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ORIGINAL REPORT

Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial

David F. Penson, Andrew J. Armstrong, Raoul Concepcion, Neeraj Agarwal, Carl Olsson, Lawrence Karsh, Curtis Dunshee, Fong Wang, Kenneth Wu, Andrew Krivoshik, De Phung, and Celestia S. Higano

See accompanying editorial on page 2075

ABSTRACT

Purpose

Enzalutamide, a potent oral androgen receptor inhibitor, improves survival in men with metastatic castration-resistant prostate cancer (CRPC) before and after chemotherapy. Bicalutamide, a nonsteroidal antiandrogen, is widely used to treat men with nonmetastatic or metastatic CRPC. The efficacy and safety of these drugs were compared in this randomized, double-blind, phase II study of men with CRPC.

Patients and Methods

A total of 396 men with nonmetastatic (n = 139) or metastatic (n = 257) CRPC were randomly assigned to enzalutamide 160 mg per day (n = 198) or bicalutamide 50 mg per day (n = 198). Androgen deprivation therapy was continued in both arms. The primary end point was progression-free survival (PFS).

Results

Enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (hazard ratio [HR], 0.24; 95% CI, 0.18 to 0.32; $P < .001$). Median PFS was 19.4 months with enzalutamide versus 5.7 months with bicalutamide. Enzalutamide resulted in significant improvements in all key secondary end points: time to prostate-specific antigen progression (HR, 0.19; 95% CI, 0.14 to 0.26; $P < .001$); proportion of patients with a ≥ 50% prostate-specific antigen response (81% *v* 31%; $P < .001$); and radiographic PFS in metastatic patients (HR, 0.32; 95% CI, 0.21 to 0.50; $P < .001$). Beneficial effects with enzalutamide were observed in both nonmetastatic and metastatic subgroups. The observed adverse event profile was consistent with that from phase III enzalutamide trials.

Conclusion

Enzalutamide significantly reduced risk of prostate cancer progression or death compared with bicalutamide in patients with nonmetastatic or metastatic CRPC.

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David F. Penson, Vanderbilt University Medical Center and Tennessee Valley Veterans Administration Medical Center Geriatric Research, Education, and Clinical Center; Raoul Concepcion, Urology Associates PC, Nashville, TN; Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC; Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Carl Olsson, Icahn School of Medicine at Mount Sinai, New York, NY; Lawrence Karsh, The Urology Center of Colorado, Denver, CO; Curtis Dunshee, Urological Associates of Southern Arizona, Tucson, AZ; Fong Wang and Kenneth Wu, Medivation, San Francisco, CA; Andrew Krivoshik, Astellas Pharma Global Development, Northbrook, IL; De Phung, Astellas Pharma Global Development, Leiden, The Netherlands; and Celestia S. Higano, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA.

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Corresponding author: David F. Penson, MD, MPH, Department of Urologic Surgery, Vanderbilt University Medical Center, A-1302 Medical Center North, Nashville, TN 37232-2765; e-mail: david.penson@vanderbilt.edu.

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INTRODUCTION

Adenocarcinoma of the prostate is treated with androgen deprivation therapy (ADT) in men with metastatic disease and in many with nonmetastatic disease who present with biochemical recurrence, defined as increasing prostate-specific antigen (PSA) after localized therapy with prostatectomy and/or radiotherapy.[1] Subsequent disease progression in the setting of castrate levels of testosterone on ADT, as manifested by increasing PSA or radiographic progression in bone or soft tissue, signals the development of castration-resistant prostate cancer (CRPC).[2] Several new therapies have been approved recently to treat metastatic CRPC, including agents that target the androgen receptor signaling pathway (enzalutamide, abiraterone acetate plus prednisone), chemotherapy (cabazitaxel after previous treatment with docetaxel), immunotherapy (sipuleucel-T) and, for men with symptomatic bone metastatic CRPC but no known visceral disease, radioisotope therapy with radium-223 dichloride.[3-9] There is currently no approved therapy for nonmetastatic CRPC, and there is no evidence that the addition of bicalutamide to ongoing ADT has an impact on the outcome of metastatic CRPC.

Initial treatment of CRPC typically includes adding a second-line hormonal agent such as an antiandrogen, most commonly bicalutamide, to ADT.[1,2] Yet the practice of adding bicalutamide

to ADT in the setting of castration resistance is based on single-arm studies in a modest number of men that suggested limited benefit lasting no more than 3 to 6 months.[10-14] Furthermore, bicalutamide can function as an androgen receptor partial agonist and can fuel disease progression,[15] particularly in the setting of androgen receptor overexpression frequently observed in CRPC.[16] This agonist activity becomes clinically apparent when PSA declines upon discontinuation of bicalutamide, a phenomenon known as antiandrogen withdrawal response.[17-19]

Enzalutamide is an androgen receptor inhibitor that binds to the androgen receptor in the same way as bicalutamide but with higher affinity. Preclinical studies demonstrated that enzalutamide, unlike bicalutamide, lacks agonist activity at the wild-type androgen receptor[20,21] and impairs nuclear translocation of the androgen receptor and its binding to DNA, which leads to reduced expression of androgen-dependent genes.[21,22] Two large multinational phase III trials in men with metastatic CRPC demonstrated improved overall survival over placebo in both prechemotherapy (PREVAIL [A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer][4]) and postchemotherapy (AFFIRM [Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy][3]) settings. The demonstrated clinical benefit of enzalutamide in patients with metastatic CRPC and its superior activity in suppressing androgen receptor signaling in preclinical models suggested that enzalutamide might confer clinical benefit compared with bicalutamide in patients with either nonmetastatic or metastatic CRPC who would ordinarily be treated with the addition of bicalutamide.

PATIENTS AND METHODS

STRIVE (Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men With Prostate Cancer) was a multicenter, randomized, double-blind phase II trial of enzalutamide versus bicalutamide in men with nonmetastatic or metastatic CRPC. The review boards of all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent to participate in the study.

Study Participants

Enrolled men had histologically or cytologically confirmed adenocarcinoma of the prostate, serum testosterone level ≤ 50 ng/dL (1.73 nmol/L), and progressive disease despite ADT. Disease progression was defined as at least one of the following three criteria: PSA progression (≥ 2 increasing PSA values with an interval of ≥ 1 week between determinations and PSA doubling time ≤ 10 months if the central laboratory screening PSA was ≥ 2 and < 5 ng/mL), soft-tissue disease progression, or bone disease progression. Key exclusion criteria included prior disease progression while receiving bicalutamide, prior chemotherapy, or radiation for distant metastasis; systemic corticosteroids for prostate cancer; and history of seizure. A complete list of inclusion and exclusion criteria is provided in Appendix Table A1 (online only).

Patients were randomly assigned 1:1 to enzalutamide (160 mg per day as four 40-mg capsules plus one placebo capsule) or bicalutamide (50 mg per day as one capsule plus four placebo capsules), stratified by disease stage (M0/N0, M0/N1, or M1). M0/N0 signified absence of bone metastases on bone scan and absence of soft-tissue disease; M0/N1 signified absence of bone metastases on bone scan and distant soft-tissue metastases but with nodal metastases below the aortic bifurcation; and M1 signified bone metastases on bone scan or soft-tissue metastases (including nodal) above the aortic bifurcation. ADT was maintained throughout the study, and concurrent use of bisphosphonates and denosumab was permitted. Patients were to continue receiving study drug at least until confirmed PSA or radiographic progression or until an adverse event that would lead to undue risk if dosing had continued.

Study End Points

The primary end point was progression-free survival (PFS), defined as the time from random assignment to a progression event or death as a result of any cause. Progression events included PSA progression per Prostate Cancer Clinical Trials Working Group 2 guidelines[23] or investigator-assessed radiographic progression (Appendix Table A2, online only). Key secondary end points included time to PSA progression, PSA response of ≥ 50% (defined as ≥ 50% reduction in PSA at any postbaseline assessment), and radiographic progression-free survival (rPFS) for patients with metastatic disease only. Other end points included best overall soft-tissue response (per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1][24]) in metastatic patients with measurable disease at screening, time to a 10-point or greater decline of the global score of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire, and PSA response of ≥ 90% (defined as ≥ 90% reduction in PSA at any postbaseline assessment). Definitions and associated analyses for all end points are detailed in Appendix Table A2.

Statistical Analysis

The intent-to-treat population included all randomly assigned patients. A minimum of 231 PFS events provided 90% power to detect a hazard ratio (HR) of 0.65 based on a two-sided log-rank test with a significance level of 0.05. Time-to-event end points, including the primary end point of PFS as well as time to PSA progression and rPFS, were compared between the two treatment arms by using a two-sided log-rank test stratified by disease stage (nonmetastatic [M0N0 and M0N1] or metastatic) where applicable. Kaplan-Meier curves and medians were calculated for these end points, and HRs were estimated by using a Cox regression model stratified by disease stage where applicable. A two-sided Cochran-Mantel-Haenszel test was used to compare PSA response rates for enzalutamide and bicalutamide. Hypothesis testing for primary and key secondary end points was performed with an overall significance level of 0.05 and multiple testing was accounted for. The safety population was defined as all randomly assigned patients who received at least one dose of study drug. Safety data were not adjusted for time on study drug.

RESULTS

Patients and Treatment Duration

A total of 396 patients at 62 sites in the United States were randomly assigned between August 2012 and March 2014 to receive enzalutamide (n = 198) or bicalutamide (n = 198). Figure 1 shows the flow of patients through the study. Baseline demographic and disease characteristics were well balanced between groups (Table 1 and Appendix Table A3 [online only]). Median time on treatment was 14.7 months for the enzalutamide group compared with 8.4 months for the bicalutamide group. More patients in the enzalutamide group than in the bicalutamide group received ≥ 12 months of treatment (68% *v* 35%) and continued on study treatment at the February 9, 2015, data cutoff date (53% *v* 20%).

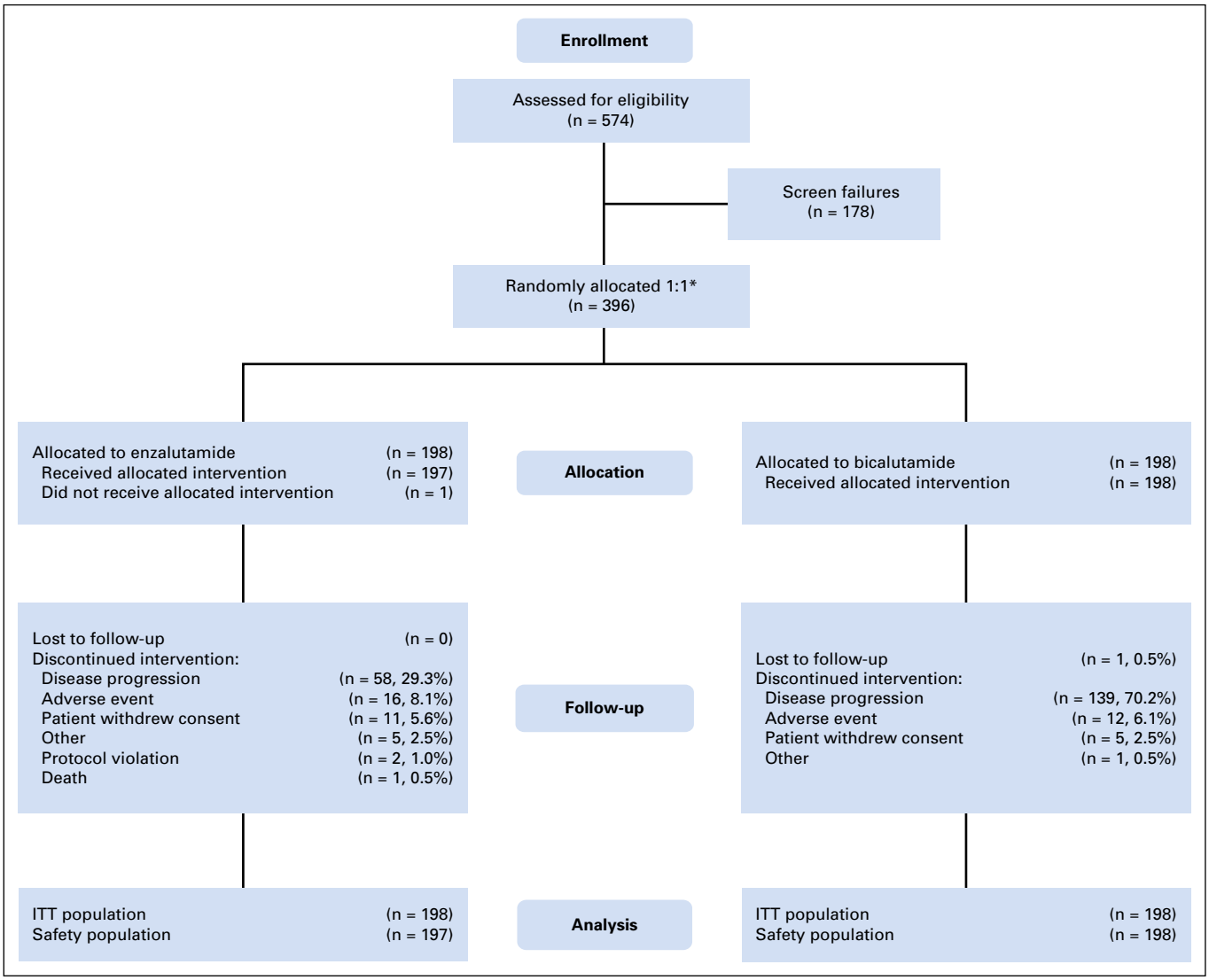

Fig 1. CONSORT diagram. (*) Random allocation was stratified by disease stage (M0/N0 [absence of bone metastases on bone scan and absence of soft-tissue disease per RECIST 1.1], M0/N1 [absence of bone metastases on bone scan and distant soft-tissue metastases, but with clinically determined nodal metastases below the aortic bifurcation], or M1 [bone metastases anywhere on bone scan or soft-tissue metastases, including nodal, above the aortic bifurcation]) at entry. ITT, intent-to-treat.

Efficacy

Primary end point. All efficacy analyses were conducted on the intent-to-treat population unless otherwise stated. Treatment with enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (HR, 0.24; 95% CI, 0.18 to 0.32; $P < .001$). Median PFS was 19.4 months with enzalutamide and 5.7 months with bicalutamide (Fig 2A and Table 2). The treatment effect of enzalutamide on PFS was consistently favorable across all prespecified subgroups (Fig 2B), including disease state (nonmetastatic *v* metastatic) at study entry. In patients with nonmetastatic CRPC, median PFS was not reached with enzalutamide compared with 8.6 months with bicalutamide (HR, 0.24; 95% CI, 0.14 to 0.42). In patients with metastatic CRPC, median PFS was 16.5 months with enzalutamide and 5.5 months with bicalutamide (HR, 0.24; 95% CI, 0.17 to 0.34; Table 2).

Key secondary end points. Analyses of all key secondary end points found enzalutamide to be significantly superior to bicalutamide (Table 2). Enzalutamide was associated with a decrease in the risk of radiographic progression or death compared with bicalutamide in both metastatic and nonmetastatic disease: 68% (HR, 0.32; 95% CI, 0.21 to 0.50; $P < .001$; Fig 2C and Table 2) and 76% (HR, 0.24; 95% CI, 0.10 to 0.56; Table 2), respectively. The median rPFS in those with metastatic disease was not reached with enzalutamide compared with 8.3 months with bicalutamide.

Enzalutamide was associated with an 81% reduction in the risk of PSA progression (HR, 0.19; 95% CI, 0.14 to 0.26; $P < .001$; Fig 3A). Median time to PSA progression was not reached with enzalutamide compared with 8.3 months with bicalutamide (Table 2). Among patients with at least one postbaseline PSA value, a PSA response $\geq$ 50% was achieved by 156 (81%) of 192 patients in the enzalutamide group compared with 61 (31%) of 195 patients in the bicalutamide group ($P < .001$; Fig 3B). In addition, secondary outcomes favored enzalutamide in both the nonmetastatic and metastatic subgroups (Table 2).

Other end points. Among patients with measurable soft-tissue metastatic disease at baseline, 21 (60%) of 35 patients in the

Table 1. Baseline Patient and Disease Characteristics (intent-to-treat population)

Baseline Characteristic	Enzalutamide (n = 198) No. (%)*	Bicalutamide (n = 198) No. (%)*
Age, years		
< 65	39 (19.7)	25 (12.6)
65-74	82 (41.4)	76 (38.4)
≥ 75	77 (38.9)	97 (49.0)
Age, years		
Median	72	74
Range	46-92	50-91
Race		
Black or African American	29 (14.6)	24 (12.1)
White	160 (80.8)	169 (85.4)
Other	9 (4.5)	5 (2.5)
Baseline weight, kg		
Median	91.4	89.1
Range	58.5-249.7	45.8-181.8
Baseline ECOG PS		
0	148 (74.7)	145 (73.2)
1	50 (25.3)	53 (26.8)
Baseline pain score as assessed by Brief Pain Inventory–Short Form question 3		
0-1	165 (83.3)	158 (79.8)
2-3	33 (16.7)	40 (20.2)
Baseline serum PSA, μg/L		
Median	11.0	13.2
Range	0.0-1499.7	0.2-2849.7
Baseline FACT–P global score		
Median	125.7	124.0
Range	37.0-154.0	51.0-156.0
Total Gleason score category at initial diagnosis		
Low (2-4)	0	2 (1.0)
Medium (5-7)	90 (45.5)	93 (47.0)
High (8-10)	100 (50.5)	97 (49.0)
Missing†	8 (4.0)	6 (3.0)
Disease stage at study entry per CRF		
M0	70 (35.4)	69 (34.8)
M0/N0 (nonnodal)	61 (30.8)	60 (30.3)
M0/N1 (nodal)	9 (4.5)	9 (4.5)
M1	128 (64.6)	129 (65.2)
Disease localization at screening		
Bone only	61 (30.8)	66 (33.3)
Soft tissue only	29 (14.6)	30 (15.2)
Both bone and soft tissue	48 (24.2)	42 (21.2)
None	60 (30.3)	60 (30.3)
Soft-tissue disease at screening		
Measurable disease‡	41 (20.7)	50 (25.3)
Target only	16 (8.1)	18 (9.1)
Target and nontarget	25 (12.6)	32 (16.2)
Nontarget only	36 (18.2)	22 (11.1)
Distribution of disease at screening§		
Bone	109 (55.1)	108 (54.5)
Lymph node	63 (31.8)	61 (30.8)
Visceral disease (lung or liver)	11 (5.6)	13 (6.6)
Liver	4 (2.0)	3 (1.5)
Lung	7 (3.5)	10 (5.1)
Lung and liver	0	0
Other soft tissue	18 (9.1)	11 (5.6)
Bone metastases at screening		
0	89 (44.9)	90 (45.5)
1	23 (11.6)	21 (10.6)
2-4	35 (17.7)	18 (9.1)
5-9	26 (13.1)	25 (12.6)
10-20	14 (7.1)	22 (11.1)
> 20	11 (5.6)	22 (11.1)

NOTE. M0/N0 indicates absence of bone metastases on bone scan and absence (per RECIST 1.1) of soft-tissue disease; M0/N1 indicates absence of bone metastases on bone scan and distant soft-tissue metastases, but with clinically determined nodal metastases below the aortic bifurcation; and M1 indicates bone metastases anywhere on bone scan or soft-tissue metastases (including nodal) above the aortic bifurcation.

Abbreviations: CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; FACT–P, Functional Assessment of Cancer Therapy–Prostate; M0, nonmetastatic; M1, metastatic; PSA, prostate-specific antigen.

*All data are No. (%), unless otherwise noted.

†Missing, patients with missing primary, secondary, and total Gleason scores.

‡Measurable soft-tissue disease was defined as at least one target lesion identified per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

§Patients could be summarized for more than one category, but only counted once for each category.

enzalutamide group compared with six (14%) of 43 patients in the bicalutamide group had an objective response (four [11%] complete responses and 17 [49%] partial responses in the enzalutamide group; no complete responses and six [14%] partial responses in the bicalutamide group; $P < .001$). Median time to decline of the FACT-P global score was 8.4 months with enzalutamide and 8.3 months with bicalutamide (HR, 0.91; 95% CI, 0.70 to 1.19; $P = .49$).

Among patients with at least one postbaseline PSA value, a PSA response of ≥ 90% was achieved by 124 (65%) of 192 patients treated with enzalutamide compared with 17 (9%) of 195 patients treated with bicalutamide ($P < .001$; Fig 3B).

Safety

Adverse events are summarized in Tables 3 and 4. Serious adverse events, grade ≥ 3 adverse events, and adverse events resulting in death were reported at similar rates in both treatment groups. Among the common adverse events (ie, occurring in ≥ 10% of patients in either treatment group, with a difference between groups of ≥ 2%), those reported more frequently with enzalutamide than with bicalutamide included fatigue, back pain, hot flashes, falls, hypertension, dizziness, and decreased appetite. Common adverse events reported more frequently with bicalutamide than with enzalutamide included constipation, diarrhea, anemia, and urinary tract infection. One patient in the enzalutamide group experienced a seizure; this patient had a previously undisclosed history of multiple seizures before study entry.

DISCUSSION

STRIVE is the first randomized, double-blind, head-to-head trial of bicalutamide versus enzalutamide in men with nonmetastatic or metastatic CRPC. Enzalutamide significantly reduced the risk of disease progression or death by 76% compared with bicalutamide, and the benefit of enzalutamide over bicalutamide was robust, with a more than 1-year prolongation of median PFS. Although the

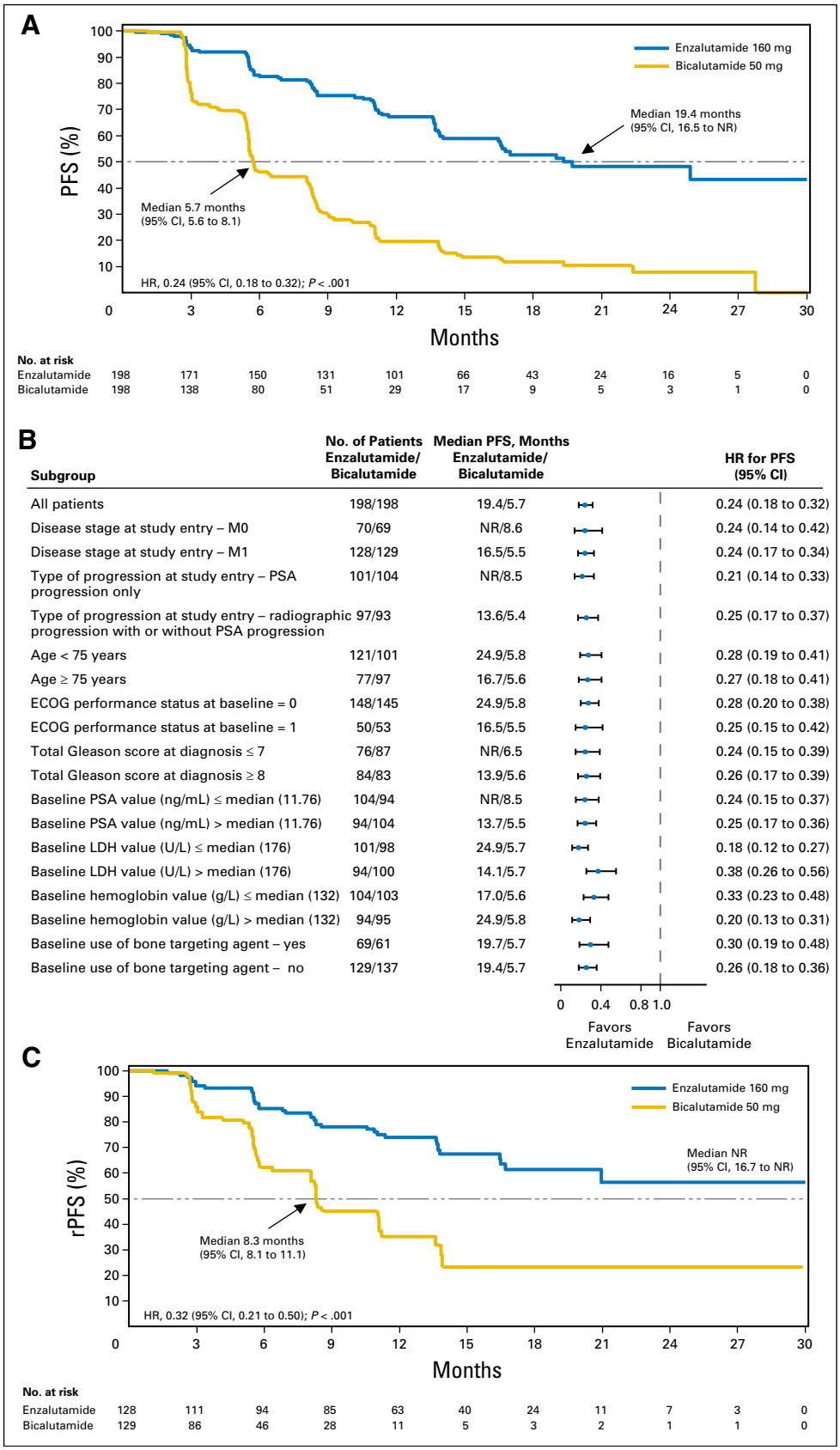

Fig 2. (A) Kaplan-Meier estimates of progression-free survival (PFS); (B) subgroup analyses; (C) Kaplan-Meier estimates of radiographic progression-free survival (rPFS). (A and B) Data for PFS (primary end point). (A) The dashed line indicates the median. (B) Hazard ratios (HRs) are based on a Cox regression model (with treatment as the only covariate) and are relative to bicalutamide, with less than 1.0 favoring enzalutamide. For A and the analysis of all patients in B, the Cox regression model used to estimate the HRs was stratified by disease stage at study entry. (C) Data for the key secondary end point analysis of rPFS in the metastatic subgroup; the dashed line indicates the median. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M0, nonmetastatic; M1, metastatic; NR, not reached; PSA, prostate-specific antigen.

Table 2. Efficacy End Points Overall and by Disease State (nonmetastatic *v* metastatic)

End Point	Enzalutamide		Bicalutamide				
	No./Total (%)	95% CI	No./Total (%)	95% CI	HR	95% CI	*P*
Overall	(n = 198)		(n = 198)				
Median PFS, months	19.4	16.5 to NR	5.7	5.6 to 8.1	0.24	0.18 to 0.32	< .001*
Median time to PSA progression, months	NR	19.4 to NR	8.3	5.7 to 8.5	0.19	0.14 to 0.26	< .001†
PSA response							
Patients with ≥ 1 postbaseline PSA assessment	192		195				
Confirmed PSA decline ≥ 50% from baseline	156/192 (81)		61/195 (31)				< .001†
Confirmed PSA decline ≥ 90% from baseline	124/192 (65)		17/195 (9)				< .001
rPFS	198		198				
Median, months	NR	NR to NR	11.2	8.4 to 16.6	0.30	0.21 to 0.44	< .001
Nonmetastatic	(n = 70)		(n = 69)				
Median PFS, months‡	NR	19.4 to NR	8.6)	8.1 to 11.1	0.24	0.14 to 0.42	< .001
Median time to PSA progression, months	NR	NR to NR	11.1	8.4 to 13.9	0.18	0.10 to 0.34	< .001
PSA response							
Patients with ≥ 1 postbaseline PSA assessment	66		69				
Confirmed PSA decline ≥ 50% from baseline	60/66 (91)		29/69 (42)				< .001
Confirmed PSA decline ≥ 90% from baseline	50/66 (76)		8/69 (12)				< .001
Median rPFS, months	NR	NR to NR	NR	14.1 to NR	0.24)	0.10 to 0.56	< .001
Metastatic	(n = 128)		(n = 129)				
Median PFS, months§	16.5	11.7 to 24.9	5.5	5.3 to 5.7	0.24	0.17 to 0.34	< .001
Median time to PSA progression, months	24.9	16.6 to NR	5.7	5.6 to 8.3	0.19	0.13 to 0.28	< .001
PSA response							
Patients with ≥ 1 postbaseline PSA assessment	126		126				
Confirmed PSA decline ≥ 50% from baseline	96/126 (76)		32/126 (25)				< .001
Confirmed PSA decline ≥ 90% from baseline	74/126 (59)		9/126 (7)				< .001
Median rPFS, months	NR	16.7 to NR	8.3	8.1 to 11.1	0.32	0.21 to 0.50	< .001†

Abbreviations: HR, hazard ratio; NR, not reached; PFS, progression-free survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.
*Primary end point analysis. Median PFS follow-up (months): enzalutamide 16.7; bicalutamide 16.8.
†Key secondary end point analysis.
‡Median PFS follow-up (months) for M0 (nonmetastatic) patients: enzalutamide 16.8; bicalutamide 17.3.
§Median PFS follow-up (months) for M1 (metastatic) patients: enzalutamide 16.6; bicalutamide 16.6.

median PFS for enzalutamide of 19.4 months exceeded study design projections, the limited 5.7-month benefit of bicalutamide was expected. The benefit associated with enzalutamide was seen across all subgroups, including disease state (nonmetastatic and metastatic) at study entry. The superiority of enzalutamide relative to bicalutamide was also observed across all key secondary end points, including time to PSA progression and PSA response. Although it is unknown whether earlier treatment with enzalutamide could lead to resistance to subsequent therapies, these data suggest that enzalutamide should replace bicalutamide in the treatment of men with CRPC.

In practice, bicalutamide 50 mg per day is commonly used for patients for whom ADT has failed despite the lack of randomized clinical trials showing a durable or widely experienced clinical benefit in the setting of castration resistance. The original approval in Europe of bicalutamide 150 mg per day for locally advanced prostate cancer was based on the results of the Early Prostate Cancer trial, which found that bicalutamide 150 mg plus standard therapy significantly reduced the risk of progressive disease in patients with early prostate cancer compared with standard care alone.[25] Bicalutamide 50 mg per day was approved for use in the United States on the basis of a trial of men with hormone-naïve metastatic disease in which flutamide served as comparator; both were administered in combination with luteinizing hormone-releasing hormone analog therapy,[26] and no differences in overall survival or time to progression were reported.[27] In the absence of approved therapies, the use of bicalutamide migrated to the treatment of castration-resistant disease. However, men with CRPC treated with bicalutamide second-line hormonal therapy, even at a higher dose of 150 mg per day, have experienced relatively short response durations,[14] which may result from the partial agonist activity of bicalutamide coupled with overexpression of the androgen receptor, a primary mechanism in the development of castration-resistant disease.[16]

Enzalutamide overcomes the limitations of bicalutamide, such as suboptimal clinical results resulting from low affinity for the androgen receptor at which bicalutamide exerts partial agonist activity. Enzalutamide has a 10-fold greater affinity for the androgen receptor than bicalutamide, lacks agonist activity unlike bicalutamide, and now in two prospective, randomized blinded studies has shown an overall survival benefit in men with metastatic CRPC.[3,4,21] The STRIVE study enrolled patients earlier in the course of the disease, before resistance to bicalutamide therapy had developed and, in some patients, before metastatic disease had developed. The stabilization of CRPC by enzalutamide in the study overall, as demonstrated by a prolongation in PFS, was consistently observed in both the nonmetastatic and metastatic subgroups. This is the first study to indicate a benefit of enzalutamide in patients with nonmetastatic CRPC. The phase III PROSPER (NCT02003924; Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer) trial is now evaluating the impact of enzalutamide versus placebo on metastasis-free survival in patients with nonmetastatic CRPC.

Data from the STRIVE study suggest that patients with nonmetastatic CRPC in the enzalutamide arm did better than those with metastatic CRPC in terms of duration of stable disease (median PFS

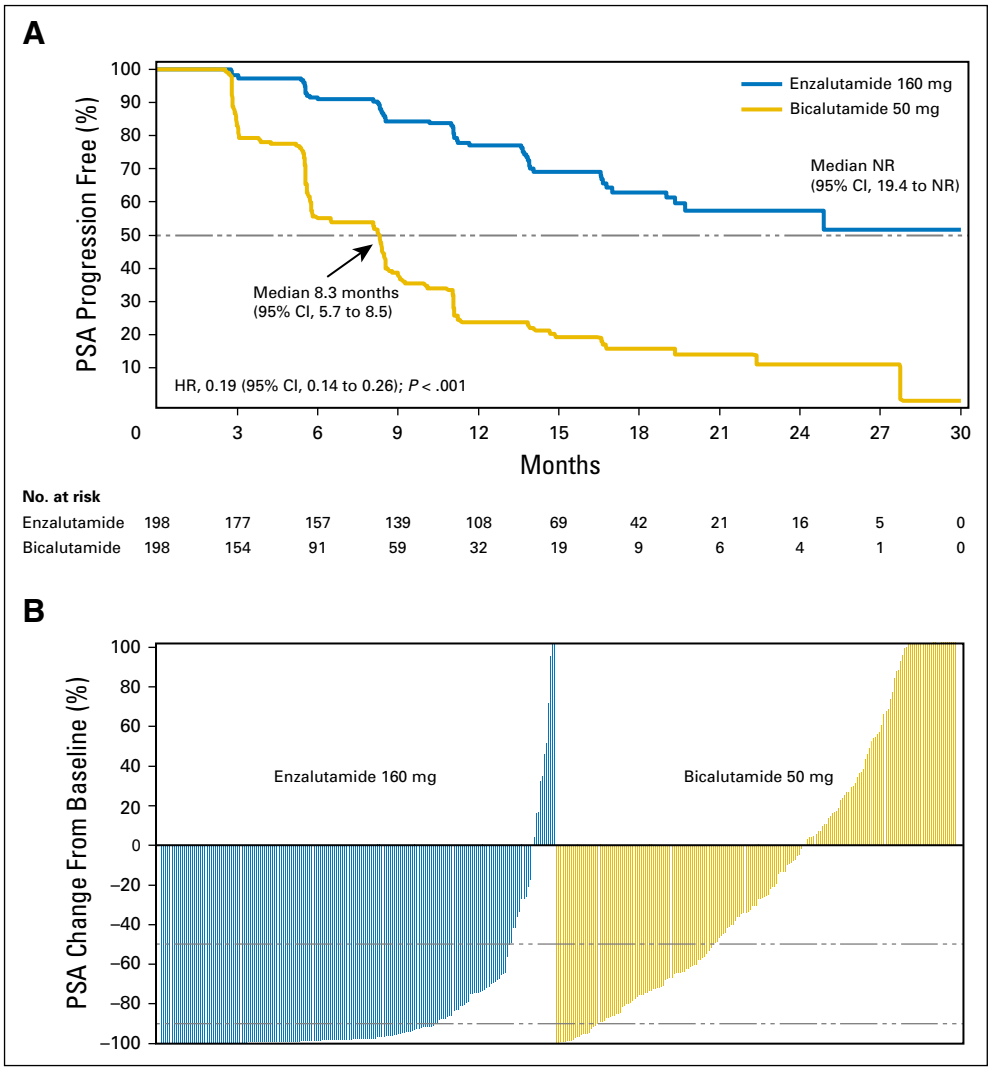

Fig 3. (A) Kaplan-Meier estimates of time to prostate-specific antigen (PSA) progression and (B) PSA response waterfall plots. (A) Data for time to PSA progression; the dashed line indicates the median. Hazard ratio (HR) is based on a Cox regression model (with treatment as the only covariate), stratified by disease stage at study entry and is relative to bicalutamide with less than 1.0 favoring enzalutamide. (B) Largest PSA decline from baseline for each patient for bicalutamide and enzalutamide, respectively. NR, not reached.

not reached *v* 16.5 months) and longer time to PSA progression and improved PSA response. These findings might be expected on the basis of the smaller tumor burden in the nonmetastatic subgroup, and they support the importance of early disease detection.

For men with measurable soft-tissue metastatic disease at study entry in STRIVE, meaningful tumor shrinkage (overall response rates by RECIST 1.1) with enzalutamide was demonstrated in the majority of patients (60%) compared with 14% in the bicalutamide arm. The soft-tissue response rate observed in STRIVE is consistent with the 59% response rate observed with enzalutamide in the PREVAIL study of chemotherapy-naïve metastatic CRPC.

Enzalutamide and bicalutamide were generally well tolerated in this study, with enzalutamide demonstrating a safety profile consistent with that reported in two large placebo-controlled phase III trials in metastatic CRPC.[3,4] In STRIVE, both drugs were associated with reports of fatigue and hot flash adverse events, although to a greater extent with enzalutamide, which is consistent with more effective androgen receptor signaling inhibition without a significant difference in quality of life as assessed by the FACT-P questionnaire. A slightly higher proportion of patients with hypertension entered STRIVE in the enzalutamide group compared with the bicalutamide group (74.2% *v* 68.7%). Adverse events of hypertension were reported by 12.2% and 5.1% of patients in the enzalutamide and bicalutamide groups, respectively, and were reported at grade 3 (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg) in 5.1% versus 1.5% of patients, respectively.

A limitation of this study was that it did not address the benefit of sequential therapy with bicalutamide followed by enzalutamide. However, the suggestion from the cross-trial comparisons mentioned

Table 3. Summary of Adverse Events

Adverse Event Summary	Enzalutamide (n = 197) No. (%)	Bicalutamide (n = 198) No. (%)
Median duration of treatment, months	14.7	8.4
Any adverse event	184 (93)	177 (89)
Any grade ≥ 3 adverse event	70 (36)	72 (36)
Any serious adverse event	58 (29)	56 (28)
Any adverse event as primary reason for treatment discontinuation	15 (8)	12 (6)
Any adverse event leading to death	6 (3)	6 (3)

Table 4. Summary of Most Common Adverse Events

Most Common Adverse Events*	Enzalutamide (n = 197) No. (%)		Bicalutamide (n = 198) No. (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Fatigue	74 (38)	9 (5)	56 (28)	5 (3)
Back pain	35 (18)	3 (2)	31 (16)	2 (1)
Hot flashes	31 (16)	0	19 (10)	1 (< 1)
Fall	27 (14)	3 (2)	16 (8)	3 (2)
Hypertension	24 (12)	10 (5)	10 (5)	3 (2)
Dizziness	24 (12)	1 (< 1)	14 (7)	1 (< 1)
Decreased appetite	23 (12)	0	17 (9)	4 (2)
Constipation	20 (10)	0	33 (17)	1 (< 1)
Diarrhea	17 (9)	3 (2)	28 (14)	2 (1)
Anemia	13 (7)	6 (3)	21 (11)	10 (5)
Urinary tract infection	10 (5)	2 (1)	22 (11)	6 (3)

*At least 10% of patients in either treatment group and a difference between groups of ≥ 2%.

before suggest that earlier use of enzalutamide results in a greater benefit. In addition, this trial was not designed to assess overall survival, and it is not known whether earlier treatment with enzalutamide results in longer survival compared with later treatment. However, available evidence suggests that for drugs such as enzalutamide that target the androgen-androgen receptor pathway, a large magnitude of improvement in radiographic PFS such as is observed in this study and in the TERRAIN (A Randomized, Double-Blind, Phase 2, Efficacy and Safety Study of Enzalutamide Versus Bicalutamide in Metastatic Castrate Resistant Prostate Cancer: TERRAIN Trial) study is associated with an improvement in overall survival.[28] The ongoing phase III PROSPER study of enzalutamide versus placebo in patients with nonmetastatic CRPC is evaluating this question.

Data from enzalutamide-treated patients across the CRPC spectrum suggest a disease continuum with a longer time to disease progression in those treated with enzalutamide earlier in the disease course of CRPC. Median time to PSA progression with enzalutamide was 8.3 months in men with late-stage metastatic CRPC treated after chemotherapy in AFFIRM, 11.2 months in men with metastatic CRPC treated before chemotherapy in PREVAIL, and 19.4 months in men with metastatic CRPC for whom bicalutamide therapy had not failed in TERRAIN; it was not reached (lower bound of 95% CI, 19.4 months) in men with nonmetastatic or metastatic CRPC for whom bicalutamide therapy had not failed in STRIVE (Appendix Table A4, online only). New classifications of disease states within CRPC based on sensitivity and resistance to androgen receptor inhibition rather than the absence or presence of radiographically evident metastases or history of chemotherapy use might better guide treatment and prognosis because the findings from STRIVE suggest that CRPC may be addressed without regard to these latter factors.

In conclusion, the improved clinical outcomes with enzalutamide compared with bicalutamide in patients with nonmetastatic or metastatic CRPC in the STRIVE study add to the growing body of evidence supporting the use of enzalutamide in patients across a broad CRPC spectrum.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: David F. Penson, Andrew J. Armstrong, Raoul Concepcion, De Phung, Celestia S. Higano
Provision of study materials or patients: David F. Penson, Andrew J. Armstrong, Carl Olsson, Lawrence Karsh, Curtis Dunshee, Celestia S. Higano
Collection and assembly of data: Andrew J. Armstrong, Neeraj Agarwal, Carl Olsson, Fong Wang, Kenneth Wu
Data analysis and interpretation: David F. Penson, Andrew J. Armstrong, Carl Olsson, Lawrence Karsh, Curtis Dunshee, Fong Wang, Kenneth Wu, Andrew Krivoshik, De Phung, Celestia S. Higano
Manuscript writing: All authors
Final approval of manuscript: All authors

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Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial

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David F. Penson
Consulting or Advisory Role: Astellas Pharma, Medivation
Research Funding: Medivation (Inst), Astellas Pharma (Inst)

Andrew J. Armstrong
Honoraria: Dendreon, Sanofi Oncology
Consulting or Advisory Role: Bayer Healthcare Pharmaceuticals, Sanofi Oncology, Novartis, Dendreon, Medivation, Janssen Biotech
Speakers' Bureau: Dendreon, Sanofi Oncology
Research Funding: Dendreon (Inst), Sanofi Oncology (Inst), Bayer Healthcare Pharmaceuticals (Inst), Pfizer (Inst), Novartis (Inst), Bristol-Myers Squibb (Inst), KangLaiTe (Inst), Janssen Biotech (Inst), Medivation (Inst), Astellas Pharma (Inst), ImClone Systems (Inst)
Patents, Royalties, Other Intellectual Property: Circulating tumor cell novel capture technology (Inst)
Travel, Accommodations, Expenses: Dendreon, Medivation, Janssen Biotech

Raoul Concepcion
Consulting or Advisory Role: Bayer Healthcare Pharmaceuticals, Dendreon, Astellas Pharma, Medivation, Sanofi Oncology
Speakers' Bureau: Bayer Healthcare Pharmaceuticals, Dendreon, Astellas Pharma, Medivation, GHI Pharma, Amgen, Janssen Biotech, Sanofi Oncology
Research Funding: Bayer Healthcare Pharmaceuticals, Astellas Pharma, Janssen Biotech, BN ImmunoTherapeutics, Medivation, Dendreon, MDxHealth

Neeraj Agarwal
Consulting or Advisory Role: Pfizer, Exelixis, Argos Therapeutics

Carl Olsson
Stock or Other Ownership: Medivation (I), Exelixis (I)
Research Funding: Medivation (Inst), Dendreon (Inst), Astellas Pharma (Inst)
Patents, Royalties, Other Intellectual Property: Reverse-transcription-polymerase chain reaction technology for staging prostate cancer

Lawrence Karsh
Honoraria: Astellas Pharma, Bayer Healthcare Pharmaceuticals, Dendreon, Janssen Biotech, Medivation
Consulting or Advisory Role: Astellas Pharma, Bayer Healthcare Pharmaceuticals, Dendreon, Janssen Biotech, Medivation
Speakers' Bureau: Astellas Pharma, Bayer Healthcare Pharmaceuticals, Dendreon, Janssen Biotech, Medivation
Research Funding: Astellas Pharma, Dendreon, Janssen Biotech, Medivation
Travel, Accommodations, Expenses: Astellas Pharma, Dendreon, Janssen Biotech, Medivation

Curtis Dunshee
Consulting or Advisory Role: Cardinal Health

Fong Wang
Employment: Medivation
Stock or Other Ownership: Medivation
Travel, Accommodations, Expenses: Medivation

Kenneth Wu
Employment: Medivation, Veracyte (I)
Stock or Other Ownership: Medivation

Andrew Krivoshik
Employment: Astellas Pharma
Stock or Other Ownership: Abbott/AbbVie, Merck (I), Johnson & Johnson (I)
Patents, Royalties, Other Intellectual Property: Abbott/AbbVie

De Phung
Employment: Astellas Pharma

Celestia S. Higano
Employment: CTI BioPharma (I)
Leadership: CTI BioPharma (I)
Stock or Other Ownership: CTI BioPharma (I)
Consulting or Advisory Role: Dendreon, Bayer Healthcare Pharmaceuticals, Medivation, Ferring Pharmaceuticals, AbbVie, Genentech, Pfizer, BHR Pharma, Orion, Sanofi Oncology, Emergent BioSolutions, MorphoSys, Churchill Pharmaceuticals, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics
Research Funding: Algeta/Bayer (Inst), Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Dendreon (Inst), Genentech (Inst), Medivation (Inst), Millennium Pharmaceuticals (Inst), Sanofi Oncology (Inst), Teva Pharmaceuticals (Inst), Exelixis (Inst), OncoGenex (Inst), Emergent BioSolutions (Inst)
Travel, Accommodations, Expenses: Bayer Healthcare Pharmaceuticals, Medivation, Dendreon, Ferring Pharmaceuticals, Pfizer, Johnson & Johnson, AbbVie, Genentech, Amgen, Orion, Ockham, Teva Pharmaceuticals, Sanofi Oncology, Astellas Pharma, Emergent BioSolutions, MorphoSys, Churchill Pharmaceuticals, Clovis Oncology, Astellas Pharma, Blue Earth Diagnostics

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Appendix

Additional STRIVE Investigators

The following investigators participated in STRIVE: Alabama: G. Bolger; Arizona: C. Dunshee, A. Buresh, C. DiSimone; California: F. Chu, C. Evans, J. Polikoff, T. Kolevska, M. Rettig, E. Uchio, S. Srinivas, F. Wolk, R. David; Colorado: T. Flaig, L. Karsh; District of Columbia: J. Aragon-Ching; Florida: D. Swartz, M. Grable, A. Cantwell, E. Gurevitch; Indiana: J. Bailen; Louisiana: J. Henderson, S. Bardot, J. Gurtler; Maryland: R. Tutrone; Michigan: K. Kernen; Minnesota: P. Flynn; Missouri: B. Roth; North Carolina; A. Armstrong, D. Lipsitz, K.C. Balaji, J. Wrenn; Nebraska: L. Nordquist; New Jersey: R. Alter; New York: C. Olsson, E. Goldfischer, J. Bass; Ohio: J. Garcia, I. Dumbadze; Oregon: B. Mehlhaff; Pennsylvania: P. Sieber, L. Gomella, H. Miller, L. Appleman; South Carolina: N. Shore, G. Keogh; Tennessee: R. Concepcion, D. Penson; Texas: J. Cochran, D. Saltzstein, T. Hutson, G. Doshi; Utah: N. Agarwal; Virginia: R. Given, M. Fleming; Washington: C. Higano, K. Chatta; Wisconsin: G. Liu

Methods

The study was designed by academic prostate cancer experts and representatives of the sponsors (Medivation and Astellas Pharma Global Development). Authors were responsible for writing the manuscript and deciding to submit the manuscript for publication and for assuming responsibility for the accuracy of the data and adherence to the study protocol. Professional writers, funded by the sponsors, helped the authors prepare and finalize the manuscript. All authors and participating institutions have agreements with the sponsors regarding the confidentiality of the data.

Adverse events, serious adverse events, adverse events leading to permanent discontinuation of study drug, and deaths were summarized descriptively by treatment arm and assessed for their relationship to the study drug.

Table A1. Inclusion and Exclusion Criteria

Study Criteria
Inclusion criteria
Patients eligible to participate in this study met all of the following inclusion criteria:
1. Males age 18 years or older and willing and able to provide informed consent
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell, small-cell, or ductal features
3. Ongoing androgen deprivation therapy for prostate cancer with a GnRH analog at a stable dose and schedule as of 4 weeks immediately before day 1, or bilateral orchiectomy (ie, medical or surgical castration). Prior intermittent therapy with a GnRH analog was allowed.
4. Patients who did not have a bilateral orchiectomy must maintain effective continuous GnRH analog therapy for the duration of the trial.
5. Serum testosterone level $\leq$ 50 ng/dL (1.73 nmol/L) at the screening visit
6. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was receiving primary androgen deprivation therapy as defined in inclusion criterion No. 3:
PSA progression defined by a minimum of two increasing PSA values (one of which could be the screening PSA value) with an interval of $\geq$ 1 week between each determination and a PSA value at the screening visit of $\geq$ 5 μg/L (5 ng/mL) or a PSA doubling time of $\leq$ 10 months if screening PSA was $\geq$ 2 μg/L (2 ng/mL)
Soft-tissue disease progression based on CT or MRI
Bone disease progression based on bone scan
7. Asymptomatic or mildly symptomatic as a result of prostate cancer (ie, the score on Brief Pain Inventory–Short Form question 3 must be $<$ 4)
8. ECOG PS of 0 or 1 at screening and on day 1 visit
9. Estimated life expectancy of $\geq$ 12 months
10. Able to swallow the study drug and comply with study requirements
11. Must use a condom if having sex with a pregnant woman
12. Male patient and his female partner of childbearing potential must use two acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control include the following:
Condom (barrier method of contraception)
AND
One of the following:
Established use of oral, injected, or implanted hormonal method of contraception by the female partner
Placement of an intrauterine device or intrauterine system by the female partner
Additional barrier method such as occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository by the female partner

(continued on following page)

Table A1. Inclusion and Exclusion Criteria (continued)

Study Criteria
Tubal ligation in the female partner
Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy) for more than 6 months
Exclusion criteria
Patients must NOT have met any of the following exclusion criteria:
1. Severe concurrent disease, infection, or comorbidity that, in the judgment of the investigator, would make the patient inappropriate for enrollment
2. Known or suspected brain metastasis or active leptomeningeal disease
3. History of another invasive cancer within 5 years of random assignment, with the exceptions of nonmelanoma skin cancers and of American Joint Committee on Cancer stage 0 or stage 1 cancers that have a remote probability of recurrence, in the opinion of the investigator, in consultation with the sponsor
4. Absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL, or hemoglobin < 9 g/dL (5.6 mmol/L) at the screening visit (Note: patients may not have received any growth factors or blood transfusions within 7 days of the hematologic laboratory values obtained at the screening visit.)
5. Total bilirubin, ALT, or AST > 2.5 times the upper limit of normal at the screening visit
6. Creatinine > 2 mg/dL (177 μmol/L) at the screening visit
7. Albumin < 3.0 g/dL (30 g/L) at the screening visit
8. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke, significant brain trauma) at any time in the past or history of loss of consciousness or transient ischemic attack within 12 months of enrollment (day 1 visit)
9. Clinically significant cardiovascular disease including:
Myocardial infarction within 6 months before screening
Uncontrolled angina within 3 months before screening
NYHA class 3 or 4 congestive heart failure or patients with history of NYHA class 3 or 4 congestive heart failure in the past, unless an echocardiogram or multigated acquisition scan performed within 3 months demonstrated a left ventricular ejection fraction ≥ 45%
History of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes)
History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
Hypotension as indicated by systolic blood pressure < 86 mm Hg at the screening visit
Bradycardia as indicated by a heart rate of < 50 beats per minute on the screening electrocardiogram and on physical examination
Uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit
10. Gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within last 3 months)
11. Major surgery within 4 weeks of enrollment (day 1 visit)
12. Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrollment (day 1 visit)
13. Radiation therapy for treatment of the primary tumor within 3 weeks of enrollment (day 1 visit)
14. Radiation or radionuclide therapy for treatment of distant metastasis
15. Prior ketoconazole, abiraterone, or cytotoxic chemotherapy for prostate cancer
16. Use of antiandrogens within 4 weeks before enrollment (day 1 visit). In the event of prior antiandrogen use, screening PSA value must be obtained after washout of any antiandrogen.
17. Prior disease progression, as assessed by the investigator, while receiving bicalutamide. Disease progression defined as PSA progression, radiographic progression, and/or clinical deterioration
18. Treatment with hormonal therapy (eg, 5α-reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone targeting agents and GnRH analog therapy) within 4 weeks of enrollment (day 1 visit)
19. Participation in a previous clinical trial of enzalutamide or an investigational agent that inhibits the androgen receptor or androgen synthesis (patients who received placebo are acceptable)
20. Use of an investigational agent within 4 weeks of enrollment (day 1 visit)
21. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA values (eg, saw palmetto) or systemic corticosteroids for prostate cancer within 4 weeks of enrollment (day 1 visit)
22. Any condition or reason that, in the opinion of the investigator, interfered with the ability of the patient to participate in the trial, which placed the patient at undue risk, or complicated the interpretation of safety data

Abbreviations: CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PSA, prostate-specific antigen.

Table A2. All End Point Definitions and Associated Analyses

End Point Variable	Definition and Analysis Method
Progression-free survival*	Progression-free survival, the primary end point, was defined as the time from random assignment to the earliest objective evidence of PSA progression, radiographic disease progression, or death on study (death as a result of any cause up to and including 30 days after treatment discontinuation), whichever occurred first. PSA progression was defined according to PCWG2 guidelines. The PSA progression date was defined as the date that a ≥ 25% increase in PSA with an absolute increase of ≥ 2 ng/mL above the nadir (or baseline for patients with no PSA decline at week 13) was documented, which was confirmed by a second consecutive value obtained at least 3 weeks later. Radiographic disease progression included soft-tissue disease progression as defined by RECIST 1.1 and bone disease progression per PCWG2 guidelines. Bone disease progression was defined as the appearance of two or more new bone lesions on bone scan. Bone disease progression at or before week 13 required a consecutive confirmatory bone scan at least 5 weeks later with at least two additional bone lesions. If bone disease progression was confirmed, the date of bone disease progression would be the date of the initial scan suggesting progression. Soft-tissue disease progression did not require confirmation. All radiographic assessments were locally based. Generally, patients who had not progressed or died by the data cutoff date were censored on the date of the last available PSA or radiographic assessment. A two-sided log-rank test stratified by disease stage at study entry (M0 or M1) was used to compare progression-free survival between the treatment groups (enzalutamide and bicalutamide).
Time to PSA progression†	Time to PSA progression was defined as the time from random assignment to the earliest evidence of PSA progression per PCWG2 guidelines. The PSA progression date was defined as the date that a ≥ 25% increase in PSA with an absolute increase of ≥ 2 ng/mL above the nadir (or baseline for patients with no PSA decline at week 13) was documented, which was confirmed by a second consecutive value obtained at least 3 weeks later. A log-rank test stratified by disease stage at study entry (M0 or M1) was used to compare the time to PSA progression between the treatment groups.
PSA response†‡	Confirmed PSA responses, defined as ≥ 50%† and ≥ 90%‡ reductions in PSA from baseline at any postbaseline assessment, were calculated by treatment group for patients with a baseline PSA value and at least one postbaseline PSA value. Confirmation of these PSA responses was required at a consecutive assessment obtained at least 3 weeks later. A Cochran-Mantel-Haenszel mean score test stratified by disease stage at study entry (M0 or M1) was used to compare the response rates between the treatment groups.
Radiographic progression-free survival†‡	Radiographic progression-free survival was defined as the time from randomization to the first objective evidence of radiographic disease progression or death on study (death as a result of any cause up to and including 30 days after treatment discontinuation), whichever occurred first. Radiographic disease progression included soft-tissue disease progression as defined by RECIST 1.1 and bone disease progression per PCWG2 guidelines. Bone disease progression was defined as the appearance of two or more new bone lesions on bone scan. Bone disease progression at or before week 13 required a consecutive confirmatory bone scan at least 5 weeks later with at least two additional bone lesions. If bone disease progression was confirmed, the date of bone disease progression would be the date of the initial scan suggesting progression. Soft-tissue disease progression did not require confirmation. Generally, patients who had not progressed or died by the data cutoff date were censored on the date of the last available radiographic assessment. An unstratified log-rank test was used to compare radiographic progression-free survival between the treatment groups separately for M1 patients† and M0 patients‡.
Functional Assessment of Cancer Therapy–Prostate (FACT-P)‡	FACT-P is a multidimensional, self-reported quality-of-life instrument specifically designed for use with prostate cancer. It consists of 27 core items that assess patient function in four domains—physical, social/family, emotional, and functional well-being—supplemented by 12 site-specific items to assess for prostate cancer symptoms. Each item is rated on a Likert-type scale of 0 to 4 and then combined to produce subscale scores for each domain as well as a global quality-of-life score (higher scores represent better quality of life). Time to degradation of FACT-P was defined as the time from random assignment to the date of the first assessment with at least a 10-point decrease from baseline in the global score. A log-rank test stratified by disease stage at study entry (M0 or M1) was used to compare the time to degradation of FACT-P between the treatment groups.
Best overall soft-tissue response‡	The best overall soft-tissue response was assessed by using RECIST 1.1 and was defined as a best overall soft-tissue response of CR or PR. Only patients with measurable (at least one target lesion) M1 soft-tissue disease at screening were included in the analysis. The proportion of patients with objective response (CR or PR) were compared between the treatment groups with an unstratified Cochran-Mantel-Haenszel mean score test.

Abbreviations: CR, complete response; M0, no distant metastasis (could have regional nodal metastasis); M1, presence of distant metastasis; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PR, partial response; PSA, prostate-specific antigen; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
*Primary end point.
†Key secondary end point.
‡Other prespecified secondary or exploratory end point.

Table A3. Other Baseline Patient and Disease Characteristics (ITT population)

Baseline Characteristic	Enzalutamide (n = 198)	Bicalutamide (n = 198)
Baseline hemoglobin, g/L		
Median	131.5	132.0
Range	91.0-160.0	91.0-161.0
Baseline alkaline phosphatase, U/L		
Median	78.0	75.0
Range	35.0-561.0	27.0-549.0
Baseline lactate dehydrogenase, U/L		
Median	175.0	177.0
Range	97.0-2,033.0	68.0-391.0
Baseline serum albumin, g/L		
Median	39.0	39.0
Range	30.0-46.0	26.0-46.0
Baseline creatinine, U/L		
Median	104.5	85.5
Range	21.0-648.0	19.0-552.0
Time from initial diagnosis to random assignment, months		
Median	73.2	79.1
Range	4.3-400.7	1.3-277.2
Primary tumor assessment at initial diagnosis	No. (%)	No. (%)
Clinical tumor stage		
Tx	10 (5.1)	7 (3.5)
T0	2 (1.0)	2 (1.0)
T1	45 (22.7)	43 (21.7)
T2	55 (27.8)	56 (28.3)
T3	35 (17.7)	43 (21.7)
T4	8 (4.0)	8 (4.0)
Unknown	43 (21.7)	39 (19.7)
Pathologic tumor stage		
pT1	20 (10.1)	13 (6.6)
pT2	55 (27.8)	52 (26.3)
pT3	46 (23.2)	46 (23.2)
pT4	3 (1.5)	3 (1.5)
Unknown	74 (37.4)	84 (42.4)
Regional lymph node assessment at initial diagnosis		
Clinical tumor stage		
Nx	64 (32.3)	54 (27.3)
N0	71 (35.9)	81 (40.9)
N1	29 (14.6)	24 (12.1)
Unknown	34 (17.2)	39 (19.7)
Pathologic tumor stage		
pNx	58 (29.3)	52 (26.3)
pN0	55 (27.8)	49 (24.7)
pN1	18 (9.1)	20 (10.1)
Unknown	67 (33.8)	77 (38.9)
Distant metastasis at initial diagnosis		
Mx	39 (19.7)	18 (9.1)
M0	100 (50.5)	120 (60.6)
M1	37 (18.7)	37 (18.7)
Unknown	22 (11.1)	23 (11.6)
PSA progression at study entry		
Yes	182 (91.9)	177 (89.4)
No	16 (8.1)	21 (10.6)
Type of disease progression at study entry		
No disease progression per protocol	0	1 (0.5)
PSA progression only	101 (51.0)	104 (52.5)
Radiographic progression only	16 (8.1)	20 (10.1)
Bone only	11 (5.6)	12 (6.1)
Soft tissue only	1 (0.5)	6 (3.0)
Bone and soft tissue	4 (2.0)	2 (1.0)
PSA and radiographic progression	81 (40.9)	73 (36.9)
PSA and bone disease progression	40 (20.2)	39 (19.7)
PSA and soft-tissue disease progression	23 (11.6)	16 (8.1)
PSA and bone and soft-tissue disease progression	18 (9.1)	18 (9.1)

Abbreviations: ITT, intent-to-treat; M0, no distant metastasis (could have regional nodal metastasis); M1, presence of distant metastasis; Mx, metastatic status unknown; PSA, prostate-specific antigen.

Table A4. Baseline PSA and Time to PSA Progression in CRPC Studies With Enzalutamide

	CRPC Study			
	STRIVE	TERRAIN	PREVAIL	AFFIRM
Population	M0, M1	M1	M1	M1
Previous chemotherapy for prostate cancer	No	No	No	Yes
Progression on previous bicalutamide therapy	Not allowed	Not allowed	Allowed	Allowed
Median baseline PSA for patients randomly assigned to enzalutamide, ng/mL	8.2 (M0); 15.1 (M1)	20.6	54.1	107.7
Median time to PSA progression, months	Not reached	19.4	11.2	8.3

Abbreviations: AFFIRM, Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy; CRPC, castration-resistant prostate cancer; M0, no distant metastasis (could have regional nodal metastasis); M1, presence of distant metastasis; PREVAIL, A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer; PSA, prostate-specific antigen; STRIVE, Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men With Prostate Cancer; TERRAIN, A Randomized, Double-Blind, Phase 2, Efficacy and Safety Study of Enzalutamide vs. Bicalutamide in Metastatic Castrate Resistant Prostate Cancer: TERRAIN Trial.