ORIGINAL ARTICLE

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

ABSTRACT

BACKGROUND

Enzalutamide, an androgen-receptor inhibitor, has been associated with improved overall survival in men with castration-resistant prostate cancer. It is not known whether adding enzalutamide to testosterone suppression, with or without early docetaxel, will improve survival in men with metastatic, hormone-sensitive prostate cancer.

METHODS

In this open-label, randomized, phase 3 trial, we assigned patients to receive testosterone suppression plus either open-label enzalutamide or a standard nonsteroidal antiandrogen therapy (standard-care group). The primary end point was overall survival. Secondary end points included progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival, and adverse events.

RESULTS

A total of 1125 men underwent randomization; the median follow-up was 34 months. There were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group (hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.86; P=0.002). Kaplan–Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard-care group. Better results with enzalutamide were also seen in PSA progression-free survival (174 and 333 events, respectively; hazard ratio, 0.39; P<0.001) and in clinical progression-free survival (167 and 320 events, respectively; hazard ratio, 0.40; P<0.001). Treatment discontinuation due to adverse events was more frequent in the enzalutamide group than in the standard-care group (33 events and 14 events, respectively). Fatigue was more common in the enzalutamide group; seizures occurred in 7 patients in the enzalutamide group (1%) and in no patients in the standard-care group.

CONCLUSIONS

Enzalutamide was associated with significantly longer progression-free and overall survival than standard care in men with metastatic, hormone-sensitive prostate cancer receiving testosterone suppression. The enzalutamide group had a higher incidence of seizures and other toxic effects, especially among those treated with early docetaxel. (Funded by Astellas Scientific and Medical Affairs and others; ENZAMET (ANZUP 1304) ANZCTR number, ACTRN12614000110684; ClinicalTrials.gov number, NCT02446405; and EU Clinical Trials Register number, 2014-003190-42.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Davis at Level 2, 5 Arnold St., Box Hill, VIC 3128, Australia, or at ian.davis@monash.edu.

*A full list of the investigators in the ENZAMET Trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 2, 2019, and updated on June 11, 2019, at NEJM.org.

N Engl J Med 2019;381:121-31.
DOI: 10.1056/NEJMoa1903835

Several randomized trials have established the benefits of adding docetaxel or abiraterone to testosterone suppression in men with metastatic, hormone-sensitive prostate cancer.[1-10] The survival benefits associated with docetaxel early in the course of treatment, particularly in men with high-volume metastatic disease,[7] are substantially larger than the survival benefits associated with using docetaxel later after castration resistance has developed.[11-13] The addition of abiraterone to testosterone suppression also improved overall survival in hormone-sensitive prostate cancer, regardless of the burden of metastatic disease.[9,10] A recent post hoc comparison indicated that men who were given abiraterone or docetaxel early in the course of treatment had similar outcomes with respect to overall survival.[14]

Enzalutamide is an orally administered, small-molecule inhibitor of the androgen receptor that is designed to overcome acquired resistance to first-generation nonsteroidal antiandrogens, including bicalutamide, nilutamide, and flutamide. Previous trials have shown that enzalutamide improved overall survival in castration-resistant prostate cancer, regardless of whether it was used before or after docetaxel chemotherapy.[15,16]

We hypothesized that adding enzalutamide to first-line therapy would delay the emergence of castration resistance and thereby improve overall survival. In the ENZAMET (Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer) trial, our aim was to determine the effects of adding enzalutamide to first-line treatment that included testosterone suppression with or without early docetaxel.

Methods

Trial Design

The primary objective of this multinational, open-label, randomized, phase 3 trial was to determine the effects of early enzalutamide treatment on overall survival in men with metastatic, hormone-sensitive prostate cancer. Secondary objectives were to determine the effects on progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival (based on imaging, symptoms, signs, or changes in therapy), and adverse events. Effects on health-related quality of life, resource use, and incremental cost-effectiveness will be reported separately.

Patients and Treatment

Eligible patients had prostatic adenocarcinoma with metastases on computed tomography (CT), bone scanning with technetium-99, or both and a score of 2 or less on the Eastern Cooperative Oncology Group (ECOG) performance-status scale, which ranges from 0 (no disability) to 5 (death). Testosterone suppression was initiated up to 12 weeks before randomization. Previous adjuvant testosterone suppression for up to 24 months was allowed if the treatment had been completed at least 12 months earlier. The trial protocol and Supplementary Appendix are available with the full text of this article at NEJM.org.

Eligible patients were randomly assigned in a 1:1 ratio to receive enzalutamide (at a dose of 160 mg daily) or a standard nonsteroidal antiandrogen drug (bicalutamide, nilutamide, or flutamide) (standard-care group) until the occurrence of clinical disease progression or prohibitive toxic effects. In the two groups, background therapy included continuous testosterone suppression. After the enrollment of 88 patients (mainly from Australia and New Zealand), the early administration of docetaxel with testosterone suppression was permitted in protocol version 2 (as revised on November 2014) as a stratification factor before randomization, according to evidence showing improved survival with this approach.[1] The decision to initiate early treatment with docetaxel was left up to the individual patients and their physicians. If docetaxel was administered, the regimen consisted of 75 mg per square meter of body-surface area, without prednisone or prednisolone, given every 3 weeks for a maximum of six cycles. Up to two cycles of docetaxel were permitted before randomization.

The central randomization system implemented minimization with a random component. Randomization was stratified according to the volume of disease (high [defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis] or low), planned use of early docetaxel (yes or no), planned use of bone antiresorptive therapy (yes or no), the score on the Adult Comorbidity Evaluation 27 (ACE-27)[17] (with

coexisting conditions rated as 0 [none] or 1 [mild] vs. 2 [moderate] or 3 [severe or multiple conditions]), and trial site.

TRIAL OVERSIGHT

The trial was led by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney. Regional sponsorship and coordination was performed by Cancer Trials Ireland in Ireland and the United Kingdom, the Canadian Cancer Trials Group in Canada, and the Dana–Farber Cancer Institute in the United States. The trial was designed by the ANZUP investigators. Data were collected and analyzed by the NHMRC Clinical Trials Centre. The authors were solely responsible for the writing of the manuscript.

Astellas Pharma provided enzalutamide and financial support for trial conduct; representatives of the company reviewed drafts of the protocol and trial report but were not otherwise involved in any aspects of the trial design, data accrual, data analysis, or manuscript preparation. Testosterone suppression, standard antiandrogen drugs, docetaxel, and all subsequent treatments were accessed according to local standard practice. The authors vouch for the accuracy and completeness of the reported data and for the fidelity of the trial to the protocol.

An independent data and safety monitoring committee reviewed the progress and results of the trial. The trial was conducted in accordance with the principles of Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was independently reviewed and approved as required at each participating institution. All the patients provided written informed consent.

END POINTS

The primary end point of overall survival was measured as the interval from randomization to death from any cause or to the date at which the patient was last known to be alive. The secondary end point of PSA progression-free survival was measured as the interval from randomization to the earliest event of PSA progression according to the criteria of the Prostate Cancer Working Group 2 (a confirmed relative increase in the PSA level from the nadir value by ≥25% and by ≥2 ng per milliliter),[18] clinical progression, death from any cause, or the last known date of follow-up without PSA progression. The secondary end point of clinical progression was defined as the earliest sign of radiographic progression according to the criteria of the Prostate Cancer Working Group 2 for bone lesions and the Response Evaluation Criteria in Solid Tumors, version 1.1,[19] for soft-tissue lesions; the development of symptoms attributable to cancer progression; or the initiation of another anticancer treatment for prostate cancer. Imaging by means of CT and bone scanning was recommended to confirm clinical suspicion of progressive disease. Imaging reports (but not the images themselves) were reviewed centrally. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02. Adverse-event data were collected during the treatment period, with a final safety assessment performed 30 to 42 days after the cessation of the trial regimen.

STATISTICAL ANALYSIS

We determined that the enrollment of 1100 patients (with 470 deaths) would provide a power of at least 80% to detect a 25% lower hazard of death in the enzalutamide group than in the standard-care group (hazard ratio, 0.75), with a two-sided type I error rate of 0.05. In these calculations, we assumed a 3-year survival rate of 65% in the standard-care group on the basis of two previous studies of enzalutamide in men with metastatic, castration-resistant prostate cancer.[15,16] Protocol versions 1 and 2 called for an interim analysis of overall survival after the occurrence of 67% of the prespecified 470 deaths with the use of the Lan–DeMets alpha-spending function. Protocol version 3, which was written after external evidence became available for improved overall survival with early abiraterone treatment,[8,9] added interim analyses of overall survival after the occurrence of 50% and 80% of the prespecified 470 deaths. The trial executive committee made these decisions without any knowledge of outcomes in each treatment group.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Enzalutamide (N = 563)	Standard Care (N = 562)
Age — yr		
Mean	68.9±8.1	68.8±8.3
Median (IQR)	69.2 (63.2–74.5)	69.0 (63.6–74.5)
Region — no. (%)		
Australia	324 (58)	321 (57)
Canada	97 (17)	107 (19)
Ireland	39 (7)	43 (8)
New Zealand	20 (4)	19 (3)
United Kingdom	63 (11)	50 (9)
United States	20 (4)	22 (4)
Planned use of early docetaxel — no. (%)	254 (45)	249 (44)
Volume of disease — no. (%)		
High	291 (52)	297 (53)
Low	272 (48)	265 (47)
Visceral metastases — no. (%)	62 (11)	67 (12)
No. of months since diagnosis of metastasis		
Mean	2.9±6.9	3.1±7.2
Median (IQR)	1.9 (0.9–2.8)	1.9 (1.0–2.8)
Gleason score — no. (%)†		
≤7	152 (27)	163 (29)
8–10	335 (60)	321 (57)
Missing data	76 (13)	78 (14)
Previous therapy — no. (%)		
Adjuvant androgen-deprivation therapy	58 (10)	40 (7)
Antiandrogen therapy‡	285 (51)	316 (56)
LHRHA‡	411 (73)	418 (74)
Bilateral orchiectomy	5 (1)	8 (1)
Docetaxel‡	95 (17)	83 (15)

* Plus–minus values are means ±SD. Patients in the standard-care group received standard nonsteroidal antiandrogen therapy. Patients in the two groups also received testosterone suppression. Additional details are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and LHRHA luteinizing-hormone–releasing hormone agonist or antagonist.

† Gleason scores for the histologic pattern of carcinoma range from 2 to 10, with higher scores indicating a higher-grade tumor.

‡ This therapy was initiated within 12 weeks before randomization.

Efficacy analyses were based on the intention-to-treat principle and included all the patients who had undergone randomization. The relevant follow-up times of patients who did not have an event were included in time-to-event analysis as censored observations. These analyses included patients who were lost to follow-up or who withdrew consent for continued follow-up after the date of consent withdrawal. Patients who had undergone randomization and received a dose of any trial drug were included in analyses of drug exposure and safety.

We used the Kaplan–Meier method to summarize time-to-event end points and to calculate event probabilities at 3 years. An unadjusted log-rank test was used for the primary comparison of randomly assigned trial groups. We used Cox proportional-hazards regression to estimate hazard ratios, their 95% confidence intervals, and interactions between group assignment and prespecified baseline characteristics. The proportional-hazards assumption was tested. All P values and confidence intervals are two-sided.

We prespecified that consistency of the treatment effect would be evaluated across the following subgroups: Gleason score (≤7 vs. 8 to 10); age at trial entry (<70 years or ≥70 years); ECOG performance status score (0 vs. 1 or 2); the presence or absence of visceral metastases in the lung, liver, or other organs; volume of disease (high or low); planned use or nonuse of early docetaxel treatment; planned use or nonuse of bone antiresorptive therapy; the ACE-27 comorbidity score (0 or 1 vs. 2 or 3); prior local treatment (radiation, surgery, or neither); and geographic region (Australia or New Zealand vs. North America vs. Ireland or United Kingdom). We prespecified that the effects of enzalutamide according to the volume of disease and the use of early docetaxel treatment were of particular interest. We used the Benjamini–Hochberg method to account for multiple comparisons associated with subgroup analyses.

RESULTS

PATIENTS

From March 2014 through March 2017, we assigned 1125 men to receive either enzalutamide (563 patients) or standard care (562 patients) at 83 sites (Fig. S1 and Table S1 in the Supplementary Appendix). A total of 14 patients — 2 who were lost to follow-up and 12 who withdrew consent for continued follow-up — were included in the time-to-event analyses with censored times as appropriate.

The baseline characteristics of all the patients are summarized in Table 1 and detailed in the Supplementary Appendix. High-volume disease was present in 52% of the patients in the two groups. Early docetaxel treatment was planned in 45% of the patients (including in 61% of those with high-volume disease and in 27% of those with low-volume disease) but was not administered to 22 patients, 11 in each of the randomly assigned treatment groups. The full planned course of six cycles of docetaxel was given to 159 of 243 patients (65%) in the enzalutamide group and 181 of 238 (76%) in the standard-care group.

OVERALL SURVIVAL

The first interim analysis of the primary end point occurred on February 28, 2019, after the occurrence of 235 deaths. On March 7, 2019, the independent data and safety monitoring committee recommended that the unblinded results be provided to the trial executive committee so that plans for definitive analyses could be implemented. The observed P value of 0.0016 met the rejection boundary of 0.0031 for the null hypothesis that was specified for this interim analysis. The results that are reported here include 10 additional deaths (for a total of 245) after a review to ascertain the survival status of all the patients as of February 28, 2019, after a median follow-up of 34 months.

At the time of this analysis, there were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group (hazard ratio for death, 0.67; 95% confidence interval [CI], 0.52 to 0.86; P=0.002) (Fig. 1A). The results were unaffected by adjustments for geographical region, volume of disease, use of early docetaxel treatment, bone antiresorptive therapy, and coexisting conditions. The median survival time was not yet estimable in either trial group. The Kaplan–Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard-care group.

PROGRESSION-FREE SURVIVAL

The effects of enzalutamide on PSA progression-free survival and clinical progression-free survival were larger than its effect on overall survival. For PSA progression-free survival, there were 174 events in the enzalutamide group and 333 events in the standard-care group (rate of event-free survival at 3 years, 67% and 37% respectively; hazard ratio, 0.39; 95% CI, 0.33 to 0.47; P<0.001) (Fig. 1B). For clinical progression-free survival, there were 167 events in the enzalutamide group and 320 events in the standard-care group (rate of event-free survival at 3 years, 68% and 41%, respectively; hazard ratio, 0.40; 95% CI, 0.33 to 0.49; P<0.001) (Fig. 1C). P values for analyses of the between-group difference in PSA progression-free survival and clinical progression-free survival remained highly significant after adjustment for multiple comparisons.

SUBGROUP ANALYSES

The effects of enzalutamide on overall survival were smaller among the patients in the stratified subgroups with respect to bone antiresorptive therapy, planned early docetaxel treatment, and high-volume disease (Fig. 2, and Table S3 in the Supplementary Appendix). After adjustment for multiple comparisons, P values for heterogeneity of the treatment effect of enzalutamide were 0.14 for volume of disease, 0.14 for early docetaxel treatment, and 0.06 for the use of bone antiresorptive therapy.

We anticipated that the smaller number of deaths would limit the reliability of subgroup analyses of overall survival. Thus, we specified in the analysis plan that subgroup analyses of progression-free survival would also be performed to take advantage of the larger number of events for this secondary end point. The effects of enzalutamide on clinical progression-free survival were noted in all predefined subgroups, including those with early docetaxel treatment (Fig. 3, and Fig. S2 in the Supplementary Appendix). The analyses of treatment effects on clinical progression-free survival according to the volume of disease and planned early docetaxel treatment showed consistently smaller effects of enzalutamide in patients with high-volume disease and in those with early docetaxel treatment. However, P values for heterogeneity of the treatment effect of enzalutamide were no longer significant after adjustment for multiple comparisons (Figs. S2, S3, and S4 in the Supplementary Appendix).

SUBSEQUENT ANTICANCER THERAPIES

Treatment after progression was initiated at the discretion of the patients and their physicians. The number of patients who received anticancer

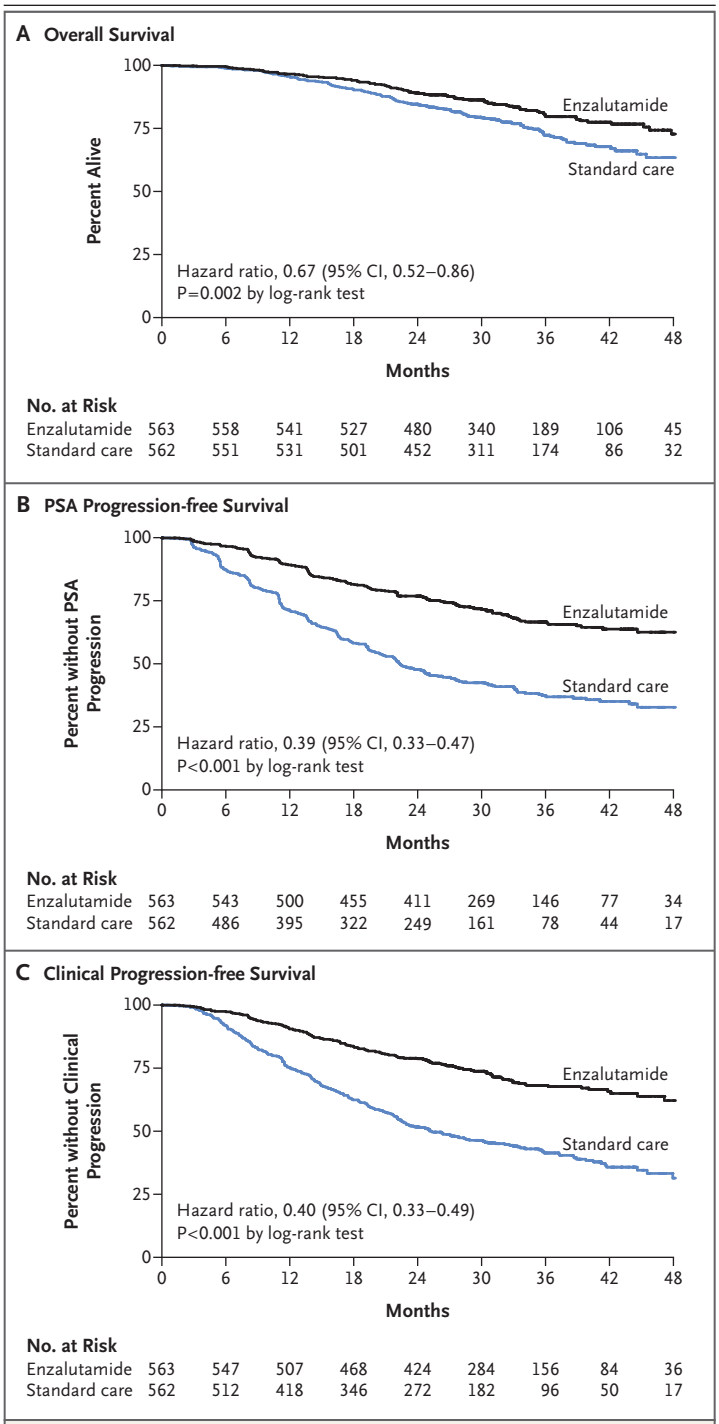

Figure 1. Overall Survival, PSA Progression-free Survival, and Clinical Progression-free Survival.

Among the patients who received enzalutamide and those who received standard nonsteroidal antiandrogen therapy (standard-care group), shown are Kaplan–Meier curves for overall survival (Panel A), progression-free survival as determined by the prostate-specific antigen (PSA) level (Panel B), and clinical progression-free survival as determined by results on imaging, symptoms, signs, or changes in therapy (Panel C).

therapies after the trial regimen was 113 in the enzalutamide group and 275 in the standard-care group, a finding that was commensurate with the higher incidence of clinical progression in the standard-care group. Among the patients who had clinical progression, 112 of 167 (67%) in the enzalutamide group and 271 of 320 (85%) in the standard-care group received one or more subsequent life-prolonging therapies (Table S4 in the Supplementary Appendix).

TREATMENT DURATION

At 3 years, the percentage of patients who were still receiving a trial regimen was 62% in the enzalutamide group and 34% in the standard-care group (Table S5 in the Supplementary Appendix). Disease progression or death was the reason for discontinuation in 133 of 201 patients (66%) in the enzalutamide group and in 251 of 356 (71%) in the standard-care group who discontinued treatment. Discontinuation for reasons other than disease progression occurred in 68 of 563 patients (12%) and 105 of 558 patients (19%) in the respective groups. Early docetaxel treatment was administered in 227 of 487 patients (47%) who subsequently had clinical progression and in 91 of 203 (45%) who died from prostate cancer. Of the patients who died from prostate cancer without receiving subsequent therapy, early docetaxel treatment was administered in 13 of 28 (46%) in the enzalutamide group and in 3 of 13 (23%) in the standard-care group.

ADVERSE EVENTS

Adverse events during the follow-up period were consistent with the stage of disease, the age of the patients, and known safety profiles of the trial regimen (Table 2; and Tables S6, S7, and S8 in the Supplementary Appendix). During the first 6 months, adverse events of grades 1 to 3 were reported by more patients in the enzalutamide group than in the standard-care group (Table S8 in the Supplementary Appendix).

The number of patients with febrile neutropenia was similar in the two treatment groups (37 with enzalutamide and 32 with standard care), and all but 2 of these events (67 of 69) occurred during early docetaxel treatment. Seizures occurred more frequently in patients in the enzalutamide group (7 vs. 0). Six patients discontinued enzalutamide because of seizure; 1 discontinued enzalutamide because of clinical progression before the seizure event. Fatigue of any grade was

Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)	P Value for Interaction	Adjusted P Value
	no. of events/total no.				
All patients	102/563	143/562	0.67 (0.52–0.86)		
Volume of disease				0.04	0.14
Low	22/272	46/265	0.43 (0.26–0.72)		
High	80/291	97/297	0.80 (0.59–1.07)		
Early docetaxel planned				0.04	0.14
Yes	52/254	55/249	0.90 (0.62–1.31)		
No	50/309	88/313	0.53 (0.37–0.75)		
ACE-27 score				0.73	0.81
2 or 3	31/141	42/143	0.73 (0.46–1.16)		
0 or 1	71/422	101/419	0.65 (0.48–0.88)		
Antiresorptive therapy				0.006	0.06
Yes	17/55	11/58	1.77 (0.83–3.77)		
No	85/508	132/504	0.59 (0.45–0.77)		
Region				0.25	0.42
Ireland and United Kingdom	22/102	22/93	1.04 (0.57–1.88)		
North America	21/117	31/129	0.72 (0.41–1.25)		
Australia and New Zealand	59/344	90/340	0.58 (0.42–0.81)		
Gleason score				0.66	0.81
≤7	13/152	23/163	0.59 (0.30–1.16)		
8 to 10	66/335	84/321	0.70 (0.50–0.96)		
ECOG performance status				0.96	0.96
1 or 2	44/158	59/157	0.66 (0.45–0.98)		
0	58/405	84/405	0.66 (0.47–0.92)		
Age				0.16	0.33
≥70 yr	47/257	79/257	0.56 (0.39–0.81)		
<70 yr	55/306	64/305	0.81 (0.56–1.15)		
Visceral metastases				0.16	0.33
Yes	18/62	18/67	1.05 (0.54–2.02)		
No	84/501	125/495	0.62 (0.47–0.82)		
Previous local treatment				0.72	0.81
Yes	39/238	49/235	0.72 (0.47–1.09)		
No	63/325	94/327	0.65 (0.47–0.89)		

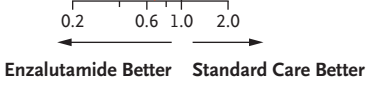

Figure 2. Subgroup Analysis of Overall Survival.

Shown are the results of subgroup analysis of overall survival in 10 key subgroups of patients in the enzalutamide group and the standard-care group. Hazard ratios and 95% confidence intervals are provided. The size of the gray shaded boxes is proportional to the number of events in the subgroup. The dashed vertical line indicates the overall hazard ratio in all the patients. Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 (no disability) to 5 (death). Scores on the Adult Comorbidity Evaluation 27 (ACE-27) are 0 (none) or 1 (mild) vs. 2 (moderate) or 3 (severe).

more common with enzalutamide than with standard care (465 patients and 363 patients, respectively). Grade 2 (clinically significant) fatigue was reported in 142 patients (25%) in the enzalutamide group and in 80 (14%) in the standard-care group.

Adverse events that occurred during the first 6 months among the patients who received early docetaxel treatment are shown in Table S8 in the Supplementary Appendix. Among those who received early docetaxel treatment, grade 2 peripheral sensory neuropathy was reported in 24 of 254 patients (9%) in the enzalutamide group and in 7 of 246 (3%) in the standard-care group. Among those who did not receive early docetaxel treatment, grade 2 peripheral neuropathy was reported in none of 309 patients in the enzalutamide group and in 2 of 312 (1%) in the standard-care group; grade 3 peripheral sensory neuropathy with docetaxel occurred in 3 patients in the enzalutamide group and in 1 in the standard-care group.

There were 385 serious adverse events reported in 235 patients in the enzalutamide group and 297 in 189 patients in the standard-care group.

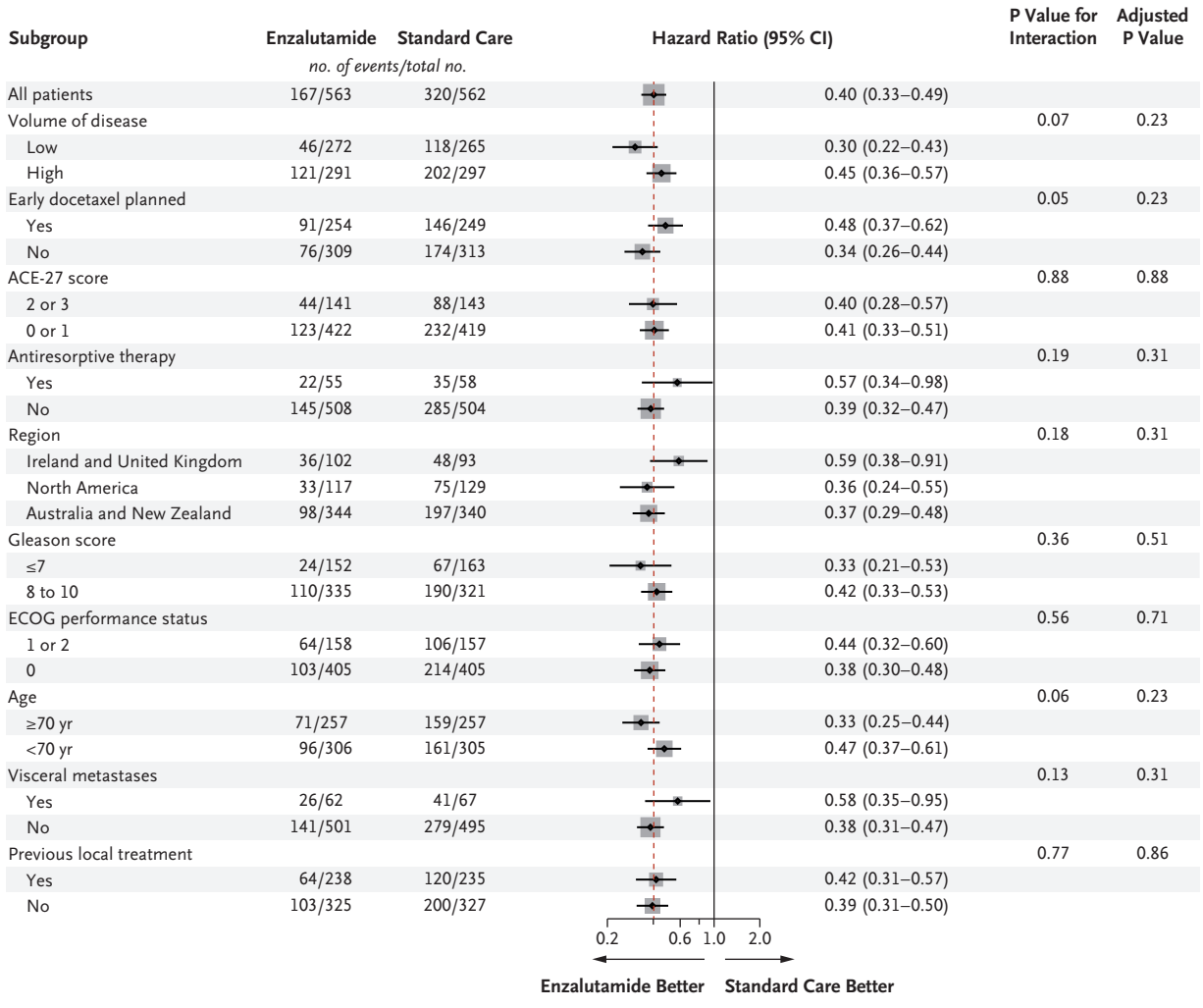

Figure 3. Subgroup Analysis of Clinical Progression-free Survival.

Shown are the results of subgroup analysis of clinical progression-free survival in 10 key subgroups of patients in the enzalutamide group and standard-care group. Clinical progression-free survival was determined by results on imaging, symptoms, signs, or changes in therapy.

The larger number of serious adverse events associated with enzalutamide was commensurate with the longer duration of trial treatment. The frequency of serious adverse events per person-year of exposure to a trial regimen was similar in the two groups (Table 2).

DISCUSSION

Enzalutamide was associated with longer overall survival and progression-free survival than standard care with nonsteroidal antiandrogen therapy in men with metastatic, hormone-sensitive prostate cancer. All the patients received testosterone suppression, plus the addition of docetaxel when appropriate. The control group in this trial was treated with standard antiandrogen therapy to provide a stringent comparator. All the patients had access to further effective therapies if the cancer progressed, and a high proportion of the patients in the standard-care group received enzalutamide or abiraterone after disease progression. The frequency of early docetaxel treatment was similar in the two groups. Thus, the

Table 2. Adverse Events.

Adverse Event	Enzalutamide (N = 563)	Standard Care (N = 558)
Any adverse event — no. of patients (%)*		
Grade 1	40 (7)	77 (14)
Grade 2	202 (36)	230 (41)
Grade 3	277 (49)	194 (35)
Grade 4	38 (7)	40 (7)
Grade 5	6 (1)	7 (1)
Serious adverse event		
No. of patients (%)	235 (42)	189 (34)
No. of events	385	297
Rate during treatment exposure (95% CI) — no./yr†	0.34 (0.29–0.40)	0.33 (0.28–0.39)
Adverse event leading to treatment discontinuation at any time — no. of patients	33	14
Grade 3 to 5 adverse event — no. of patients (%)‡		
Febrile neutropenia	37 (7)	32 (6)
Hypertension	43 (8)	25 (4)
Neutrophil count decreased	31 (6)	16 (3)
Fatigue	31 (6)	4 (1)
Syncope	20 (4)	6 (1)
Surgical or medical procedure	13 (2)	10 (2)
Anemia	4 (1)	5 (1)
Fall	6 (1)	2 (<1)
Thromboembolic event	4 (1)	4 (1)
Acute coronary syndrome	3 (1)	4 (1)
Myocardial infarction	5 (1)	2 (<1)
Chest pain from cardiac cause	3 (1)	2 (<1)
Stroke	1 (<1)	2 (<1)
Seizure§	2 (<1)	0
Delirium	0	1 (<1)

* When a patient had multiple events identified by a particular term, the worst grade is shown.
† The rate of serious adverse events per year of treatment exposure was estimated with the use of a negative binomial regression model.
‡ These adverse events occurred in at least 2% of the patients in either group or were selected as being events of special interest. In the enzalutamide group, 6 grade 5 adverse events were reported: death from an unknown cause in 2 patients and 1 patient each with stroke, myocardial infarction, aspiration pneumonia, and acidosis. In the standard-care group, 7 grade 5 adverse events were reported: sepsis in 2 patients and 1 patient each with cardiac arrest, sudden death from an unknown cause, gastric hemorrhage, urinary tract infection, and symptomatic progression of prostate cancer.
§ Seizure of any grade occurred in 7 patients in the enzalutamide group and in no patients in the standard-care group.

observed benefits of early enzalutamide therapy are not explained by differences in access to or use of subsequent therapies.

We found that adding early enzalutamide to testosterone suppression was associated with a higher frequency of toxic effects, especially peripheral neuropathy associated with the concomitant use of docetaxel. Patients who were treated with enzalutamide reported more fatigue and more often discontinued therapy before disease progression. Seven patients (1%) in this group had seizures, a known potential side effect of enzalutamide.

The effect of enzalutamide on overall survival appeared to be smaller in the subgroup with early docetaxel treatment. However, this trial was neither designed nor powered to reliably analyze the results in this subgroup. The effects of enzalutamide on clinical progression-free survival, an earlier end point with considerably more events and consequently greater statistical reliability, remained substantial regardless of early docetaxel treatment. This finding indicates that longer follow-up is needed to determine the effects of enzalutamide on overall survival beyond 3 years in those with early docetaxel treatment. Our current data support the claim that early enzalutamide prolongs survival within 3 years in the entire trial population but provide limited support that it prolongs overall survival within 3 years in patients who received early docetaxel treatment.

The main limitations of this trial are consequences of the detection of evidence of benefit at the first planned interim analysis. This early analysis may have overestimated the eventual treatment benefit.[20] There was no central review of actual imaging, but this factor would have no effect on the rate of death, the primary end point. The median follow-up of 34 months is sufficient to provide evidence about the effects within this interval but not beyond it. The sample size and number of events allow for strong conclusions about the effects of enzalutamide on survival in the entire trial population and the effects on progression-free survival in some subgroups; however, we cannot determine the effects on overall survival in any of the prespecified subgroups.

In conclusion, in men with metastatic hormone-sensitive prostate cancer receiving testosterone suppression, the addition of enzalutamide resulted in longer overall survival, PSA progression-free survival, and clinical progression-free survival within 3 years than the use of standard nonsteroidal antiandrogen therapy. However, enzalutamide was associated with some additional toxic effects, including fatigue and a small risk of seizures. Among the patients who also received early docetaxel treatment, the addition of enzalutamide was associated with additional toxic effects and longer progression-free survival but not longer overall survival.

Supported by Astellas Scientific and Medical Affairs, a grant (704970) from the Canadian Cancer Society, the Support for Cancer Clinical Trials Program of Cancer Australia, and a practitioner fellowship (APP1102604) and program grants (1037786 and 1150467) from the National Health and Medical Research Council of the Australian Government Department of Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Ian D. Davis, M.B., B.S., Ph.D., Andrew J. Martin, Ph.D., Martin R. Stockler, M.B., B.S., Stephen Begbie, M.B., B.S., Kim N. Chi, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Xanthi Coskinas, M.Med.Sc., Mark Frydenberg, M.B., B.S., Wendy E. Hague, M.B., B.S., Ph.D., Lisa G. Horvath, M.B., B.S., Ph.D., Anthony M. Joshua, M.B., B.S., Ph.D., Nicola J. Lawrence, M.B., Ch.B., Gavin Marx, M.B., B.S., John McCaffrey, M.B., B.Ch., Ray McDermott, M.D., Ph.D., Margaret McJannett, R.N., Scott A. North, M.D., Francis Parnis, M.B., B.S., Wendy Parulekar, M.D., David W. Pook, M.B., B.S., M.D., M. Neil Reaume, M.D., Shahneen K. Sandhu, M.B., B.S., Alvin Tan, M.B., Ch.B., T. Hsiang Tan, M.B., B.S., Alastair Thomson, B.M., Emily Tu, Ph.D., Francisco Vera-Badillo, M.D., Scott G. Williams, M.B., B.S., M.D., Sonia Yip, Ph.D., Alison Y. Zhang, M.B., B.S., Robert R. Zielinski, M.B., B.S., and Christopher J. Sweeney, M.B., B.S.

The authors' affiliations are as follows: Monash University (I.D.D., M.F., D.W.P.), Eastern Health (I.D.D.), Australian Urology Associates (M.F.), Monash Health (D.W.P.), and the Peter MacCallum Cancer Centre and the University of Melbourne (S.K.S., S.G.W.), Melbourne, VIC, the National Health and Medical Research Council Clinical Trials Centre, University of Sydney (A.J.M., M.R.S., X.C., W.E.H., E.T., S.Y., A.Y.Z.), the Chris O'Brien Lifehouse (M.R.S., L.G.H., A.Y.Z.), the University of Sydney (L.G.H., G.M.), Royal Prince Alfred Hospital (L.G.H.), Kinghorn Cancer Centre, St. Vincent's Hospital, and Garvan Institute of Medical Research (A.M.J.), Macquarie University (A.Y.Z.), and Western Sydney University (R.R.Z.), Sydney, Concord Cancer Centre, Concord Repatriation General Hospital, Concord, NSW (M.R.S.), Port Macquarie Base Hospital and Mid North Coast Cancer Institute Port Macquarie, Port Macquarie, NSW (S.B.), Sydney Adventist Hospital, Wahroonga, NSW (G.M.), the ANZUP Cancer Trials Group, Camperdown, NSW (M.M.), the Adelaide Cancer Centre and the University of Adelaide (F.P.) and the Royal Adelaide Hospital (T.H.T.), Adelaide, SA, and Orange Health Service, Central West Cancer Care Centre, Orange, NSW (R.R.Z.) — all in Australia; BC Cancer and the University of British Columbia, Vancouver (K.N.C.), the Cross Cancer Institute and the University of Alberta, Edmonton (S.A.N.), Canadian Cancer Trials Group, Queen's University (W.P., F.V.-B.), and the Kingston Health Sciences Center (F.V.-B.), Kingston, ON, and the University of Ottawa and the Ottawa Hospital Research Institute, Ottawa (M.N.R.) — all in Canada; Guy's and St. Thomas' NHS Foundation Trust Biomedical Research Centre, Cancer Research UK and King's College London, and Sarah Cannon Research UK, London (S.C.), and the Royal Cornwall Hospital, Truro (A. Thomson) — all in the United Kingdom; Auckland City Hospital, Auckland (N.J.L.), and the Waikato District Health Board, Hamilton (A. Tan) — both in New Zealand; Cancer Trials Ireland (J.M., R.M.), Mater Misericordiae University Hospital (J.M.), and St. Vincent's University Hospital and University College Dublin (R.M.D.) — all in Dublin; and Dana–Farber Cancer Institute and Harvard Medical School (C.J.S.) — both in Boston.

REFERENCES

1. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737-46.
2. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080-7.
3. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-77.
4. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149-58.
5. Gravis G, Boher JM, Joly F, et al. Androgen-deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016;70:256-62.
6. Vale CL, Burdett S, Rydzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016;17:243-56.
7. Gravis G, Boher J-M, Chen Y-H, et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. Eur Urol 2018;73:847-55.
8. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352-60.
9. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338-51.
10. Hoyle AP, Ali SA, James ND, et al. Effects of abiraterone acetate plus prednisone/prednisolone in high and low risk metastatic hormone sensitive prostate cancer. Ann Oncol 2018;29:Suppl 8:LBA4. abstract.
11. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
12. Berthold DR, Pond GR, de Wit R, Eisenberger M, Tannock IF. Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa. Ann Oncol 2008;19:1749-53.
13. Prostate Cancer Trialists Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000;355:1491-8.
14. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol 2018;29:1235-48.
15. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.
16. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424-33.
17. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291:2441-7.
18. 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.
19. 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.
20. Pocock SJ, Hughes MD. Practical problems in interim analyses, with particular regard to estimation. Control Clin Trials 1989;10:Suppl:209S-221S.