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# Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

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## ABSTRACT

### BACKGROUND

Enzalutamide (formerly called MDV3100) targets multiple steps in the androgen-receptor–signaling pathway, the major driver of prostate-cancer growth. We aimed to evaluate whether enzalutamide prolongs survival in men with castration-resistant prostate cancer after chemotherapy.

### METHODS

In our phase 3, double-blind, placebo-controlled trial, we stratified 1199 men with castration-resistant prostate cancer after chemotherapy according to the Eastern Cooperative Oncology Group performance-status score and pain intensity. We randomly assigned them, in a 2:1 ratio, to receive oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients). The primary end point was overall survival.

### RESULTS

The study was stopped after a planned interim analysis at the time of 520 deaths. The median overall survival was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary end points: the proportion of patients with a reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2%, P<0.001), the soft-tissue response rate (29% vs. 4%, P<0.001), the quality-of-life response rate (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001). Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group. Seizures were reported in five patients (0.6%) receiving enzalutamide.

### CONCLUSIONS

Enzalutamide significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy. (Funded by Medivation and Astellas Pharma Global Development; AFFIRM ClinicalTrials.gov number, NCT00974311.)

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*The AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Prostate cancer is an androgen-dependent disease that initially responds but later becomes resistant to established therapies that reduce circulating testosterone levels or inhibit androgen binding to the androgen receptor.[1-4] Reactivation of the disease despite castrate levels of testosterone represents a transition to the lethal phenotype of castration-resistant prostate cancer.[5,6] This state was previously called androgen-independent or hormone-refractory prostate cancer but is now recognized to be driven by androgen-receptor signaling, in part due to overexpression of the androgen receptor itself.[7,8] In preclinical models of prostate cancer, androgen-receptor overexpression shortens the period of tumor latency and confers resistance to conventional antiandrogen agents, such as bicalutamide.[9]

Enzalutamide (formerly MDV3100) is an androgen-receptor–signaling inhibitor chosen for clinical development on the basis of activity in prostate-cancer models with overexpression of the androgen receptor. Enzalutamide is distinct from the currently available antiandrogen agents in that it inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment. It also has a greater affinity for the receptor, induces tumor shrinkage in xenograft models (in which conventional agents only retard growth), and has no known agonistic effects.[10,11]

In a phase 1–2 trial enrolling men with castration-resistant prostate cancer (some of whom had undergone previous chemotherapy) conducted by the Prostate Cancer Clinical Trials Consortium,[12] enzalutamide had significant antitumor activity regardless of previous chemotherapy status. On the basis of these findings, a dose of enzalutamide was identified for further study.[13] In our phase 3 trial, we evaluated whether enzalutamide would prolong life in men with progressive castration-resistant prostate cancer after chemotherapy. The design incorporated the recommendations of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2)[14] to avoid premature study-drug discontinuation and to help address previously identified difficulties in assessing outcomes in clinical trials involving men with prostate cancer.

## Methods

### Study Design and Conduct

AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was an international, phase 3, randomized, double-blind, placebo-controlled study of enzalutamide in patients with prostate cancer who had previously been treated with one or two chemotherapy regimens, at least one of which contained docetaxel.

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.

The study was designed and the protocol was written by the senior academic authors and representatives of one of the sponsors (Medivation). The first draft of the manuscript was written by the first author, and the manuscript was then completed and approved by all the authors. All the authors were responsible for writing the manuscript and for the decision to submit the manuscript for publication, and all the authors assume responsibility for the completeness and integrity of the data and the fidelity of the study to the protocol and analysis plan (available with the full text of this article at NEJM.org). All the authors or authors' institutions had agreements with the sponsor regarding confidentiality of the data. No one who is not an author contributed to the writing of the manuscript.

### Study Participants

The study was conducted at 156 sites in 15 countries. Patients were eligible for enrollment if they had a histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per liter]), previous treatment with docetaxel, and progressive disease defined according to PCWG2 criteria (see the Study End Points section below), including three increasing values for prostate-specific antigen (PSA) or radiographically confirmed progression with or without a rise in the PSA level.[14] A complete list of inclusion and exclusion criteria is provided in the protocol.

Patients were enrolled from September 2009 through November 2010 and were randomly assigned to a study treatment centrally by means of an interactive voice-response system after stratification according to the baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1 vs. 2) and the Brief Pain Inventory–Short Form (BPI-SF) question 3 score ad-



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dressing the average pain over the 7 days before randomization (0 to 3 [no pain to mild pain] vs. 4 to 10 [moderate-to-severe pain]).

ECOG performance scores range from 0 to 5, with 0 indicating full activity, 1 indicating a restriction in strenuous activity but the ability to be ambulatory and do light work, and 2 indicating an ability to be ambulatory but an inability to work.[15] Scores on BPI-SF question 3, which asks about the worst pain in the previous 24 hours, range from 0 to 10, with higher scores reflecting a greater severity of pain.[16]

Patients were randomly assigned in a 2:1 ratio to receive enzalutamide (160 mg orally once daily as four 40-mg capsules) or matched placebo capsules. Permuted-block randomization was used. The use of prednisone or other glucocorticoids was permitted but not required, and the study drug was given without regard to food intake. Investigators were encouraged to continue study treatment until radiographically confirmed disease progression requiring initiation of new systemic antineoplastic therapy. The safety and efficacy data that were collected are described in the Supplementary Appendix, available at NEJM.org.

### STUDY END POINTS

The primary end point was overall survival, which was defined as the time from randomization to death from any cause. Secondary end points included measures of response (in the PSA level, in soft tissue, and in the quality-of-life score) and measures of progression (time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event[17]).

We used the following definitions of the secondary end points (as detailed in Table 1S in the Supplementary Appendix): PSA-level response was defined as a reduction in the PSA level from baseline by 50% or more or 90% or more, as confirmed on an additional PSA evaluation performed 3 or more weeks later.[14] Objective soft-tissue response was defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[18] Quality-of-life response was defined as a 10-point improvement in the global score on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart.[19,20] The FACT-P is a 39-item questionnaire on which the score for each item can range from 0 to 4, with higher scores indicating a better quality of life.

For the analysis of progression-free survival, we used the following measures of progression (as indicated by the results of computed tomography or magnetic resonance imaging of soft tissue and of radionuclide bone scanning): progression of soft-tissue disease according to RECIST, version 1.1[18]; progression of osseous disease according to bone scans showing two or more new lesions per PCWG2; and death from any cause. Progression in bone at the first scheduled assessment, at week 13, required a confirmatory scan performed 6 or more weeks later showing additional new lesions.[14] The times to PSA progression and the first skeletal-related event were also recorded. PSA progression was defined as an increase by a factor of 1.25 over the baseline level (for patients in whom the PSA level had not decreased) or over the nadir level (for patients in whom the PSA level had decreased) and an increase in the absolute PSA level by at least 2 ng per milliliter, which was confirmed by a repeat measurement.[14] A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.[17]

### STATISTICAL ANALYSIS

All analyses were performed by the sponsor using data obtained as of the cutoff date of September 25, 2011. The primary efficacy end point was a between-group comparison of the time from randomization to death from any cause (overall survival) in the intention-to-treat population (all randomly assigned patients). The study was designed to have a power of 90% to detect a hazard ratio of 0.76 for death in the enzalutamide group, as compared with the placebo group, with a two-sided type I error rate of 0.05. We planned to enroll approximately 1170 patients, assuming a median survival of 15.7 months in the enzalutamide group and 12.0 months in the placebo group, an accrual period of approximately 12 months, and a total study duration of approximately 30 months to observe the required 650 events.

A single interim analysis was planned to be performed after 520 deaths (80% of the 650 total events) had occurred. The analysis was done according to a group sequential design with the use of a Lan–DeMets implementation of the O'Brien–Fleming stopping boundary ($P<0.02$). In the primary analysis, we used a log-rank test to evaluate overall survival, with stratification according to the ECOG performance-status score



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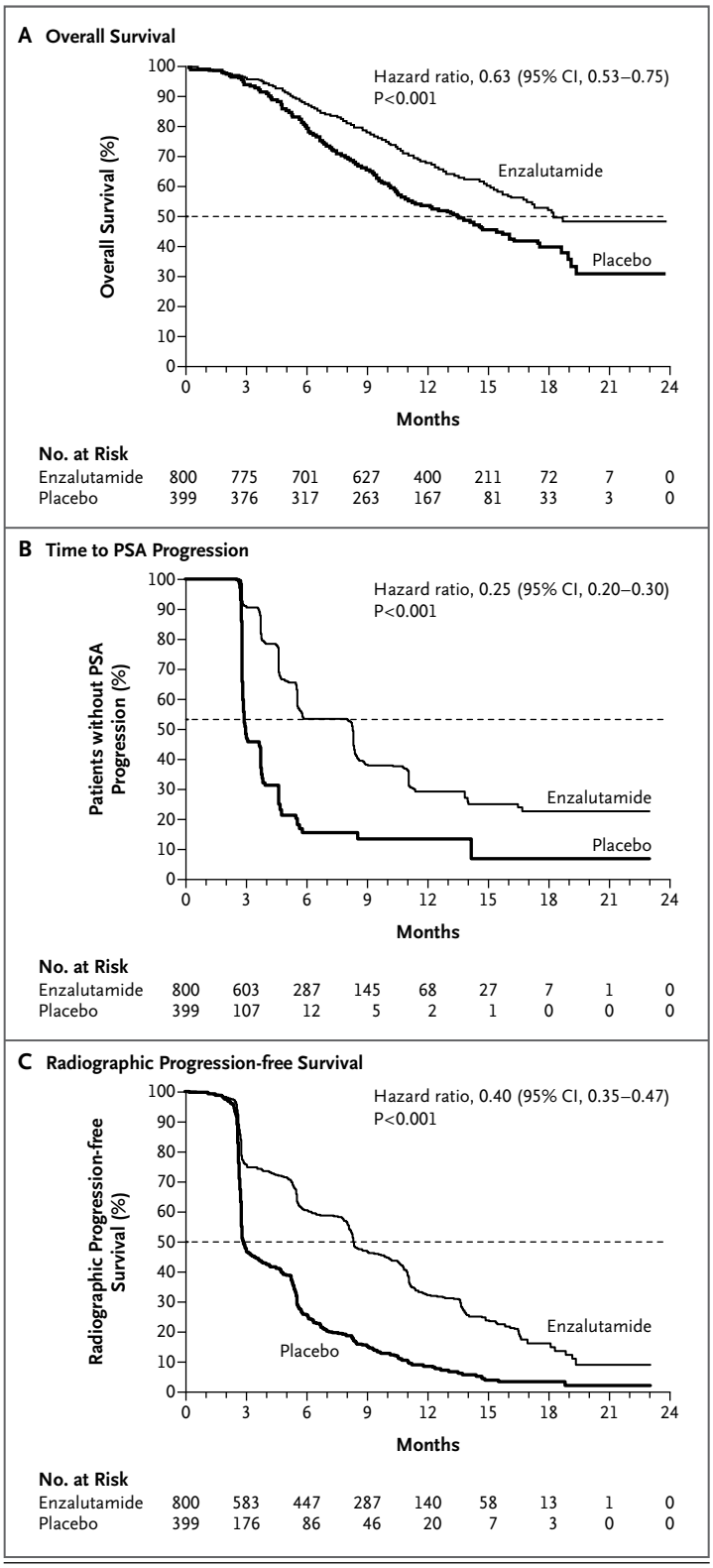



**Figure 1. Kaplan–Meier Estimates of Primary and Secondary End Points in the Intention-to-Treat Population.**

Shown are data for overall survival, the primary end point (Panel A), and for two secondary end points, the time to prostate-specific antigen (PSA) progression (Panel B) and radiographic progression-free survival (Panel C), in the enzalutamide group, as compared with the placebo group. CI denotes confidence interval.

and the baseline mean pain score (as measured by the BPI-SF score); the results are presented as Kaplan–Meier curves. Supportive analyses of overall survival were performed with the use of the unstratified log-rank test and Cox proportional-hazards models. Subgroup analyses were conducted to determine whether treatment effects were consistent across patient subgroups. A multivariate analysis was also performed.

Only if the overall survival analysis showed statistical superiority of enzalutamide over placebo was the testing of the key secondary end points to be undertaken, in the rank-prioritized order — the time to PSA progression, radiographic progression-free survival, and the time to the first skeletal-related event — with the significance of the previous end point gating further testing. These end points were tested by means of the stratified log-rank test in a protected hierarchical manner, each at the two-sided significance level of 0.05.

## RESULTS

### PATIENTS AND TREATMENT

The study enrolled 1199 patients who were randomly assigned to receive either enzalutamide (800 patients) or placebo (399 patients). The enrollment, follow-up, and data analysis of patients are shown in Figure 1S in the Supplementary Appendix. Baseline characteristics were well matched between groups in terms of demographic characteristics, previous treatment history, and extent of disease (Table 2S in the Supplementary Appendix). At the time of the interim analysis, the median time on treatment was 8.3 months in the enzalutamide group and 3.0 months in the placebo group. The median duration of follow-up to ascertain survival status was 14.4 months.

### EFFICACY

The median overall survival was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) among patients receiving enzalutamide and 13.6 months (95% CI, 11.3 to 15.8) among patients receiving placebo (Fig. 1A). At the time of the prespecified interim analysis, the use of enzalu-



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| Subgroup | No. of Patients | Enzalutamide | Placebo | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| | | *median overall survival (mo)* | | |
| All patients | 1199 | 18.4 | 13.6 | 0.63 (0.53–0.75) |
| Age | | | | |
| <65 yr | 362 | — | 12.4 | 0.63 (0.46–0.87) |
| ≥65 yr | 837 | 18.4 | 13.9 | 0.63 (0.51–0.78) |
| Baseline ECOG performance status score | | | | |
| 0–1 | 1097 | — | 14.2 | 0.62 (0.52–0.75) |
| 2 | 102 | 10.5 | 7.2 | 0.65 (0.39–1.07) |
| Baseline mean pain score on BPI–SF (question no. 3) | | | | |
| <4 | 858 | — | 16.2 | 0.59 (0.47–0.74) |
| ≥4 | 341 | 12.4 | 9.1 | 0.71 (0.54–0.94) |
| Geographic region | | | | |
| North America | 395 | 17.4 | 12.3 | 0.63 (0.47–0.83) |
| Other | 804 | — | 14.4 | 0.64 (0.51–0.80) |
| No. of previous hormonal treatments | | | | |
| ≤2 | 587 | 18.8 | 11.2 | 0.59 (0.46–0.75) |
| >2 | 605 | 18.3 | 14.7 | 0.68 (0.53–0.88) |
| No. of previous chemotherapy regimens | | | | |
| 1 | 875 | — | 14.2 | 0.59 (0.48–0.73) |
| ≥2 | 324 | 15.9 | 12.3 | 0.74 (0.54–1.03) |
| Type of progression at study entry | | | | |
| PSA progression only | 490 | — | 19.5 | 0.62 (0.46–0.83) |
| Radiographic progression with or without PSA progression | 704 | 17.3 | 13.0 | 0.64 (0.52–0.80) |
| No. of bone lesions | | | | |
| ≤20 | 746 | — | 16.2 | 0.59 (0.46–0.75) |
| >20 | 453 | 13.1 | 9.5 | 0.67 (0.52–0.87) |
| Visceral (liver or lung) disease at baseline | | | | |
| No | 921 | — | 14.2 | 0.56 (0.46–0.69) |
| Yes | 278 | 13.4 | 9.5 | 0.78 (0.56–1.09) |
| Baseline PSA level | | | | |
| ≤Median | 600 | — | 19.2 | 0.67 (0.50–0.89) |
| >Median | 599 | 15.3 | 10.3 | 0.62 (0.50–0.78) |
| Baseline LDH level | | | | |
| ≤Median | 603 | — | 19.2 | 0.63 (0.46–0.86) |
| >Median | 594 | 12.4 | 8.5 | 0.61 (0.50–0.76) |

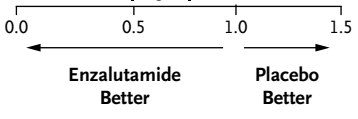



**Figure 2. Subgroup Analyses of Hazard Ratios for Death in the Two Study Groups.**

Hazard ratios are based on a nonstratified proportional-hazards model. Dashes indicate that the median time to death had not been reached for the indicated subgroup. The size of the circles is proportional to the size of the subgroup. The horizontal bars represent 95% confidence intervals. The Eastern Cooperative Oncology Group (ECOG) grades the performance status of patients with respect to activities of daily living, with 0 indicating that the patient is fully active and able to carry out all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature; and 2 indicating that the patient is ambulatory and up and about for more than 50% of waking hours and is capable of self-care but unable to carry out work activities. Scores on the Brief Pain Inventory–Short Form (BPI-SF) range from 0 to 10, with scores of 0 to 3 indicating that clinically significant pain is absent and scores of 4 to 10 indicating that clinically significant pain is present, and with higher scores indicating greater pain. LDH denotes lactate dehydrogenase, and PSA prostate-specific antigen.

tamide resulted in a 37% reduction in the risk of death, as compared with placebo (hazard ratio for death, 0.63; 95% CI, 0.53 to 0.75; P<0.001). On the basis of these results, an independent data and safety monitoring committee recommended that the study be halted and unblinded, with eligible patients in the placebo group offered treatment with enzalutamide. These results were confirmed at the time that the database was locked and are presented here.



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In the intention-to-treat population, 308 of 800 patients (39%) died in the enzalutamide group and 212 of 399 patients (53%) died in the placebo group. When the study was unblinded, 231 patients (29%) in the enzalutamide group were receiving the study drug, as compared with only 19 patients (5%) in the placebo group.

The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region, and type of disease progression at entry (Fig. 2), and it was maintained in the supportive analyses of overall survival performed with the use of the unstratified log-rank test and the Cox proportional-hazards model. The effect of enzalutamide on overall survival was maintained after adjustment for stratification factors and baseline prognostic factors, as shown in Table 1 in a multivariate analysis (hazard ratio for death, 0.58; 95% CI, 0.49 to 0.70; P<0.001). Systemic antineoplastic treatments were used for prostate cancer after the study drug was discontinued in a large proportion of patients, more commonly in the placebo group (in 61% of patients) than in the enzalutamide group (in 42% of patients). Among patients receiving at least one therapy after discontinuation of the study drug, the agents used included abiraterone acetate in 21% of patients in the enzalutamide group and in 24% of those in the placebo group and cabazitaxel in 10% and 14%, respectively. Both agents have been shown to confer a survival benefit for men with this disease state (see Table 3S in the Supplementary Appendix).

The superiority of enzalutamide over placebo was shown for all secondary end points, including PSA-level response rate (54% vs. 2%, P<0.001), soft-tissue response rate (29% vs. 4%, P<0.001), FACT-P quality-of-life response (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001) (Fig. 1B), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001) (Fig. 1C), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001) (Table 2).

### SAFETY

Though the period of observation for the enzalutamide group was more than twice that for the placebo group, the rates of adverse events were similar in the two groups (Table 3). The enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3%, vs. 53.1% in the placebo group). The median time to the first

**Table 1. Multivariate Analysis of Hazard Ratios for Death.***

| Variable | Measurement Estimates | | Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | Coefficient | P Value | |
| Study treatment (enzalutamide vs. placebo) | −0.54±0.09 | <0.001 | 0.58 (0.49–0.70) |
| ECOG performance score (0 or 1 vs. 2) | −0.33±0.14 | 0.02 | 0.72 (0.55–0.95) |
| Mean pain score on BPI-SF (question no. 3) (<4 vs. ≥4)† | −0.23±0.10 | 0.02 | 0.79 (0.65–0.97) |
| Progression at study entry (PSA only vs. radiographic) | −0.29±0.09 | 0.002 | 0.75 (0.62–0.90) |
| Visceral disease at screening (no vs. yes) | −0.47±0.10 | <0.001 | 0.63 (0.52–0.76) |
| Baseline serum lactate dehydrogenase (per increase of 1 U per liter) | 0.00±0.00 | <0.001 | 1.002 (1.001–1.002) |
| Baseline hemoglobin (per increase of 1 g per liter) | −0.03±0.00 | <0.001 | 0.97 (0.97–0.98) |

* Data with respect to survival for patients who were alive at the time of analysis were censored at the date the patient was last known to be alive. Hazard ratios for death were calculated after adjustment for prognostic factors. Several factors were entered into a Cox proportional-hazards model, and a stepwise selection method was used in which nonsignificant factors were eliminated at entry into the model (P≥0.10) and further eliminated after the contribution to the model was assessed (P≥0.25). These included the factors listed in the table as well as age (<65 years vs.≥65 years), region (North America vs. other), number of previous chemotherapy regimens (1 vs. 2), and baseline serum prostate-specific antigen (PSA) level (per increase of 1 ng per milliliter). The Gleason score for prostate tumors was excluded owing to a large number of missing values. CI denotes confidence interval, and ECOG Eastern Cooperative Oncology Group.

† Scores on the Brief Pain Inventory–Short Form (BPI-SF) range from 0 to 10, with scores of 0 to 3 indicating that clinically significant pain is absent and scores of 4 to 10 indicating that clinically significant pain is present, and with higher scores indicating greater pain.



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**Table 2. Secondary End Points Related to Response and Disease Progression.***

| End Point | Enzalutamide (N=800) | Placebo (N=399) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| Confirmed PSA decline† | | | | |
| Patients with ≥1 postbaseline PSA assessment — no. (%) | 731 (91) | 330 (83) | | |
| PSA response — no./total no. (%) | | | | |
| Decline ≥50% from baseline | 395/731 (54) | 5/330 (2) | | <0.001 |
| Decline ≥90% from baseline | 181/731 (25) | 3/330 (1) | | <0.001 |
| Soft-tissue objective response | | | | |
| Patients with measurable disease — no. (%) | 446 (56) | 208 (52) | | |
| Complete or partial objective response — no./total no. (%) | 129/446 (29) | 8/208 (4) | | <0.001 |
| FACT-P quality-of-life response† | | | | |
| Patients with ≥1 postbaseline assessment — no. (%) | 651 (81) | 257 (64) | | |
| Quality-of-life response — no./total no. (%)‡ | 281/651 (43) | 47/257 (18) | | <0.001 |
| Progression indicators | | | | |
| Time to PSA progression — mo | | | 0.25 (0.20–0.30) | <0.001 |
| Median | 8.3 | 3.0 | | |
| 95% CI | 5.8–8.3 | 2.9–3.7 | | |
| Radiographic progression-free survival — mo | | | 0.40 (0.35–0.47) | <0.001 |
| Median | 8.3 | 2.9 | | |
| 95% CI | 8.2–9.4 | 2.8–3.4 | | |
| Time to first skeletal-related event — mo | | | 0.69 (0.57–0.84) | <0.001 |
| Median | 16.7 | 13.3 | | |
| 95% CI | 14.6–19.1 | 9.9–NYR | | |

* For a complete definition of end points, see Table 1S in the Supplementary Appendix. FACT-P denotes Functional Assessment of Cancer Therapy–Prostate, NYR not yet reached, and PSA prostate-specific antigen.
† Only patients with both baseline and postbaseline assessments are included.
‡ The quality-of-life response was defined as a 10-point improvement in the global score on the FACT-P questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart.

such adverse event was 12.6 months in the enzalutamide group, as compared with 4.2 months in the placebo group (Fig. 2S in the Supplementary Appendix). There was a higher incidence of all grades of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache in the enzalutamide group than in the placebo group. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo (with cardiac disorders of grade 3 in 1% and 2%, respectively). Hypertension or increased blood pressure was observed in 6.6% of patients in the enzalutamide group and 3.3% of those in the placebo group. There were no significant between-group imbalances in the rates of other adverse events, such as hyperglycemia, weight gain, hyperlipidemia, or glucose intolerance. Therefore, there was no evidence to suggest the development of a metabolic syndrome associated with enzalutamide, although the study was not designed to formally evaluate this event. Liver-function abnormalities were reported as adverse events in 1% of patients receiving enzalutamide and in 2% of those receiving placebo.

A comprehensive evaluation of electrocardiographic data, including the QT interval and the QT interval corrected for heart rate (QTc), revealed no clinically relevant changes in heart rate, atrioventricular conduction, cardiac depolarization, or effect on cardiac repolarization as determined by means of the QTc according to Fridericia's formula.[21]



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**Table 3. Adverse Events, According to Grade.**

| Adverse Event | Enzalutamide (N=800) | | Placebo (N=399) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number of patients (percent)* | | | |
| ≥1 Adverse event | 785 (98) | 362 (45) | 390 (98) | 212 (53) |
| Any serious adverse event | 268 (34) | 227 (28) | 154 (39) | 134 (34) |
| Discontinuation owing to adverse event | 61 (8) | 37 (5) | 39 (10) | 28 (7) |
| Adverse event leading to death | 23 (3) | 23 (3) | 14 (4) | 14 (4) |
| Frequent adverse events more common with enzalutamide* | | | | |
| Fatigue | 269 (34) | 50 (6) | 116 (29) | 29 (7) |
| Diarrhea | 171 (21) | 9 (1) | 70 (18) | 1 (<1) |
| Hot flash | 162 (20) | 0 | 41 (10) | 0 |
| Musculoskeletal pain | 109 (14) | 8 (1) | 40 (10) | 1 (<1) |
| Headache | 93 (12) | 6 (<1) | 22 (6) | 0 |
| Clinically significant adverse events | | | | |
| Cardiac disorder | | | | |
| Any | 49 (6) | 7 (1) | 30 (8) | 8 (2) |
| Myocardial infarction | 2 (<1) | 2 (<1) | 2 (<1) | 2 (<1) |
| Abnormality on liver-function testing† | 8 (1) | 3 (<1) | 6 (2) | 3 (<1) |
| Seizure | 5 (<1) | 5 (<1) | 0 | 0 |

* Included in this category are adverse events that occurred in more than 10% of patients in the enzalutamide group and that occurred in the enzalutamide group at a rate that was at least 2 percentage points higher than that in the placebo group.

† Abnormalities on liver-function testing included hyperbilirubinemia and increased levels of aspartate aminotransferase or alanine aminotransferase.

Five of the 800 patients in the enzalutamide group (0.6%) were reported by the investigators to have had a seizure; no seizures were reported in the placebo group. One case of status epilepticus (confusion associated with partial complex-status epilepticus) required medical intervention; the four other seizures were self-limited and did not recur after study-drug discontinuation. Four of the seizures were witnessed. Potentially predisposing factors were present in several patients. Two patients had brain metastases, 1 of whom had a seizure reported 26 days after the last dose of enzalutamide. One patient had inadvertently been administered lidocaine intravenously immediately before the seizure, and 1 patient with brain atrophy had an unwitnessed event classified as a seizure, in the context of a history of heavy alcohol use, after initiation of haloperidol 7 days beforehand. One additional adverse event reported by the investigator as a syncope had several features suggestive of seizure.

## DISCUSSION

In this phase 3 study, we found that enzalutamide, an oral androgen-receptor–signaling inhibitor, significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy by a median of 4.8 months and reduced the risk of death from any cause by 37% versus placebo. In a multivariate analysis, the survival benefit was seen in all patient subgroups, including those stratified according to age and ECOG performance status, the geographic location of the study center, the extent of disease on diagnostic imaging, and biochemical measurements that included PSA and lactate dehydrogenase, even after adjustment for baseline factors.

These data confirm the central role of the androgen receptor and androgen-receptor signaling in the progression of prostate cancer throughout the spectrum of disease. Castration-resistant



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disease was previously considered to be a hormone-refractory disease. The survival benefit in this study substantiates preclinical work showing that androgen-receptor signaling contributes to disease progression despite castrate levels of testosterone and previous conventional antiandrogen therapy. This result, coupled with the recent report of a survival benefit from abiraterone acetate plus prednisone (probably resulting from further reduction in androgen levels),[22] establishes that these tumors are not refractory to hormones, even after chemotherapy has been administered. Changes in the androgen receptor, including overexpression, not only are oncogenic in model systems but also are associated with growth-stimulatory effects from the available antiandrogen agents.[7-9] Enzalutamide, unlike bicalutamide and flutamide, has no known agonist activity,[11] and enzalutamide therapy was able to slow disease progression despite the presence of low levels of circulating androgens.

At the time that this placebo-controlled study was designed and initiated, no life-prolonging treatment was available for men with progressive prostate cancer after docetaxel therapy; however, during the study period, both cabazitaxel[23] and abiraterone acetate plus prednisone[21] were approved for use. The benefits of enzalutamide were observed even though a greater proportion of patients in the placebo group received subsequent systemic therapies for prostate cancer that have been shown to prolong life (42% of those receiving enzalutamide and 61% of those receiving placebo). PSA levels increased in a majority of patients who had disease progression while receiving enzalutamide, a finding that suggests the tumors remained driven by androgen and androgen receptors and potentially sensitive to further hormonal interventions.

The analyses of the reported secondary outcome measures were supportive of the observed survival benefit. Enzalutamide was superior to placebo both in early measures of response (as assessed by improvements in PSA level, radiographically measurable disease, and quality-of-life scores) and in time-to-event measures of progression (as defined by PSA level, diagnostic imaging results, and delay in the development of skeletal-related events), as outlined in the PCWG2 guidelines.[14] The significantly higher response rates, as well as the prolonged progression-free survival, with enzalutamide as compared with placebo are consistent with the overall clinical benefit of enzalutamide.

The median time to any initial adverse event of grade 3 or higher was 8.4 months longer in the enzalutamide group than in the placebo group (12.6 vs. 4.2 months), owing to improved long-term control of disease-related symptoms without an increase in drug reactions of grade 3 or higher. The most common adverse events that were reported more frequently in the enzalutamide group included fatigue, diarrhea, and hot flashes. Although all men had castrate levels of circulating testosterone, further inhibition of androgen-receptor signaling in noncancerous tissues probably explains some of these side effects.[24,25]

Seizures were reported in 5 of 800 patients (0.6%) receiving enzalutamide, several of whom had predisposing conditions or concomitant treatments. Convulsions are a dose-dependent toxic effect of enzalutamide given at doses above the clinical therapeutic range in animals,[26] and seizures were seen in the phase 1–2 enzalutamide trial in each of the cohorts, beginning at daily doses of 360 mg of enzalutamide or more.[13] Inhibition of the $\gamma$-aminobutyric acid–gated chloride channel is a hypothesized mechanism by which enzalutamide lowers the seizure threshold.[27] Caution should be used in administering enzalutamide to patients with a history of seizure or who have other predisposing factors, including underlying brain injury, stroke, brain metastases, or alcoholism, or to patients receiving concomitant medication that may lower the seizure threshold. In this study, enzalutamide was discontinued in patients who were reported to have had a seizure. Treatment with enzalutamide did not result in an increase in the rate of cardiac disorders or hepatic dysfunction.

Enzalutamide, a once-daily oral hormonal treatment, is administered without the need for concomitant prednisone, which has been postulated to activate androgen-receptor signaling.[28] This novel agent is anticipated to join the therapeutic armamentarium of anticancer drugs with diverse mechanisms of action that confer a survival benefit in men with castration-resistant prostate cancer.[22,23,29] These results validate androgen-receptor signaling as a key therapeutic target throughout the clinical spectrum of prostate cancer, including in men who have received previous chemotherapy. Clinical trials of enzalutamide in earlier-stage prostate cancer are ongoing.



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In conclusion, enzalutamide significantly prolonged survival in men with metastatic castration-resistant prostate cancer after chemotherapy.

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## APPENDIX

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## REFERENCES

1. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer 2001;1:34-45.
2. Grossmann ME, Huang H, Tindall DJ. Androgen receptor signaling in androgen-refractory prostate cancer. J Natl Cancer Inst 2001;93:1687-97.
3. Pienta KJ, Bradley D. Mechanisms underlying the development of androgen-independent prostate cancer. Clin Cancer Res 2006;12:1665-71.
4. Scher HI, Sawyers CL. Biology of progressive castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005;23:8253-61.
5. Attard G, Richards J, de Bono JS. New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway. Clin Cancer Res 2011;17:1649-57.



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**6.** Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. Endocr Relat Cancer 2004;11:459-76.
**7.** Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164:217-27.
**8.** Visakorpi T, Hyytinen E, Koivisto P, et al. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. Nat Genet 1995;9:401-6.
**9.** Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004;10:33-9.
**10.** Jung ME, Ouk S, Yoo D, et al. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). J Med Chem 2010;53:2779-96.
**11.** Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324:787-90.
**12.** Morris MJ, Basch EM, Wilding G, et al. Department of Defense prostate cancer clinical trials consortium: a new instrument for prostate cancer clinical research. Clin Genitourin Cancer 2009;7:51-7.
**13.** Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010;375:1437-46.
**14.** Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-59.
**15.** Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
**16.** Atkinson TM, Rosenfeld BD, Sit L, et al. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). J Pain Symptom Manage 2011;41:558-65.
**17.** Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-68.
**18.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
**19.** Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health 2009;12:124-9.
**20.** Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-Prostate instrument. Urology 1997;50:920-8.
**21.** Morganroth J. A definitive or thorough phase 1 QT ECG trial as a requirement for drug safety assessment. J Electrocardiol 2004;37:25-9.
**22.** de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
**23.** de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-54.
**24.** Grossmann M, Zajac JD. Management of side effects of androgen deprivation therapy. Endocrinol Metab Clin North Am 2011;40:655-71.
**25.** Kumar RJ, Barqawi A, Crawford ED. Adverse events associated with hormonal therapy for prostate cancer. Rev Urol 2005;7:Suppl 5:S37-S43.
**26.** Foster WR, Car BD, Shi H, et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. Prostate 2011;71:480-8.
**27.** Treiman DM. GABAergic mechanisms in epilepsy. Epilepsia 2001;42:Suppl 3:8-12.
**28.** Richards J, Lim AC, Hay CW, et al. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res 2012;72:2176-82.
**29.** Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
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