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Prostate Cancer

Efficacy and Safety of Darolutamide in Patients with Nonmetastatic Castration-resistant Prostate Cancer Stratified by Prostate-specific Antigen Doubling Time: Planned Subgroup Analysis of the Phase 3 ARAMIS Trial

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Abstract

Background: Patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) have a high risk of progression to metastatic disease, particularly if their prostate-specific antigen doubling time (PSADT) is ≤6 mo. However, patients remain at a high risk with a PSADT of >6 mo.
Objective: To evaluate the efficacy and safety of darolutamide versus placebo in patients stratified by PSADT >6 or ≤6 mo.
Design, setting, and participants: A planned subgroup analysis of a global multicenter, double-blind, randomized, phase 3 trial in men with nmCRPC and PSADT ≤10 mo was conducted.
Intervention: Patients were randomized 2:1 to oral darolutamide 600 mg twice daily or placebo, while continuing androgen-deprivation therapy.
Outcome measurements and statistical analysis: The primary endpoint was metastasis-free survival (MFS). Secondary endpoints were overall survival (OS) and times to pain progression, first cytotoxic chemotherapy, and symptomatic skeletal events. Quality of life (QoL) was measured using validated prostate-relevant tools. Safety was recorded throughout the study.

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Overall survival
Prostate-specific antigen doubling time
Quality of life

Results and limitations: Of 1509 patients enrolled, 469 had PSADT >6 mo (darolutamide n = 286; placebo n = 183) and 1040 had PSADT ≤6 mo (darolutamide n = 669; placebo n = 371). Baseline characteristics were balanced between subgroups. Darolutamide significantly prolonged MFS versus placebo in both subgroups (unstratified hazard ratio [95% confidence interval]: PSADT >6 mo, 0.38 [0.26–0.55]; PSADT ≤6 mo, 0.41 [0.33–0.52]). OS and other efficacy and QoL endpoints favored darolutamide with significant improvement over placebo in both subgroups. The incidence of adverse events, including events commonly associated with androgen receptor inhibitors (fractures, falls, hypertension, and mental impairment), and discontinuations due to adverse events were low and similar to placebo. Limitations include small subgroup populations.

Conclusions: In patients with nmCRPC and PSADT >6 mo (maximum 10 mo), darolutamide provided a favorable benefit/risk ratio, characterized by significant improvements in MFS, OS, and other clinically relevant endpoints; maintenance of QoL; and favorable tolerability.

Patient summary: In patients with prostate cancer that has stopped responding to standard hormonal therapy (indicated by an increase in prostate-specific antigen [PSA] levels), there is a risk that the cancer will spread to other parts of the body. This risk is highest when the time it takes for the PSA level to double (ie, "PSA doubling time" [PSADT]) is less than 6 mo. However, there is still a risk that the cancer will spread even if the PSADT is longer than 6 mo. In a group of patients whose PSADT was more than 6 mo but no more than 10 mo, treatment with darolutamide slowed the cancer spread and allowed them to live longer than patients who received placebo (inactive drug). Darolutamide treatment did not cause many side effects and helped maintain patients' quality of life without disruptions.

1. Introduction

Nonmetastatic castration-resistant prostate cancer (nmCRPC) is diagnosed when a patient's prostate-specific antigen (PSA) rises despite surgical or medical castration, without evidence of metastasis on conventional imaging [1]. Many patients have high risks of disease progression and development of metastatic disease [2]. Patients with nmCRPC are usually asymptomatic from their disease [1], although they often have adverse events from local treatment of the primary tumor and androgen-deprivation therapy (ADT), such as urinary and sexual dysfunction, hot flushes, and fatigue [3].

In the absence of clinically apparent signs of progressive disease, PSA level and rate of change, as quantified by PSA doubling time (PSADT), offer the best prognostic indicators of progression and survival outcome [4–9]. Any increase in PSA, no matter how small, warrants monitoring [8] because the window of opportunity to treat patients before progression to metastatic disease can be narrow [2]. There is evidence that a shorter PSADT indicates a higher risk of progression, which is associated with reduced survival [6,7,9,10]. Various thresholds have been proposed to distinguish between high and low risk of metastatic progression [11–15]; PSADT <6 mo is sometimes proposed as a cutoff to identify the need for more aggressive therapy [14,16,17]. However, international evidence-based guidelines recommend treatment with a new-generation androgen receptor inhibitor (ARI; ie, apalutamide, enzalutamide, or darolutamide) in addition to standard ADT when the PSADT is ≤10 mo [18,19].

Given the poorer prognosis in patients with metastatic disease and the fact that patients with nmCRPC are often asymptomatic from their cancer, the goals of treatment are to delay progression to metastatic disease and prolong survival, while minimizing treatment-related toxicity that can limit patients' daily activities and health-related quality of life (HRQoL) [3,18,20–23]. Darolutamide is a structurally distinct ARI [21,22,24] that demonstrated significant improvements in metastasis-free survival (MFS) and overall survival (OS) versus placebo in patients with nmCRPC in the phase 3 ARAMIS trial [21,25]. The safety profile of darolutamide is consistently favorable, with ≤2% difference versus placebo in the incidence of most ARI-associated adverse events and a low risk of central nervous system–related adverse events, likely due to its low blood–brain barrier penetration [21,22,24,26,27]. Darolutamide also has a low potential for drug–drug interactions (DDIs) with medications commonly used to treat comorbidities in patients with nmCRPC [28,29]. Minimizing the risks of adverse events and DDIs is an important component of optimal disease management in patients with nmCRPC, allowing them to maintain their QoL, while prolonging survival and delaying disease progression [23].

The pivotal phase 3 trial for darolutamide (ARAMIS) enrolled patients with PSADT ≤10 mo [21]. The aim of this preplanned ARAMIS subgroup analysis was to evaluate the efficacy and safety of darolutamide versus placebo in patients stratified by PSADT >6 versus ≤6 mo to help inform therapeutic decision-making, particularly in patients with PSADT 6–10 mo in whom there may be uncertainty about the benefit versus risk of treatment.

2. Patients and methods

ARAMIS was a global, multicenter, double-blind, randomized, phase 3 trial of darolutamide versus placebo plus ADT in men with nmCRPC (NCT02200614). The full methods have been reported previously [21,25] and are summarized briefly here.

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2.1. Patients

The study enrolled men aged ≥18 yr with histologically or cytologically confirmed prostate adenocarcinoma, who had a PSA level of ≥2 ng/ml and a PSADT of ≤10 mo at screening and an Eastern Cooperative Oncology Group performance status of 0 or 1 at baseline. Patients with evidence of metastases or a history of metastatic disease on conventional bone scan, computed tomography, or magnetic resonance imaging were excluded. Patients with a previous seizure disorder or predisposition to seizure could be included.

2.2. Study design

Patients were randomized 2:1 to double-blind treatment with oral darolutamide 600 mg twice daily or matched placebo, while continuing ADT. Randomization was stratified by PSADT (>6 vs ≤6 mo) and use of osteoclast-targeted therapy (yes vs no). The PSADT for each patient was initially calculated locally during screening, but was recomputed centrally by the sponsor for this analysis to ensure consistency in the calculations. Treatment was continued until patients experienced protocol-defined progression or intolerable adverse events, commenced another anticancer treatment, or withdrew consent.

Unblinding occurred after the primary analysis, at which point patients initially randomized to darolutamide could continue open-label darolutamide, while those initially randomized to placebo could switch to open-label darolutamide or another treatment of the investigators' choice.

2.3. Study endpoints

The study had two planned analyses: the primary analysis was performed after 437 MFS events; the final analysis was performed after 254 OS events. The primary efficacy endpoint was MFS [21]. Secondary endpoints were OS, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal event (SSE). Progression-free survival (PFS) was an exploratory efficacy endpoint.

Throughout the study, HRQoL was measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) total and prostate cancer subscale scores (higher scores indicate better HRQoL), European Organisation for Research and Treatment of Cancer Quality of Life–Prostate cancer questionnaire (EORTC-QLQ-PR25) urinary symptom subscale scores (a higher score indicates a greater impact of symptoms on HRQoL), and Brief Pain Inventory–Short Form (BPI-SF) questionnaire scores for pain interference (higher scores indicate greater impact of pain) and pain severity (higher scores indicate greater pain).

Safety was assessed throughout the study. The incidence of treatment-emergent adverse events (TEAEs) was recorded, with the event type coded according to the Medical Dictionary for Regulatory Activities version 21.0 and severity graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

In this planned subgroup analysis, we report findings separately in patients with PSADT >6 or ≤6 mo.

2.4. Statistical analyses

Full details of the statistical analyses were published previously and are available in the statistical analysis plan at clinicaltrials.gov/ProvidedDocs/14/NCT02200614/SAP_001.pdf.

The efficacy and HRQoL analyses were based on the intention-to-treat (ITT) population, defined as all randomized patients, grouped according to treatment allocation. Missing event occurrence dates were imputed as the earliest possible dates. HRQoL analyses excluded patients with missing baseline data. Safety analyses were based on the safety population, defined as all randomized patients who received one or more doses of study medication, grouped according to the treatment actually received.

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA). Time-to-event endpoints were estimated using the Kaplan–Meier method, and were reported as medians with range and 95% confidence intervals (CIs). Hazard ratios (HRs) and 95% CIs, based on Cox regression modeling and log-rank testing without stratification, were reported for comparisons between the darolutamide and placebo treatment arms within each PSADT subgroup and for a univariate analysis of MFS by baseline age, race, and region. For HRQoL measures, differences between treatment arms were reported as least squares mean (LSM) differences in time-adjusted area under the curve (AUC) using analysis of covariance. Changes in HRQoL measures over time were reported descriptively.

2.5. Study ethics

The study protocol was approved by the institutional review board at each participating center. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent for participation. Unblinded safety data were reviewed by an independent data and safety monitoring board.

3. Results

3.1. Patients

The data cutoff dates for the primary and final analyses were September 3, 2018 [21], and November 15, 2019 [25], respectively. The median follow-up duration for OS was 29 mo. The overall ITT population comprised 1509 patients (darolutamide n = 955; placebo n = 554), of whom 469 had a PSADT of >6–≤10 mo (darolutamide n = 286; placebo n = 183) and 1040 had a PSADT of ≤6 mo (darolutamide n = 669; placebo n = 371).

Baseline characteristics were generally well balanced between the PSADT subgroups (Table 1), although the median time from the initial diagnosis was longer in the PSADT >6 mo subgroup (darolutamide arm 97 mo; placebo arm 95 mo) than in the PSADT ≤6 mo subgroup (darolutamide arm 82 mo; placebo arm 79 mo). The proportions of patients with prior local therapy were generally similar between treatment arms in both subgroups. In the PSADT >6 mo subgroup, 19% of patients who received darolutamide and 18% of patients who received placebo had previously undergone prostatectomy; in the PSADT ≤6 mo subgroup, the proportions were 28% and 27%, respectively. For prior radiotherapy, the proportions were 18% and 13%, respectively, in the PSADT >6 mo subgroup and 19% and 18%, respectively, in the PSADT ≤6 mo subgroup.

3.2. Efficacy

At the primary analysis, darolutamide significantly reduced the risk of metastasis or death versus placebo by 62% in the PSADT >6 mo subgroup (unstratified HR 0.38, 95% CI 0.26–0.55) and by 59% in the PSADT ≤6 mo subgroup (unstratified HR 0.41, 95% CI 0.33–0.52; Fig. 1). The MFS benefit with darolutamide versus placebo was consistent across PSADT

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Table 1 – Patient demographics and clinical characteristics at baseline

Baseline characteristic[a]	PSADT >6 mo		PSADT ≤6 mo	
	Darolutamide (*n* = 286[b])	Placebo (*n* = 183)	Darolutamide (*n* = 669)	Placebo (*n* = 371)
Age (yr), median (IQR)	76 (70–81)	75 (70–80)	74 (68–79)	72 (67–79)
Age (yr), *n* (%)				
<65	31 (11)	20 (11)	82 (12)	64 (17)
65–74	94 (33)	61 (33)	279 (42)	155 (42)
75–84	134 (47)	81 (44)	250 (37)	128 (35)
≥85	27 (9)	21 (11)	58 (9)	24 (7)
ECOG performance status, *n* (%)				
0	187 (65)	126 (69)	463 (69)	265 (71)
1	99 (35)	57 (31)	206 (31)	106 (29)
Gleason score at initial diagnosis, *n* (%)				
<7	69 (24)	48 (26)	148 (22)	94 (25)
≥7	208 (73)	127 (69)	503 (75)	268 (72)
Time from initial diagnosis (mo), median (IQR)	97 (62–129)	95 (57–147)	82 (47–126)	79 (44–130)
Primary tumor classification, *n* (%)				
T2: tumor confined within the prostate	30 (10)	16 (9)	80 (12)	42 (11)
T3a: unilateral or bilateral extracapsular extension	25 (9)	19 (10)	88 (13)	30 (8)
Pathological lymph nodes on central imaging review, *n* (%)	23 (8)	14 (8)	77 (12)	52 (14)
Serum PSA (ng/ml), median (IQR)	8.9 (4.4–18)	9.3 (4.7–19)	9.2 (4.5–21)	10 (5.1–22)
PSADT (mo), median (IQR)[c]	7.8 (6.9–9.0)	7.3 (6.6–8.2)	3.5 (2.5–4.6)	3.6 (2.5–4.7)
Serum testosterone (nmol/l), median (IQR)	0.54 (0.46–0.71)	0.54 (0.44–0.69)	0.56 (0.47–0.71)	0.56 (0.47–0.75)
Prior hormonal therapy, *n* (%)				
1	58 (20)	30 (16)	119 (18)	73 (20)
≥2	209 (73)	139 (76)	518 (77)	281 (76)
NA	19 (7)	14 (8)	32 (5)	17 (5)
Prior local therapy, *n* (%)				
Prostatectomy	53 (19)	33 (18)	186 (28)	101 (27)
Radiotherapy	51 (18)	23 (13)	126 (19)	66 (18)

ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; NA = not applicable; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.

[a] Data are missing for some patients and categories.

[b] In the initial ARAMIS report [21], 288 patients had PSADT >6 mo based on local calculations at screening. PSADT was recomputed centrally by the sponsor for this analysis to ensure consistency in the calculations, resulting in some discrepancies versus the values recorded during screening.

[c] Although patients had to have a PSADT of ≤10 mo at screening, as calculated locally by the investigator, recalculation of all PSADTs centrally by the sponsor and changes in PSADT between screening and the start of treatment resulted in some patients having a PSADT of >10 mo at baseline.

quartiles, with HRs ranging from 0.33 to 0.48 (Supplementary Table 1). When evaluating MFS by baseline characteristics, the results were generally consistently in favor of darolutamide over placebo, regardless of age, race, or region, although 95% CIs were wide, and crossed 1 for age 74–79 yr (*n* = 140), age 47–67 yr (*n* = 81), non-White race (*n* = 82), and Asia-Pacific region (*n* = 43) in the PSADT >6 mo subgroup (Fig. 2).

At the final analysis, darolutamide significantly prolonged OS versus placebo in both PSADT subgroups (Fig. 1). The risk of death was reduced by 45% in the PSADT >6 mo subgroup ($p = 0.01$) and by 26% in the PSADT ≤6 mo subgroup ($p = 0.04$) with darolutamide versus placebo. The OS benefit of darolutamide over placebo was consistent across PSADT quartiles, although CIs were wide and often overlapping 1 (Supplementary Table 2).

The benefit of darolutamide over placebo was seen in both PSADT subgroups for all other efficacy endpoints (Fig. 3). For time to pain progression and PFS, significant differences were achieved at the primary analysis in both subgroups. For time to first cytotoxic chemotherapy and time to first SSE, significant differences were achieved at the final analysis, except for the time to first SSE in the PSADT >6 mo subgroup ($p = 0.06$).

3.3. *Health-related quality of life*

HRQoL was maintained with darolutamide versus placebo in both subgroups (Supplementary Fig. 1 and Supplementary Table 3). For all HRQoL subscale measures, LSM differences in time-adjusted AUC showed a positive trend for darolutamide versus placebo, although these did not meet the minimally important differences required to be clinically meaningful.

3.4. *Safety and tolerability*

The median duration of study drug administration was generally consistent between subgroups. In patients randomized to darolutamide, the median duration of darolutamide treatment was 18 mo in the PSADT >6 mo subgroup versus 19 mo in the PSADT ≤6 mo subgroup during the double-blind period, and 26 mo in each subgroup across the double-blind and open-label periods. In patients randomized to placebo, the median duration of study treatment was 15 mo (PSADT >6 mo subgroup) versus 11 mo (PSADT ≤6 mo subgroup) for placebo during the double-blind period and 11 mo in each subgroup for darolutamide during the open-label period.

The safety profile of darolutamide was consistent between the PSADT subgroups, with a low incidence of grade 3–4 events and discontinuations due to TEAEs in both subgroups (Table 2 and Supplementary Table 4). During double-blind treatment, most TEAEs commonly associated with ARIs (including fractures, falls, hypertension, and mental impairment disorders) showed a difference of ≤3% between darolutamide and placebo in both subgroups; fatigue was the only adverse event with an incidence of >10% in

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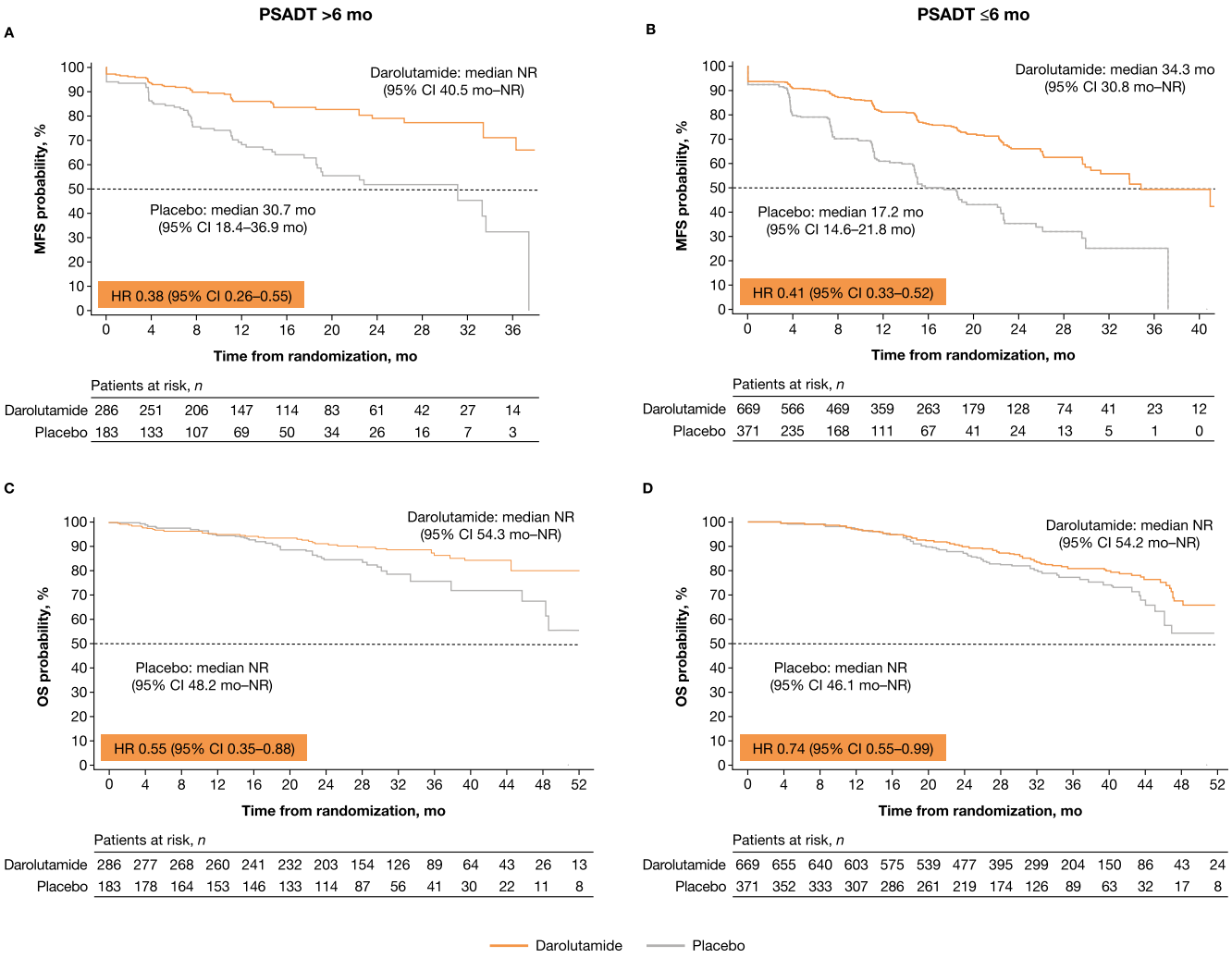

Fig. 1 – Darolutamide efficacy by PSADT subgroup. Kaplan–Meier estimates of metastasis-free survival (primary analysis): (A) PSADT >6 mo subgroup and (B) PSADT ≤6 mo subgroup; and overall survival (final analysis): (C) PSADT >6 mo subgroup and (D) PSADT ≤6 mo subgroup. HRs and 95% CIs were based on a Cox regression model, without stratification. CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; NR = not reached; OS = overall survival; PSADT = prostate-specific antigen doubling time.

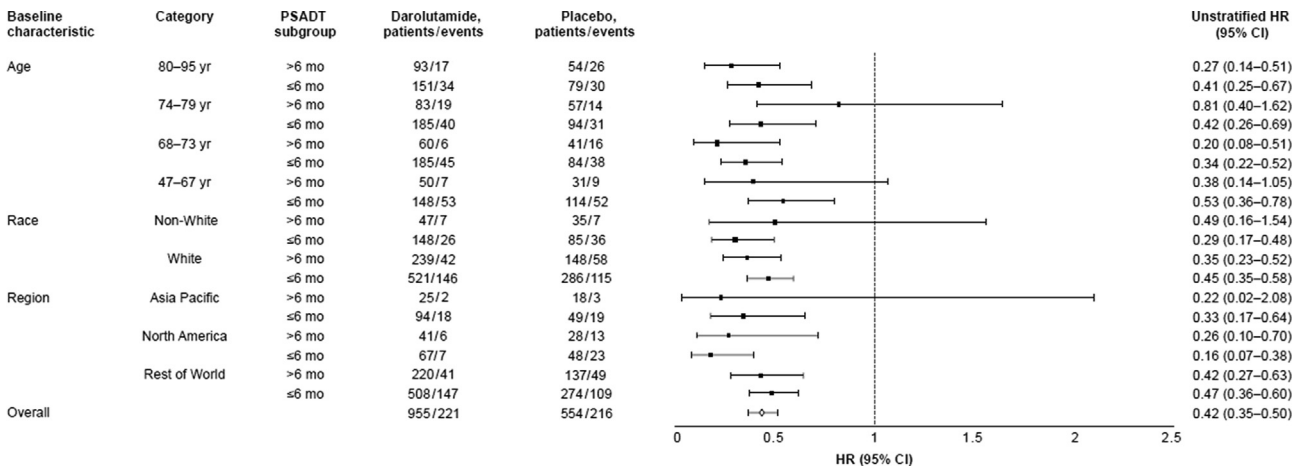

Fig. 2 – Metastasis-free survival analyses by baseline characteristics. Nominal 95% CIs are provided without controlling for multiple inferences. CI = confidence interval; HR = hazard ratio; PSADT = prostate-specific antigen doubling time.

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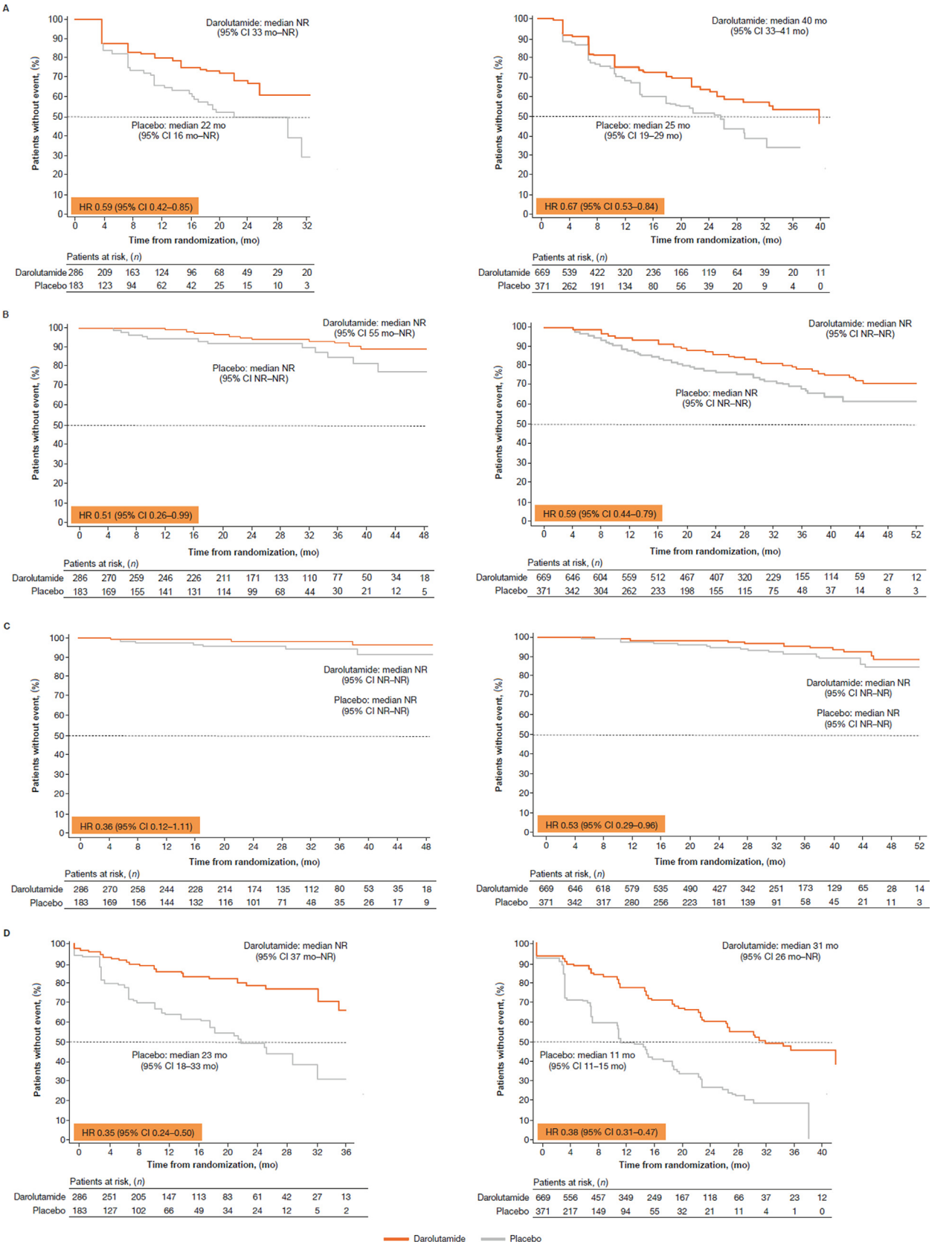

Fig. 3 – Secondary and exploratory endpoint outcomes during double-blind treatment by PSADT subgroup: >6 mo (left-hand column) and ≤6 mo (right-hand column): (A) Time to pain progression[a], (B) time to initiation of first cytotoxic chemotherapy, (C) time to first symptomatic skeletal event, and (D) progression-free survival[a]. Nominal inferential statistics are presented without controlling for multiple inferential analyses. CI = confidence interval; NR = not reached; PSADT = prostate-specific antigen doubling time. [a]Primary analysis.

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Table 2 – TEAEs of interest in the safety population during the double-blind period[a]

TEAE	PSADT >6 mo						PSADT ≤6 mo					
	Darolutamide (*n* = 286)			Placebo (*n* = 183)			Darolutamide (*n* = 668)			Placebo (*n* = 371)		
	Any grade, *n* (%)	Grade 3/4, *n* (%)[b]	EAIR[c]	Any grade, *n* (%)	Grade 3/4, *n* (%)[b]	EAIR[c]	Any grade, *n* (%)	Grade 3/4, *n* (%)[b]	EAIR[c]	Any grade, *n* (%)	Grade 3/4, *n* (%)[b]	EAIR[c]
Fatigue	42 (15)	1 (0.35)	9.0	19 (10)	2 (1.1)	8.1	84 (13)	3 (0.45)	8.0	27 (7.3)	3 (0.81)	6.9
Bone fracture[d]	16 (5.6)	2 (0.70)	3.4	12 (6.6)	5 (2.7)	5.1	36 (5.4)	8 (1.2)	3.4	8 (2.2)	0	2.1
Falls (including accidents)	17 (5.9)	2 (0.70)	3.6	12 (6.6)	2 (1.1)	5.1	33 (4.9)	7 (1.0)	3.1	15 (4.0)	2 (0.54)	3.9
Weight decreased	13 (4.5)	0	2.8	7 (3.8)	0	3.0	27 (4.0)	0	2.6	7 (1.9)	0	1.8
Asthenic conditions[e]	13 (4.5)	0	2.8	8 (4.4)	1 (0.5)	3.4	29 (4.3)	2 (0.30)	2.8	15 (4.0)	2 (0.54)	3.9
Rash[f]	8 (2.8)	0	1.7	1 (0.55)	0	0.4	22 (3.3)	2 (0.30)	2.1	5 (1.3)	0	1.3
Mental impairment disorders[g]	5 (1.7)	0	1.1	5 (2.7)	0	2.1	14 (2.1)	3 (0.45)	1.3	5 (1.3)	0	1.3
Depressed mood disorders[g]	5 (1.7)	1 (0.35)	1.1	3 (1.6)	0	1.3	16 (2.4)	0	1.5	7 (1.9)	0	1.8
Hypertension	18 (6.3)	5 (1.7)	3.8	13 (7.1)	5 (2.7)	5.5	56 (8.4)	28 (4.2)	5.3	23 (6.2)	8 (2.2)	5.9
Hot flush[h]	17 (5.9)	0	3.6	8 (4.4)	0	3.4	40 (6.0)	0	3.8	17 (4.6)	0	4.4
Cardiac arrhythmia[g]	24 (8.4)	3 (1.0)	5.1	11 (6.0)	2 (1.1)	4.7	46 (6.9)	14 (2.1)	4.4	13 (3.5)	2 (0.54)	3.3
Coronary artery disorders[g]	14 (4.9)	8 (2.8)	3.0	5 (2.7)	2 (1.1)	2.1	24 (3.6)	11 (1.6)	2.3	10 (2.7)	0	2.6
Heart failure[g]	3 (1.0)	1 (0.35)	0.6	3 (1.6)	0	1.3	15 (2.2)	3 (0.45)	1.4	2 (0.54)	0	0.5

EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PSADT = prostate-specific antigen doubling time; TEAE = treatment-emergent adverse event.

[a] TEAEs of interest commonly associated with androgen receptor inhibitors.

[b] EAIR is for any-grade TEAE per 100 patient-years.

[c] The following grade 5 TEAEs were recorded: cardiac arrhythmia (PSADT >6 mo subgroup: darolutamide *n* = 1 [0.35%], placebo *n* = 2 [1.1%]; PSADT ≤6 mo subgroup: darolutamide *n* = 1 [0.15%], placebo *n* = 1 [0.27%]), coronary artery disorders (PSADT >6 mo subgroup: darolutamide *n* = 2 [0.70%], placebo *n* = 0; PSADT ≤6 mo subgroup: darolutamide *n* = 1 [0.15%], placebo *n* = 1 [0.27%]), and heart failure (PSADT >6 mo subgroup: darolutamide *n* = 0; placebo *n* = 2 [1.1%]; PSADT ≤6 mo subgroup: darolutamide *n* = 5 [0.75%], placebo *n* = 1 [0.27%]).

[d] This category combines the following MedDRA version 22.1 terms: any fractures and dislocations; limb fractures and dislocations; pelvic fractures and dislocations; skull fractures, facial bone fractures, and dislocations; spinal fractures and dislocations; and thoracic cage fractures and dislocations.

[e] This category combines the following MedDRA terms: asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, and asthenia.

[f] This category combines the following MedDRA terms: rash, macular rash, maculopapular rash, papular rash, and pustular rash.

[g] This category is a MedDRA high-level group term.

[h] This category combines the following MedDRA terms: flushing, hot flush, and vasodilatation.

the darolutamide arm (15% in the PSADT >6 mo subgroup and 13% in the PSADT ≤6 mo subgroup vs 10% and 7.3%, respectively, in the placebo arm; Table 2); most fatigue events were of grade 1 (PSADT >6 mo subgroup: darolutamide 8.7% and placebo 7.7%; PSADT ≤6 mo subgroup: darolutamide 9.1% and placebo 5.4%). When adjusted for exposure, differences in the incidence of these TEAEs of interest between darolutamide and placebo were minimal in both subgroups. The incidence of TEAEs that occurred in ≥5% of patients in either treatment group was generally similar in both subgroups, with the most frequently reported TEAEs in either subgroup being fatigue, back pain, and arthralgia (Supplementary Table 4). In both subgroups, the types of TEAEs reported in patients who crossed over from placebo to darolutamide during the open-label period were consistent with those observed with darolutamide treatment during the double-blind period (Supplementary Table 4).

4. Discussion

In patients with nmCRPC, PSADT is a prognostic factor for progression to metastatic disease, with a shorter PSADT indicating a higher risk of progression [9]. This preplanned subgroup analysis of ARAMIS demonstrated that patients with PSADT >6 mo benefited from darolutamide treatment to a similar extent to those with PSADT ≤6 mo, with significant improvements in MFS and OS, as well as favorable trends in other efficacy endpoints and HRQoL. Age, race, and region had no impact on MFS outcomes, with consistent benefits in favor of darolutamide over placebo, although some 95% CIs in the PSADT >6 mo subgroup were wide and crossed 1, reflecting the small sample sizes. Most darolutamide-induced improvements in HRQoL were smaller than the minimally important differences for the scales employed; however, the overall trends toward improvement of patient-reported outcome measures of HRQoL were encouraging. Darolutamide was well tolerated, and the safety profile was similar across the two PSADT subgroups and comparable to that of the overall population. The incidence of most TEAEs was consistently low and similar to the placebo arm, indicating that treatment with darolutamide may have minimal negative impact on patients' HRQoL.

The ARAMIS study was restricted to patients with PSADT ≤10 mo, which is the accepted cutoff to define a high risk of progression and early mortality in patients with nmCRPC [6,7,18]. The association between rapid PSADT and poor prognosis is widely recognized [4,5,9,30–37], and PSADT ≤6 mo indicates the highest risk of progression to metastatic disease [9,30]. However, the potentially negative impact of drug-induced adverse events on HRQoL is an important consideration in men with nmCRPC and PSADT >6 mo, given the anticipated long treatment duration; the risk of experiencing adverse events is especially higher in elderly men with comorbidities. We show that in patients with PSADT >6–≤10 mo, darolutamide offers significant MFS and OS benefits, as well as improvement in other patient-relevant endpoints, without imposing undue toxicity burden or adversely affecting HRQoL. In the pivotal phase 3 studies of other ARIs, findings from PSADT subgroup analyses were less clear. A subgroup analysis of PROSPER using a PSADT cutoff of ≥6 versus <6 mo indicated MFS benefits with enzalutamide versus placebo in both PSADT subgroups, whereas for OS, the 95% CI crossed 1 in the PSADT ≥6 mo subgroup [6,38]. In a subgroup analysis of SPARTAN using a PSADT cutoff of >6 versus ≤6 mo, apalutamide showed MFS benefits versus placebo in both PSADT subgroups; for OS, the 95% CI crossed 1 in the PSADT ≤6 mo subgroup [7,39].

As a subgroup analysis, the statistical power is reduced due to the smaller patient populations in each treatment arm within each subgroup compared with the overall population. Nonetheless, because PSADT was a stratification factor for randomization, the groups were well balanced, minimizing the selection bias. Furthermore, we cannot rule out that patients might have had evidence of metastases on newer imaging modalities, such as prostate-specific membrane antigen positron-emission tomography/computed tomography or whole-body diffusion-weighted magnetic resonance imaging. All patients, however, met the entry criterion of nmCRPC on conventional imaging, and the balanced baseline characteristics between treatment arms suggest that the findings apply regardless of metastases that were not evident on conventional imaging. ARAMIS was restricted to patients with a PSADT of ≤10 mo; therefore, conclusions from the PSADT >6 mo subgroup should not be extrapolated to patients with nmCRPC and a PSADT of >10 mo. Finally, the low reported rate of prior local therapy, which is similar to other reported large datasets [40], might be a potential limitation, but reflects the patient population enrolled in this trial.

5. Conclusions

In conclusion, in patients with nmCRPC and a PSADT of >6 mo, darolutamide provided a markedly favorable benefit-to-risk ratio, characterized by significant improvement in survival and other clinically relevant endpoints; maintained HRQoL; and demonstrated a favorable tolerability profile. Thus, early initiation of life-prolonging therapy with an ARI is warranted in these patients.

Author contributions: Martin Bögemann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shore, Smith, Verholen, Le Berre, Ortiz, Mohamed, Fizazi.
Acquisition of data: Bögemann, Shore, Smith, Tammela, Ulys, Vjaters, Polyakov, Jievaltas, Luz, Alekseev, Lebret, Schostak, Fizazi.
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***Data sharing*:** Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union (EU), as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information are provided in the study sponsors' section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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