

ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

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ABSTRACT

BACKGROUND

Preliminary trial results showed that enzalutamide significantly improved metastasis-free survival among men who had nonmetastatic, castration-resistant prostate cancer and rapidly increasing prostate-specific antigen (PSA) levels while taking androgen-deprivation therapy. Results from the final analysis of overall survival have not yet been reported.

METHODS

In this double-blind, phase 3 trial, men with nonmetastatic, castration-resistant prostate cancer (defined on the basis of conventional imaging and a PSA doubling time of ≤ 10 months) who were continuing to receive androgen-deprivation therapy were randomly assigned (in a 2:1 ratio) to receive enzalutamide at a dose of 160 mg or placebo once daily. Overall survival was assessed with a group sequential testing procedure and an O'Brien–Fleming–type alpha-spending function.

RESULTS

As of October 15, 2019, a total of 288 of 933 patients (31%) in the enzalutamide group and 178 of 468 (38%) in the placebo group had died. Median overall survival was 67.0 months (95% confidence interval [CI], 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89; $P=0.001$). The exposure-adjusted rate of adverse events of grade 3 or higher was 17 per 100 patient-years in the enzalutamide group and 20 per 100 patient-years in the placebo group. Adverse events in the enzalutamide group were consistent with those previously reported for enzalutamide; the most frequently reported events were fatigue and musculoskeletal events.

CONCLUSIONS

Enzalutamide plus androgen-deprivation therapy resulted in longer median overall survival than placebo plus androgen-deprivation therapy among men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising PSA level. The risk of death associated with enzalutamide was 27% lower than with placebo. Adverse events were consistent with the established safety profile of enzalutamide. (Funded by Pfizer and Astellas Pharma; PROSPER ClinicalTrials.gov number, NCT02003924.)

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ENZALUTAMIDE, AN ORAL ANDROGEN-receptor inhibitor, in combination with androgen-deprivation therapy was approved by the Food and Drug Administration to treat nonmetastatic, castration-resistant prostate cancer in 2018 on the basis of a significantly lower risk of metastasis or death without radiographic progression than with androgen-deprivation therapy alone (hazard ratio, 0.29; 95% confidence interval [CI], 0.24 to 0.35; $P < 0.001$) in the phase 3 PROSPER trial.^{1,2} Enzalutamide had a safety profile consistent with that shown in multiple previous phase 3 trials.^{1,3-5} Enzalutamide was associated with a better health-related quality of life and with a significantly lower risk of prostate-specific antigen (PSA) progression (hazard ratio, 0.07; 95% CI, 0.05 to 0.08; $P < 0.001$), as well as with a longer time to use of subsequent antineoplastic therapy (hazard ratio, 0.21; 95% CI, 0.17 to 0.26; $P < 0.001$),¹ than androgen-deprivation therapy alone.⁶

It is estimated that bone metastases develop in one third of patients with nonmetastatic, castration-resistant prostate cancer within 2 years after diagnosis.⁷ Because metastatic, castration-resistant prostate cancer is associated with decreased overall survival,^{5,8} worsening quality of life,⁹ and increased health care-related costs,¹⁰ delaying the time to metastasis is a clinically relevant goal.^{11,12}

Although delaying metastasis and maintaining quality of life are meaningful outcomes, overall survival has long been considered an important end point and the standard for regulatory approval. At the primary analysis in the PROSPER trial, after 23 months of follow-up, the data on overall survival were immature, with 165 deaths during the trial (28% of 596 prespecified events for the final analysis). Median overall survival was not reached in either treatment group (hazard ratio, 0.80; 95% CI, 0.58 to 1.09; $P = 0.15$).¹ Here, we report results from the prespecified third interim analysis of overall survival.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this multinational, double-blind, randomized, placebo-controlled phase 3 trial, which was approved by the independent review

boards at more than 300 sites in 32 countries, in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent before participating. An independent data and safety monitoring committee reviewed safety data in an unblinded fashion at regular intervals.

The trial was designed and written in collaboration with the principal investigators and employees of the sponsors — Medivation (a Pfizer company) and Astellas Pharma, the codevelopers of enzalutamide. Local site investigators treated patients, conducted follow-up, and collected data, which were first analyzed by the sponsors. Data analyses were conducted by the sponsors and were provided to the authors, who wrote the manuscript. The authors vouch for the accuracy and completeness of the data and its analysis and for the adherence of the trial to the protocol, available with the full text of this article at [NEJM.org](https://www.nejm.org). A medical writer and medical editor were paid by the sponsors and assisted in the preparation of the manuscript that was submitted.

The trial design has been described previously.¹ To be eligible for participation, men had to have pathologically confirmed prostate adenocarcinoma with an increasing PSA despite castrate levels of testosterone (serum testosterone level, ≤ 1.73 nmol per liter [0.50 ng per milliliter]), a baseline PSA level of 2 ng or greater per milliliter, and a PSA doubling time of 10 months or less. Patients had no previous or current evidence of metastatic disease, as assessed with computed tomography or magnetic resonance imaging for soft-tissue disease and with whole-body radionuclide bone scan, with results confirmed by independent central reviewers. Patients were stratified according to PSA doubling time (< 6 months or ≥ 6 months) and previous or current use of a bone-targeting agent at baseline (yes or no) and were randomly assigned in a 2:1 ratio to continue receiving androgen-deprivation therapy (either with a gonadotropin-releasing hormone agonist or antagonist or with previous bilateral orchiectomy) plus either enzalutamide at a dose of 160 mg or placebo once daily until radiographic progression, unacceptable toxic effects, or death. Patients and investigators were unaware of the PSA levels during the trial. Dis-

continuation of the trial regimen solely because of an increase in PSA level was discouraged. After the trial was unblinded, patients in the placebo group were given the option to enroll in an open-label extension in which they would receive enzalutamide. All enrolled patients were followed for survival and for the use of subsequent therapies after discontinuation of the trial regimen.

TRIAL END POINTS

The primary end point was metastasis-free survival, defined as time from randomization to imaging-based progression, as determined by central review at any time, or as the time to death from any cause without evidence of imaging-based progression during the period from randomization to 112 days after discontinuation of the trial regimen, whichever occurred first. Secondary end points included overall survival, defined as the time from randomization to death from any cause, time to PSA progression, PSA response rate, time to first use of a subsequent antineoplastic therapy, time to first use of cytotoxic chemotherapy, chemotherapy-free survival, time to pain progression, health-related quality of life, and the frequency and severity of adverse events. Definitions of the end points are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

At the primary analysis (data cutoff date, June 28, 2017), the results with respect to metastasis-free survival, time to PSA progression, and time to first use of a new subsequent antineoplastic therapy met the criteria for significance; therefore, in accordance with the protocol, the analysis of these end points was considered final.¹ Patients were then followed for safety and overall survival; two additional interim analyses of overall survival (after approximately 285 deaths and 440 deaths) and a final analysis (after approximately 596 deaths) were planned. Updated analyses of time to first use of subsequent therapy, time to first use of cytotoxic chemotherapy, and chemotherapy-free survival were also performed.

STATISTICAL ANALYSIS

Efficacy end points were analyzed in the intention-to-treat population, defined as all patients who underwent randomization. Patients who

had been randomly assigned to receive placebo who crossed over to receive enzalutamide during the open-label extension (the crossover group) were included in the placebo group for all efficacy analyses. Safety was analyzed in all patients who received at least one dose of enzalutamide or placebo. The analysis of safety included events that occurred from the time of the first dose of enzalutamide or placebo to 30 days after the last dose or to the day before initiation of a new antineoplastic therapy, whichever occurred first.

For the final analysis of overall survival, we calculated that 590 deaths were required to provide 85% power to detect a hazard ratio of 0.77 at a two-sided significance level of 0.05. Overall survival was assessed with the use of a group sequential testing procedure based on an O'Brien–Fleming–type alpha-spending function with three preplanned interim analyses. If an interim analysis of overall survival crossed the significance boundary, it would be reported as the final analysis and no subsequent analyses would be performed. The results of the first and second (data not shown) interim analyses of overall survival did not cross the significance boundary.¹ This was the third preplanned interim analysis, performed after approximately 440 deaths had occurred. After adjustment for multiplicity, a P value of 0.021 or less was required to indicate statistical significance.

The trial groups were compared with the use of a log-rank test with stratification according to the same factors that were used in randomization. The Kaplan–Meier method was used to estimate medians. A stratified Cox regression model was used to estimate hazard ratios and 95% confidence intervals, which were not adjusted for multiplicity.

RESULTS

PATIENTS

From November 26, 2013, to June 28, 2017, a total of 1401 eligible patients were enrolled and underwent randomization; 933 were assigned to the enzalutamide group and 468 were assigned to the placebo group (Fig. S1). Demographic and baseline characteristics were well balanced between the groups.¹ The median age was 74 years in the enzalutamide group and 73 years in the

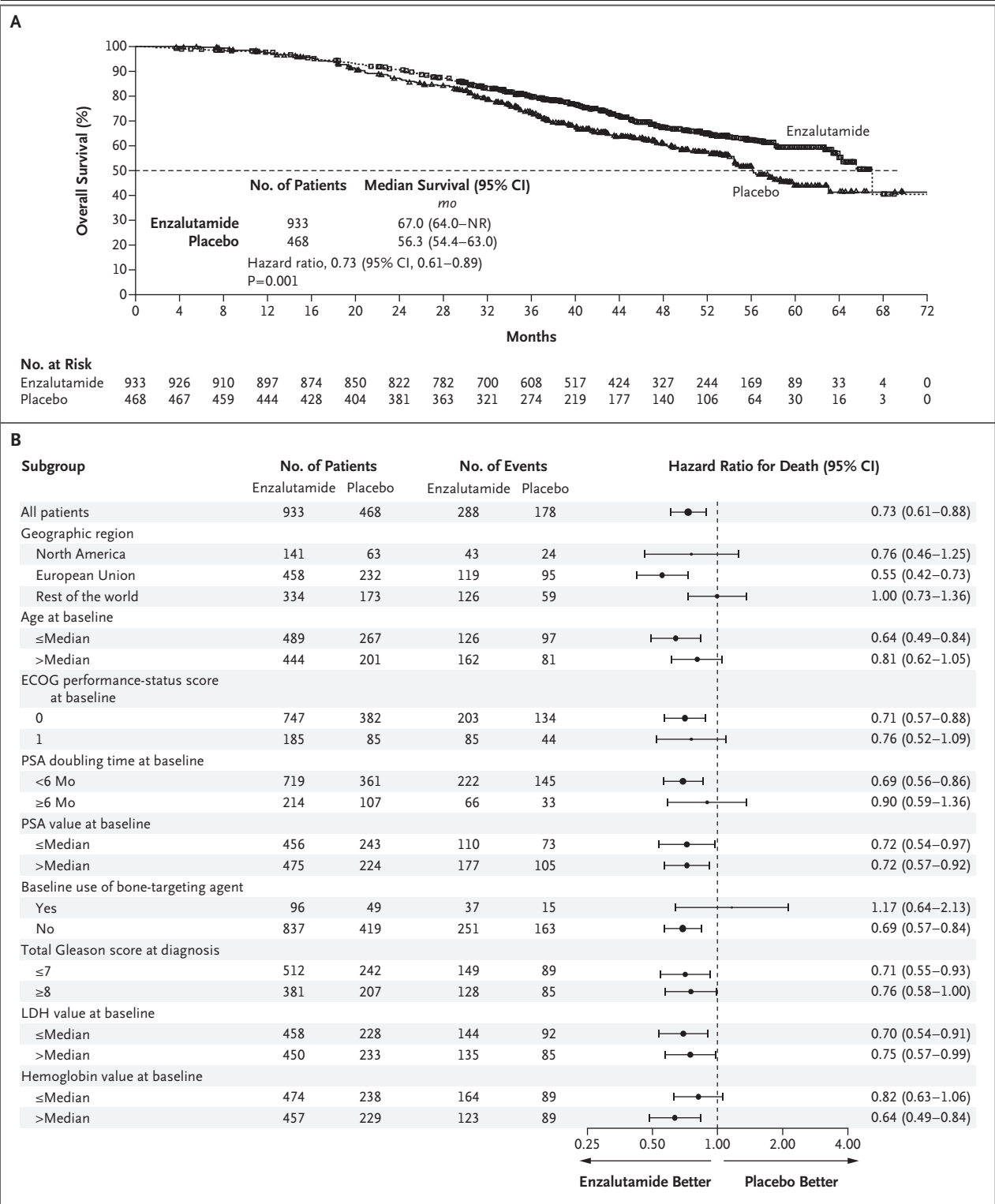


Figure 1 (facing page). Kaplan–Meier Estimates and Subgroup Analysis of Overall Survival.

Panel A shows the data for the final Kaplan–Meier analysis of overall survival. The hazard ratio was based on a Cox regression model stratified according to prostate-specific antigen (PSA) doubling time (<6 months or ≥6 months) and previous or current use of a bone-targeting agent (yes or no), with trial group as the only covariate and a value of less than 1.00 favoring enzalutamide treatment. The dashed line indicates the median, and symbols indicate censored data in the Kaplan–Meier curve. NR denotes not reached. Panel B shows the subgroup analysis of overall survival. The analyses of all subgroups were unstratified, and 95% confidence intervals were not adjusted for multiplicity. The size of each circle reflects the number of patients in the subgroup. At baseline, the median age of the patients was 74 years, the median PSA level was 10.75 ng per milliliter, the median lactate dehydrogenase (LDH) level was 1.78 U per liter, and the median hemoglobin level was 134 g per liter. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Gleason scores range from 6 to 10, with higher scores indicating more aggressive cancer.

placebo group had died. In the enzalutamide group, 178 deaths (19%) were prostate cancer-related, and 110 (12%) were not prostate cancer-related, as compared with 136 deaths (29%) and 42 deaths (9%), respectively, in the placebo group. Median overall survival was 67.0 months (95% CI, 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (Fig. 1A). Enzalutamide plus androgen-deprivation therapy was associated with a significant 27% lower risk of death than placebo plus androgen-deprivation therapy (hazard ratio, 0.73; 95% CI, 0.61 to 0.89; $P=0.001$). Because the O'Brien–Fleming significance boundary was crossed, this became the final analysis. The treatment effect of enzalutamide was generally consistent across prespecified subgroups, with the possible exception of patients receiving bone-sparing agents, although the number of such patients was small (Fig. 1B). In an unplanned analysis, the percentage of patients alive at 3 years was 80% (95% CI, 77 to 83) in the enzalutamide group and 73% (95% CI, 69 to 77) in the placebo group.

placebo group (Table S2). The median PSA doubling time was 3.8 months in the enzalutamide group and 3.6 months in the placebo group.

After the primary analysis was completed, the trial data were unblinded, and patients in the placebo group were given the opportunity to receive enzalutamide (crossover began on February 12, 2018). Of the 114 patients in the placebo group who were still receiving treatment when crossover began, 87 received enzalutamide in the open-label extension. At the data cutoff (October 15, 2019), 552 of 933 patients (59%) from the enzalutamide group and 17 of 87 patients (20%) from the crossover group had discontinued enzalutamide. The most common reason for discontinuation was disease progression in the enzalutamide group (288 of 552 patients; 31% of total patients assigned to enzalutamide and 52% of patients assigned to enzalutamide who discontinued) and in the placebo group (247 of 465; 53%), and adverse events were the most common reason in the crossover group (10 of 17; 59%). Median follow-up for the trial was 48 months.

OVERALL SURVIVAL

At the data cutoff, 288 patients (31%) in the enzalutamide group and 178 patients (38%) in the

SUBSEQUENT THERAPY

Enzalutamide was associated with a delay in the use of a new subsequent antineoplastic therapy (hazard ratio for the use of any subsequent antineoplastic therapy, 0.29; 95% CI, 0.25 to 0.35) (Fig. S2A). The median time to first use of new antineoplastic therapy was 66.7 months in the enzalutamide group and 19.1 months in the placebo group. A total of 310 patients in the enzalutamide group (33% of all patients assigned to enzalutamide and 56% of those who discontinued treatment) and 303 patients in the placebo group (65%) received at least one subsequent antineoplastic therapy after discontinuation of the trial regimen (Table 1). The median time from discontinuation to the start of a subsequent antineoplastic therapy was 30 days in the enzalutamide group and 22 days in the placebo group. The most common subsequent antineoplastic therapy was docetaxel (185 patients, 60%) in the enzalutamide group and abiraterone (178 patients, 59%) in the placebo group.

SAFETY

The median treatment duration was 33.9 months (95% CI, 0.2 to 68.8) in the enzalutamide group

Table 1. Antineoplastic Therapy Received after Discontinuation of Enzalutamide or Placebo.

Subsequent Therapy	Enzalutamide Group (N=930)	Placebo Group (N=465)
	no. of patients (%)	
At least one antineoplastic agent	310 (33)	303 (65)
Agents used by ≥5% of patients in either treatment group*		
Abiraterone acetate	152 (49)	178 (59)
Docetaxel	185 (60)	141 (47)
Enzalutamide	44 (14)	109 (36)†
Cabazitaxel	46 (15)	49 (16)
Bicalutamide	28 (9)	41 (14)

* Percentages are based on the number of patients who received at least one antineoplastic agent after discontinuation of the trial regimen (310 in the enzalutamide group and 303 in the placebo group).

† A total of 87 patients who received enzalutamide in the crossover group after the trial was unblinded were not included in this analysis, since they received enzalutamide as open-label treatment. After inclusion of these 87 patients, the total number of patients randomly assigned to placebo who received at least one subsequent antineoplastic agent increased to 390 (84%), and the total number of patients who received subsequent treatment with enzalutamide was 196.

and 14.2 months (95% CI, 0.1 to 51.3) in the placebo group. The incidences of adverse events within the first 3 months and 6 months were higher in the enzalutamide group than in the placebo group. However, after adjustment for exposure, the rates of adverse events per 100 patient-years were similar in the two groups (Table 2). Cumulative incidence plots showed a similar onset of grade 3 or 4 adverse events and serious adverse events in the enzalutamide and placebo groups, whereas adverse events of special interest (Table 3) had a steeper rate of initial onset in the enzalutamide group (Fig. S3). The most frequently reported adverse events were consistent with those reported in the primary analysis¹ (Tables S3 and S4), primarily fatigue and musculoskeletal events.

The adverse events of special interest with exposure-adjusted rates that were 3 or more events per 100 patient-years higher in the enzalutamide group than in the placebo group were falls (9 vs. 4 events per 100 patient-years) and fractures (9 vs. 5 events per 100 patient-years) (Table S5). The most frequently reported adverse

Table 2. Summary of Adverse Events, Irrespective of Relationship to Enzalutamide or Placebo.*

Adverse Event	Enzalutamide Group (N=930)		Placebo Group (N=465)	
	Patients	Events	Patients	Events
	no. (%)	no. (no./100 patient-yr)	no. (%)	no. (no./100 patient-yr)
Any adverse event	876 (94)	876 (34)	380 (82)	380 (60)
Within the first 3 mo	609 (65)	—	241 (52)	—
Within the first 6 mo	703 (76)	—	298 (64)	—
Any grade ≥3 adverse event	446 (48)	446 (17)	126 (27)	126 (20)
Within the first 3 mo	89 (10)	—	22 (5)	—
Within the first 6 mo	140 (15)	—	56 (12)	—
Any serious adverse event†	372 (40)	372 (14)	100 (22)	100 (16)
Any adverse event leading to discontinuation of trial regimen	158 (17)	158 (6)	41 (9)	41 (6)
Any adverse event leading to death	51 (5)	51 (2)	3 (1)	3 (<1)

* Total patient-years of exposure were 2613.41 for the enzalutamide group and 634.45 for the placebo group. The event rate was calculated as 100×number of events/total patient-years of exposure for the treatment group.

† Serious adverse events were events that resulted in death, were life-threatening, resulted in or prolonged hospitalization, resulted in the inability to conduct normal life functions, or led to a congenital anomaly or birth defect. A full definition is provided in the protocol.

events leading to death during the entire trial period were cardiovascular events (14 [2%] in the enzalutamide group and 2 [$<1\%$] in the placebo group) (the full list is provided in Table 4). In the enzalutamide group, 10 of 14 patients with a cardiovascular event leading to death had clinically significant previous or ongoing cardiovascular disease. Seventeen adverse events leading to death occurred after the primary analysis; the group of men who were affected had a median age of 80 years (range, 63 to 93). None of the cardiovascular events that led to death in the trial were considered by the investigators to be related to treatment with enzalutamide.

CROSSOVER GROUP

A total of 87 patients received enzalutamide in the crossover group. The median treatment duration with enzalutamide after crossover treatment began was 14.5 months (95% CI, 0.4 to 18.8), a shorter period than among patients who had been randomly assigned to enzalutamide from the outset. Four patients (5%) received subsequent therapy after discontinuation of enzalutamide (docetaxel, abiraterone, enzalutamide, and sipuleucel-T were received by 1 patient each). The exposure-adjusted rates of adverse events and adverse events of special interest were consistent with those in the enzalutamide group (Table S6). The most frequently reported adverse events (occurring in $\geq 10\%$ of the patients) were fatigue (15%) and asthenia (11%) (Table S7). Four patients (5%) had adverse events leading to death after crossover began; none of these events were considered by the investigators to be related to enzalutamide (Table S8).

DISCUSSION

In this final analysis of overall survival in the PROSPER trial, treatment with enzalutamide was associated with a significant 27% lower risk of death than placebo in men with nonmetastatic, castration-resistant prostate cancer and a rapidly increasing PSA levels who were receiving androgen-deprivation therapy, despite the use of subsequent life-prolonging antineoplastic therapies (including enzalutamide) by patients in the placebo group. The time to subsequent antineoplastic therapy, time to cytotoxic chemotherapy,

Table 3. Adverse Events of Special Interest, Irrespective of Relationship to Enzalutamide or Placebo.

Adverse Event	Enzalutamide Group (N = 930)	Placebo Group (N = 465)
	no. of patients (%)	
Fatigue*	424 (46)	103 (22)
Musculoskeletal event†	315 (34)	107 (23)
Fracture‡	168 (18)	29 (6)
Hypertension§	167 (18)	28 (6)
Fall	164 (18)	25 (5)
Cognitive and memory impairment¶	73 (8)	10 (2)
Cardiovascular events	60 (6)	11 (2)
Ischemic heart disease**	60 (6)	8 (2)
Second primary cancer	48 (5)	7 (2)
Rash††	38 (4)	13 (3)
Loss of consciousness‡‡	34 (4)	4 (1)
Angioedema§§	20 (2)	4 (1)
Hepatic disorder¶¶	16 (2)	15 (3)
Renal disorder	14 (2)	8 (2)
Thrombocytopenia	12 (1)	4 (1)
Neutropenia	12 (1)	1 (<1)
Severe cutaneous adverse reaction	1 (<1)	0
Seizure	3 (<1)	0
Posterior reversible encephalopathy syndrome	0	0

* Fatigue events included asthenia.

† Musculoskeletal events included back pain, arthralgia, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal stiffness, muscular weakness, and muscle spasms.

‡ Fracture events included bone and joint injuries.

§ Hypertension events included hypertensive retinopathy, increased blood pressure, systolic hypertension, and hypertensive crisis.

¶ Events of cognitive and memory impairment included disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, dementia, senile dementia, mental impairment, and vascular dementia.

|| Cardiovascular events included hemorrhagic central nervous system vascular conditions, ischemic central nervous system vascular conditions, and cardiac failure.

** Events of ischemic heart disease included myocardial infarction and other ischemic heart disease.

†† Rash events included maculopapular rash, generalized rash, macular rash, papular rash, and pruritic rash.

‡‡ Loss-of-consciousness events included syncope and presyncope.

§§ Angioedema events included urticaria, eyelid edema, periorbital edema, swollen tongue, swollen lip, face edema, laryngeal edema, pharyngeal edema.

¶¶ Hepatic disorders included hepatic failure; fibrosis, cirrhosis, and other liver damage-related conditions; and hepatitis and liver-related investigations, signs, and symptoms.

||| Thrombocytopenia events included decreases in platelet count.

Table 4. Adverse Events Leading to Death, Irrespective of Relationship to Enzalutamide or Placebo.

Adverse Event	Enzalutamide Group (N=930)	Placebo Group (N=465)
At least one adverse event leading to death — no. of patients (%) [*]	51 (5)	3 (1)
Adverse events leading to death — no. (events/100 patient-yr) [†]	57 (2)	3 (<1)
Specific events leading to death — no. (%)		
Cardiovascular event [‡]	14 (2)	2 (<1)
Second primary cancer [§]	7 (1)	1 (<1)
Stroke [¶]	4 (<1)	0
Sudden death	4 (<1)	0
Disease progression	3 (<1)	0
Pneumonia ^{**}	3 (<1)	0
Septic shock ^{††}	3 (<1)	0
Hemorrhage ^{‡‡}	2 (<1)	0
General deterioration of physical health ^{§§}	2 (<1)	0
Intestinal congestion	1 (<1)	0
Mesenteric-vein thrombosis	1 (<1)	0
Malaise	1 (<1)	0
Hepatic failure	1 (<1)	0
Lung infection	1 (<1)	0
Gangrene in small intestine	1 (<1)	0
Pelvic fracture	1 (<1)	0
Renal impairment	1 (<1)	0
Urinary retention	1 (<1)	0
Interstitial lung disease	1 (<1)	0
Pleurisy	1 (<1)	0
Anemia	1 (<1)	0
Type 2 diabetes mellitus	1 (<1)	0

^{*} Patients with multiple events resulting in death for a given adverse-event term were counted only once per term.

[†] The total patient-years of exposure were 2613.41 for the enzalutamide group and 634.45 for the placebo group. The event rate was calculated as 100×number of events/total patient-years of exposure for the treatment group.

[‡] Cardiovascular events included acute myocardial infarction, myocardial infarction, cardiac failure, cardiac arrest, cardiorespiratory arrest, cardiogenic shock, cardiovascular insufficiency, coronary artery disease, ventricular arrhythmia, and left ventricular failure. Ten patients in the enzalutamide group had a history of cardiovascular disease.

[§] Second primary cancers included acute myeloid leukemia, brain neoplasm, malignant neoplasm of unknown primary site, mesothelioma, metastasis to liver, metastasis to peritoneum, neoplasm progression, metastatic pancreatic carcinoma, prostate cancer, and small-cell lung cancer.

[¶] Stroke events included cerebrovascular accident, cerebral infarction, hemorrhagic stroke, and ischemic stroke.

^{||} Sudden deaths included death, sudden death, and sudden cardiac death. One death was considered by the investigators to be related to enzalutamide.

^{**} Pneumonia events included pneumonia and aspiration pneumonia.

^{††} Septic shock events included septic shock and sepsis.

^{‡‡} Hemorrhage events included hemorrhage and duodenal ulcer hemorrhage. The duodenal ulcer hemorrhage was considered by the investigators to be related to enzalutamide.

^{§§} This event was considered by the investigators to be related to enzalutamide in 1 patient.

and chemotherapy-free survival were also longer in the enzalutamide group than in the placebo group.

In line with recent studies,^{13,14} these results add to the growing body of evidence that androgen-receptor inhibitors not only delay the time to metastasis but also improve overall survival among men with nonmetastatic, castration-resistant prostate cancer. Enzalutamide prolongs survival in both nonmetastatic and metastatic castration-resistant prostate cancer.^{3,5}

The treatment effect of enzalutamide was consistent across all prespecified subgroups, except in patients who had received bone-targeting agents at baseline; however, the number of patients in this subgroup was low, which makes interpretation of this result difficult. Further research is necessary.

As treatments are evaluated at earlier stages of disease and more life-prolonging therapies are available, it is increasingly difficult to show improvements in overall survival in clinical trials. Metastasis-free survival has been shown to be a surrogate for overall survival among patients with intermediate-risk, high-risk, clinically localized prostate cancer.¹⁵ These results provide clinical validation for the use of metastasis-free survival as a meaningful end point and as a potential surrogate for overall survival among patients with nonmetastatic, castration-resistant prostate cancer.

Our trial had several limitations. Conventional imaging has been used in our trial as well as in the SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) and ARAMIS (Androgen Receptor Antagonizing Agent for Metastasis-free Survival) phase 3 clinical trials in nonmetastatic, castration-resistant prostate cancer to obtain diagnoses and monitor patients' conditions.^{1,16,17} More sensitive techniques are becoming available, allowing for earlier detection of metastasis, which may affect the classification of patients as having nonmetastatic disease.¹⁸ Data on the time to progression while receiving the next subsequent therapy were not collected, so we cannot evaluate whether treatment with enzalutamide also translated into differences in treatment effects of subsequent therapies.

After a median of 15 additional months of treatment, the safety profile of enzalutamide with androgen-deprivation therapy was similar

to that reported at the time of the primary analysis,¹ which includes an increase in falls, fatigue, hypertension, and deaths from cardiovascular causes. The exposure-adjusted rates of cardiovascular events were slightly higher in the enzalutamide group than in the placebo group (3 vs. 2 per 100 patient-years). Three events of seizures were reported at the time of the primary analysis, but no subsequent events were reported. Men, especially those who are asymptomatic, should consider whether the increased risk of adverse events is acceptable before initiating treatment.

Although adverse events leading to death were more common in the enzalutamide group than in the placebo group, it is important to consider the significantly longer median treatment duration in the enzalutamide group (33.9 months vs. 14.2 months). The most frequently reported adverse events leading to death in the enzalutamide group were cardiovascular events. Most men who died from a cardiovascular event had a clinically significant history of cardiovascular disease. The World Health Organization reports that the leading cause of death among men older than 70 years of age in 2016 was ischemic heart disease.¹⁹ The longer follow-up interval, history of cardiovascular risk factors, and advanced age in patients treated with enzalutamide may explain this finding in our trial. Although none of the cardiovascular deaths were attributed to enzalutamide by the investigators, physicians should be aware of the increased risk when determining whether a patient with pre-existing cardiovascular disease should receive enzalutamide, and patients receiving this treatment should be followed closely.

In our trial, enzalutamide treatment in men with nonmetastatic, castration-resistant prostate cancer and rapidly increasing PSA levels resulted in a significantly longer overall survival than placebo. The adverse event profile was similar to the established safety profile of enzalutamide.^{3,5,20,21}

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