Genitourinary Masterclass

Impactful data in mHSPC over the last year

Prof. Stéphane Oudard
Prof. Antonio Alcaraz
Prof. Ugo de Giorgi

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Xtandi™ enzalutamide

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XTANDI™ (enzalutamide) indications

XTANDI is indicated, as per the EMA SmPC:

- As monotherapy or in combination with ADT for the treatment of adult men with high-risk biochemical recurrent nmHSPC who are unsuitable for salvage radiotherapy
- In combination with ADT for the treatment of adult men with mHSPC
- For the treatment of adult men with high-risk nmCRPC
- For the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated
- For the treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy

XTANDI is subject to medicinal prescription.
Astellas Pharma B.V., Sylviusweg 62, 2333 BE Leiden, The Netherlands.
ADT, androgen deprivation therapy; EMA, European Medicines Agency; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; nmHSPC, nonmetastatic hormone-sensitive prostate cancer; SmPC, Summary of Product Characteristics.
XTANDI (enzalutamide). Summary of Product Characteristics.
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Genitourinary Masterclass

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ARANOTE study: Review of the results in the light of doublet in mHSPC

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Disclosures

Research funding:

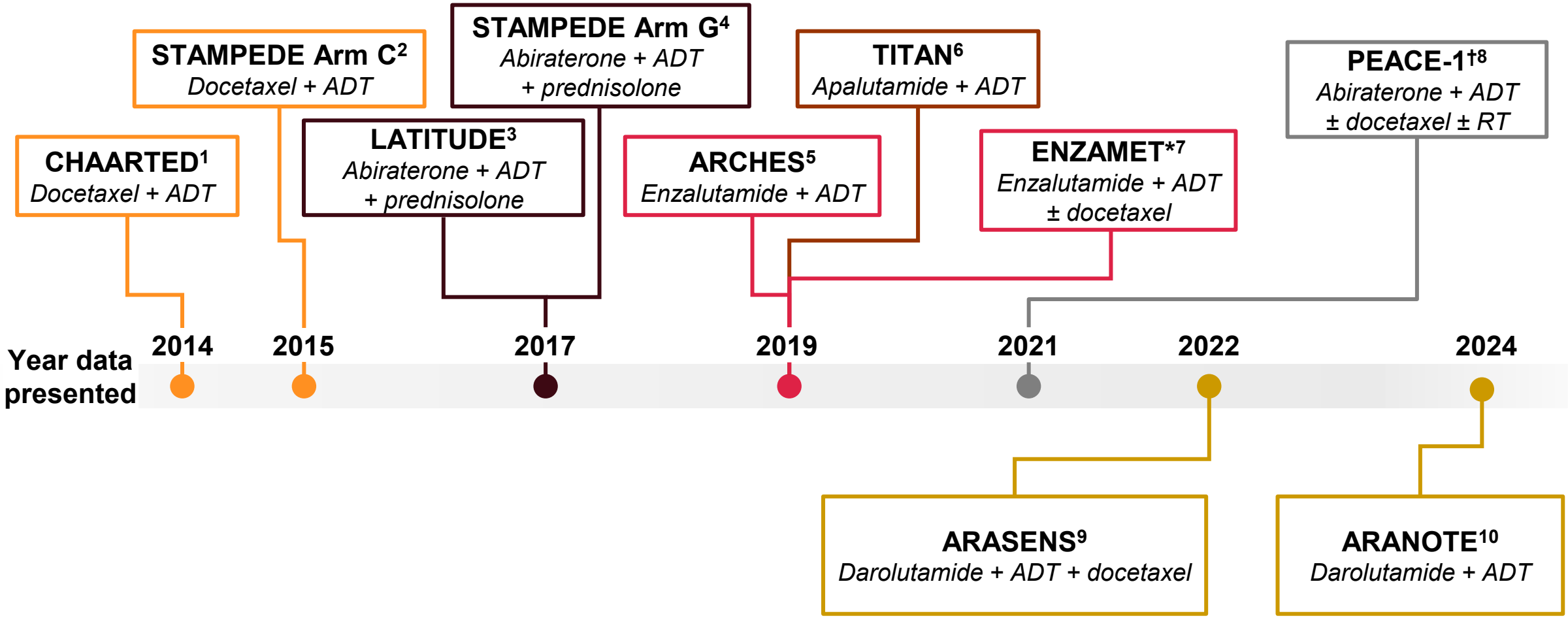
- AstraZeneca, Bayer, BMS, Ipsen, Novartis, Pfizer

Consultancy:

- Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck/MSD, Novartis, Pfizer, Roche

The presenter has received an honorarium for this presentation.

Evolution of care for patients with mHSPC



*ENZAMET was not powered to analyse the results of overall survival in individual subgroups. Therefore, an improvement in overall survival cannot be demonstrated formally in any subgroup, including mHSPC patients taking XTANDI + LHRH therapy with or without concomitant docetaxel. †Please note this combination is not licensed in the UK or Europe for mHSPC.

ADT, androgen deprivation therapy; LHRH, luteinising hormone releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; RT, radiotherapy.

1. Sweeney C, et al. *J Clin Oncol* 2014;32(suppl):LBA2; 2. James ND, et al. *J Clin Oncol* 2015;33(15 suppl):5001; Fizazi K, et al. *J Clin Oncol* 2017;35(suppl):LBA3; 4. James ND, et al. *J Clin Oncol* 2017;35(suppl):LBA5003; 5. Armstrong AJ, et al. *J Clin Oncol* 2019;37(suppl 7):687; 6. Chi KN, et al. *J Clin Oncol* 2019;37(15 suppl):5006; 7. Sweeney C, et al. *J Clin Oncol* 2019;37(18 suppl):LBA2; 8. Fizazi K, et al. *Ann Oncol* 2021;32(5 suppl):LBA5; 9. Smith MR, et al. *J Clin Oncol* 2022;40(suppl 6):13; 10. Saad F, et al. *Ann Oncol* 2024;35(2 suppl):LBA68.

MAT-NL-XTD-2025-00031 | July 2025

Recommendations for the management of mHSPC (EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines 2025)

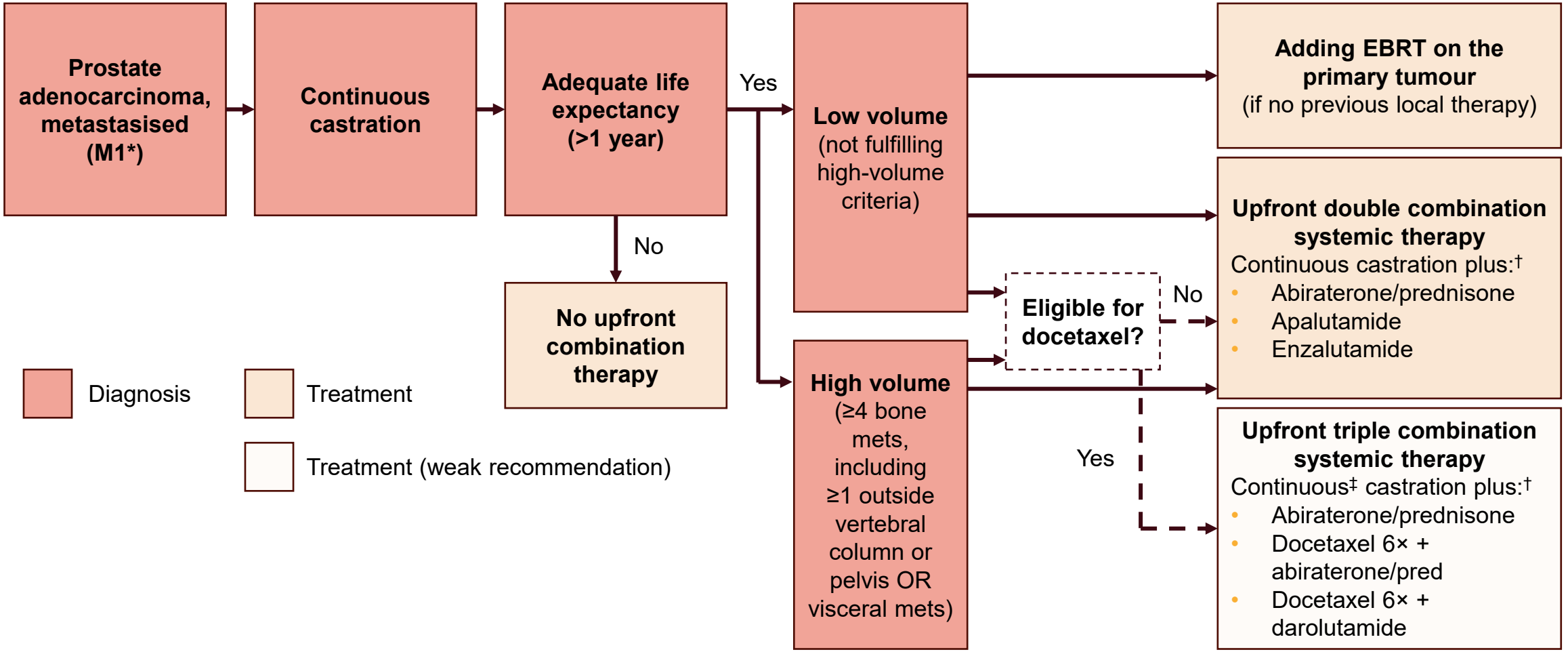


Image adapted from Cornford P, et al., 2025.
*Based on staging using combination of bone scan and CT; †Alphabetical order; ‡Not for low volume metachronous disease.
CT, computed tomography; EBRT, external beam radiotherapy; mHSPC, metastatic hormone-sensitive prostate cancer.
Cornford P, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Available at: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2025_2025-03-24-120144_rinw.pdf. Last accessed: June 2025.

Recommendations for the management of mHSPC (EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines 2025)

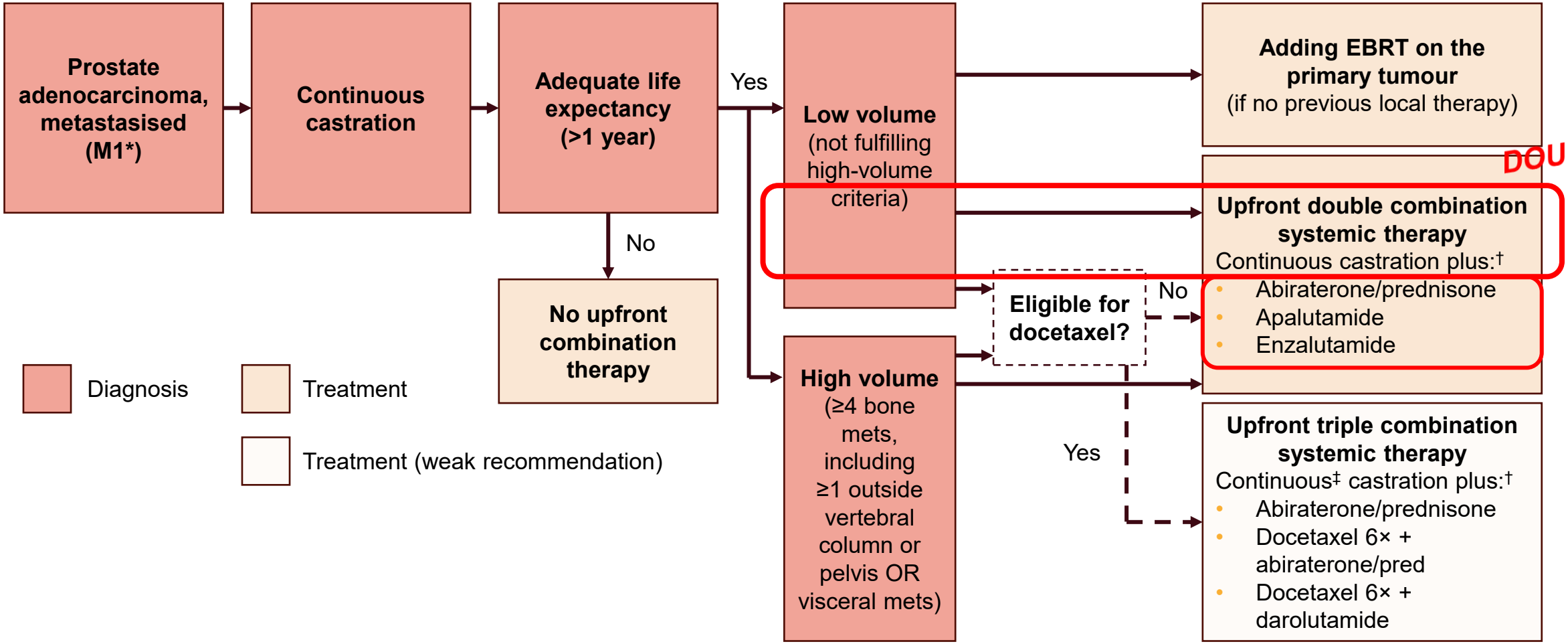


Image adapted from Cornford P, et al., 2025.
*Based on staging using combination of bone scan and CT; †Alphabetical order; ‡Not for low volume metachronous disease.
CT, computed tomography; EBRT, external beam radiotherapy; mHSPC, metastatic hormone-sensitive prostate cancer.
Cornford P, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Available at: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2025_2025-03-24-120144_rinw.pdf. Last accessed: June 2025.

Data from the ARANOTE study (DARO/ADT doublet)

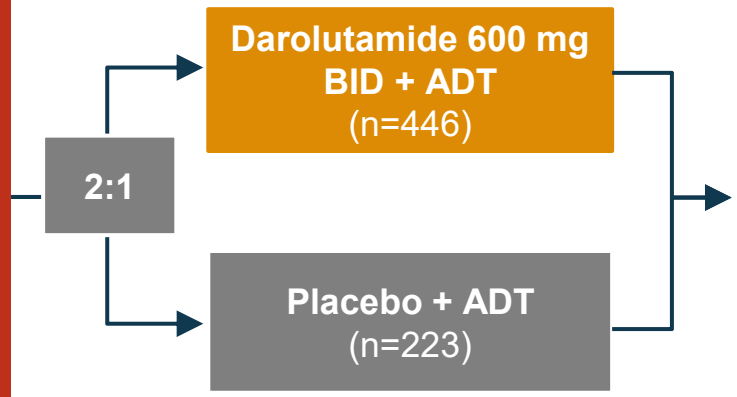
A randomised, double-blind, placebo-controlled Phase III study

Patients (N=669)

- mHSPC*
- ECOG PS ≤2

Stratification factors

- Presence/absence of visceral metastases (assessed by central review)
- Prior local therapy: Yes/no



Data cutoff: June 7, 2024

Primary endpoint

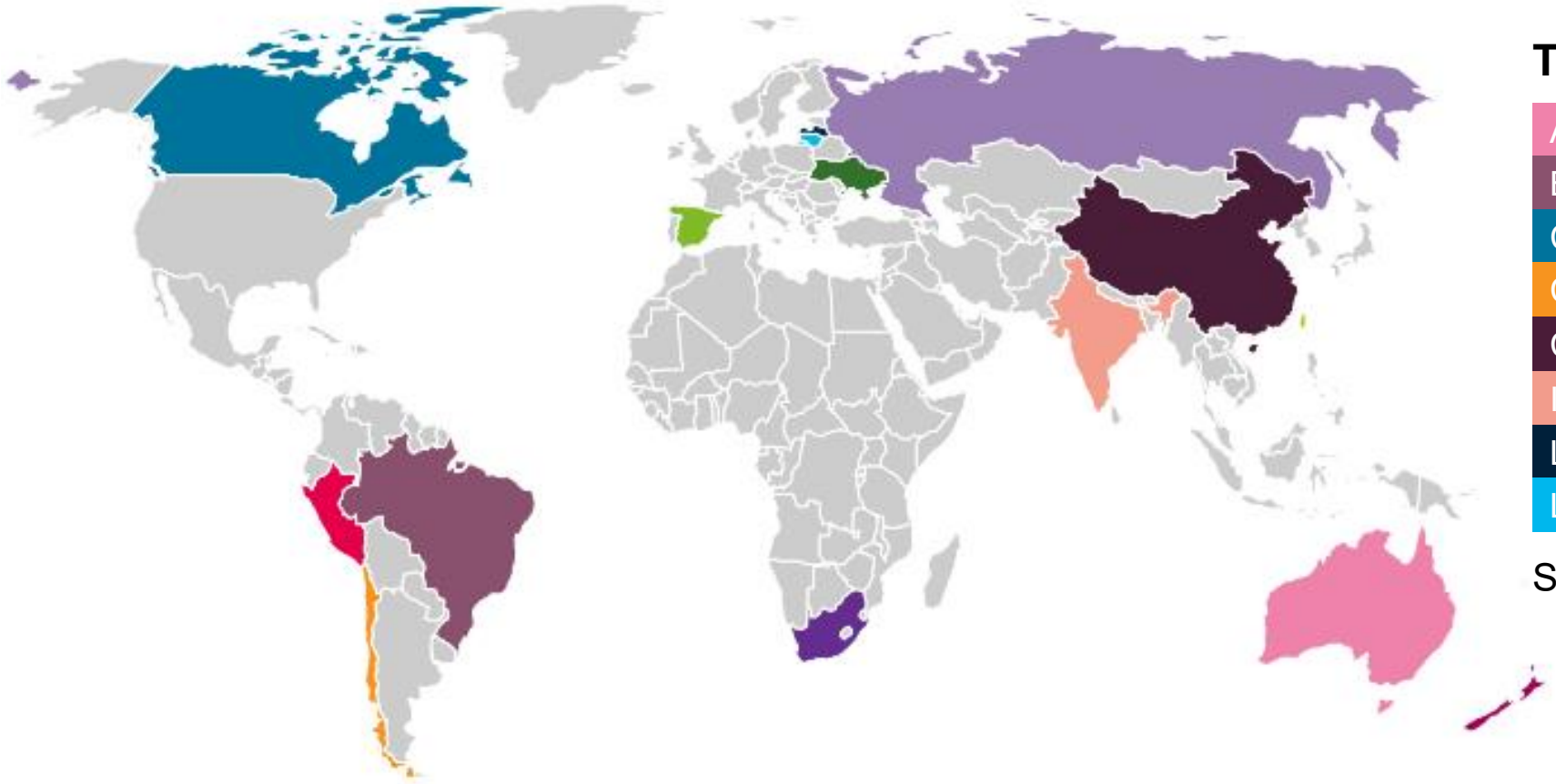
- rPFS (assessed by central review)

Secondary endpoints

- OS
- Time to mCRPC
- Time to initiation of subsequent anticancer therapy
- Time to PSA progression
- Rates of undetectable PSA (<0.2 ng/mL)
- Time to pain progression (BPI-SF)
- Safety profile

Image adapted from Saad F, et al. 2024.
*Metastatic disease confirmed by conventional imaging method, either by a positive ^{99m}Tc-phosphonate bone scan, or soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by central review.
ADT, androgen deprivation therapy; BID, twice daily; BPI-SF, Brief Pain Inventory-Short Form; CRPC, castration-resistant prostate cancer; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.

ARANOTE: Trial conducted in 15 countries



Trial sites (133)

Australia	New Zealand
Brazil	Peru
Canada	Russian Federation
Chile	South Africa
China	Spain
India	Taiwan
Latvia	Ukraine
Lithuania	

Study conducted in 15 countries

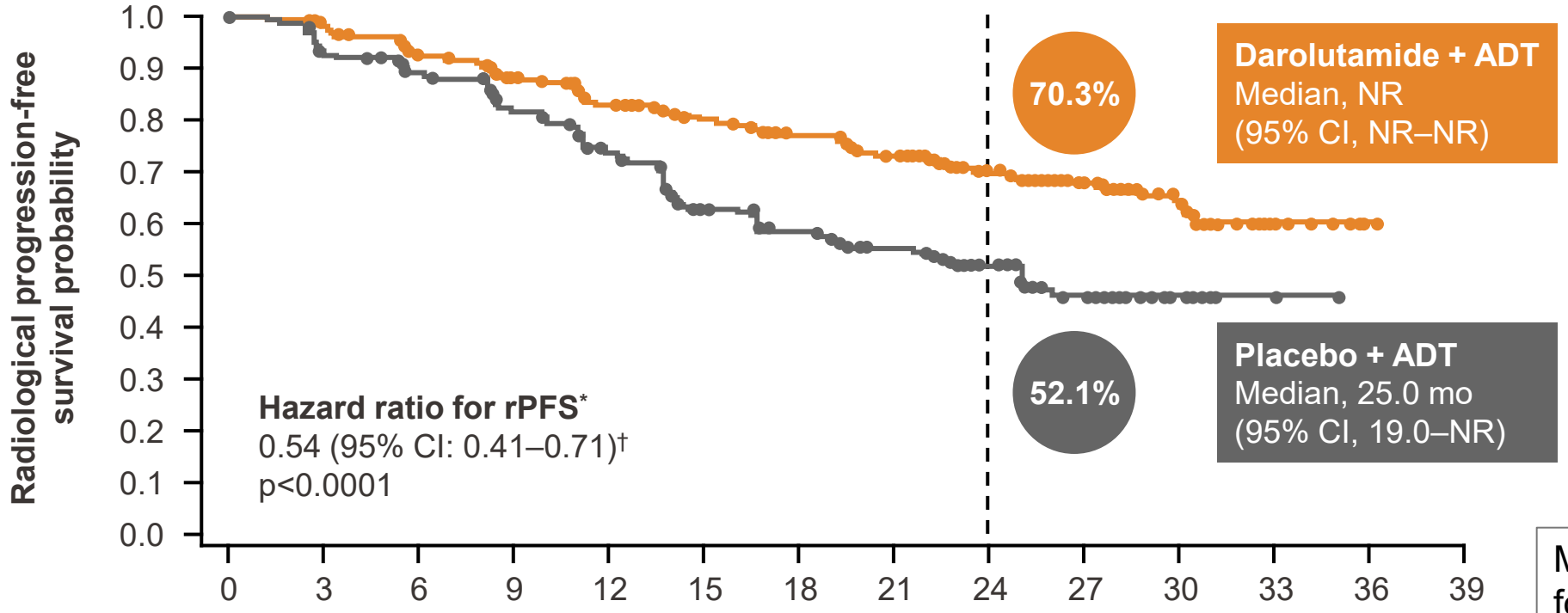
Image adapted from Saad F, et al. 2024.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.
MAT-NL-XTD-2025-00031 | July 2025

ARANOTE: Patient characteristics

Characteristic		Darolutamide + ADT (n=446)	Placebo + ADT (n=223)
Age, years	Median (range)	70 (43–93)	70 (45–91)
Race, n (%)	White	251 (56.3)	125 (56.1)
	Asian	144 (32.3)	65 (29.1)
	Black	41 (9.2)	24 (10.8)
	Other	10 (2.2)	9 (4.0)
Region, n (%)	Asia	141 (31.6)	63 (28.3)
	Latin America	119 (26.7)	72 (32.3)
	Europe and Rest of World	186 (41.7)	88 (39.5)
ECOG PS, n (%)	0	235 (52.7)	98 (43.9)
	1/2	211 (47.3)	125 (56.1)
Gleason score at initial diagnosis, n (%)	≥8	311 (69.7)	146 (65.5)
Serum PSA, ng/mL	Median (range)	21.4 (0.02–15,915)	21.2 (0.02–8533)
Metastases at initial diagnosis, n (%)	Yes [*de novo*]	317 (71.1)	168 (75.3)
	No [recurrent]	100 (22.4)	45 (20.2)
Disease volume,* n (%)	High	315 (70.6)	157 (70.4)
	Low	131 (29.4)	66 (29.6)
Visceral metastases, n (%)	Yes	53 (11.9)	27 (12.1)
	No	393 (88.1)	196 (87.9)
Prior local therapy, n (%)	Yes	80 (17.9)	40 (17.9)
	No	366 (82.1)	183 (82.1)

Table adapted from Saad F, et al. 2024.
*Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis.
ADT, androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.

ARANOTE: 46% reduction in the risk of radiological progression



No. of patients at risk

Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

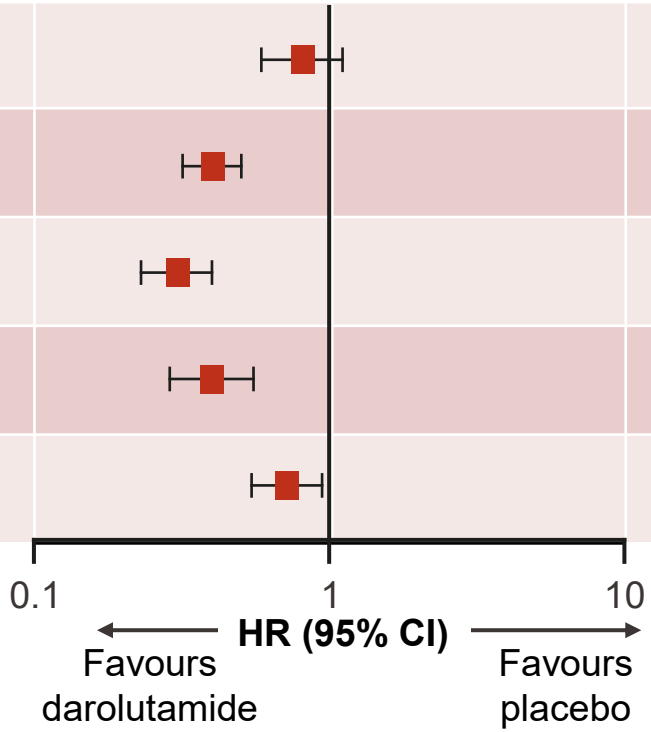
Median follow-up for rPFS:

- Darolutamide + ADT 25.3 months
- Placebo + ADT 25.0 months

Figure adapted from Saad F, et al. 2024.
*'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).
ADT, androgen deprivation therapy; CI, confidence interval; mo, months; NR, not reached; rPFS, radiological progression-free survival.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.
MAT-NL-XTD-2025-00031 | July 2025

ARANOTE: Benefit on secondary endpoints (immature OS at the time of presentation)

Endpoint	Darolutamide + ADT (n=446)		Placebo + ADT (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 PCa	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)**

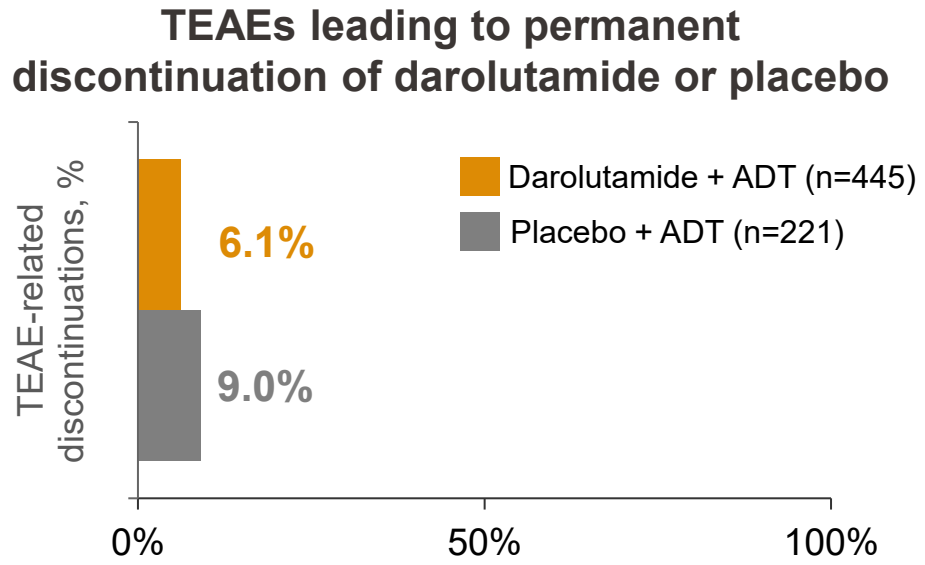


- At the time of primary analysis, OS data were immature

Figure adapted from Saad F, et al. 2024.
ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; OS, overall survival; PCa, prostate cancer; PSA, prostate-specific antigen.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.

ARANOTE: Tolerance profile

TEAE	Darolutamide + ADT (n=445*)	Placebo + ADT (n=221*)
Patients, n (%)		
Any AE	405 (91.0)	199 (90.0)
Worst grade, n (%)		
Grade 3 or 4 AE	137 (30.8)	67 (30.3)
Grade 5 AE	21 (4.7)	12 (5.4)
Serious AE, n (%)	105 (23.6)	52 (23.5)



- Median treatment duration was 24.2 months in the darolutamide arm vs. 17.3 months in the placebo arm

Table and figure adapted from Saad F, et al. 2024.
*Two patients who were randomised to the placebo group but received darolutamide are analysed in the darolutamide group for the safety analysis set.
ADT, androgen deprivation therapy; AE, adverse event; TEAE, treatment-emergent adverse event.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.

ARANOTE: A benefit was observed across subgroups (regardless of disease volume) in rPFS

Subgroup		Darolutamide + ADT (n=446)		Placebo + ADT (n=223)		Stratified HR* (95% CI)
		Events/patients, n/N	Median, months	Events/patients, n/N	Median, months	
Overall population		128/446	NR	94/223	25.0	**0.54 (0.41–0.71)**
Age subgroups	<65 years	37/118	NR	32/65	14.2	**0.44 (0.27–0.71)**
	65–74 years	53/193	NR	35/96	NR	**0.64 (0.41–0.98)**
	75–84 years	29/117	NR	22/52	NR	**0.48 (0.27–0.83)**
	≥85 years	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)**

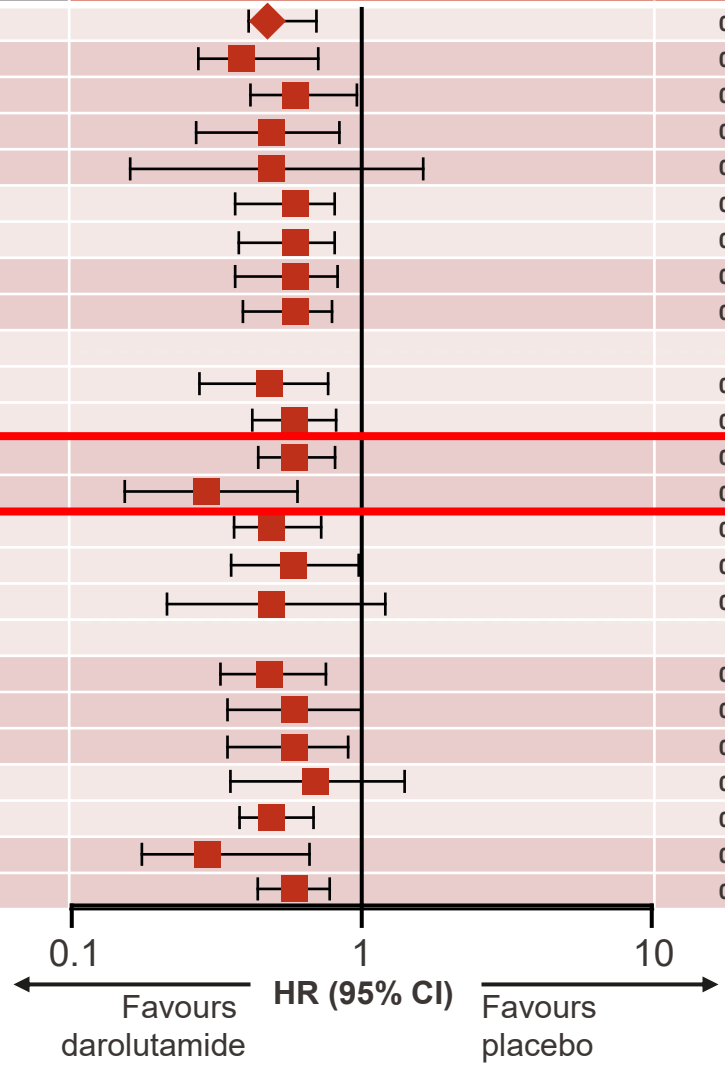


Table adapted from Saad F, et al. 2024.
*HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.
ADT, androgen deprivation therapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PSA, prostate-specific antigen; RoW, rest of world.
Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68.
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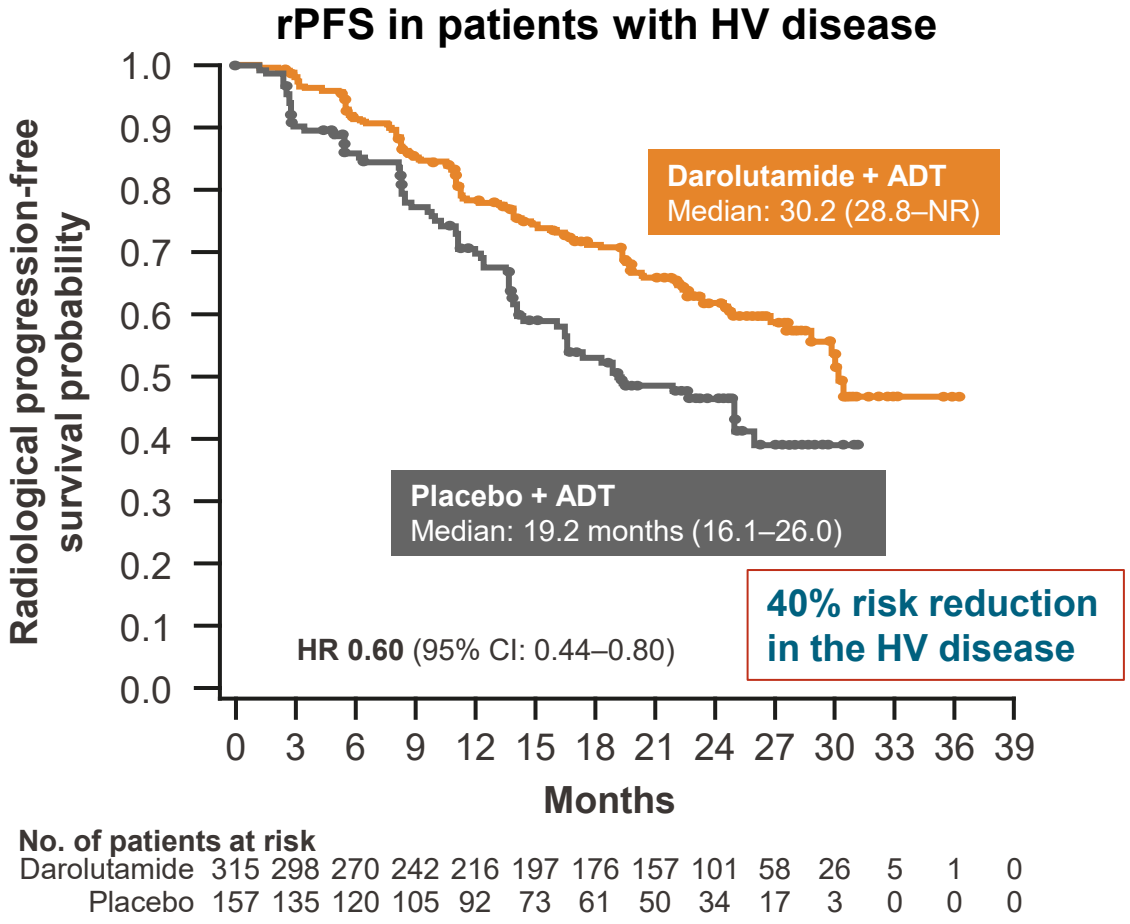
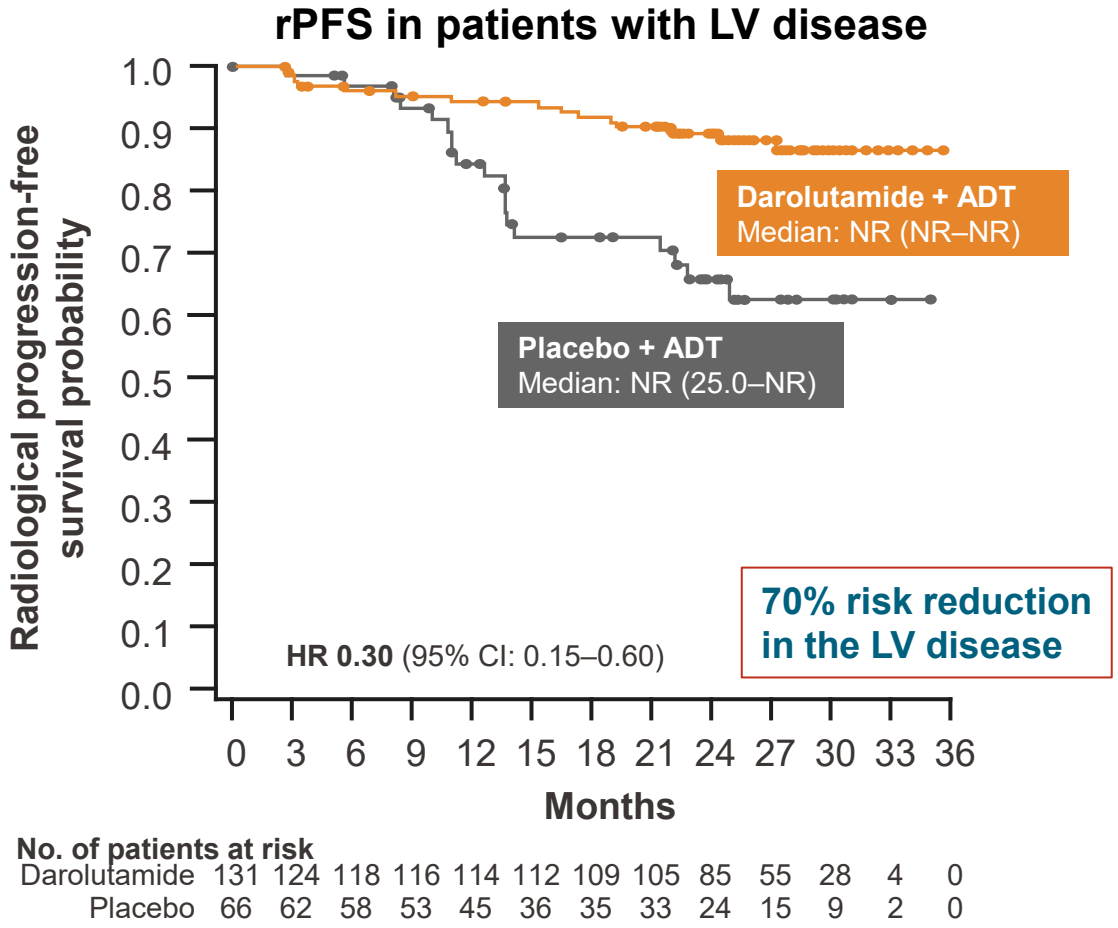
Efficacy of ADT + darolutamide doublet by disease volume: rPFS

- *Post hoc* analysis of the ARANOTE study (ASCO-GU 2025)





Figures adapted from Saad F, et al. 2025.

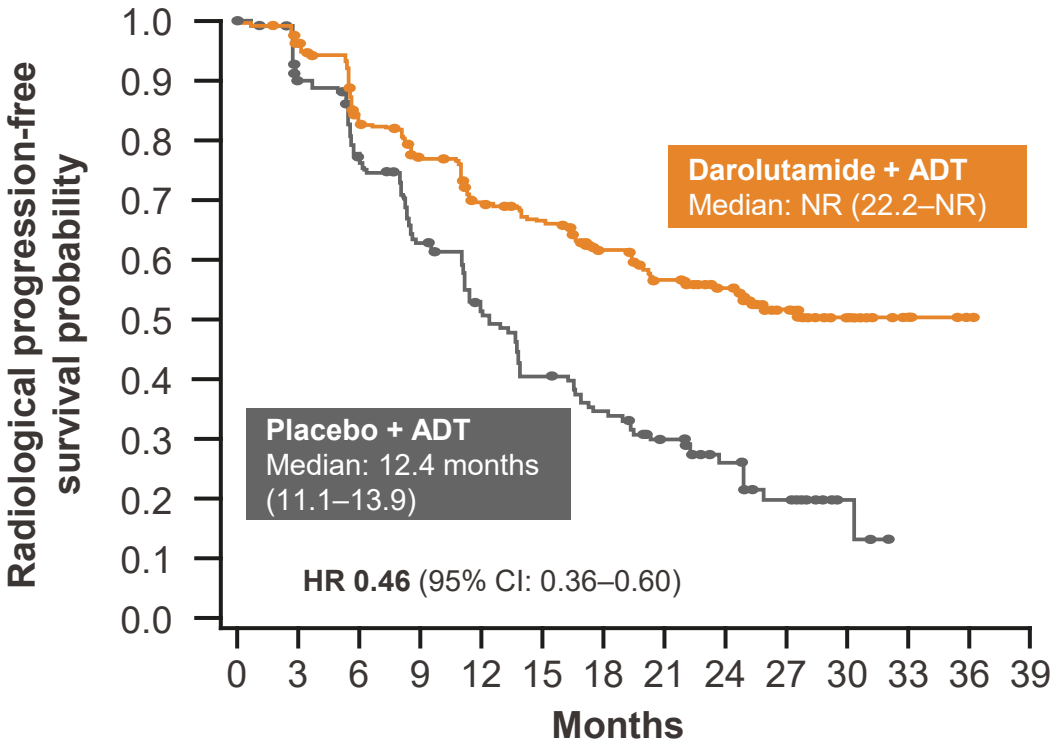
ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; HV, high volume; LV, low volume; NR, not reached; rPFS, radiologic progression-free survival.

Saad F, et al. Presented at ASCO GU 2025, February 13–15, 2025, San Francisco, CA, USA, Abstract 151 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-prostate-cancer/158132-asco-gu-2025-darolutamide-adt-in-patients-with-mhspc-by-disease-volume-subgroup-analysis-of-the-phase-3-aranote-trial.html. Last accessed June 2025.

Efficacy of ADT + darolutamide doublet by disease volume: Time to mCRPC

- *Post hoc* analysis of the ARANOTE study (ASCO-GU 2025)

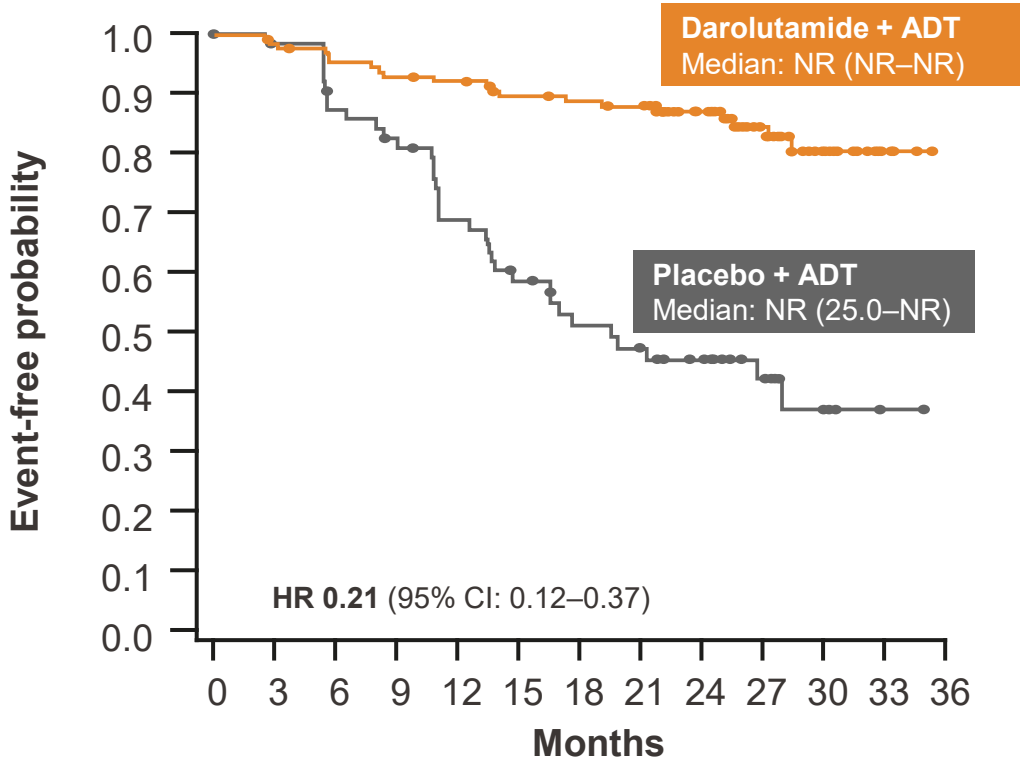
Time to mCRPC in patients with HV disease



No. of patients at risk

Darolutamide	315	293	245	223	198	185	162	141	94	54	25	7	2	0
Placebo	157	135	113	90	70	55	46	36	22	11	3	0	0	0

Time to mCRPC in patients with LV disease



No. of patients at risk

Darolutamide	131	124	119	116	114	108	106	104	83	56	26	7	0	
Placebo	66	62	54	49	40	33	27	25	20	14	7	2	0	

Figures adapted from Saad F, et al. 2025.

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; HV, high volume; LV, low volume; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached.

Saad F, et al. Presented at ASCO GU 2025, February 13–15, 2025, San Francisco, CA, USA, Abstract 151 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-prostate-cancer/158132-asco-gu-2025-darolutamide-adt-in-patients-with-mhspc-by-disease-volume-subgroup-analysis-of-the-phase-3-aranote-trial.html. Last accessed June 2025.

ARANOTE: Impact on deep PSA response (1/2)

- Overall, 62.6% of patients had low PSA levels (<0.2 ng/mL) when treated with darolutamide + ADT doublet vs. only 18.5% treated with ADT alone[1]

- As a reminder, 60% of patients treated with darolutamide + ADT + docetaxel in the ARASENS trial had low PSA levels (<0.2 ng/mL) at 1 year[2]

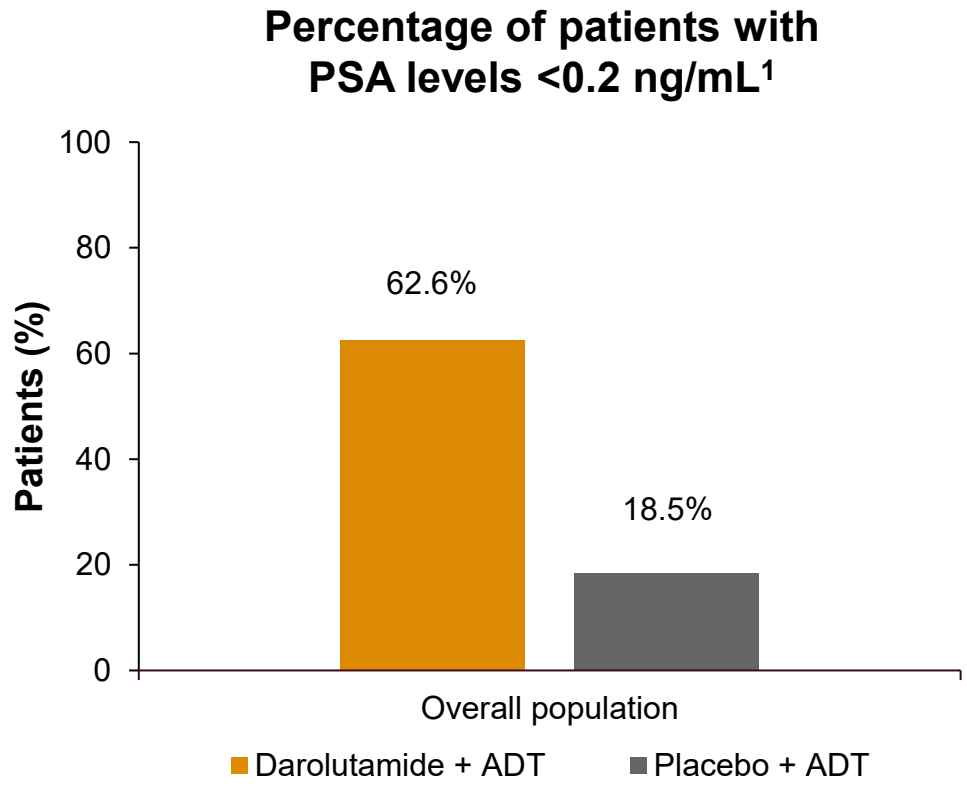


Figure adapted from Saad F, et al. 2024.
ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
1. Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68; 2. Saad F, et al. *Eur Urol* 2024;86:329–339.
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ARANOTE: Impact on deep PSA response (2/2)

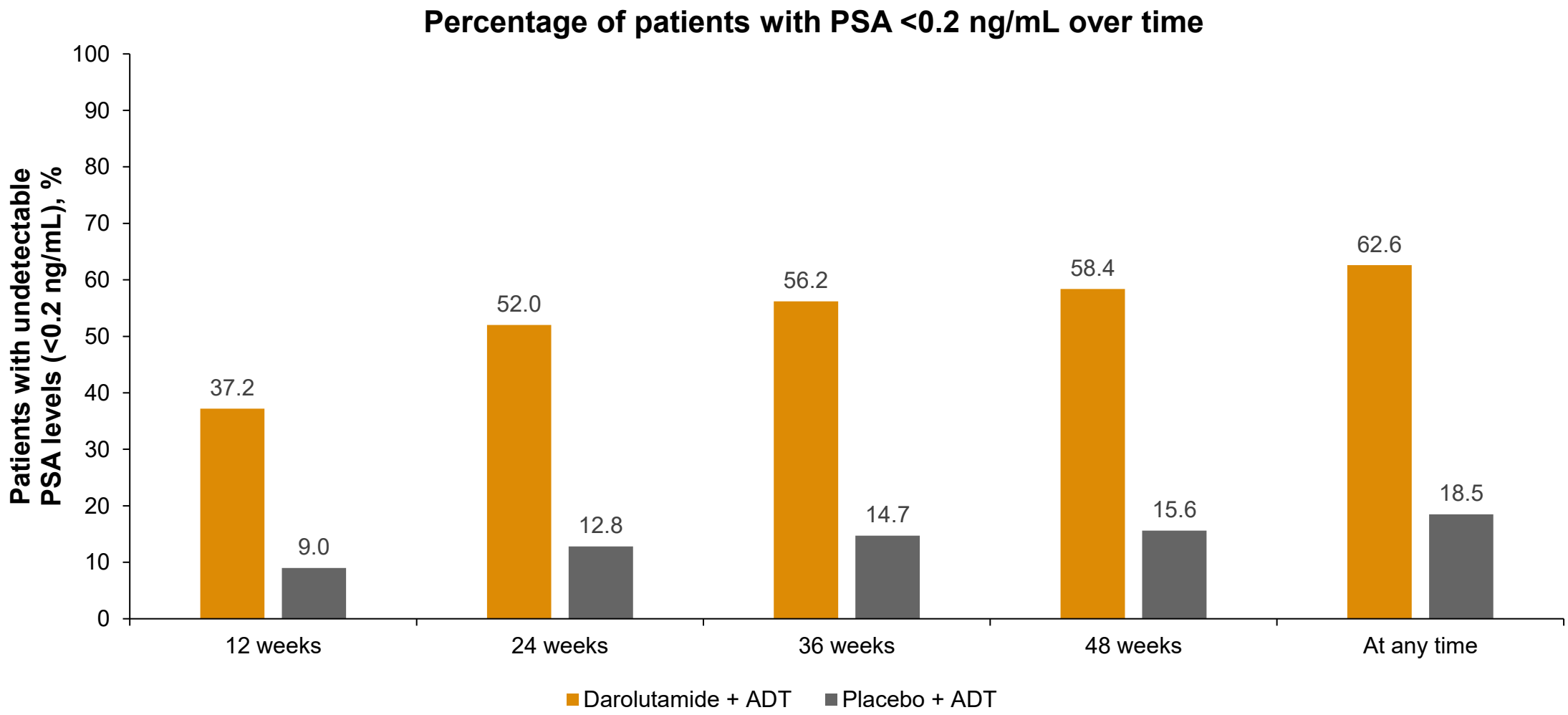
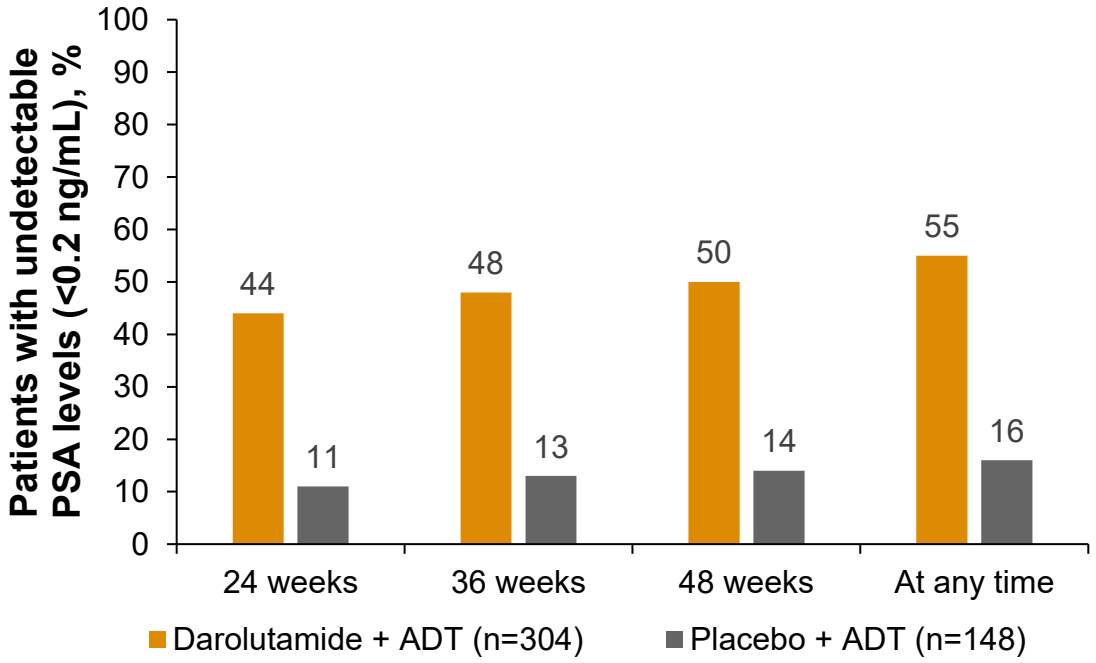


Figure adapted from Saad F, et al. 2025.
ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
Saad F, et al. Presented at EAU 2025, March 21–24, 2025, Madrid, Spain, Abstract GC11 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/eau-2025/eau-2025-prostate-cancer/159221-eau-2025-psa-response-with-darolutamide-plus-adt-in-patients-with-mhspc-in-aranote.html. Last accessed June 2025.

ARANOTE: Impact on deep PSA response by volume of disease

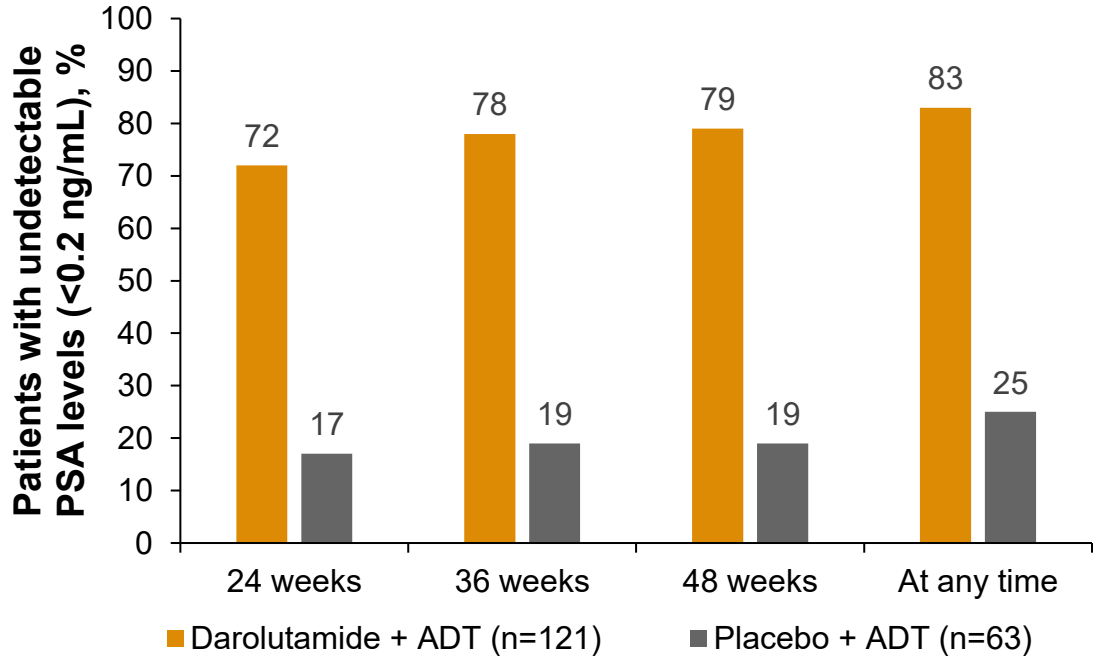
High volume

Patients with undetectable PSA (<0.2 ng/mL) in the HV subgroup (of those with baseline PSA ≥0.2 ng/mL)



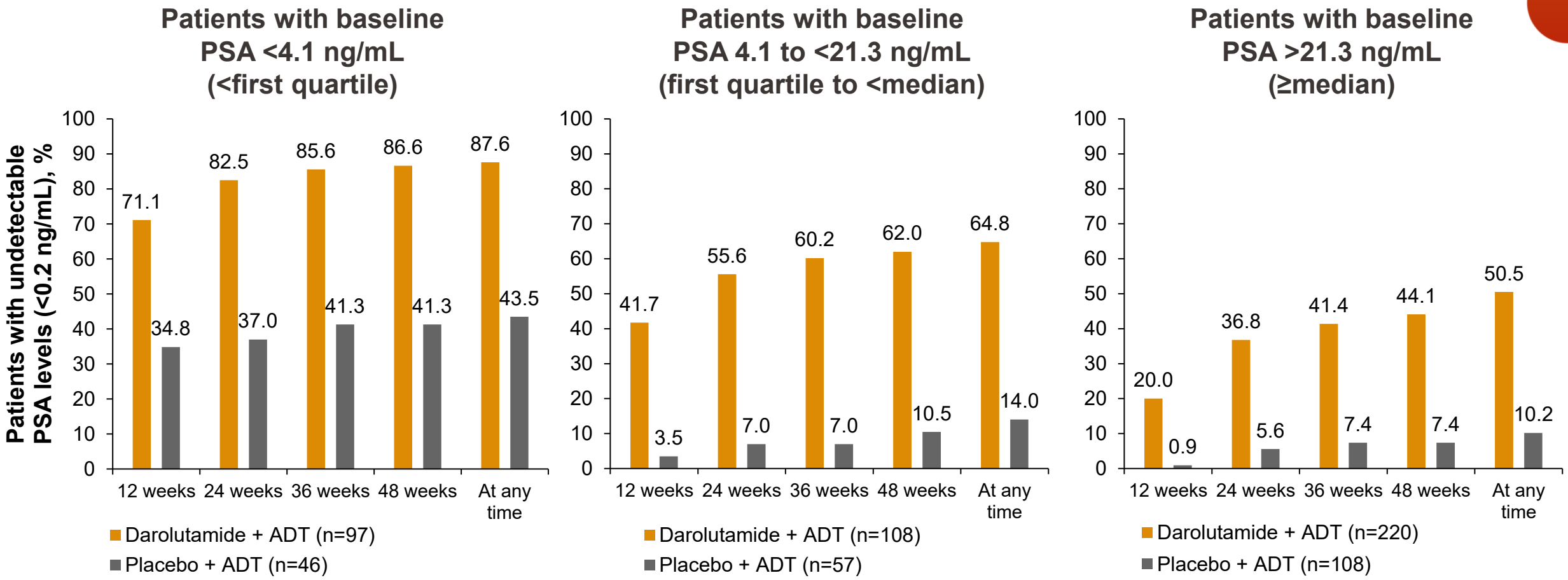
Low volume

Patients with undetectable PSA (<0.2 ng/mL) in the LV subgroup (of those with baseline PSA ≥0.2 ng/mL)



Figures adapted from Saad F, et al. 2025.
ADT, androgen deprivation therapy; HV, high volume; LV, low volume; PSA, prostate-specific antigen.
Saad F, et al. Presented at ASCO GU 2025, February 13–15, 2025, San Francisco, CA, USA, Abstract 151 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-prostate-cancer/158132-asco-gu-2025-darolutamide-adt-in-patients-with-mhspc-by-disease-volume-subgroup-analysis-of-the-phase-3-aranote-trial.html. Last accessed June 2025.

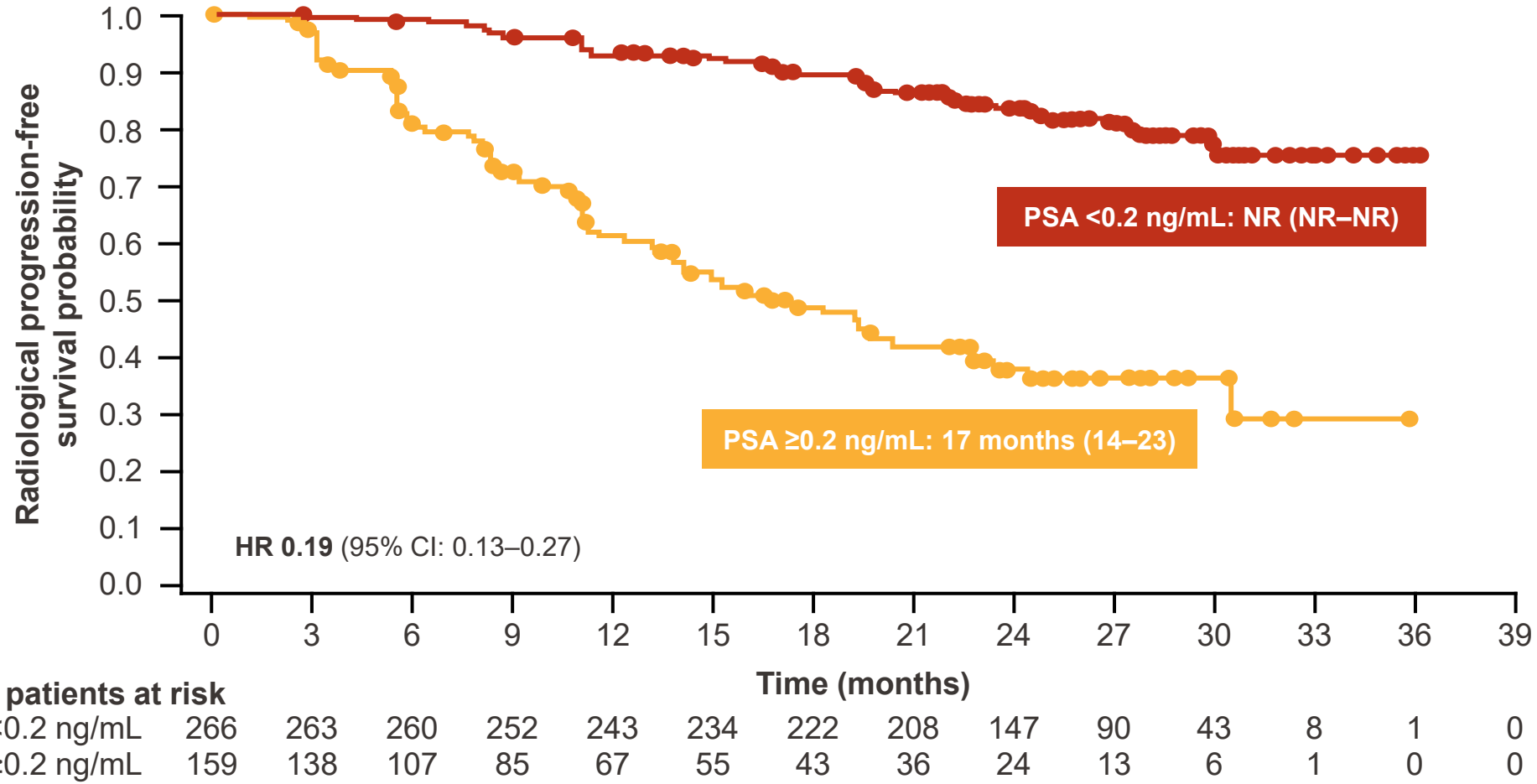
ARANOTE: PSA response as a function of baseline PSA



ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

Saad F, et al. Presented at EAU 2025, March 21–24, 2025, Madrid, Spain, Abstract GC11 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/eau-2025/eau-2025-prostate-cancer/159221-eau-2025-psa-response-with-darolutamide-plus-adt-in-patients-with-mhspc-in-aranote.html. Last accessed June 2025.

ARANOTE: rPFS according to PSA response



No. of patients at risk

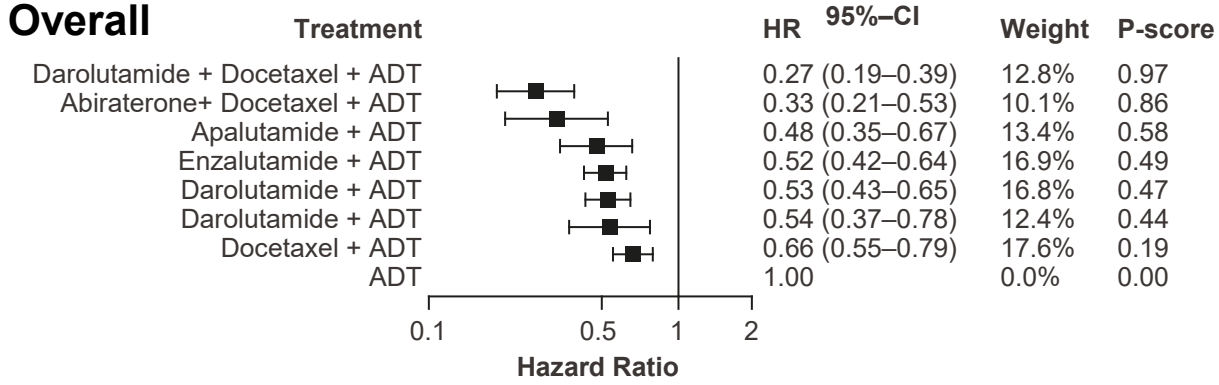
PSA <0.2 ng/mL	266	263	260	252	243	234	222	208	147	90	43	8	1	0
PSA ≥0.2 ng/mL	159	138	107	85	67	55	43	36	24	13	6	1	0	0

Figure adapted from Saad F, et al. 2025.
CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.
Saad F, et al. Presented at EAU 2025, March 21–24, 2025, Madrid, Spain, Abstract GC11 – as reported in UroToday. Available at: https://www.urotoday.com/conference-highlights/eau-2025/eau-2025-prostate-cancer/159221-eau-2025-psa-response-with-darolutamide-plus-adt-in-patients-with-mhspc-in-aranote.html. Last accessed June 2025.

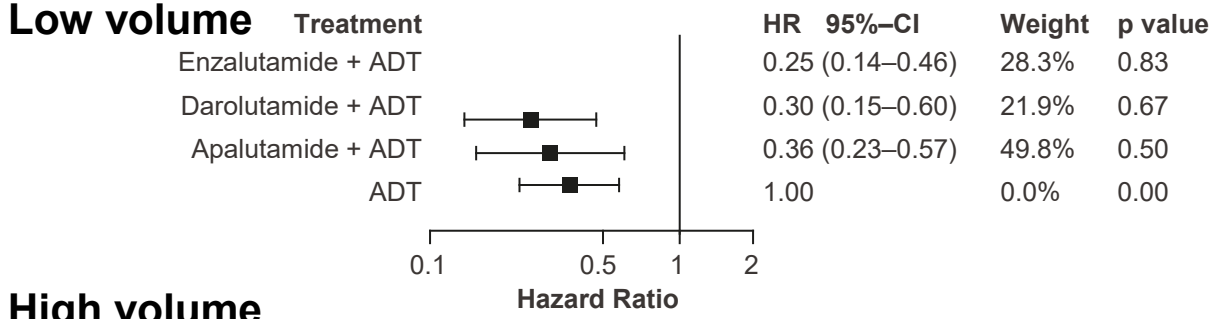
Triplet or Doublet Therapy in Metastatic Hormone-sensitive Prostate Cancer Patients: An Updated Network Meta-analysis Including ARANOTE Data

Benefit in rPFS

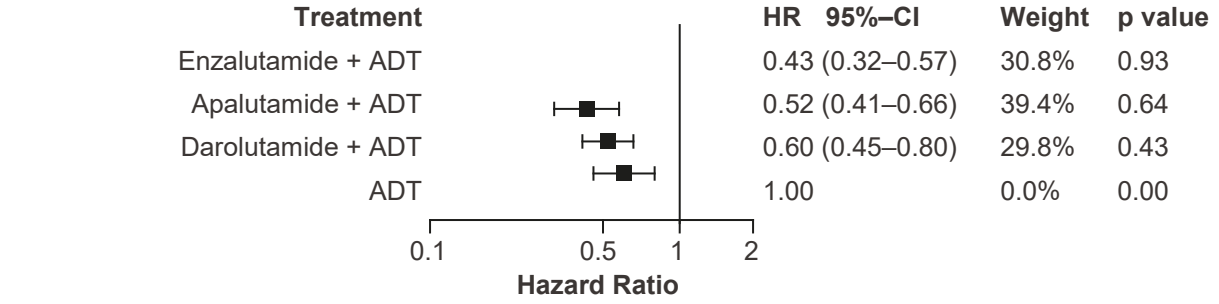
Overall



Low volume

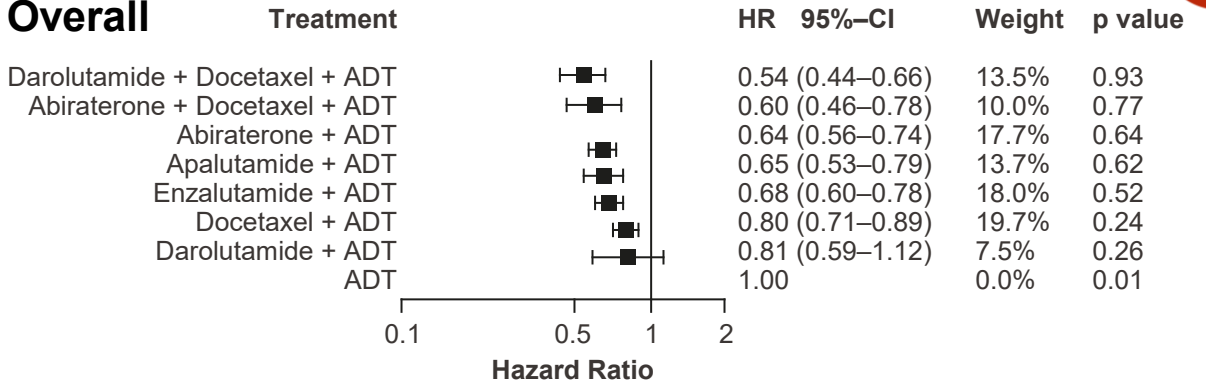


High volume



Benefit in OS

Overall



- Darolutamide + ADT demonstrated comparable rPFS to established doublet therapies (ADT + apalutamide, enzalutamide, abiraterone, or docetaxel)

The current data suggest that the combination of darolutamide + ADT offers another treatment option for mHSPC, demonstrating comparable rPFS to other ADT-based doublet therapies and an acceptable safety profile

Figures adapted from Hoeh B, et al. 2025.
ADT, androgen deprivation therapy; CI, confidence interval; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival.
Hoeh B, et al. *Eur Urol* 2025; doi:10.1016/j.euf.2024.11.004 [Epub ahead of print].
MAT-NL-XTD-2025-00031 | July 2025

Conclusion on ARANOTE in mHSPC

- Darolutamide + ADT demonstrated a clinically significant delay in rPFS vs placebo + ADT with minimal treatment burden[1]
- The results of ARANOTE confirm the efficacy and well-established acceptable safety profile of darolutamide, including a low discontinuation rate due to AEs[1]
- The results of this second pivotal trial of darolutamide add to the body of evidence from ARASENS, supporting a potential role for darolutamide as a doublet therapy alongside its indication as a triplet with ADT and docetaxel[1]

While not yet incorporated into guidelines, darolutamide + ADT doublet has recently been granted a license for use in patients with mHSPC[2]

ADT, androgen deprivation therapy; AE, adverse event; mHSPC, metastatic hormone-sensitive prostate cancer; rPFS, radiographic progression-free survival.

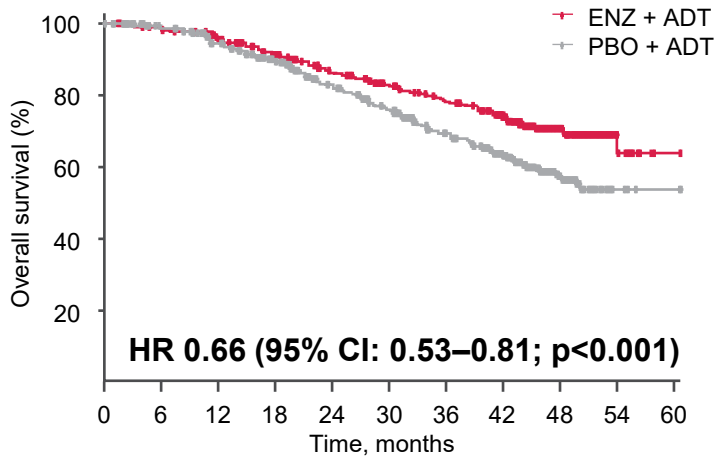
1. Saad F, et al. Presented at ESMO 2024, September 13–17, 2024, Barcelona, Spain, Abstract LBA68; 2. US FDA. FDA approves darolutamide for metastatic castration-sensitive prostate cancer [Website[. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darolutamide-metastatic-castration-sensitive-prostate-cancer#:~:text=sensitive%20prostate%20cancer-,FDA%20approves%20darolutamide%20for%20metastatic%20castration%2Dsensitive%20prostate%20cancer,Efficacy%20and%20Safety. Last accessed: June 2025.

Recent update: ARANOTE OS

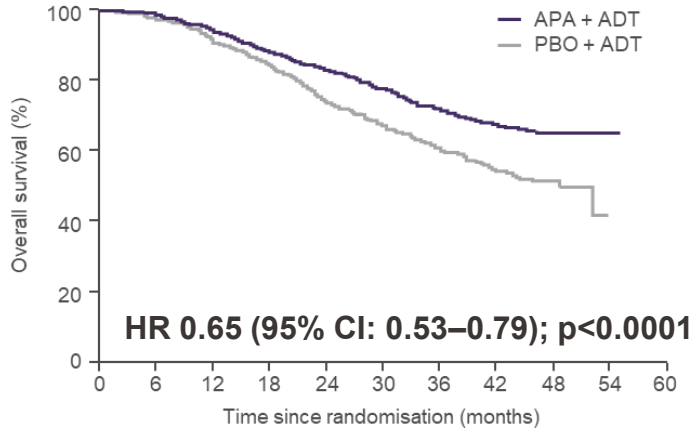
ARANOTE (darolutamide + ADT vs. PBO + ADT)[1]

"There was no statistically significant improvement in OS at the final analysis (HR 0.78; 95% CI: 0.58, 1.05)."

ARCHES (enzalutamide + ADT vs. PBO + ADT)
Data from 2022, median follow-up 44.6 months[2]



TITAN (apalutamide + ADT vs. PBO + ADT)
Data from 2021, median follow-up 44.0 months[3]



Figures adapted from Armstrong AJ, et al., 2022 and Chi KN, et al. 2021.[2,3]
Data shown are for illustrative purposes only, and direct comparisons should not be drawn. Studies differed in terms of design and duration of follow-up.
ADT, androgen deprivation therapy; APA, apalutamide; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; OS, overall survival; PBO, placebo.
1. US FDA. FDA approves darolutamide for metastatic castration-sensitive prostate cancer [Website[. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darolutamide-metastatic-castration-sensitive-prostate-cancer#:~:text=sensitive%20prostate%20cancer-,FDA%20approves%20darolutamide%20for%20metastatic%20castration%2Dsensitive%20prostate%20cancer,Efficacy%20and%20Safety. Last accessed: June 2025;
2. Armstrong AJ, et al. *J Clin Oncol* 2022;40:1616–16223; 3. Chi KN, et al. *N Engl J Med* 2021;39:2294–2303.

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Relevance of ARCHES 5-year Follow-up Overall Survival

Antonio Alcaraz, MD, PhD

Chair, Department of Urology – Hospital Clinic Barcelona
Professor of Urology – University of Barcelona

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Disclosures

Professor Alcaraz has acted as a speaker for the following companies:

- Astellas, Bayer, Casen Recordati, Ipsen, Janssen and Olympus

The presenter has received an honorarium for this presentation.

Images freely available from Microsoft PowerPoint.

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There are multiple systemic treatment options available today for patients with mHSPC

Monotherapy
(ADT alone)

Doublet therapy
(ADT + ARPI)

Triplet therapy
(ADT + ARPI + DOC)

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; DOC, docetaxel; EAU, European Association of Urology; mHSPC, metastatic hormone-sensitive prostate cancer.

EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.

MAT-NL-XTD-2025-00031 | July 2025

Real-world evidence suggests that most patients with mHSPC are not receiving guideline-recommended treatment

- The first evidence of an OS benefit with ADT + ARPI for patients with mHSPC was seen in 2017[1,2]
- The 2025 EAU guidelines recommend offering ADT + ARPI for patients with mHSPC who are fit for the regimen[3]
- However, real-world data have shown that 76% of patients with mHSPC are receiving treatments not recommended by guidelines[4]

Country-specific analysis of the proportion of patients with mHSPC receiving non-guideline-recommended treatments between 2018 and 2020[4]

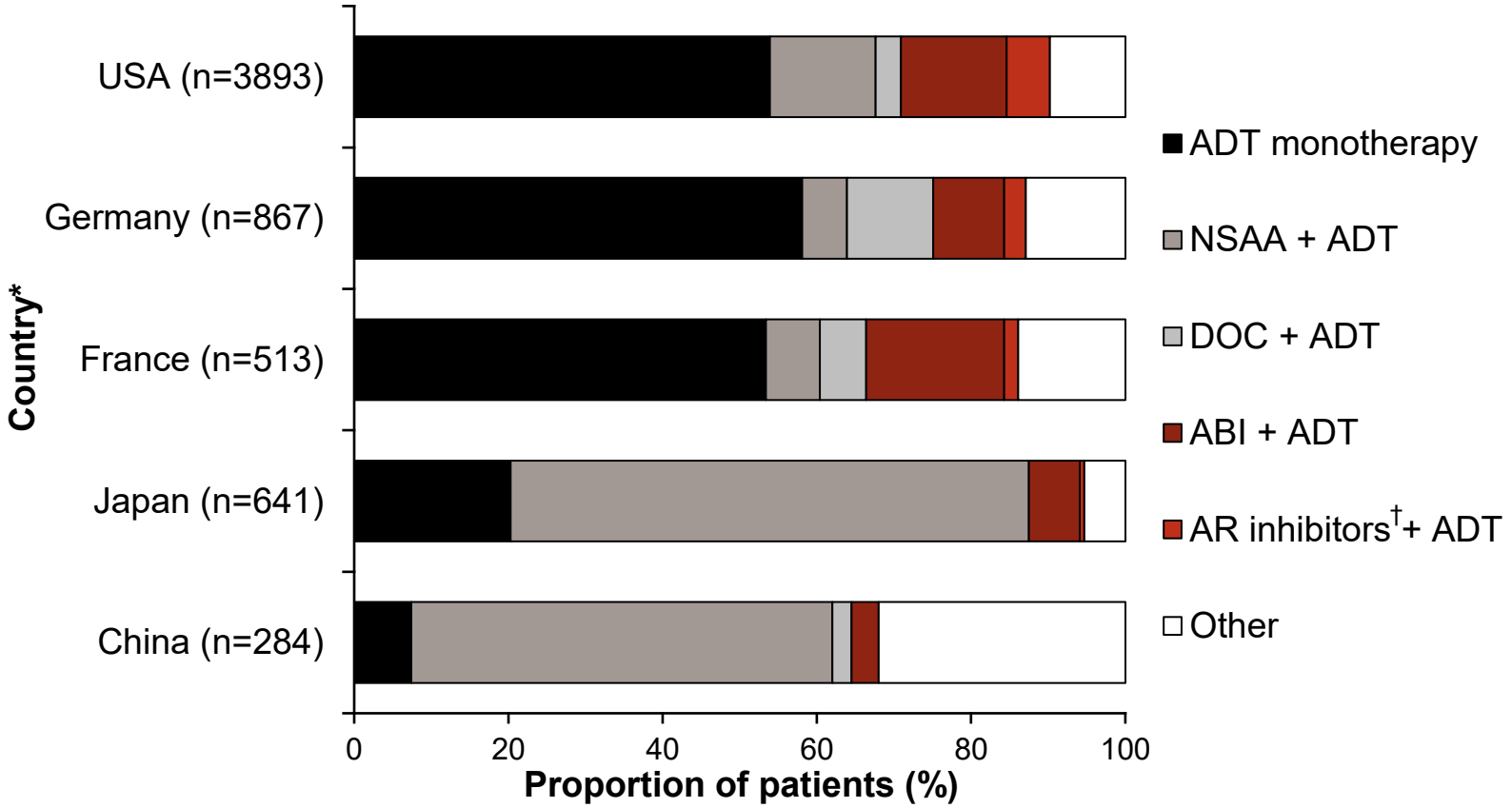

Figure adapted from Goebell PJ, et al. 2024.
*Study time frame of January 2018 through December 2019 for China vs. June 2020 for other countries due to data availability;[2] †Apalutamide, darolutamide or enzalutamide.[2]
ABI, abiraterone; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; DOC, docetaxel; EAU, European Association of Urology; mHSPC, metastatic hormone-sensitive prostate cancer; nmHSPC, non-metastatic hormone-sensitive prostate cancer; NSAA, non-steroidal anti-androgen; OS, overall survival.

1. Fizazi K, et al. *N Engl J Med* 2017;377:352–360; 2. James ND, et al. *N Engl J Med* 2017;377:338–351;
3. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025;
4. Goebell PJ, et al. Future Oncol 2024; doi:10.2217/fon-2023-0814 [Epub ahead of print].

MAT-NL-XTD-2025-00031 | July 2025

Real-world evidence suggests that most patients with mHSPC are not receiving guideline-recommended treatment

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Analysis of the proportion of patients with mHSPC in Australia receiving non-guideline-recommended treatments[5]

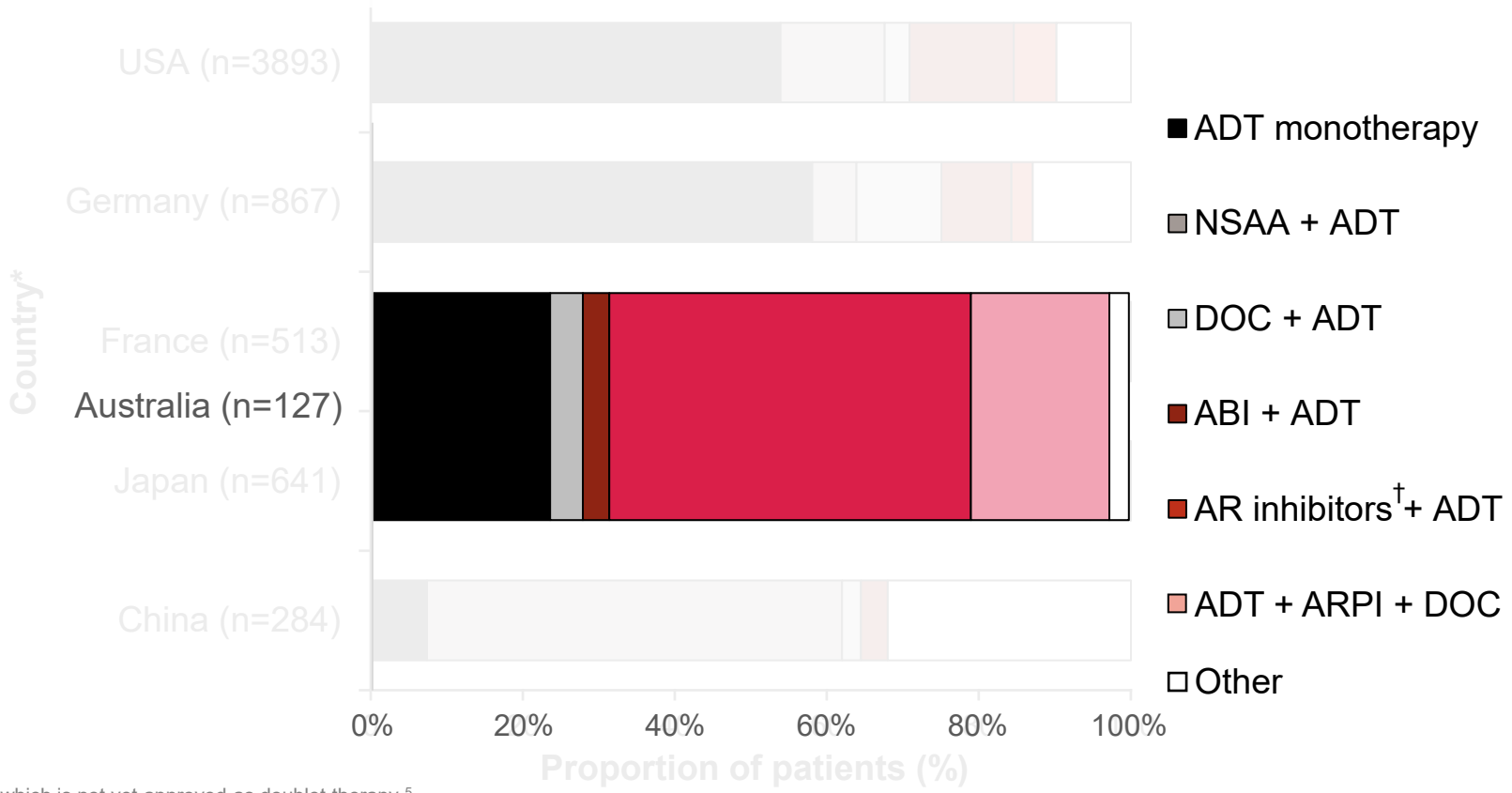

Figure adapted from Inderjeeth AJ, et al. 2024.
*Study time frame from after January 2023;[5] †These data include darolutamide, which is not yet approved as doublet therapy.[5]
ABI, abiraterone; ADT, androgen deprivation therapy; AR, androgen receptor; ARPI, androgen receptor pathway inhibitor; DOC, docetaxel; EAU, European Association of Urology; mHSPC, metastatic hormone-sensitive prostate cancer; NSAA, non-steroidal anti-androgen; OS, overall survival.

1. Fizazi K, et al. *N Engl J Med* 2017;377:352–360; 2. James ND, et al. *N Engl J Med* 2017;377:338–351;
3. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: March 2025;
4. Goebell PJ, et al. *Future Oncol* 2024; doi:10.2217/fon-2023-0814 [Epub ahead of print]. 5. Inderjeeth AJ, et al. Presented at ANZUP ASM 2024, 21–23 July 2024, Gold Coast, Australia. Poster abs22.

Data show an OS benefit with ARPIs vs. PBO + ADT in patients with mHSPC regardless of disease volume or timing of metastases

Trial	Arms	High-volume disease	Low-volume disease
ARCHES[1]	**ENZ + ADT** vs. PBO + ADT	**HR 0.66** (95 CI: 0.52–0.83)	**HR 0.66** (95 CI: 0.43–1.03)
ENZAMET*[2] (Population without concomitant docetaxel)	**ENZ + ADT** vs. NSAA + ADT	Synchronous: **HR 0.70** (95% CI: 0.47–1.04)	Synchronous: **HR 0.58** (95% CI: 0.32–1.04) Metachronous: **HR 0.47** (95% CI: 0.28–0.79)
TITAN[3]	**APA + ADT** vs. PBO + ADT	Synchronous: **HR 0.68** (95% CI: 0.53–0.87) Metachronous: **HR 0.69** (95% CI: 0.33–1.44)	Synchronous: **HR 0.65** (95% CI: 0.40–1.05) Metachronous: **HR 0.22** (95% CI; 0.09–0.55)
STAMPEDE[4]	**AAP + ADT** vs. ADT monotherapy	**HR 0.60** (95% CI: 0.46–0.78)	**HR 0.64** (95% CI: 0.42–0.97)
LATITUDE[5]	**AAP + ADT** vs. PBO + ADT	**HR 0.62** (95% CI: 0.52–0.74)	**HR 0.72** (95% CI: 0.47–1.10)

Data shown are for illustrative purposes only, and direct comparisons should not be drawn. *Concomitant use of enzalutamide and docetaxel is not authorised in Europe. The overall patient population in ENZAMET included those who received or did not receive concomitant docetaxel, and the efficacy and safety of enzalutamide in combination with docetaxel is not established. ENZAMET was neither designed nor powered to analyse the results of OS in individual subgroups. Therefore, an improvement in OS cannot be established in any subgroup, including patients with mHSPC taking enzalutamide + LHRH therapy alone or with or without concomitant docetaxel.

AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; APA, apalutamide; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; NSAA, non-steroidal anti-androgen; OS, overall survival; PBO, placebo.

1. Armstrong AJ, et al. *J Clin Oncol* 2022;40:1616–1622; 2. Sweeney CS, et al. *Lancet Oncol* 2023;24:323–334 (supplementary); 3. Merseburger AS, et al. *Eur J Cancer* 2023;193:113290; 4. Hoyle AP, et al. *Eur Urol* 2019;76:719–728; 5. Fizazi K, et al. *Lancet Oncol* 2019;20:686–700.

MAT-NL-XTD-2025-00031 | July 2025

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New learnings from ASCO 2025

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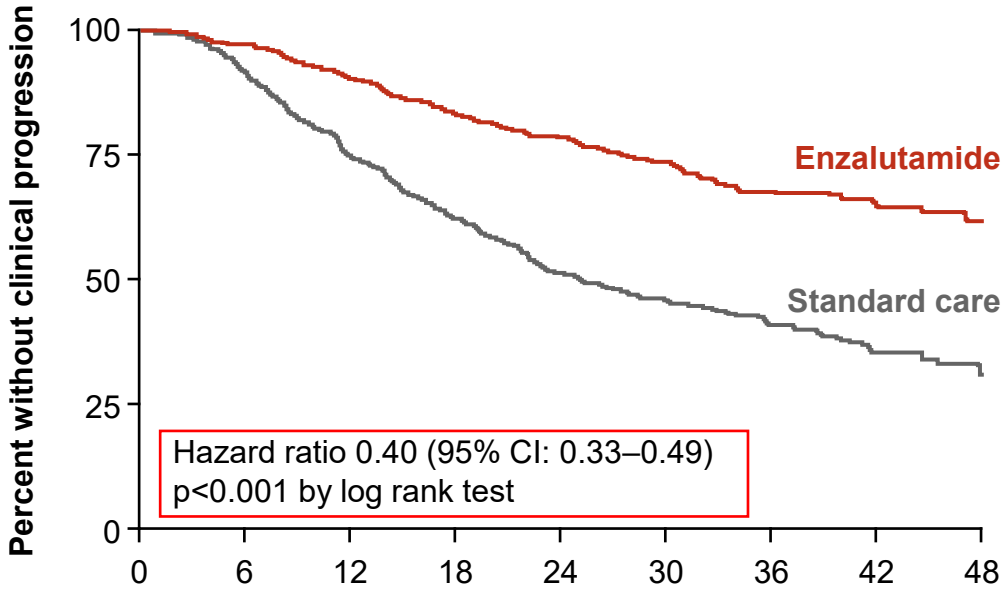
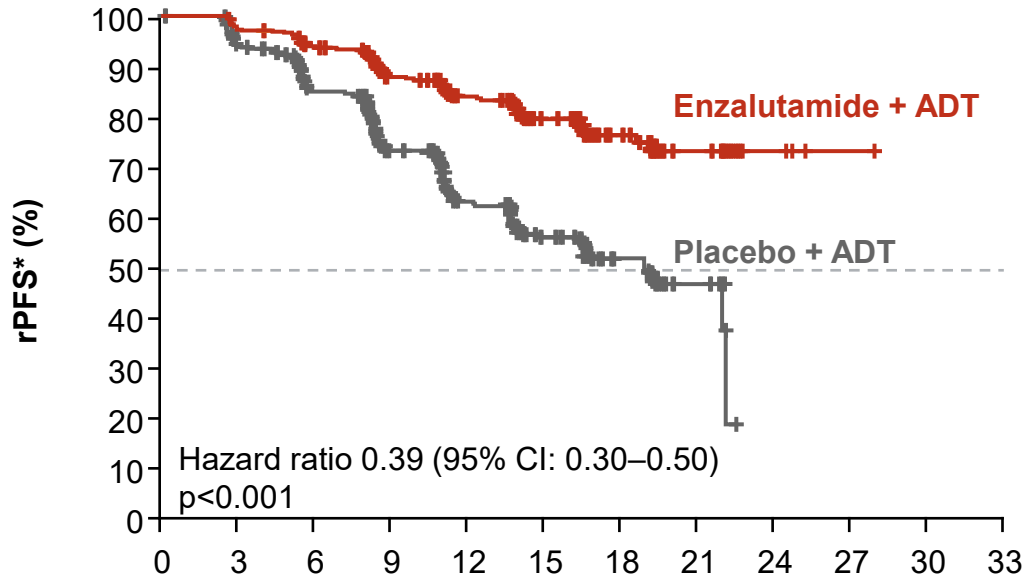
ENZAMET:* cPFS[1]



Number at risk									
Enzalutamide	563	547	507	468	424	284	156	84	36
Standard care	562	512	418	346	272	182	96	50	17

ARCHES: rPFS[2]



Number at risk												
Enzalutamide + ADT	574	5416	493	370	256	144	62	23	4	1	0	0
Placebo + ADT	576	511	445	314	191	106	39	10	0	0	0	0

Figures adapted from David ID, et al. 2019 and Armstrong AJ, et al. 2019.

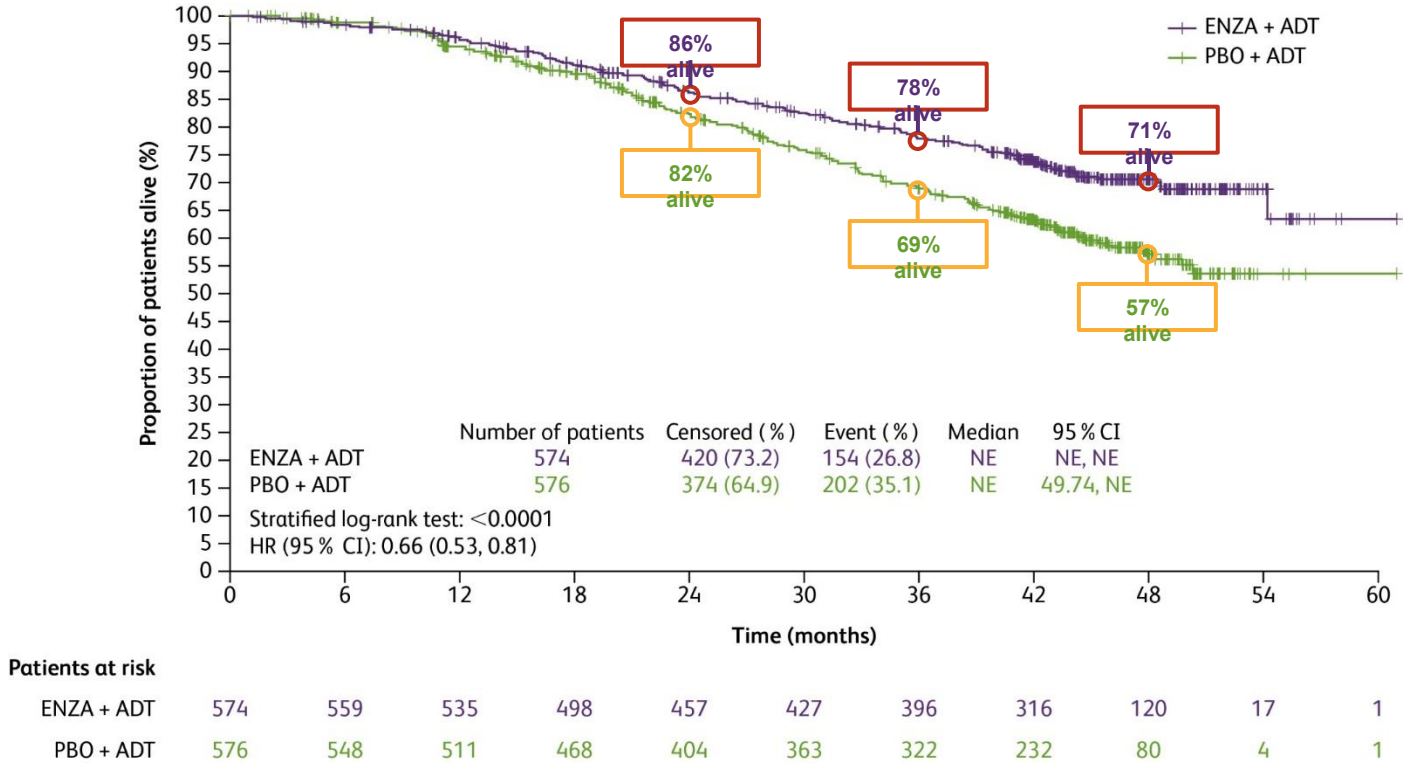
*Concomitant use of enzalutamide and docetaxel is not authorised in Europe. The overall patient population in ENZAMET included those who received or did not receive concomitant docetaxel, and the efficacy and safety of enzalutamide in combination with docetaxel is not established. ENZAMET was neither designed nor powered to analyse the results of OS in individual subgroups. Therefore, an improvement in OS cannot be established in any subgroup, including patients with mHSPC taking enzalutamide + LHRH therapy alone or with or without concomitant docetaxel.

ADT, androgen deprivation therapy; CI, confidence interval; cPFS, clinical progression-free survival; HR, hazard ratio; NR, not reached; rPFS, radiographic progression-free survival.

1. Davis ID, et al. *N Engl J Med* 2019;381:121–131; 2. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974–2986.

MAT-NL-XTD-2025-00031 | July 2025

ARCHES: Overall survival (ITT)



- **As of May 28, 2021: 356 deaths (enzalutamide plus ADT, 154; placebo plus ADT, 202) were observed**
- **Median follow-up time: 44.6 months**
- **Median treatment duration:**
  - **Enzalutamide plus ADT: 40.2 months**
  - **Placebo plus ADT: 13.8 months**
  - **Placebo plus ADT crossover: 23.9 months**

Enzalutamide plus ADT significantly improved overall survival by 34% vs. placebo plus ADT

Figure adapted from Armstrong AJ, et al. 2021.
ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; PBO, placebo.
Armstrong AJ, t al. Presented at ESMO 2021, 16–21 September 2021, Virtual Meeting;abstract LBA25.

2025 ASCO® ANNUAL MEETING

ARCHES 5-year follow-up overall survival (OS) analysis of enzalutamide (ENZA) plus androgen-deprivation therapy (ADT) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC)

Andrew J. Armstrong, MD, ScM, FACP[1], Daniel P. Petrylak, MD[2], Neal D. Shore, MD, FACS[3], Russell Z. Szmulewitz, MD[4], Jeffrey Holzbeierlein, MD[5], Arnauld Villers, MD, PhD[6], Antonio Alcaraz, MD, PhD[7], Boris Alekseev, MD[8], Taro Iguchi, MD, PhD[9], Francisco Gomez-Veiga, MD, PhD[10], Ruslan Croitoru, MD[11], Ruishan Wu, MS[11], Matko Kalac, MD, PhD[12], Yiyun Tang, PhD[12], Arnulf Stenzl, MD[13], Arun A. Azad, MBBS, PhD, FRACP[14]

[1]Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC, USA; [2]Yale School of Medicine, New Haven, CT, USA; [3]Atlantic Urology Clinics, Myrtle Beach, SC, USA; [4]Department of Medicine, University of Chicago, Chicago, IL, USA; [5]University of Kansas Medical Center, Kansas City, KS, USA; [6]Department of Urology, University of Lille, Lille, France; [7]Department of Urology, Hospital Clínic de Barcelona, Barcelona, Spain; [8]P. Hertsen Moscow Oncology Research Institute, Moscow, Russia; [9]Kanazawa Medical University, Ishikawa, Japan; [10]Complexo Hospitalario Universitario de A Coruña, Coruña, Spain; [11]Astellas Pharma Inc., Northbrook, IL, USA; [12]Pfizer Inc., South San Francisco, CA, USA; [13]Department of Urology, University of Tübingen, Tübingen, Germany; [14]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.
MAT-NL-XTD-2025-00031 | July 2025

Background

- The primary analysis of ARCHES (NCT02677896), conducted in October 2018, showed that ENZA + ADT significantly reduced the risk of rPFS or death in patients with mHSPC by 61% (median not reached vs 19.0 months; HR 0.39; 95% CI: 0.30–0.50; *P*<0.001) after a median follow-up of 14.4 months
- After a median follow-up of 44.6 months (May 2021), ENZA + ADT significantly reduced the risk of death by 34% compared with PBO + ADT (medians not reached in either group; HR 0.66; 95% CI: 0.53–0.81; *P*<0.0001)

The objective of this *post hoc* analysis was to describe the 5-year survival outcomes and safety of ENZA + ADT vs PBO + ADT for all randomised patients (data cutoff: July 31, 2024)

ADT, androgen-deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; PBO, placebo; rPFS, radiographic progression-free survival; vs, versus.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.

Methods: Study design

An international, phase 3, randomized, double-blind, PBO-controlled trial

mHSPC patient population:

- N = 1,150
- mHSPC confirmed by bone, CT, or MRI scan; histologically confirmed adenocarcinoma
- ECOG PS 0–1
- Current ADT duration ≤3 months in the metastatic setting, unless prior DOC was received, then ≤6 months

Stratification factors:

- Disease volume (low vs high)
- Prior DOC use for mHSPC (none, 1–5 cycles, or 6 cycles)

Randomization 1:1

ENZA group
ENZA 160 mg QD + ADT (n = 574)

PBO group
PBO + ADT (n = 576)

After primary analysis, PBO + ADT crossed over to ENZA + ADT in an open-label extension (n = 182)

Treatment continued until clinical progression, prohibitive toxicity, or initiation of alternative investigational therapy for PC

Primary endpoint[1]:

- rPFS

Key secondary endpoints[1]:

- OS
- PSA PFS
- Time to initiation of new antineoplastic therapy
- Undetectable PSA rate
- Objective response rate
- Time to deterioration in urinary symptoms

5-year follow-up analysis:

- Effect of ENZA compared with PBO was based on stratified log-rank test. HR was estimated from stratified Cox regression model. Kaplan–Meier methods were used to summarize OS endpoint by treatment group
- Cox regression model stratified by prior DOC use and disease volume with 95% CI was estimated using the Brookmeyer–Crowley method
- RPSFT model was used to estimate the adjusted HR to assess the impact of treatment crossover

Primary rPFS analysis: October 2018 (84 deaths/progressions). Median follow-up: 14.4 months[1]
Final prespecified OS analysis: May 2021 (356 deaths). Median follow-up: 44.6 months[2]
5-year follow-up analysis: July 31, 2024 (414 deaths). Median follow-up: 61.4 months

Figure adapted from Armstrong AJ, et al. 2025.
ADT, androgen-deprivation therapy; CI, confidence interval; CT, computer tomography; DOC, docetaxel; ENZA, enzalutamide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; N, total population; n, sample size; OS, overall survival; PBO, placebo; PC, prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen; QD, once daily; rPFS, radiographic progression-free survival; RPSFT, rank-preserving structural failure time; vs, versus
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.

Results: baseline characteristics (ITT)

Data cutoff: July 31, 2024

Characteristic, n (%) unless stated otherwise	ENZA + ADT (n = 574)	PBO + ADT (n = 576)	PBO crossover (n = 184)*
Age, years, median (range)	70.0 (46–92)	70.0 (42–92)	69.0 (51–89)
Age <65 years	148 (25.8)	152 (26.4)	39 (21.2)
65–74 years	256 (44.6)	255 (44.3)	96 (52.2)
≥75 years	170 (29.6)	169 (29.3)	49 (26.6)
Race†			
White	466 (81.2)	460 (79.9)	140 (76.1)
Asian	75 (13.1)	80 (13.9)	38 (20.7)
Black	8 (1.4)	8 (1.4)	4 (2.2)
Region			
Europe	341 (59.4)	344 (59.7)	102 (55.4)
Asia Pacific	104 (18.1)	113 (19.6)	49 (26.6)
North America	86 (15.0)	77 (13.4)	18 (9.8)
South America	32 (5.6)	30 (5.2)	11 (6.0)

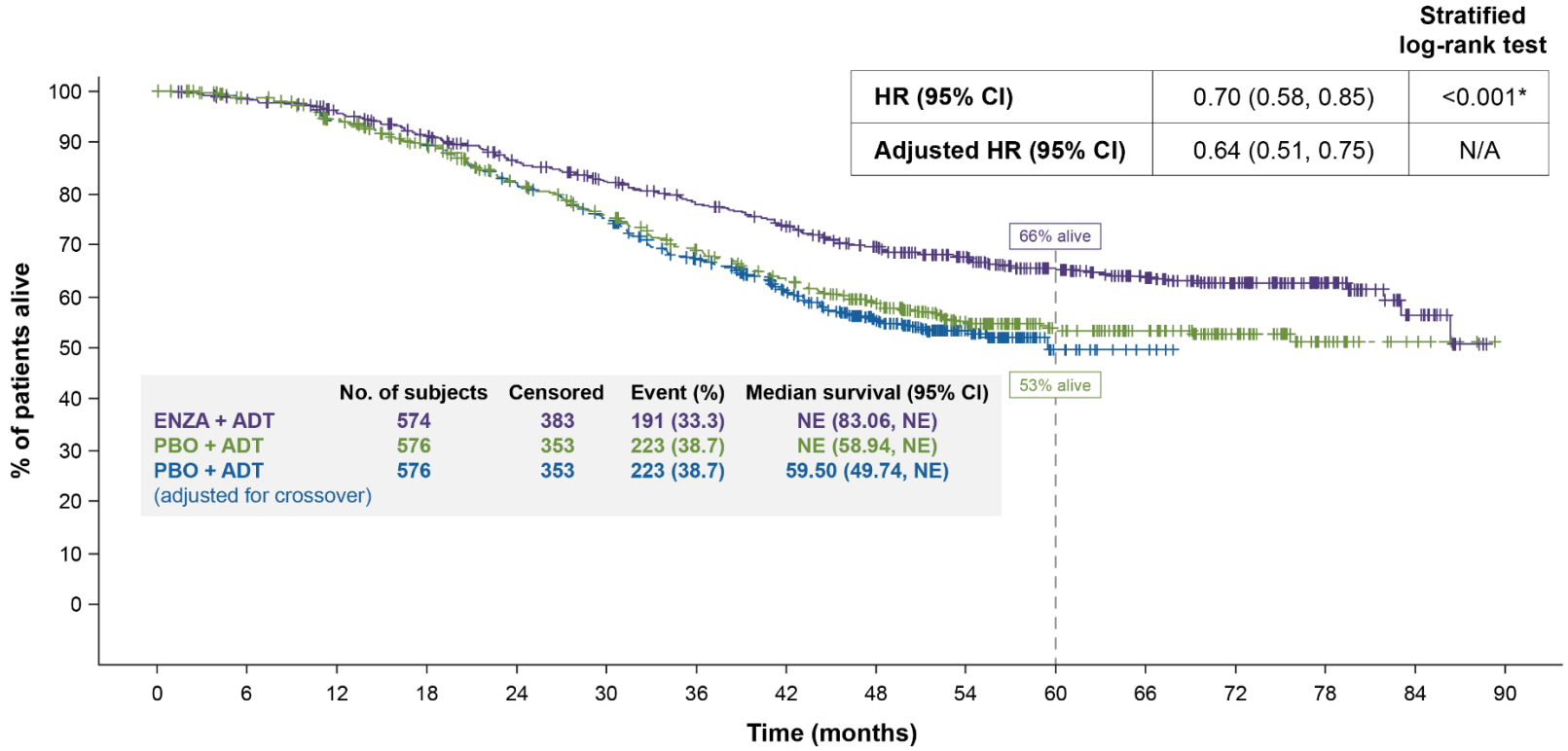
Characteristic, n (%) unless stated otherwise	ENZA + ADT (n = 574)	PBO + ADT (n = 576)	PBO crossover (n = 184)*
ECOG PS 0	448 (78.0)	443 (76.9)	155 (84.2)
Gleason score ≥8 at diagnosis	386 (67.2)	373 (64.8)	108 (58.7)
Median PSA (range), ng/mL‡	5.3 (0–4,823.5)	5.1 (0–19,000.0)	3.6 (0–3,192.0)
Sites of metastases			
Bone only	268 (46.7)	245 (42.5)	80 (43.5)
Soft tissue only	51 (8.9)	45 (7.8)	18 (9.8)
Bone and soft tissue	217 (37.8)	241 (41.8)	59 (32.1)
Visceral ± bone or lymph node	88 (15.3)	101 (17.5)	34 (18.5)
Synchronous (de novo)	438 (76.3)	439 (76.2)	138 (75.0)
High-volume disease	354 (61.7)	373 (64.8)	92 (50.0)
Prior docetaxel use	103 (17.9)	102 (17.7)	29 (15.7)

Tables adapted from Armstrong AJ, et al. 2025.
*182 patients received ENZA + ADT in the OLE.
†By country regulations, data regarding patient race are not collected in France.
‡Patients who had baseline PSA results at data cutoff (ENZA + ADT, n = 573; PBO + ADT, n = 575; PBO crossover, n = 184).
ADT, androgen-deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENZA, enzalutamide; IQR, interquartile range; ITT, intent-to-treat; n, sample size; OLE, open-label extension; PBO, placebo; PSA, prostate-specific antigen.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.

Results: 5-year overall survival (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)

Figure adapted from Armstrong AJ, et al. 2025.
*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; vs, versus.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.
MAT-NL-XTD-2025-00031 | July 2025

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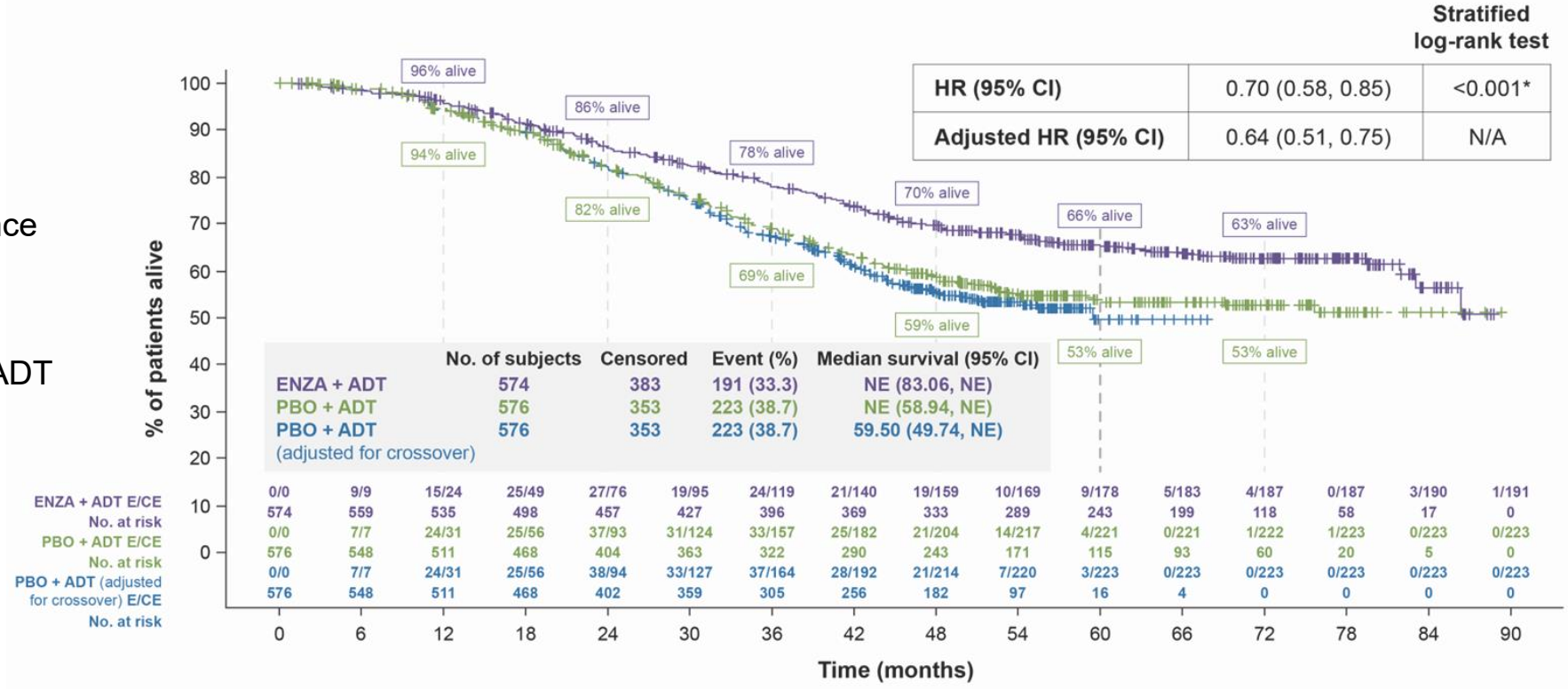

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ADT, androgen-deprivation therapy; CI, confidence interval; E/CE, events/cumulative events; ENZA, enzalutamide; HR, hazard ratio; ITT, intent-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; n, sample size; N/A, not applicable; NE, not estimable; No., number; OS, overall survival; PBO, placebo; RPSFT, rank-preserving structural failure time; vs, versus.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.
MAT-NL-XTD-2025-00031 | July 2025

Results: ENZA extended estimated median OS in patients with high-volume disease vs PBO by 3 years

Data cutoff: July 31, 2024

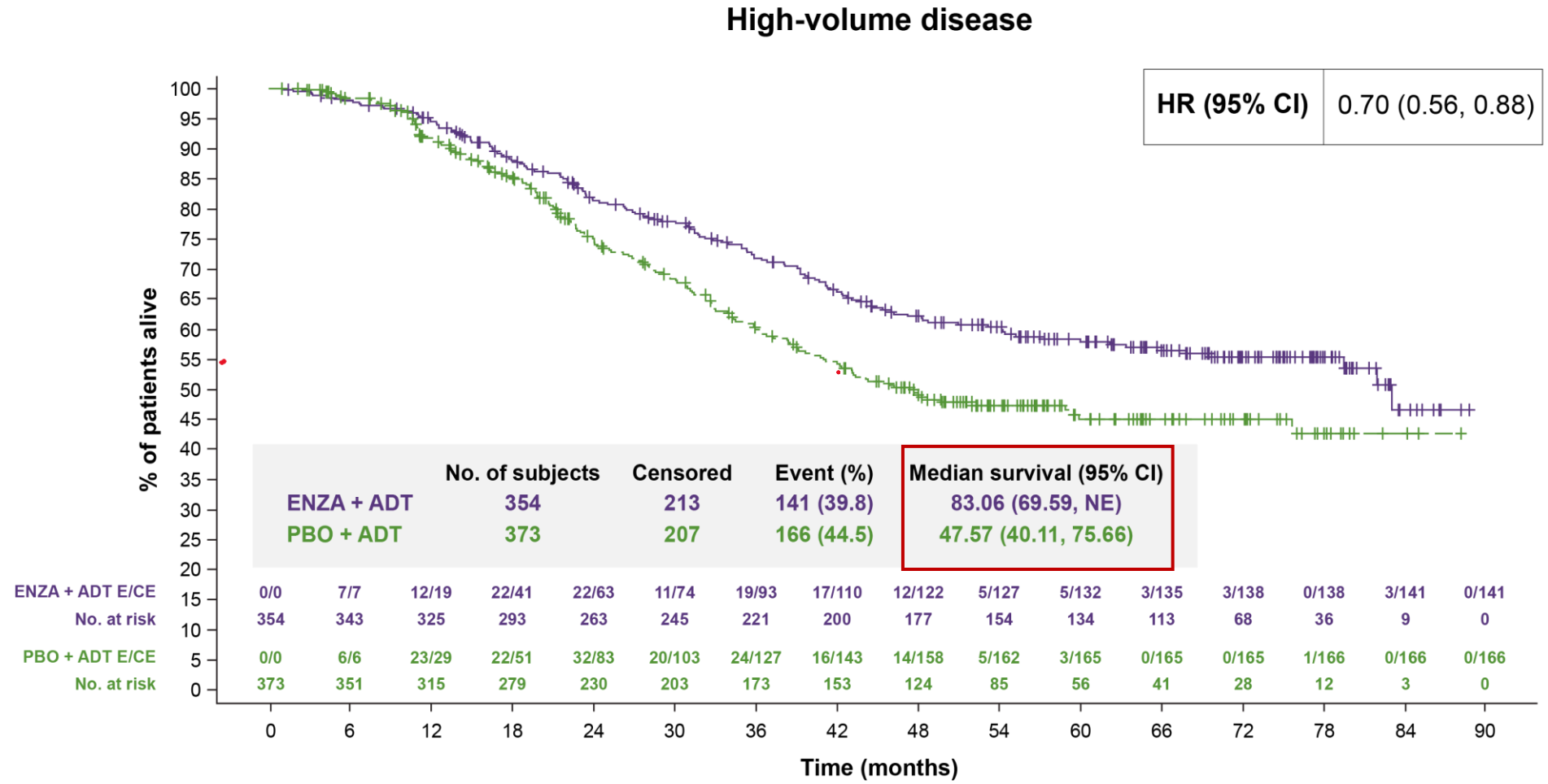


Figure adapted from Armstrong AJ, et al. 2025.

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; vs, versus.

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

Results: similar relative improvement in OS in patients with low-volume disease

Data cutoff: July 31, 2024

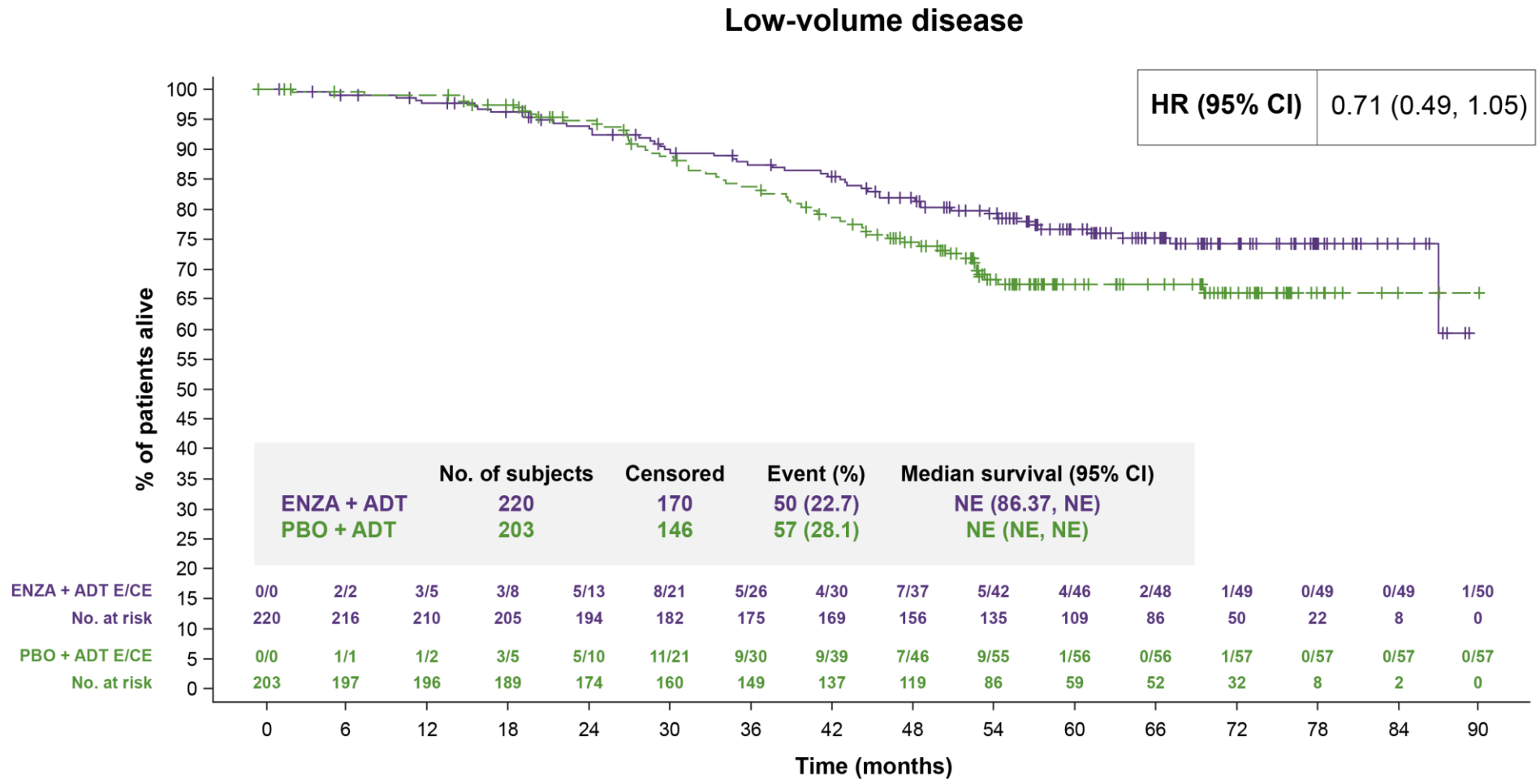


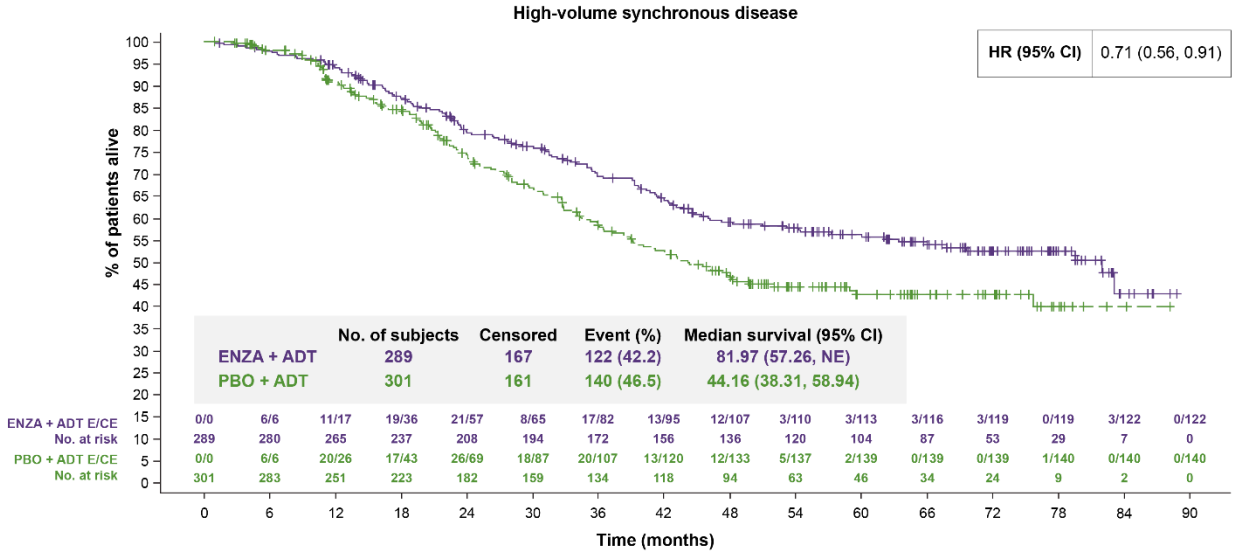
Figure adapted from Armstrong AJ, et al. 2025.

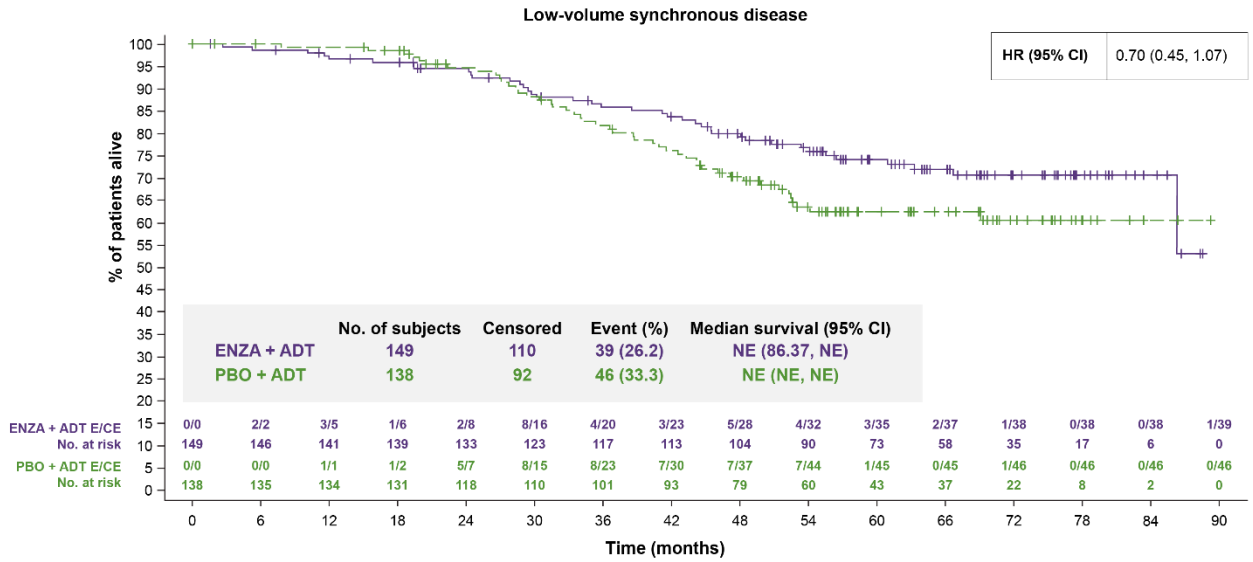
ADT, androgen-deprivation therapy; CI, confidence interval; E/CE, events/cumulative events; ENZA, enzalutamide; HR, hazard ratio; NE, not estimable; No., number; OS, overall survival; PBO, placebo; vs, versus.

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

Results: OS in high- and low-volume synchronous disease

Data cutoff: July 31, 2024





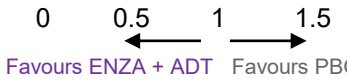
- Treatment with ENZA + ADT resulted in meaningfully prolonged median survival (82 months) vs PBO + ADT (44 months) in patients with **high-volume synchronous disease**
- In patients with **low-volume synchronous disease**, OS was longer with ENZA + ADT than with PBO + ADT but CI included 1.0

Figures adapted from Armstrong AJ, et al. 2025.
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; vs, versus.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.
MAT-NL-XTD-2025-00031 | July 2025

Results: overall survival by prespecified subgroups

Data cutoff: July 31, 2024

Subgroup	ENZA + ADT / PBO + ADT No. (events)	Median (mo)	HR (95% CI)
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 No. (events)	Median (mo)	HR (95% CI)
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 (de novo)	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

Tables adapted from Armstrong AJ, et al. 2025.
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.
MAT-NL-XTD-2025-00031 | July 2025

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
- None of the 48 TEAEs leading to death in the ENZA + ADT group were considered related to the study treatment by the investigator,
- whereas one TEAE leading to death in both the PBO + ADT and PBO crossover groups (deterioration in general physical health) was considered related to the study treatment by the investigator
- No new safety signals were identified

Table adapted from Armstrong AJ, et al. 2025.
*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; vs, versus.
Armstrong AJ, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, US:abstract 5005.

Results: TEAEs of special interest* (safety population)

Data cutoff: July 31, 2024

Patient incidence, n (rate per 100 pt-years)	ENZA + ADT (n = 572)	PBO + ADT (n = 574)	PBO crossover (n = 182)
Convulsions	3 (0.1)	3 (0.4)	1 (0.2)
Hypertension	106 (5.1)	41 (5.6)	20 (3.5)
Decreased neutrophil count	10 (0.5)	6 (0.8)	3 (0.5)
Cognitive/memory impairment	50 (2.4)	15 (2.0)	17 (2.9)
Ischemic heart disease	45 (2.2)	14 (1.9)	11 (1.9)
Other selected cardiovascular events	50 (2.4)	11 (1.5)	12 (2.1)
Posterior reversible encephalopathy syndrome	0	0	0
Fatigue	232 (11.2)	127 (17.4)	52 (9.0)
Renal disorder	37 (1.8)	10 (1.4)	2 (0.3)

Patient incidence, n (rate per 100 pt-years)	ENZA + ADT (n = 572)	PBO + ADT (n = 574)	PBO crossover (n = 182)
Second primary malignancies	35 (1.7)	16 (2.2)	9 (1.6)
Falls	108 (5.2)	20 (2.7)	30 (5.2)
Fractures	147 (7.1)	36 (4.9)	45 (7.8)
Loss of consciousness	18 (0.9)	2 (0.3)	4 (0.7)
Thrombocytopenia	7 (0.3)	3 (0.4)	0
Musculoskeletal events	461 (22.3)	255 (34.8)	81 (14.0)
Severe cutaneous adverse reactions	1 (0.0)	1 (0.1)	0
Angioedema	13 (0.6)	1 (0.1)	1 (0.2)
Rash	27 (1.3)	12 (1.6)	9 (1.6)
Hepatic disorder	49 (2.4)	55 (7.5)	17 (2.9)

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

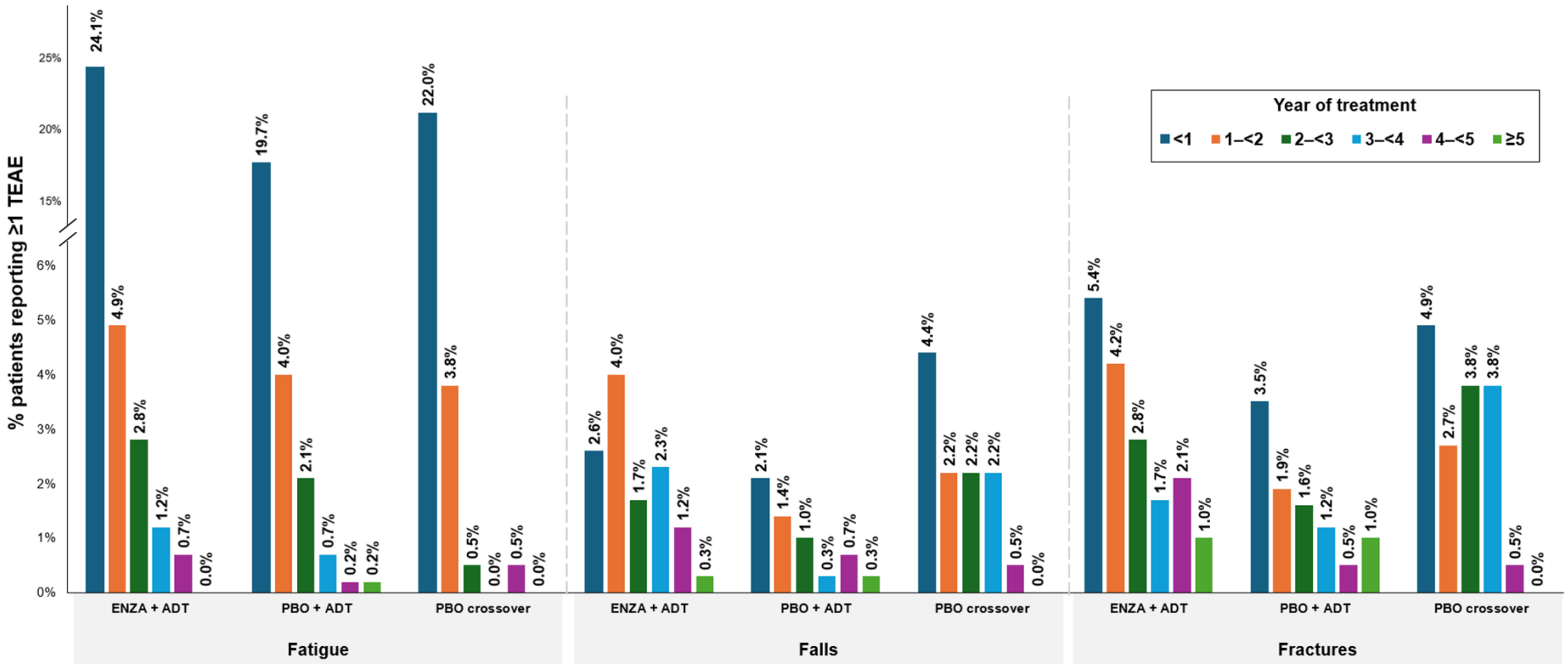
Tables adapted from Armstrong AJ, et al. 2025.
*TEAEs of special interest were based on prespecified combinations of preferred terms (MedDRA version 23.0) and were graded on the basis of NCI-CTCAE (version 4.03) by the investigator.
ADT, androgen-deprivation therapy; ENZA, enzalutamide; MedDRA, Medical 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.

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



Figures adapted from Armstrong AJ, et al. 2025.

ADT, androgen-deprivation therapy; ENZA, enzalutamide; PBO, placebo; TEAEs, treatment-emergent adverse events; vs, versus.

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

Key takeaway points/conclusions

1. This 5-year median follow-up from the ARCHES study showed that ENZA + ADT was associated with a **66% probability of survival at 5 years** and **a significant reduction in the risk of death by 30%** in patients with mHSPC compared with PBO + ADT, despite substantial crossover
   - Patients on ENZA + ADT with **high-volume disease** had a significantly longer median OS by 3 years vs those on PBO + ADT
   - Absolute 5-year survival rate improved by 13% in high-volume disease and 9% in low-volume disease
   - These data represent one of the longest OS follow-up analyses conducted to date in the mHSPC setting, and provide compelling long-term OS data in this context, particularly for patients with high-volume disease
2. ENZA + ADT provided substantial and durable survival benefits across a wide range of patient characteristics, with no evidence of heterogeneity by disease volume, prior docetaxel use, or synchronous vs metachronous metastatic disease
3. This improvement in long-term survival was accompanied by an increase in ENZA-associated TEAEs, which tended to diminish substantially over time

ADT, androgen-deprivation therapy; ENZA, enzalutamide; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PBO, placebo; TEAEs, treatment-emergent adverse events; vs, versus.

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

Genitourinary Masterclass

astellas

Impactful data in mHSPC over the last year: HRR mutations and the AMPLITUDE study

Professor Ugo de Giorgi

IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy

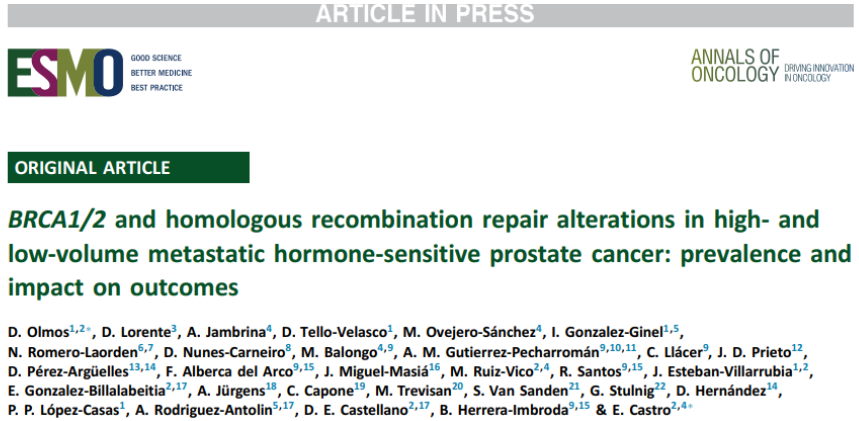
MAT-NL-XTD-2025-00031 | July 2025

Ugo De Giorgi - Disclosures

- Consultant/advisory board member for Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Janssen, Merck, MSD, Novartis, PharmaMar, Pfizer, and Roche
- Travel support from AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen and Pfizer
- Research funding from AstraZeneca, Roche and Sanofi (paid to institution)
- The presenter has received an honorarium for this presentation

Impact of somatic/germline homologous recombination repair (HRR) alterations on metastatic hormone-sensitive prostate cancer (mHSPC)

- Alterations in *BRCA1/2* (BRCA) and other HRR genes have previously been shown to exert a negative impact on outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC)[1]
- Poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPis), the only treatment demonstrated to improve the prognosis of these patients with mCRPC,[2–5] are also being developed for the treatment of patients with mHSPC
- Somatic and germline alterations in HRR genes (including BRCA) in patients with mHSPC, and their impact on disease-onset characteristics and clinical outcomes, specifically exploring the associations between these mutations and tumour burden, have been recently presented at ASCO 2025 and published on Ann Oncol[6] Adv online June 2, 2025: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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

***BRCA1/2* and homologous recombination repair alterations in high- and low-volume metastatic hormone-sensitive prostate cancer: prevalence and impact on outcomes**

D. Olmos[1,2*], D. Lorente[3], A. Jambrina[4], D. Tello-Velasco[1], M. Ovejero-Sánchez[4], I. Gonzalez-Ginel[1,5], N. Romero-Laorden[6,7], D. Nunes-Carneiro[8], M. Balongo[4,9], A. M. Gutierrez-Pecharromán[9,10,11], C. Llácer[9], J. D. Prieto[12], D. Pérez-Argüelles[13,14], F. Alberca del Arco[9,15], J. Miguel-Masiá[16], M. Ruiz-Vico[2,4], R. Santos[9,15], J. Esteban-Villarrubia[1,2], E. Gonzalez-Billalabeitia[2,17], A. Jürgens[18], C. Capone[19], M. Trevisan[20], S. Van Sanden[21], G. Stulnig[22], D. Hernández[14], P. P. López-Casas[1], A. Rodriguez-Antolin[5,17], D. E. Castellano[2,17], B. Herrera-Imbroda[9,15] & E. Castro[2,4*]

HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor .

1. Olmos D, et al. *Ann Oncol*. 2024;35:458–472; 2. De Bono JS, et al. *Lancet Oncol*. 2021;22(9):1250–1264; 3. Mateo J, et al. *Lancet Oncol*. 2020;21:162–174; 4. Chi KN, et al. *Ann Oncol*. 2023;34(9):772–782; 5. Clarke NW, et al. *Eur Urol* Oncol. 2025:8:394–406; 6. Olmos D, et al. *Ann Oncol* 2025;In press DOI: 10.1016/j.annonc.2025.05.534.

The prevalence of somatic and germline alterations in HRR genes (including BRCA) in patients with mHSPC

- Distribution of subgroups according to mutation type (A) and frequency of HRR alterations by germline versus somatic in the subgroups of patients with high- and low-volume (B)

- Of 556 patients, 159 (28.6%) had HRR gene alterations: 69 (12.4%) with BRCA and 90 (16.2%) with HRR non-BRCA mutations
- mHSPC was classified by conventional imaging as high volume in 306 (55.0%) and low volume in 250 (45.0%) patients per CHAARTED criteria
- mHSPC was synchronous in 451 patients (81.1%) and metachronous in 105 patients (18.9%)

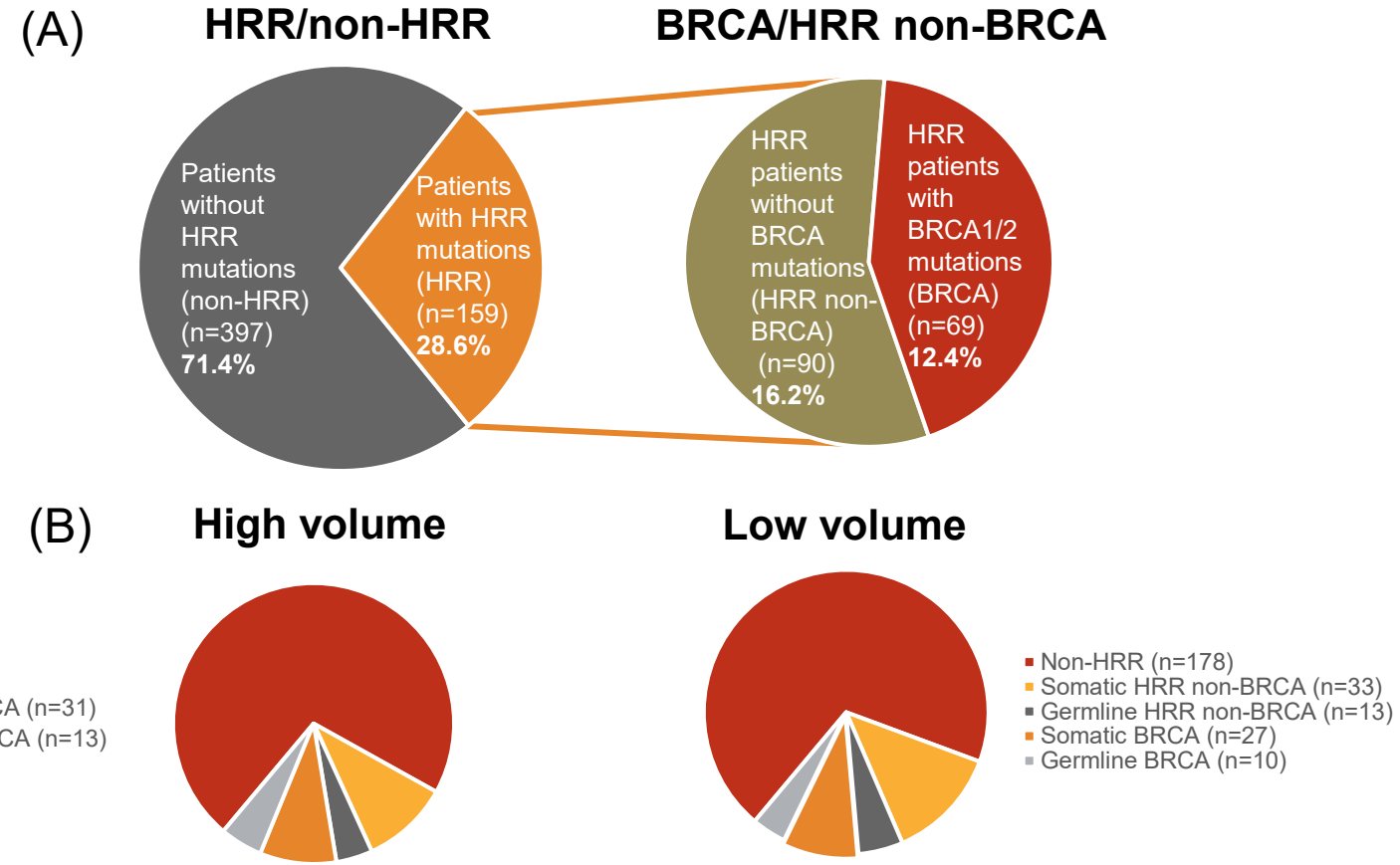
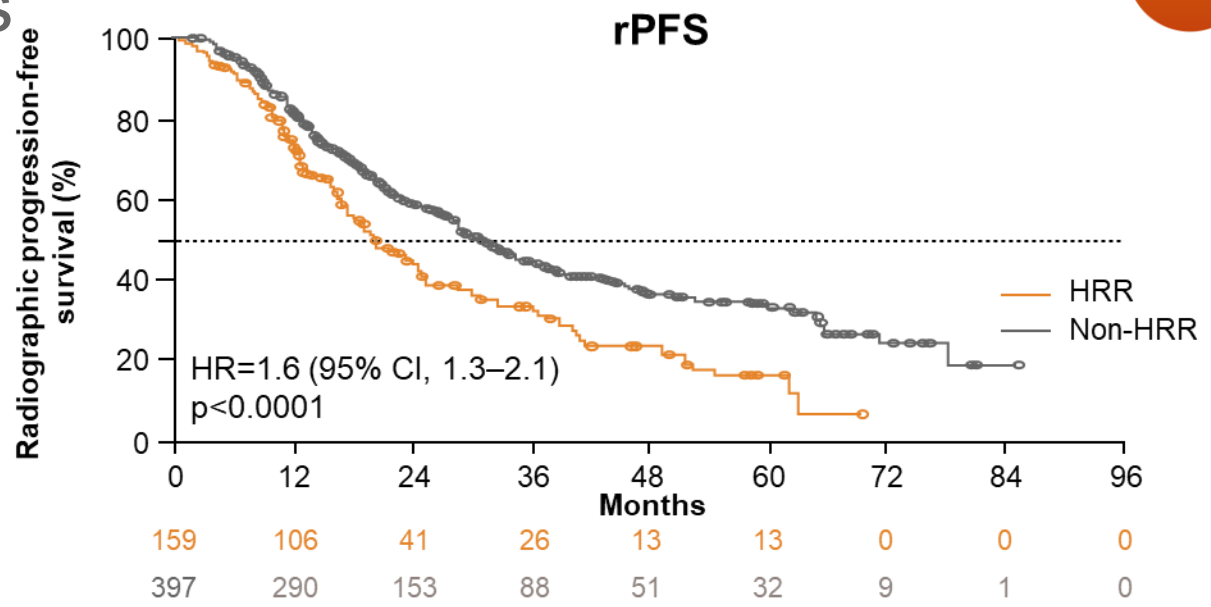
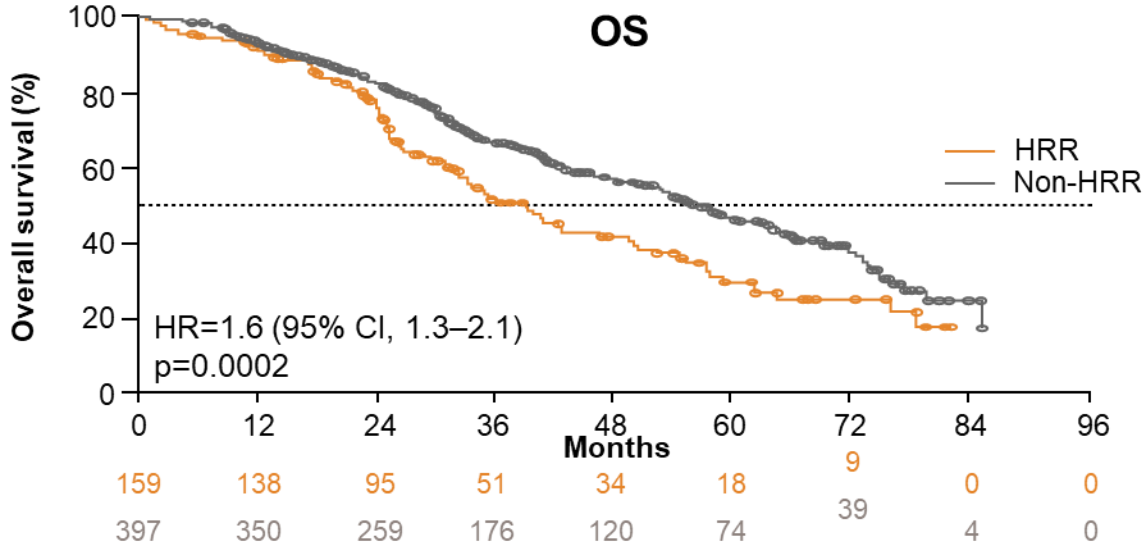


Figure adapted from Olmos D, et al. 2025.
HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer.
Olmos D, et al. Poster presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract 5094.

mHSPC with homologous recombination repair (HRR) gene alterations has a poor prognosis

- The most common treatment regimen was ADT + ARPI (44.8%), while 30.4% received docetaxel + ADT, and 11.3% were treated with triplet therapy. Only 13.5% received ADT alone
- Baseline patient characteristics and treatments administered were similar across all subgroups after adjustment





Figures adapted from Olmos D, et al. 2025.
ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer.
Olmos D, et al. Poster presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract 5094.

Impact of somatic/germline homologous recombination repair (HRR) alterations on mHSPC outcomes by disease volume

Comparison of outcomes between mutational subgroups by tumour burden

- The presence of **BRCA and HRR alterations was associated with poor prognosis in both low- and high-volume subgroups**
- This adverse impact was stronger in the low-volume population

Treatment outcomes by high-volume and low-volume disease: BRCA versus non-BRCA (A) and HRR versus non-HRR (B)

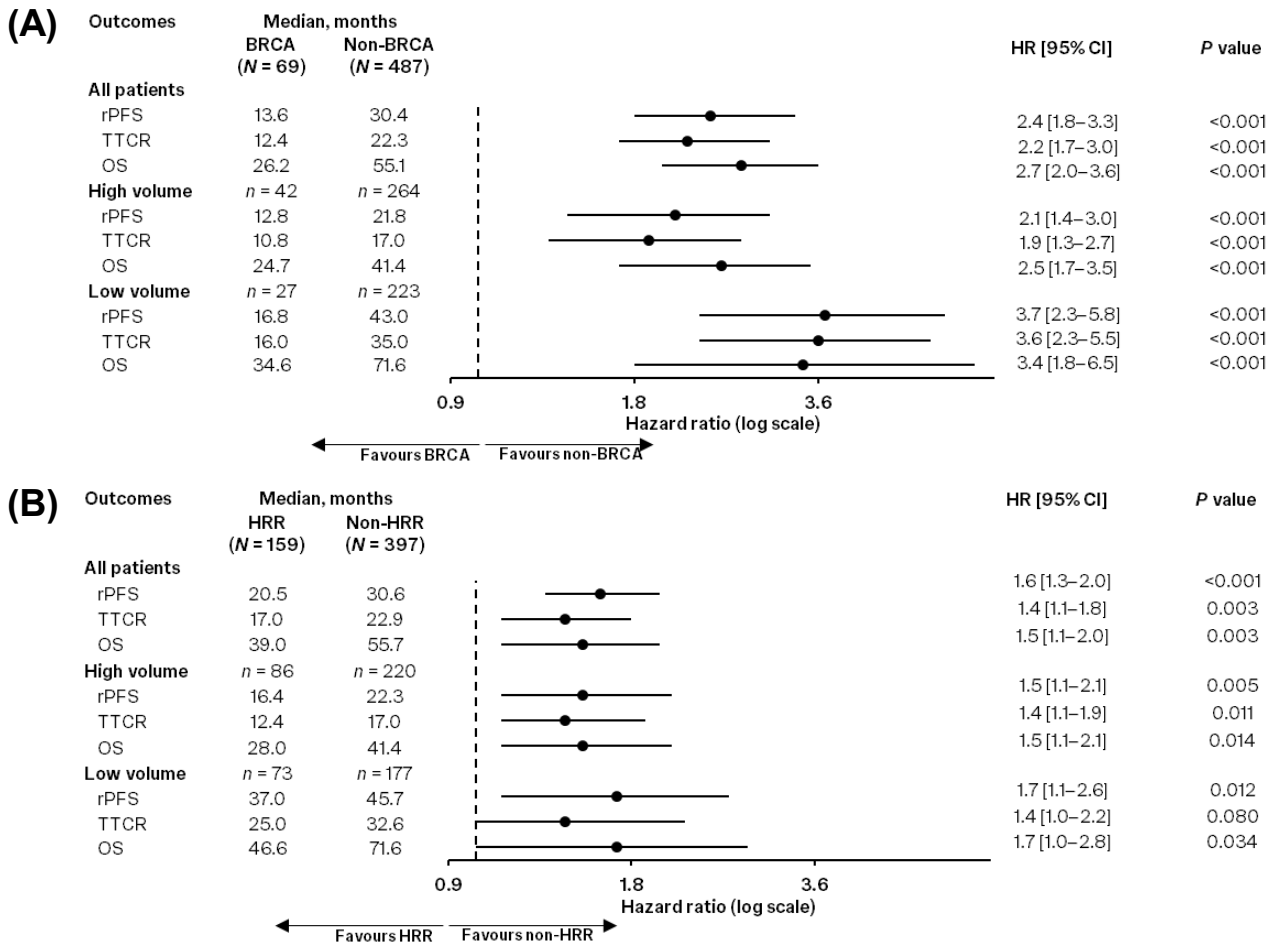


Figure adapted from Olmos D, et al. 2025.
HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; TTCR, time to castration-resistant prostate cancer.
Olmos D, et al. Poster presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract 5094.
MAT-NL-XTD-2025-00031 | July 2025

Phase 3 AMPLITUDE trial:
Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

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Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

MAT-NL-XTD-2025-00031 | July 2025

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes (Clinical data cutoff: 7 January 2025)

AMPLITUDE: Randomised, double-blind, placebo-controlled trial in HRRm mHSPC

First and final radiographic progression-free survival (rPFS) analysis and first interim analysis of time to symptomatic progression and overall survival (OS).
Median follow-up: 30.8 months

Key inclusion criteria:

- mHSPC*
- Alteration in ≥1 HRR eligible gene:† *BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54Lb*
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2

Key exclusion criteria:

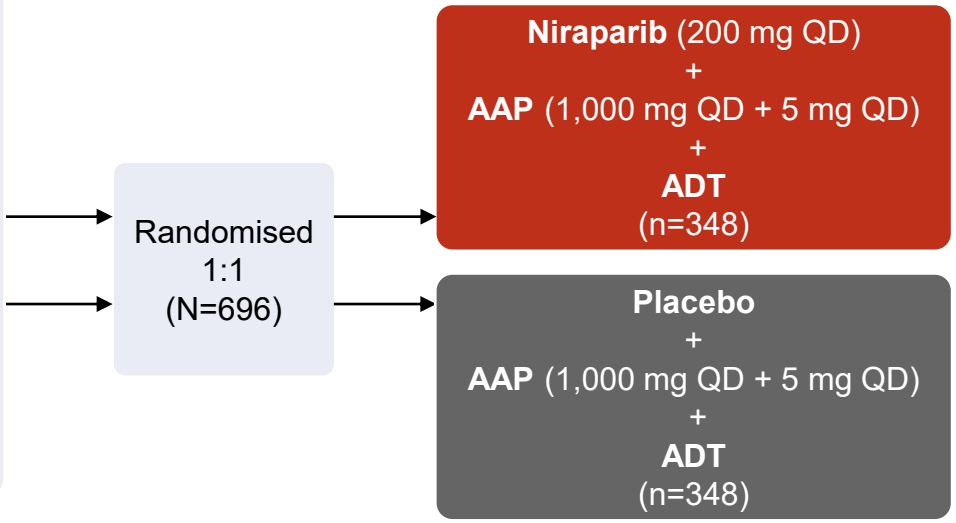
- Any prior
  - PARP inhibitor (PARPi)
  - ARPI other than AAP

Prior allowed treatments in mHSPC:

- ADT ≤6 months
- Docetaxel ≤6 cycles‡
- AAP ≤45 days
- Palliative radiotherapy

Stratification factors:

- *BRCA2* vs. *CDK12* vs. all other alterations
- Prior docetaxel (yes vs. no)
- Disease volume (high vs. low)



Primary endpoint

- rPFS by investigator review

Key secondary endpoints

- Time to symptomatic progression
- OS
- Safety

Clinical data cutoff: 7 January 2025.

Figure adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

*Patients with lymph node–only disease are not eligible. †HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. ‡Last dose ≤3 months prior to randomization.
AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BRCA, BReast CAncer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; PARPi, poly ADP-ribose polymerase inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; QD, once daily.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Baseline characteristics

		Niraparib + AAP (n=348)	Placebo + AAP (n=348)
Median age (range), years		68 (40–88)	67 (40–92)
Median prostate-specific antigen (PSA) at initial diagnosis (range), ng/mL		112 (0.1–17,475)*	102 (0.1–15,900)†
ECOG PS score, n (%)	0 ≥1	242 (70) 106 (30)	218 (63) 130 (37)
Gleason score at initial diagnosis, n (%)	≥8	276 (79)	262 (75)
Metastatic stage at diagnosis, n (%)	M1 (synchronous)	301 (86)	302 (87)
Disease volume, n (%)	High	269 (77)	271 (78)
Prior docetaxel use in mHSPC, n (%)		54 (16)	56 (16)
Site of metastases,‡ n (%)	Bone only Visceral Lymph nodes	146 (42) 57 (16) 173 (50)	154 (44)** 54 (16)** 161 (46)**
BRCA alteration, n (%)		191 (55)	196 (56)

- Characteristics were well balanced between arms

Table adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

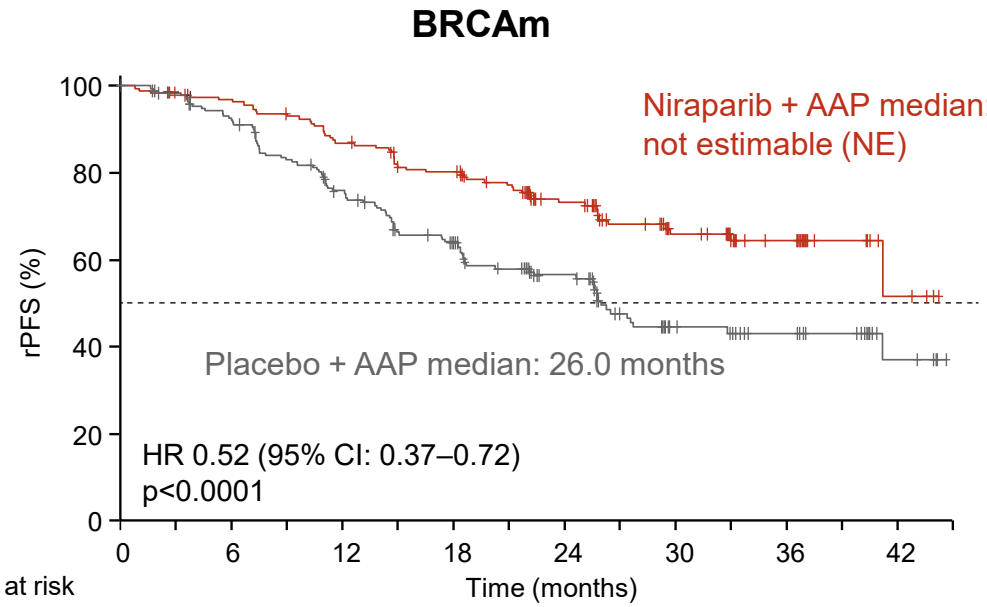
*n=258. † n=275. ‡ Non-mutually exclusive. **n=347.

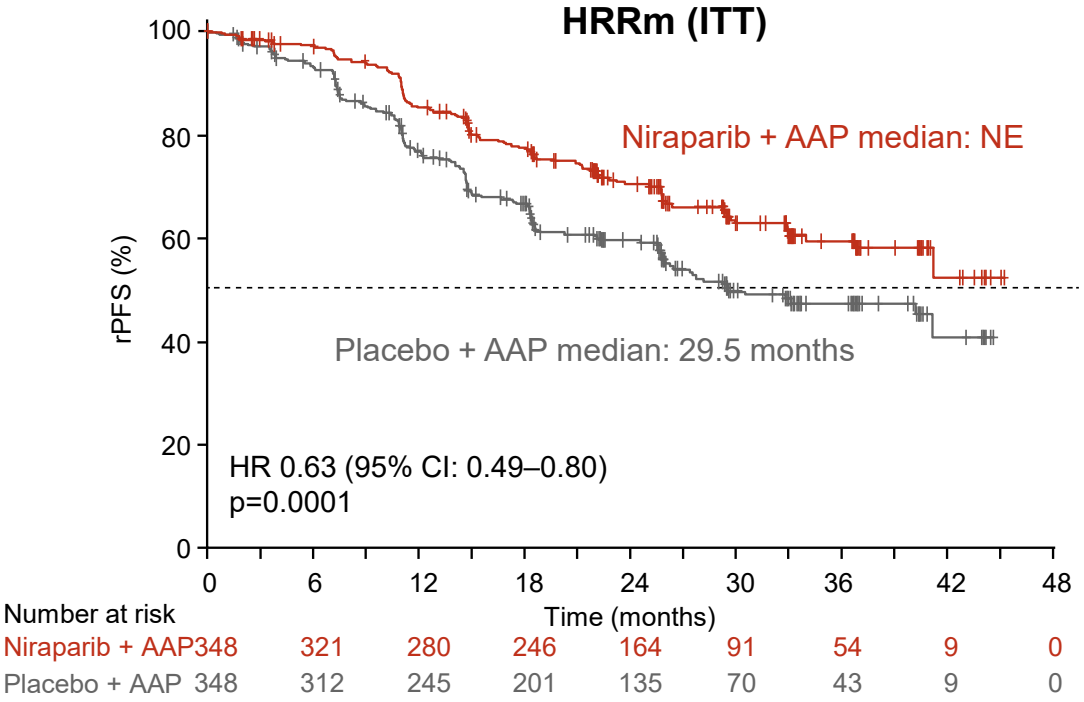
AAP, abiraterone acetate plus prednisone; BRCA, BReast CAncer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Primary endpoint: rPFS*





AMPLITUDE met the primary endpoint: Niraparib + AAP significantly reduced the risk of radiographic progression* or death by 48% in BRCAm group and by 37% in HRRm group

Figures adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

*rPFS by investigator review. The results for rPFS by BICR were similar: HR=0.51 (95% CI: 0.37–0.72) and 0.61 (95% CI: 0.47–0.79) for BRCAm and HRRm groups.

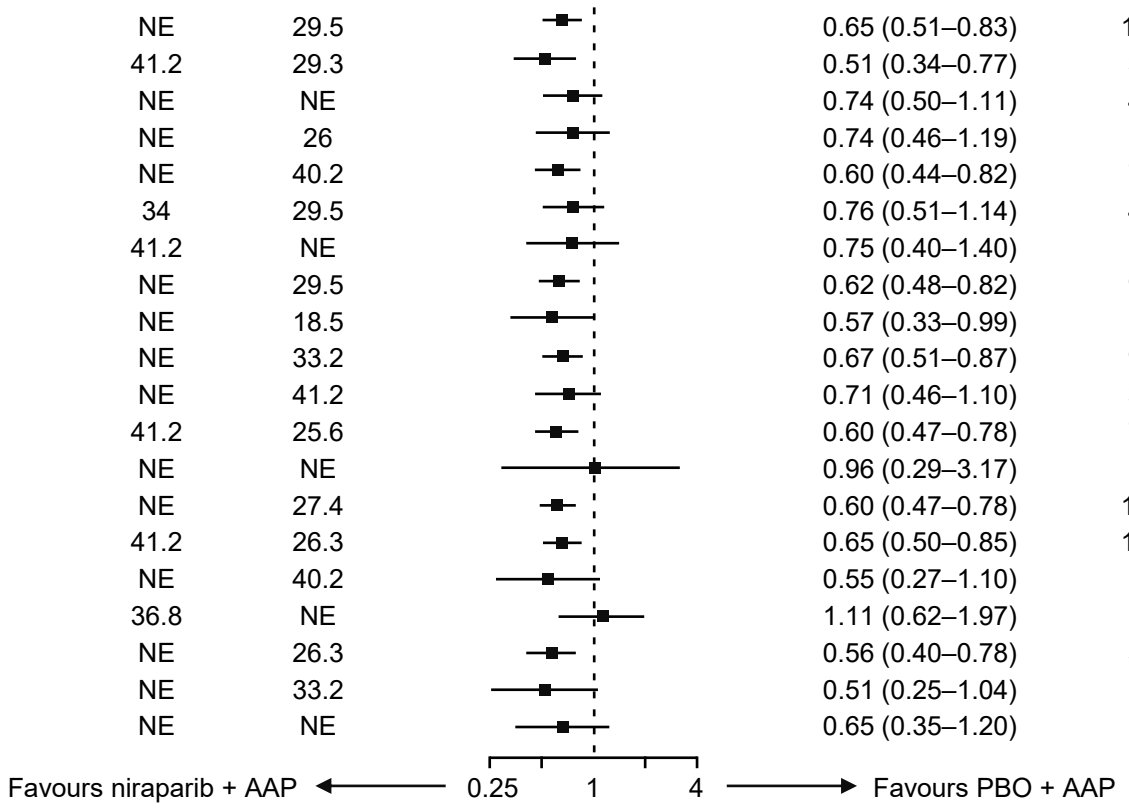
AAP, abiraterone acetate plus prednisone; BICR, blinded independent central review; BRCAm, BReast CAncer gene mutation; CI, confidence interval; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; ITT, intention-to-treat; NE, not estimable; rPFS, radiographic progression-free survival.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Prespecified subgroup analysis of rPFS

Variable	Subgroup	Median, months		HR (95% CI)	Events/N	
		Niraparib + AAP	PBO + AAP		Niraparib + AAP	PBO + AAP
All patients		NE	29.5	0.65 (0.51–0.83)	113/348	151/348
Age	<65 years	41.2	29.3	0.51 (0.34–0.77)	35/116	62/135
	65–74 years	NE	NE	0.74 (0.50–1.11)	45/148	52/139
	≥75 years	NE	26	0.74 (0.46–1.19)	33/84	37/74
ECOG at PS baseline	0	NE	40.2	0.60 (0.44–0.82)	72/242	93/218
	≥1	34	29.5	0.76 (0.51–1.14)	41/106	58/130
Prior docetaxel use	Yes	41.2	NE	0.75 (0.40–1.40)	18/54	23/56
	No	NE	29.5	0.62 (0.48–0.82)	95/294	128/292
Visceral metastases	Yes	NE	18.5	0.57 (0.33–0.99)	22/57	30/54
	No	NE	33.2	0.67 (0.51–0.87)	91/291	121/294
Bone-only metastases at baseline	Yes	NE	41.2	0.71 (0.46–1.10)	36/146	48/154
	No	41.2	25.6	0.60 (0.47–0.78)	77/202	103/194
Metastases state at diagnosis	M0	NE	NE	0.96 (0.29–3.17)	5/32	6/36
	M1	NE	27.4	0.60 (0.47–0.78)	100/301	142/302
Disease volume at baseline	High	41.2	26.3	0.65 (0.50–0.85)	100/269	130/271
	Low	NE	40.2	0.55 (0.27–1.10)	13/79	21/77
Regions	Asia	36.8	NE	1.11 (0.62–1.97)	26/72	21/63
	Europe	NE	26.3	0.56 (0.40–0.78)	56/168	86/177
	North America	NE	33.2	0.51 (0.25–1.04)	14/45	18/44
	Rest of World	NE	NE	0.65 (0.35–1.20)	17/63	26/64



Benefit from niraparib + AAP is generally consistent across prespecified subgroups

Figure adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination. Results in small subgroups should be interpreted with caution.

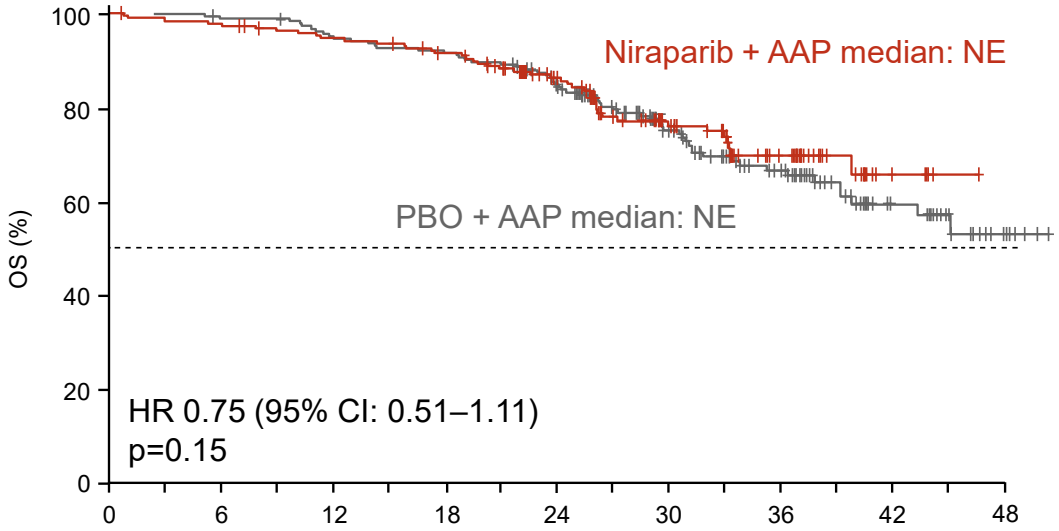
AAP, abiraterone acetate plus prednisone; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not estimable; PBO, placebo.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

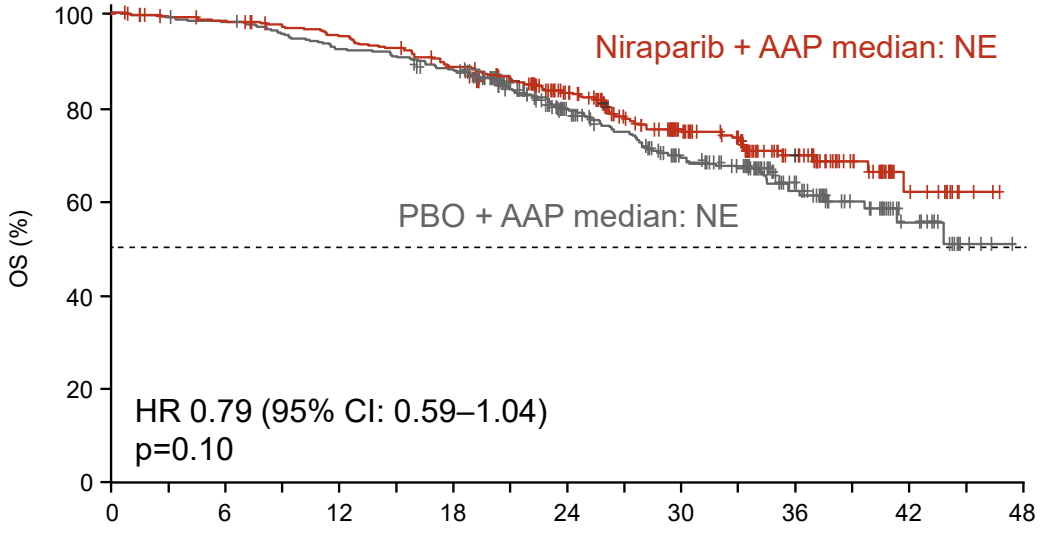
Secondary endpoint: Overall survival (first interim analysis)*

BRCAm



Number at risk									
Niraparib + AAP	191	186	177	168	126	75	38	6	0
PBO + AAP	196	193	180	174	124	72	39	12	0

HRRm (ITT)



Number at risk									
Niraparib + AAP	348	335	320	293	218	133	71	13	0
PBO + AAP	348	340	319	304	219	131	70	18	0

The first interim analysis (≈50% of total needed events) estimates show niraparib + AAP reduced risk of death by 25% in BRCAm group and by 21% in HRRm group

Figures adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

*The first interim analysis for OS was conducted when 193 patients had died (of a target of 389, an information fraction of 50%), 85 of 348 (24%) in the niraparib + AAP arm and 108 of 348 (31%) in the PBO + AAP arm.

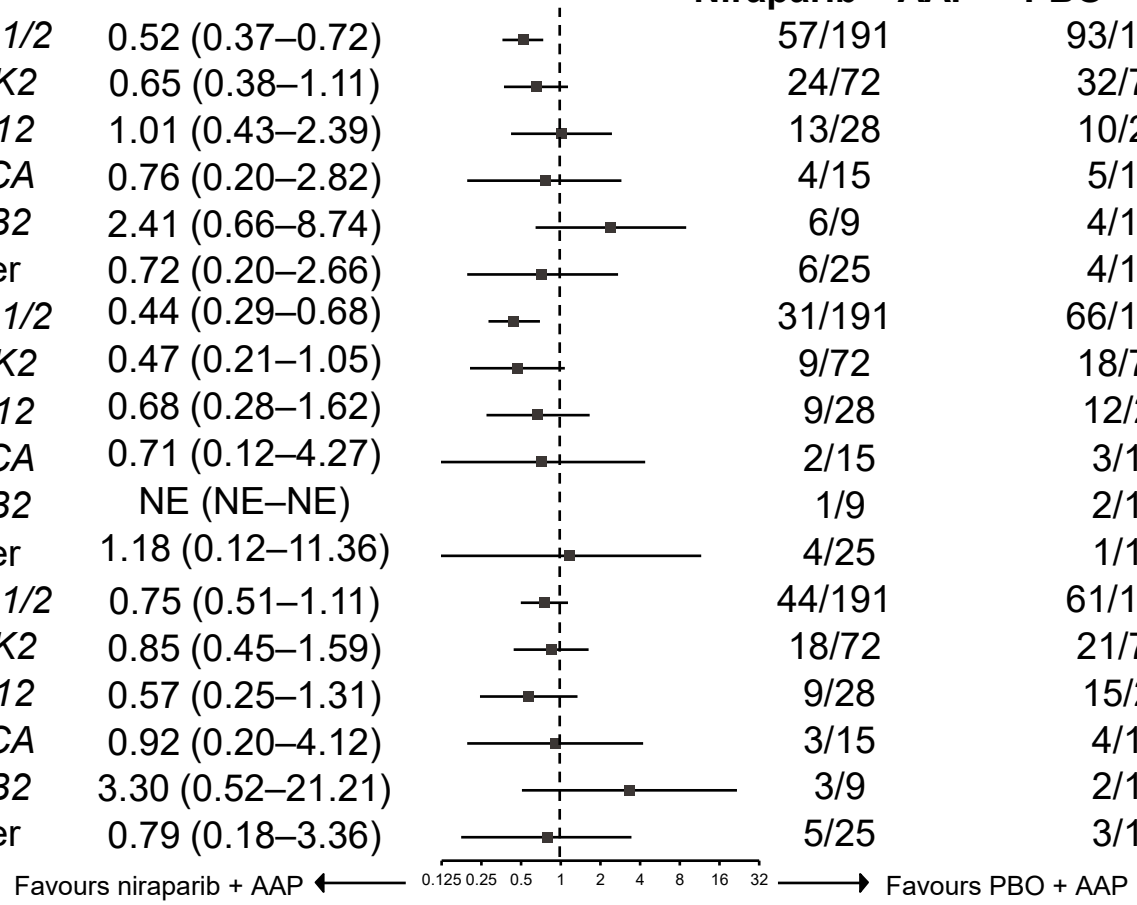
AAP, abiraterone acetate plus prednisone; BRCAm, BReast CAncer gene mutation; CI, confidence interval; HR, hazard ratio; HRRm, homologous recombination repair mutation; NE, not estimable; OS, overall survival; PBO, placebo.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Subgroup analysis by BRCA and non-BRCA alterations

Endpoint	Subgroup	HR (95% CI)	Events/N Niraparib + AAP	Events/N PBO + AAP
rPFS	*BRCA1/2*	0.52 (0.37–0.72)	57/191	93/196
	CHEK2	0.65 (0.38–1.11)	24/72	32/76
	CDK12	1.01 (0.43–2.39)	13/28	10/28
	FANCA	0.76 (0.20–2.82)	4/15	5/15
	PALB2	2.41 (0.66–8.74)	6/9	4/13
	Other	0.72 (0.20–2.66)	6/25	4/15
Time to symptomatic progression	*BRCA1/2*	0.44 (0.29–0.68)	31/191	66/196
	CHEK2	0.47 (0.21–1.05)	9/72	18/76
	CDK12	0.68 (0.28–1.62)	9/28	12/28
	FANCA	0.71 (0.12–4.27)	2/15	3/15
	PALB2	NE (NE–NE)	1/9	2/13
	Other	1.18 (0.12–11.36)	4/25	1/15
OS*	*BRCA1/2*	0.75 (0.51–1.11)	44/191	61/196
	CHEK2	0.85 (0.45–1.59)	18/72	21/76
	CDK12	0.57 (0.25–1.31)	9/28	15/28
	FANCA	0.92 (0.20–4.12)	3/15	4/15
	PALB2	3.30 (0.52–21.21)	3/9	2/13
	Other	0.79 (0.18–3.36)	5/25	3/15



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*The first interim analysis for OS was conducted when 193 patients had died (of a target of 389, an information fraction of 50%), 85 of 348 (24%) in the niraparib + AAP arm and 108 of 348 (31%) in the PBO + AAP arm.

Non-BRCA subgroups were not statistically powered for formal testing in this exploratory analysis. Hazard ratios were stratified by disease volume (high vs. low).

Other: RAD54L, BRIP1, RAD51B.

AAP, abiraterone acetate plus prednisone; BRCA, BReast CAncer gene; CI, confidence interval; HR, hazard ratio; OS, overall survival; PBO, placebo; rPFS, radiographic progression-free survival..

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

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*The first interim analysis (≈50% of total needed events) estimates show niraparib + AAP reduced risk of death by 25% in BRCAm group and by 21% in HRRm group

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Subsequent therapy for prostate cancer

Patients, n (%)	Niraparib + AAP (n=347)*	PBO + AAP (n=348)
Discontinued treatment due to progressive disease (denominator for any subsequent therapy)	93 (27)	149 (43)
Any subsequent therapy (denominator for below)	72 (77)	120 (81)
Chemotherapy†	60 (83)	91 (76)
ARPI	19 (26)	27 (23)
PARPi	**8 (11)**	**43 (36)**
Radiopharmaceuticals	6 (8)	8 (7)
Immunotherapy	2 (3)	6 (5)
Other‡	6 (8)	13 (11)

Table adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

*One randomised patient never received the study treatment. †Of patients with any subsequent therapy, 14% in the niraparib + AAP arm and 11% in the PBO + AAP arm also received carboplatin. ‡Capivasertib, ODM 208, AMG 509, vobramitamab duocarmazine, ZEN 3694, cabozantinib, datopotamab deruxtecan, enfortumab vedotin, investigational antineoplastic drugs, NUV 868 or zanzalintinib.

AAP, abiraterone acetate plus prednisone; ARPI, androgen receptor pathway inhibitor; PARPi, poly ADP-ribose polymerase inhibitor; PBO, placebo.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

MAT-NL-XTD-2025-00031 | July 2025

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Overview of AMPLITUDE safety profile

Safety population, n (%)	Niraparib + AAP (n=347)*	PBO + AAP (n=348)
Treatment-emergent adverse events (TEAEs)	346 (>99)	341 (98)
Treatment-related TEAEs†	309 (89)	257 (74)
Grade 3 or 4 TEAEs	261 (75)	205 (59)
Treatment-related grade 3 or 4 TEAEs	193 (56)	105 (30)
Serious adverse events (SAEs)	136 (39)	96 (28)
Treatment-related SAEs	44 (13)	11 (3)
TEAEs leading to treatment discontinuation‡	**51** (15)**	**36 (10)**
TEAEs leading to dose reduction	76 (22)	24 (7)
TEAEs leading to death††	14‡‡ (4)	7 (2)

<5% increase in rate of discontinuation due to toxicity of niraparib + AAP versus PBO + AAP

Table adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

Median duration of treatment was 25.3 months in the niraparib + APP arm and 22.5 months in the PBO + APP arm.

*One randomised patient never received the study treatment. † AE is categorised as related if assessed by the investigator as related to study treatment (niraparib/PBO or AA/PBO or prednisone). ‡ An AE is counted as leading to discontinuation of study treatment if it leads to withdrawal of niraparib/PBO or AA/PBO or prednisone. **Includes one case of MDS. †† AE leading to death based on AE outcome of fatal. ‡‡ TEAE leading to death included 4 cases of respiratory infection, including 2 attributed as related to COVID-19, 4 attributed to cardiac causes, 3 classified as sudden death and 1 each of sepsis, subdural hematoma and multiorgan dysfunction syndrome.

AAP, abiraterone acetate plus prednisone; AE, adverse event; MDS, myelodysplastic syndrome; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Adverse events of special interest

Selected categories of TEAEs of interest, n (%)		Niraparib + AAP (n=347)		PBO + AAP (n=348)	
		All grades	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 AE of interest		306 (88)	217 (63)	261 (75)	132 (38)
Hematologic	**Anaemia** Neutropenia Thrombocytopenia MDS	**179 (52)** 76 (22) 66 (19) 1 (<1)	**101 (29)** 33 (10) 24 (7) 1 (<1)	**83 (24)** 28 (8) 20 (6) 0 (0)	**16 (5)** 7 (2) 1 (<1) 0 (0)
Cardiovascular	**Hypertension** Arrhythmia Cardiac failure	**155 (45)** 68 (20) 20 (6)	**93 (27)** 19 (5) 9 (3)	**113 (33)** 28 (8) 6 (2)	**64 (18)** 11 (3) 4 (1)
Other	Hypokalaemia Hepatotoxicity	92 (27) 46 (13)	40 (12) 8 (2)	70 (20) 71 (20)	38 (11) 19 (5)

- Other common AEs of any grade: Constipation (35% vs. 16%), nausea (31% vs. 14%), fatigue (26% vs. 18%) and arthralgia (21% vs. 21%) in the niraparib + AAP vs. placebo + AAP arms, respectively

Table adapted from Attard G, et al. 2025.

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the patient with the worst toxicity is used.
If a patient has missing toxicity for a specific AE, the patient is only counted in the total column for that AE.
AAP, abiraterone acetate plus prednisone; AE, adverse event; MDS, myelodysplastic syndrome; PBO, placebo; TEAE, treatment-emergent adverse event.
Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006.

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Conclusions[1]

- The AMPLITUDE trial met its primary endpoint of rPFS and is the first trial to show efficacy of a PARPi + ARPI combination in mHSPC with HRR alterations, with the greatest benefit likely observed in patients with BRCA alterations
- Improvements in rPFS are supported by a statistically significant benefit in time to symptomatic progression and a trend toward improved OS
- The safety profile of niraparib + AAP was consistent with that previously observed in the MAGNITUDE trial,[2] with a <5% increase in patients discontinuing treatment due to toxicity than in those receiving placebo
- AMPLITUDE supports niraparib + AAP as a potential option for patients with mHSPC and HRR gene alterations

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AAP, abiraterone acetate plus prednisone; ARPI, androgen receptor pathway inhibitor; BRCA, BReast CAncer gene; HRR, homologous recombination repair gene; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PARPi, poly ADP-ribose polymerase inhibitor; rPFS, radiographic progression-free survival.

1. Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006; 2. Chi KN, et al. *J Clin Oncol*. 2023;41:3339-3351.

MAT-NL-XTD-2025-00031 | July 2025

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Takeaways[1]

- AMPLITUDE met its primary endpoint of rPFS
- AMPLITUDE is the first trial to show efficacy of the combination of a PARPi and an ARPI in mHSPC with HRR alterations, with greatest benefit in patients with BRCA alterations
- Improvements in rPFS are supported by a statistically significant benefit in time to symptomatic progression
- The safety profile of niraparib + abiraterone acetate plus prednisone was consistent with that previously observed in the MAGNITUDE trial,[2] with a <5% increase in patients discontinuing treatment due to toxicity versus those receiving placebo + abiraterone acetate plus prednisone

Niraparib is not licenced for the treatment of mHSPC; this is an investigational combination.

ARPI, androgen receptor pathway inhibitor; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; rPFS, radiographic progression-free survival.

1. Attard G, et al. Presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract LBA5006; 2. Chi KN, et al. *J Clin Oncol*. 2023;41:3339-3351.

MAT-NL-XTD-2025-00031 | July 2025

Impact of somatic/germline homologous recombination repair (HRR) alterations on metastatic hormone-sensitive prostate cancer (mHSPC)

- The presence of HRR mutations, particularly BRCA alterations, significantly worsened prognosis, regardless of disease volume or treatment regimen
- These findings highlight the need for early HRR screening and underscore the importance of integrating tumour biology for accurate risk stratification in mHSPC and the design of new treatment strategies

HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer.

Olmos D, et al. Poster presented at ASCO 2025, 30 May–03 June 2025, Chicago, IL, USA: Abstract 5094.

MAT-NL-XTD-2025-00031 | July 2025

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EMA, European Medicines Agency; SmPC, Summary of Product Characteristics.
MAT-NL-XTD-2025-00031 | July 2025