Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial

DR. DHARMPAL JAKHAR

TATA MEMORIAL HOSPITAL, MUMBAI

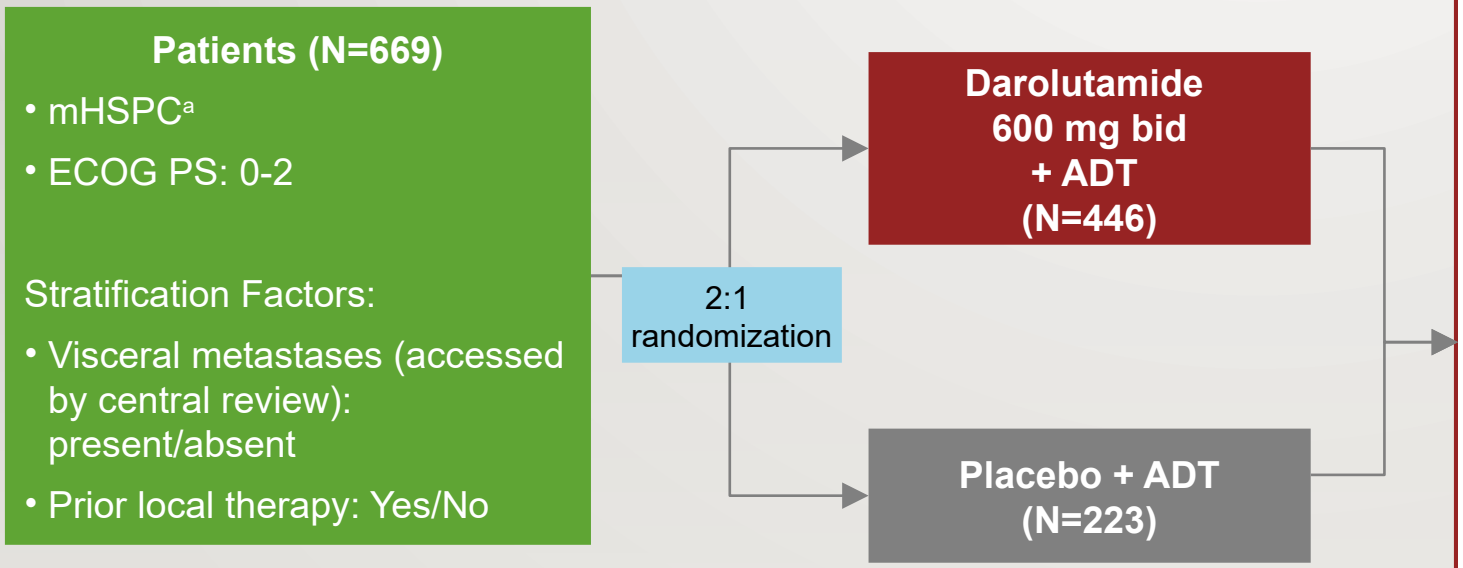
Introduction:-

- Several phase III trials have demonstrated improved overall survival (OS) and delayed progression to mCRPC when ADT is combined with an ARPI (abiraterone acetate, enzalutamide, or apalutamide)
- The ARASENS and PEACE-1 trials have demonstrated survival benefits with the triplet combination of darolutamide or abiraterone, respectively, plus ADT and docetaxel.

However, these doublet and triplet regimens are underutilized, and many patients with mHSPC continue to receive treatment with ADT alone because of concerns about drug accessibility, tolerability, safety, drug-drug interactions, and health care provider education.

Thus, an unmet need remains for treatments that delay progression to mCRPC with recognized tolerability.

ARANOTE Is a Phase 3 Double-Blind Study That **Investigated the Clinical Benefit and Tolerability of Darolutamide + ADT for Patients With mHSPC**[1-4]



Primary Endpoint: rPFS (central blinded review)

Secondary Endpoints:

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

1. Clinicaltrials.gov identifier: NCT04736199. Accessed September 9, 2024. https://clinicaltrials.gov/study/NCT04736199. 2. Haresh KP, et al. Poster presented at: The American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. Abstract #TPS200. 3. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68. 4. Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798.

Data cutoff: June 7, 2024

ARANOTE Had Broad Eligibility Criteria to Ensure the Study Population Is Representative of Current Real-World Patients With mHSPC

Key Eligibility Criteria[1,2]

Inclusion Criteria

- Documented metastatic disease confirmed by conventional imaging method - central review[a]
- Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first-generation anti-androgen (≤12 weeks before randomization)
- ECOG performance status 0, 1, or 2
- Adequate bone marrow, liver, and renal function
- Included both de novo & recurrent disease

Exclusion Criteria

- Regional lymph node metastases only (N1, below the aortic bifurcation)
- Baseline superscan
- Prior treatment with:
  - LHRH agonist or antagonist started >12 weeks before study treatment starts except neoadjuvant and/or adjuvant therapy for a duration of ≤24 months and completed ≥12 months prior to randomization
  - Second-generation ARIs or other investigational ARis
  - CYP17 enzyme inhibitors as antineoplastic treatment
  - Chemotherapy (docetaxel or immunotherapy for PC)
  - Radiotherapy in the 2 weeks prior to randomization

[a]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.

1. Haresh KP, et al. Poster presented at: The American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. Abstract #TPS200. 2. Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798.

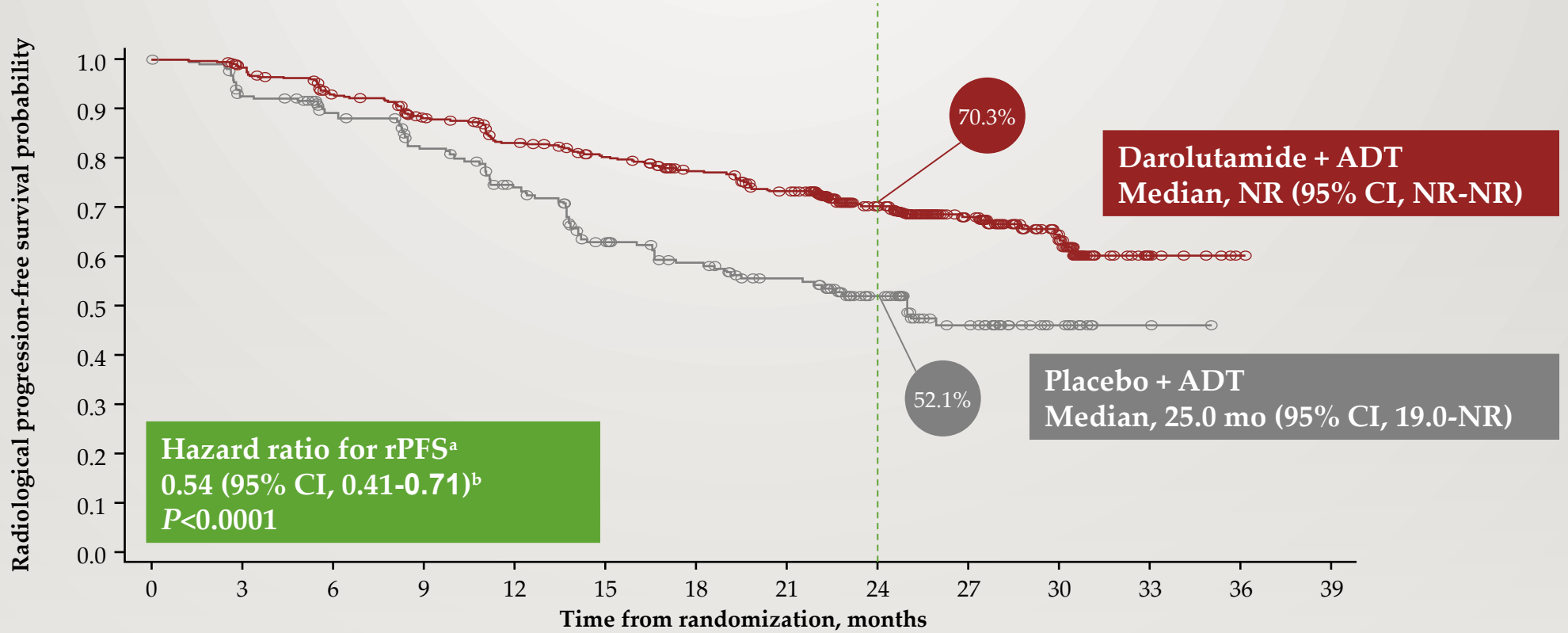
ARANOTE Included a Diverse Range of Patients, With Approximately 70% Having De Novo Disease and 70% Having High-Volume Disease

		Darolutamide + ADT (N=446)	Placebo + ADT (N=223)
Age, median (range), years		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)
EGOG PS, n (%)	0	235 (52.7)	98 (43.9)
	1-2	211 (47.3)	125 (56.1)
Gleason score ≥8 at initial diagnosis, n (%)		311 (69.7)	146 (65.5)
Serum PSA, median (range), ng/mL		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 (%)[a]	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)

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis (Sweeney CJ, et al. *N Engl J Med*. 2015;373:737-746).

Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

Darolutamide + ADT Significantly Reduced the Risk of Radiological Progression or Death by 46%



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

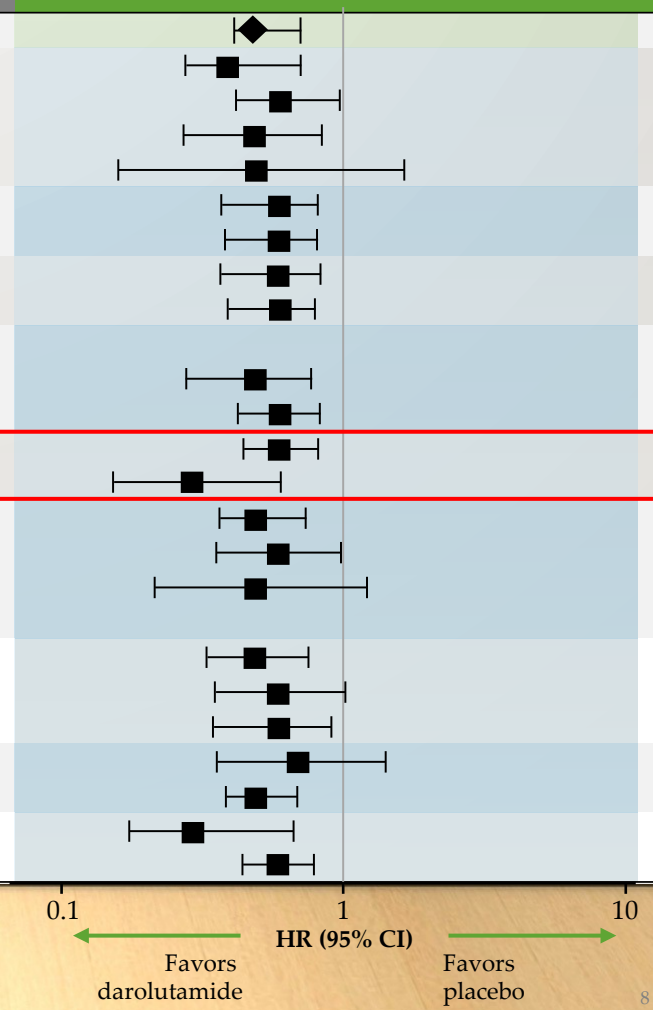
- Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

[a]Primary analysis occurred after 222 events (darolutamide 128; placebo 94). [b]HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).
Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.
For Internal Training Only

Darolutamide Showed a Consistent Benefit Across Subgroups

Subgroup analyses of rPFS

		Darolutamide (n=446)		Placebo (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, years	**<65**	37/118	NR	32/65	14.2	0.44 (0.27-0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41-0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27-0.83)
	≥85	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)

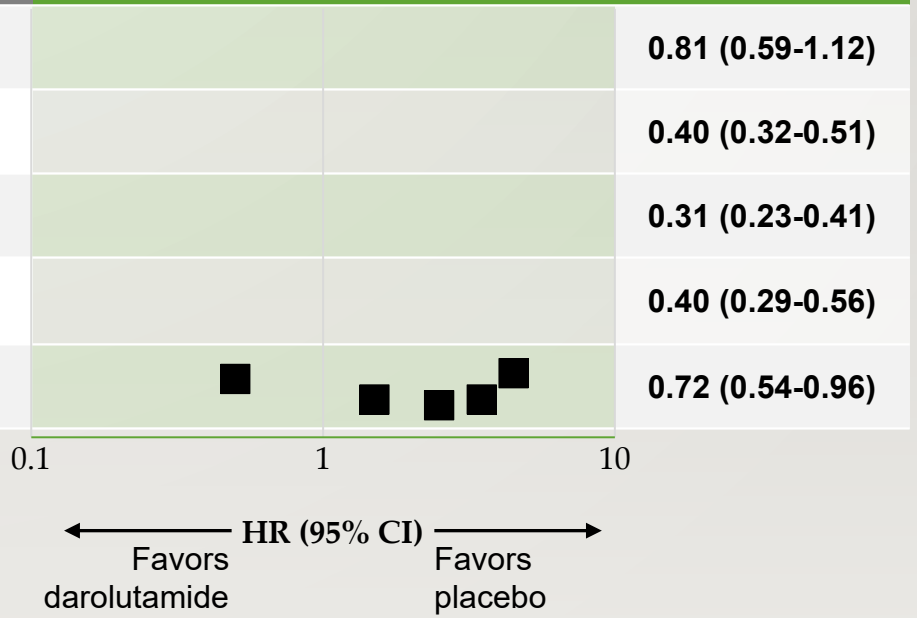


HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.

Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

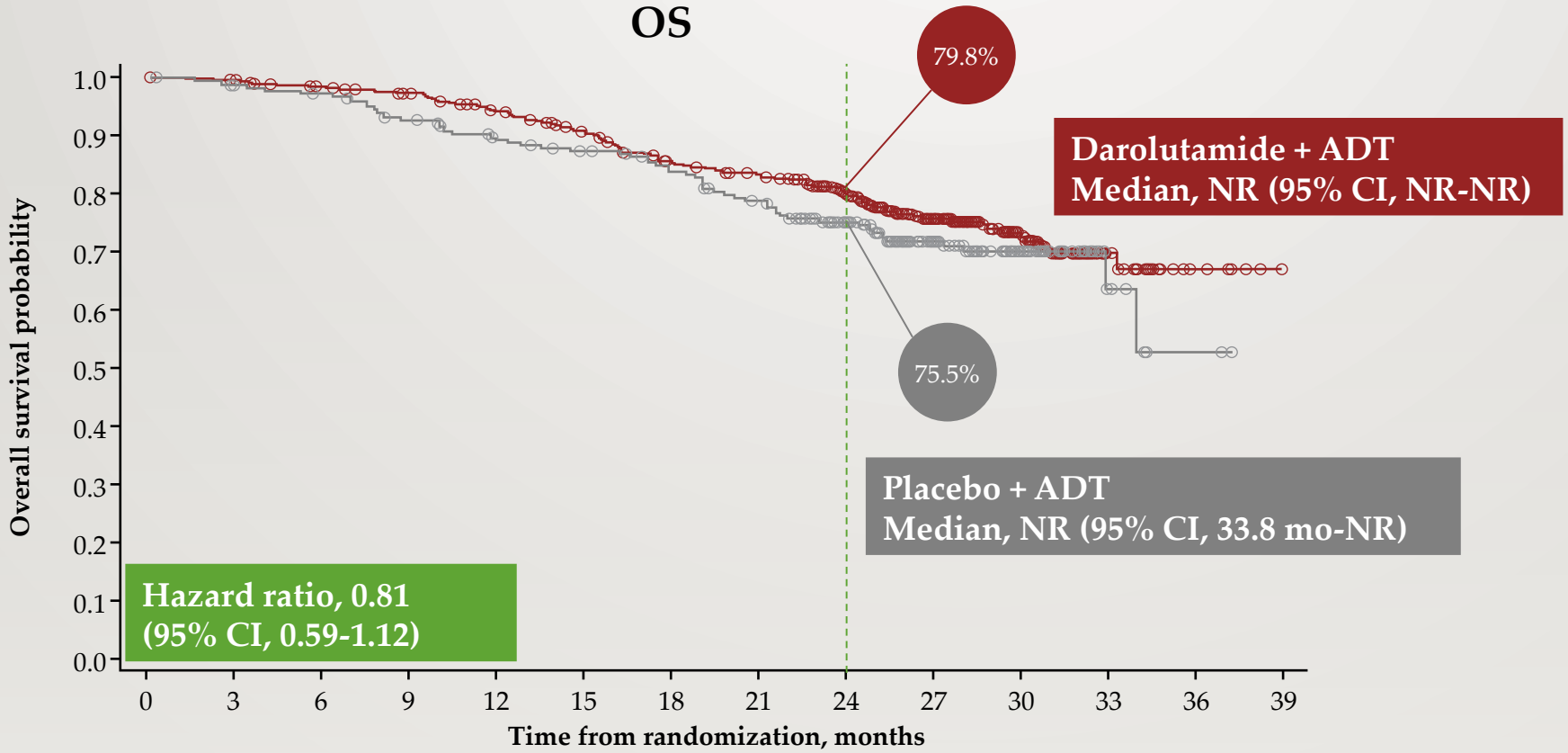
Darolutamide Showed a Benefit Across All Secondary Endpoints

Endpoint	Darolutamide (n=446)		Placebo (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 prostate cancer	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 are immature

Although OS Is Immature, Darolutamide + ADT Reduced the Risk of Death by 19%



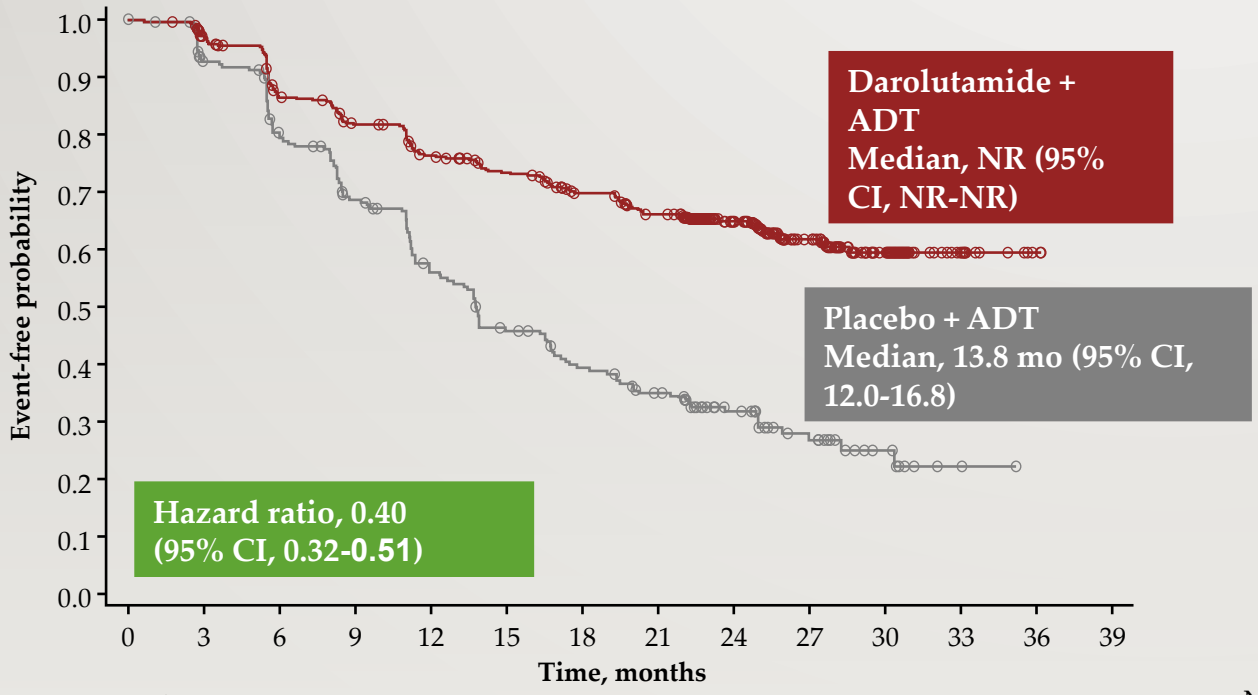
No. of patients at risk

Darolutamide	446	440	429	417	399	374	346	332	269	169	91	26	7	0
Placebo	223	217	213	200	188	180	170	156	127	85	41	8	2	0

Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798.

Darolutamide Delayed Time to CRPC and Time to Pain Progression, Which Are Both **Key Patient-Relevant Endpoints**

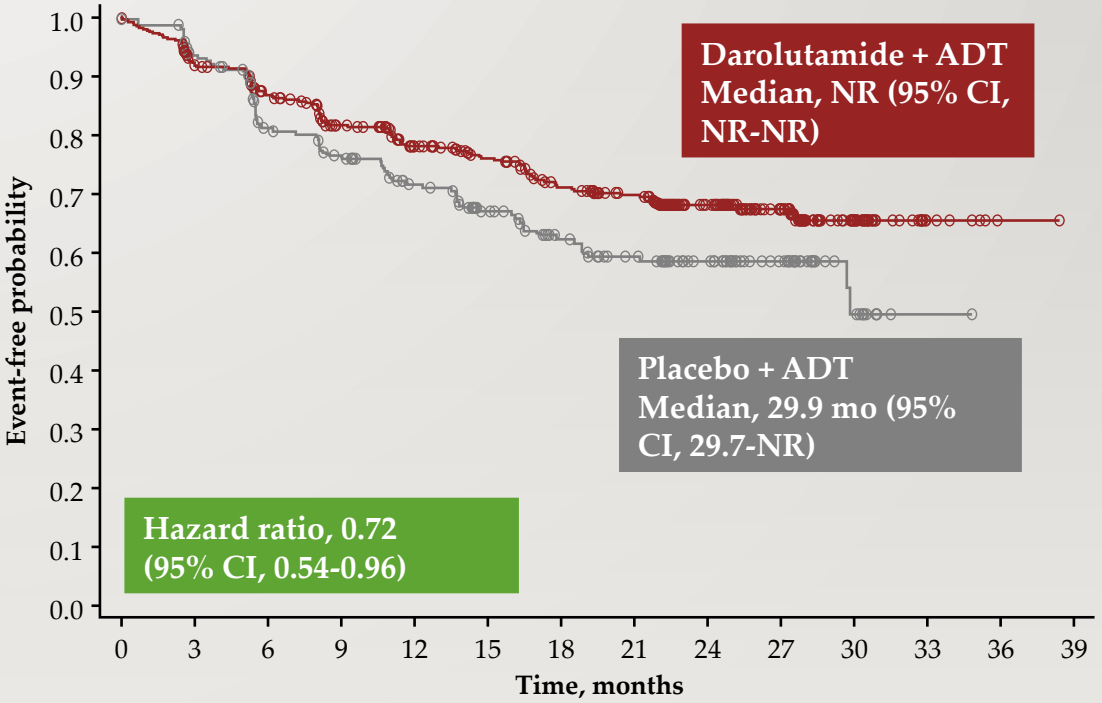
Time to mCRPC[1,2]



No. of patients at risk

Darolutamide	446	417	364	339	312	293	268	245	177	110	51	14	2	0
Placebo	223	197	167	139	110	88	73	61	42	25	10	2	0	0

Time to Pain Progression[2]



No. of patients at risk

Darolutamide	446	385	349	310	278	254	225	209	150	90	36	7	1	0
Placebo	223	195	159	146	127	106	87	74	55	31	11	1	0	0

1. Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798. 2. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

A Greater Proportion of Patients in the Placebo arm (42.5%) Versus NUBEQA + ADT arm (32.5%) Received Subsequent Systemic Life Prolonging Therapy

Subsequent Life-Prolonging Anticancer Therapy[a]

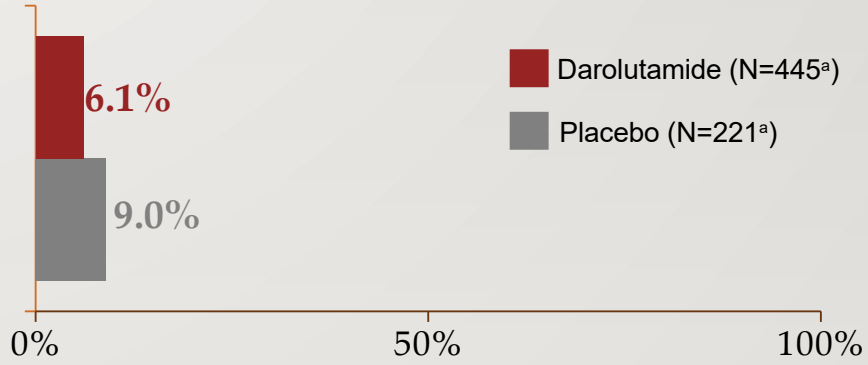
No. (%) of patients[b]	Darolutamide + ADT (N=446)	Placebo + ADT (N=223)
Discontinued study treatment, n (%)	203 (45.5)	160 (71.7)
Received subsequent life-prolonging anticancer therapy,[c] n/n (%)	66/203 (32.5)	68/160 (42.5)
Docetaxel	46/203 (22.7)	46/160 (28.8)
Abiraterone acetate	26/203 (12.8)	21/160 (13.1)
Enzalutamide	6/203 (3.0)	12/160 (7.5)
Apalutamide	3/203 (1.5)	0
Cabazitaxel	2/203 (1.0)	1/160 (0.6)
Radium-223	2/203 (1.0)	0
Olaparib	1/203 (0.5)	0

[a]Subsequent life-prolonging therapies for prostate cancer are defined as abiraterone acetate, apalutamide, enzalutamide, docetaxel, cabazitaxel, radium-223, sipuleucel-T, lutetium-177–PSMA-617, rucaparib, and olaparib.
[b]Patients could receive more than one subsequent life-prolonging anticancer therapy. [c]Four patients who started life-prolonging therapy before study treatment discontinuation are included.
Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798. For Internal Training Only

Similar Rates of TEAEs Across Treatment Arms
Lower Rate of Discontinuation Due to AEs in the Darolutamide Arm

TEAE, no. of patients (%)	Darolutamide + ADT (N=445[a])	Placebo + ADT (N=221[a])
Any AE	405 (91.0)	199 (90.0)
Serious AE	105 (23.6)	52 (23.5)
Grade 3 or 4 AE	137 (30.8)	67 (30.3)
Grade 5 AE	21 (4.7)	12 (5.4)

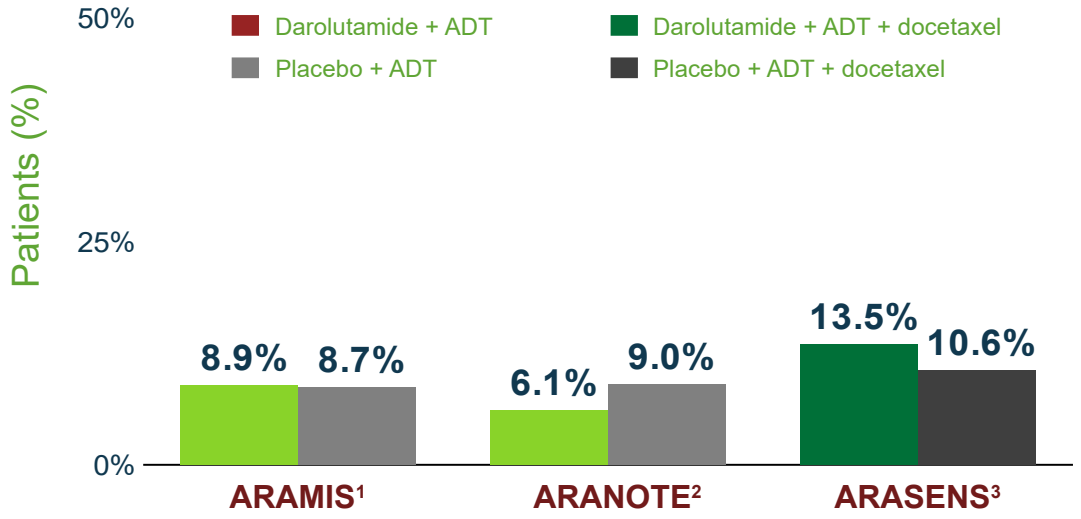
TEAEs Leading to Permanent Discontinuation of Darolutamide/Placebo



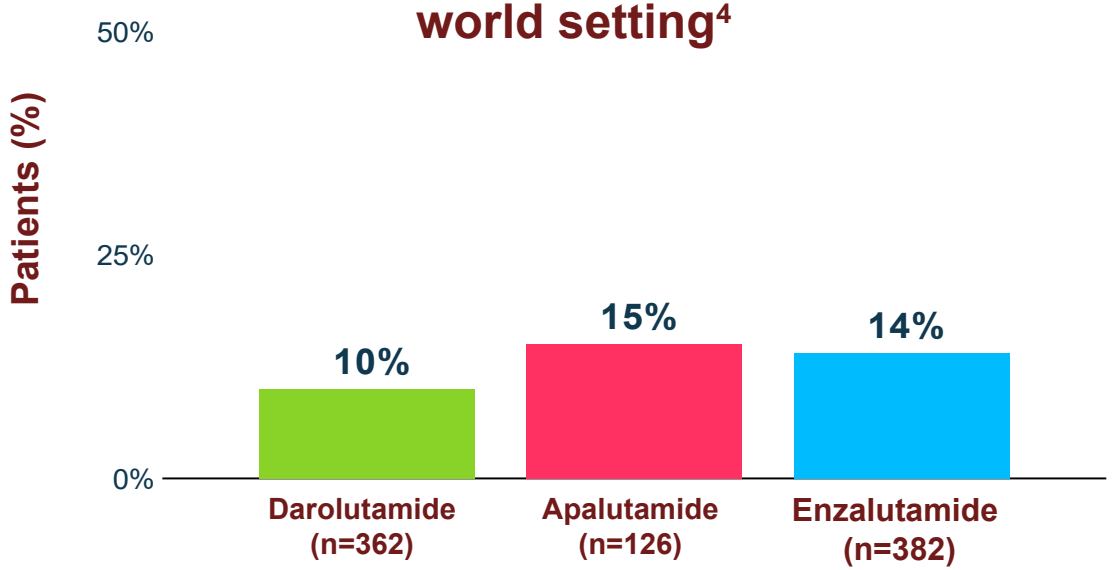
[a]Two patients who were randomized to the placebo group but received darolutamide are analyzed in the darolutamide group for the safety analysis set.

1. Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.01798. 2. Fizazi K, et al. *N Engl J Med*. 2017;377(4):352-360. 3. Fizazi K, et al. *Lancet Oncol*. 2019;20(5):686-700. 4. Armstrong AJ, et al. *J Clin Oncol*. 2019;37(32):2974-2986. 5. Armstrong AJ, et al. Presented at European Society for Medical Oncology, Annual Meeting. September 16-20, 2021. Virtual. Abstract LBA25. 6. Chi KN, et al. *N Engl J Med*. 2019;381(1):13-24. 7. Chi KN, et al. *J Clin Oncol*. 2021;39(20):2294-2303. 8. Smith M, et al. *N Engl J Med*. 2022;386(12):1132-1142. 9. Fizazi K. et al. *Lancet*. 2022;399(10336):1695-1707. 10. Davis ID, et al. *N Engl J Med*. 2019;381:121-131. 11. Sweeney CJ, et al. *Lancet Oncol*. 2023;24:323-334. 12. Sternberg CN, et al. *N Engl J Med*. 2020;382(23):2197-2206. 13. Smith MR, et al. *Eur Urol*. 2021;79:150-158. 14. Fizazi K, et al. *N Engl J Med*. 2020;383(11):1040-1049.

Darolutamide Allows Patients to Stay on Treatment – Discontinuation Rates Due to AEs Are Consistently Low Across Trials



Darolutamide's proven tolerability is supported by low discontinuations due to AEs in the real-world setting[4]



ADT, androgen deprivation therapy; AEs, adverse events; nmCRPC, nonmetastatic castration-resistant prostate cancer; RWE, real-world evidence.

1. Fizazi K, et al. N Engl J Med. 2020;383:1040-1049. 2. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68 . 3. Smith MR, et al. N Engl J Med. 2022;386(12):1132-1142.4. Shore N, et al. Poster presented at: American Urological Association Annual Meeting; April 28-May 1, 2023. Abstract #MP29-13.

Darolutamide Has Low Potential for DDIs With Common Comedications in Prostate Cancer

Potential DDIs with ARis[4]

Common comedications in prostate cancer[1-3]	Example treatment	Darolutamide	Apalutamide	Enzalutamide
Depression	nefazodone		Monitor	Monitor
Cardiovascular	rivaroxaban		Avoid	Consider modifying
Hypertension	verapamil	**No action**	Consider modifying	Consider modifying
Dyslipidemia	rosuvastatin	Consider modifying	Monitor	
Diabetes mellitus	repaglinide	Monitor	Monitor	Monitor
Sexual dysfunction	sildenafil		Monitor	Monitor

None Minor

Moderate Major

Shaded boxes represent potential DDIs

Patients with prostate cancer are typically >65 years of age and often take medications for comorbidities – putting them at increased risk for DDIs

ARi, androgen receptor inhibitor; DDIs, drug-drug interactions.

1. Shore N, et al. Target Oncol. 2019;14:527-539. 2. Fuentes AV, et al. Pharmacy (Basel). 2018;6(2):43. 3. Pirschel C. ONSVoice. Accessed June 10, 2024. https://voice.ons.org/news-and-views/comorbidities-in-cancer-patient-care. 4. Lexi-Interact. Lexicomp app. UpToDate Inc. Accessed July 11, 2024.

- Out of all patients included in this trial:
  - 70% of patients had Gleasons score ≥8
  - 71% had de novo disease,
  - 71% had high-volume disease, and
  - 20% had visceral metastasis.
- These patients met the criteria for a trial testing triplet therapy, but some were randomly assigned to receive ADT alone (plus placebo) as the control treatment in the ARANOTE trial.
- The authors attempt to justify this choice of control arm by arguing that treatment intensification is underutilized and 30% of patients in the real world with metastatic HSPC receive ADT alone.

To conclude..
Darolutamide + ADT in mHSPC

Established Efficacy

- Darolutamide + ADT **significantly reduced the risk of radiological progression or death by 46%** compared to placebo + ADT in patients with mHSPC
  - This benefit was consistent across all prespecified subgroups
- Darolutamide was associated with a **19% reduction in the risk of death,** although **OS was immature** at this primary analysis
- The data are supported by a **benefit across all other secondary endpoints**

Differentiated Tolerability

- Treatment-Emergent Adverse Events (TEAEs) were low and similar to the placebo group
- Discontinuations due to adverse events, a measure of treatment tolerability, was lower in patients receiving darolutamide versus placebo

Thank You