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STUDY REVIEW

Prostate-specific antigen response with darolutamide in metastatic hormone-sensitive prostate cancer and its impact on treatment outcomes

Making Education Easy 2026

Independent expert commentary provided by Professor Anthony Joshua
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Abbreviations used in this review:

ADT = androgen deprivation therapy;
nmCRPC = nonmetastatic castration-resistant prostate cancer;
mCRPC = metastatic castration-resistant prostate cancer;
mHSPC = metastatic hormone-sensitive prostate cancer;
PSA = prostate-specific antigen.

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This review summarises an ARASENS clinical trial data sub-analysis by Saad et al.[1,2] as well as a *post hoc* analysis by Morgans et al.[3] The ARASENS trial originally investigated the effect of the addition of darolutamide to standard-of-care androgen deprivation therapy (ADT) and docetaxel establishing the triplet as a new standard of care for men with metastatic hormone-sensitive prostate cancer (mHSPC). These sub-analyses provide insights into the associations between prostate-specific antigen (PSA) dynamics and patient outcomes in certain subgroups. Darolutamide-treated patients were more likely to have long-lasting undetectable PSA levels compared with the placebo group, and these PSA responses were associated with better patient outcomes.[1,2] Furthermore, lower baseline PSA levels were linked to better patient outcomes in the darolutamide group, and darolutamide-treated patients had better outcomes than placebo-treated patients regardless of baseline PSA levels.[3] Adverse reactions to darolutamide treatment were similar to those of placebo treatment regardless of PSA response[1,2] or baseline PSA level[3]. Together, these findings will help clinicians to improve patient outcomes in mHSPC. The data were presented in *European Urology*,[1] *Future Oncology*,[2] and at the 40th Annual European Association of Urology Congress, held in March 2025 in Madrid, Spain.[3]
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Background

Darolutamide is a potent androgen receptor inhibitor[4] that, in combination with ADT, can decrease the risk of death and increase metastasis-free survival in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).[5,6] In the phase 3 ARASENS trial, researchers investigated the efficacy and safety of darolutamide, in combination with ADT and docetaxel, to treat patients with metastatic hormone sensitive prostate cancer (mHSPC). In the ARASENS trial 1,306 patients with mHSPC were randomised 1:1 with ADT and docetaxel combined with either darolutamide (the darolutamide group; n=651) or placebo (the placebo group; n=655).[7]

In this phase 3 trial, darolutamide significantly reduced the risk of death by 32.5% compared with placebo in all patients (hazard ratio [HR] 0.68; 95% confidence interval [CI], 0.57 to 0.80; P<0.001),[7] including those with high-volume disease (classified as patients with visceral metastasis or four or more tumours in the bones with ≥1 beyond vertebral bodies and pelvis) and low-volume disease.[8] Darolutamide also improved clinically relevant secondary endpoints compared with placebo.[7,8]

Serum PSA were measured every 3 months in the ARASENS trial and their evaluation such as PSA response rates was included in the prespecified exploratory analyses,[1] the data on PSA stratification and response presented here were not included in the preliminary study reports.[7,8] By exploring the associations among baseline PSA levels, PSA responses, and patient outcomes in the ARASENS cohort, these two new studies contribute valuable insights to inform clinical decision-making in mHSPC management, potentially leading to improved treatment choices and patient outcomes.[1–3]

Methods

The ARASENS study was an international, randomised, double-blind, placebo-controlled trial of 1,306 patients with mHSPC.[7] Patients were eligible if they were aged ≥18 years old and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1; histologically or cytologically confirmed prostate cancer; and metastases detected on bone scanning, contrast-enhanced computed tomography, or magnetic resonance imaging.[7] Patients were excluded if they had received ADT >12 weeks before randomisation; second-generation androgen-receptor pathway inhibitors, chemotherapy, or immunotherapy before randomisation; or radiotherapy ≤2 weeks before randomisation.[7] The following two analyses[1–3] were performed using the ARASENS trial data.

Associations between PSA levels and patient outcomes[1,2]

In the first analysis, researchers aimed to identify the association between the PSA responses of patients and the following treatment outcomes: 1) overall survival (the time from randomisation to death); 2) time to metastatic castration-resistant prostate cancer (mCRPC; the time from randomisation to occurrence of the following events, whichever occurred first: PSA progression with serum testosterone at a castrate level [<0.5 ng/mL] or radiological progression); and 3) time to PSA progression (the time from randomisation to the date of first PSA progression defined as a relative PSA increase of ≥25% above the PSA nadir and an absolute increase of ≥2 ng/ml).

Associations between baseline PSA and patient outcomes[3]

In the second analysis presented at EAU 2025, researchers examined the association between baseline PSA levels (bPSA was measured after the start of ADT for ~90% of patients; median time from start of ADT to bPSA measurement was approximately 30 days) and the following clinical outcomes: 1) achievement of undetectable PSA (defined as <0.2 ng/mL) at key predetermined timepoints; 2) time to PSA progression; and 3) time to mCRPC. In this analysis, patients were classified into three groups based on the baseline PSA quartile distribution (i.e., low quartile [<4.80 ng/ml], middle quartile [4.80–27.55ng/ml], and the highest two quartiles combined [≥27.55ng/ml).

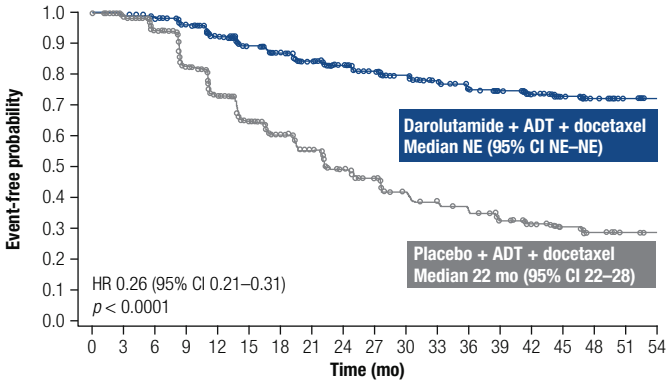
Expert comment

Further prognostic biomarkers in mHSPC are sorely needed to guide discussions with patients about potential morbidity and mortality. These two sub-analyses of the original ARASENS study use PSA values and dynamics, both well validated and easily measured, and add to existing risk factors used in clinical practice for a variety of clinically meaningful endpoints.

Results

Associations between PSA levels and patient outcomes[1,2]

More than twice as many patients in the darolutamide group had undetectable PSA (<0.2 ng/mL) at any time in the trial compared with the placebo group (67% in the darolutamide group vs 29% in the placebo group). Similar results were observed in both the high-volume (62% vs 26%, respectively) and low-volume (84% vs 38%, respectively) patient subgroups. Patients in the darolutamide group also had a longer time to PSA progression compared with the placebo group (**Figure 1**). By the end of the trial, only 21% of patients in the darolutamide group had reached PSA progression compared with 47% in the placebo group. In the high- and low-volume patient subgroups, 25% and 6.5% of patients in the darolutamide group had reached PSA progression by the end of the trial (vs 49% and 42% in the placebo group), respectively.



Number of patients at risk

Darolutamide group	651	608	585	552	513	477	449	416	393	373	358	339	319	295	214	139	55	17	5
Placebo group	654	605	542	432	354	293	253	220	186	167	144	132	114	104	77	38	14	4	1

Figure 1. Time to prostate-specific antigen (PSA) progression in the overall study population (n=1305). Adapted from Saad et al. (2025).[1]
ADT = androgen deprivation therapy; **CI** = confidence interval; **HR** = hazard ratio; **NE** = not evaluable.

Patients in the darolutamide group who had undetectable PSA at 6 months after the trial began had a 51% lower risk of death (HR 0.49, 95% CI 0.36–0.65), a 50% lower risk of mCRPC (HR 0.50, 95% CI 0.37–0.68), and a 72% lower risk of increased PSA levels (HR 0.28, 95% CI 0.18–0.42) (**Figure 2**). Similar results were seen in the high- and low-volume subgroups (**Figure 2**) and with undetectable PSA levels at 9 months after the trial began (patients in the darolutamide group with undetectable PSA at 9 months had a 62% lower risk of death, a 58% lower risk of mCRPC, and a 77% lower risk of increased PSA levels). Furthermore, in patients who had undetectable PSA at 6 months after the trial began, the overall survival rates were 80% and 72% (vs 56% and 52% in the detectable PSA group) at 3 and 4 years later.

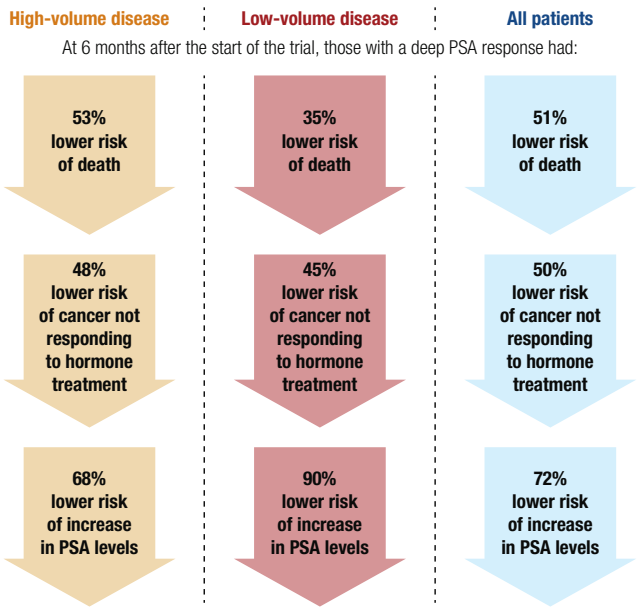


Figure 2. Risk of death, cancer not responding to hormone treatment, and increased PSA levels in patients who achieved undetectable PSA at any time during the study. Adapted from Saad et al. (2025).[2]
PSA = prostate-specific antigen.
Note: A deep PSA response refers to the achievement of undetectable PSA (<0.2 ng/mL) at any time during the study. High-volume disease refers to patients with visceral metastasis or four or more tumours in the bones. Low-volume disease refers to patients with no visceral metastasis and less than four tumours in the bones.

The demographic and baseline characteristics of patients who achieved undetectable PSA levels were similar to those of patients who did not achieve undetectable PSA levels. Adverse events were also analysed, and similar percentages of patients experienced adverse events in the darolutamide and placebo groups regardless of whether they achieved undetectable PSA levels during the trial (**Figure 3**). In patients who achieved undetectable PSA levels, similar frequencies of patients in the darolutamide and placebo groups discontinued treatment because of an adverse event (**Figure 4**).

	Patients who achieved deep PSA response		Patients who did not achieve a deep PSA response	
Percentage of patients who:	Darolutamide out of 439 patients	Placebo out of 186 patients	Darolutamide out of 213 patients	Placebo out of 464 patients
had an adverse event	99.7% (438)	100% (186)	99% (211)	99% (457)
had a serious adverse event	43% (190)	36% (66)	48% (102)	45% (209)
stopped receiving daralutamide or placebo because of an adverse event	7.7% (34)	7.5% (14)	25% (54)	12% (55)

Figure 3. Adverse events in response to darolutamide and placebo treatments in patients who did and did not achieve undetectable PSA at any time during the study. Adapted from Saad et al. (2025).[2]
PSA = prostate-specific antigen.
Note: Deep PSA response refers to the achievement of undetectable PSA (<0.2 ng/mL) at any time during the study.

Adverse event	Patients who achieved deep PSA response: Darolutamide out of 439 patients	Patients who achieved deep PSA response: Placebo out of 186 patients	Patients who did not achieve a deep PSA response: Darolutamide out of 213 patients	Patients who did not achieve a deep PSA response: Placebo out of 464 patients
Had a grade 3 or 4 adverse event	**67% (295)**	**64% (119)**	**64% (136)**	**63% (294)**
Neutropenia	36% (159)	37% (68)	29% (61)	33% (154)
Febrile neutropenia	9.1% (40)	8.6% (16)	5.2% (11)	6.9% (32)
Hypertension	7.7% (34)	3.8% (7)	3.8% (8)	3% (14)
Anemia	4.6% (20)	2.7% (5)	5.2% (11)	6% (28)
Hyperglycaemia	3.2% (14)	5.9% (11)	1.9% (4)	2.8% (13)
Pneumonia	3.2% (14)	1.1% (2)	3.3% (7)	3.9% (18)
Increased levels of alanine aminotransferase (ALT), a sign of liver inflammation	2.1% (9)	1.6% (3)	4.2% (9)	1.7% (8)

Figure 4. Grade 3 and 4 adverse events reported by >2% of all patients in response to darolutamide and placebo treatments in patients who did and did not achieve undetectable PSA at any time during the study. Adapted from Saad et al. (2025).[2]
PSA = prostate-specific antigen.
Note: Deep PSA response refers to the achievement of undetectable PSA (<0.2 ng/mL) at any time during the study.

Associations between baseline PSA and patient outcomes[3]

In this *post hoc* analysis, patients were classified using the baseline PSA quartile distribution (**Table 1**). Across all baseline PSA groups, darolutamide treatment was consistently associated with higher rates of undetectable PSA levels (**Figure 5**). Furthermore, lower baseline PSA levels were associated with higher rates of achieving undetectable PSA at any time (**Figure 4**). In addition, darolutamide-treated patients with low baseline PSA levels had a longer time to both PSA progression and mCRPC development compared with those with high baseline PSA levels (**Table 2**).

Table 1. Patient classification by baseline PSA levels.[3]

Low: Q1 <4.80 ng/mL	Middle: Q2 4.80–27.55 ng/mL	High: Q3 & Q4 ≥27.55 ng/mL
Darolutamide n=156 Placebo n=168	Darolutamide n=159 Placebo n=169	Darolutamide n=336 Placebo n=316

Q = quartile.

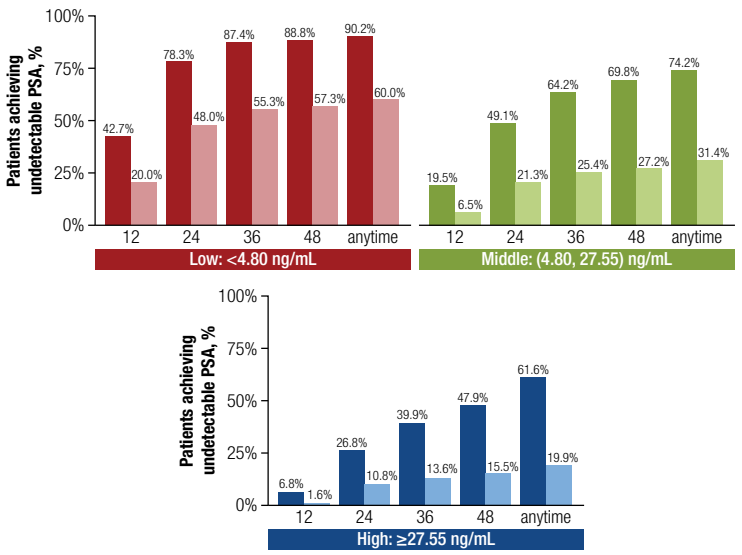


Figure 5. Patients with low, middle, and high baseline PSA levels in the darolutamide and placebo groups who achieved undetectable PSA levels during the study. Adapted from Morgans et al. (2025).[3]
PSA = prostate-specific antigen.
Note: Solid colours represent the darolutamide group; shaded colours represent the placebo group.

Table 2. Associations between baseline PSA levels and time to PSA progression or mCRPC. Adapted from Morgans et al. (2025).[3]

		HR (95% CI)	
	Baseline PSA comparison	Darolutamide	Placebo
Time to PSA progression	Low vs high (<4.80 ng/mL vs ≥27.55 ng/mL)	0.41 (0.25–0.68)	0.50 (0.37–0.68)
	Middle vs high (4.80–27.55 ng/mL vs ≥27.55 ng/mL)	0.66 (0.43–1.01)	0.97 (0.75–1.26)
Time to mCRPC	Low vs high (<4.80 ng/mL vs ≥27.55 ng/mL)	0.67 (0.47–0.94)	0.63 (0.49–0.82)
	Middle vs high (4.80–27.55 ng/mL vs ≥27.55 ng/mL)	0.90 (0.66–1.24)	1.01 (0.80–1.28)

CI = confidence interval; **mCRPC** = metastatic castration-resistance prostate cancer; **HR** = hazard ratio; **PSA** = prostate-specific antigen.

In this *post hoc* analysis, the safety profile of darolutamide was similar to that of previous reports and was not associated with baseline PSA levels (**Table 3**).

Table 3. Safety profile of darolutamide treatment stratified by baseline PSA levels. Adapted from Morgans et al. (2025).[3]

	Low baseline PSA (<4.80 ng/mL)		Middle baseline PSA (4.80–27.55 ng/mL)		High baseline PSA (≥27.55 ng/mL)		All patients	
	DARO n=156	Placebo n=166	DARO n=159	Placebo n=168	DARO n=336	Placebo n=316	DARO N=651	Placebo N=650
Any TEAE	155, 99.4%	166, 100%	158, 99.4%	166, 98.8%	335, 99.7%	311, 98.4%	648, 99.5%	643, 98.9%
Grade 3/4 TEAE	100, 64.1%	91, 54.8%	105, 66.0%	119, 70.8%	226, 67.3%	203, 64.2%	431, 66.2%	413, 63.5%
Any serious TEAE	66, 42.3%	65, 39.2%	81, 50.9%	64, 38.1%	145, 43.2%	146, 46.2%	292, 44.9%	275, 42.3%
Any TEAE leading to treatment discont.	19, 12.2%	18, 10.8%	25, 15.7%	14, 8.3%	44, 13.1%	37, 11.7%	88, 13.5%	69, 10.6%

DARO = darolutamide; **discont.** = discontinuation; **PSA** = prostate-specific antigen; **TEAE** = treatment-emergent adverse events.
Note: Data are displayed as n, %.

Expert comment

Although these analyses are *post hoc*, they replicate similar analyses carried out in pivotal trials such as TITAN and LATITUDE. These PSA-based analyses also serve as benchmarks for several ongoing clinical trials examining the utility of de-escalation trials in men who achieve a robust PSA response to the initial treatment, further advancing the paradigm of personalised care in prostate cancer.

Take-home messages

- Patients with mHSPC who received a combination of ADT, docetaxel, and darolutamide were more than twice as likely to have undetectable PSA levels (<0.2 ng/mL) at any time during the ARASENS study compared with those who received combined ADT, docetaxel, and placebo.
- Patients who had undetectable PSA levels at any time during the ARASENS study had a lower risk of death, a lower risk of developing mCRPC, and a longer time to PSA progression.
- Patients who had undetectable PSA at 24 weeks had better overall survival rates up to 4 years later.
- Regardless of baseline PSA levels, more patients who received darolutamide achieved undetectable PSA at any time.
- Compared with patients who had high baseline PSA levels, those with lower baseline PSA levels who received darolutamide had higher rates of achieving undetectable PSA at any time, had a longer time to PSA progression, and took longer to develop mCRPC.
- Adverse reactions to darolutamide were not associated with the achievement of undetectable PSA levels or baseline PSA levels.
- These insights can aid in decision-making when selecting treatments and monitoring responses in patients with mHSPC, and will help to improve patient outcomes.

Expert's concluding remarks

Although secondary analyses of published trials have inherent limitations, the results of these analyses are aligned with existing literature on darolutamide and other agents and thus confirm the utility of inter- and intra-patient PSA dynamics as contributing to prognostication, and provide important benchmarks. The equivalency in safety outcomes is also reassuring for treating doctors and nurses. To date, however, there are no clinical trials that have directly tested the addition or not of docetaxel to an ADT + ARSI backbone, which is currently a difficult clinical issue to discuss with patients and where further research is needed. Generally, the addition of docetaxel is considered in younger men with de novo high-risk disease, but is a case-by-case consideration.

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