ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

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abstract

PURPOSE Enzalutamide, a potent androgen-receptor inhibitor, has demonstrated significant benefits in metastatic and nonmetastatic castration-resistant prostate cancer. We evaluated the efficacy and safety of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).

METHODS ARCHES (ClinicalTrials.gov identifier: NCT02677896) is a multinational, double-blind, phase III trial, wherein 1,150 men with mHSPC were randomly assigned 1:1 to enzalutamide (160 mg/day) or placebo, plus androgen deprivation therapy (ADT), stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-free survival.

RESULTS As of October 14, 2018, the risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (hazard ratio, 0.39; 95% CI, 0.30 to 0.50; $P < .001$; median not reached v 19.0 months). Similar significant improvements in radiographic progression-free survival were reported in prespecified subgroups on the basis of disease volume and prior docetaxel therapy. Enzalutamide plus ADT significantly reduced the risk of prostate-specific antigen progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression. More men achieved an undetectable prostate-specific antigen level and/or an objective response with enzalutamide plus ADT ($P < .001$). Patients in both treatment groups reported a high baseline level of quality of life, which was maintained over time. Grade 3 or greater adverse events were reported in 24.3% of patients who received enzalutamide plus ADT versus 25.6% of patients who received placebo plus ADT, with no unexpected adverse events.

CONCLUSION Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time versus placebo plus ADT in men with mHSPC, including those with low-volume disease and/or prior docetaxel, with a safety analysis that seems consistent with the safety profile of enzalutamide in previous clinical trials in castration-resistant prostate cancer.

INTRODUCTION

Globally, prostate cancer was the most common cancer for men, with 1.4 million patients in 2016; mortality was 381,000.[1] In the United States, 174,650 new cases of prostate cancer are expected in 2019, with 31,620 anticipated deaths.[2] The majority of deaths from prostate cancer are due to metastatic disease, identified either at diagnosis or after relapse following local therapies.[3]

Metastatic hormone-sensitive prostate cancer (mHSPC), defined as patients with metastatic disease who have not yet received, or are continuing to respond to, hormone therapy, accounts for up to 5% of annual prostate cancer incidence in the United States.[4] Androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone agonist/receptor antagonist or bilateral orchiectomy has been the standard of care (SOC) for men with mHSPC.[5] However, the majority of men with mHSPC who receive ADT alone progress to castration-resistant disease within 1 to 3 years, despite experiencing an initial response.[5-7]

Previous trials in men with mHSPC combining ADT with other treatments such as docetaxel chemotherapy[6,8] or the selective androgen biosynthesis inhibitor abiraterone acetate,[9-11] hereafter referred to as abiraterone,

have demonstrated significant clinical benefits, including significantly improved overall survival (OS), and these combinations are now included in treatment guidelines as part of the SOC.[12,13] Abiraterone plus ADT is approved in combination with prednisone for men with metastatic high-risk castration-sensitive prostate cancer,[14,15] on the basis of the LATITUDE trial (ClinicalTrials.gov identifier: NCT01715285),[10] which exclusively enrolled men with high-risk mHSPC and excluded previous chemotherapy.

The efficacy and safety of enzalutamide, a potent androgen-receptor (AR) inhibitor,[16] has been demonstrated across the spectrum of castration-resistant prostate cancer (CRPC) by numerous, large-scale, randomized, controlled clinical trials.[17-21] In addition, a phase II, open-label, single-arm study investigating enzalutamide monotherapy in patients with hormone-naïve prostate cancer demonstrated long-term reductions in prostate-specific antigen (PSA) levels, with minimal changes in overall bone mineral density and global health status.[22-24]

Two recent studies that investigated abiraterone in addition to ADT excluded men with prior docetaxel chemotherapy and did not include prospective evaluation of results by disease volume (high *v* low).[10,11] ARCHES (Clinical-Trials.gov identifier: NCT02677896) aimed to assess efficacy and safety of enzalutamide plus ADT in men with mHSPC, regardless of prior docetaxel or disease volume. We hypothesized that enzalutamide, in combination with ADT, would prolong radiographic progression-free survival (rPFS) in men with mHSPC, compared with ADT alone.

METHODS

Study Design and Conduct

ARCHES is a multinational, double-blind, randomized, placebo-controlled, phase III trial. The study protocol was approved by local independent review boards and conducted according to provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent. An independent Data Safety Monitoring Board (DSMB) evaluated unblinded safety data on an ongoing basis. Please refer to the Disclosures for full information on data sharing.

Patients and Treatments

Eligible patients were adult (defined according to local regulation) males with pathologically confirmed prostate adenocarcinoma, without neuroendocrine differentiation, signet-cell, or small-cell features, and an Eastern Cooperative Oncology Group performance status score of 0 or 1. Eligible patients had hormone-sensitive metastatic disease, either de novo or after recurrence after prior local therapy, documented by a positive bone scan, or metastatic lesions on computed tomography or magnetic resonance imaging. Enrollment was based on investigator-assessed metastases; after study entry, metastasis was evaluated by independent central review. Prior ADT and up to six cycles of prior docetaxel chemotherapy were permitted. Patients who experienced disease progression prior to randomization while receiving ADT and/or docetaxel were excluded. Additional details regarding inclusion/exclusion criteria are provided in the Data Supplement.

Patients were centrally randomized 1:1 to enzalutamide (160 mg/day) plus ADT or placebo plus ADT, stratified by disease volume (low *v* high) and prior docetaxel chemotherapy for prostate cancer (no cycles, one to five cycles, or six cycles). High-volume disease was defined as presence of metastases involving the viscera, or in the absence of visceral lesions, four or more bone lesions, one or more of which must have been in a bony structure beyond the vertebral column and pelvic bone, per CHAARTED (ClinicalTrials.gov identifier: NCT00309985) criteria.[6] Treatment continued until occurrence of unacceptable toxicity, radiographic progression (confirmed by independent central review), or initiation of an investigational agent or new prostate cancer therapy. Subsequent therapy after treatment discontinuation was permitted per local practice. On the basis of the primary analysis results and DSMB recommendation of study continuation, eligible patients were offered the opportunity to transition to an open-label extension.

End Points

The primary end point was rPFS, defined as the time from randomization to the first objective evidence of radiographic disease progression, as assessed by independent central review or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurred first. The cutoff of 24 weeks from study drug discontinuation (ie, the second long-term follow-up visit) for deaths (in the absence of disease progression) ensured a similar follow-up period as for monitoring of radiographic progression (ie, two 12-week radiologic assessment cycles post-treatment discontinuation). In addition, sensitivity analyses for rPFS were performed, including all deaths (in the absence of evidence of radiographic progression) regardless of timing, and radiographic progression documented by central review according to Prostate Cancer Working Group 2 criteria,[25] to assess the robustness of the primary analysis; additional details are provided in Data Supplement Table A1. Key secondary end points were time to PSA progression, time to initiation of new antineoplastic therapy (including cytotoxic and hormone therapies), PSA undetectable rate, objective response rate, time to deterioration in urinary symptoms, and OS. Other secondary end points included time to first symptomatic skeletal event, time to castration resistance, patient-reported outcomes (PROs), time to deterioration of quality of life (QoL), and time to pain progression. Additional prespecified analyses, per a separate PRO statistical analysis plan (SAP),

included QoL over time and sensitivity analyses of time to pain progression (using other clinically meaningful threshold criteria). Safety was also assessed. End point definitions are provided in Data Supplement Table A1.

Assessments

Efficacy assessments included sequential radiographic imaging performed at screening, at week 13, and every subsequent 12 weeks. Radiographic progression events were confirmed by independent central review; details regarding the definition of radiographic progression, including confirmatory scans required for new bone lesions observed over time, are provided in Data Supplement Table A2. PSA levels were measured at screening, at weeks 1, 5, and 13, every subsequent 12 weeks, and 30 days after the last dose or prior to initiation of new antineoplastic therapy for prostate cancer, whichever occurred first. PRO assessments, such as Functional Assessment of Cancer Therapy–Prostate,[26] Quality of Life Prostate-Specific questionnaire 25,[27] and Brief Pain Inventory–Short Form (BPI-SF), were completed at baseline, week 13, and every 12 weeks thereafter. Adverse events (AEs) were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Statistical Analysis

The final rPFS analysis was planned to occur after 262 events, to detect a hazard ratio (HR) of 0.67 with 90% power, on the basis of a two-sided log-rank test and 5% significance level. To adjust for multiplicity, a parallel testing strategy was applied to the key secondary end points (Appendix Fig A1, online only). Key secondary end points, other than OS, were sequentially tested at a 1% significance level. A final OS analysis will be performed when 342 deaths have occurred to provide 80% power to detect an HR of 0.73 at a 4% significance level. An interim OS analysis was performed at the time of the final rPFS analysis at a significance level calculated using the O'Brien-Fleming function to control the overall alpha. Additional details regarding the statistical analyses (original and final) are provided in the Data Supplement (Fig A1 and Table A1) and Protocol (including SAP).

RESULTS

Patients and Treatment

From March 21, 2016, to January 12, 2018, a total of 1,150 patients were randomly assigned 1:1 from 202 centers in North and Latin America, Europe, and Asia; 1,146 patients received at least one dose of the study drug (Fig 1). Baseline demographics were well balanced between treatment groups (Table 1); 727 patients (63.2%) had high-volume disease, and 205 (17.9%) received prior docetaxel chemotherapy. Use of concomitant antiandrogens as prostate cancer therapy during the study was reported by

34 patients (5.9%) in the enzalutamide plus ADT group and 43 patients (7.5%) in the placebo plus ADT group.

As of the data cutoff on October 14, 2018, median follow-up time was 14.4 months. Overall, 377 patients (32.8%) discontinued study treatment (enzalutamide plus ADT, n = 135 [23.5%]; placebo plus ADT, n = 242 [42.0%]). The primary reason for treatment discontinuation was progressive disease (enzalutamide plus ADT, n = 65 [11.3%] v placebo plus ADT, n = 171 [29.7%]), followed by patient withdrawal (n = 25 [4.4%] v n = 30 [5.2%], respectively; Fig 1).

rPFS

At data cutoff, 292 radiographic disease progression events or deaths without radiographic disease progression within 24 weeks of treatment discontinuation had occurred (enzalutamide plus ADT, n = 91 [15.9%]; placebo plus ADT, n = 201 [34.9%]; Table 2). Overall, enzalutamide plus ADT significantly reduced the risk of radiographic disease progression or death compared with placebo plus ADT by 61% (HR, 0.39; 95% CI, 0.30 to 0.50; $P < .001$; Fig 2A). Median rPFS was not reached (NR) with enzalutamide plus ADT (95% CI, NR to NR) versus 19.0 months (95% CI, 16.6 to 22.2 months) with placebo plus ADT. The treatment effect of enzalutamide plus ADT was consistent across all prespecified subgroups, including disease volume and prior docetaxel chemotherapy (Fig 2B). A sensitivity analysis of rPFS, including all deaths (in the absence of evidence of radiographic disease progression) regardless of timing, and a sensitivity analysis of radiographic progression documented by central review according to Prostate Cancer Working Group 2 criteria[25] were both consistent with the primary analysis (Table 2).

Secondary End Points

The superiority of enzalutamide plus ADT over placebo plus ADT was shown for the key secondary end points of time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, and objective response rate (Table 2; Fig 3). Although the median time to initiation of a new antineoplastic agent of 30.2 months in the enzalutamide arm is not a reliable estimate because it resulted from an event observed in the only remaining patient at risk, the treatment effect was robust, as evidenced by the HR of 0.28 (95% CI, 0.20 to 0.40; $P < .001$). Of the patients who initiated new antineoplastic therapy, the most common therapy was abiraterone (n = 13; 28.3%) followed by docetaxel (n = 11; 23.9%) in the enzalutamide plus ADT group and docetaxel (n = 52; 39.1%) followed by abiraterone and enzalutamide (n = 28 each; 21.1%) in the placebo plus ADT group (Data Supplement Table A3). At this interim OS analysis, data were immature, with 84 deaths (enzalutamide plus ADT, n = 39; placebo plus ADT, n = 45; median duration of OS was NR in either treatment group (HR, 0.81; 95% CI, 0.53 to 1.25; $P = .3361$; Table 2; Data Supplement Fig A2). Enzalutamide plus ADT also significantly reduced the risk of a first symptomatic skeletal
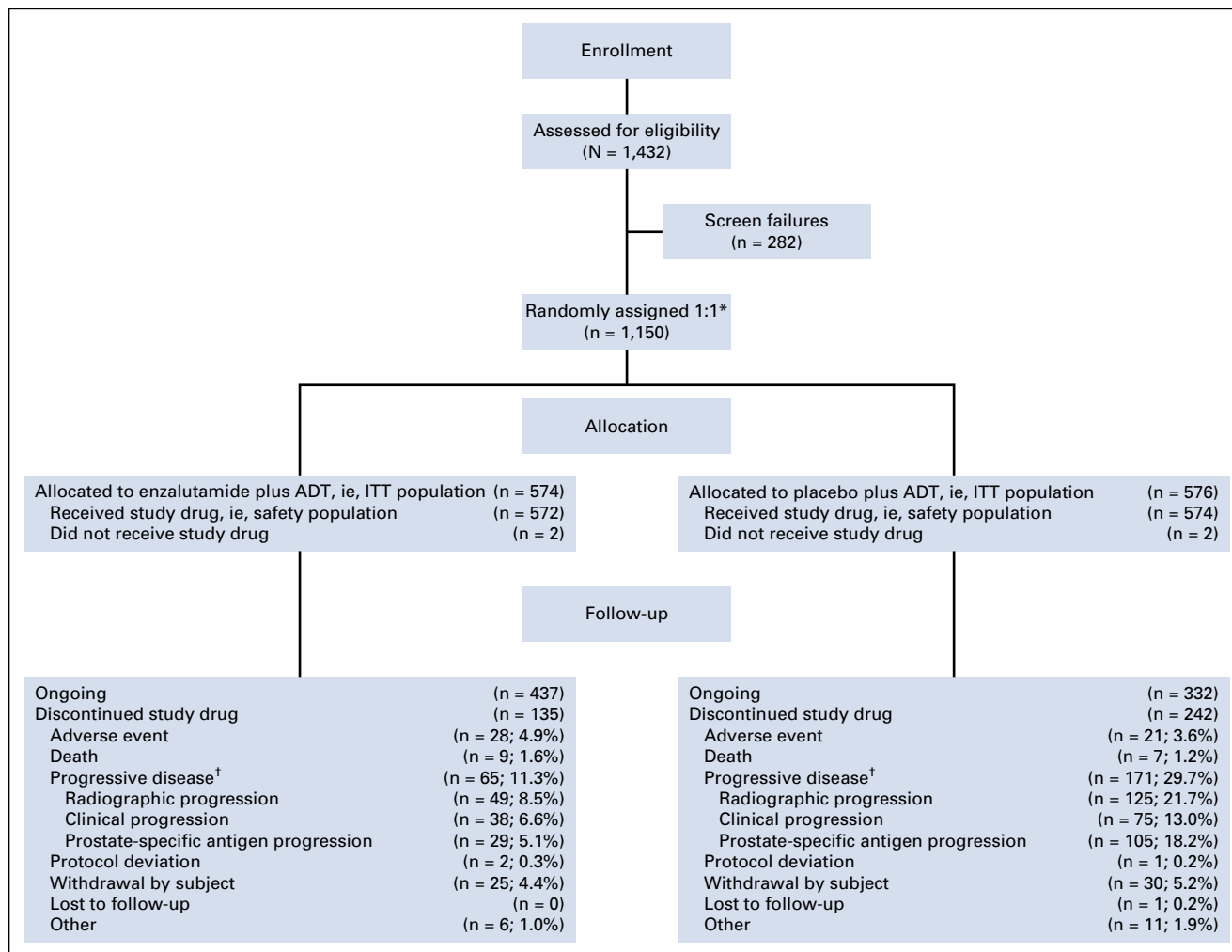
FIG 1. CONSORT diagram. (*) Randomization 1:1 was stratified by volume of disease (low *v* high) and prior docetaxel therapy for prostate cancer (no cycles, one to five cycles, or six cycles); high volume of disease was defined as presence of metastases involving the viscera, or in the absence of visceral lesions, four or more bone lesions, one or more of which must have been in a bony structure beyond the vertebral column and pelvic bone, per CHAARTED (ClinicalTrials.gov identifier: NCT00309985) criteria.[6] (†) Progressive disease types are not mutually exclusive; the same patient may be reported in multiple categories. ADT, androgen deprivation therapy; ITT, intent-to-treat.

event (Table 2; Fig 3) and castration resistance (Table 2; Data Supplement Fig A3).

Mean Functional Assessment of Cancer Therapy–Prostate total score, as a global indicator of QoL, was high at baseline for both treatment groups (Table 1) and remained high over time (Data Supplement Fig A4). Enzalutamide plus ADT did not significantly affect time to deterioration in urinary symptoms or QoL compared with placebo plus ADT (Table 2). Although the analysis of time to pain progression, with progression defined as a 30% or greater increase from baseline in average BPI-SF pain severity score, was not delayed (Table 2), prespecified sensitivity analyses from the PRO SAP, using a clinically significant 2-point or greater increase from baseline in average BPI-SF score as the progression threshold, demonstrated that enzalutamide plus ADT delayed time to pain progression for worst pain

and pain severity versus placebo plus ADT (Table 2; Data Supplement Fig A5).

Safety

Median treatment duration was 12.8 months (range, 0.2 to 26.6 months) in the enzalutamide plus ADT group and 11.6 months (range, 0.2 to 24.6 months) in the placebo plus ADT group. Grade 3 or greater AEs, serious AEs, and AEs leading to treatment discontinuation were reported in similar proportions of patients in both treatment groups (Table 3). There were no unexpected AEs; of the 14 AEs (2.4%) leading to death in the enzalutamide plus ADT group and 10 (1.7%) in the placebo plus ADT group, none were assessed by the investigator to be related to treatment in the enzalutamide plus ADT group, whereas one event (general physical health deterioration)

TABLE 1. Baseline Demographics

Characteristic	Enzalutamide Plus ADT (n = 574)	Placebo Plus ADT (n = 576)
Age (years)		
Median	70.0	70.0
Range	46-92	42-92
Age category, years		
< 65	148 (25.8)	152 (26.4)
65-74	256 (44.6)	255 (44.3)
≥ 75	170 (29.6)	169 (29.3)
Race[a]		
White	466 (81.2)	460 (79.9)
Asian	75 (13.1)	80 (13.9)
Black or African American	8 (1.4)	8 (1.4)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	2 (0.3)	3 (0.5)
Missing	23 (4.0)	25 (4.3)
Geographic region		
Europe	341 (59.4)	344 (59.7)
Asia-Pacific	104 (18.1)	113 (19.6)
North America	86 (15.0)	77 (13.4)
South America	32 (5.6)	30 (5.2)
Other	11 (1.9)	12 (2.1)
ECOG performance status score on day 1		
0	448 (78.0)	443 (76.9)
1	125 (21.8)	133 (23.1)
Total Gleason score at initial diagnosis		
< 8	171 (29.8)	187 (32.5)
≥ 8	386 (67.2)	373 (64.8)
Confirmed metastases at screening[b]		
Yes	536 (93.4)	531 (92.2)
No	34 (5.9)	45 (7.8)
Unknown	4 (0.7)	0
Localization of confirmed metastases at screening[b]		
Bone only	268 (46.7)	245 (42.5)
Soft tissue only	51 (8.9)	45 (7.8)
Bone and soft tissue	217 (37.8)	241 (41.8)
Distant metastasis at initial diagnosis		
M1	402 (70.0)	365 (63.4)
M0	83 (14.5)	86 (14.9)
MX/unknown	88 (15.3)	125 (21.7)
Disease volume		
High[c]	354 (61.7)	373 (64.8)
Low	220 (38.3)	203 (35.2)
(continued on following page)		

TABLE 1. Baseline Demographics (continued)

Characteristic	Enzalutamide Plus ADT (n = 574)	Placebo Plus ADT (n = 576)
Prior local therapy		
Radical prostatectomy	72 (12.5)	89 (15.5)
Radiation therapy	73 (12.7)	72 (12.5)
No. of cycles of prior docetaxel chemotherapy		
0	471 (82.1)	474 (82.3)
1-5	14 (2.4)	11 (1.9)
6	89 (15.5)	91 (15.8)
Previous use of ADT[d]		
None	39 (6.8)	61 (10.6)
≤ 3 months	414 (72.1)	394 (68.4)
> 3 months	121 (21.1)	120 (20.8)
Unknown[e]	0	1 (0.2)
Median duration of prior ADT, months (range)[f]	1.6 (0.03-55.3)	1.6 (0.03-198.8)
Previous use of antiandrogen[g]	205 (35.8)	229 (39.9)
Median PSA, ng/mL (range)[g]	5.4 (0-4,823.5)	5.1 (0-19,000.0)
Modified QLQ-PR25 urinary symptoms score, mean (SD)[h]	35.2 (25.3)	35.8 (25.4)
FACT-P total score, mean (SD)[i]	113.9 (19.8)	112.7 (19.0)
BPI-SF item 3 (worst pain), mean (SD)[j]	1.8 (2.4)	1.8 (2.3)
BPI-SF pain severity score, mean (SD)[j]	1.4 (1.8)	1.4 (1.7)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory–Short Form; ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy–Prostate; MX, distant metastasis cannot be assessed (not evaluated by any modality); M0, no distant metastasis; M1, distant metastasis; PSA, prostate-specific antigen; QLQ-PR25, Quality of Life Prostate-Specific questionnaire; SD, standard deviation.

[a]By country regulations, race is not collected in France.

[b]Assessed by independent central review after investigator assessment at study entry.

[c]Defined by CHAARTED criteria[6] as presence of metastases involving the viscera, or, in the absence of visceral lesions, four or more bone lesions, one or more of which must be in a bony structure beyond the vertebral column and pelvic bone; some study sites incorrectly reported disease volume information for some patients at the time of randomization, which was corrected during medical review on study entry, resulting in a difference of approximately 20 patients with either high or low disease volume between the treatment arms.

[d]Includes the time since bilateral orchiectomy for patients who had prior bilateral orchiectomy.

[e]The patient had prior ADT; however, the duration of ADT use was unknown.

[f]Intent-to-treat patients who had received prior ADT (enzalutamide plus ADT, n = 535; placebo plus ADT, n = 514).

[g]Safety-analysis-set patients (enzalutamide plus ADT, n = 572; placebo plus ADT, n = 574).

[h]Intent-to-treat patients who had a baseline modified QLQ-PR25 urinary symptoms score (enzalutamide plus ADT, n = 539; placebo plus ADT, n = 546). Only items Q31-Q33 from the urinary symptoms subscale were assessed. All items and scale scores of the QLQ-PR25 are linearly transformed to a 0 to 100 scale. A higher score in the urinary symptoms subscale indicates more symptoms.[27]

[i]Intent-to-treat patients who had a baseline Functional Assessment of Cancer Therapy–Prostate total score (enzalutamide plus ADT, n = 550; placebo plus ADT, n = 553). The Functional Assessment of Cancer Therapy–Prostate total score ranges from 0 to 156, with the higher scores indicating more favorable quality of life.[26]

[j]Intent-to-treat patients who had baseline average Brief Pain Inventory–Short Form worst pain and pain severity scores (enzalutamide plus ADT, n = 542; placebo plus ADT, n = 552). The Brief Pain Inventory–Short Form average score ranges from 0 to 10, with higher scores indicating worse pain.

was assessed by the investigator to be related in the placebo plus ADT group.

DISCUSSION

In this phase III trial involving men with mHSPC, adding enzalutamide to ADT significantly reduced the risk of radiographic disease progression or death by 61% compared with placebo plus ADT (HR, 0.39; $P < .001$). Significant improvements with enzalutamide plus ADT were also observed in secondary efficacy end points. OS data are immature and will be analyzed when 342 deaths have occurred. Preliminary safety analysis showed an acceptable safety profile that seems consistent with that in

TABLE 2. Primary and Secondary End Points

End Point	Enzalutamide Plus ADT (n = 574)	Placebo Plus ADT (n = 576)	HR (95% CI)	P
Primary end point				
Median rPFS, months	NR	19.0	0.39 (0.30 to 0.50)	< .001
Radiographic progression	79 (13.8)	188 (32.6)		
Prespecified sensitivity analysis (using PCWG2)[a]	NR	19.4	0.39 (0.30 to 0.50)	< .001
Death within 24 weeks of treatment discontinuation in the absence of radiographic progression	12 (2.1)	13 (2.3)		
Prespecified sensitivity analysis (all deaths)[b]	NR	19.0	0.39 (0.30 to 0.50)	< .001
Key secondary end points				
Median time to PSA progression (months)	NR	NR	0.19 (0.13 to 0.26)	< .001
Median time to initiation of new antineoplastic therapy (months)	30.2	NR	0.28 (0.20 to 0.40)	< .001
PSA undetectable (< 0.2 ng/mL) rate[c]	348 (68.1)	89 (17.6)		< .001
Objective response rate[d]	147 (83.1)	116 (63.7)		< .001
Complete response	65 (36.7)	42 (23.1)		
Partial response	82 (46.3)	74 (40.7)		
Stable disease	17 (9.6)	43 (23.6)		
Progressive disease	7 (4.0)	9 (4.9)		
NE/NA	6 (3.4)	14 (7.7)		
Median time to deterioration of urinary symptoms (months)[e]	NR	16.8	0.88 (0.72 to 1.08)	.2162
Median OS (months)	NR	NR	0.81 (0.53 to 1.25)	.3361
Other secondary end points				
Median time to first SSE, months	NR	NR	0.52 (0.33 to 0.80)	.0026
Median time to castration resistance, months	NR	13.8	0.28 (0.22 to 0.36)	< .001
Median time to deterioration of QoL (months)[f]	11.3	11.1	0.96 (0.81 to 1.14)	.6548
Median time to pain progression (months)[g]	8.3	8.3	0.92 (0.78 to 1.07)	.2715
Prespecified sensitivity analyses of time to pain progression from the PRO SAP				
Median time to worst pain (item 3) (months)[h]	14.1	11.1	0.82 (0.69 to 0.98)	.0322
Median time to pain severity (months)[h]	19.4	16.8	0.79 (0.65 to 0.97)	.0209

NOTE. All data are No. (%) unless otherwise specified.

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; NA, not applicable; NE, not evaluable; NR, not reached; OS, overall survival; PCWG2, Prostate Cancer Working Group 2; PRO, patient-reported outcome; PSA, prostate-specific antigen; QoL, quality of life; rPFS, radiographic progression-free survival; SAP, statistical analysis plan; SSE, symptomatic skeletal event.

[a]Radiographic progression was documented by central review according to Prostate Cancer Working Group 2 criteria for bone assessment.[25]

[b]All deaths (in the absence of evidence of radiographic progression), regardless of timing, were included.

[c]This analysis was conducted using intent-to-treat patients who had detectable PSA values at baseline (enzalutamide plus ADT, n = 511; placebo plus ADT, n = 506).

[d]Objective response is defined as patients achieving a complete or partial response in their soft tissue disease using the Response Evaluation Criteria in Solid Tumors (version 1.1).[28] Patients with no postbaseline assessment at any visit are reported in the NE category. This analysis was conducted using intent-to-treat patients who had measurable soft tissue disease at baseline (enzalutamide plus ADT, n = 177; placebo plus ADT, n = 182).

[e]A deterioration in urinary symptoms is defined as an increase in the urinary symptoms subscale score by ≥ 50% of the standard deviation observed in the urinary symptoms subscale score at baseline (ie, Q31-Q33).

[f]A deterioration of QoL is defined as a decrease of ≥ 10 points in the total Functional Assessment of Cancer Therapy–Prostate score from baseline.

[g]Pain progression is defined an increase of ≥ 30% from baseline in the average Brief Pain Inventory–Short Form pain severity score.

[h]Pain progression is defined as an increase of ≥ 2 points from baseline in the average Brief Pain Inventory–Short Form score.

previously reported clinical trials involving patients with CRPC,[17,18] with maintenance of QoL at the high level reported at baseline. These efficacy and safety results prompted the DSMB to recommend crossing patients treated with placebo plus ADT over to enzalutamide plus ADT.
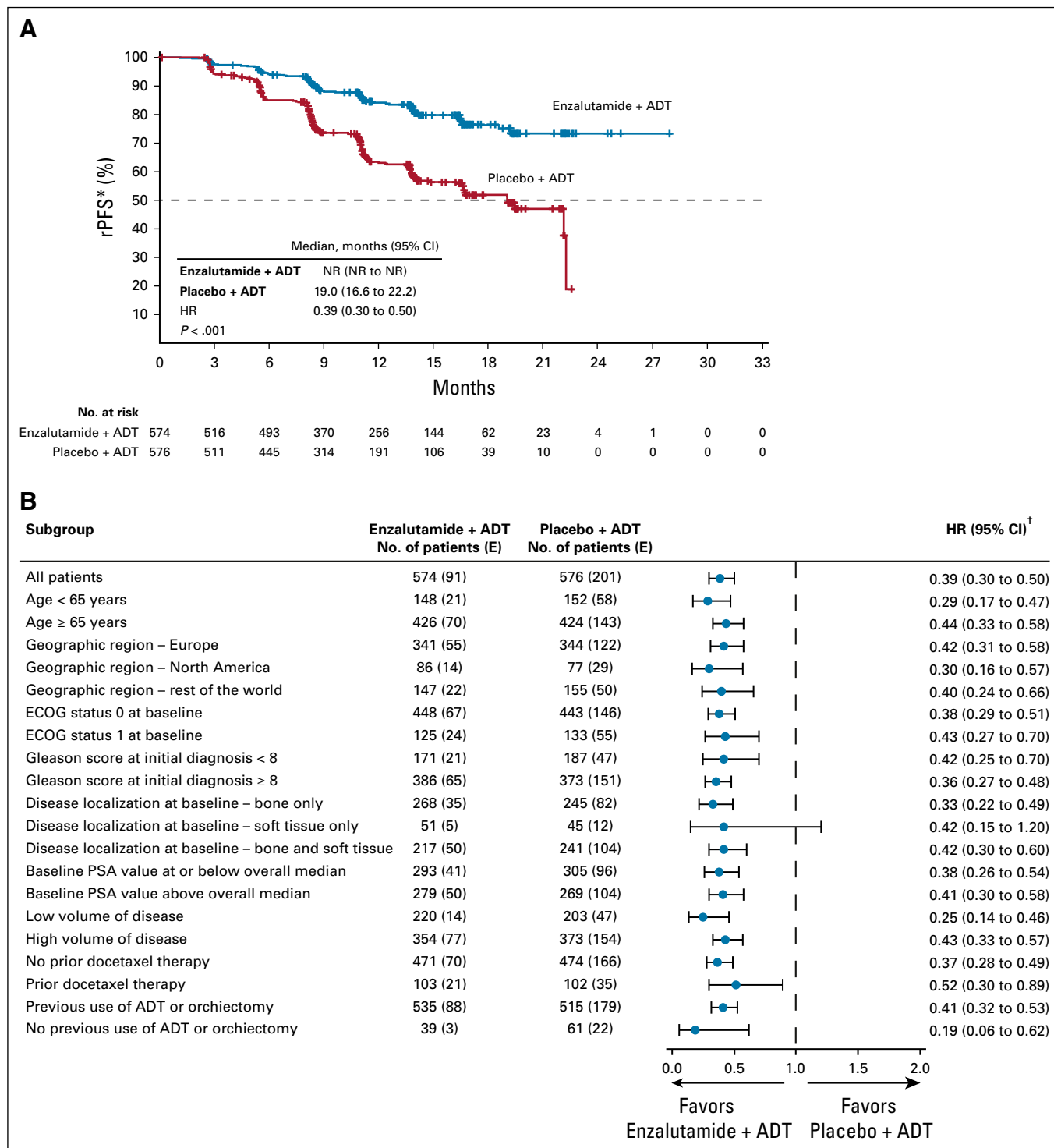
A

B

Subgroup	Enzalutamide + ADT No. of patients (E)	Placebo + ADT No. of patients (E)		HR (95% CI)[†]
All patients	574 (91)	576 (201)		0.39 (0.30 to 0.50)
Age < 65 years	148 (21)	152 (58)		0.29 (0.17 to 0.47)
Age ≥ 65 years	426 (70)	424 (143)		0.44 (0.33 to 0.58)
Geographic region – Europe	341 (55)	344 (122)		0.42 (0.31 to 0.58)
Geographic region – North America	86 (14)	77 (29)		0.30 (0.16 to 0.57)
Geographic region – rest of the world	147 (22)	155 (50)		0.40 (0.24 to 0.66)
ECOG status 0 at baseline	448 (67)	443 (146)		0.38 (0.29 to 0.51)
ECOG status 1 at baseline	125 (24)	133 (55)		0.43 (0.27 to 0.70)
Gleason score at initial diagnosis < 8	171 (21)	187 (47)		0.42 (0.25 to 0.70)
Gleason score at initial diagnosis ≥ 8	386 (65)	373 (151)		0.36 (0.27 to 0.48)
Disease localization at baseline – bone only	268 (35)	245 (82)		0.33 (0.22 to 0.49)
Disease localization at baseline – soft tissue only	51 (5)	45 (12)		0.42 (0.15 to 1.20)
Disease localization at baseline – bone and soft tissue	217 (50)	241 (104)		0.42 (0.30 to 0.60)
Baseline PSA value at or below overall median	293 (41)	305 (96)		0.38 (0.26 to 0.54)
Baseline PSA value above overall median	279 (50)	269 (104)		0.41 (0.30 to 0.58)
Low volume of disease	220 (14)	203 (47)		0.25 (0.14 to 0.46)
High volume of disease	354 (77)	373 (154)		0.43 (0.33 to 0.57)
No prior docetaxel therapy	471 (70)	474 (166)		0.37 (0.28 to 0.49)
Prior docetaxel therapy	103 (21)	102 (35)		0.52 (0.30 to 0.89)
Previous use of ADT or orchiectomy	535 (88)	515 (179)		0.41 (0.32 to 0.53)
No previous use of ADT or orchiectomy	39 (3)	61 (22)		0.19 (0.06 to 0.62)

0.0   0.5   1.0   1.5   2.0

← Favors Enzalutamide + ADT   Favors Placebo + ADT →

FIG 2. Kaplan-Meier estimate of (A) radiographic progression-free survival (rPFS) and (B) forest plot of rPFS for prespecified subgroups (intent-to-treat population). The dashed line at the 50th percentile indicates the median. Crosses indicate censored data. (*) For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cutoff date. (†) 95% CIs provided are not adjusted for the number of subgroups summarized. ADT, androgen deprivation therapy; E, No. of events; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen.

Importantly, the significant reduction in the risk of radiographic disease progression or death with enzalutamide plus ADT in this study (P < .001) was observed in all prespecified subgroups, including men with or without prior docetaxel chemotherapy and those with a low or high volume of metastatic disease. These data support the
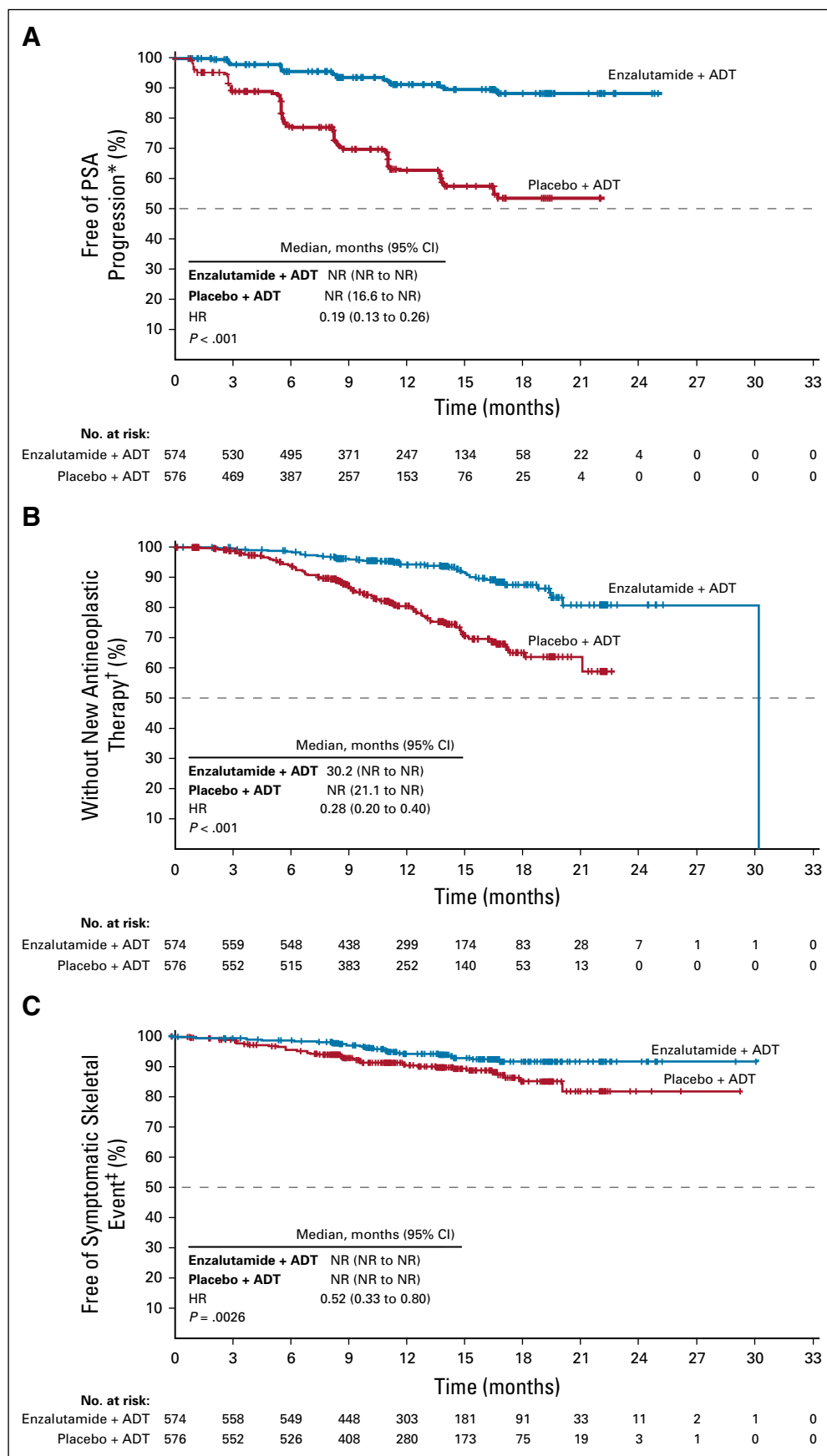
FIG 3. Kaplan-Meier estimates of time to (A) prostate-specific antigen (PSA) progression, (B) initiation of new antineoplastic therapy, and (C) first symptomatic skeletal event (intent-to-treat population). The dashed line at the 50th percentile indicates the median. Crosses indicate censored data. (*) In patients with no PSA progression, time to PSA progression was censored on the date of the last PSA sample taken. Patients without PSA progression before two or more consecutive missed PSA assessments were censored on the date of last PSA assessment before the assessments missed. (†) In patients with no new antineoplastic therapy initiated for prostate cancer after randomization, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomization, whichever occurred last. The median for the enzalutamide plus androgen deprivation therapy (ADT) group was not a reliable estimate because it resulted from an event observed in the only remaining patient at risk at approximately 30 months, leading to the vertical drop at the end of the Kaplan-Meier curve. The hazard ratio (HR; 95% CI) is a more accurate depiction of the differences between treatment arms. (‡) In patients with no symptomatic skeletal event by the time of the data cutoff point, time to symptomatic skeletal event was censored on the last visit date or the date of randomization, whichever occurred last. HR, hazard ratio; NR, not reached.

TABLE 3. Summary of AEs

Event	Enzalutamide Plus ADT (n = 572)			Placebo Plus ADT (n = 574)		
AEs leading to withdrawal of treatment	41 (7.2)			30 (5.2)		
Drug-related serious AEs	22 (3.8)			16 (2.8)		
AEs leading to death	14 (2.4)			10 (1.7)		
	All Grades	**Grade ≥ 3**		**All Grades**	**Grade ≥ 3**	
AEs	487 (85.1)	139 (24.3)		493 (85.9)	147 (25.6)	
Serious AEs	104 (18.2)	84 (14.7)		112 (19.5)	90 (15.7)	
Most common AEs, occurring in ≥ 5% of patients*						
Hot flash	155 (27.1)	2 (0.3)		128 (22.3)	0	
Fatigue	112 (19.6)	5 (0.9)		88 (15.3)	6 (1.0)	
Arthralgia	70 (12.2)	2 (0.3)		61 (10.6)	4 (0.7)	
Back pain	43 (7.5)	5 (0.9)		62 (10.8)	3 (0.5)	
Increased weight	35 (6.1)	2 (0.3)		44 (7.7)	1 (0.2)	
Hypertension	46 (8.0)	19 (3.3)		32 (5.6)	10 (1.7)	
Diarrhea	34 (5.9)	0		33 (5.7)	1 (0.2)	
Edema, peripheral	29 (5.1)	1 (0.2)		38 (6.6)	1 (0.2)	
Nausea	37 (6.5)	1 (0.2)		29 (5.1)	0	
Asthenia	31 (5.4)	6 (1.0)		28 (4.9)	3 (0.5)	
Constipation	28 (4.9)	0		31 (5.4)	0	
Musculoskeletal pain	36 (6.3)	1 (0.2)		23 (4.0)	1 (0.2)	
Dizziness	29 (5.1)	0		20 (3.5)	0	
AEs of special interest†						
Convulsion	2 (0.3)	2 (0.3)		2 (0.3)	2 (0.3)	
Hypertension	49 (8.6)	19 (3.3)		36 (6.3)	12 (2.1)	
Neutrophil count decreased	5 (0.9)	2 (0.3)		4 (0.7)	2 (0.3)	
Cognitive/memory impairment	26 (4.5)	4 (0.7)		12 (2.1)	0	
Ischemic heart disease	10 (1.7)	3 (0.5)		8 (1.4)	6 (1.0)	
Other selected cardiovascular events	13 (2.3)	6 (1.0)		9 (1.6)	5 (0.9)	
Posterior reversible encephalopathy syndrome	0	0		0	0	
Fatigue	138 (24.1)	10 (1.7)		112 (19.5)	9 (1.6)	
Fall	21 (3.7)	2 (0.3)		15 (2.6)	1 (0.2)	
Fractures	37 (6.5)	6 (1.0)		24 (4.2)	6 (1.0)	
Loss of consciousness	9 (1.6)	6 (1.0)		1 (0.2)	1 (0.2)	
Thrombocytopenia	3 (0.5)	0		3 (0.5)	0	
Musculoskeletal events	151 (26.4)	9 (1.6)		159 (27.7)	12 (2.1)	
Severe cutaneous adverse reactions	0	0		1 (0.2)	0	
Angioedema	7 (1.2)	1 (0.2)		1 (0.2)	0	
Rash	15 (2.6)	0		9 (1.6)	0	
Second primary malignancies	11 (1.9)	9 (1.6)		11 (1.9)	7 (1.2)	

NOTE. All data are No. (%). AEs were recorded in the electronic case report form and graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03) by the study investigator.

Abbreviations: ADT, androgen deprivation therapy; AE, adverse event.

*AEs reported in at least 5% of the patients in either treatment group, listed in descending order by preferred term. None of the most common AEs was grade 5.

†AEs of special interest were based on prespecified combinations of preferred terms (Medical Dictionary for Regulatory Activities, version 21.0) related to the AE of special interest; for example, the combination of preferred terms used to define fatigue as an AE of special interest was fatigue and asthenia. Two of the AEs of special interest in the enzalutamide plus ADT group were grade 5 (ischemic heart disease, n = 1; other selected cardiovascular events, n = 1).

consideration of enzalutamide in addition to ADT for men with mHSPC, including patients with prior docetaxel treatment and regardless of disease volume. Although OS data remain immature, these findings have clear clinical implications for the current management of these patients.

PROs from assessments of daily living have also been shown to predict survival in prostate cancer.[29] In this population of men with mHSPC, we observed maintenance of high QoL over time, similar to that observed in the population with nonmetastatic castration-resistant disease.[30] Baseline average BPI-SF scores were low overall, with almost half of patients reporting scores of zero. Consequently, no significant difference between treatment groups in risk of pain progression, defined as a 30% or greater increase in average BPI-SF pain severity score, was observed. However, when using a more clinically meaningful definition of pain progression (≥ 2-point threshold)[31] during the prespecified sensitivity analyses from the PRO SAP, enzalutamide plus ADT showed a delay in pain progression versus placebo plus ADT. Ultimately, no significant difference between treatment groups in risk of deterioration of urinary symptoms or QoL was observed, suggesting there was no negative impact on PROs due to the addition of enzalutamide to ADT. Additional analyses of the PROs are ongoing and are also planned as part of the long-term follow-up.

Currently, ARCHES is the first trial to demonstrate clinically meaningful benefits of potent AR inhibition with a second-generation nonsteroidal antiandrogen (enzalutamide) in combination with ADT, including a subgroup of men with mHSPC after docetaxel chemotherapy. Whereas some previous studies focused on patients with high risk and entirely excluded patients with previous chemotherapy,[6-8,10,11] the specific inclusion of patients with prior docetaxel chemotherapy in ARCHES provides unique insight into this important patient subgroup with unmet clinical needs.

Both rPFS and metastasis-free survival are accepted by the US Food and Drug Administration as primary efficacy end points in metastatic CRPC and nonmetastatic CRPC, respectively.[32,33] However, although rPFS has not yet been established as a surrogate for OS in mHSPC, it is an acceptable regulatory end point, and reducing the risk of radiographic progression or death is of clinical importance, given the strong positive correlation reported for rPFS and

OS in patients with metastatic CRPC[34,35] and the direct impact of additional metastatic progression in this setting on patient management. Furthermore, rPFS requires shorter follow-up periods and fewer patients compared with OS as a result of the higher event rate, accelerating trial completion.[36] It is also in the interest of patients to unblind trials earlier, on the basis of robust rPFS evidence, especially when supported by strong secondary end points, to allow crossover to active treatment. Therefore, ARCHES was accelerated, with rPFS analysis conducted after only 262 events, despite an immature OS analysis. At the time of manuscript submission, a phase III study investigating the addition of enzalutamide versus a first-generation nonsteroidal antiandrogen, such as bicalutamide, to ADT, with or without docetaxel chemotherapy, in men with mHSPC[37] is currently ongoing and will provide additional data on the clinical benefits of enzalutamide plus ADT, including the impact on OS.

Several therapies have recently been shown to be effective in men with mHSPC; therefore, ADT alone may no longer be an appropriate control arm in this patient population. However, docetaxel plus ADT only became part of the global SOC for mHSPC in 2016, after patients were already enrolling in ARCHES,[12] and thus, docetaxel could not have been considered as part of the comparator arm in the current study. Furthermore, patients with high-volume disease who had completed prior docetaxel were eligible for trial entry by study design, and for those with low-volume disease, the benefit of early treatment with docetaxel combined with ADT has not been established.[13,38,39]

In conclusion, in comparison with placebo, the addition of enzalutamide to ADT for men with mHSPC provided clinically meaningful improvements across key efficacy end points while maintaining the high level of QoL reported at baseline. Enzalutamide was generally well tolerated, with a preliminary safety analysis seeming to be consistent with the safety profile of enzalutamide in previous clinical trials in CRPC. Enzalutamide plus ADT should therefore be considered as a treatment option for men with mHSPC, including those with low-volume disease or who had received prior docetaxel. Additional studies are necessary to clarify whether combination or sequential approaches with AR-targeted therapies or chemotherapy are favored for initial management.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer

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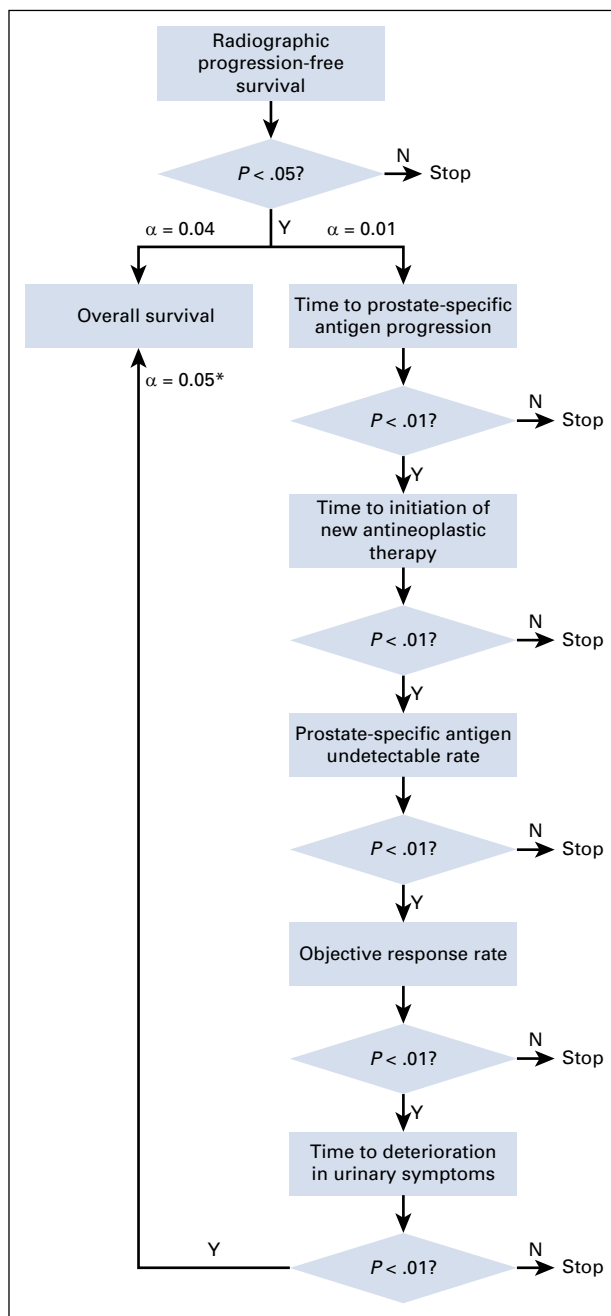No other potential conflicts of interest were reported.

APPENDIX

FIG A1. Multiplicity adjustment strategy. (*) Overall survival will be tested at 0.05 only if all the other five secondary end points analyses are statistically significant at 0.01, otherwise it will be tested at 0.04. N, no; Y, yes.