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Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial

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abstract

PURPOSE For patients with metastatic hormone-sensitive prostate cancer, metastatic burden affects outcome. We examined efficacy and safety from the ARASENS trial for subgroups by disease volume and risk.

METHODS Patients with metastatic hormone-sensitive prostate cancer were randomly assigned to darolutamide or placebo plus androgen-deprivation therapy and docetaxel. High-volume disease was defined as visceral metastases and/or ≥ 4 bone metastases with ≥ 1 beyond the vertebral column/pelvis. High-risk disease was defined as ≥ 2 risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and presence of measurable visceral metastases.

RESULTS Of 1,305 patients, 1,005 (77%) had high-volume disease and 912 (70%) had high-risk disease. Darolutamide increased overall survival (OS) versus placebo in patients with high-volume (hazard ratio [HR], 0.69; 95% CI, 0.57 to 0.82), high-risk (HR, 0.71; 95% CI, 0.58 to 0.86), and low-risk disease (HR, 0.62; 95% CI, 0.42 to 0.90), and in the smaller low-volume subgroup, the results were also suggestive of survival benefit (HR, 0.68; 95% CI, 0.41 to 1.13). Darolutamide improved clinically relevant secondary end points of time to castration-resistant prostate cancer and subsequent systemic antineoplastic therapy versus placebo in all disease volume and risk subgroups. Adverse events (AEs) were similar between treatment groups across subgroups. Grade 3 or 4 AEs occurred in 64.9% of darolutamide patients versus 64.2% of placebo patients in the high-volume subgroup and 70.1% versus 61.1% in the low-volume subgroup. Among the most common AEs, many were known toxicities related to docetaxel.

CONCLUSION In patients with high-volume and high-risk/low-risk metastatic hormone-sensitive prostate cancer, treatment intensification with darolutamide, androgen-deprivation therapy, and docetaxel increased OS with a similar AE profile in the subgroups, consistent with the overall population.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 19, 2023 and published at ascopubs.org/journal/jco on February 16, 2023: DOI https://doi.org/10.1200/JCO.23.00041

INTRODUCTION

In patients with metastatic hormone-sensitive prostate cancer, early treatment intensification with a combination of androgen-deprivation therapy (ADT) plus either docetaxel or an androgen receptor pathway inhibitor improved survival versus ADT alone in several randomized controlled trials.[1-6] The combination of ADT, docetaxel, and an androgen receptor pathway inhibitor was evaluated in several phase III trials (PEACE-1, ENZAMET, and ARASENS) with varying results.[7-9] PEACE-1 was a randomized, open-label trial using a 2 × 2 factorial design that was conducted in patients with de novo metastatic hormone-sensitive prostate cancer.[8] In a preplanned analysis of patients who received docetaxel, longer survival was observed with abiraterone in combination with ADT and docetaxel versus ADT and docetaxel alone (hazard ratio [HR], 0.75; 95% CI, 0.59 to 0.95).[8] The ENZAMET trial allowed for early administration of docetaxel with enzalutamide.[7] Among patients who received docetaxel, the effect of enzalutamide on overall survival (OS) appeared to be smaller (HR, 0.82; 95% CI, 0.63 to 1.06) than that observed for all patients (HR, 0.70; 95% CI, 0.58 to 0.84).[10] In ARASENS, patients with metastatic hormone-sensitive prostate cancer were randomly assigned to double-blind treatment with either darolutamide or placebo, in combination with ADT and docetaxel. The darolutamide group had a significant reduction in the risk of death by 32.5% (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .0001$) compared with the placebo group.[9]

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CONTEXT

Key Objective

We evaluated efficacy and safety outcomes from ARASENS in patients with metastatic hormone-sensitive prostate cancer by disease volume and disease risk to determine if specific subgroups of patients would achieve greater benefit from the combination of darolutamide, androgen-deprivation therapy (ADT), and docetaxel compared with ADT and docetaxel.

Knowledge Generated

These subgroup analyses of ARASENS showed that darolutamide plus ADT and docetaxel improves overall survival in high-volume and high- and low-risk patients with hazard ratios consistent across all subgroups and similar to the overall population. Darolutamide did not increase the toxicity associated with ADT and docetaxel in disease volume and risk subgroups.

Relevance *(M.A. Carducci)*

Triplet therapy for predominantly de novo docetaxel fit metastatic hormone-sensitive prostate cancer is supported by this subgroup analysis of the ARASENS study. This study provides useful information to guide providers and patients as to volume of disease and risk category.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD.

Timing of metastatic presentation and disease volume and risk have been used to assess prognosis in patients with metastatic hormone-sensitive prostate cancer.[11-14] The presence of metastatic disease at initial diagnosis (de novo or synchronous disease) is associated with poorer outcomes compared with developing metastases after local therapy (recurrent or metachronous disease). Disease burden has been defined on the basis of extent (volume) of metastases as described in the CHAARTED trial.[1,15] In the LATITUDE trial, a benefit of adding an androgen receptor pathway inhibitor to ADT was demonstrated in patients with high-risk metastatic hormone-sensitive prostate cancer on the basis of factors associated with poor prognosis, including metastatic burden and Gleason score.[2]

In ARASENS, the treatment effect of darolutamide on OS was favorable in patients with de novo (HR, 0.71; 95% CI, 0.59 to 0.85) and recurrent (HR, 0.61; 95% CI, 0.35 to 1.05) metastatic hormone-sensitive prostate cancer.[9] When ARASENS was designed, the final analysis of CHAARTED had not been reported nor had data from LATITUDE been reported. Thus, subgroups on the basis of volume and risk categorizations were not prespecified in ARASENS.[16] We conducted these subgroup analyses post hoc to determine if specific subgroups of patients by disease volume or risk would achieve greater benefit from the combination of darolutamide, ADT, and docetaxel. We present efficacy and safety outcomes from ARASENS in patients with metastatic hormone-sensitive prostate cancer by disease volume and disease risk according to CHAARTED and LATITUDE criteria, respectively.

METHODS

Trial Design

ARASENS was a randomized, double-blind, placebo-controlled, phase III trial conducted at 286 centers in 23 countries between November 2016 and June 2018. Complete study design and methodology have been published.[9] The trial met ethical and clinical practice guidelines with approval from the institutional review boards of each participating center and informed consent received from all patients. All authors have reviewed and approved the manuscript that was submitted for publication and assume responsibility for its completeness and accuracy of the data.

In brief, adult patients were eligible for enrollment into ARASENS if they had metastatic prostate cancer (beyond regional lymph nodes only) and were candidates for ADT and docetaxel on the basis of the investigator's assessment. Enrolled patients were randomly assigned (1:1) to oral darolutamide 600 mg twice daily or matched placebo, in combination with ADT and docetaxel. Random assignment was stratified by metastatic stage according to the TNM system (M1a, nonregional lymph node metastases only; M1b, bone metastases with or without lymph node metastases, or M1c, visceral metastases with or without lymph node or bone metastases) and alkaline phosphatase level. Patients were evaluated every 12 weeks for efficacy outcomes and AEs. Contrast-enhanced chest, abdomen, and pelvic computed tomography or magnetic resonance imaging and bone scans were conducted at baseline, within 30 days of the last docetaxel cycle, and yearly during trial treatment.

For this analysis, patient subgroups on the basis of disease volume and disease risk were assessed. High-volume disease was defined as visceral metastases and/or four or more bone metastases with one or more beyond the vertebral column and pelvis.[1] High-risk disease was defined as two of the following risk factors associated with poor prognosis: Gleason score $\geq$ 8, three or more bone metastases, and presence of measurable visceral metastasis.[2] Low-volume and low-risk disease were defined as not meeting the

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respective high-volume and high-risk criteria. High-volume/high-risk groups further included patients with diffusely increased skeletal metastases with superscan.[17]

Study Assessments

OS was the primary end point. Secondary efficacy end points included time to castration-resistant prostate cancer, time to pain progression on the basis of the Brief Pain Inventory Short-Form questionnaire, symptomatic skeletal event-free survival, time to first symptomatic-skeletal event, time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms as measured by the Functional Assessment of Cancer Therapy–Prostate (National Comprehensive Cancer Network) symptom index 17-item questionnaire, and time to initiation of opioid use for 7 or more days. Safety was assessed by AEs, which were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

This subgroup analysis used Kaplan-Meier estimates to determine medians and 95% CIs. Treatment groups were compared by HRs and associated 95% CIs on the basis of an unstratified Cox regression model. The Cox models used HR estimation on the basis of fitting separate models for each volume/risk subgroup (four models overall). AEs were summarized by treatment group for the subgroups of patients by disease volume and disease risk.

RESULTS

Patient Characteristics

As previously reported, a total of 1,306 patients were randomly assigned, and 1,305 patients were included in

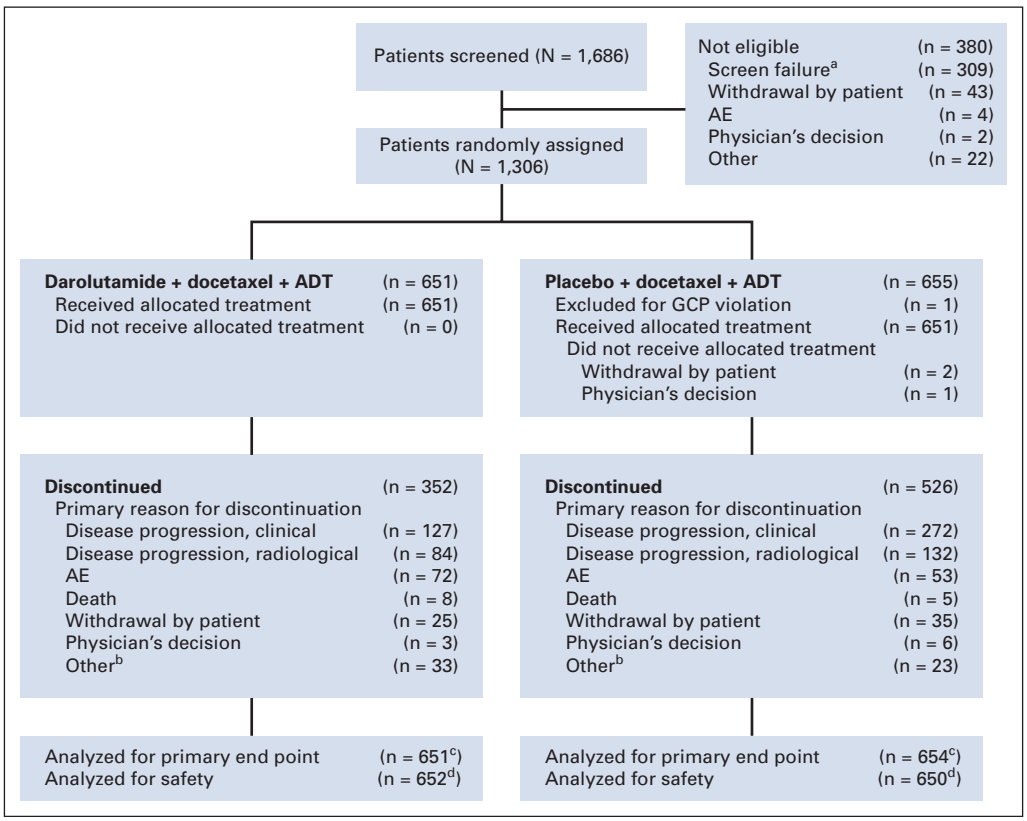

FIG 1. CONSORT flow diagram. [a]Patient had signed informed consent but did not meet inclusion/exclusion criteria. [b]Other includes noncompliance, additional primary malignancy, lost to follow-up, protocol violation, and other. [c]The primary end point (OS) was assessed after 533 patients had died (229 in the darolutamide group and 304 in the placebo group). Most deaths were related to disease progression (415 of 533 [77.9%] in the overall population, 172 of 229 [75.1%] in the darolutamide group, and 243 of 304 [79.9%] in the placebo group). [d]One patient was randomly assigned in the placebo arm but received darolutamide. The patient was included in the darolutamide arm for the safety analysis and the placebo arm for the full analysis set. AE, adverse event; ADT, androgen-deprivation therapy; GCP, good clinical practice; HR, hazard ratio; OS, overall survival. From N Engl J Med, Smith MR, Hussain M, Saad F, et al, Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer, 386(12), 1132-1142,[9] Copyright © 2022, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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the full analysis set of ARASENS (Fig 1). Of them, 1,005 (77%) patients had high-volume disease and 300 (23%) had low-volume disease; 912 (70%) patients had high-risk disease, and 393 (30%) had low-risk disease (Table 1). Baseline demographics and patient characteristics were well balanced between treatment groups in disease volume and risk subgroups. Among those with high-volume disease, most had bone metastases and 23% had visceral metastases. Patients with high-volume disease had higher baseline median serum prostate-specific antigen levels, and a greater proportion of patients had elevated alkaline phosphatase levels than patients with low-volume disease. For those with high-risk disease, approximately 77% had three or more bone metastases, and almost all (95%) had a Gleason score ≥ 8.

Patients receiving darolutamide had longer duration of treatment versus those receiving placebo in high-volume (32.9 *v* 15.3 months) and low-volume subgroups (43.6 *v* 26.5 months). Similar results were observed in patients with high- and low-risk metastatic hormone-sensitive prostate cancer (darolutamide *v* placebo, 33.1 *v* 15.2 months; 43.3 *v* 22.5 months). A higher proportion of patients receiving darolutamide across all subgroups were ongoing with study treatment at the time of study analysis versus patients receiving placebo (high-volume, 39.4% *v* 15.9%; low-volume, 66.9% *v* 30.1%; high-risk, 41.4% *v* 15.2%; low-risk, 56.3% *v* 28.4%).

Primary End Point

OS. A benefit in OS was shown with darolutamide compared with placebo for patients with high-volume disease (HR, 0.69; 95% CI, 0.57 to 0.82; Fig 2). Median survival was not reached in the darolutamide group and was 42.4 months (95% CI, 39.7 to 46.0 months) in the placebo group. In patients with low-volume disease, the results are suggestive of a survival benefit with darolutamide (HR, 0.68; 95% CI, 0.41 to 1.13). Median survival was not reached in either treatment group for low-volume patients. A test for interaction showed that the treatment effect was homogeneous across high- and low-volume subgroups (ratio of HRs, 0.99; 95% CI, 0.58 to 1.69).

The improvement in survival with darolutamide was observed despite more than 70% of patients in the placebo group receiving subsequent life-prolonging systemic therapies, primarily different androgen receptor pathway inhibitors (76.1% with high-volume and 73.1% with low-volume disease) compared with those in the darolutamide group (59.8% with high-volume and 38.6% with low-volume disease; Appendix Table A1, online only). The effect of darolutamide treatment on OS across prespecified subgroups, including de novo and recurrent disease, was favorable across all subgroups of patients with high-volume and almost all subgroups with low-volume disease (Appendix Fig A1, online only).

In both high-risk and low-risk metastatic hormone-sensitive prostate cancer subgroups, darolutamide provided an OS benefit compared with placebo (high-risk, HR, 0.71; 95% CI, 0.58 to 0.86; low-risk, HR, 0.62; 95% CI, 0.42 to 0.90; Fig 3). In patients with high-risk disease, median survival was not reached in the darolutamide group versus 43.2 months (95% CI, 40.0 to 48.9 months) in the placebo group. In patients with low-risk disease, median survival was not reached in either treatment group.

Secondary Efficacy End Points

Darolutamide prolonged time to castration resistance compared with placebo in patients with high-volume (HR, 0.41; 95% CI, 0.34 to 0.49) and low-volume metastatic hormone-sensitive prostate cancer (HR, 0.21; 95% CI, 0.14 to 0.33) as well as in those with high-risk (HR, 0.38; 95% CI, 0.32 to 0.46) and low-risk metastatic hormone-sensitive prostate cancer (HR, 0.32; 95% CI, 0.23 to 0.45; Fig 3). The effects of darolutamide on other key clinically relevant secondary efficacy end points are shown in Table 2.

Safety. The incidence of AEs was similar between treatment groups across all high-volume and low-volume disease and high-risk and low-risk disease subgroups (Table 3). Incidences of serious AEs in patients receiving darolutamide compared with placebo were 45.4% versus 43.5% for those with high-volume disease, 42.9% versus 38.2% for patients with low-volume disease, 45.3% versus 42.9% for patients with high-risk disease, and 43.7% versus 40.9% for patients with low-risk disease. Discontinuations of darolutamide and placebo due to AEs occurred respectively in 13.3% and 10.7% of high-volume, 14.3% and 10.4% of low-volume, 12.8% and 9.8% of high-risk, and 15.1% and 12.4% of low-risk patients. Incidences of the most common AEs, occurring in 25% or more of patients, were similar between treatment groups across subgroups by disease volume and risk. The safety profile of darolutamide was confirmed on the basis of the exposure-adjusted incidence rates that account for the longer duration of treatment with darolutamide versus placebo (Table 3). AEs of special interest commonly associated with androgen receptor pathway inhibitors were consistent for disease volume and disease risk subgroups (Table 4).

DISCUSSION

Two previous studies have investigated the combination of an androgen receptor pathway inhibitor with ADT and docetaxel, with conflicting results in subgroups by disease volume. In the PEACE-1 trial of patients with de novo metastatic hormone-sensitive prostate cancer, 710 of 1,173 (61%) patients received ADT and docetaxel as their standard of care, and 64% of these patients met high-volume disease criteria.[8] An improvement in OS with abiraterone, ADT, and docetaxel was observed in patients

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TABLE 1. Baseline Demographics and Patient Characteristics for the Subgroups of Patients by Disease Volume and Disease Risk in ARASENS

	High Volume[a]		Low Volume[a]		High Risk[b]		Low Risk[b]		
Characteristic at Baseline	**Darolutamide (n = 497)**	**Placebo (n = 508)**	**Darolutamide (n = 154)**	**Placebo (n = 146)**	**Darolutamide (n = 452)**	**Placebo (n = 460)**	**Darolutamide (n = 199)**	**Placebo (n = 194)**	**All Patients (N = 1,305)**
Age, median, years (range)	67.0 (41-89)	67.0 (44-86)	67.0 (41-84)	67.5 (42-81)	67.0 (41-86)	67.0 (44-86)	67.0 (41-89)	67.0 (42-85)	67.0 (41-89)
ECOG PS,[c] No. (%)									
0	343 (69.0)	349 (68.7)	123 (79.9)	113 (77.4)	317 (70.1)	318 (69.1)	149 (74.9)	144 (74.2)	928 (71.1)
1	154 (31.0)	157 (30.9)	31 (20.1)	33 (22.6)	135 (29.9)	140 (30.4)	50 (25.1)	50 (25.8)	375 (28.7)
Missing	0	2 (0.4)	0	0	0	2 (0.4)	0	0	2 (0.2)
Gleason score at initial diagnosis,[d] No. (%)									
< 8	96 (19.3)	87 (17.1)	26 (16.9)	31 (21.2)	16 (3.5)	16 (3.5)	106 (53.3)	102 (52.6)	240 (18.4)
≥ 8	381 (76.7)	403 (79.3)	124 (80.5)	113 (77.4)	428 (94.7)	440 (95.7)	77 (38.7)	76 (39.2)	1,021 (78.2)
Missing	20 (4.0)	18 (3.5)	4 (2.6)	2 (1.4)	8 (1.8)	4 (0.9)	16 (8.0)	16 (8.2)	44 (3.4)
Metastasis stage at initial diagnosis, No. (%)									
De novo mHSPC	432 (86.9)	445 (87.6)	126 (81.8)	121 (82.9)	416 (92.0)	419 (91.1)	142 (71.4)	147 (75.8)	1,124 (86.1)
Recurrent mHSPC	58 (11.7)	59 (11.6)	28 (18.2)	23 (15.8)	33 (7.3)	39 (8.5)	53 (26.6)	43 (22.2)	168 (12.9)
Missing	7 (1.4)	4 (0.8)	0	2 (1.4)	3 (0.7)	2 (0.4)	4 (2.0)	4 (2.1)	13 (1.0)
Metastasis stage at screening, No. (%)									
M1a, nonregional LN only	0	0	23 (14.9)	15 (10.3)	0	0	23 (11.6)	15 (7.7)	38 (2.9)
M1b, bone metastases ± LN	386 (77.7)	390 (76.8)[e]	131 (85.1)	131 (89.7)	345 (76.3)	354 (77.0)[e]	172 (86.4)	167 (86.1)	1,038 (79.5)
M1c, visceral metastases ± LN or bone	111 (22.3)	118 (23.2)	0	0	107 (23.7)	106 (23.0)	4 (2.0)	12 (6.2)	229 (17.5)
Serum PSA level,[f] ng/mL, median (range)	38.7 (0-9,219.0)	27.9 (0-11,947.0)	11.7 (0-3,771.0)	14.5 (0-3,372.9)	34.0 (0-9,219.0)	30.0 (0-11,947.0)	19.2 (0-4,173.0)	12.4 (0-3,372.9)	27.6 (0-11,947.0)
Serum ALP level,[f] U/L, median (range)	199.0 (46-4,885)	172.0 (41-7,680)	84.5 (40-2,116)	87.5 (36-735)	183.0 (44-4,885)	161.5 (41-7,680)	99.0 (40-4,793)	97.0 (36-3,227)	143.0 (36-7,680)
ALP < ULN, No. (%)	168 (33.8)	176 (34.6)	122 (79.2)	115 (78.8)	165 (36.5)	166 (36.1)	125 (62.8)	125 (64.4)	581 (44.5)
ALP ≥ ULN, No. (%)	329 (66.2)	332 (65.4)	32 (20.8)	31 (21.2)	287 (63.5)	294 (63.9)	74 (37.2)	69 (35.6)	724 (55.5)

Abbreviations: ADT, androgen-deprivation therapy; ALP, alkaline phosphatase; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; ULN, upper level of normal.

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases or ≥ 4 bone metastases with ≥ 1 beyond vertebral bodies and pelvis (Sweeney et al).[1]

[b]Disease risk defined by LATITUDE criteria (two of the following three factors): Gleason score of ≥ 8, the presence of ≥ 3 bone lesions, or the presence of measurable visceral metastasis (Fizazi et al).[2]

[c]ECOG PS scores range from 0 to 5, with higher scores indicating greater disability.

[d]Gleason scores for the histologic pattern of carcinoma range from 6 to 10, with higher scores indicating a more aggressive form of prostate cancer.

[e]One patient had lymph node metastasis alone per direct entry in case report form but was categorized as M1b in the high-volume subgroup using detailed tumor data.

[f]These values were centrally assessed. Samples were obtained while patients were receiving ADT.

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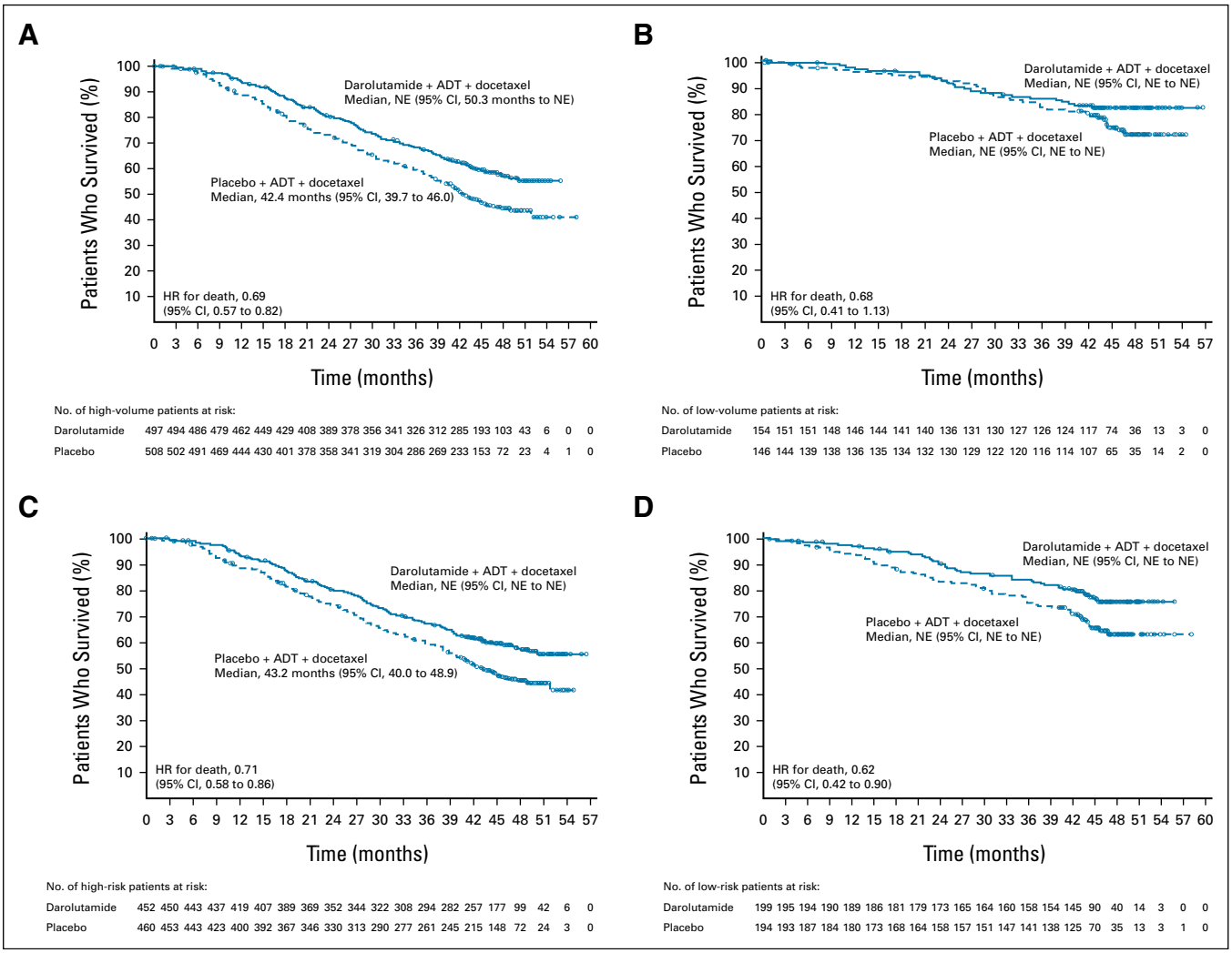

FIG 2. OS in subgroups of patients by (A) high-volume disease, (B) low-volume disease, (C) high-risk disease, and (D) low-risk disease in ARASENS. High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis.[1] High-risk disease was defined by two of the following three risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastases.[2] ADT, androgen-deprivation therapy; HR, hazard ratio; OS, overall survival; NE, not estimable.

with high-volume disease, with a risk reduction of 28% (HR, 0.72; 95.1% CI, 0.55 to 0.95). The risk reduction in patients with low-volume disease was 17% (HR, 0.83; 95.1% CI, 0.50 to 1.39), and data are currently immature for this subgroup. The open-label ENZAMET trial allowed for the use of docetaxel in patients with metastatic hormone-sensitive prostate cancer as a protocol amendment.[7] Among 503 of 1,125 (45%) patients who received docetaxel, 359 (71%) patients had high-volume disease.[10] Exploratory analyses of OS for those who received docetaxel showed a 13% risk reduction for enzalutamide versus control in patients with high-volume disease (HR, 0.87; 95% CI, 0.66 to 1.17) and a 39% risk reduction in patients with low-volume disease (HR, 0.61; 95% CI, 0.33 to 1.10).[10] A post hoc subgroup analysis suggested benefit of enzalutamide, ADT, and docetaxel in patients with de novo, high-volume disease (HR, 0.79; 95% CI, 0.57 to 1.10).

The results of this post hoc analysis of the ARASENS trial, in which all patients received docetaxel, show that darolutamide in combination with ADT and docetaxel increases OS in patients with metastatic hormone-sensitive prostate cancer. HRs were consistent across all disease volume and risk subgroups, with risk reductions of 31% and 32% for high- and low-volume disease and 29% and 38% for high- and low-risk disease, and similar to the overall ARASENS population. The small sample size in the low-volume subgroup (23% of ARASENS population) may have contributed to the HR CIs crossing 1.0 (HR, 0.68; 95% CI 0.41 to 1.13). Key patient-relevant secondary efficacy end points of time to castration-resistant prostate cancer and time to initiation of subsequent systemic antineoplastic therapy were consistently improved with darolutamide versus placebo in high- and low-disease volume and risk subgroups. Time to pain progression and symptomatic skeletal events showed improvement with HRs

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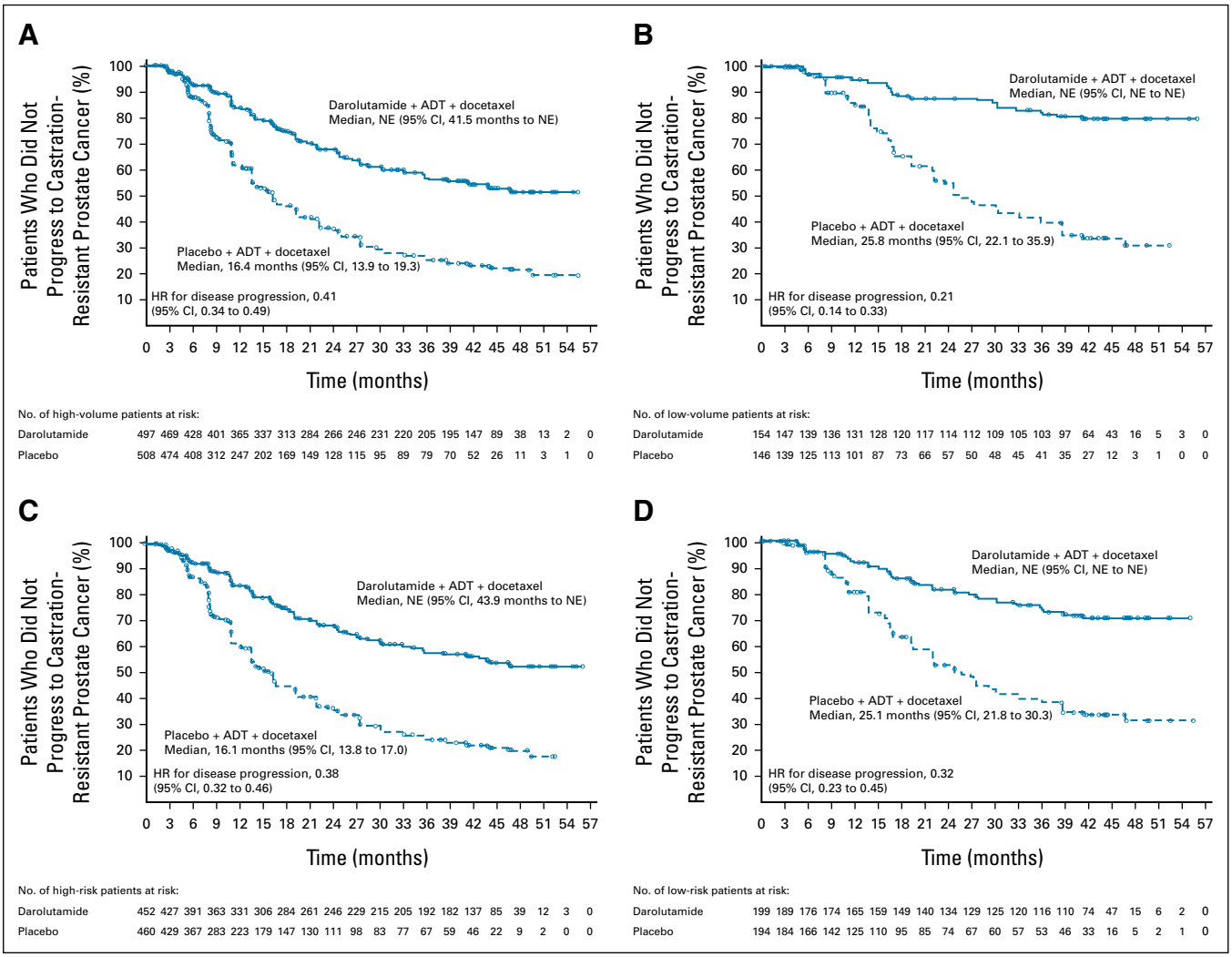

FIG 3. Time to castration-resistant prostate cancer in subgroups of patients by (A) high-volume disease, (B) low-volume disease, (C) high-risk disease, and (D) low-risk disease in ARASENS. High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis.[1] High-risk disease was defined by two of the following three risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastases.[2] ADT, androgen-deprivation therapy; HR, hazard ratio; NE, not estimable.

below one across all volume and risk subgroups, with greater variability in the low-volume and low-risk subgroups. These data provide important information to guide treatment selection for patients with metastatic hormone-sensitive prostate cancer, showing benefit of darolutamide, ADT, and docetaxel.

The favorable safety profile of darolutamide was confirmed in the subgroups of patients by disease volume and disease risk. Incidences of the most common AEs were similar between treatment groups by disease volume and risk subgroups, and many were known docetaxel-related AEs, such as alopecia, neutropenia, fatigue, and anemia. The incidences of most AEs commonly associated with androgen receptor pathway inhibitors in volume and risk subgroups were similar between treatment groups and consistent with the overall ARASENS population.[9] In addition, patients receiving darolutamide remained on treatment longer than those receiving placebo in all subgroups by disease volume and risk, indicating good tolerability of the combination of darolutamide with ADT and docetaxel. The PEACE-1 and ENZAMET trials did not report safety in subgroups of patients by disease volume. In PEACE-1, the addition of combination abiraterone and prednisone to ADT and docetaxel led to an 11% higher incidence of grade 3 to 5 AEs versus docetaxel plus ADT (63% *v* 52%). This difference was mostly due to hypertension and increased transaminase. Among all patients who received docetaxel in ENZAMET, the incidences of docetaxel-related AEs during the first 6 months were higher in the enzalutamide group versus the control group and could be associated with drug-drug interactions between enzalutamide and docetaxel.[7,18] Darolutamide demonstrates a low potential for clinically relevant drug-drug interactions with commonly administered drugs and docetaxel.[19] The

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TABLE 2. Secondary Efficacy End Points for the Subgroups of Patients by Disease Volume and Disease Risk in ARASENS

	High Volume[a]		Low Volume[a]		High Risk[b]		Low Risk[b]		All Patients[9] (N = 1,305)	
End Point, Median Months	**Darolutamide (n = 497)**	**Placebo (n = 508)**	**Darolutamide (n = 154)**	**Placebo (n = 146)**	**Darolutamide (n = 452)**	**Placebo (n = 460)**	**Darolutamide (n = 199)**	**Placebo (n = 194)**	**Darolutamide (n = 651)**	**Placebo (n = 654)**
Time to CRPC	NR	16.4	NR	25.8	NR	16.1	NR	25.1	NR	19.1
No. (%)[c]	198 (40)	315 (62)	27 (18)	76 (52)	175 (39)	289 (63)	50 (25)	102 (53)	225 (35)	391 (60)
HR (95% CI)	0.41 (0.34 to 0.49)		0.21 (0.14 to 0.33)		0.38 (0.32 to 0.46)		0.32 (0.23 to 0.45)		0.36 (0.30 to 0.42)	
Time to pain progression	NR	24.4	46.1	39.5	35.4	25.0	NR	28.8	NR	27.5
No. (%)[c]	161 (32)	192 (38)	61 (40)	56 (38)	155 (34)	173 (38)	67 (34)	75 (39)	222 (34)	248 (38)
HR (95% CI)	0.75 (0.61 to 0.93)		0.94 (0.66 to 1.36)		0.81 (0.65 to 1.01)		0.76 (0.55 to 1.06)		0.79 (0.66 to 0.95)	
SSE-free survival	46.1	35.7	NR	NR	47.1	35.8	NR	46.7	51.2	39.7
No. (%)[c]	225 (45)	287 (57)	32 (21)	42 (29)	205 (45)	257 (56)	52 (26)	72 (37)	257 (40)	329 (50)
HR (95% CI)	0.63 (0.53 to 0.75)		0.61 (0.38 to 0.96)		0.65 (0.54 to 0.78)		0.55 (0.39 to 0.79)		0.61 (0.52 to 0.72)	
Time to first SSE	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No. (%)[c]	82 (17)	96 (19)	13 (8)	12 (8)	78 (17)	79 (17)	17 (9)	29 (15)	95 (15)	108 (17)
HR (95% CI)	0.71 (0.53 to 0.96)		0.89 (0.40 to 1.95)		0.84 (0.61 to 1.15)		0.46 (0.25 to 0.84)		0.71 (0.54 to 0.94)	
Time to subsequent antineoplastic therapy	NR	22.7	NR	42.5	NR	21.3	NR	39.0	NR	25.3
No. (%)[c]	187 (38)	324 (64)	32 (21)	71 (49)	173 (38)	299 (65)	46 (23)	96 (49)	219 (34)	395 (60)
HR (95% CI)	0.40 (0.34 to 0.49)		0.34 (0.22 to 0.52)		0.40 (0.33 to 0.48)		0.36 (0.26 to 0.52)		0.39 (0.33 to 0.46)	
Time to worsening disease-related symptoms	22.0	22.1	11.1	11.2	19.3	16.7	19.4	24.6	19.3	19.4
No. (%)[c]	259 (52)	229 (45)	92 (60)	79 (54)	241 (53)	217 (47)	110 (55)	91 (47)	351 (54)	308 (47)
HR (95% CI)	1.05 (0.88 to 1.25)		1.04 (0.77 to 1.40)		1.01 (0.84 to 1.22)		1.13 (0.86 to 1.50)		1.04 (0.89 to 1.22)	
Time to opioid use ≥ 7 days	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No. (%)[c]	74 (15)	106 (21)	18 (12)	11 (8)	68 (15)	94 (20)	24 (12)	23 (12)	92 (14)	117 (18)
HR (95% CI)	0.63 (0.47 to 0.85)		1.46 (0.69 to 3.10)		0.66 (0.48 to 0.90)		0.94 (0.53 to 1.66)		0.69 (0.52 to 0.91)	

Abbreviations: CRPC, castration-resistant prostate cancer; mo, months; HR, hazard ratio; NR, not reached; SSE, symptomatic skeletal event.

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases or ≥ 4 bone metastases with ≥ 1 beyond vertebral bodies and pelvis (Sweeney et al).[1]

[b]Disease risk defined by LATITUDE criteria (two of the following three factors): Gleason score of ≥ 8, the presence of ≥ 3 bone lesions, or the presence of measurable visceral metastasis (Fizazi et al).[2]

[c]No. of patients with an event.

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TABLE 3. Treatment-Emergent AEs in the Subgroups of Patients by Disease Volume and Disease Risk in ARASENS

	High Volume[a]		Low Volume[a]		High Risk[b]		Low Risk[b]		All Patients[9] (N = 1302[c])	
AE	Darolutamide (n = 498)	Placebo (n = 506)	Darolutamide (n = 154)	Placebo (n = 144)	Darolutamide (n = 453)	Placebo (n = 457)	Darolutamide (n = 199)	Placebo (n = 193)	Darolutamide (n = 652)	Placebo (n = 650)
Any AE	496 (99.6)	500 (98.8)	153 (99.4)	143 (99.3)	450 (99.3)	451 (98.7)	199 (100)	192 (99.5)	649 (99.5)	643 (98.9)
Worst grade										
Grade 1	21 (4.2)	23 (4.5)	7 (4.5)	12 (8.3)	19 (4.2)	20 (4.4)	9 (4.5)	15 (7.8)	28 (4.3)	35 (5.4)
Grade 2	130 (26.1)	132 (26.1)	32 (20.8)	37 (25.7)	107 (23.6)	118 (25.8)	55 (27.6)	51 (26.4)	162 (24.8)	169 (26.0)
Grade 3	188 (37.8)	189 (37.4)	60 (39.0)	43 (29.9)	169 (37.3)	167 (36.5)	79 (39.7)	65 (33.7)	248 (38.0)	232 (35.7)
Grade 4	135 (27.1)	136 (26.9)	48 (31.2)	45 (31.3)	137 (30.2)	127 (27.8)	46 (23.1)	54 (28.0)	183 (28.1)	181 (27.8)
Grade 5 (death)[d]	21 (4.2)	20 (4.0)	6 (3.9)	6 (4.2)	17 (3.8)	19 (4.2)	10 (5.0)	7 (3.6)	27 (4.1)	26 (4.0)
Serious AE	226 (45.4)	220 (43.5)	66 (42.9)	55 (38.2)	205 (45.3)	196 (42.9)	87 (43.7)	79 (40.9)	292 (44.8)	275 (42.3)
AE leading to permanent discontinuation of trial agent										
Darolutamide or placebo	66 (13.3)	54 (10.7)	22 (14.3)	15 (10.4)	58 (12.8)	45 (9.8)	30 (15.1)	24 (12.4)	88 (13.5)	69 (10.6)
Docetaxel	39 (7.8)	54 (10.7)	13 (8.4)	13 (9.0)	38 (8.4)	45 (9.8)	14 (7.0)	22 (11.4)	52 (8.0)	67 (10.3)
Most common AEs (≥ 25%), No. (%)/EAIR										
Alopecia	192 (38.6)/15.3	202 (39.9)/23.1	72 (46.8)/15.2	62 (43.1)/18.9	191 (42.2)/16.6	183 (40.0)/23.3	73 (36.7)/12.5	81 (42.0)/19.5	264 (40.5)/15.3	264 (40.6)/22.0
Neutropenia[e]	197 (39.6)	199 (39.3)	59 (38.3)	53 (36.8)	192 (42.4)	182 (39.8)	64 (32.2)	70 (36.3)	256 (39.3)	252 (38.8)
Fatigue	166 (33.3)/13.2	165 (32.6)/18.9	50 (32.5)/10.6	49 (34.0)/15.0	141 (31.1)/12.3	130 (28.4)/16.5	75 (37.7)/12.9	84 (43.5)/20.2	216 (33.1)/12.5	214 (32.9)/17.8
Anemia	140 (28.1)/11.1	132 (26.1)/15.1	41 (26.6)/8.7	31 (21.5)/9.5	134 (29.6)/11.7	105 (23.0)/13.4	47 (23.6)/8.1	58 (30.1)/13.9	181 (27.8)/10.5	163 (25.1)/13.6
Peripheral edema	136 (27.3)/10.8	138 (27.3)/15.8	37 (24.0)/7.8	31 (21.5)/9.5	119 (26.3)/10.4	123 (26.9)/15.7	54 (27.1)/9.3	46 (23.8)/11.0	173 (26.5)/10.0	169 (26.0)/14.1
Arthralgia	134 (26.9)/10.7	134 (26.5)/15.3	44 (28.6)/9.3	40 (27.8)/12.2	125 (27.6)/10.9	118 (25.8)/15.0	53 (26.6)/9.1	56 (29.0)/13.4	178 (27.3)/10.3	174 (26.8)/14.5
Diarrhea	120 (24.1)/9.5	114 (22.5)/13.0	47 (30.5)/9.9	42 (29.2)/12.8	111 (24.5)/9.7	98 (21.4)/12.5	56 (28.1)/9.6	58 (30.1)/13.9	167 (25.6)/9.6	156 (24.0)/13.0

Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate.

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases or ≥ 4 bone metastases with ≥ 1 beyond vertebral bodies and pelvis (Sweeney et al).[1]

[b]Disease risk defined by LATITUDE criteria (two of the following three factors): Gleason score of ≥ 8, the presence of ≥ 3 bone lesions, or the presence of measurable visceral metastasis (Fizazi et al).[2]

[c]Three patients who underwent random assignment never received the assigned trial treatment; all three patients were in the placebo group. One patient who was assigned to the placebo group but received darolutamide was included in the darolutamide group of the safety analysis set.

[d]Specific grade 5 events are provided in the supplementary appendix of Smith et al.[9]

[e]Neutropenia includes preferred terms of leukopenia, neutropenia, decreased neutrophil count, and decreased white blood cell count. Exposure adjustment is not applicable, as the majority of AEs occurred during concomitant docetaxel treatment.

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TABLE 4. AEs of Special Interest for the Subgroups of Patients by Disease Volume and Disease Risk in ARASENS

	High Volume[a]		Low Volume[a]		High Risk[b]		Low Risk[b]		All Patients[c]	
AEs of Special Interest	**Darolutamide (n = 498)**	**Placebo (n = 506)**	**Darolutamide (n = 154)**	**Placebo (n = 144)**	**Darolutamide (n = 453)**	**Placebo (n = 457)**	**Darolutamide (n = 199)**	**Placebo (n = 193)**	**Darolutamide (n = 652)**	**Placebo (n = 650)**
Fatigue	166 (33.3)	165 (32.6)	50 (32.5)	49 (34.0)	141 (31.1)	130 (28.4)	75 (37.7)	84 (43.5)	216 (33.1)	214 (32.9)
Vasodilation/flushing	96 (19.3)	108 (21.3)	37 (24.0)	33 (22.9)	83 (18.3)	96 (21.0)	50 (25.1)	45 (23.3)	133 (20.4)	141 (21.7)
Rash[d]	78 (15.7)	71 (14.0)	30 (19.5)	17 (11.8)	72 (15.9)	67 (14.7)	36 (18.1)	21 (10.9)	108 (16.6)	88 (13.5)
Diabetes mellitus and hyperglycemia	69 (13.9)	70 (13.8)	30 (19.5)	23 (16.0)	60 (13.2)	63 (13.8)	39 (19.6)	30 (15.5)	99 (15.2)	93 (14.3)
Hypertension[e]	63 (12.7)	38 (7.5)	26 (16.9)	21 (14.6)	54 (11.9)	33 (7.2)	35 (17.6)	26 (13.5)	89 (13.7)	60 (9.2)
Cardiac disorder	56 (11.2)	60 (11.9)	15 (9.7)	16 (11.1)	44 (9.7)	47 (10.3)	27 (13.6)	29 (15.0)	71 (10.9)	76 (11.7)
Cardiac arrhythmia[e]	40 (8.0)	43 (8.5)	12 (7.8)	12 (8.3)	31 (6.8)	34 (7.4)	21 (10.6)	21 (10.9)	52 (8.0)	55 (8.5)
Coronary artery disorders[e]	16 (3.2)	10 (2.0)	3 (1.9)	3 (2.1)	14 (3.1)	7 (1.5)	5 (2.5)	6 (3.1)	19 (2.9)	13 (2.0)
Heart failure[e]	3 (0.6)	11 (2.2)	1 (0.6)	2 (1.4)	2 (0.4)	9 (2.0)	2 (1.0)	4 (2.1)	4 (0.6)	13 (2.0)
Bone fracture[f]	39 (7.8)	25 (4.9)	10 (6.5)	8 (5.6)	36 (7.9)	23 (5.0)	13 (6.5)	10 (5.2)	49 (7.5)	33 (5.1)
Falls, including accident	34 (6.8)	24 (4.7)	9 (5.8)	6 (4.2)	33 (7.3)	18 (3.9)	10 (5.0)	12 (6.2)	43 (6.6)	30 (4.6)
Mental impairment disorders[e]	17 (3.4)	11 (2.2)	6 (3.9)	4 (2.8)	18 (4.0)	10 (2.2)	5 (2.5)	5 (2.6)	23 (3.5)	15 (2.3)
Weight decreased	19 (3.8)	31 (6.1)	3 (1.9)	4 (2.8)	18 (4.0)	24 (5.3)	4 (2.0)	11 (5.7)	22 (3.4)	35 (5.4)
Depressed mood disorders[e]	16 (3.2)	16 (3.2)	5 (3.2)	8 (5.6)	9 (2.0)	12 (2.6)	12 (6.0)	12 (6.2)	21 (3.2)	24 (3.7)
Breast disorders/gynecomastia[e]	15 (3.0)	7 (1.4)	6 (3.9)	3 (2.1)	10 (2.2)	5 (1.1)	11 (5.5)	5 (2.6)	21 (3.2)	10 (1.5)
Cerebral ischemia	7 (1.4)	5 (1.0)	1 (0.6)	3 (2.1)	7 (1.5)	4 (0.9)	1 (0.5)	4 (2.1)	8 (1.2)	8 (1.2)
Seizure	3 (0.6)	1 (0.2)	1 (0.6)	0	2 (0.4)	0	2 (1.0)	1 (0.5)	4 (0.6)	1 (0.2)

NOTE. Data presented as No. (%).

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases or ≥ 4 bone metastases with ≥ 1 beyond vertebral bodies and pelvis (Sweeney et al).[1]

[b]Disease risk defined by LATITUDE criteria (2 of the following three factors): Gleason score of ≥ 8, the presence of ≥ 3 bone lesions, or the presence of measurable visceral metastasis (Fizazi et al).[2]

[c]Three patients who underwent random assignment never received the assigned trial treatment; all three patients were in the placebo group. One patient who was assigned to the placebo group but received darolutamide was included in the darolutamide group of the safety analysis set.

[d]This category combines the following MedDRA terms: rash, maculopapular rash, drug eruption, pruritic rash, erythematous rash, macular rash, popular rash, follicular rash, pustular rash, and vesicular rash.

[e]This category is a MedDRA High-Level Group Term.

[f]Excluding pathological fractures. This category combines the following MedDRA 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.

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median treatment duration in ARASENS was 41 months for darolutamide plus ADT and docetaxel versus 34.1 months in the docetaxel subgroup of the abiraterone group in PEACE-1 and not reported for the docetaxel subgroup in ENZAMET.

ARASENS was designed before results were reported for the LATITUDE trial, which showed an OS benefit with androgen receptor pathway inhibitors,[2] and before the long-term survival analysis of the CHAARTED trial.[15] The standard of care for patients with metastatic hormone-sensitive prostate cancer was ADT and docetaxel when ARASENS was designed. In the 2015 CHAARTED trial publication, the HR for OS in the low-volume subgroup was 0.60, with clear separation of the survival curves, and the authors concluded that docetaxel benefit was observed in all subgroups analyzed.[1] In the STAMPEDE trial, the survival effect of docetaxel was consistent for patients with low-volume (HR, 0.76; 95% CI, 0.54 to 1.07) and high-volume (HR, 0.81; 95% CI, 0.64 to 1.02) disease.[20] Consequently, the multinational ARASENS study was designed to stratify patients on the basis of the TNM staging system and alkaline phosphatase levels. However, the case report form collected all necessary information to conduct analyses by disease volume and risk post hoc to determine which patients would benefit from triple combination therapy. The high-volume and high-risk subgroups had two- to three-fold more patients than the respective low-volume and low-risk subgroups, and, therefore, for some subgroup analyses the number of events was small. Moreover, the majority of patients in ARASENS had de novo disease; thus, the volume and risk subgroups of patients with recurrent disease have insufficient power to draw definitive conclusions. Notably, the later separation in the survival curves in the low-volume subgroup is expected as these patients had better prognosis, with lower prostate-specific antigen and alkaline phosphatase levels at baseline. The late separation in the curves also indicates nonproportional hazards by treatment group for low-volume patients that may reduce the likelihood of detecting a treatment effect in this subgroup. However, it appears to represent a real treatment effect because a large proportion of patients continued in follow-up, with 124 of 154 (81%) in the darolutamide group and 114 of 146 (78%) in the placebo group still at risk beyond 3 years.

Results of ARASENS indicate an advantage to adding an androgen receptor inhibitor (darolutamide) to ADT and docetaxel, but other studies have shown that benefits are not consistent for all types of androgen receptor pathway inhibitors. Given the unique structure, benefit-risk profile, and limited drug-drug interactions of darolutamide,[9,21-23] the results of ARASENS should not be extrapolated to other second-generation androgen receptor pathway inhibitors. ARASENS was not designed to compare outcomes for triple combination therapy versus darolutamide plus ADT to evaluate whether docetaxel has added benefit in patients with metastatic hormone-sensitive prostate cancer. In patients with low-volume disease, an additional study evaluating the effect of a triple combination versus combination with ADT and androgen receptor pathway inhibitor might provide more information for optimal treatment selection.

In patients with high-volume and high-risk/low-risk metastatic hormone-sensitive prostate cancer, treatment intensification with darolutamide, ADT, and docetaxel increased OS, consistent with the overall population; the results in the low-volume subgroup were suggestive of survival benefit. The favorable safety profile of darolutamide was confirmed in the disease volume and risk subgroups.

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PRIOR PRESENTATION

Presented in part at the ASCO Genitourinary Cancer Symposium, San Francisco, CA, February 17-19, 2022; and the ASCO Genitourinary Cancer Symposium, San Francisco, CA, February 16-18, 2023.

SUPPORT

Supported by Bayer AG and Orion Pharma.

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CLINICAL TRIAL INFORMATION

NCT02799602

DATA SHARING STATEMENT

Availability of the data underlying this publication will be determined 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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00041.

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ACKNOWLEDGMENT

Statistical analyses were provided by Kevin Clark, MS, MPH, PT, of Bayer and Lei Li, MSc, of CHRESTOS Concept GmbH & Co KG. Writing and editorial support in the development of this manuscript was provided by Michelle McDermott, PharmD, and Lauren Gallagher RPh, PhD, of OPEN Health Communications, London, UK, with financial support from Bayer Healthcare. The authors retained full editorial control over the content of the manuscript and the decision to publish.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Patents, Royalties, Other Intellectual Property: TITLE: SYSTEMS AND METHODS FOR TISSUE IMAGING, 3,676 Our File: Serial Number: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753 US 8,185,186 (US patent number) Systems and methods for tissue imaging (issued patent) EP 08745653.9 (EP application number) Systems and methods for tissue imaging (pending) CA 2683805 (Canadian application number) Systems and methods for tissue imaging (pending) US 13/362,500 (US application number) Systems and Methods for Tissue Imaging (continuation application of US 8,185,186), TITLE: METHOD OF TREATING CANCER Docket No: Serial Number: 224,990/10-016P2/311,733 61/481/671 Application Filed on: 5/2/2011, TITLE: Dual Inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases. Applicant/Proprietor Exelexis, Inc Application No/Patent No. 11764665.4-1,464 Application No/Patent No. 11764656.2-1,464 Application Filed on: 26/9/2011
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No other potential conflicts of interest were reported.

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APPENDIX

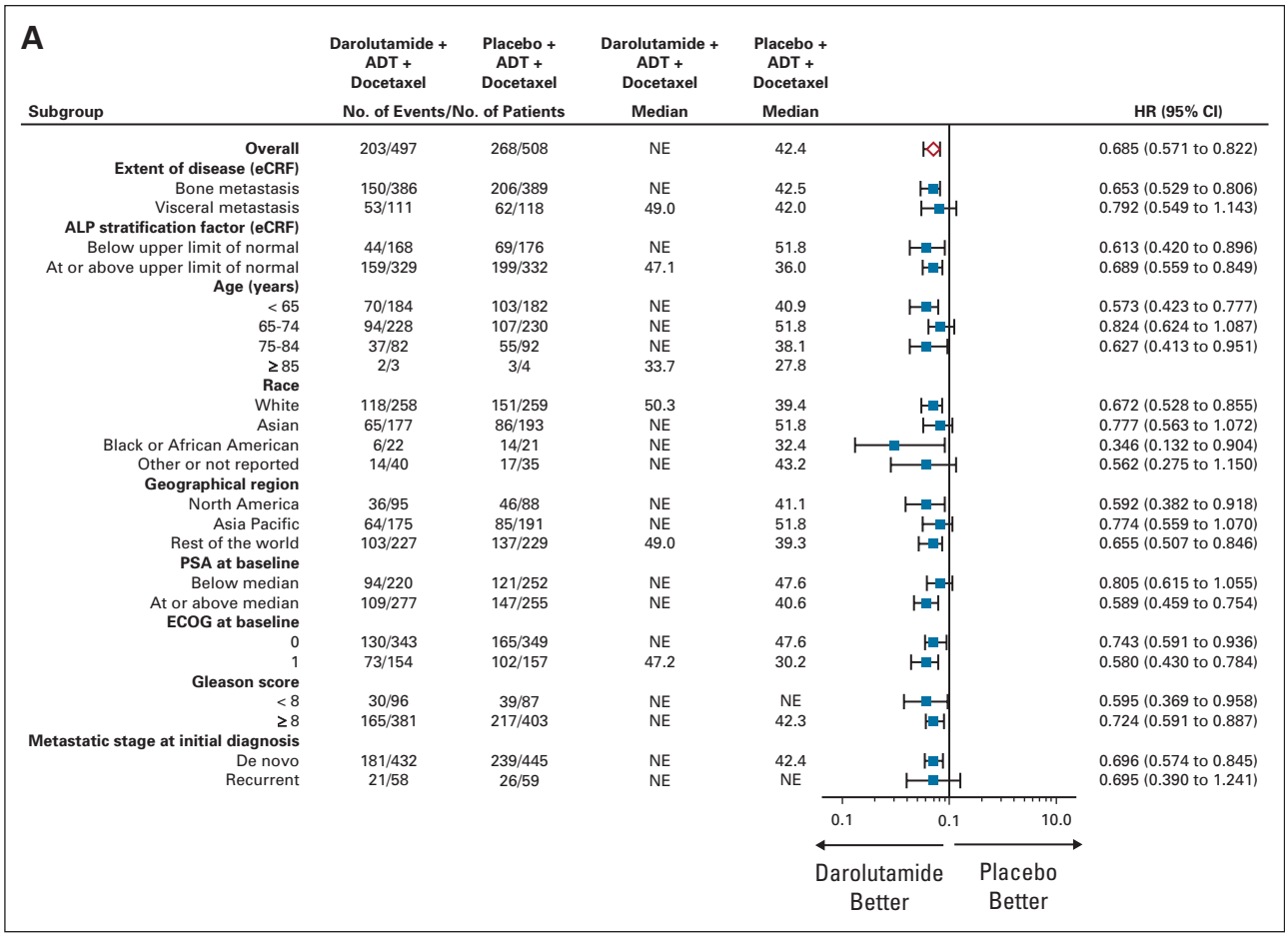

FIG A1. OS in prespecified subgroups for patients with (A) high-volume and (B) low-volume disease. HR estimates were obtained from univariate analysis using unstratified Cox regression. High-volume disease was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.[1] ADT, androgen-deprivation therapy; ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HR, hazard ratio; PSA, prostate-specific antigen; OS, overall survival; NE, not estimable. (continued on following page)

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B

Subgroup	Darolutamide + ADT + Docetaxel No. of Events/No. of Patients	Placebo + ADT + Docetaxel No. of Events/No. of Patients	Darolutamide + ADT + Docetaxel Median	Placebo + ADT + Docetaxel Median	HR (95% CI)
Overall	26/154	36/146	NE	NE	0.682 (0.412 to 1.130)
Extent of disease (eCRF)					
Nonregional lymph node metastasis	5/23	5/15	NE	NE	0.602 (0.174 to 2.082)
Bone metastasis	21/131	31/131	NE	NE	0.680 (0.391 to 1.184)
ALP stratification factor (eCRF)					
Below upper limit of normal	18/122	24/115	NE	NE	0.705 (0.383 to 1.299)
At or above upper limit of normal	8/32	12/31	NE	NE	0.667 (0.272 to 1.631)
Age (years)					
< 65	10/59	14/52	NE	NE	0.681 (0.302 to 1.534)
65-74	13/75	17/76	NE	NE	0.752 (0.365 to 1.548)
75-84	3/20	5/18	NE	NE	
Race					
White	13/87	22/74	NE	NE	
Asian	9/53	7/52	NE	NE	0.461 (0.232 to 0.916)
Black or African American	2/4	2/7	NE	NE	1.444 (0.537 to 3.881)
Other or not reported	2/10	5/13	NE	45.7	
Geographical region					
North America	6/30	10/31	NE	NE	0.602 (0.219 to 1.658)
Asia Pacific	10/54	7/53	NE	NE	1.617 (0.615 to 4.251)
Rest of the world	10/70	19/62	NE	NE	0.411 (0.191 to 0.885)
PSA at baseline					
Below median	16/95	21/85	NE	NE	0.680 (0.355 to 1.303)
At or above median	10/59	15/61	NE	NE	0.690 (0.310 to 1.535)
ECOG at baseline					
0	20/123	23/113	NE	NE	0.826 (0.454 to 1.504)
1	6/31	13/33	NE	NE	0.433 (0.165 to 1.140)
Gleason score					
< 8	3/26	5/31	NE	NE	
≥ 8	22/124	31/113	NE	NE	0.641 (0.371 to 1.108)
Metastatic stage at initial diagnosis					
De novo	25/126	32/121	NE	NE	0.755 (0.447 to 1.274)
Recurrent	1/28	4/23	NE	NE	

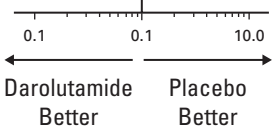

FIG A1. (Continued).

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TABLE A1. Subsequent Life-Prolonging Systemic Antineoplastic Therapy in Patient Subgroups by Disease Volume and Disease Risk in ARASENS

	High Volume[a]		Low Volume[a]		High Risk[b]		Low Risk[b]		All Patients[c]	
Subsequent Therapy[c]	**Darolutamide (n = 271)**	**Placebo (n = 402)**	**Darolutamide (n = 44)**	**Placebo (n = 93)**	**Darolutamide (n = 240)**	**Placebo (n = 364)**	**Darolutamide (n = 75)**	**Placebo (n = 131)**	**Darolutamide (n = 315)**	**Placebo (n = 495)**
Patients with subsequent life-prolonging systemic antineoplastic therapy	162 (59.8)	306 (76.1)	17 (38.6)	68 (73.1)	145 (60.4)	283 (77.7)	34 (45.3)	91 (69.5)	179 (56.8)	374 (75.6)
Abiraterone acetate	101 (37.3)	190 (47.3)	11 (25.0)	42 (45.2)	91 (37.9)	178 (48.9)	21 (28.0)	54 (41.2)	112 (35.6)	232 (46.9)
Enzalutamide	41 (15.1)	106 (26.4)	7 (15.9)	30 (32.3)	35 (14.6)	100 (27.5)	13 (17.3)	36 (27.5)	48 (15.2)	136 (27.5)
Cabazitaxel	53 (19.6)	75 (18.7)	4 (9.1)	14 (15.1)	48 (20.0)	65 (17.9)	9 (12.0)	24 (18.3)	57 (18.1)	89 (18.0)
Docetaxel	41 (15.1)	74 (18.4)	5 (11.4)	15 (16.1)	37 (15.4)	66 (18.1)	9 (12.0)	23 (17.6)	46 (14.6)	89 (18.0)
Radium-223	18 (6.6)	30 (7.5)	1 (2.3)	4 (4.3)	18 (7.5)	22 (6.0)	1 (1.3)	12 (9.2)	19 (6.0)	34 (6.9)
Sipuleucel-T	4 (1.5)	7 (1.7)	0	3 (3.2)	4 (1.7)	8 (2.2)	0	2 (1.5)	4 (1.3)	10 (2.0)
Lutetium-177 PSMA	2 (0.7)	7 (1.7)	0	0	2 (0.8)	7 (1.9)	0	0	2 (0.6)	7 (1.4)
Apalutamide	2 (0.7)	1 (0.2)	0	1 (1.1)	2 (0.8)	2 (0.5)	0	0	2 (0.6)	2 (0.4)
Other systemic antineoplastic therapy	25 (9.2)	18 (4.5)	15 (34.1)	3 (3.2)	28 (11.7)	16 (4.4)	12 (16.0)	5 (3.8)	40 (12.7)	21 (4.2)

NOTE. Data presented as No. (%).

Abbreviation: PSMA, prostate-specific membrane antigen.

[a]Disease volume defined by CHAARTED criteria: presence of visceral metastases or ≥ 4 bone metastases with ≥ 1 beyond vertebral bodies and pelvis (Sweeney et al).[1]

[b]Disease risk defined by LATITUDE criteria (2 of the following three factors): Gleason score of ≥ 8, the presence of ≥ 3 bone lesions, or the presence of measurable visceral metastasis (Fizazi et al).[2]

[c]At the data cutoff date (October 25, 2021), 45.9% of patients in the darolutamide group and 19.1% of patients in the placebo group were receiving ongoing study treatment. The denominators are the number of patients who entered active or long-term follow-up, plus one patient who did not enter follow-up but received subsequent therapy. Patients could receive > 1 subsequent life-prolonging systemic antineoplastic therapy.

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