Radiographic Progression With and Without Prostate-Specific Antigen Rise in Patients With Advanced Prostate Cancer Treated With Enzalutamide

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ABSTRACT

PURPOSE In patients who received enzalutamide, we characterized the development of radiographic progression (rPD) without prostate-specific antigen (PSA) rise or progression in metastatic hormone-sensitive prostate cancer (mHSPC) and nonmetastatic castration-resistant prostate cancer (nmCRPC).

METHODS We conducted a post hoc analysis in two phase III trials (N = 2,551; ARCHES [ClinicalTrials.gov identifier: NCT02677896]; PROSPER [ClinicalTrials.gov identifier: NCT02003924]) for co-occurrence of rPD ± Prostate Cancer Working Group 2/3-defined PSA progression, and rPD ± any PSA rise from baseline/nadir by treatment. Kaplan-Meier methods were used for overall survival (OS) outcomes.

RESULTS In ARCHES, 3.5% and 8.5% of 574 patients with mHSPC treated with enzalutamide plus androgen-deprivation therapy (ADT) had no PSA rise or PSA progression at rPD, respectively. Of 79 patients with rPD who received enzalutamide plus ADT, 25.3% had no PSA rise and 62.0% did not meet PSA progression criteria compared with 7.4% and 38.3% of 188 patients with rPD treated with ADT alone, respectively. In PROSPER, 4.4% and 10.3% of 933 patients with nmCRPC treated with enzalutamide plus ADT had no PSA rise or PSA progression, respectively, at rPD. However, of 187 patients with rPD who received enzalutamide plus ADT, 21.9% had no PSA rise and 51.3% did not meet PSA progression criteria compared with 3.6% and 18.8% of 224 patients treated with placebo/ADT, respectively. Liver metastases were >5-fold higher in enzalutamide-treated patients with rPD events versus control, although sample size was small. Compared with no rPD, enzalutamide-treated patients with rPD ± PSA rise or progression had worse OS.

CONCLUSION Given the frequent discordance and poor prognosis of imaging-based progression in the absence of PSA changes during enzalutamide treatment in mHSPC and nmCRPC, periodic surveillance using imaging is recommended.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

In patients with advanced prostate cancer (PC), androgen-deprivation therapy (ADT) plus potent androgen receptor (AR) pathway inhibitors (ARPIs) have dramatically improved survival and delayed progression.[1-15] However, the relationship between serum prostate-specific antigen (PSA) levels and radiographic progression (rPD) may become discordant over time in some patients, particularly for those treated with AR inhibition due to loss of AR dependence, where PSA production may become uncoupled from tumor growth and metastasis.[16,17] This discordance may develop in a significant minority of patients with metastatic hormone-sensitive PC (mHSPC) or nonmetastatic (nmCRPC) and metastatic castration-resistant PC (mCRPC) during treatment with ADT and ARPIs.[18-21]

Serial PSA testing, physical examination, and symptom assessments are routinely used in clinical practice to monitor disease progression. Imaging is also an important modality for therapeutic monitoring, but the value of regular imaging in the absence of rising PSA levels is unclear and is usually not done in a standardized manner.[18,22] Previous PC Working Group 2 and 3 (PCWG2/3) guidelines define PSA progression as the time from start of therapy to the first PSA increase ≥25% and ≥2 ng/mL above the nadir, confirmed by a second value 3 or more weeks later.[23,24] However, these criteria have not been validated in the context of potent ARPI therapy.[20]

CONTEXT

Key Objective

Define the prevalence and clinical impact of radiographic progression (rPD) without prostate-specific antigen (PSA) progression in patients with advanced prostate cancer during hormonal therapy.

Knowledge Generated

Although enzalutamide delays rPD and improves survival in patients with advanced prostate cancer, among patients with rPD, 22%-25% of patients receiving enzalutamide may not have PSA rise (*v* 4%-7% receiving androgen-deprivation therapy [ADT]) and a majority (51%-62%) will not meet PSA progression criteria (*v* 19%-38% receiving ADT). Liver metastases are five times more common at rPD with enzalutamide versus ADT alone. rPD with or without PSA progression is associated with poor survival.

Relevance *(A. Necchi)*

This study is important because it highlights the need to provide an accurate radiological monitoring, added to PSA tests, during the follow-up of patients with metastatic hormone-sensitive prostate cancer or nonmetastatic castration-resistant prostate cancer receiving enzalutamide treatment.*

*Relevance section written by *JCO* Associate Editor Andrea Necchi, MD.

Progression of advanced PC manifests in various ways, including a continuous rise in PSA levels, radiographic or symptomatic progression of preexisting disease, and/or appearance of metastatic disease deposits.[22] After treatment with enzalutamide, PSA levels decline due to potent AR blockade and cell death.[1,4] Although PSA decline is prognostic and associated with improved long-term outcomes,[25,26] detection of rPD could be delayed if imaging studies are only guided by PSA levels. Importantly, rPD in the absence of significant increases in PSA levels has been reported previously in the setting of neuroendocrine transformation and AR indifference,[27] and during treatment with enzalutamide plus ADT therapy in phase III trials such as PREVAIL[18] and PROSPER.[20] This post hoc analysis offers a unique opportunity to evaluate whether progression from mHSPC to mCRPC occurs without PSA rise in patients receiving enzalutamide versus control.

METHODS

Study Design and Conduct

ARCHES (ClinicalTrials.gov identifier: NCT02677896) and PROSPER (ClinicalTrials.gov identifier: NCT02003924) were randomized, phase III, international trials. The appropriate institutional review board or independent ethics committee at participating study sites approved the study designs and amendments. The studies were conducted according to principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Patients and Treatments

The study designs and methodology for ARCHES and PROSPER have been published.[1,4] In brief, 1,150 patients with mHSPC were randomly assigned (1:1) to enzalutamide plus ADT or placebo plus ADT (ADT alone) in ARCHES. For PROSPER, 1,401 patients with nmCRPC and a PSA doubling time of ≤10 months who were being treated with ADT were randomly assigned (2:1) to enzalutamide or placebo.

Post Hoc Analyses

Post hoc analysis of the co-occurrence of rPD (confirmed by independent central review) with and without PSA progression (rPD + ≤90 days, defined as PSA progression from start of treatment up to rPD date + 90 days), as defined by the PCWG2/3 criteria, and rPD with and without any rise (ie, any nonzero increase) in PSA from baseline or nadir (any PSA rise from start of treatment up to rPD date + 90 days) was assessed by treatment group for ARCHES and PROSPER. The nadir was defined as the lowest PSA value collected up to rPD + ≤90 days. In patients with rPD with and without PSA rise and progression, the following were assessed for both studies by treatment group: baseline characteristics, timing of PSA rise and progression, PSA levels, characteristics of metastatic spread, and overall survival (OS).

Assessments

For ARCHES and PROSPER, radiographic imaging was assessed using computed tomography (CT) or magnetic resonance imaging of the abdomen and pelvis, chest x-ray or CT, and bone scintigraphy. In both studies, rPD was defined by RECIST v1.1.[28] For both studies, the schedule of radiographic imaging and assessment of PSA was previously published.[1,4]

Statistical Analyses

The intention-to-treat population was used for all analyses. A landmark analysis was conducted using 9 months as the

landmark for ARCHES and 12 months as the landmark for PROSPER. These time points correspond to when each patient had completed the third imaging assessment. Kaplan-Meier methods estimated the median and 95% CIs for OS. The hazard ratio (HR) was estimated from the Cox proportional hazards model. Descriptive analyses were performed, including baseline demographics and disease characteristics, PSA levels, proportions of patients with PSA rise or progression, and rPD. To account for potential confounding factors and determine whether these characteristics were independent predictors of rPD, a multivariate analysis was performed. Additionally, a sensitivity analysis was performed using 6 months as the landmark for ARCHES and 8 months as the landmark for PROSPER. These time points correspond to when each patient had completed the second imaging scan. Statistical analyses were performed using SAS software, v9.4 (SAS Institute, Cary, NC). The data cutoff dates were October 14, 2018, for ARCHES (May 28, 2021, for OS analyses) and June 28, 2017, for PROSPER. *P* values are nominal, as this was a post hoc analysis.

Patient-Reported Outcomes

Descriptive analyses were performed to measure change from baseline in pain (Item 3, worst pain) in patients experiencing rPD, and in patients not experiencing rPD (survivors).

RESULTS

ARCHES

In patients with mHSPC, enzalutamide plus ADT significantly improved OS and delayed PSA progression and rPD-free survival compared with ADT alone.[4,5] Of the overall ARCHES population (N = 1,150), 267 patients (23.2%) developed rPD (Fig 1A; enzalutamide plus ADT, n = 79 [13.8%]; ADT alone, n = 188 [32.6%]) by the data cutoff. Overall, there was no PSA rise from baseline/nadir in 3.5% of patients (20/574) who received enzalutamide plus ADT and 2.4% of patients (14/576) who received ADT alone at rPD (Fig 2A). Of patients with rPD who received enzalutamide plus ADT, 25.3% (20/79) had no PSA rise compared with 7.4% of patients (14/188) who received ADT alone. At rPD, 21.5% of patients (17/79) treated with enzalutamide plus ADT had undetectable PSA (<0.2 ng/mL) compared with 4.8% (9/188) for ADT alone (Fig 2A, Table 1). Baseline characteristics were generally similar for patients with rPD with and without any PSA rise; however, in both treatment groups, patients with rPD (with and without any PSA rise) had more high-volume disease (per CHAARTED definition[29]) and high Gleason scores (≥8) at initial diagnosis versus patients who remained free of rPD (Table 2). Results of the multivariate analysis indicated statistical significance for volume of disease and Gleason score at initial diagnosis for ARCHES, and PSA doubling time for PROSPER (Table 2). Overall, rPD without PSA progression occurred for 8.5% of patients (49/574) who received enzalutamide plus ADT and 12.5% of patients (72/576) who received ADT alone (Fig 2A; Data Supplement, Fig S1A, online only). Of patients with rPD, 62% (49/79) who received enzalutamide plus ADT and 38% of patients (72/188) who received ADT alone did not meet PSA progression criteria. Together, these data in patients with mHSPC suggest that rPD without any PSA rise or PSA progression is relatively common in the setting of potent AR blockade, and this discordant progression is more common with enzalutamide treatment versus control (Data Supplement, Fig S1A).

PROSPER

In patients with nmCRPC, enzalutamide significantly improved metastasis-free survival (MFS) and OS, and delayed PSA progression and MFS compared with placebo.[1,2] Of the overall PROSPER study population (N = 1,401), 411 patients (29.3%) developed rPD (Fig 1B; enzalutamide, n = 187 [20.0%]; placebo, n = 224 [47.9%]) by the data cutoff. Overall, no PSA rise occurred from baseline/nadir in 4.4% of patients (41/933) who received enzalutamide and 1.7% of patients (8/468) who received placebo at rPD (Fig 2B). Of patients with rPD who received enzalutamide, 21.9% (41/187) had no PSA rise compared with 3.6% of patients (8/224) with placebo. At rPD, 5.9% of patients (11/187) treated with enzalutamide had undetectable PSA (<0.2 ng/mL) compared with 0% for placebo (Fig 2B, Table 1). No notable differences in pretreatment baseline characteristics were observed with and without PSA rise at rPD (Table 2). Overall, no PSA progression occurred for 10.3% of patients (96/933) who received enzalutamide and 9.0% of patients (42/468) who received placebo (Fig 2B; Data Supplement, Fig S1B); of patients with rPD, 51.3% (96/187) versus 18.8% (42/224) of patients treated with enzalutamide or placebo, respectively, did not meet PSA progression criteria. Together, these data suggest that despite a significant delay in MFS, rPD without PSA progression or any PSA rise is relatively common in the setting of both ADT and potent AR blockade in patients with nmCRPC. In addition, among those patients who developed rPD, discordant progression was much more common with enzalutamide versus placebo (Data Supplement, Fig S1B).

Timing of PSA Rise, rPD, and PSA Progression

The timing of rPD events did not differ among those with and without any PSA rise or progression in ARCHES or PROSPER, but these events were typically observed in the first year after treatment initiation (Data Supplement, Table S3).

Relative and Absolute Magnitude of PSA Changes at rPD

In ARCHES, the overall median PSA (ng/mL) at rPD was lower after enzalutamide plus ADT treatment versus ADT alone (3.5 [n = 79] *v* 17.8 [n = 188]; *P* < .0001). The median PSA (ng/mL) was higher in patients at rPD with any PSA rise versus no PSA rise in both treatment groups (enzalutamide plus ADT, 8.9 [n = 59] *v* 0.05 [n = 20]; ADT alone 22.3 [n = 174] *v* 2.2 [n = 14]; Table 1). These results were consistent with the median change and percentage change from

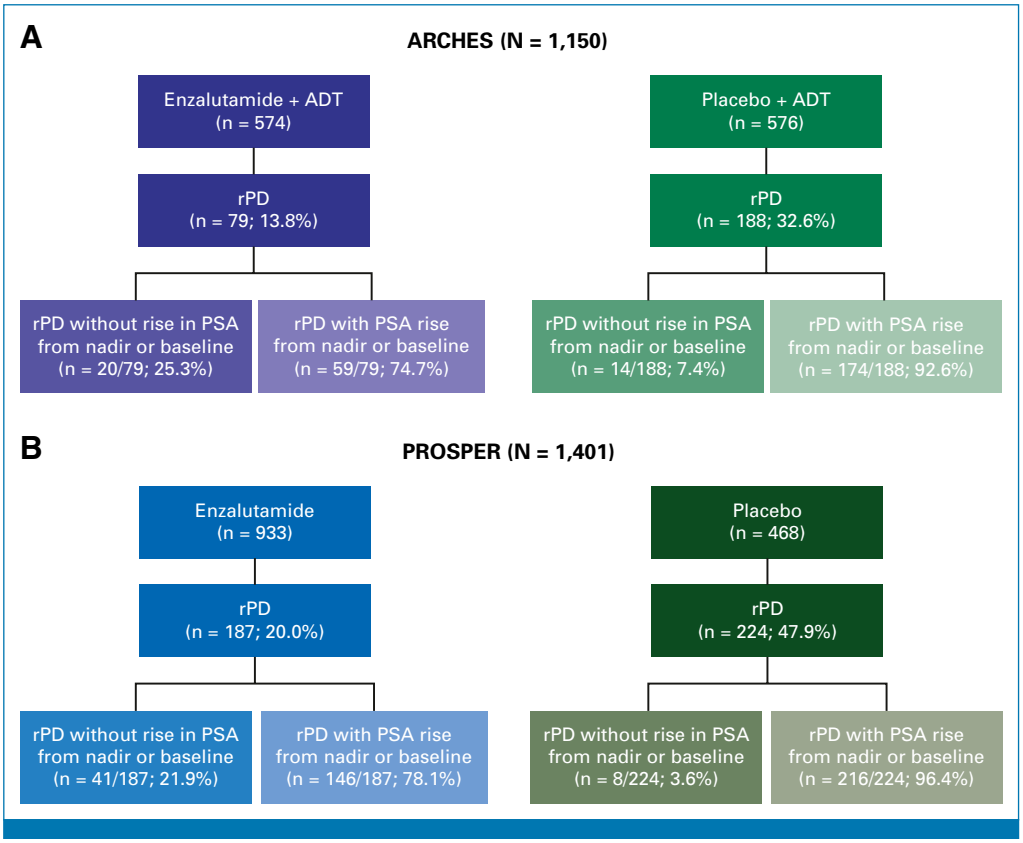

FIG 1. rPD with and without any rise in PSA in (A) ARCHES and (B) PROSPER (ITT population). PSA values were closest to the rPD date, including 90 days after rPD. The data cutoff for ARCHES was October 14, 2018; the data cutoff for PROSPER was June 28, 2017. ADT, androgen-deprivation therapy; ITT, intention-to-treat; PSA, prostate-specific antigen; rPD, radiographic progression.

nadir (Table 1). The data with and without any PSA rise were comparable with the results reported for patients with and without PSA progression (Data Supplement, Table S1).

Similar to ARCHES, in PROSPER, the overall median PSA (ng/mL) at rPD was lower after enzalutamide treatment versus placebo (11.2 [n = 187] *v* 46.3 [n = 224]). At the time of rPD, the median PSA (ng/mL) was higher in patients with any PSA rise versus no PSA rise in both treatment groups (enzalutamide, 15.2 [n = 146] *v* 1.2 [n = 41]; placebo, 47.5 [n = 216] *v* 19.5 [n = 8]; Table 1). These results were consistent with the median change and percentage change from nadir presented in Table 1. The data with and without any PSA rise were similar to the results reported for patients with and without PSA progression (Data Supplement, Table S1). Together, these data suggest that despite significant delays in rPD or death, discordant rPD with low PSA values and small PSA changes can develop in a minority of patients with mHSPC or nmCRPC, particularly with enzalutamide treatment.

Distribution of Metastases at rPD

At the time of rPD in patients with any PSA rise, most metastases were in lymph node and bone only versus visceral in both treatment groups in ARCHES (Table 3). In patients treated with enzalutamide plus ADT, 27.8% were lymph node only, 32.9% were bone only, and 10.1% were visceral metastases. In patients treated with ADT alone, 28.7% were lymph node only, 57.4% were bone only, and 3.2% were visceral metastases. In patients with rPD with any PSA rise after treatment with enzalutamide plus ADT versus ADT alone, the pattern of metastases showed that most visceral metastases were in the liver (7.6% *v* 1.1%; $P = .277$). In patients with no PSA rise, the number of visceral metastases were lower compared with patients with any PSA rise in both treatment groups. In patients treated with enzalutamide plus ADT, higher rates of metastases to all tumor locations were observed in patients with rPD without PSA progression versus rPD with PSA progression (Data Supplement, Table S4).

Similar to ARCHES, the majority of metastases at the time of rPD with any PSA rise in PROSPER were in lymph node and bone only versus visceral in both treatment groups (Table 3). Of 187 patients treated with enzalutamide, 37.4% were lymph node only, 20.3% were bone only, and 5.3% were visceral metastases; with placebo, 49.6% were lymph node only, 26.8% were bone only, and 4.9% were visceral metastases.

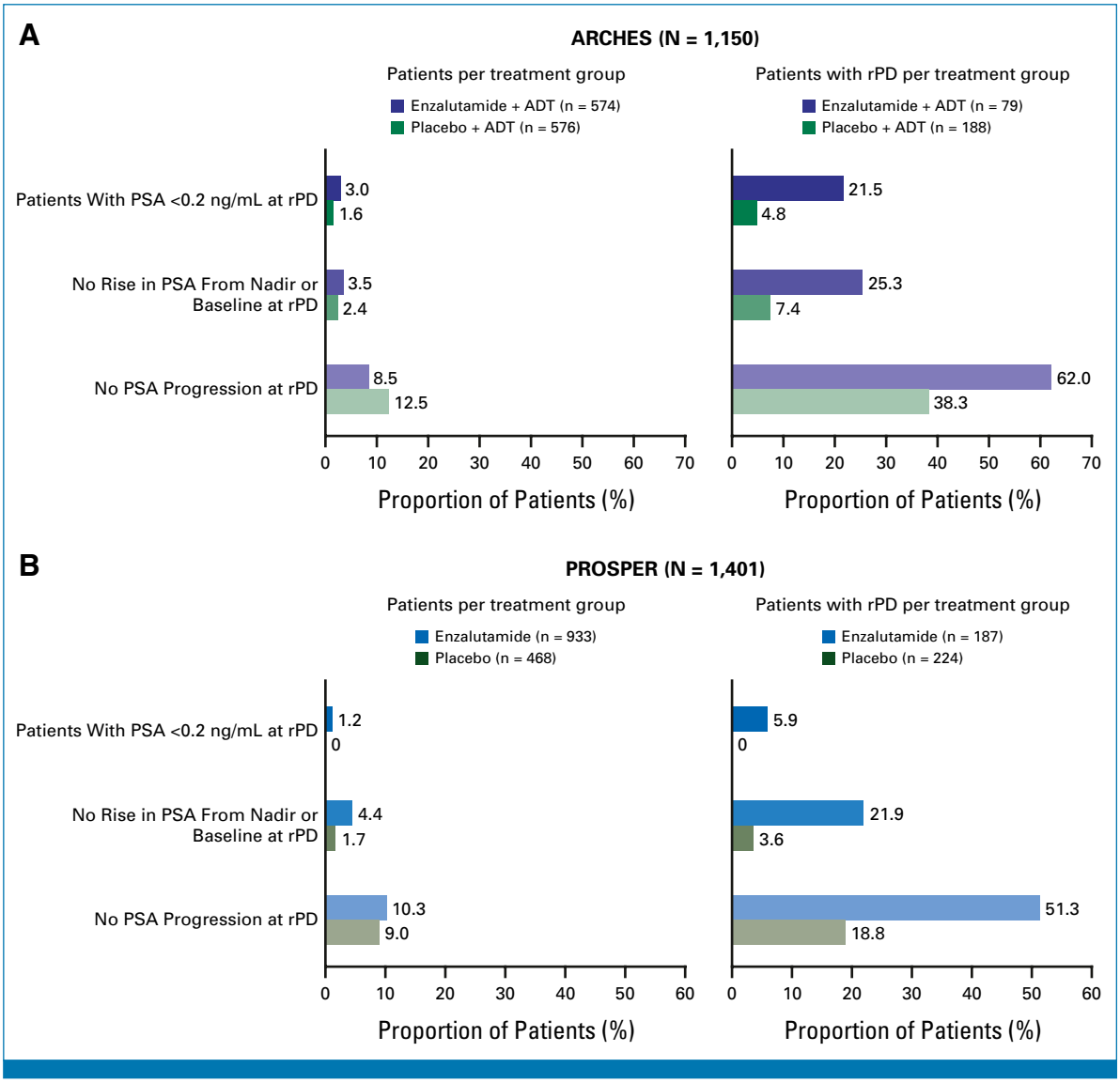

FIG 2. rPD in the absence of PCWG 2/3-defined PSA progression and any rise in PSA in (A) ARCHES and (B) PROSPER (ITT population). PSA values were closest to the rPD date including 90 days after rPD. The data cutoff for ARCHES was October 14, 2018; the data cutoff for PROSPER was June 28, 2017. ADT, androgen-deprivation therapy; ITT, intention-to-treat; PCWG, Prostate Cancer Working Group; PSA, prostate-specific antigen; rPD, radiographic progression.

Liver metastases were higher in patients with rPD and any PSA rise after treatment with enzalutamide versus placebo (4.8% *v* 0.9%; $P = .002$). However, this difference in liver metastases by treatment group was not observed for patients with no PSA rise at rPD (0.5% *v* 0%). Mixed results were reported for the distribution of metastases in patients with rPD with and without PSA progression (Data Supplement, Table S4).

Patient-Reported Outcomes

Most of the rPD events in both trials occurred without symptoms, and there was no significant difference in the median pain score or the proportion of patients with significantly worse pain at rPD with or without PSA progression or rise (Data Supplement, Tables S5 and S6).

OS Outcomes: Landmark Analyses

In ARCHES, patients who had rPD with any PSA rise or no PSA rise had worse OS in both treatment groups versus patients without rPD (reference; Fig 3). Poor OS was observed for patients with rPD with and without PSA progression versus patients without rPD (Data Supplement, Fig S2).

In PROSPER, patients treated with enzalutamide who had rPD with (HR, 2.72 [95% CI, 1.78 to 4.15]; $P < .0001$) but not without (HR, 1.79 [95% CI, 0.77 to 4.19]; $P = .1726$) any PSA rise had significantly worse OS versus patients without rPD (reference; Fig 4A). By contrast, patients treated with placebo who had rPD with or without any PSA rise had comparable OS to patients without rPD (reference; Fig 4B). Similarly, compared with patients who did not experience

TABLE 1. Characterization of PSA Levels for Patients With rPD, With or Without Any Rise in PSA From ARCHES and PROSPER (ITT Population)[a]

	ARCHES									PROSPER								
	rPD With Any PSA Rise			rPD With No PSA Rise			Total			rPD With Any PSA Rise			rPD With No PSA Rise			Total		
Parameter	Enza + ADT (n = 59)	Pbo + ADT (n = 174)	*P*[b]	Enza + ADT (n = 20)	Pbo + ADT (n = 14)	*P*[b]	Enza + ADT (n = 79)	Pbo + ADT (n = 188)	*P*[b]	Enza (n = 146)	Pbo (n = 216)	*P*[b]	Enza (n = 41)	Pbo (n = 8)	*P*[b]	Enza (n = 187)	Pbo (n = 224)	*P*[b]
Median baseline PSA, ng/mL	6.0	6.3	.777	5.2	9.7	.391	6.0	6.3	.443	15.3	11.1	.064	14.8	51.1	.050	15.2	11.3	.083
Patients with PSA <0.2 ng/mL at rPD, No. (%)[c]	7 (11.9)	4 (2.3)	—	10 (50.0)	5 (35.7)	—	17 (21.5)	9 (4.8)	—	3 (2.1)	0	—	8 (19.5)	0		11 (5.9)	0	—
Median PSA at rPD, ng/mL[c]	8.9	22.3	.0005	0.05	2.2	.028	3.5	17.8	<.0001	15.2	47.5	<.0001	1.2	19.5	.001	11.2	46.3	<.0001
Median PSA at nadir, ng/mL[d]	0.7	2.5	<.0001	0.03	0.9	.014	0.4	2.3	<.0001	2.0	22.2	<.0001	0.9	27.2	.0014	1.7	22.3	<.0001
Median % change in PSA from nadir	516.3	376.6	.513	0	5.2	.255	225.0	337.0	.144	299.2	67.4	<.0001	0	0	.744	198.8	62.1	<.0001
Median absolute change in PSA from nadir, ng/mL	7.0	14.4	.011	0	0.01	.113	1.9	11.7	<.0001	7.5	11.1	.882	0	0	.744	3.9	10.7	.135

NOTE. ARCHES data cutoff date: October 14, 2018. PROSPER data cutoff date: June 28, 2017.

Abbreviations: ADT, androgen-deprivation therapy; enza, enzalutamide; ITT, intention-to-treat; Pbo, placebo; PSA, prostate-specific antigen; rPD, radiographic progression.

[a]rPD is defined as objective evidence of protocol-specified rPD, as assessed by independent central review.

[b]From the Wilcoxon ranked-sum test.

[c]PSA value closest to rPD ± 90 days.

[d]Nadir was the lowest PSA value collected up to rPD + 90 days.

TABLE 2. Demographics and Baseline Characteristics for Patients With No rPD, Patients With rPD and Any PSA Rise, and Patients With rPD and No PSA Rise From ARCHES and PROSPER (ITT population)

	No rPD		rPD With Any PSA Rise		rPD With No PSA Rise		
ARCHES	Enzalutamide + ADT (n = 495)	Placebo + ADT (n = 388)	Enzalutamide + ADT (n = 59)	Placebo + ADT (n = 174)	Enzalutamide + ADT (n = 20)	Placebo + ADT (n = 14)	*P*[a]
Age, years, median	70.0	70.0	72.0	69.0	68.5	73.0	
Race, No. (%)[b]							
White	398 (80.4)	304 (78.4)	51 (86.4)	147 (84.5)	17 (85.0)	9 (64.3)	.301
Asian	68 (13.7)	59 (15.2)	4 (6.8)	19 (10.9)	3 (15.0)	2 (14.3)	
Black or African American	7 (1.4)	5 (1.3)	1 (1.7)	3 (1.7)	0	0	
Other[c]	22 (4.4)	20 (5.2)	3 (5.1)	5 (2.9)	0	3 (21.4)	
ECOG at study entry, No. (%)							
0	389 (78.6)	303 (78.1)	42 (71.2)	133 (76.4)	17 (85.0)	7 (50.0)	.373
1	105 (21.2)	85 (21.9)	17 (28.8)	41 (23.6)	3 (15.0)	7 (50.0)	
Volume of disease, No. (%)[d]							
Low	208 (42.0)	159 (41.0)	6 (10.2)	39 (22.4)	6 (30.0)	5 (35.7)	<.001
High	287 (58.0)	229 (59.0)	53 (89.8)	135 (77.6)	14 (70.0)	9 (64.3)	
Total GS at enrollment, No. (%)							
<8	154 (31.1)	144 (37.1)	12 (20.3)	39 (22.4)	5 (25.0)	4 (28.6)	<.001
≥8	328 (66.3)	231 (59.5)	43 (72.9)	133 (76.4)	15 (75.0)	9 (64.3)	
PROSPER	Enzalutamide (n = 746)	Placebo (n = 244)	Enzalutamide (n = 146)	Placebo (n = 216)	Enzalutamide (n = 41)	Placebo (n = 8)	*P*[a]
Age, years, median	74.0	74.0	73.0	72.0	74.0	78.5	
Race, No. (%)[b]							
White	533 (71.4)	168 (68.9)	105 (71.9)	147 (68.1)	33 (80.5)	5 (62.5)	.312
Asian	113 (15.1)	53 (21.7)	26 (17.8)	35 (16.2)	3 (7.3)	0	
Black or African American	20 (2.7)	4 (1.6)	1 (0.7)	6 (2.8)	0	0	
Other[e]	80 (10.7)	19 (7.8)	14 (9.6)	28 (13.0)	5 (12.2)	3 (37.5)	
ECOG at study entry, No. (%)							
0	606 (81.2)	192 (78.7)	111 (76.0)	184 (85.2)	30 (73.2)	6 (75.0)	.455
1	139 (18.6)	51 (20.9)	35 (24.0)	32 (14.8)	11 (26.8)	2 (25.0)	
Total GS at initial diagnosis, No. (%)							
<8	415 (55.6)	125 (51.2)	74 (50.7)	114 (52.8)	23 (56.1)	3 (37.5)	.727

(continued on following page)

TABLE 2. Demographics and Baseline Characteristics for Patients With No rPD, Patients With rPD and Any PSA Rise, and Patients With rPD and No PSA Rise From ARCHES and PROSPER (ITT population) (continued)

PROSPER	Enzalutamide (n = 746)	Placebo (n = 244)	Enzalutamide (n = 146)	Placebo (n = 216)	Enzalutamide (n = 41)	Placebo (n = 8)	*P*[a]
≥8	300 (40.2)	106 (43.4)	66 (45.2)	97 (44.9)	15 (36.6)	4 (50.0)	
PSA doubling time category, No. (%)							
<6 months	557 (74.7)	173 (70.9)	77 (84.6)	156 (85.7)	81 (84.4)	32 (76.2)	<.001
≥6 months	189 (25.3)	71 (29.1)	14 (15.4)	26 (14.3)	14 (14.6)	10 (23.8)	

NOTE. ARCHES data cutoff date: October 14, 2018. PROSPER data cutoff date: June 28, 2017.

Abbreviations: ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score; ITT, intention-to-treat; PSA, prostate-specific antigen; rPD, radiographic progression.

[a]Calculated using the Cochran-Mantel-Haenszel test.

[b]Race not collected in France per country regulations.

[c]Includes American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, other, or missing.

[d]Defined by CHAARTED criteria as the 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 random assignment, which was corrected during medical review on study entry, resulting in a difference of approximately 20 patients with either high or low volume between treatment groups.[29]

[e]Includes American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, multiple, other, or missing.

TABLE 3. Distribution of Metastases in Patients at the Time of rPD With or Without Any Rise in PSA in ARCHES and PROSPER (ITT population)

	ARCHES[b]			PROSPER[c]		
Distribution of Metastases, No. (%)[a]	Enzalutamide + ADT (n = 79)	Placebo + ADT (n = 188)	*P*[d]	Enzalutamide (n = 187)	Placebo (n = 224)	*P*[d]
Any visceral metastases	13 (16.5)	9 (4.8)		13 (7.0)	11 (4.9)	
With PSA rise	8 (10.1)	6 (3.2)		10 (5.3)	11 (4.9)	
Without PSA rise	5 (6.3)	3 (1.6)		3 (1.6)	0	
Adrenal gland	2 (2.5)	1 (0.5)		0	1 (0.4)	
With PSA rise	2 (2.5)	1 (0.5)	1.000	0	1 (0.4)	1.000
Without PSA rise	0	0		0	0	
Kidney	0	0		0	1 (0.4)	
With PSA rise	0	0		0	1 (0.4)	1.000
Without PSA rise	0	0		0	0	
Liver	9 (11.4)	4 (2.1)		10 (5.3)	2 (0.9)	
With PSA rise	6 (7.6)	2 (1.1)	.277	9 (4.8)	2 (0.9)	.002
Without PSA rise	3 (3.8)	2 (1.1)	1.000	1 (0.5)	0	
Lung	3 (3.8)	4 (2.1)		3 (1.6)	3 (1.3)	
With PSA rise	1 (1.3)	3 (1.6)	.245	1 (0.5)	3 (1.3)	.587
Without PSA rise	2 (2.5)	1 (0.5)	1.000	2 (1.1)	0	
Peritoneum	1 (1.3)	0		1 (0.5)	4 (1.8)	
With PSA rise	0	0		0	4 (1.8)	.090
Without PSA rise	1 (1.3)	0	1.000	1 (0.5)	0	
Bone only	31 (39.2)	114 (60.6)	.002	52 (27.8)	62 (27.7)	1.000
With PSA rise	26 (32.9)	108 (57.4)		38 (20.3)	60 (26.8)	
Without PSA rise	5 (6.3)	6 (3.2)		14 (7.5)	2 (0.9)	
Bone + LN	3 (3.8)	6 (3.2)	.727	12 (6.4)	17 (7.6)	.702
With PSA rise	2 (2.5)	6 (3.2)		9 (4.8)	16 (7.1)	
Without PSA rise	1 (1.3)	0		3 (1.6)	1 (0.4)	
LN only	31 (39.2)	59 (31.4)	.257	83 (44.4)	115 (51.3)	.167
With PSA rise	22 (27.8)	54 (28.7)		70 (37.4)	111 (49.6)	
Without PSA rise	9 (11.4)	5 (2.7)		13 (7.0)	4 (1.8)	
Other metastases[e]	0	0		19 (10.2)	12 (5.4)	.090
With PSA rise	0	0		12 (6.4)	12 (5.4)	
Without PSA rise	0	0		7 (3.7)	0	

NOTE. ARCHES data cutoff date: October 14, 2018. PROSPER Data cutoff date: June 28, 2017. rPD is defined as objective evidence of protocol-specified rPD, as assessed by independent central review; PSA value was the value that was collected closest to within 90 days of the rPD.

Abbreviations: ADT, androgen-deprivation therapy; ITT, intention-to-treat; LN, lymph node; PSA, prostate-specific antigen; rPD, radiographic progression.

[a]Patients with visceral metastases at multiple sites were counted once for each location.

[b]One patient was missing a tumor location.

[c]Fifteen patients were missing tumor locations.

[d]From the Fisher's exact test.

[e]Other locations include bladder, mediastinum, pelvis, pleura, prostate, retroperitoneum, and other.

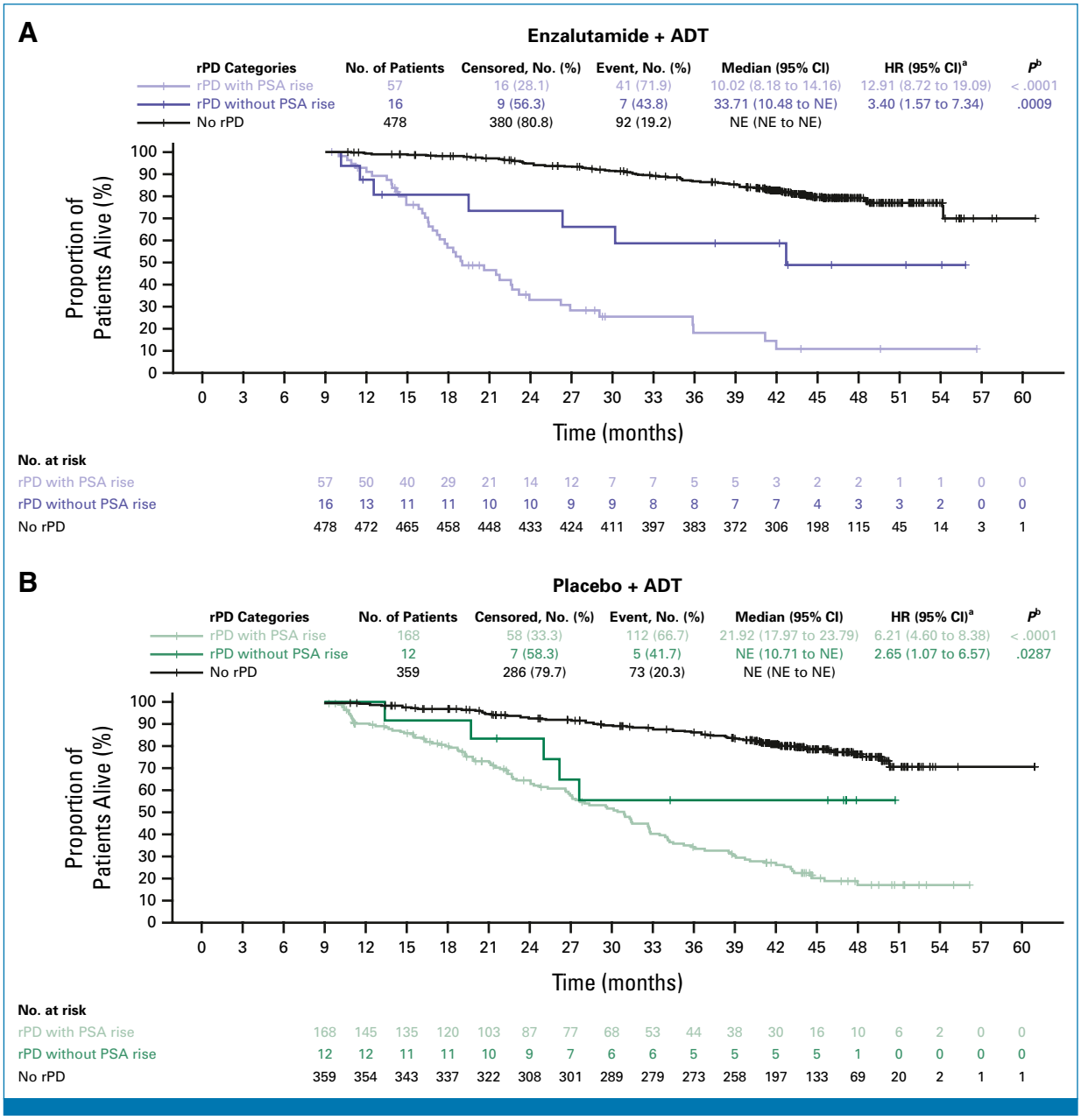

FIG 3. ARCHES: Kaplan-Meier curves of OS by rPD with and without any PSA rise in patients treated with (A) enzalutamide plus ADT or (B) placebo plus ADT (ITT population). OS is defined as the time from random assignment to death of any cause. rPD was defined by RECIST v1.1 for soft tissue disease or the appearance of ≥2 new lesions on bone scan.[28] The data cutoff for ARCHES was May 28, 2021. ADT, androgen-deprivation therapy; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PSA, prostate-specific antigen; rPD, radiographic progression. [a]No rPD is the reference. [b]From the log-rank test.

rPD, OS was significantly worse in patients who experienced rPD with and without PSA progression during enzalutamide treatment and in placebo patients who experienced rPD without PSA progression (Data Supplement, Fig S3).

In the sensitivity analysis using 6 months as the landmark, patients in ARCHES in both treatment arms with rPD, whether accompanied by PSA progression, PSA rise, or neither, had significantly shorter OS versus no rPD (Data Supplement, Fig S4). In PROSPER, using 8 months as the landmark, compared with no rPD, enzalutamide-treated patients had significantly shorter OS with rPD, both with and without PSA progression, and with and without PSA rise. In the placebo group, OS was significantly shorter only in patients with rPD without PSA progression (Data Supplement, Fig S5).

DISCUSSION

In this post hoc analysis of two phase III trials including over 2,500 patients with mHSPC and nmCRPC, rPD occurred in a

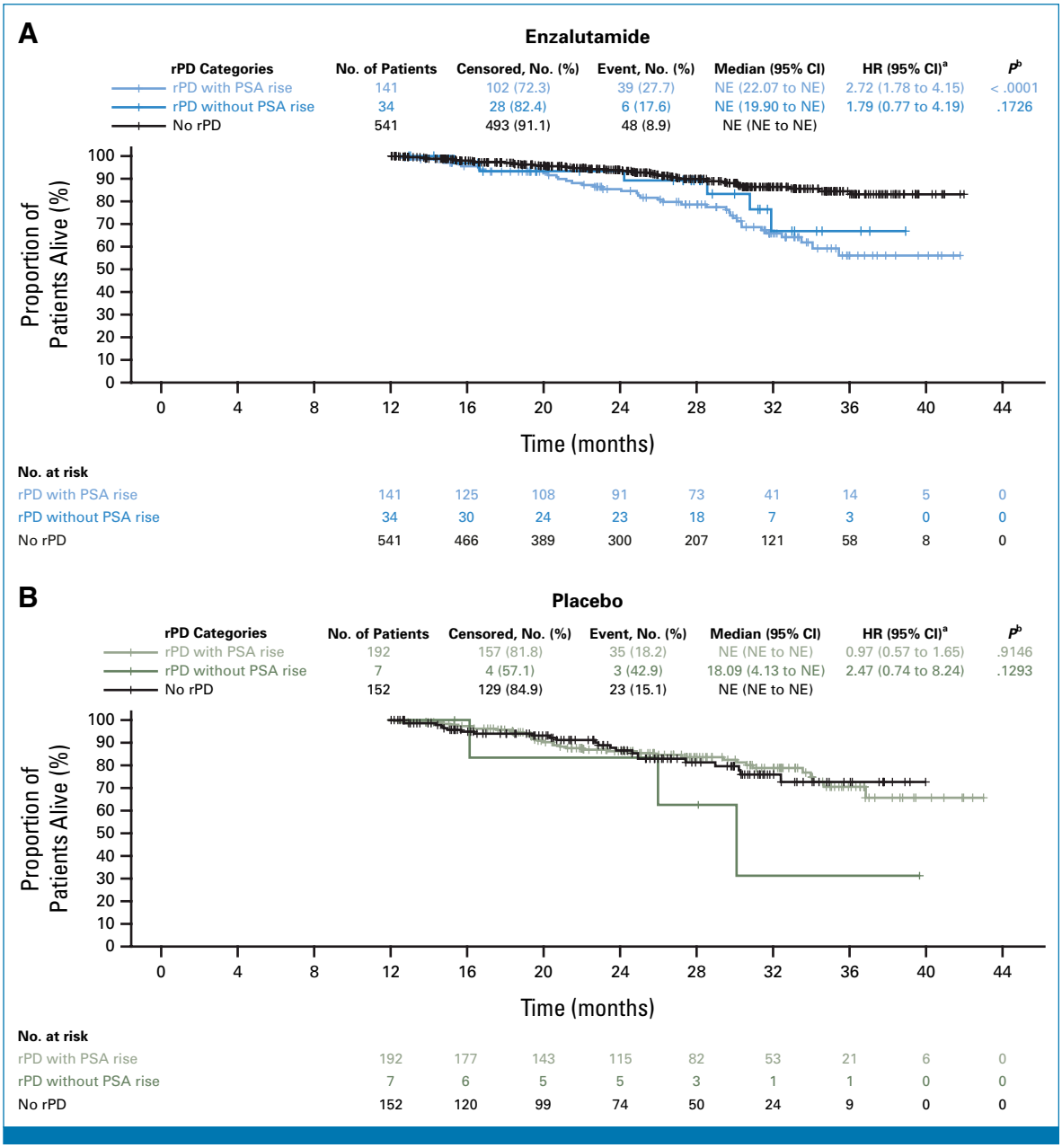

FIG 4. PROSPER: Kaplan-Meier curves of OS by rPD with and without any PSA rise in patients treated with (A) enzalutamide or (B) placebo (ITT population). OS is defined as the time from random assignment to death due to any cause. rPD was defined by RECIST v1.1 for soft tissue disease or the appearance of ≥1 new lesions on bone scan.[28] The data cutoff for PROSPER was June 28, 2017. [a]No rPD is the reference. [b]From the log-rank test. ADT, androgen-deprivation therapy; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PSA, prostate-specific antigen; rPD, radiographic progression.

significant minority of patients in the absence of concomitant rise in PSA above nadir/baseline or PSA progression, in patients treated with enzalutamide. In ARCHES, 4%, 9%, and 3% of all patients treated with enzalutamide plus ADT experienced rPD with no PSA rise, without PSA progression, and with undetectable PSA, versus 2%, 13%, and 2% of patients treated with ADT alone, respectively. In PROSPER, 4%, 10%, and 1% of all patients treated with enzalutamide experienced rPD with no PSA rise, without PSA progression, and with undetectable PSA, compared with 2%, 9%, and 0% of patients treated with placebo, respectively. However, of patients with rPD, 62% and 51% of enzalutamide-treated patients did not meet PCWG2/3-defined PSA progression, 25% and 22% had no PSA rise, and 22% and 6% of patients had an undetectable PSA in ARCHES and PROSPER, respectively. For patients with rPD versus no rPD, OS was worse irrespective of PSA rise/progression, and the vast majority of these rPD events developed without symptoms, illustrating

the clinical importance of rPD even in the absence of PSA changes or worsening symptoms in patients with mHSPC and nmCRPC.

The only baseline predictors of development of rPD were volume of disease and Gleason score at enrollment (for ARCHES) and PSA doubling time (for PROSPER). These features did not clearly predict rPD without a PSA rise. Demographics were generally similar for patients with rPD with and without PSA rise and PSA progression. However, in ARCHES, patients with rPD with and without PSA rise in both treatment groups had more high-grade and/or high-volume metastatic disease at initial diagnosis versus patients who remained free of rPD, reflecting the poor prognosis associated with heavy disease burden.

On the basis of these data, we suggest that regular bone and soft tissue imaging at least in the first 2 years of therapy should be considered to detect clinically important rPD events, particularly in the setting of potent ARPI therapies such as enzalutamide, which suppress AR and PSA production. Serial PSA monitoring alone may not be sufficient to detect rPD, and criteria for defining PSA progression in the context of ARPI treatment should be reconsidered to be any confirmed PSA rise.[22] Despite this, many patients developed rPD with no PSA rise and even with an undetectable PSA, suggesting the need for periodic imaging irrespective of PSA levels. Overall, the proportion of enzalutamide-treated patients who experienced rPD in the absence of PSA rise in both studies suggests this is a common enough occurrence to warrant monitoring in practice with frequent imaging. Whether late rPD exhibits a similar disconnect with PSA rise is unknown. Physicians often wait to order radiographic imaging studies until they observe PSA progression, and this could miss clinically important events associated with increased mortality.

Furthermore, although most metastases were located in bone and lymph nodes, visceral metastases (primarily in liver) were also identified and more commonly detected with enzalutamide treatment in both studies. The findings that liver metastases were more common in enzalutamide-treated patients with rPD, and OS was shorter in patients with rPD, irrespective of PSA rise/progression, support the need for regular soft tissue and bone radiographic imaging studies rather than relying on PSA levels alone. The landmark analysis further supports the prognostic value of rPD in the absence of PSA progression or rise. After the publication of the post hoc analyses from PROSPER and PREVAIL, it was suggested that detection of rising PSA, although it does not meet PCWG2/3-defined criteria for PSA progression, should initiate radiographic imaging studies.[18,20] This analysis from ARCHES and PROSPER supports that recommendation and expands it to include patients with undetectable PSA levels on ARPI/ADT therapy. Future guidelines should address the timing and frequency for radiographic imaging studies. We suggest that imaging every 3 months during the first 2 years is reasonable, with less frequent imaging likely needed in subsequent years, provided there is no clinical evidence of progression. Future guidelines should also seek to improve on PCWG2/3 PSA progression criteria, specifically in patients receiving ARPIs and other novel therapies, given the relatively large number of patients meeting rPD but not PSA progression criteria.

Similarly, findings from a 2024 secondary analysis published from the TITAN trial showed 52% of patients treated with apalutamide plus ADT for mHSPC experienced rPD without PCWG2/3-defined PSA progression.[19] With our findings, these data indicate that a potential mechanism for the development of castration resistance after ARPI treatment is the emergence of AR-independent clones or the induction of lineage plasticity, such as neuroendocrine transformation, with minimal or no PSA secretion enriched in visceral metastatic disease. Both AR-dependent (PSA-producing) and AR-independent (low PSA) progression events were associated with a poor prognosis, illustrating the importance of identifying these events and designing treatments to delay or overcome ARPI resistance.[30] This reinforces the need for periodic imaging in patients with mHSPC treated with potent ARPIs, highlighting a limitation of using serial PSA monitoring alone to assess disease status and detect lineage plasticity to promote earlier diagnosis and treatment of this fatal event.

A strength of this analysis is that a subpopulation of approximately 25% of patients treated with enzalutamide with mHSPC (ARCHES) and nmCRPC (PROSPER) was identified who have rPD in the absence of any PSA rise, consistent with the results for other ARPIs.[19] Additionally, this study examined two large phase III trial data sets that used ARPI therapy in mHSPC and nmCRPC to illustrate the importance of rPD and PSA discordance and the need for regular imaging across these two distinct disease settings. Overall, the inclusion of over 2,500 patients with mHSPC and nmCRPC represents an important strength of the study.

One limitation is that patients with rising PSA in ARCHES who discontinued before rPD were not included in this post hoc analysis. Another limitation is that radiographic imaging in these studies was performed with conventional imaging technologies with limited sensitivity at PSA levels <10 ng/mL.[31,32] Imaging technologies have evolved with increasing sensitivity, with detection rates of 36%-38% at PSA levels <0.5 ng/mL with prostate-specific membrane antigen positron emission tomography (PET).[33,34] As newer PET radiotracers were not available at the time that these studies were conducted, it is unclear how the increased sensitivity would have affected these data, and PET scanning has still not been incorporated in regular follow-up. Future research should investigate whether advanced imaging modalities such as PSMA PET can be validated to permit the early detection of rPD and improve patient risk stratification in the mHSPC or nmCRPC settings.

In summary, this post hoc analyses of patients with mHSPC and nmCRPC demonstrated that approximately 25% of

patients with rPD after enzalutamide treatment had no PSA rise. To identify these patients, it is important for clinicians to consider the use of periodic radiographic imaging studies in addition to monitoring PSA levels in patients receiving potent ARPIs. Future studies should explore whether PSMA PET imaging or conventional imaging is most appropriate, and in which patients, given the need to balance clinical outcomes with the economic cost of frequent PSMA PET scans.

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DISCLAIMER

Data were collected by investigators, analyzed by statisticians employed by the sponsors, and interpreted by the authors, including employees of the sponsor companies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Radiographic Progression With and Without Prostate-Specific Antigen Rise in Patients With Advanced Prostate Cancer Treated With Enzalutamide

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