DAROLUTAMIDE PLUS ANDROGEN-DEPRIVATION THERAPY IN PATIENTS WITH METASTATIC HORMONE-SENSITIVE PROSTATE CANCER: EFFICACY AND SAFETY BY DISEASE VOLUME IN THE PHASE 3 ARANOTE STUDY

Carlos Alemany[1] on behalf of Fred Saad,[2] Neal Shore,[3] Egils Vjaters,[4] David Olmos,[5] Natasha Littleton,[6] Anna Liu,[7] Isabella Testa,[8] Mindy Mo,[9] Shankar Srinivasan,[9] Kunhi Parambath Haresh[10]

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INTRODUCTION

In the Phase 3 ARANOTE study, darolutamide + androgen-deprivation therapy (ADT) significantly improved radiologic progression-free survival (rPFS) versus placebo + ADT (HR 0.54; 95% CI: 0.41–0.71; P<0.0001) in patients with metastatic hormone-sensitive prostate cancer[1]

Disease volume is an established prognostic factor in mHSPC[2,3]

OBJECTIVE

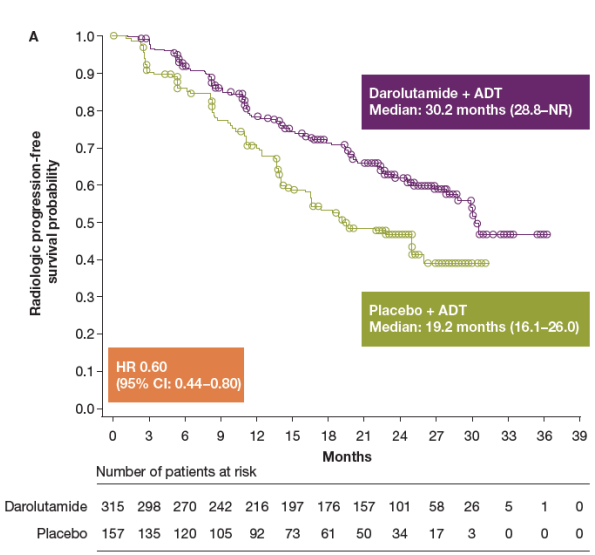
Post hoc analysis of ARANOTE evaluating the impact of disease burden on efficacy and safety outcomes in the ARANOTE study

METHODS

Patients were evaluated by disease volume (CHAARTED criteria)[4] as high volume (>4 bone metastasis with at least one beyond the axial skeleton or any visceral metastases) or low volume (did not meet high-volume criteria)

Primary endpoint: rPFS

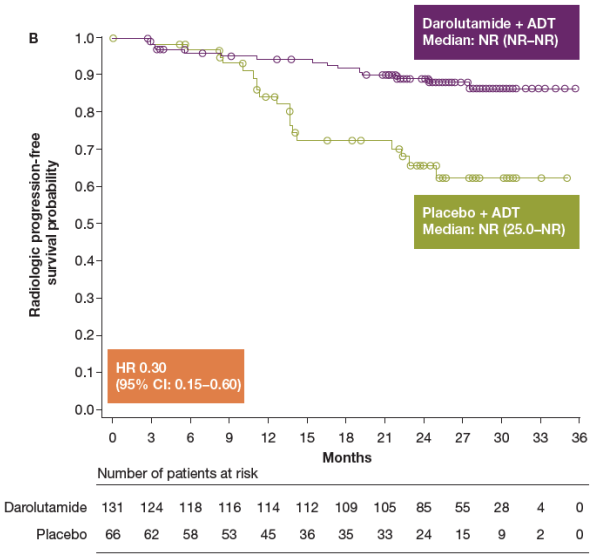
High-volume disease subgroup:
Darolutamide + ADT reduced the risk of radiologic progression or death by 40%



Number of patients at risk

Darolutamide	315	298	270	242	216	197	176	157	101	58	26	5	1	0
Placebo	157	135	120	105	92	73	61	50	34	17	3	0	0	0

Low-volume disease subgroup:
Darolutamide + ADT reduced the risk of radiologic progression or death by 70%



Number of patients at risk

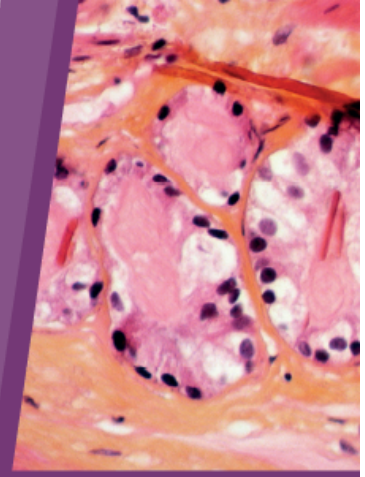
Darolutamide	131	124	118	116	114	112	109	105	85	55	28	4	0
Placebo	66	62	58	53	45	36	35	33	24	15	9	2	0

ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; NR, not reached.

Incidence of TEAEs was similar between treatment arms across disease volume subgroups

TEAEs, n (%)	High volume[a]		Low volume[a]		Overall ARANOTE population[a]	
	Darolutamide + ADT (n=314)	Placebo + ADT (n=156)	Darolutamide + ADT (n=131)	Placebo + ADT (n=65)	Darolutamide + ADT (n=445)	Placebo + ADT (n=221)
Any TEAE	292 (93.0)	143 (91.7)	113 (86.3)	56 (86.2)	405 (91.0)	199 (90.0)
Grade 3/4	98 (31.2)	50 (32.1)	39 (29.8)	17 (26.2)	137 (30.8)	67 (30.3)
Serious	89 (28.3)	40 (25.6)	16 (12.2)	12 (18.5)	105 (23.6)	52 (23.5)
TEAE leading to discontinuation of the study drug	23 (7.3)	13 (8.3)	4 (3.1)	7 (10.8)	27 (6.1)	20 (9.0)

[a]Safety analysis population in which 2 patients randomized to placebo received darolutamide and were analyzed in the darolutamide group.
ADT, androgen-deprivation therapy; TEAE, treatment-emergent adverse event.



CONCLUSIONS

- Efficacy outcomes with darolutamide + ADT were improved versus placebo + ADT, regardless of disease volume
- Darolutamide + ADT was well tolerated in high- and low-volume disease subgroups, with low treatment discontinuation rates
- Patients with low-volume mHSPC had marked treatment efficacy with minimal treatment burden

SCAN ME FOR MORE INFO

Medical writing services were provided by Kennedy Shaw, MSc, of Adelphi Communications Ltd (Bollington, UK), funded by Bayer, in accordance with Good Publication Practice 2022 guidelines.

References: 1. Saad F, et al. J Clin Oncol 2024;42:4271–4281. 2. Halabi S, et al. Ann Oncol 2024;35:S975. 3. Wenzel M, et al. Clin Prostate Cancer 2024;42:371–e11. 4. Sweeney CJ, et al. N Engl J Med 2015;373:737–746.

Poster presented at Florida Society of Clinical Oncology Spring Congress 2025, Orlando, FL, USA; April 4–5 2025

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Supplementary material

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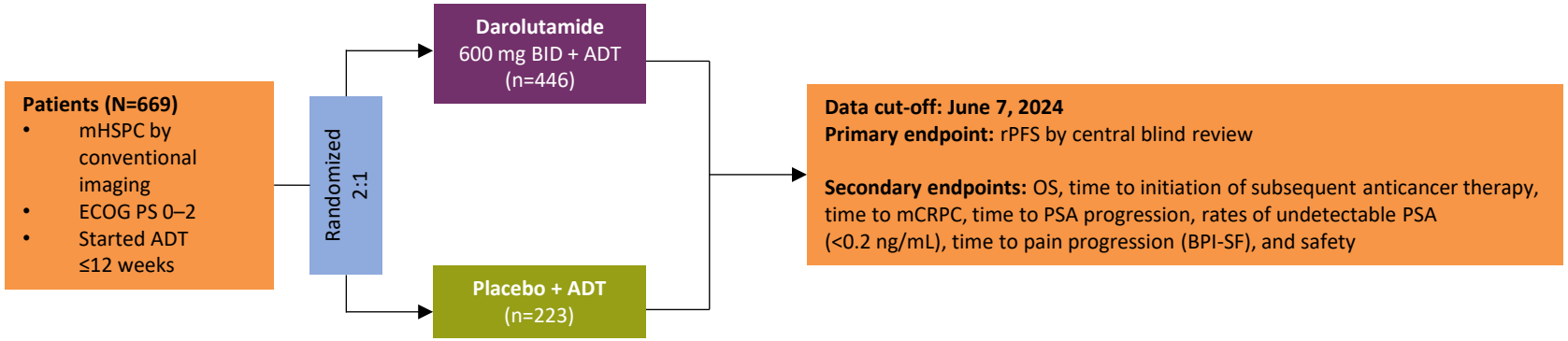
Plain language summary

- In this study, men with a type of advanced prostate cancer that has spread to other parts of the body received treatment with the combination of darolutamide plus androgen-deprivation therapy (also called ADT), which lowers male hormone levels in the body, or ADT alone
- Darolutamide plus ADT worked better than ADT alone in men no matter if the cancer had spread a little or a lot throughout the body, reducing the risk of the cancer getting worse or leading to death by 70% in men with little cancer spread and by 40% in men with a lot of cancer spread
- Darolutamide also delayed the time it took for the cancer to become resistant to hormone-lowering therapy and for prostate-specific antigen (PSA) to rise, and more men receiving darolutamide had their PSA drop to very low levels
- Adverse events were about the same for both groups of men based on the amount of cancer spread, and fewer men taking darolutamide stopped treatment because of adverse events
- Darolutamide was effective and well tolerated in men with advanced prostate cancer who had a little or a lot of cancer spread throughout their body, and men who had little cancer spread responded to darolutamide well with little treatment burden

Methods

- ARANOTE was a global, randomized, double-blind Phase 3 study of darolutamide + ADT versus placebo + ADT in patients with mHSPC
- In this post hoc analysis, patients were evaluated by disease volume, which was defined according to CHAARTED criteria[1]:
  - High-volume: Presence of visceral metastases and/or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
  - Low-volume: Disease that does not meet high-volume criteria



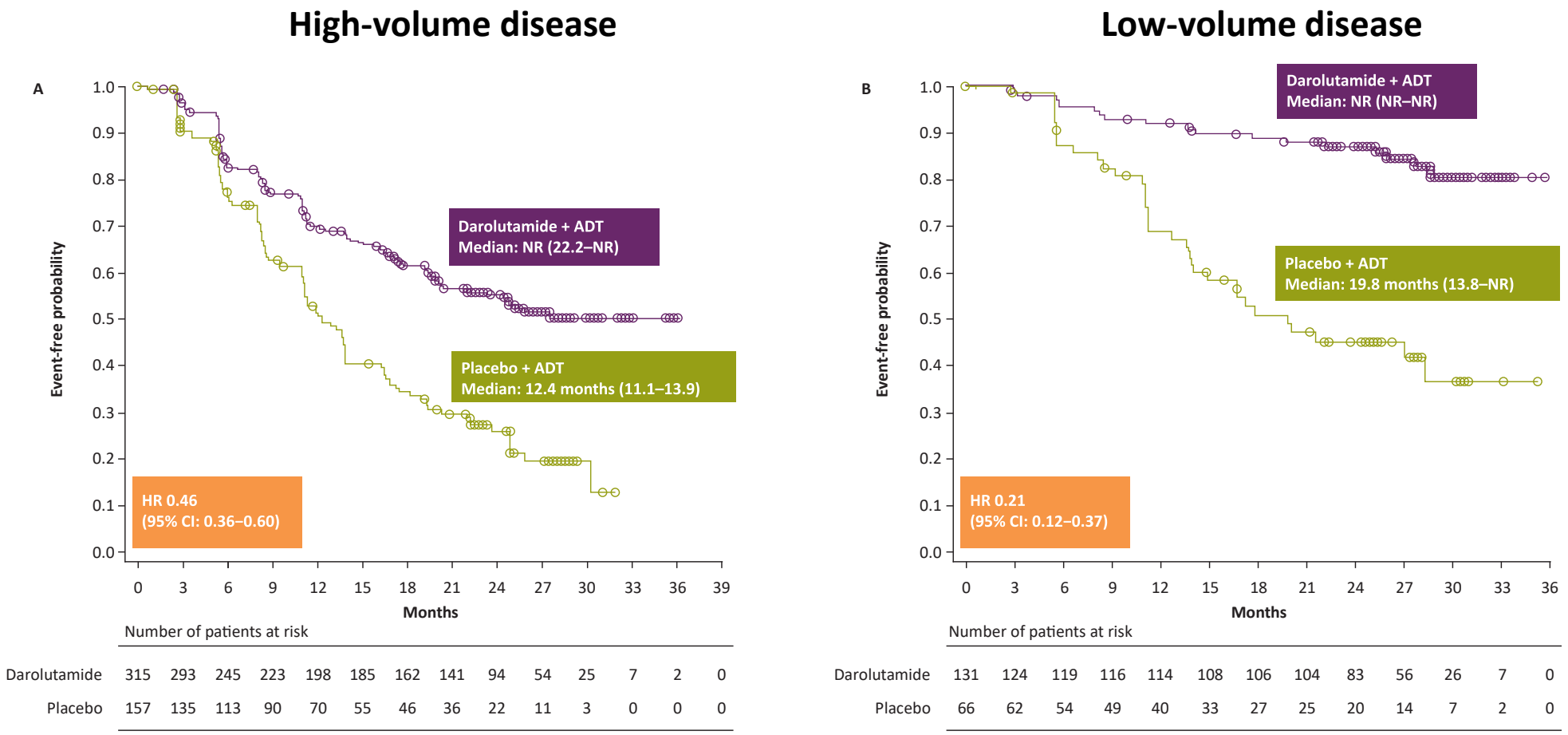
1. Sweeney CJ, et al. N Engl J Med 2015;373:737–746.

ADT, androgen-deprivation therapy; BID, twice a day; BPI-SF, Brief Pain Inventory (Short Form); ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiologic progression-free survival.

Baseline demographics and disease characteristics

	High-volume		Low-volume		All patients (N=669)
	Darolutamide + ADT (n=315)	Placebo + ADT (n=157)	Darolutamide + ADT (n=131)	Placebo + ADT (n=66)	
Age, median (range), years	69.0 (43–93)	69.0 (47–89)	71.0 (47–89)	70.0 (45–91)	70.0 (43–93)
ECOG PS 0, n (%)	149 (47.3)	59 (37.6)	86 (65.6)	39 (59.1)	333 (49.8)
Gleason score of ≥8 at initial diagnosis, n (%)	236 (74.9)	110 (70.1)	75 (57.3)	36 (54.5)	457 (68.3)
Metastasis stage at initial diagnosis, n (%) De novo	245 (77.8)	121 (77.1)	72 (55.0)	47 (71.2)	485 (72.5)
Serum PSA level, median (range), ng/mL	28.9 (0.09–15,915)	27.0 (0.03–8533)	10.9 (0.02–3915)	15.6 (0.02–7050)	21.3 (0.02–15,915)
Visceral metastases (centrally assessed), n (%)	53 (16.8)	27 (17.2)	0	0	80 (12.0)
Received prior local therapy, n (%)	52 (16.5)	26 (16.6)	28 (21.4)	14 (21.2)	120 (17.9)

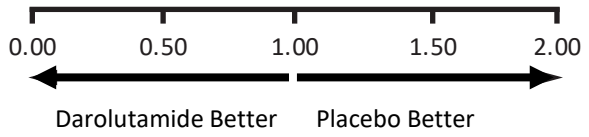
Darolutamide delayed time to mCRPC



CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached.

ARANOTE secondary efficacy endpoints by disease volume

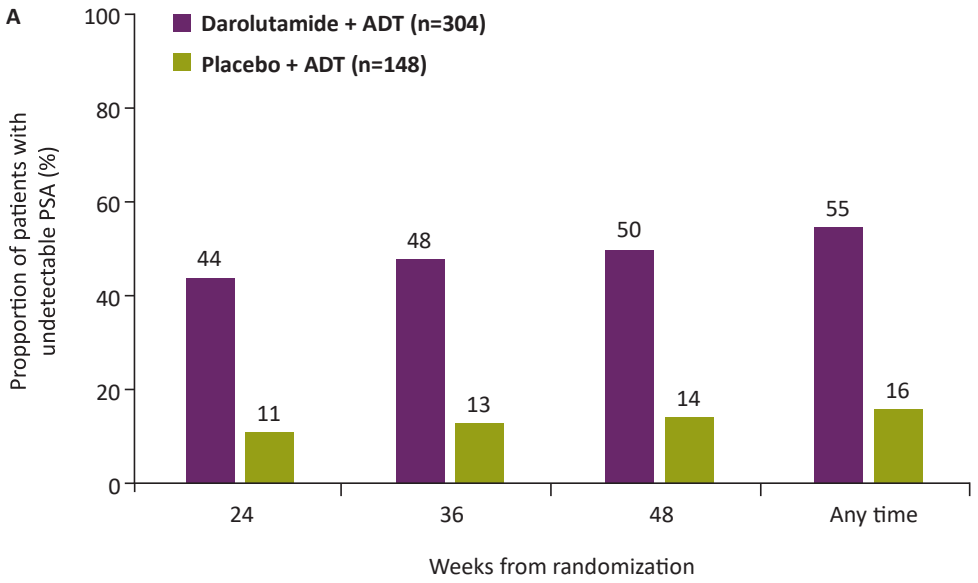
Secondary endpoint	Patient subgroup	Number of events/number of patients		Median (95% CI), months		HR (95% CI)[a]
		Darolutamide	Placebo	Darolutamide	Placebo	
Time to initiation of subsequent systemic anticancer therapy	All patients[b]	68/446	74/223	NR (NR–NR)	NR (27.7–NR)	0.40 (0.29–0.56)
	High-volume	60/315	55/157	NR (NR–NR)	29.6 (25.2–NR)	0.47 (0.32–0.68)
	Low-volume	8/131	19/66	NR (NR–NR)	NR (NR–NR)	0.19 (0.08–0.43)
Time to PSA progression	All patients[b]	93/446	108/223	NR (NR–NR)	16.8 (13.9–20.1)	0.31 (0.23–0.41)
	High-volume	79/315	82/157	NR (NR–NR)	13.9 (12.0–17.3)	0.34 (0.25–0.46)
	Low-volume	14/131	26/66	NR (NR–NR)	28.3 (16.8–NR)	0.19 (0.10–0.37)
Time to pain progression	All patients[b]	124/446	79/223	NR (NR–NR)	29.9 (29.7–NR)	0.72 (0.54–0.96)
	High-volume	104/315	62/157	NR (NR–NR)	29.7 (18.9–NR)	0.78 (0.57–1.06)
	Low-volume	20/131	17/66	NR (NR–NR)	NR (NR–NR)	0.53 (0.28–1.01)



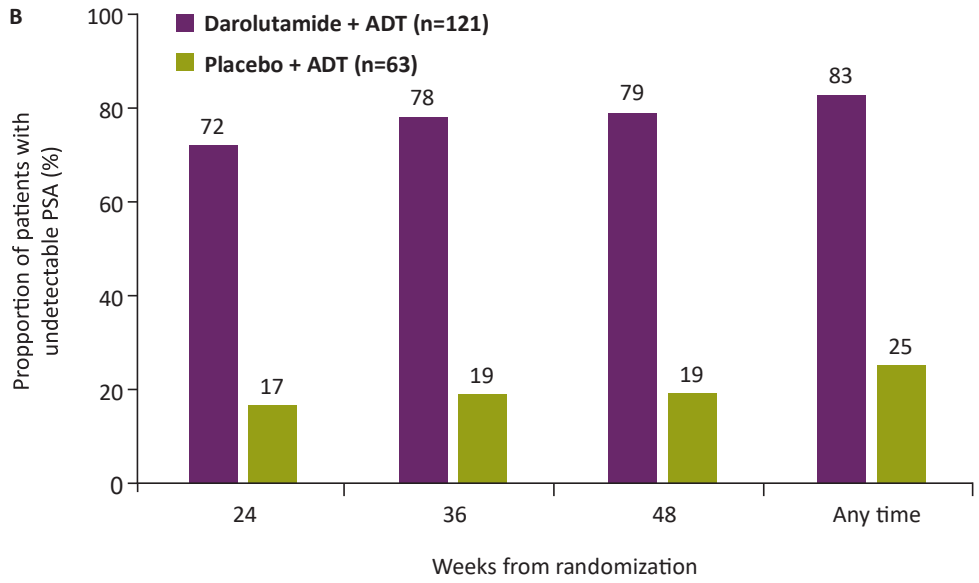
[a]Based on unstratified Cox regression model for high/low volume subgroups. [b]Includes all randomized patients according to planned treatment.

Patients with undetectable PSA <0.2 ng/mL) in the high-volume and low-volume subgroups[a]

High-volume disease



Low-volume disease



[a]Of those with baseline PSA ≥0.2 ng/mL.