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Prostate-specific antigen response with darolutamide plus androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer in ARANOTE

Prof Fred SAAD on behalf of the ARANOTE Investigators

Conflict of Interest Disclosure

I have the following potential conflict(s) of interest to report:

- Honoraria: Astellas Pharma, Janssen Oncology, Sanofi, Bayer, AstraZeneca, AbbVie, Myovant Sciences, Pfizer, BMS, Novartis, Advanced Accelerator Applications, Merck, Knight Therapeutics, Tolmar
- Consulting or Advisory Role: Astellas Pharma, Janssen Oncology, Sanofi, AstraZeneca/MedImmune, Bayer, Pfizer, Myovant Sciences, AbbVie, Novartis, Advanced Accelerator Applications, Knight Therapeutics, Tolmar
- Research Funding: Astellas Pharma (Inst), Bayer (Inst), Janssen Oncology (Inst), Sanofi (Inst), AstraZeneca (Inst), Pfizer (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Advanced Accelerator Applications (Inst), Merck (Inst)

Introduction

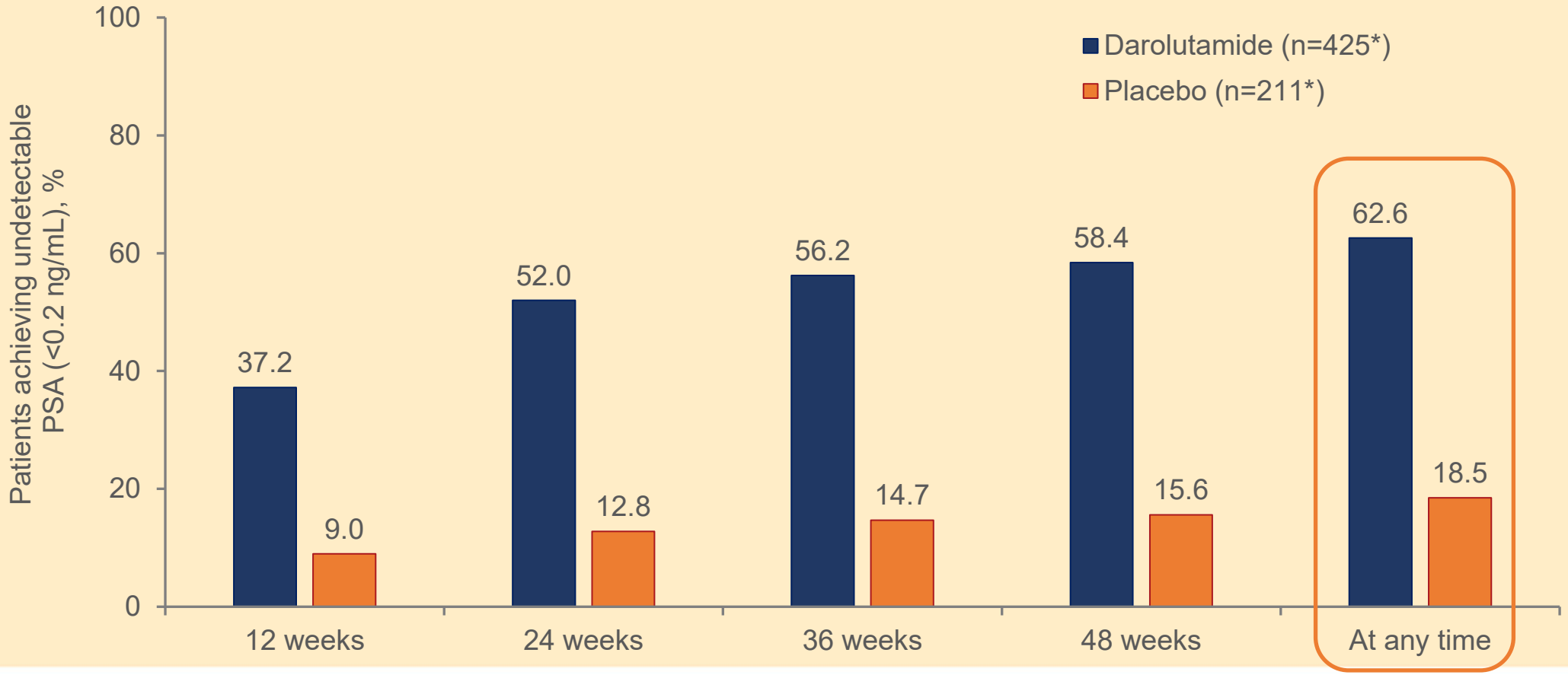
- In the phase 3 ARANOTE study (NCT04736199), darolutamide + ADT reduced the risk of radiological progression or death by 46% (HR 0.54; 95% CI 0.41–0.71; *P*<0.0001) versus placebo + ADT in patients with mHSPC[1]
- The incidence of treatment-emergent adverse events was low and similar between groups[1]
- Patients achieving undetectable PSA (<0.2 ng/mL) at any time had better ECOG performance status, lower Gleason score, and lower baseline PSA values versus patients who did not

- **We report post-hoc analyses of ARANOTE correlating PSA response with outcomes overall and by baseline PSA level**

1. Saad F et al. *J Clin Oncol.* 2024;42(36):4271–4281.

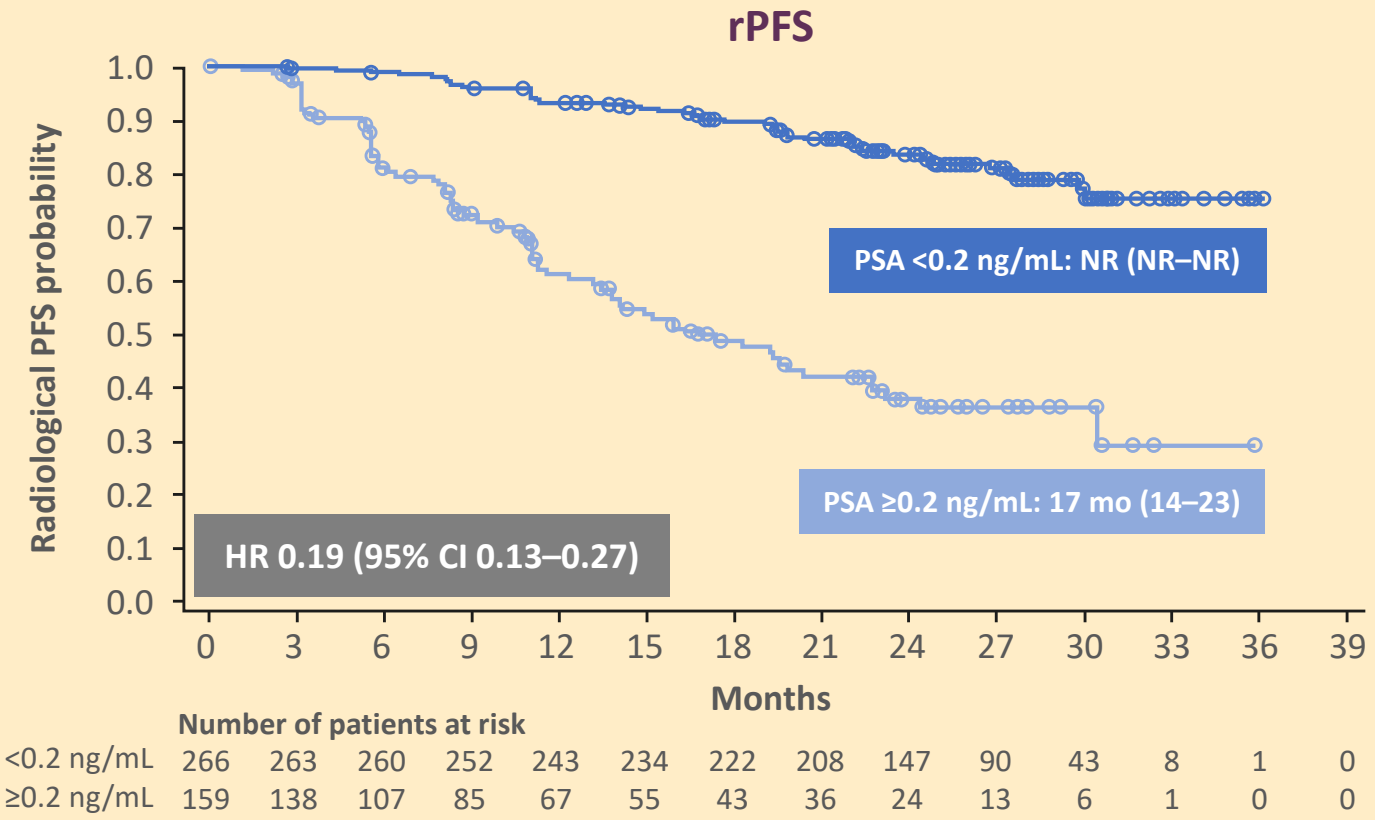
ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

Darolutamide resulted in a deep PSA response: Three times as many patients achieved undetectable PSA (<0.2 ng/mL) at any time vs those on placebo



PSA, prostate-specific antigen. *Excludes patients with undetectable PSA (<0.2 ng/mL) at baseline (darolutamide n=11; placebo n=8).

Patients on darolutamide who achieved undetectable PSA (<0.2 ng/mL) had a lower risk of radiological progression or death



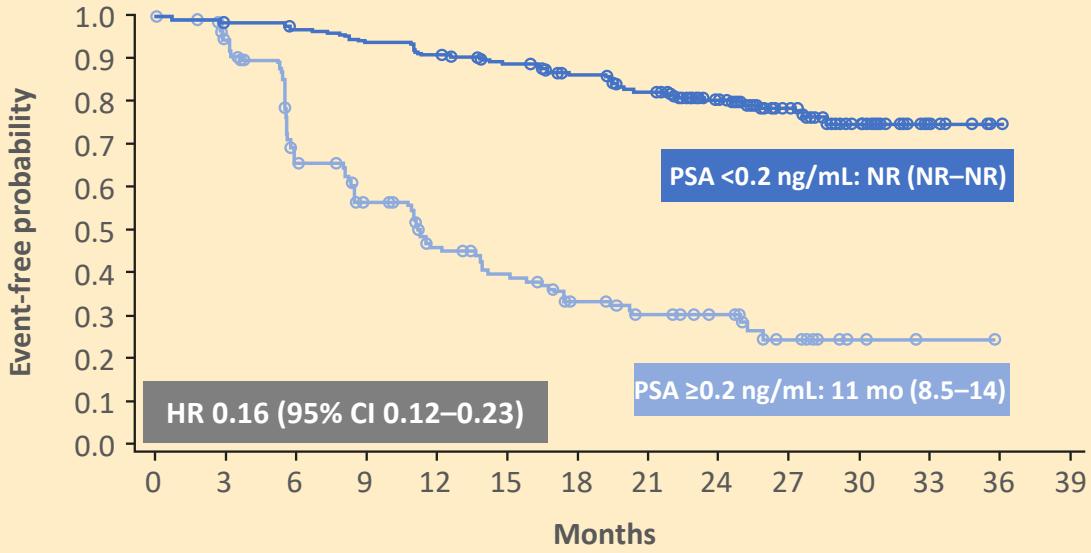
Number of patients at risk

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

CI, confidence interval; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen; rPFS, radiological progression-free survival.

Patients on darolutamide who achieved undetectable PSA (<0.2 ng/mL) had longer time to mCRPC and time to PSA progression

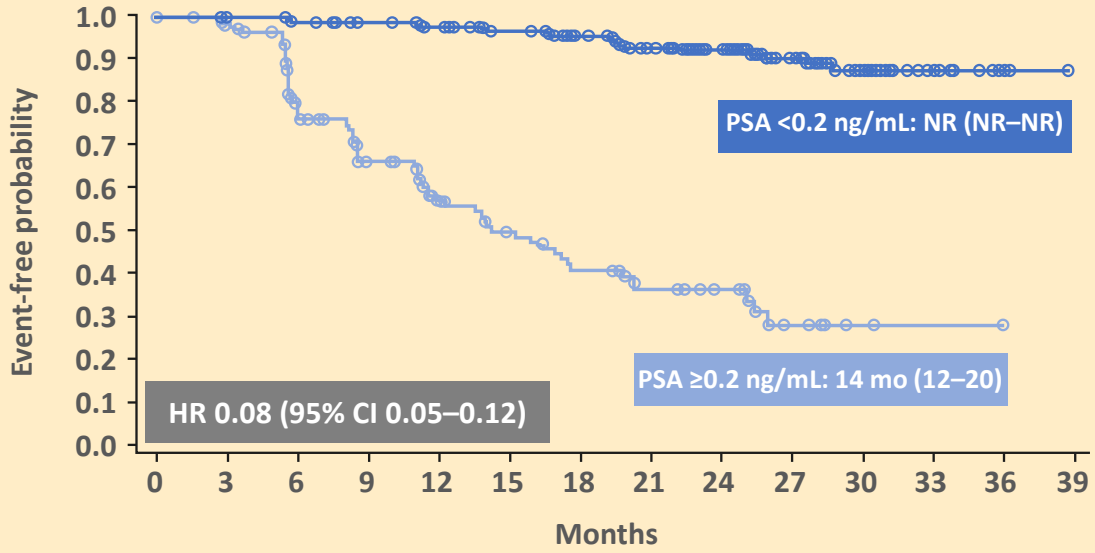
Time to mCRPC progression



Number of patients at risk

PSA <0.2 ng/mL	266	260	255	247	239	230	216	202	144	92	44	13	2	0
PSA ≥0.2 ng/mL	159	137	89	72	54	44	33	26	19	9	3	1	0	0

Time to PSA progression

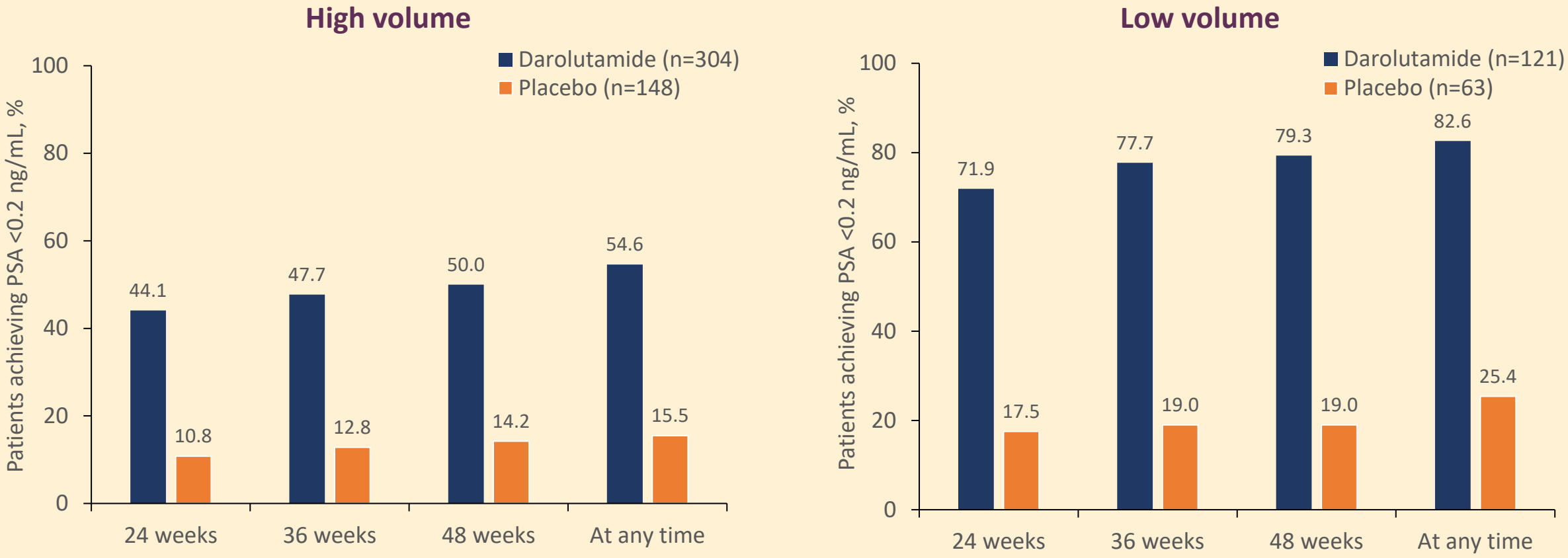


Number of patients at risk

PSA <0.2 ng/mL	266	261	256	250	241	231	215	188	134	86	45	11	2	0
PSA ≥0.2 ng/mL	159	136	90	69	49	39	31	23	17	6	2	1	0	0

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

A higher proportion of patients achieved undetectable PSA (<0.2 ng/mL) with darolutamide versus placebo in both high-volume and low-volume subgroups



PSA, prostate-specific antigen.

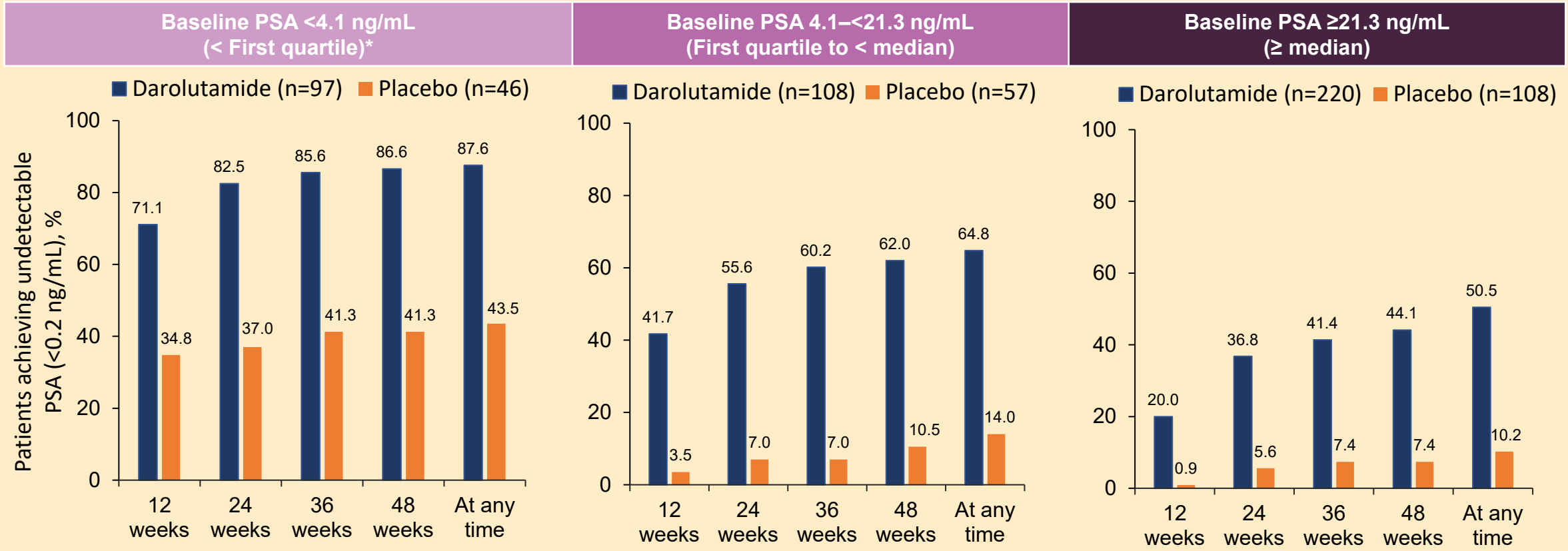
Of all randomized patients, median baseline PSA was 21 ng/mL; fewer patients with baseline PSA <4.1 ng/mL had de novo disease versus groups with baseline PSA ≥4.1 ng/mL

Characteristic at baseline	Baseline PSA <4.1 ng/mL (First quartile)		Baseline PSA 4.1–<21.3 ng/mL (First quartile to < median)		Baseline PSA ≥21.3 ng/mL (≥ median)	
	Darolutamide (n=108)	Placebo (n=54)	Darolutamide (n=108)	Placebo (n=57)	Darolutamide (n=220)	Placebo (n=108)
Age, median (range), years	70 (48–87)	70 (50–91)	70 (49–93)	70 (45–89)	70 (43–93)	69 (47–89)
ECOG PS=0/1, n (%)	63 (58.3) / 42 (38.9)	35 (64.8) / 18 (33.3)	65 (60.2) / 40 (37.0)	21 (36.8) / 32 (56.1)	101 (45.9) / 113 (51.4)	40 (37.0) / 65 (60.2)
Gleason score at initial diagnosis, ≥8, n (%)	71 (65.7)	34 (63.0)	78 (72.2)	36 (63.2)	156 (70.9)	74 (68.5)
PSA , median (range), ng/mL	1.3 (0.0–4.0)	0.7 (0.0–3.7)	9.1 (4.1–21.1)	9.4 (4.1–21.2)	115.2 (21.3–15,915.0)	134.7 (21.7–8533.0)
De novo mHSPC at initial diagnosis, n (%)	66 (61.1)	28 (51.9)	77 (71.3)	47 (82.5)	168 (76.4)	90 (83.3)
Visceral metastases, n (%)	10 (9.3)	7 (13.0)	10 (9.3)	4 (7.0)	32 (14.5)	15 (13.9)
Received prior local therapy, n (%)	24 (22.2)	17 (31.5)	21 (19.4)	7 (12.3)	31 (14.1)	16 (14.8)

ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

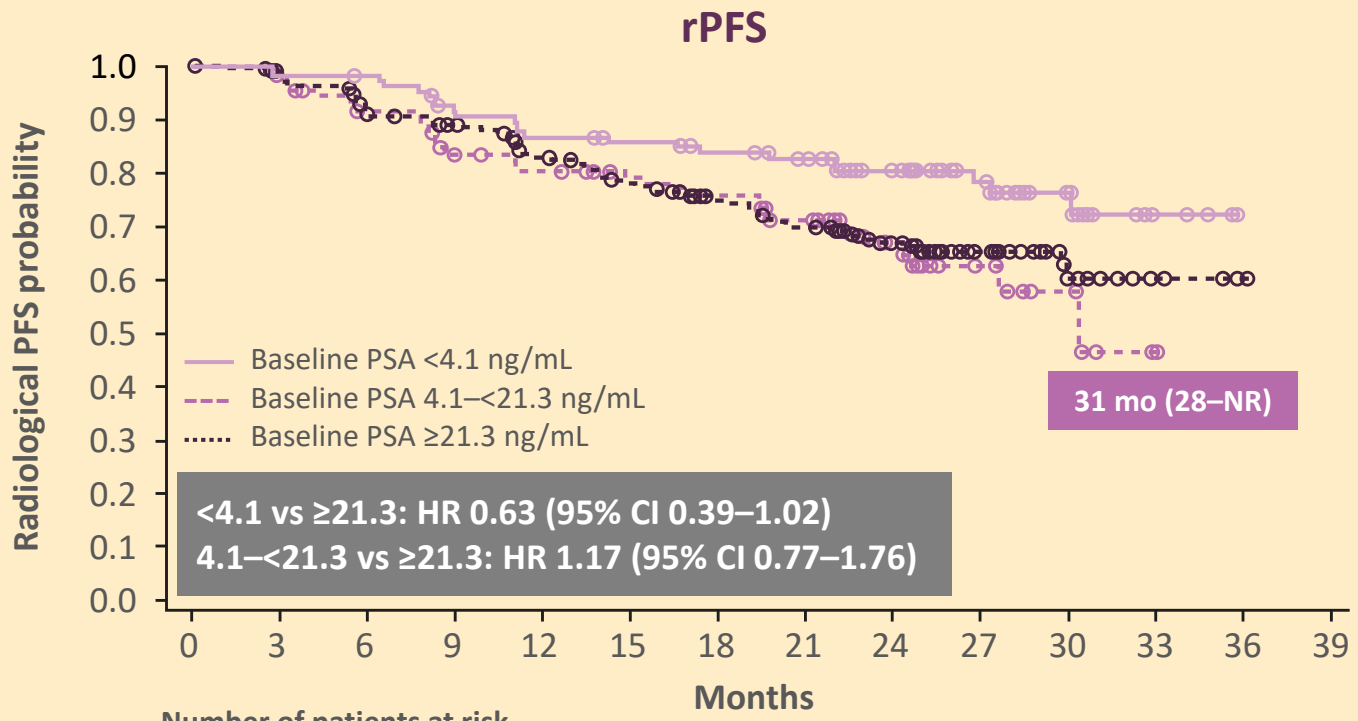
Regardless of baseline PSA, more patients on darolutamide vs placebo achieved undetectable PSA (<0.2 ng/mL) at any time

- A greater proportion of patients with low baseline PSA achieved undetectable PSA at any time



PSA, prostate-specific antigen.
*Excludes patients with undetectable PSA (<0.2 ng/mL) at baseline (darolutamide n=11; placebo n=8).

Patients on darolutamide with low baseline PSA (<4.1 ng/mL) had a lower risk of radiological progression or death vs patients with baseline PSA ≥21.3 ng/mL



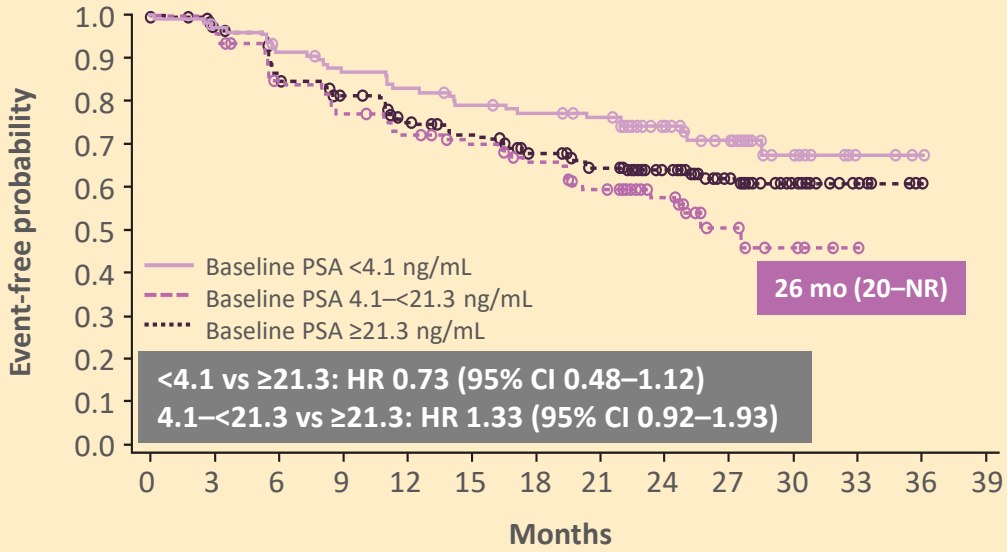
Number of patients at risk

Baseline PSA <4.1 ng/mL	108	105	103	93	89	86	81	76	56	39	20	4	0	0
Baseline PSA 4.1–<21.3 ng/mL	108	102	91	79	75	70	66	59	36	16	8	1	0	0
Baseline PSA ≥21.3 ng/mL	220	205	184	176	157	144	129	119	87	53	24	4	1	0

CI, confidence interval; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen; rPFS, radiological progression-free survival.

Patients on darolutamide with low baseline PSA (<4.1 ng/mL) had longer time to mCRPC and time to PSA progression vs patients with baseline PSA ≥21.3 ng/mL

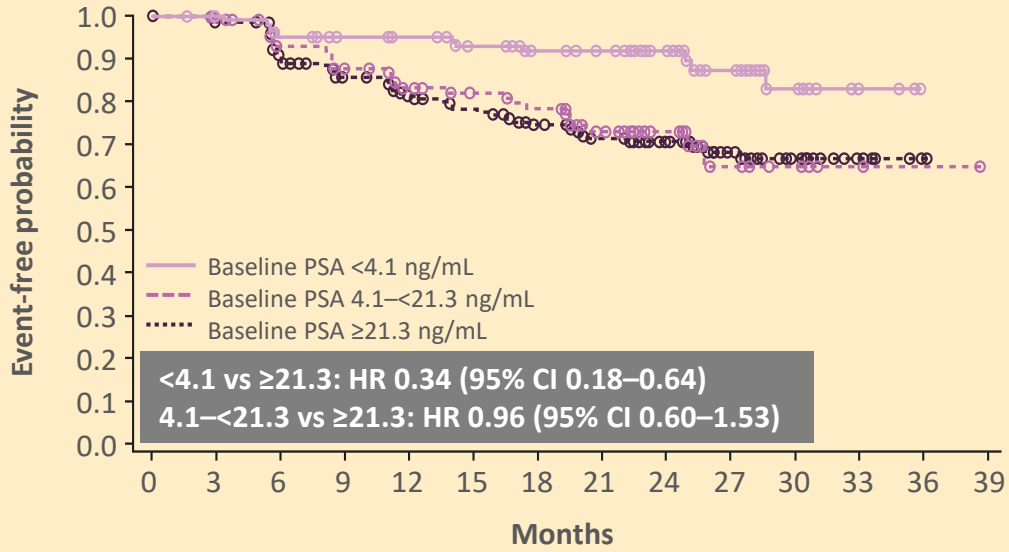
Time to mCRPC progression



Number of patients at risk

Baseline PSA <4.1 ng/mL	108	104	96	90	86	81	78	75	54	37	17	4	1	0
Baseline PSA 4.1–<21.3 ng/mL	108	102	86	78	72	67	61	52	32	14	7	2	0	0
Baseline PSA ≥21.3 ng/mL	220	202	173	162	146	137	121	111	85	54	25	8	1	0

Time to PSA progression



Number of patients at risk

Baseline PSA <4.1 ng/mL	108	104	92	92	89	83	76	70	52	35	18	3	0	0
Baseline PSA 4.1–<21.3 ng/mL	108	103	89	82	72	66	62	46	30	12	8	3	1	0
Baseline PSA ≥21.3 ng/mL	220	201	172	156	140	131	118	104	76	48	22	6	1	0

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

The favorable safety profile of darolutamide was independent of baseline PSA

TEAEs, n (%)	Darolutamide (n=434)*†			Placebo (n=218)*†			Overall ARANOTE population*	
	Baseline PSA							
	<4.1 ng/mL (n=109)	4.1–<21.3 ng/mL (n=106)	≥21.3 ng/mL (n=219)	<4.1 ng/mL (n=53)	4.1–<21.3 ng/mL (n=57)	≥21.3 ng/mL (n=108)	Darolutamide (n=445)	Placebo (n=221)
Any TEAE	99 (90.8)	96 (90.6)	199 (90.9)	48 (90.6)	54 (94.7)	94 (87.0)	405 (91.0)	199 (90.0)
Grade 3/4	31 (28.4)	32 (30.2)	69 (31.5)	13 (24.5)	15 (26.3)	37 (34.3)	137 (30.8)	67 (30.3)
Serious	24 (22.0)	23 (21.7)	53 (24.2)	11 (20.8)	11 (19.3)	30 (27.8)	105 (23.6)	52 (23.5)
TEAEs leading to discontinuation of study drug	6 (5.5)	5 (4.7)	14 (6.4)	5 (9.4)	5 (8.8)	10 (9.3)	27 (6.1)	20 (9.0)

*Safety analysis population in which 3 patients in the darolutamide group were not treated, and 2 patients randomized to placebo received darolutamide and were analyzed in the darolutamide group.
†Excludes patients with PSA <0.02 ng/mL at baseline.
PSA, prostate-specific antigen; TEAEs, treatment-emergent adverse events.

Conclusions

- Darolutamide provided deep and durable PSA responses in the overall population and across baseline PSA subgroups
  - Three times as many patients reached undetectable PSA (<0.2 ng/mL) vs placebo
  - Undetectable PSA was achieved in a greater proportion regardless of baseline PSA
- Undetectable PSA with darolutamide correlated with clinical benefit in terms of radiological progression or death and longer times to mCRPC and PSA progression
- The safety profile of darolutamide was consistent across subgroups, regardless of PSA response and baseline PSA

Acknowledgments

We thank the patients and their families, and all of the investigators involved in the ARANOTE study

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