Abstract Session 31 - Systemic treatment of metastatic prostate cancer
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Impact of baseline prostate-specific antigen (PSA) on clinical outcomes in patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with darolutamide triplet therapy in ARASENS

Morgans A.[1], Smith M.[2], Tombal B.[3], Hussain M.[4], Sternberg C.N.[5], Chen S.[6], Wang A.[7], Verholen F.[8], Saad F.[9]

[1]Dana-Farber Cancer Institute, Survivorship Program, Boston, United States of America, [2]Massachusetts General Hospital, Genitourinary Malignancies Program, Boston, United States of America, [3]Université Catholique de Louvain (UCL), Cliniques Universitaires Saint-Luc, Dept. of Surgery and Dept. of Urology, Brussels, Belgium, [4]Northwestern University Feinberg School of Medicine, Dept. of Medicine (hematology and oncology), Chicago, United States of America, [5]Weill Cornell Medicine, Dept. of Medicine-Hematology/Oncology, New York, United States of America, [6]Bayer Healthcare Pharmaceuticals, Inc., Dept. of Access Marketing & Strategy, Whippany, United States of America, [7]Analysis Group Inc., Dept. of Health Economics and Outcomes Research, New York, United States of America, [8]Bayer Healthcare Pharmaceuticals Inc., Dept. of Gu Franchise, Basel, Switzerland, [9]University of Montreal, Dept. of Surgery, Montréal, Canada

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Dr. Alicia Morgans

Disclosures:

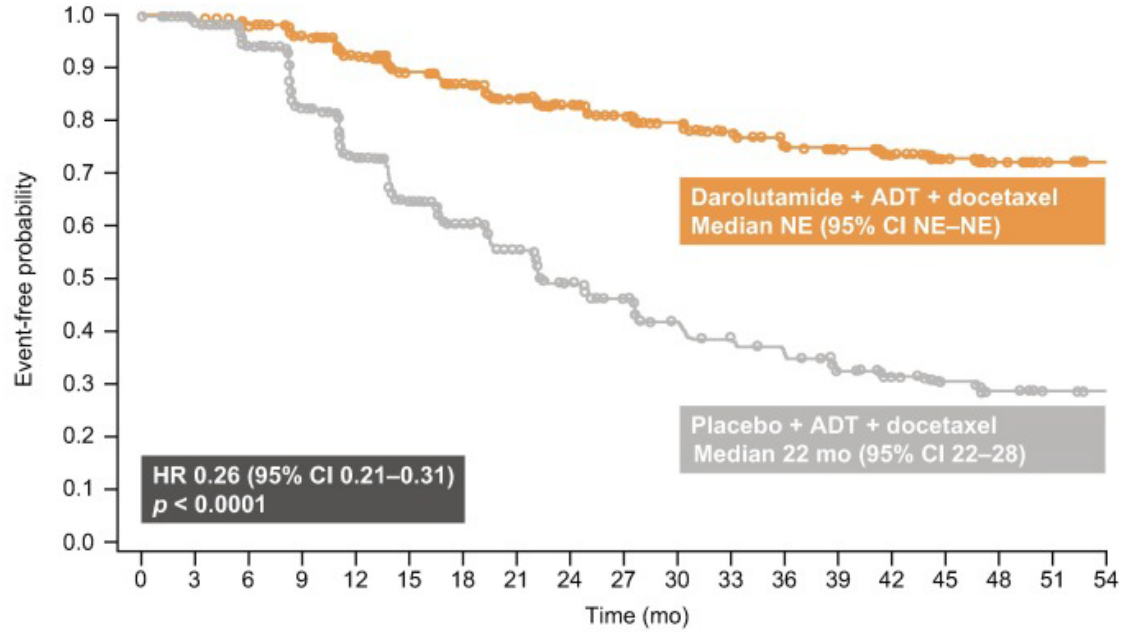
I have the following potential conflicts of interest to report

- Honoraria: AstraZeneca, Astellas, Bayer, Janssen, Sanofi, Genentech, and Seattle Genetics
- Research funding: Bayer, Genentech, and Seattle Genetics

Introduction

- In the phase 3 ARASENS study (NCT02799602), **ADT+ docetaxel + darolutamide (DARO triplet)** significantly reduced the risk of death by 32.5% (HR 0.68; 95% CI 0.57-0.80; *P*<0.001) vs **ADT + docetaxel + placebo (Control)** in patients with mHSPC[1]
- DARO triplet achieved deep and durable PSA responses, with **67% of patients reaching undetectable PSA** (<0.20 ng/mL) at any time compared to 29% in the Control group, along with a **significantly longer time to PSA progression**[2]

Time to PSA progression in the ARASENS study: DARO triplet vs Control



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

1. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022;386(12):1132-1142. doi:10.1056/NEJMoa2119115
2. Saad F, Hussain MHA, Tombal B, et al. Deep and Durable Prostate-specific Antigen Response to Darolutamide with Androgen Deprivation Therapy and Docetaxel, and Association with Clinical Outcomes for Patients with High- or Low-volume Metastatic Hormone-sensitive Prostate Cancer: Analyses of the Randomized Phase 3 ARASENS Study. Eur Urol. 2024;86(4):329-339. doi:10.1016/j.eururo.2024.03.036

Objectives

- This post-hoc analysis examined the **association between baseline PSA (bPSA) levels and key clinical outcomes** in patients treated with DARO triplet vs Control:
  - Achievement of undetectable PSA (<0.20 ng/mL) at predefined landmark time points
  - Time to PSA progression
  - Time to castration-resistant prostate cancer (CRPC)

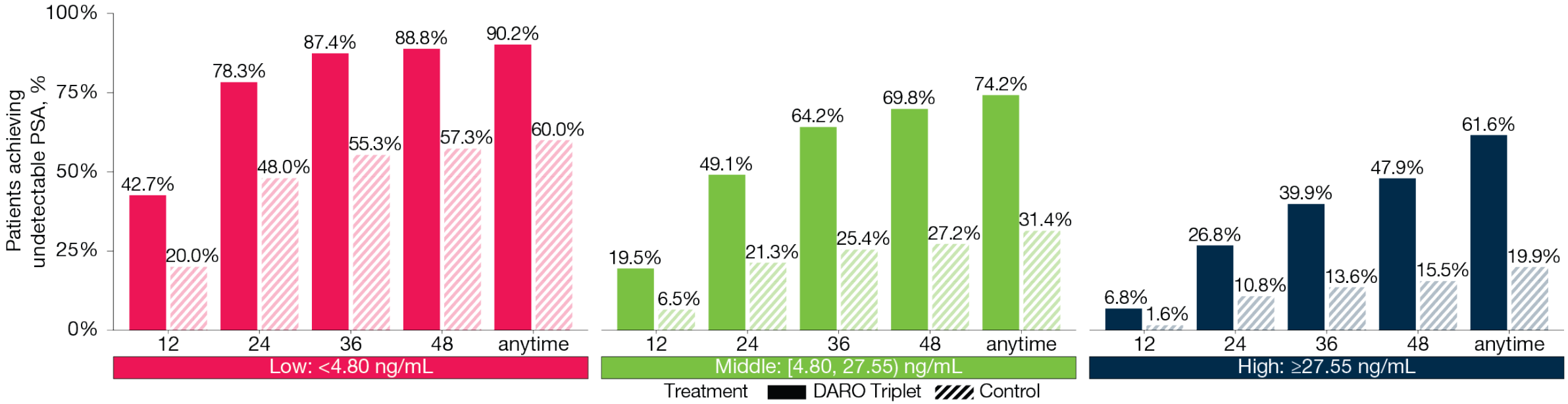
Patients were categorized into three groups based on the bPSA quartile distribution of the ARASENS population*:

Q1: 4.80 ng/mL | **Median: 27.55 ng/mL**

Low: Q1	Middle: Q2	High: Q3 & Q4
<4.80 ng/mL DARO triplet n=156 Control n=168	**[4.80, 27.55) ng/mL** DARO triplet n=159 Control n=169	**≥27.55 ng/mL** DARO triplet n=336 Control n=316

*bPSA was measured after the start of ADT for ~90% of patients. Median time from start of ADT to bPSA measurement was 31.0 days in the DARO triplet arm and 34.0 days in Control arm.

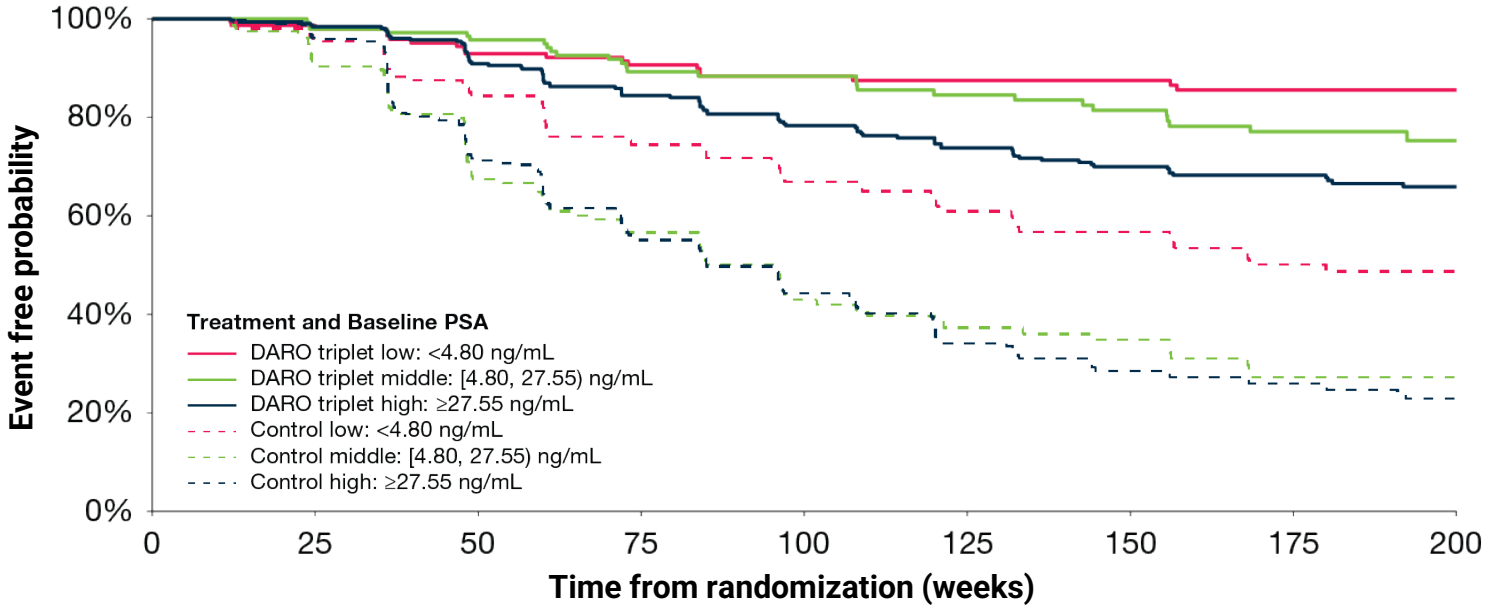
Regardless of bPSA, more patients on DARO triplet vs placebo achieved **undetectable PSA (<0.20 ng/mL) at any time**



- Lower bPSA was associated with higher rates of achieving undetectable PSA (<0.2 ng/mL) at any time
- Treatment with DARO triplet (vs. Control) led to improvement in deep PSA response consistently across all bPSA groups

Abbreviations: bPSA, baseline PSA; DARO, darolutamide; PSA, prostate-specific antigen.

Patients on DARO triplet with **low bPSA (<4.80 ng/mL) had longer time to PSA progression** vs patients with high bPSA (≥27.55 ng/mL)

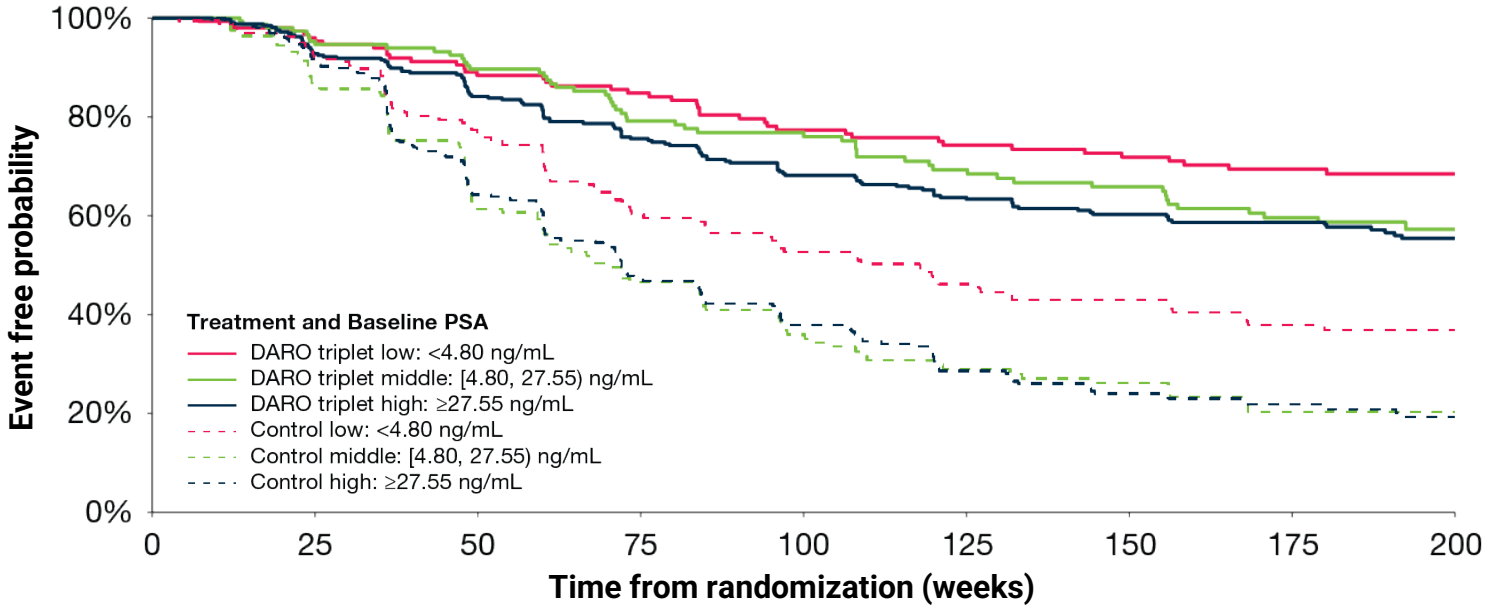


Patients at risk									
DARO triplet									
Low <4.80 ng/mL	156	142	126	117	100	94	90	82	36
Middle [4.80, 27.55) ng/mL	159	139	125	103	94	80	75	66	33
High ≥27.55 ng/mL	336	292	247	219	189	169	153	140	61
Control									
Low <4.80 ng/mL	168	140	105	79	67	57	52	42	13
Middle [4.80, 27.55) ng/mL	169	135	88	61	43	31	28	20	9
High ≥27.55 ng/mL	316	264	158	103	79	57	46	40	16

bPSA Comparison	HR (95% CI) DARO triplet	HR (95% CI) Control
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)

Abbreviations: bPSA, baseline prostate-specific antigen; CI, confidence interval; DARO, darolutamide; HR, hazard ratio; PSA, prostate-specific antigen.

Patients on DARO triplet with **low bPSA (<4.80 ng/mL) had longer time to CRPC** vs patients with high bPSA (≥27.55 ng/mL)



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Patients at risk

	HR (95% CI)	
bPSA Comparison	**DARO triplet**	**Control**
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)

Abbreviations: bPSA, baseline prostate-specific antigen; CI, confidence interval; DARO, darolutamide; HR, hazard ratio; PSA, prostate-specific antigen.

The safety profile of DARO triplet was consistent with previous data and independent of baseline PSA

bPSA	Low: <4.80 ng/mL		Middle: [4.80, 27.55) ng/mL		High: ≥27.55 ng/mL		Overall	
TEAE	**DARO triplet (N=156)**	**Control (N=166)**	**DARO triplet (N=159)**	**Control (N=168)**	**DARO triplet (N=336)**	**Control (N=316)**	**DARO triplet (N=651)**	**Control (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 discontinuation	19 (12.2%)	18 (10.8%)	25 (15.7%)	14 (8.3%)	44 (13.1%)	37 (11.7%)	88 (13.5%)	69 (10.6%)

Abbreviations: bPSA, baseline prostate-specific antigen; DARO, darolutamide; TEAE, treatment-emergent adverse events.

Conclusions

- Lower bPSA was associated with
  - ✓ Higher rates of achieving undetectable PSA (<0.2 ng/mL) at any time
  - ✓ Longer time to PSA progression
  - ✓ Longer time to CRPC progression.
- Treatment with DARO triplet was consistently associated with
  - ✓ **Higher rates of undetectable PSA** (<0.2 ng/mL) over time
  - ✓ **Longer time to PSA progression** vs Control
  - ✓ **Longer time to CRPC progression** vs Control

  with patients benefiting regardless of bPSA levels.

This analysis shows the **efficacy benefit and importance of adding DARO** to ADT and docetaxel in appropriate patients **across a wide range of bPSA,** including those with low bPSA.

Acknowledgments

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

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Appendix

Baseline Demographic and Clinical Characteristics by bPSA and Treatment (Table 1/3)

bPSA	Low: <4.80 ng/mL		Middle: [4.80, 27.55) ng/mL		High: ≥27.55 ng/mL	
Characteristic	**DARO triplet (N=156)**	**Control (N=168)**	**DARO triplet (N=159)**	**Control (N=169)**	**DARO triplet (N=336)**	**Control (N=316)**
Median age (range) - yr	68.0 (41.0, 86.0)	67.0 (42.0, 82.0)	67.0 (44.0, 85.0)	68.0 (47.0, 82.0)	67.0 (41.0, 89.0)	67.0 (44.0, 86.0)
ECOG performance-status score - no. (%)						
0	120 (76.9%)	119 (70.8%)	118 (74.2%)	128 (75.7%)	228 (67.9%)	214 (67.7%)
1	36 (23.1%)	48 (28.6%)	41 (25.8%)	40 (23.7%)	108 (32.1%)	102 (32.3%)
Data missing	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Race - no. (%)						
White	100 (64.1%)	93 (55.4%)	85 (53.5%)	101 (59.8%)	160 (47.6%)	138 (43.7%)
Asian	37 (23.7%)	53 (31.5%)	54 (34.0%)	50 (29.6%)	139 (41.4%)	142 (44.9%)
Black or African American	5 (3.2%)	5 (3.0%)	7 (4.4%)	8 (4.7%)	14 (4.2%)	15 (4.7%)
Other	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (1.8%)	2 (0.6%)
Not reported	13 (8.3%)	17 (10.1%)	13 (8.2%)	10 (5.9%)	17 (5.1%)	19 (6.0%)
Data missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Region - no. (%)						
North America	43 (27.6%)	48 (28.6%)	27 (17.0%)	31 (18.3%)	55 (16.4%)	40 (12.7%)
Asia-Pacific	38 (24.4%)	52 (31.0%)	54 (34.0%)	49 (29.0%)	137 (40.8%)	143 (45.3%)
Rest of the world	75 (48.1%)	68 (40.5%)	78 (49.1%)	89 (52.7%)	144 (42.9%)	133 (42.1%)
Data missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: bPSA: baseline prostate-specific antigen; DARO, darolutamide; ECOG, Eastern Cooperative Oncology Group; no., number; Control, placebo; yr, year.

Baseline Demographic and Clinical Characteristics by bPSA and Treatment (Table 2/3)

bPSA	Low: <4.80 ng/mL		Middle: [4.80, 27.55) ng/mL		High: ≥27.55 ng/mL	
Characteristic	**DARO triplet (N=156)**	**Control (N=168)**	**DARO triplet (N=159)**	**Control (N=169)**	**DARO triplet (N=336)**	**Control (N=316)**
Gleason score at initial diagnosis - no. (%) <8 ≥8 Data missing	 28 (17.9%) 125 (80.1%) 3 (1.9%)	 39 (23.2%) 124 (73.8%) 5 (3.0%)	 31 (19.5%) 123 (77.4%) 5 (3.1%)	 25 (14.8%) 136 (80.5%) 8 (4.7%)	 63 (18.8%) 257 (76.5%) 16 (4.8%)	 54 (17.1%) 255 (80.7%) 7 (2.2%)
Metastasis stage at initial diagnosis - no. (%) M1, distant metastasis M0, no distant metastasis MX, distant metastasis not assessed	 112 (71.8%) 42 (26.9%) 2 (1.3%)	 132 (78.6%) 35 (20.8%) 1 (0.6%)	 145 (91.2%) 14 (8.8%) 0 (0.0%)	 148 (87.6%) 20 (11.8%) 1 (0.6%)	 301 (89.6%) 30 (8.9%) 5 (1.5%)	 285 (90.2%) 27 (8.5%) 4 (1.3%)
Metastasis stage at screening - no. (%) M1a, nonregional LN only M1b, bone B1 LN M1c, visceral B1 LN or bone	 4 (2.6%) 131 (84.0%) 21 (13.5%)	 3 (1.8%) 133 (79.2%) 32 (19.0%)	 8 (5.0%) 120 (75.5%) 31 (19.5%)	 1 (0.6%) 139 (82.2%) 29 (17.2%)	 11 (3.3%) 266 (79.2%) 59 (17.6%)	 12 (3.8%) 247 (78.2%) 57 (18.0%)
Median serum PSA level (range) - ng/ml	1.5 (0.0, 4.7)	1.4 (0.0, 4.7)	10.6 (4.8, 26.9)	11.9 (4.8, 27.5)	148.7 (28.4, 9,219.0)	123.3 (27.6, 11,947.0)
Median serum ALP level (range) - U/ml	97.0 (43.0, 1,995.0)	103.0 (36.0, 1,201.0)	131.0 (40.0, 3,348.0)	134.0 (41.0, 7,680.0)	208.0 (44.0, 4,885.0)	184.5 (49.0, 4,854.0)
ALP category - no. (%) <ULN ≥ULN	 105 (67.3%) 51 (32.7%)	 103 (61.3%) 65 (38.7%)	 78 (49.1%) 81 (50.9%)	 74 (43.8%) 95 (56.2%)	 107 (31.8%) 229 (68.2%)	 114 (36.1%) 202 (63.9%)
Visceral metastases - no. (%)	21 (13.5%)	32 (19.0%)	31 (19.5%)	29 (17.2%)	59 (17.6%)	57 (18.0%)

Abbreviations: ALP, alkaline phosphatase; bPSA: baseline prostate-specific antigen; DARO, darolutamide; LN, lymph node; no., number; Control, placebo; PSA, prostate-specific antigen; ULN, upper limit of the normal range.

Baseline Demographic and Clinical Characteristics by bPSA and Treatment (Table 3/3)

bPSA	Low: <4.80 ng/mL		Middle: [4.80, 27.55) ng/mL		High: ≥27.55 ng/mL	
Characteristic	**DARO triplet (N=156)**	**Control (N=168)**	**DARO triplet (N=159)**	**Control (N=169)**	**DARO triplet (N=336)**	**Control (N=316)**
Patients who received prior ADT - no. (%)	156 (100.0%)	163 (97.0%)	155 (97.5%)	163 (96.4%)	326 (97.0%)	313 (99.1%)
Duration of prior ADT - days Median Range	 65.0 (5.0, 85.0)	 62.0 (2.0, 85.0)	 50.0 (2.0, 85.0)	 55.0 (6.0, 85.0)	 36.0 (1.0, 85.0)	 36.0 (1.0, 85.0)
ADT before baseline PSA measurement, n(%)	153 (98.1%)	157 (93.5%)	144 (90.6%)	157 (92.9%)	286 (85.1%)	275 (87.0%)
Time from start of ADT to baseline PSA measurement, days Median Range	 48.0 (6.0, 80.0)	 45.0 (4.0, 83.0)	 36.0 (3.0, 75.0)	 36.0 (2.0, 85.0)	 19.5 (2.0, 81.0)	 22.0 (2.0, 78.0)
Time from baseline PSA measurement to randomization, days Median Range	 18.0 (1.0, 31.0)	 18.0 (3.0, 29.0)	 19.0 (3.0, 29.0)	 19.0 (0.0, 29.0)	 21.0 (4.0, 29.0)	 20.0 (4.0, 29.0)
Testosterone, ng/mL Testosterone <0.5 ng/mL Testosterone ≥0.5 ng/mL	 120 (77.4%) 35 (22.6%)	 131 (79.9%) 33 (20.1%)	 95 (59.7%) 64 (40.3%)	 92 (54.4%) 77 (45.6%)	 124 (37.1%) 210 (62.9%)	 128 (40.8%) 186 (59.2%)

Abbreviations: ADT, androgen deprivation therapy; bPSA: baseline prostate-specific antigen; DARO, darolutamide; Control, placebo; PSA: prostate-specific antigen.