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Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D., Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Aude Fléchon, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

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.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Scher at Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at scherh@mskcc.org.

*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-

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

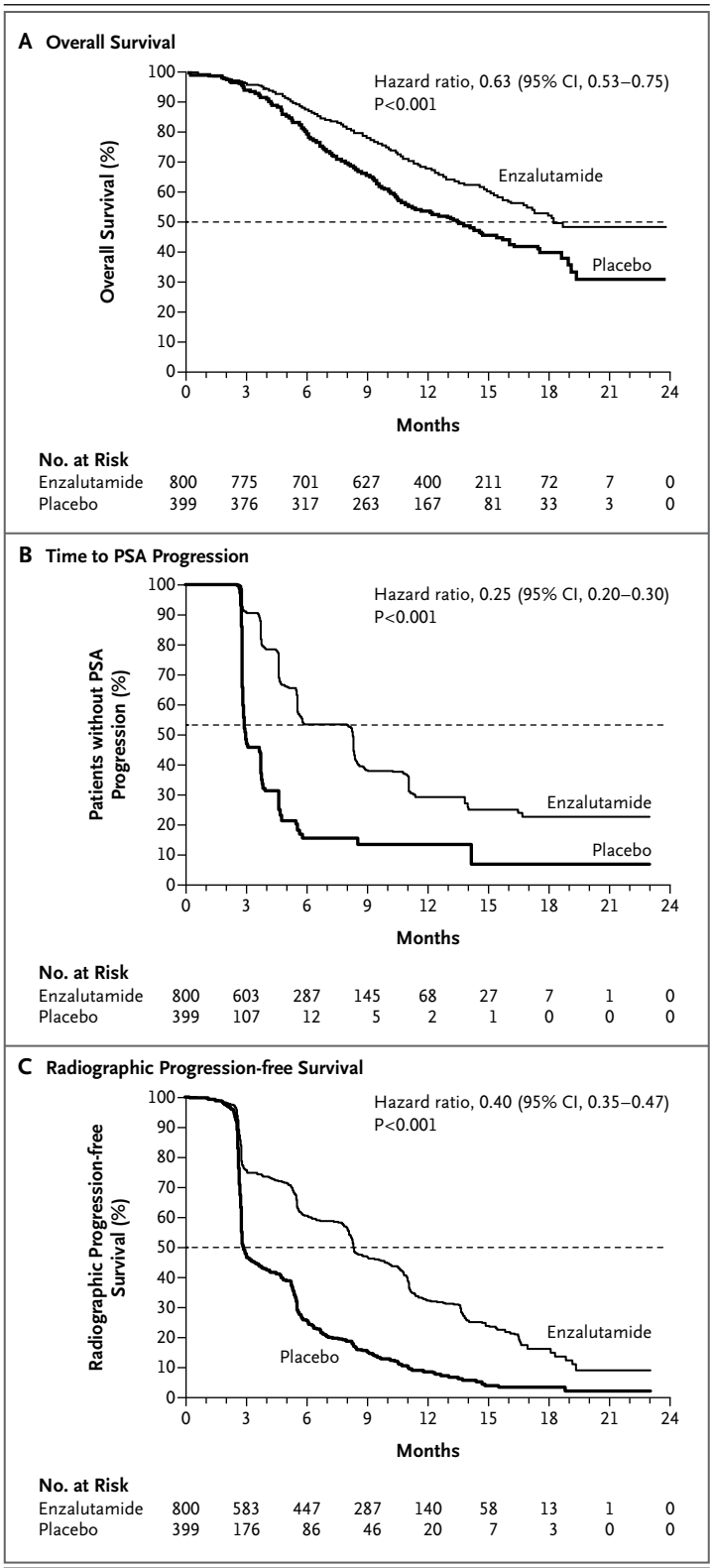

Figure 1. Kaplan–Meier Estimates of Primary and Secondary End Points in the Intention-to-Treat Population.
Shown are data for overall survival, the primary end point (Panel A), and for two secondary end points, the time to prostate-specific antigen (PSA) progression (Panel B) and radiographic progression-free 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-

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)

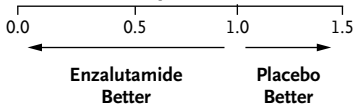

Figure 2. Subgroup Analyses of Hazard Ratios for Death in the Two Study Groups.

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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