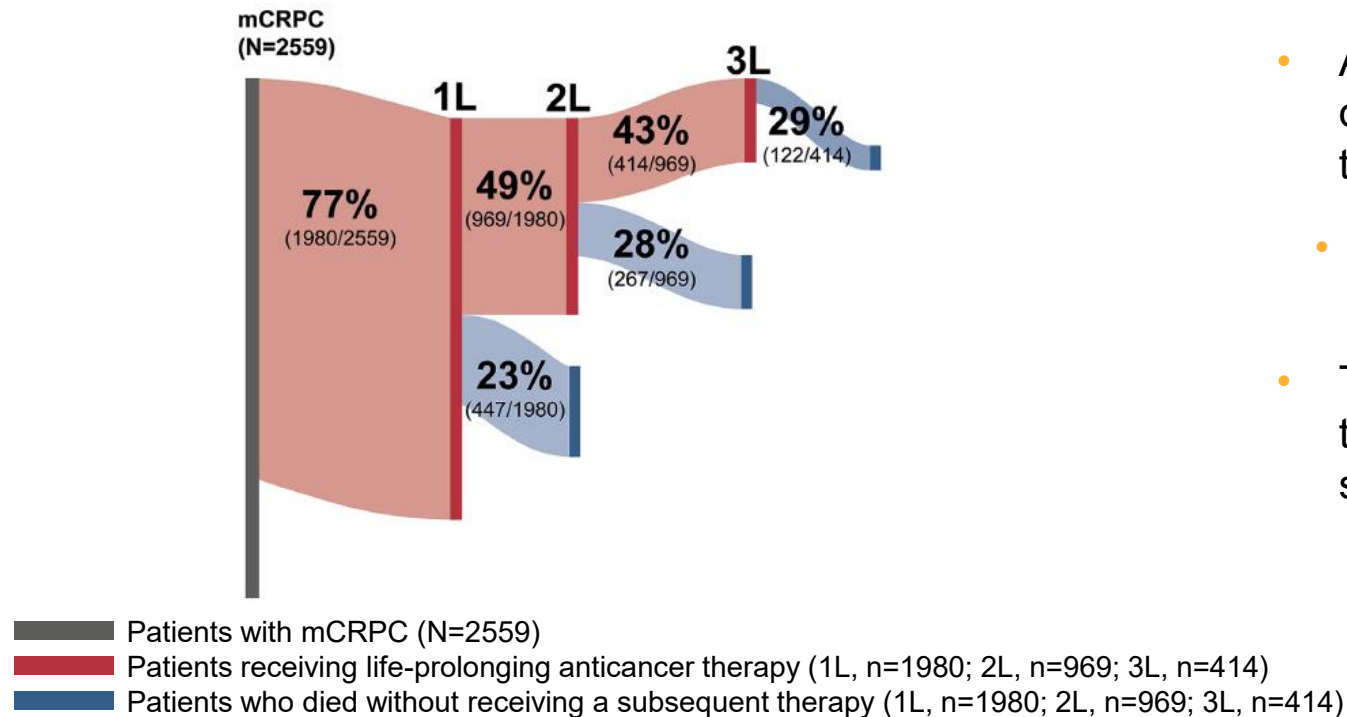


If or how **patient circumstances** or **preferences** will **change** throughout treatment

As a result of these unknown factors, an optimal treatment sequence cannot be predicted in advance for individual patients with advanced prostate cancer¹

Do not save the drug considered to be the most potent for later as that opportunity may never arrive

Proportion of patients with mCRPC receiving life-prolonging anticancer therapies¹



- An analysis of the FLATIRON HEALTH[®] technology database of patients with confirmed mCRPC found that only 49% of patients with mCRPC received a 2L¹
- A quarter of patients died without receiving a second treatment
- Therefore, an ideal sequence of two or more treatments does not reflect the situation commonly seen in clinical practice¹

Saving 'the most efficacious' treatment until 2L or later will not benefit most patients.¹
The most appropriate treatment should be utilized in the 1L setting²

Given that many factors are unknown, optimal treatment sequence cannot be predicted

- Identifying an optimal treatment sequence would imply future knowledge of all these factors:
 - Prostate cancer-related factors
 - Non-prostate cancer-related factors
 - Treatment-related factors
 - Patient-related factors
- Treatment should be personalized to each patient based on their individual circumstances

Although we cannot predict a treatment sequence, the sequential use of ARPIs is not recommended



The sequential use of ARPIs is **not a recommended SOC** in international guidelines or expert opinion^{1–4}

- EAU guidelines state that the use of **sequential ARPIs should be avoided** due to:¹
 - Risk of cross-resistance
 - Availability of other treatments (eg, chemotherapy, PARP inhibitors, and Lu-PSMA)
- There was a consensus at APCCC 2024 that **directly switching to another ARPI** after progressing on 1L ARPI should be **avoided**⁴
 - Overall panelists did not recommend switching directly from one ARPI to another

Is treatment sequencing reflective of your experiences in clinical practice?

1L, first line; APCCC, Advanced Prostate Cancer Consensus Conference; ARPI, androgen receptor pathway inhibitor; EAU, European Association of Urology; Lu, lutetium-177; PARP, poly (ADP-ribose) polymerase; PSMA, prostate specific membrane antigen; SOC, standard of care.

1. EAU, EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: <https://uroweb.org/guidelines/prostate-cancer>. Last accessed: June 2025;

2. Referenced with permission from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Prostate Cancer, Version 2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed 30 June 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way; 3. Parker C, et al. *Ann Oncol* 2020;31:1119–1134; 4. Gillessen S, et al. *Eur Urol* 2025;87:157–216.

Patient preference may evolve over time, due to their experience from receiving individual treatments

Patients want a treatment that:



Is effective

+



Is safe

+



Maintains/improves QoL

- **However**, a patient's preferred treatment may not be the most appropriate one for them
 - For example, DOC may be the most appropriate treatment for the patient, but may be refused due to individual circumstances or personal preference

Expectations also change within and across disease states

ADT + ARPIs: SOC in patients with mHSPC



	Trial	Experimental arm	Control arm	Number of enrolled patients (experimental vs. control)	Population characteristics	Median follow-up (months)	OS		
							Experimental	Control	HR (95% CI); p value
DOUBLET THERAPY	LATITUDE ¹	Abiraterone + prednisone + ADT	ADT + placebo	1,199 (597 vs. 602)	Newly diagnosed mHSPC ≥2 of the following high-risk factors: Gleason score ≥8, ≥3 bone lesions, and measurable visceral metastasis	51.8	53.3 months	36.5 months	0.66 (0.56–0.78); p<0.0001
	STAMPEDE ²	Abiraterone + prednisolone + ADT	ADT	1,917 (960 vs. 957)	Newly diagnosed metastatic, node-positive, or high-risk locally advanced (N0M0, ≥2 of the following: T3 or T4, Gleason score 8–10, and PSA ≥40 ng/mL), or recurrent disease after local therapy with high-risk features or metastasis	40.0	-	-	0.61 (0.49–0.75); p<0.001
	TITAN ³	Apalutamide + ADT	ADT + placebo	1,052 (525 vs. 527)	Prior docetaxel or ADT were allowed	44.0	NR	52.2 months	0.65 (0.53–0.79); p<0.0001
	ENZAMET ⁴	Enzalutamide + testosterone suppression	Testosterone suppression + standard nonsteroidal antiandrogen therapy	1,125 (563 vs. 562)	Testosterone suppression initiated up to 12 weeks before randomization; administration of docetaxel was allowed	68.0	OS at 5 years: 67%	OS at 5 years: 57%	0.70 (0.58–0.84); p<0.0001
	ARCHES ⁵	Enzalutamide + ADT	ADT + placebo	1,150 (574 vs. 576)	Prior docetaxel or ADT were allowed	44.6	NE	NE	0.66 (0.53–0.81); p<0.001
TRIPLET THERAPY	ARASENS ⁶	Darolutamide + docetaxel + ADT	ADT + docetaxel	1,306 (651 vs. 655)	Synchronous disease: 86% High-volume disease: 77%	43.7	NE	48.9	0.68 (0.57–0.80); p<0.001
	PEACE-1 ⁷	Abiraterone + prednisone + docetaxel + ADT	ADT + docetaxel	710 (355 vs. 355)	Only patients with synchronous disease were included	45.6	NR	52.8	0.75 (0.59–0.95); p=0.017
							High-volume disease OS HR 0.72 (0.55–0.95); p=0.019 Low-volume disease OS HR 0.83 (0.5–1.39); p=0.66		

ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; OS, overall survival; SOC, standard of care.

1. Fizazi K, et al. *Lancet Oncol* 2019;20:686–700; 2. James ND, et al. *N Engl J Med* 2017;377:338–351; 3. Chi KN, et al. *J Clin Oncol* 2021;39:2294–2303; 4. Sweeney CJ, et al. *Lancet Oncol* 2023;24: 323–34; 5. Armstrong AJ, et al. *J Clin Oncol* 2022;40:1616–1622; 6. Smith MR, et al. *N Engl J Med* 2022;386:1132–1142; 7. Fizazi K, et al. *Lancet* 2022;399:1695–1707.

So which 1L treatment should we choose?

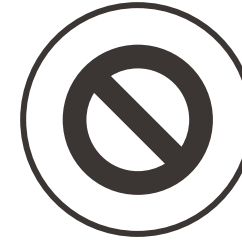
ADT monotherapy is only suitable in a limited number of situations^{1–3}



Frail patients



**Patients with
≤1-years'
life expectancy**

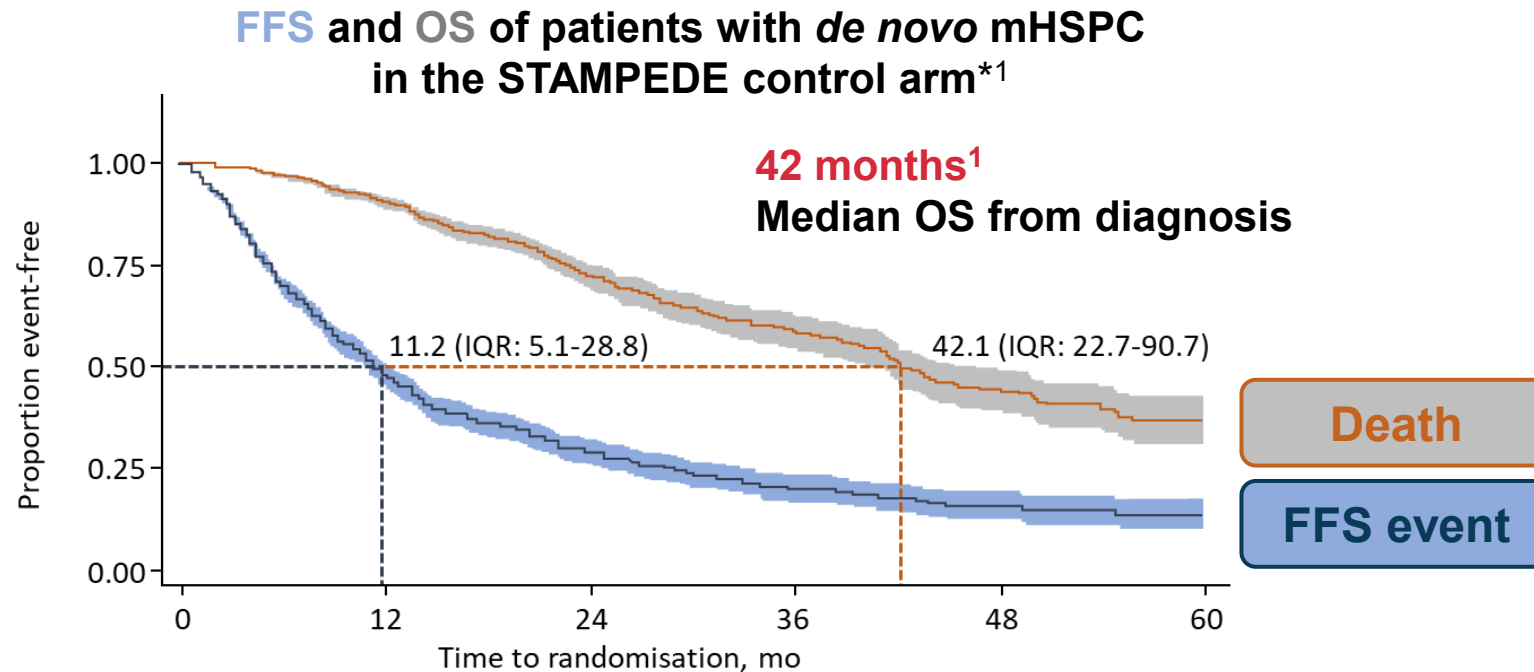


**Patients with clear
contraindications to
all combination
therapies**

ADT, androgen deprivation therapy.

1. Cornford P, et al. *Eur Urol* 2024;86:148–163; 2. Parker C, et al. *Ann Oncol* 2020;31:1119–1134; 3. Referenced with permission from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Prostate Cancer, Version 2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed 30 June 2025. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org). NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Treatment with ADT monotherapy results in a short OS for most of patients



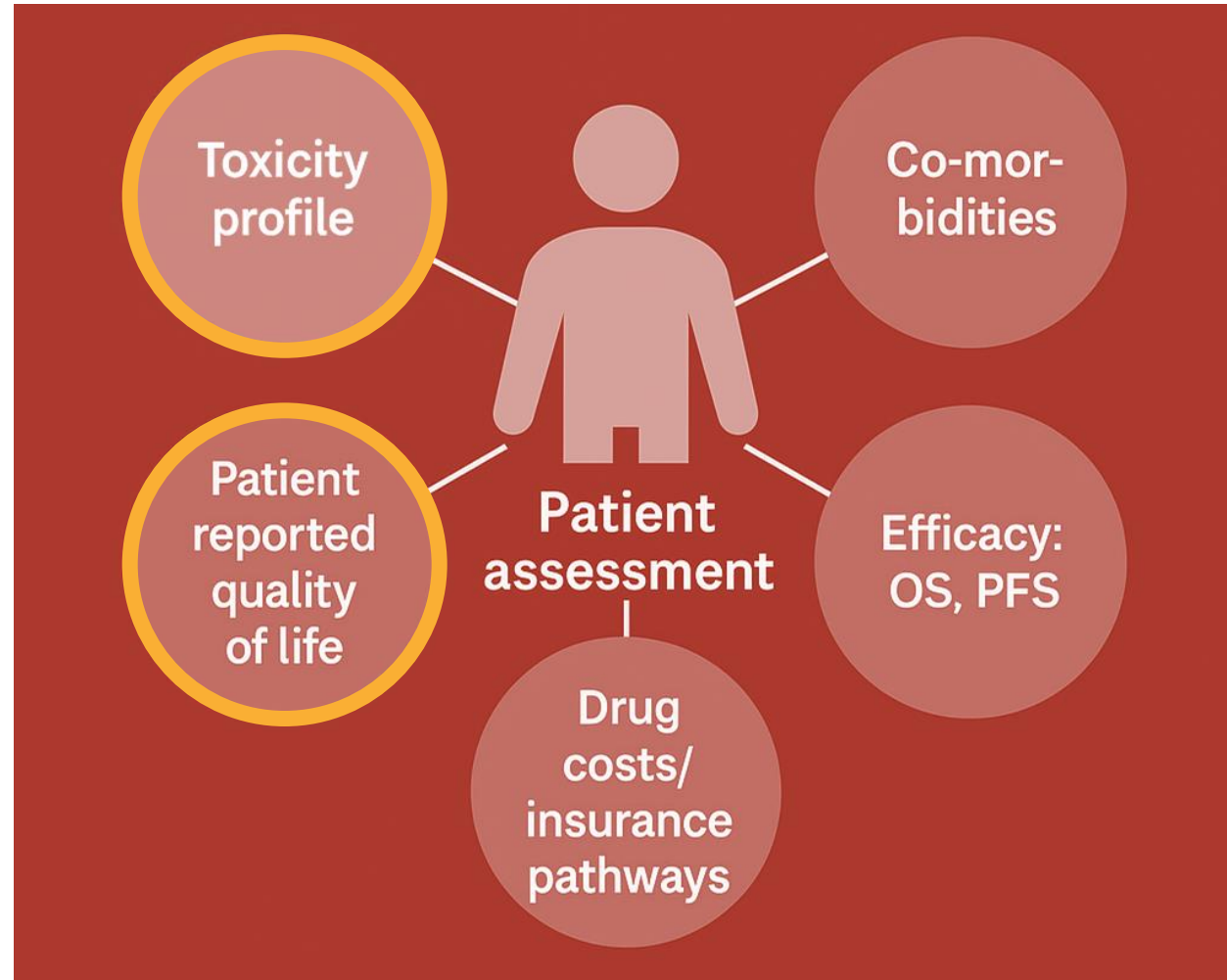
ADT monotherapy is not recommended as the SOC for patients with mHSPC^{†2-4}

*Patients with newly diagnosed mHSPC received either orchidectomy or LHRH agonists or antagonists with or without long-term NSAAs;¹ [†]Except in certain cases as detailed in the EAU guidelines.²

ADT, androgen deprivation therapy; FFS, failure-free survival; IQR, interquartile range; LHRH, luteinizing hormone-releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; mo, month; NSAA, non-steroidal anti-androgen; OS, overall survival; SOC, standard of care.

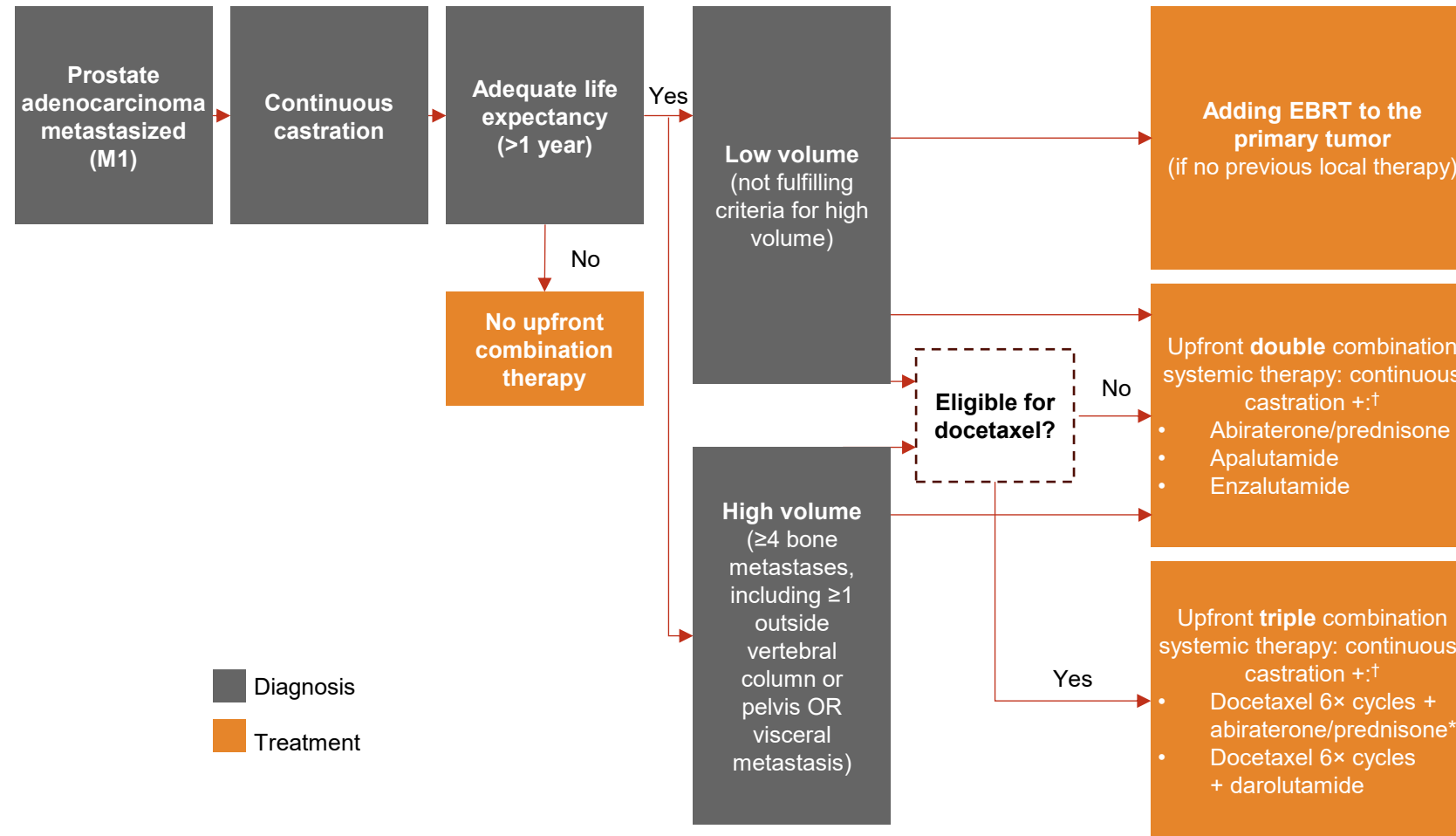
1. James ND, et al. *Eur Urol* 2015;67:1028–1038; 2. Cornford P, et al. *Eur Urol* 2024;86:148–163; 3. Parker C, et al. *Ann Oncol* 2020;31:1119–1134; 4. Referenced with permission from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines[®]) for Prostate Cancer, Version 2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed 30 June 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Factors influencing patient treatment decisions



EAU¹ and ESMO² guidelines recommend ADT + ARPI for the 1L treatment of mHSPC

EAU guidelines¹



ESMO guidelines²

- The other treatment option for men with mHSPC is **NHA + ADT** (ADT-abiraterone-prednisone [ESMO-MCBS v1.1 score: 4], **ADT-apalutamide** [ESMO-MCBS v1.1 score: 4] or **ADT-enzalutamide** [ESMO-MCBS v1.1 score: 4]), **which is recommended for 1L treatment**. Both strategies (NHA-ADT vs. triplet therapy) have not been directly compared
- In men with mHSPC, **ADT alone should be used only in vulnerable men who cannot tolerate treatment intensification**

1L, first line; ARPI, androgen receptor pathway inhibitor; ADT, androgen deprivation therapy; MCBS, Magnitude of Clinical Benefit Scale; EBRT, external beam radiation therapy; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; NHA, novel hormone agent; mHSPC, metastatic hormone-sensitive prostate cancer.

1. EAU guideline. Available at: <https://uroweb.org/guidelines/prostate-cancer/chapter/treatment>. Last accessed June 2025; 2. Fizazi K, et al. *Ann Oncol* 2023;34:557–563.

Multiple ARPIs improve OS and rPFS in mHSPC vs. ADT alone

Study	Drug	Comparison	OS	rPFS
STAMPEDE ¹	Abiraterone	Placebo	0.63	0.40
LATITUDE ²	Abiraterone	Placebo	0.62	0.47
TITAN ³	Apalutamide	Placebo	0.67	0.48
ENZAMET ⁴	Enzalutamide	NSAA	0.67	0.39*
ARCHES ^{5,6}	Enzalutamide	Placebo	0.70	0.39
ARANOTE ⁷	Darolutamide	Placebo	0.81	0.54

ADT + ARPI is SOC for patients with mHSPC⁸

Data are for reference only: trials are not to be compared directly.

*Data for PSA PFS.

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; NSAA, nonsteroidal antiandrogen therapy; PSA, prostate-specific antigen; PFS, progression-free survival; r, radiographic; SOC, standard of care.

1. James ND, et al. *N Engl J Med* 2017;377:338–351; 2. Fizazi K, et al. *N Engl J Med* 2017;377:352–360; 3. Chi KN, et al. *N Engl J Med* 2019;381:13–24; 4. Davis ID, et al. *N Engl J Med* 2019;381:121–131;

5. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974–2986; 6. Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005; 7. Saad F, et al. *J Clin Oncol* 2024;42:4271–4281;

8. EAU, EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: <https://uroweb.org/guidelines/prostate-cancer>. Last accessed: July 2025.

There are safety considerations for ARPIs such as abiraterone

		Abiraterone	AE frequency*
Monitoring requirement	Prednisone requirement	Yes	—
	Liver and electrolyte monitoring	Yes	—
	Blood pressure monitoring	Yes	—
AE	Mineralocorticoid excess	Yes	—
	Cardiovascular risk†	Yes	Very common
	Seizure risk	—	—
	Bone health	Fractures Bone density loss	Common —
	Rash	Yes	Common
	Sepsis	Yes	Common
	Hypothyroidism	—	—
	Cognitive disorder	—	—

Please note '—' is reflective of no corresponding information in the SmPC.

*Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); and not known (frequency cannot be estimated from the available data); †Including hypertension.

AE, adverse event; ARPI, androgen receptor pathway inhibitor; SmPC, summary of product characteristic.

ZYTIGA (abiraterone acetate). Summary of Product Characteristics.

There are safety considerations for ARPIs such as apalutamide

		Apalutamide	AE frequency*
Monitoring requirement	Prednisone requirement	—	—
	Liver and electrolyte monitoring	—	—
	Blood pressure monitoring	Yes	—
AE	Mineralocorticoid excess	—	—
	Cardiovascular risk†	Yes	Very common
	Seizure risk	Caution for patients with a history of seizures and strokes	Uncommon
	Bone health	Fractures	Very common
	Rash	Yes	Very common
	Fatigue	Yes	Very common
	Hypothyroidism	Yes	Common
	Falls	Yes	Very common
	Cognitive disorder	—	—

Please note '—' is reflective of no corresponding information in the SmPC.

*Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); and not known (frequency cannot be estimated from the available data); †Including hypertension.

AE, adverse event; ARPI, androgen receptor pathway inhibitor.

ERLEADA (apalutamide). Summary of Product Characteristics.

There are safety considerations for ARPIs such as enzalutamide

		Enzalutamide	AE frequency*
Monitoring requirement	Prednisone requirement	—†	—
	Liver and electrolyte monitoring	—	—
	Blood pressure monitoring	Yes	—
AE	Mineralocorticoid excess	—	—
	Cardiovascular risk‡	Yes	Very common
	Seizure risk	—	Uncommon
	Bone health	Fractures	Very common
	Rash‡	—	Not known
	Fatigue	Yes	Very common
	Hypothyroidism	—	—
	Falls	Yes	Very common
	Cognitive disorder	Yes	Common

Please note '—' is reflective of no corresponding information in the SmPC.

*Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); and not known (frequency cannot be estimated from the available data); †In clinical studies patients were allowed, but not required, to take prednisone; ‡Including hypertension and ischemic hearts disease; §SCARs have been reported with enzalutamide, and dry skin and pruritus are common in frequency.

AE, adverse event; ARPI, androgen receptor pathway inhibitor; SCAR, severe cutaneous adverse reaction.

XTANDI (enzalutamide). Summary of Product Characteristics.

There are safety considerations for ARPIs such as darolutamide

		Darolutamide	AE frequency*
Monitoring requirement	Prednisone requirement	–	–
	Liver and electrolyte monitoring	ALT/AST elevations noted	Very common
	Blood pressure monitoring	Yes	Very common
AE	Mineralocorticoid excess	–	–
	Cardiovascular risk	Yes	Common
	Seizure risk	–	–
	Bone health	Yes	Common
	Rash	Yes	Very common
	Fatigue	Yes	Very common
	Hypothyroidism	–	–
	Falls	–	–
	Cognitive disorder	–	–

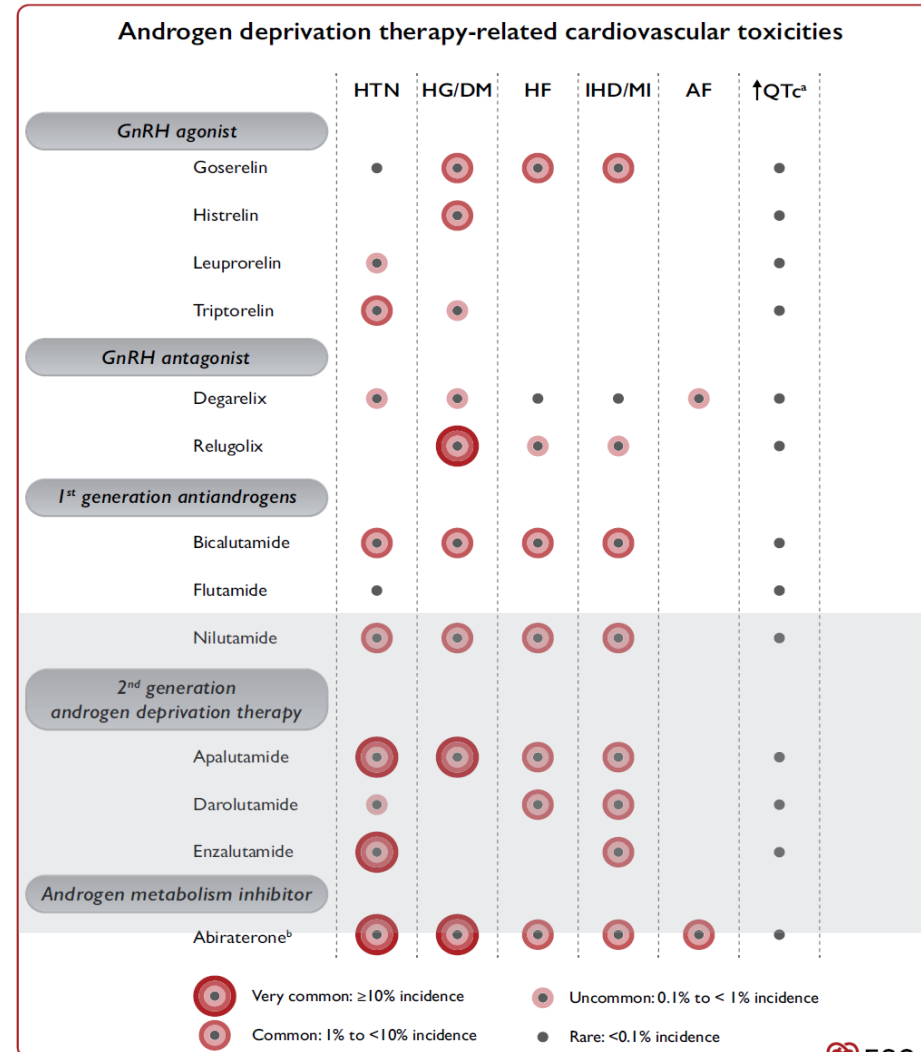
Please note '–' is reflective of no corresponding information in the SmPC or not reported.

*Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); and not known (frequency cannot be estimated from the available data).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARPI, androgen receptor pathway inhibitor; SCAR, severe cutaneous adverse reaction.

NUBEQA (darolutamide). Summary of Product Characteristics.

There are notable differences between ARPIs for risk of CV-related toxicities

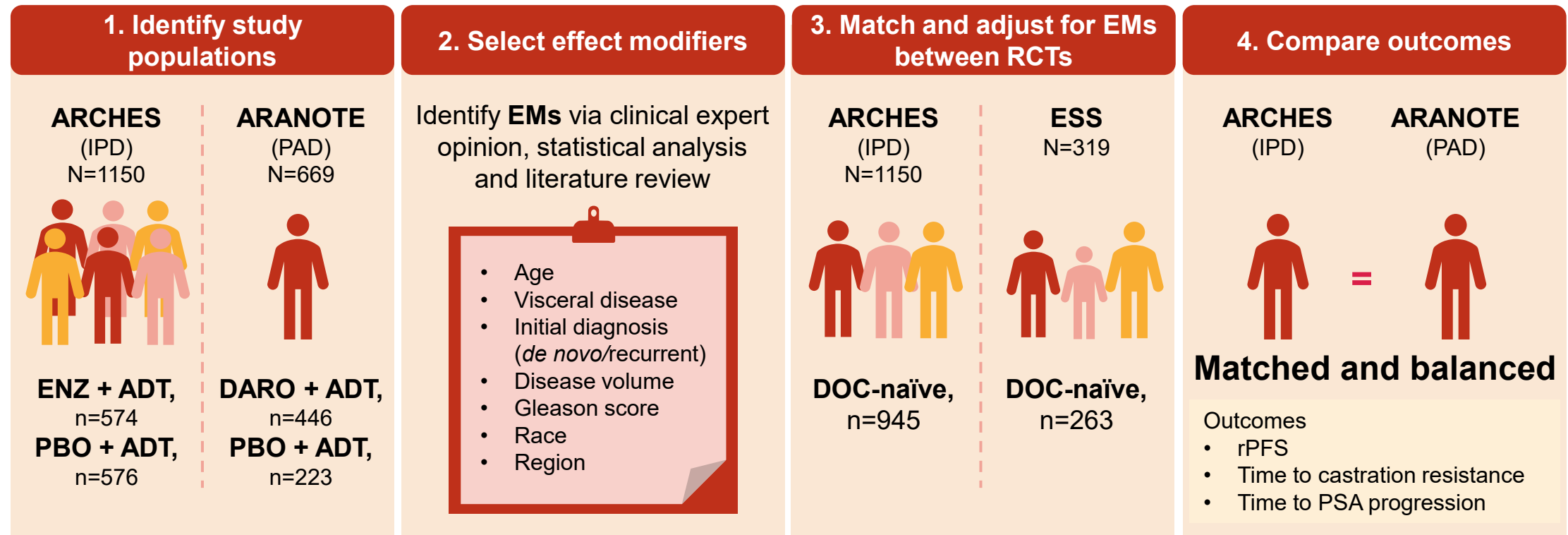


ADT, androgen deprivation therapy; AF, atrial fibrillation; CV cardiovascular; DM, diabetes mellitus; EMA, European Medicines Agency; FDA, Food and Drug Administration; GnRH, gonadotropin-releasing hormone; HF, heart failure; HG, hyperglycemia; HTN, hypertension; IHD, ischemic heart disease; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; ↑QTc, corrected QT interval prolongation; TdP, torsade de pointes. Lyon, et al. *Eur Heart J* 2022;43:4229–4361.

Comparative efficacy of ENZ + ADT vs. DARO + ADT in the treatment of patients with mHSPC using the MAIC methodology

- In the absence of head-to-head trials, **MAIC analyses** can be used to make indirect comparisons in efficacy by adjusting for differences between trials in effect modifiers and minimizing any biases due to differences in patient populations^{1–3}

MAIC analysis to compare efficacies of ENZ + ADT and DARO + ADT⁴



ADT, androgen deprivation therapy; DARO, darolutamide; DOC, docetaxel; EM, effect modifier; ENZ, enzalutamide; ESS, effect sample size; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; mHSPC, metastatic hormone-sensitive cancer; PAD, published aggregate data; PBO, placebo; PSA, prostate-specific antigen; RCT, randomized controlled trial; rPFS, radiographic progression-free survival.

1. Signorovitch JE, et al. *Value Health* 2012;15:940–947; 2. Phillippo DM, et al. *Med Decis Making* 2018;38:200–211; 3. Tanaka S, et al. *Value Health* 2024;27:1179–1190;

4. Azad A, et al. Presented at EAU 2025, 21–24 March 2025, Madrid, Spain, Abstract P181.

Indirect treatment comparison of ENZA + ADT vs. DARO + ADT favors ENZA for efficacy endpoints

Outcome	Population	ESS	Matching-adjusted estimates, forest plot*	Matching-adjusted estimate, HR* (95% CI); p value	Unadjusted Bucher estimate,† HR* (95% CI); p value
rPFS	Total population	319		0.54 (0.32–0.93); 0.03	0.72 (0.50–1.05); 0.09
	DOC-naïve population	263		0.47 (0.26–0.84); 0.01	0.69 (0.46–1.01); 0.06
Time to castration resistance	Total population	319		0.57 (0.34–0.94); 0.03	0.70 (0.50–0.98); 0.04
	DOC-naïve population	263		0.46 (0.27–0.79); 0.01	0.63 (0.44–0.90); 0.01
Time to PSA progression	Total population	319		0.61 (0.29–1.30); 0.20	0.61 (0.39–0.96); 0.03
	DOC-naïve population	263		0.48 (0.21–1.10); 0.08	0.58 (0.37–0.91); 0.02

In the MAIC analysis of the total population, patients receiving ENZA + ADT showed a significantly lower risk of radiographic progression or death by 46% (HR 0.54 [95% CI: 0.32–0.93; p=0.03]) and of progression to castration resistance by 43% (HR 0.57 [95% CI: 0.34–0.94; p=0.03]) than those receiving DARO + ADT

Similar results were observed in the DOC-naïve population: compared with DARO + ADT, patients receiving ENZA + ADT had a significantly lower risk of radiographic progression or death by 53% (HR 0.47 [95% CI: 0.26–0.84; p=0.01]) and of progression to castration resistance by 54% (HR 0.46 [95% CI: 0.27–0.79; p=0.01])

Time to PSA progression for ENZA + ADT was similar to DARO + ADT in both the total population (HR 0.61 [95% CI: 0.29–1.30; p=0.20]) and the DOC-naïve population (HR 0.48 [95% CI: 0.21–1.10; p=0.08])

In sensitivity analyses, the comparative effectiveness of ENZA + ADT and DARO + ADT remained similar in direction and significance for all outcomes; however, adjusting for ECOG PS yielded a reduction in ESS (n=196)

*DARO + ADT served as the reference treatment for all comparisons; †Estimates from the Bucher method should be interpreted with caution due to the assumption that patient populations should be balanced in EMs between trials. The direction of relative effects was aligned between the two methods.

ADT, androgen-deprivation therapy; CI, confidence interval; DARO, darolutamide; DOC, docetaxel; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EMs, effect modifiers; ENZA, enzalutamide; ESS, effective sample size; HR, hazard ratio; PSA, prostate-specific antigen; MAIC, matching-adjusted indirect comparison; rPFS, radiographic progression-free survival.

Azad A, et al. Presented at EAU 2025, 21–24 March 2025, Madrid, Spain, Abstract P181.

STOPCAP meta-analyses provides evidence that adding ARPI to SOC substantially improves outcomes

- The analysis includes 70% of available IPD across eligible trials (7778 participants)
 - The analysis includes 100% of IPD from eligible abiraterone trials
 - The analysis includes 48% of IPD from 'amide' ARPI trials
- The study methodology is more reliable and thorough than meta-analyses based on summary data

Median follow-up and control arm survival

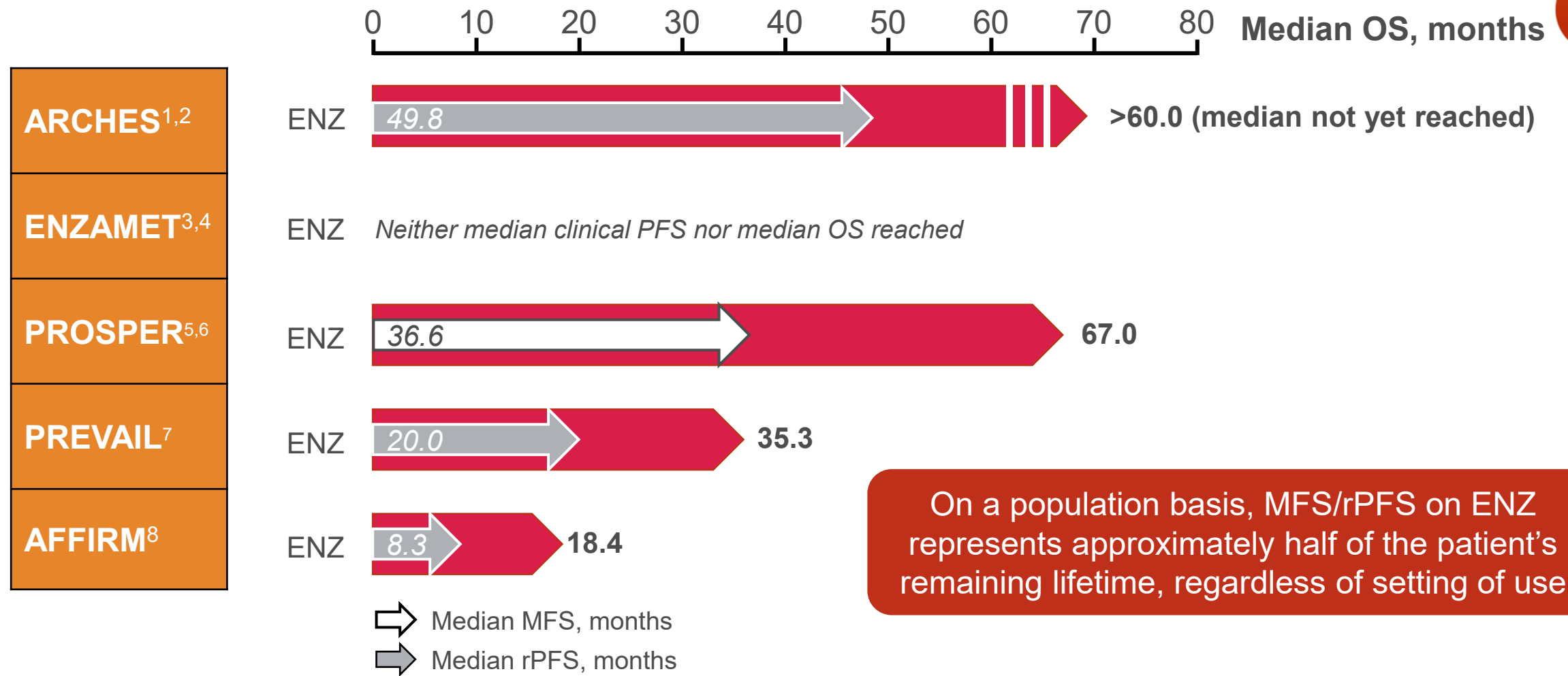
Trial	No. of participants	Follow-up, years	Control arm survival, years
STAMPEDE (abi)	1003	8.0	3.8
LATITUDE (abi)	1199	4.3	3.0
PEACE-1 (abi)	1172	6.0	4.6
ENZAMET (enza)	1125	5.7	6.1
TITAN (apa)	1052	3.7	4.4
STAMPEDE (abi + enza)	916	6.0	4.3
SWOG 1216 (ort)	1311	6.9	6.3

No difference in patient preference between darolutamide and enzalutamide

ODENZA study

- Patients with mCRPC, N=200
- 12 weeks of darolutamide → 12 weeks of enzalutamide or vice versa
- Asked which agent they prefer:
 - 49% darolutamide
 - 40% enzalutamide
 - 12% no preference
 - $p=0.92$ (no significant difference)

The earlier the treatment, the greater the clinical outcome



Results from independent trials: data are for illustrative purpose only.

ENZ, enzalutamide; MFS, metastatic-free survival; OS, overall survival; PFS, progression-free survival; rPFS, radiographic PFS.

1. Armstrong AJ, et al. *J Clin Oncol* 2022;40:1616–1622; 2. Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005; 3. Davis ID, et al. *N Engl J Med* 2019;381:121–131;

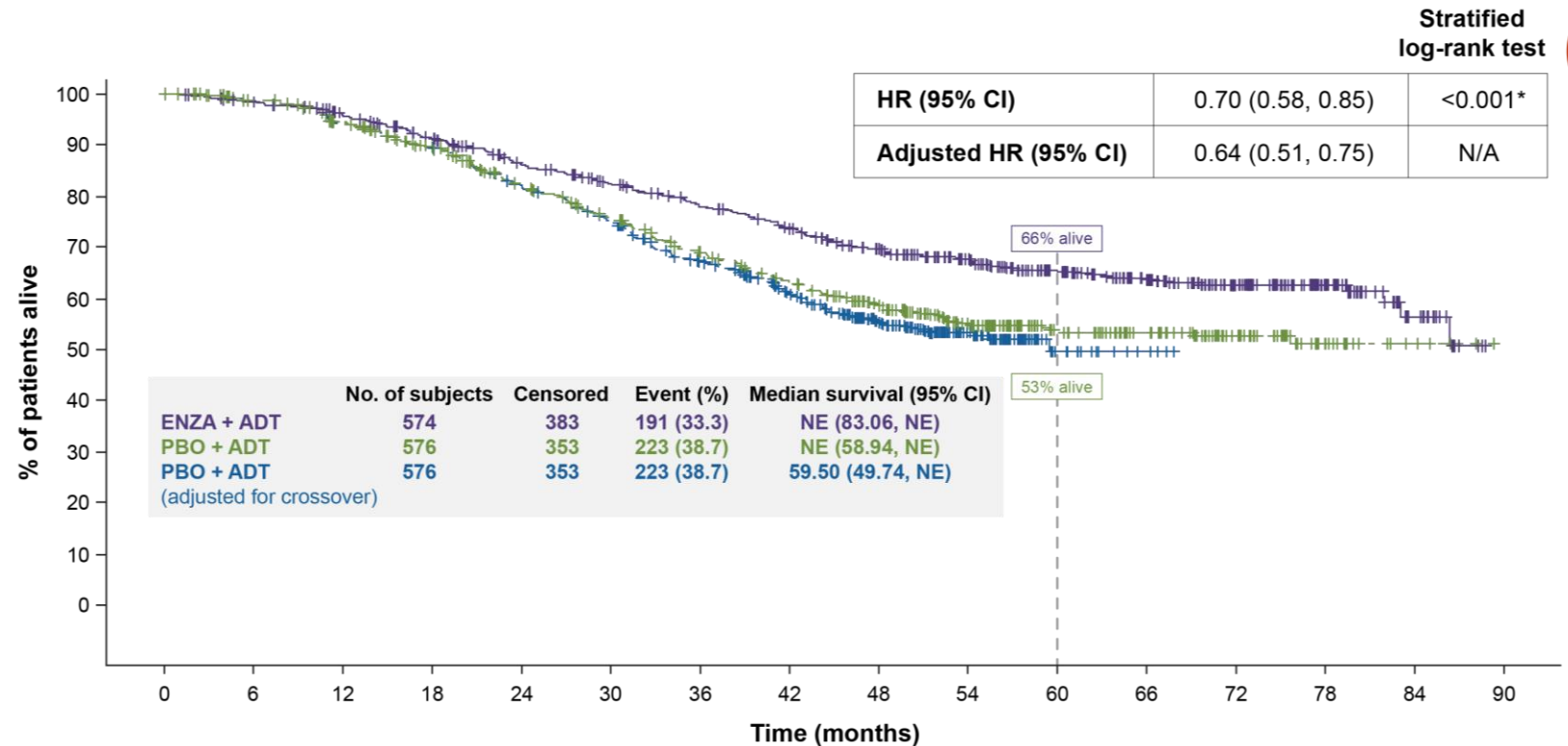
4. Sweeney CJ, et al. *Lancet Oncol* 2023;24:323–334; 5. Hussain M, et al. *N Engl J Med* 2018;378:2465–2474; 6. Sternberg CN, et al. *N Engl J Med* 2020;382:2197–2206; 7. Beer TM, et al. *Eur Urol* 2017;71:151–154;

8. Scher H, et al. *N Engl J Med* 2012;367:1187–1197.

ARCHES results: 5-year OS (ITT)

Data cutoff: July 31, 2024

- Median follow-up (range): **61.4 months** (0.03–89.33)
- Only 11 patients were lost to follow-up, with no clear evidence of informative censoring
- Significantly prolonged OS in patients treated with ENZA + ADT vs. PBO + ADT (**HR 0.70** [95% CI: 0.58–0.85; $p < 0.001$])
- Sensitivity analysis using RPSFT method showed a similar treatment effect (**HR 0.64** [95% CI: 0.51–0.75])



Initial treatment with ENZA + ADT showed a sustained long-term survival benefit compared with PBO + ADT in patients with mHSPC, despite a substantial crossover after study-wide unblinding (n=182, 32%; crossover start: Month 18)

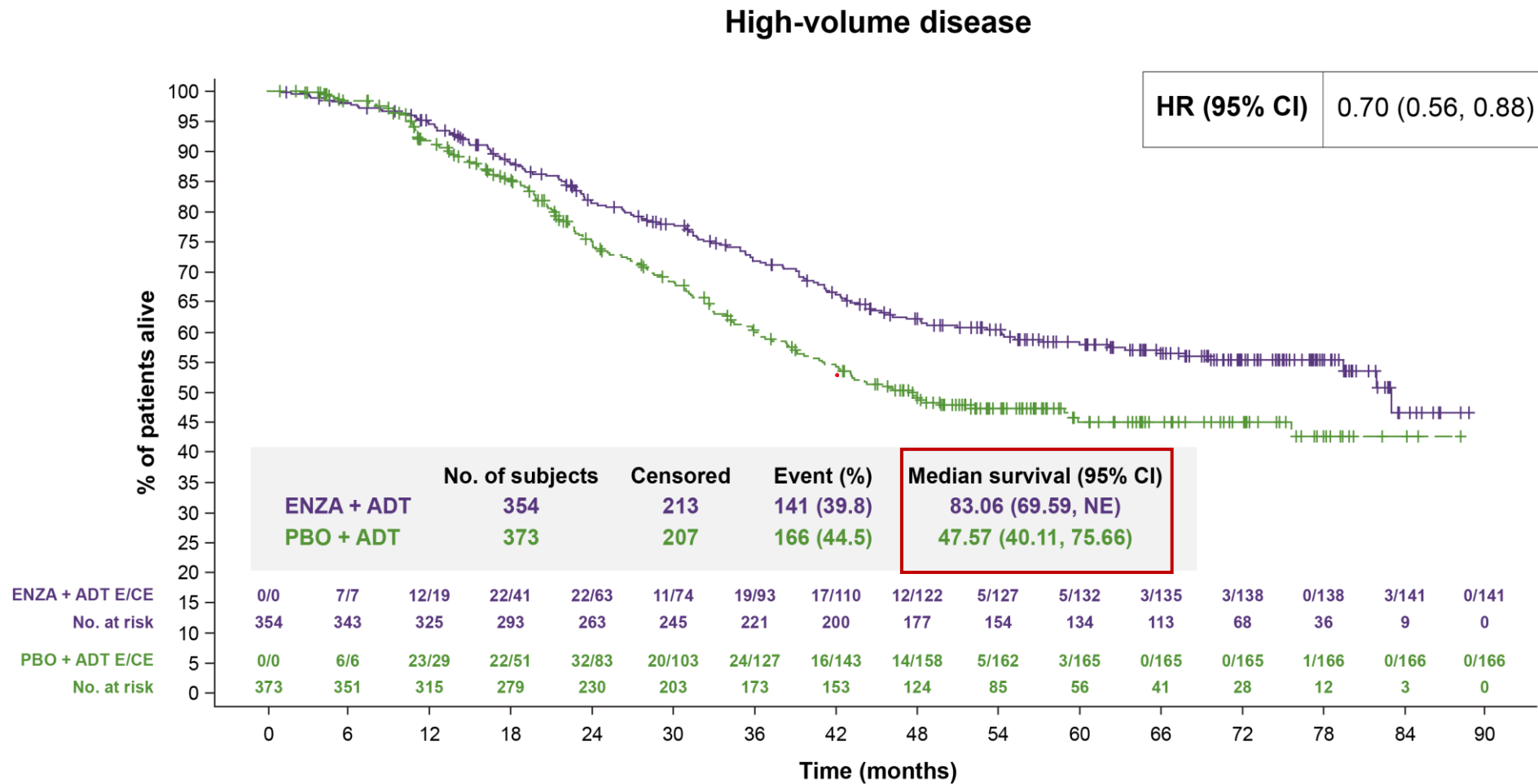
*p value is nominal.

ADT, androgen-deprivation therapy; CI, confidence interval; E/CE, events/cumulative events; ENZA, enzalutamide; HR, hazard ratio; ITT, intent-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; n, sample size; N/A, not applicable; NE, not estimable; No., number; OS, overall survival; PBO, placebo; RPSFT, rank-preserving structural failure time.

Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

ARCHES results: ENZA extended estimated median OS for patients with high-volume disease vs. PBO by 3 years

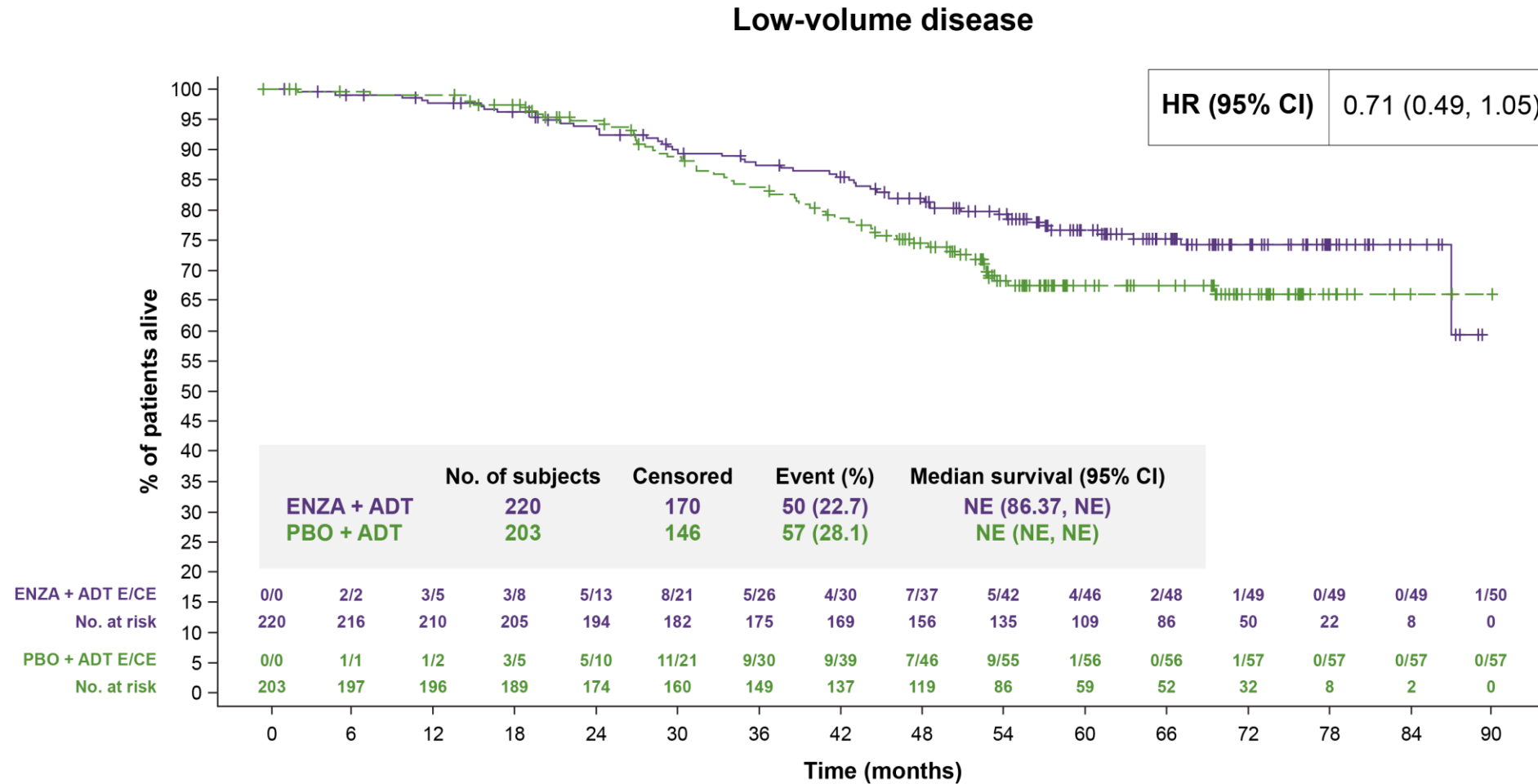
Data cutoff: July 31, 2024



ADT, androgen-deprivation therapy; CI, confidence interval; E/CE, events/cumulative events; ENZA, enzalutamide; HR, hazard ratio; NE, not estimable; No., number; OS, overall survival; PBO, placebo.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

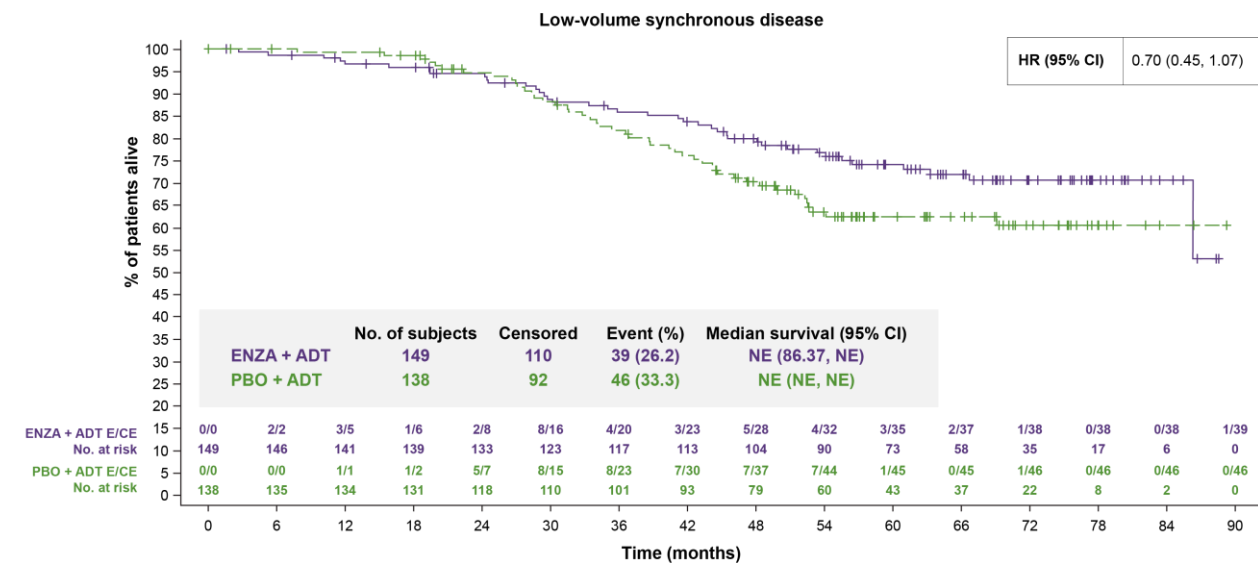
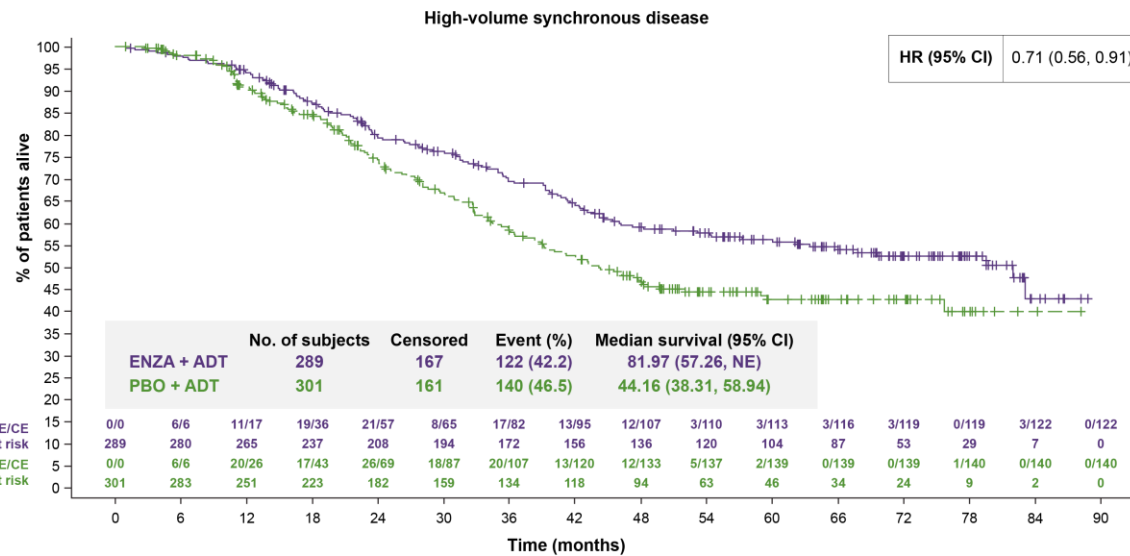
ARCHES results: Similar relative improvement in OS for patients with low-volume disease

Data cutoff: July 31, 2024



ARCHES results: OS in high- and low-volume synchronous disease

Data cutoff: July 31, 2024



- Treatment with ENZA + ADT resulted in meaningfully prolonged median survival (82 months) vs. PBO + ADT (44 months) in patients with **high-volume synchronous disease**
- In patients with **low-volume synchronous disease**, OS was longer with ENZA + ADT than with PBO + ADT but CI included 1.0

ARCHES results: 5-year survival probability (ITT)

Data cutoff: July 31, 2024



- 5-year survival rate was greater in the ENZA + ADT group vs. PBO + ADT group in all clinically relevant subgroups
- Improvement in OS at 5 years ranged from 9% to 17% based on disease volume, prior chemotherapy, and metastatic disease presentation

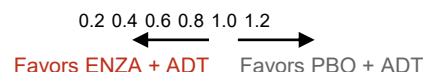
ADT, androgen-deprivation therapy; CI, confidence interval; E/CE, events/cumulative events; ENZA, enzalutamide; HR, hazard ratio; ITT, intent-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; n, sample size; No., number; OS, overall survival; PBO, placebo; RPSFT, rank-preserving structural failure time.

Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

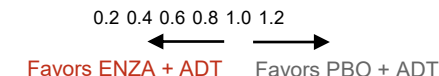
ARCHES results: OS by prespecified subgroups

Data cutoff: July 31, 2024

Subgroup	ENZA + ADT/PBO + ADT		HR (95% CI)
	No. (events)	Median (mo)	
All subgroups	574 (191)/576 (223)	NR/NR	0.70 (0.58–0.85)
Age <65 years	148 (46)/152 (55)	86.4/NR	0.63 (0.42–0.93)
Age 65–74 years	256 (73)/255 (96)	NR/NR	0.65 (0.48–0.89)
Age ≥75 years	170 (72)/169 (72)	69.6/58.9	0.83 (0.60–1.15)
Geographic region			
Europe	341 (123)/344 (140)	86.4/75.7	0.76 (0.60–0.97)
North America	86 (28)/77 (29)	83.1/NR	0.57 (0.34–0.97)
Rest of the world	147 (40)/155 (54)	NR/NR	0.65 (0.43–0.97)
Hispanic or Latino	46 (16)/37 (17)	NR/41.0	0.47 (0.23–0.93)
Not Hispanic or Latino	504 (164)/514 (195)	86.4/NR	0.72 (0.58–0.88)
Gleason score <8	171 (45)/187 (55)	NR/NR	0.75 (0.50–1.11)
Gleason score ≥8	386 (136)/373 (162)	86.4/52.7	0.65 (0.52–0.82)
ECOG PS 0	448 (139)/443 (161)	NR/NR	0.70 (0.56–0.88)
ECOG PS 1	125 (52)/133 (62)	83.1/47.7	0.73 (0.50–1.06)



Subgroup	ENZA + ADT/PBO + ADT		HR (95% CI)
	No. (events)	Median (mo)	
PSA at baseline			
≤ overall median	294 (89)/305 (107)	86.4/NR	0.73 (0.55–0.97)
> overall median	279 (102)/270 (116)	NR/52.0	0.67 (0.51–0.87)
LV disease	220 (50)/203 (57)	NR/NR	0.71 (0.49–1.05)
HV disease	354 (141)/373 (166)	83.1/47.6	0.70 (0.56–0.88)
Prior docetaxel	103 (34)/102 (44)	83.1/59.5	0.67 (0.43–1.05)
No prior docetaxel	471 (157)/474 (179)	NR/NR	0.71 (0.57–0.88)
Previous ADT or orchiectomy			
Yes	535 (180)/515 (198)	NR/NR	0.72 (0.59–0.88)
No	39 (11)/61 (25)	NR/59.9	0.56 (0.28–1.14)
Synchronous (<i>de novo</i>)	438 (161)/439 (186)	86.4/58.9	0.71 (0.57–0.88)
Metachronous (relapsed)	132 (29)/136 (37)	NR/NR	0.66 (0.41–1.08)



OS treatment benefit with ENZA + ADT was consistent across most prespecified subgroups

ADT, androgen-deprivation therapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ENZA, enzalutamide; HR, hazard ratio; HV, high-volume; LV, low-volume; mo, months; No., number; NR, not reached; OS, overall survival; PBO, placebo; PSA, prostate-specific antigen.

Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

ARCHES results: Overview of safety (safety population)

Data cutoff: July 31, 2024

Patient incidence, n (%) unless otherwise stated	ENZA + ADT (n=572)	PBO + ADT (n=574)	PBO crossover (n=182)
Median treatment duration, months (range)	41.7 (0.2–88.7)	13.8 (0.2–27.6)	44.2 (0.2–62.2)
Total exposure, patient-years	2,070.0	731.9	579.0
TEAE*	531 (92.8)	505 (88.0)	167 (91.8)
Grade 3–4 TEAE	263 (46.0)	163 (28.4)	90 (49.5)
Grade 5 TEAE (death)	190 (33.2)	197 (34.3)	27 (14.8)
Study drug-related TEAE	347 (60.7)	273 (47.6)	99 (54.4)
Study drug-related TEAE leading to death	0	1 (0.2)	1 (0.5)
TEAE of special interest	434 (75.9)	328 (57.1)	127 (69.8)

- Incidence of all TEAEs was similar between all treatment groups
- Incidence of Grade 3–4, study-drug related, and TEAEs of special interest were higher in ENZA + ADT group vs. PBO + ADT group
- No new safety signals were identified

*TEAE is defined as an adverse event that occurs or worsens at any time from the first study drug intake up to the date of end of treatment +30 days, study discontinuation, or the start of new antineoplastic therapy, whichever occurs first.

Adverse event grading is based on NCI-CTCAE (version 4.03).

ADT, androgen-deprivation therapy; ENZA, enzalutamide; n, sample size; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; PBO, placebo; TEAE, treatment-emergent adverse event.

Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

ARCHES results: TEAEs of special interest* (safety population)

Data cutoff: July 31, 2024

Patient incidence, n (%)	ENZA + ADT (n=572)	PBO + ADT (n=574)	PBO crossover (n=182)
Convulsions	3 (0.5)	3 (0.5)	1 (0.5)
Hypertension	95 (16.6)	40 (7.0)	20 (11.0)
Decreased neutrophil count	8 (1.4)	4 (0.7)	3 (1.6)
Cognitive/memory impairment	41 (7.2)	15 (2.6)	14 (7.7)
Ischemic heart disease	33 (5.8)	11 (1.9)	8 (4.4)
Other selected cardiovascular events	37 (6.5)	10 (1.7)	11 (6.0)
Posterior reversible encephalopathy syndrome	0	0	0
Fatigue	193 (33.7)	119 (20.7)	49 (26.9)
Renal disorder	28 (4.9)	8 (1.4)	2 (1.1)

Patient incidence, n (%)	ENZA + ADT (n=572)	PBO + ADT (n=574)	PBO crossover (n=182)
Second primary malignancies	31 (5.4)	13 (2.3)	9 (4.9)
Falls	70 (12.2)	19 (3.3)	21 (11.5)
Fractures	99 (17.3)	31 (5.4)	29 (15.9)
Loss of consciousness	17 (3.0)	2 (0.3)	4 (2.2)
Thrombocytopenia	3 (0.5)	3 (0.5)	0
Musculoskeletal events	247 (43.2)	169 (29.4)	53 (29.1)
Severe cutaneous adverse reactions	1 (0.2)	1 (0.2)	0
Angioedema	12 (2.1)	1 (0.2)	1 (0.5)
Rash	23 (4.0)	10 (1.7)	8 (4.4)
Hepatic disorder	38 (6.6)	34 (5.9)	9 (4.9)

- The incidence of TEAEs of special interest was consistent with prior ARCHES analyses
- No new safety signals were identified

*TEAEs of special interest were based on prespecified combinations of preferred terms (MedDRA version 23.0) and were graded on the basis of NCI-CTCAE (version 4.03) by the investigator.

ADT, androgen-deprivation therapy; ENZA, enzalutamide; MedDRA, Medical Dictionary for Regulatory Activities; n, sample size; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; PBO, placebo; TEAE, treatment-emergent adverse event.

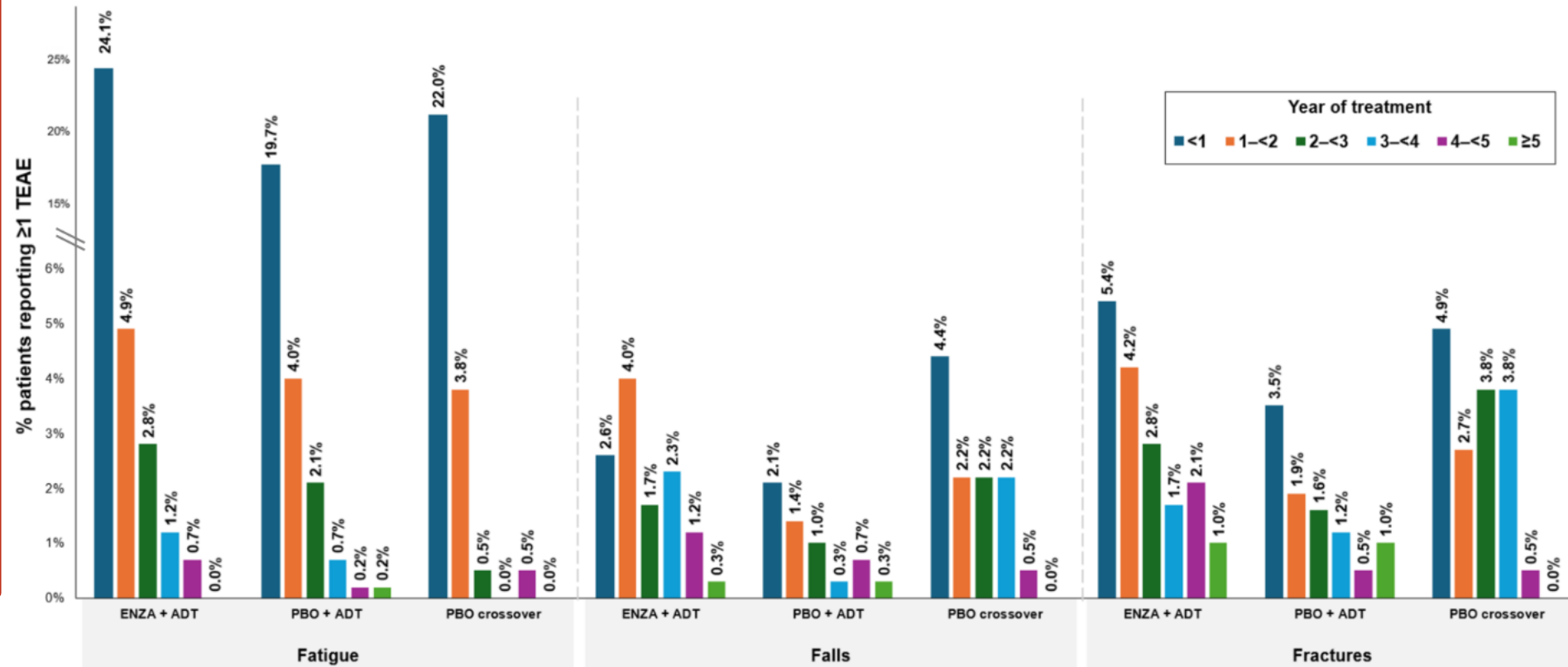
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US: abstract 5005.

ARCHES results: ENZA-associated TEAEs tended to diminish substantially over time

Data cutoff: July 31, 2024

- First onset of fatigue was slightly more common in ENZA + ADT and PBO crossover vs. PBO + ADT group during the first year and decreased thereafter
- A lower incidence in fatigue, falls, and fractures was generally observed in the PBO + ADT group vs. the ENZA + ADT and PBO crossover groups
- Mostly reported in the first couple of years

Summary of patients reporting ≥ 1 TEAE by year



But how do we minimize the risk of toxicities?

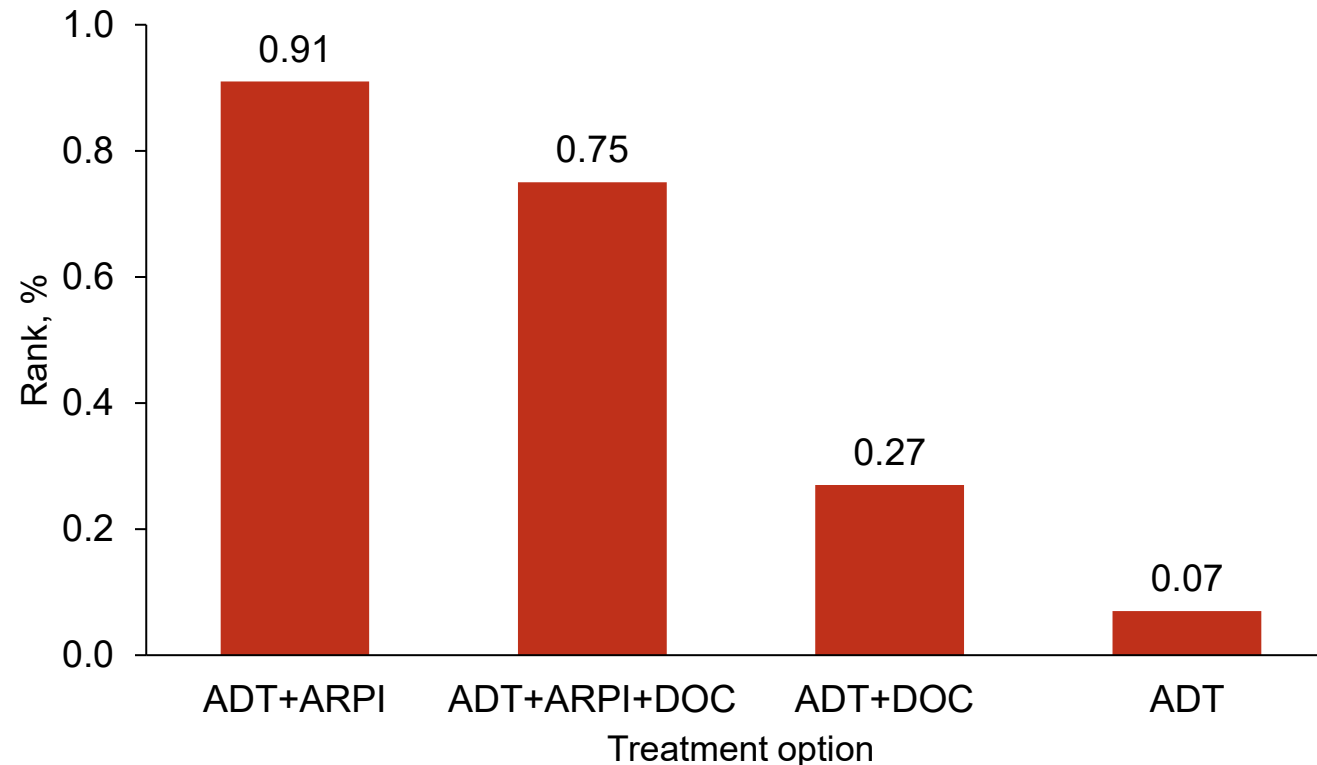
- Diabetes
- Cardiovascular disease
- Reduction in bone mineral density
- Hypothyroidism (unique to apalutamide)
- Corticosteroid effects (unique to abiraterone)

Specific situations may require the addition of a third treatment to SOC

- Low-volume mHSPC
 - RT
- High-volume mHSPC
 - Risk of additional toxicities
 - Not all patients are eligible, or want to receive docetaxel

In low-volume mHSPC, ADT + ARPI is potentially the most efficacious treatment vs. ADT + ARPI + DOC

Rank plot for OS in patients with low-volume disease



ARPI included DAR or ABI
for triplet therapy

Relative treatment rankings
show the treatment likely to
be the most efficacious

This slide includes information on drugs for indication(s) that are pending price and reimbursement.

This slide includes information on drug(s) or drug combinations outside of their approved indication; they are mentioned for illustrative purposes only.

What other treatment options can we consider for patients with low-volume mHSPC?



RT to the primary tumor

**STAMPEDE and HORRAD¹,
PEACE-1,² SWOG³**

Significant OS benefit of RT + ADT in patients with ≤4 bone metastases;^{*1}
rPFS benefit of RT + SOC + AAP²



MDT[§]

**STOMP⁴, ORIOLE⁵
and EXTEND⁶**

Improvements in the median time to palliative ADT or death^{†4},
median PFS ^{†‡5,6}, and eugonadal PFS^{**6}



Surgery

TRoMbone⁷ and SWOG³

Ongoing studies/recommended future Phase 3 trials

Which of these options would you select for this patient, and why?

^{*}Compared with ADT monotherapy; [†]Compared with surveillance/observation; [‡]Compared with the SOC, intermittent hormonal therapy; [§]MDT to patients with M1 disease is not recommended outside of the clinical trial setting or well-designed prospective cohort study.⁸

AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; MDT, metastasis-directed therapy; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; r, radiographic; RT, radiotherapy; SOC, standard of care.

1. Burdett S, et al. *Eur Urol* 2019;76:115–124; 2. Bossi A, et al. *J Clin Oncol* 2023;41:LBA5000; 3. NCT03678025. Available at: <https://classic.clinicaltrials.gov/ct2/show/study/NCT03678025>. Last accessed July 2025; 4. Ost P, et al. *J Clin Oncol* 2018;36:446–453; 5. Philips R, et al. *JAMA Oncol* 2020;6:650–659; 6. Tang C, et al. *JAMA Oncol* 2023;9:825–834; 7. Sooriakumaran P, et al. *BJU Int* 2022;130:43–53; 8. EAU, EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: <https://uroweb.org/guidelines/prostate-cancer>. Last accessed: July 2025.

Not all patients are fit enough to receive DOC or all six cycles of treatment



Patient preference should be considered¹



Due to its toxicity profile, not all patients are **fit enough to receive DOC**²



Not all patients receive **six cycles** of treatment in routine practice, which may **affect OS outcomes**

- In routine practice, as few as **43.9% of patients with mHSPC** complete six cycles of DOC treatment³

Monitoring and management of major AE therapy side effects



CV



Fracture



Fall



SSE



Fatigue

Risk

Management/monitoring



Monitor



Calcium, vitamin D,
exercise



Exercise

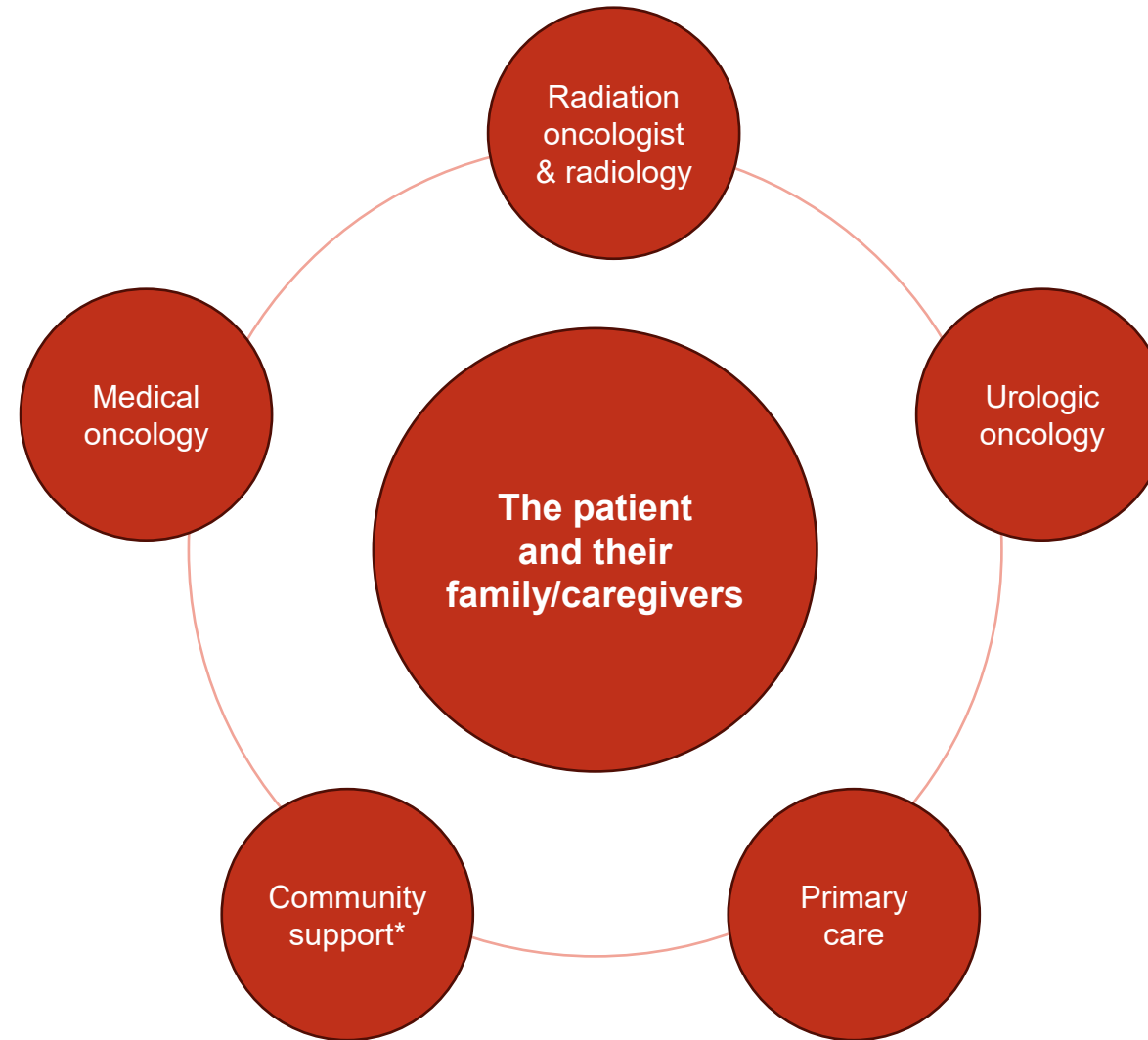


Reduce bone turnover

Lifestyle recommendations

1. **Achieve and maintain a healthy body weight:** (BMI <25, waist circumference <40")
2. **Engage in regular physical activity:** Avoid inactivity, 150 minutes/week moderate intensity exercise or 75 minutes/week vigorous activity at minimum, combination of strength and conditioning aerobic activity
3. **Eat a healthy diet:** Limit processed foods, red meat, and trans fats; eat 2.5 cups or more of vegetables or fruits daily, whole grains; avoid added sugar. Many healthy diets such as Mediterranean, low carb. Moderate fish/nut intake, cruciferous vegetables (e.g., broccoli, cauliflower, bok choy, brussels sprouts, broccolini, etc.)
4. **Limit alcohol, avoid tobacco**
5. **Bone health:** Regular exercise, Ca 1200 mg/d plus D3 800 IU/d
6. **Avoid mega vitamins (eat real food)**
7. **Manage stress, depression, anxiety:** Support groups, churches, social groups, professional support, spouses and family
8. **Cardiovascular care:** Cardiovascular disease remains the number one killer among men with prostate cancer. Blood pressure and lipid monitoring

Multidisciplinary care



*Community support includes pathology, nutrition, and social work.
Lama DJ et al, *J Clin Imaging Sci* 2021;11:1–9

What's next?

Future-gazing in advanced prostate cancer

A **PSA nadir** between 6–12 months of treatment has consistently emerged as a strong prognostic biomarker for both PFS and OS in mHSPC in multiple trials

The **IRONMAN registry** highlights a strong association between a suboptimal PSA nadir ≥ 0.2 ng/mL and decreased OS

The treatment landscape for mHSPC is evolving

A032101 'A-DREAM' trial evaluates treatment interruption in patients with stable or falling PSA < 0.2 ng/mL after 18–24 months of ADT (minimum 12 months of ARPI)

There are two key ongoing trials aiming to refine treatment strategies in mHSPC

TRIPLE-SWITCH (CCTG-PR26) trial endpoints focus on clinically meaningful outcomes including improvement in OS, delayed time to CRPC and clinical progression, and preservation of QoL

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen. QoL, quality of life.

Aggarwal RR, et al. ASCO 2025: Discussion: Tailoring Therapy in Castration-Sensitive Prostate Cancer: Do Biomarkers Make the Cut? Available at: <https://www.urotoday.com/conference-highlights/asco-2025/asco-2025-prostate-cancer/161095-asco-2025-discussion-tailoring-therapy-in-castration-sensitive-prostate-cancer-do-biomarkers-make-the-cut.html>. Last accessed: June 2025.

Treatment options for mHSPC are expanding and genomic features may aid with treatment selection

- Genomic features associated with prognosis in mHSPC that may aid in molecular classification and treatment selection¹
 - Specific **oncogenic signaling pathways** may be a potentially targetable biologic underpinning of this poor prognosis subtype (genomic alterations)¹
 - The AMPLITUDE study supports **early genomic testing** and niraparib + AAP as a new treatment option for patients with mHSPC and HRR gene alterations²
- An ancillary study of the STAMPEDE trials highlighted that **combining docetaxel and hormone therapy** can improve OS but is not appropriate for all patients with mHSPC³
 - Prostate tumors classified as high Decipher and PTEN inactive have a 45% reduction in hazard of death when docetaxel is added to ADT and this biomarker should be tested in patients considered for triplet therapy of ADT + abiraterone + docetaxel

Final remarks

Conclusions and take-home messages

- ADT + ARPI is the backbone of SOC treatment for mHSPC¹
- 1L treatment in mHSPC has the greatest clinical outcome vs. later treatment lines²
- Predetermined treatment sequencing is unreliable; as we cannot predict the future, patients should receive the most appropriate treatment first, not save it for later³
- All patients should receive the treatment most appropriate for them¹
 - Most patients should receive ADT + ARPI
 - Only a minority of patients should receive ADT monotherapy
 - Some patients may benefit from the addition of a third treatment (RT or DOC)
- Not all ARPIs are the same
- mHSPC treatment is evolving³
 - We will use biological and molecular predictors for treatment guidance
 - Maybe the best candidates for docetaxel and ARPI triplet will be found by the PSA response

1L, first-line; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BRCA, BRCA1/2 gene; DOC, docetaxel; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog tumor suppressor; RT, radiotherapy; SOC, standard of care.

1. EAU. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025; 2. George DJ, et al. *Clin Genitourin Cancer* 2020;18:284–294;

3. Speaker's own experience.

Thank you!

Please refer to the Korean PI for
XTANDI[®] (enzalutamide) via the
following link or QR Code:

<XTANDI soft capsule 40mg>

