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Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

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ABSTRACT

BACKGROUND

Patients with prostate cancer who have high-risk biochemical recurrence have an increased risk of progression. The efficacy and safety of enzalutamide plus androgen-deprivation therapy and enzalutamide monotherapy, as compared with androgen-deprivation therapy alone, are unknown.

METHODS

In this phase 3 trial, we enrolled patients with prostate cancer who had high-risk biochemical recurrence with a prostate-specific antigen doubling time of 9 months or less. Patients were randomly assigned, in a 1:1:1 ratio, to receive enzalutamide (160 mg) daily plus leuprolide every 12 weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group). The primary end point was metastasis-free survival, as assessed by blinded independent central review, in the combination group as compared with the leuprolide-alone group. A key secondary end point was metastasis-free survival in the monotherapy group as compared with the leuprolide-alone group. Other secondary end points were patient-reported outcomes and safety.

RESULTS

A total of 1068 patients underwent randomization: 355 were assigned to the combination group, 358 to the leuprolide-alone group, and 355 to the monotherapy group. The patients were followed for a median of 60.7 months. At 5 years, metastasis-free survival was 87.3% (95% confidence interval [CI], 83.0 to 90.6) in the combination group, 71.4% (95% CI, 65.7 to 76.3) in the leuprolide-alone group, and 80.0% (95% CI, 75.0 to 84.1) in the monotherapy group. With respect to metastasis-free survival, enzalutamide plus leuprolide was superior to leuprolide alone (hazard ratio for metastasis or death, 0.42; 95% CI, 0.30 to 0.61; P<0.001); enzalutamide monotherapy was also superior to leuprolide alone (hazard ratio for metastasis or death, 0.63; 95% CI, 0.46 to 0.87; P=0.005). No new safety signals were observed, with no substantial between-group differences in quality-of-life measures.

CONCLUSIONS

In patients with prostate cancer with high-risk biochemical recurrence, enzalutamide plus leuprolide was superior to leuprolide alone with respect to metastasis-free survival; enzalutamide monotherapy was also superior to leuprolide alone. The safety profile of enzalutamide was consistent with that shown in previous clinical studies, with no apparent detrimental effect on quality of life. (Funded by Pfizer and Astellas Pharma; EMBARK ClinicalTrials.gov number, NCT02319837.)

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A Quick Take is available at NEJM.org

The American Cancer Society estimated that there would be 288,300 new cases of prostate cancer and 34,700 deaths from prostate cancer in the United States in 2023.[1] Within 10 years after definitive therapy for prostate cancer, approximately 20 to 50% of patients have biochemical disease recurrence characterized by a rise in prostate-specific antigen (PSA) levels.[2-4] A rise in PSA levels can also represent the presence of micrometastatic, localized, regional, or distant disease (or more than one of these), which increases the likelihood of illness and death related to prostate cancer.[2-5] Level 1 clinical evidence regarding the treatment of biochemically recurrent prostate cancer is limited; therefore, patients generally receive a treatment strategy involving risk stratification.[6,7] Patients with a PSA doubling time of less than 9 months are considered to be at high risk for rapid disease progression and at increased risk for death from prostate cancer.[2,8,9] Indeed, men with a PSA doubling time of less than 3 months have a median survival of 6 years after biochemical recurrence.[2,8,10]

Evidence from prospective, phase 3 clinical trials has shown that treatment intensification with next-generation hormonal therapies, such as enzalutamide, prolongs imaging-based progression-free survival and overall survival, delays the development of castration-resistant prostate cancer, and maintains quality of life in patients with metastatic hormone-sensitive prostate cancer as compared with androgen-deprivation therapy alone.[11-14] It is noteworthy that the nadir PSA level after treatment with enzalutamide and other next-generation hormonal therapies is correlated with improved clinical outcomes at every stage of prostate disease. Therefore, PSA could be a biomarker to identify patients who would have a good therapeutic response when strategies to deintensify therapy may be warranted.[15-21] Furthermore, in a phase 2 study, enzalutamide monotherapy in patients with nonmetastatic or metastatic hormone-sensitive prostate cancer produced durable reductions in PSA levels (≥80%). However, evidence from phase 3 trials regarding next-generation hormonal monotherapy is lacking.[22-25] The objective of the EMBARK trial was to evaluate the efficacy and safety of enzalutamide plus leuprolide and enzalutamide monotherapy, as compared with leuprolide alone, in patients with prostate cancer who have had high-risk biochemical recurrence.

Methods

Trial Design and Conduct

This international, randomized, phase 3 trial was sponsored by Pfizer and Astellas Pharma. The trial design has been published previously.[26] The trial was designed by the protocol steering committee, in collaboration with the clinical development teams. The trial design and amendments were approved by the institutional review board or independent ethics committee at each site. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All the patients provided written informed consent.

Data were collected by the investigators, analyzed by statisticians who were employed by the sponsors, and interpreted by the authors, some of whom are employees of the sponsors. Periodic monitoring of safety data was conducted by an independent, external safety monitoring committee composed of experts in prostate cancer, safety-data monitoring, and statistics. After signing a data confidentiality agreement, authors had full access to the data and were responsible for all the content and editorial decisions related to preparation of the manuscript. The sponsors provided and funded editorial and medical writing support for the preparation of the manuscript. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org.

Patients and Interventions

Adult patients with prostate cancer who had had biochemical recurrence after local therapy were eligible if at the time of the initial biopsy before primary definitive therapy they had histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell features, or small-cell features. Patients also had to meet the following criteria at screening: high-risk disease (defined as a PSA doubling time of ≤9 months and a PSA level of ≥2 ng per milliliter above nadir after radiation

therapy or ≥1 ng per milliliter after radical prostatectomy with or without postoperative radiation therapy), a serum testosterone level of at least 150 ng per deciliter, and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability).

Patients were excluded if they had undergone previous cytotoxic chemotherapy, had a history of seizure or a condition that may confer a predisposition to seizure, showed evidence of distant metastatic disease on conventional imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI], or bone scans), or if after radical prostatectomy they were considered by the investigator to be a candidate for salvage radiation therapy. Patients who received previous hormonal therapy were excluded, except for the following indications: neoadjuvant or adjuvant therapy at the time of definitive radiation therapy for no more than 36 months and at least 9 months before randomization or a single dose or short course (≤6 months) of hormonal therapy administered for rising PSA levels at least 9 months before randomization.

Patients were randomly assigned in a 1:1:1 ratio to receive enzalutamide plus leuprolide (combination group, double-blind), placebo plus leuprolide (leuprolide-alone group, double-blind), or enzalutamide monotherapy (monotherapy group, open-label) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to PSA level at screening, PSA doubling time, and previous hormonal therapy. Enzalutamide (at a dose of 160 mg) or placebo was administered orally once daily with or without food, and leuprolide (at a dose of 22.5 mg) was given as a single intramuscular or subcutaneous injection every 12 weeks. Treatment was suspended at week 37 if the PSA level was less than 0.2 ng per milliliter and was restarted when the PSA level was at least 5.0 ng per milliliter (if the patient had not had previous radical prostatectomy) or at least 2.0 ng per milliliter (if the patient had previously had radical prostatectomy). Patients continued to receive their assigned treatments until imaging-based disease progression (confirmed by central review), an unacceptable adverse event, seizure, or death occurred, nonadherence due to protocol violation was documented, or the patient or physician decided to discontinue the regimen.

END POINTS

The primary end point was metastasis-free survival in the combination group as compared with the leuprolide-alone group and was defined as the time from randomization to the date of earliest objective evidence of imaging-based progression according to central imaging or death from any cause. Key secondary end points were metastasis-free survival in the monotherapy group as compared with the leuprolide-alone group, the time to PSA progression, the time to use of new antineoplastic therapy, and overall survival. Additional secondary end points were safety and the time to the following: distant metastasis, resumption of hormonal therapy, development of castration resistance, symptomatic progression, first symptomatic skeletal event, and first deterioration in quality of life, as assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) total score. The definitions of the secondary efficacy end points are provided in the Supplementary Appendix.

ASSESSMENTS

Details regarding baseline assessments, efficacy assessments, and adverse events, including the assessment schedule, are provided in Table S1. Metastasis-free survival was determined on the basis of imaging-based assessment of disease and monitoring of survival status. Imaging-based assessment of disease, defined according to Response Evaluation Criteria for Solid Tumors, version 1.1, was determined by blinded independent central review with the use of conventional CT or MRI and whole-body radionuclide bone scans to identify bone disease. Baseline evaluations were performed within 4 weeks before the start of the trial treatment. Patients were assessed for progression approximately every 6 months after randomization.

PSA and testosterone levels were quantified by a central laboratory. Patients and site investigators were unaware of the PSA levels during the treatment period. The trial sites were notified if any PSA levels were considered to be undetectable (<0.2 ng per milliliter at week 36) or if criteria for PSA progression were met. PSA progression was defined as a PSA doubling time of 10

months or less. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

STATISTICAL ANALYSIS

For the primary end point, we calculated that a target enrollment of 1068 patients and the occurrence of at least 197 events (metastasis or death) in the three groups combined would give the trial 90% power to detect a hazard ratio for metastasis or death of 0.58 for the comparison of the combination group with the leuprolide-alone group, at a two-sided alpha level of 0.05. For the analyses of the key secondary end points, the significance level was strongly controlled with the use of a hierarchical testing plan (Fig. S2). Analyses of non–key secondary end points were descriptive.

All efficacy end points were analyzed with the use of the intention-to-treat principle. Safety was assessed in the as-treated population, with patients evaluated according to the treatment they received. For all time-to-event efficacy end points, P values derived from a stratified log-rank test were used for between-group comparisons. The stratification factors were PSA level at screening (≤10 ng per milliliter or >10 ng per milliliter), PSA doubling time (≤3 months or >3 to ≤9 months), and previous hormonal therapy (yes or no). Hazard ratios and associated 95% confidence intervals for the treatment effects were estimated with the use of a stratified Cox regression model.

RESULTS

PATIENTS

From January 2015 through August 2018, a total of 1068 patients at 244 sites in 17 countries were enrolled and underwent randomization: 355 patients were assigned to receive enzalutamide plus leuprolide, 358 to receive leuprolide alone, and 355 to receive enzalutamide monotherapy (Fig. 1). The data-cutoff date was January 31, 2023. The baseline characteristics were well balanced among the groups (Table 1). Most patients were White (83.2%). The median age was 69 years (range, 49 to 93), the median PSA doubling time was 4.9 months (range, 0.9 to 18.9), and the median PSA level was 5.2 ng per milliliter (range, 1.0 to 308.3). The representativeness of the trial population is shown in Table S2.

EFFICACY

The median follow-up in all three groups was 60.7 months. According to blinded independent central review, 45 patients (12.7%) in the combination group and 92 patients (25.7%) in the leuprolide-alone group had imaging-based progression or died. The 5-year metastasis-free survival was 87.3% (95% confidence interval [CI], 83.0 to 90.6) in the combination group and 71.4% (95% CI, 65.7 to 76.3) in the leuprolide-alone group. The risk of metastasis or death was 57.6% lower in the combination group than in the leuprolide-alone group, a difference that was significant (hazard ratio, 0.42; 95% CI, 0.30 to 0.61; P<0.001) (Fig. 2A). Among all 12 prespecified subgroups of sufficient size for analysis, including the subgroups of patients with shorter PSA doubling times (≤3 months and >3 months to ≤6 months), a benefit with respect to metastasis-free survival was seen with enzalutamide plus leuprolide as compared with leuprolide alone (Fig. S3).

According to blinded independent central review, 63 patients (17.7%) in the monotherapy group had imaging-based progression or died. The percentage of patients with 5-year metastasis-free survival was 80.0% (95% CI, 75.0 to 84.1) in the monotherapy group. The risk of metastasis or death was 36.9% lower in the monotherapy group than in the leuprolide-alone group, a difference that was significant (hazard ratio for metastasis or death, 0.63; 95% CI, 0.46 to 0.87; P=0.005) (Fig. 2B).

The estimated percentage of patients who were free from PSA progression at 5 years was 97.4% (95% CI, 94.7 to 98.8) in the combination group, 70.0% (95% CI, 64.1 to 75.1) in the leuprolide-alone group, and 88.9% (95% CI, 84.6 to 92.1) in the monotherapy group. The estimated percentage of patients who were free from antineoplastic therapy at 5 years was 83.0% (95% CI, 78.3 to 86.8) in the combination group, 61.7% (95% CI, 56.1 to 66.8) in the leuprolide-alone group, and 75.7% (95% CI, 70.6 to 80.0) in the monotherapy group. Patients in the combination group and the monotherapy group had a significantly lower risk of PSA progression than those in the leuprolide-alone group (hazard ratio in the combination group, 0.07; 95% CI, 0.03 to

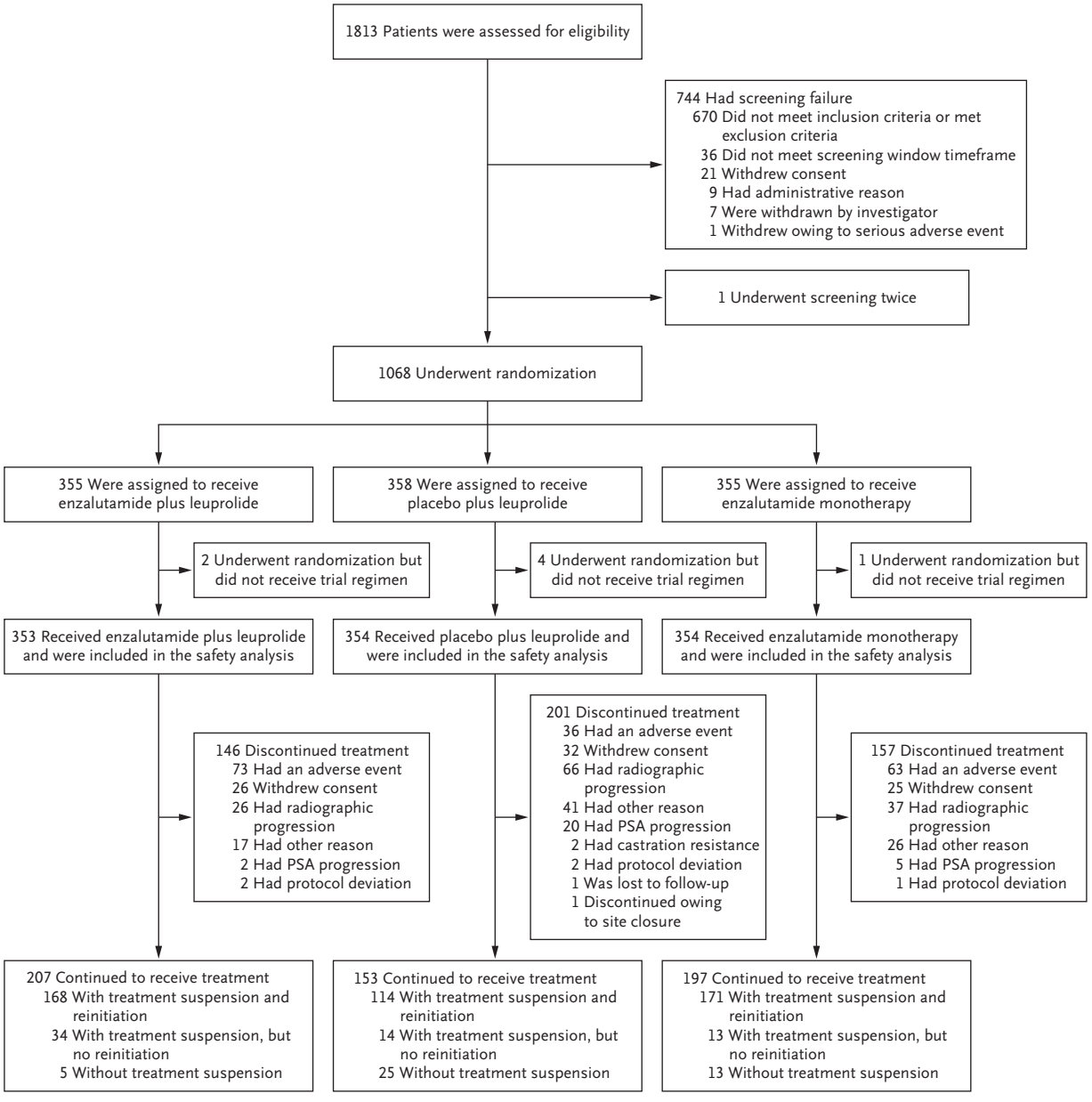


Figure 1. Enrollment, Randomization, and Treatment.

PSA denotes prostate-specific antigen.

0.14; P<0.001; hazard ratio in the monotherapy group, 0.33; 95% CI, 0.23 to 0.49; P<0.001) (Fig. 3). The time to first use of new antineoplastic therapy was longer in the combination group and the monotherapy group than in the leuprolide-alone group (hazard ratio in the combination group, 0.36; 95% CI, 0.26 to 0.49; P<0.001; hazard ratio in the monotherapy group, 0.54; 95% CI, 0.41 to 0.71; P<0.001). As compared with leuprolide alone, enzalutamide plus leuprolide and enzalutamide monotherapy resulted in a longer time to distant metastasis, symptomatic progression, and first symptomatic skeletal event. Enzalutamide plus leuprolide also result-

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Enzalutamide + Leuprolide (N = 355)	Leuprolide Alone (N = 358)	Enzalutamide Monotherapy (N = 355)
Median age (range) — yr	69 (51–87)	70 (50–92)	69 (49–93)
Age group — no. (%)			
<65 yr	81 (22.8)	91 (25.4)	91 (25.6)
65 to <75 yr	201 (56.6)	180 (50.3)	174 (49.0)
≥75 yr	73 (20.6)	87 (24.3)	90 (25.4)
Race or ethnic group — no. (%)†			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
American Indian or Alaska Native	4 (1.1)	1 (0.3)	0
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
Other	5 (1.4)	9 (2.5)	5 (1.4)
Not reported	10 (2.8)	5 (1.4)	14 (3.9)
Geographic region — no. (%)			
North America	144 (40.6)	137 (38.3)	133 (37.5)
Europe	130 (36.6)	128 (35.8)	146 (41.1)
Rest of the world	81 (22.8)	93 (26.0)	76 (21.4)
ECOG performance-status score — no. (%)‡			
0	328 (92.4)	336 (93.9)	321 (90.4)
1	26 (7.3)	21 (5.9)	34 (9.6)
>1	1 (0.3)	0	0
Missing data	0	1 (0.3)	0
PSA doubling time — no. (%)			
≤3 mo	69 (19.4)	80 (22.3)	76 (21.4)
>3 to 6 mo	187 (52.7)	142 (39.7)	164 (46.2)
>6 to 9 mo	98 (27.6)	135 (37.7)	114 (32.1)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)
Median PSA doubling time (range) — mo§	4.6 (0.9–9.6)	5.0 (1.1–10.8)	5.0 (1.0–18.9)
Median serum PSA level (range) — ng/ml	5.0 (1.0–308.3)	5.5 (1.1–163.3)	5.3 (1.1–37.0)
Previous hormonal therapy — no. (%)			
Yes	107 (30.1)	113 (31.6)	112 (31.5)
No	248 (69.9)	245 (68.4)	243 (68.5)
Primary definitive therapy — no. (%)			
Prostatectomy alone	90 (25.4)	75 (20.9)	99 (27.9)
Radiation therapy alone	86 (24.2)	104 (29.1)	90 (25.4)
Prostatectomy and radiation therapy	179 (50.4)	179 (50.0)	166 (46.8)

* Percentages may not total 100 because of rounding. PSA denotes prostate-specific antigen.
† Race or ethnic group was reported by the patients. The "Other" category includes patients who identified as multiple races or ethnic groups.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ PSA doubling time at baseline was calculated on the basis of a sequence of PSA values tested over time during the enrollment period. Some baseline PSA doubling time values exceeded the enrollment threshold of less than 9 months owing to discrepancies in the PSA values captured in the case-report forms as compared with the values used for the enrollment calculation.

ed in a lower risk of castration resistance and resumption of any hormonal therapy than leuprolide alone. No substantial difference was noted in the time to first deterioration of FACT-P total scores in the combination group or the monotherapy group as compared with the leuprolide-alone group.

Death occurred in 33 patients in the combination group, 55 patients in the leuprolide-alone group, and 42 patients in the monotherapy group. The 5-year overall survival was 92.2% (95% CI, 88.7 to 94.7) in the combination group, 87.2% (83.0 to 90.4) in the leuprolide-alone group, and 89.5% (85.6 to 92.4) in the monotherapy group. At the time of an interim analysis of overall survival, 130 of 271 patients (48.0%) had died. The hazard ratio for death in the comparison of enzalutamide plus leuprolide with leuprolide alone was 0.59 (95% CI, 0.38 to 0.91; P=0.02 [interim efficacy boundary, P≤0.0001]), and the hazard ratio for death in the comparison of enzalutamide monotherapy with leuprolide alone was 0.78 (95% CI, 0.52 to 1.17; P=0.23) (Fig. S4). Death due to disease progression occurred in 12 patients (3.4%) in the combination group, 22 patients (6.1%) in the leuprolide-alone group, and 19 patients (5.4%) in the monotherapy group.

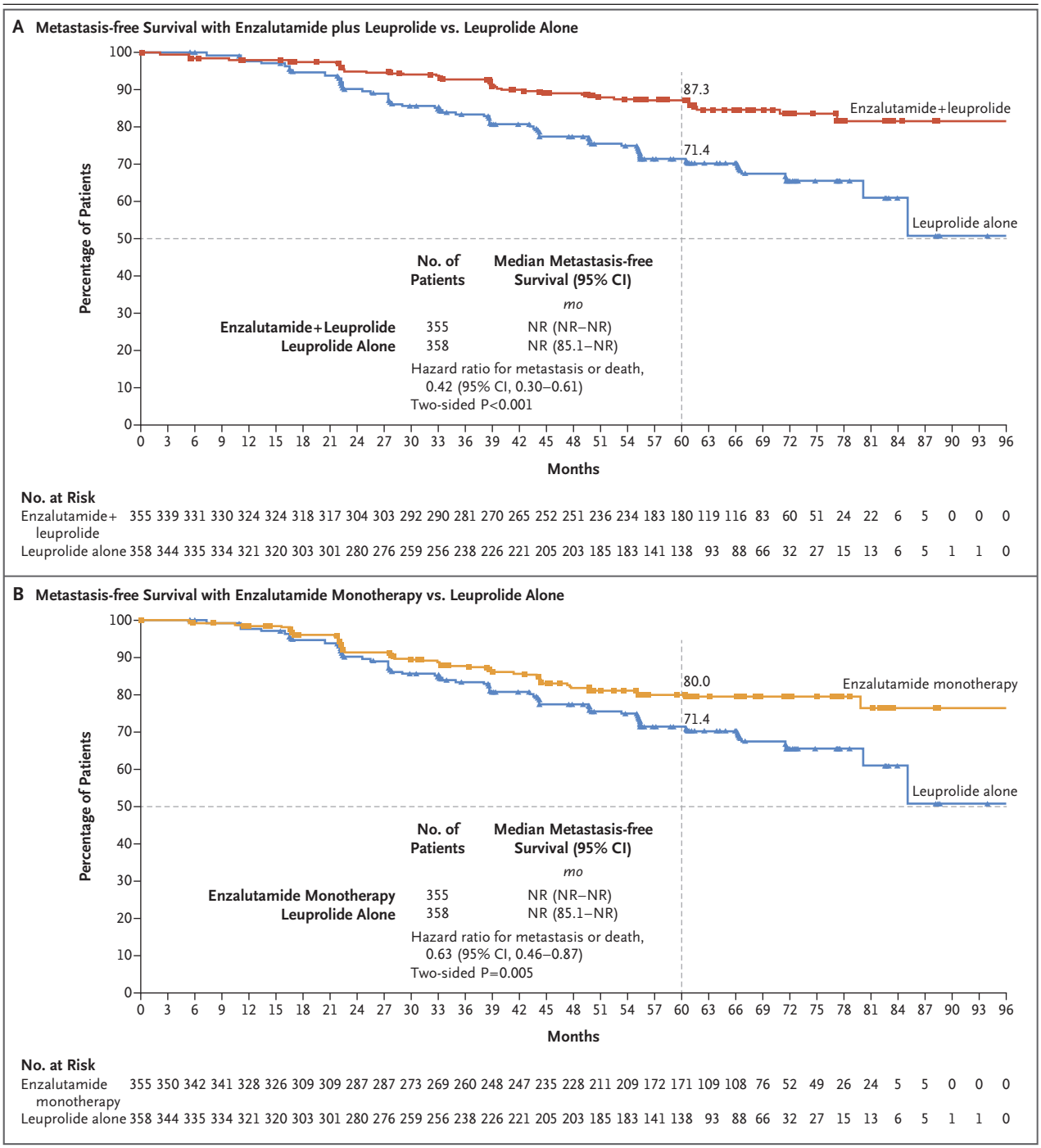
Patients whose PSA levels reached undetectable levels (<0.2 ng per milliliter) at week 36 had their treatment suspended (Fig. S5). In the combination group, 90.9% of the patients (321 of 353 patients) had treatment suspended for a median of 20.2 months (range, 5.7 to 87.9); 43.9% of these patients did not receive treatment for more than 24 months. A total of 67.8% of the patients (240 of 354 patients) in the leuprolide-alone group had treatment suspended (median, 16.8 months [range, 3.4 to 83.0]); 32.1% did not receive treatment for more than 24 months. In the monotherapy group, 85.9% of the patients (304 of 354 patients) had treatment suspended for a median of 11.1 months (range, 2.3 to 84.9); 20.4% did not receive treatment for 24 months.

In the monotherapy group, as compared with baseline, the mean testosterone levels were supraphysiologic until treatment suspension at week 37. When treatment was resumed, testosterone levels remained high. In contrast, during treatment suspension in the combination group and the leuprolide-alone group, testosterone recovered slightly, but not to baseline levels. Once treatment resumed in both groups, testosterone levels were reduced (Fig. S6).

SAFETY

The median duration of treatment, excluding treatment suspension, in all groups was 38.7 months (range, 0.1 to 88.9). No new safety signals were reported. More than 97% of the patients in all the groups had an adverse event (Table 2). The most common adverse events (occurring in ≥10% of patients) in the combination group and the leuprolide-alone group were hot flashes and fatigue. The most common adverse events (occurring in ≥30% of the patients) in the monotherapy group were gynecomastia, hot flashes, and fatigue. These events were considered by the investigator to be related to treatment; most were less than grade 3 in severity. Nipple pain and breast tenderness were more common in the monotherapy group than in the combination group and the leuprolide-alone group. Nipple pain occurred in 3.1% of the patients in the combination group, 1.1% in the leuprolide-alone group, and 15.3% in the monotherapy group. Breast tenderness occurred in 1.4% of the patients in the combination group, 1.1% in the leuprolide-alone group, and 14.4% in the monotherapy group. Treatment was discontinued due to adverse events in 73 of 353 patients (20.7%) in the combination group, 36 of 354 patients (10.2%) in the leuprolide-alone group, and 63 of 354 patients (17.8%) in the monotherapy group. The most common adverse event leading to discontinuation was fatigue (in 12 patients [3.4%] in the combination group, 4 patients [1.1%] in the leuprolide-alone group, and 8 patients [2.3%] in the monotherapy group). In all the groups, adverse events leading to death were not considered by the site investigators to be related to treatment.

Clustered adverse events (events of similar type grouped together) of special interest were reported in 304 patients (86.1%) in the combination group, in 286 (80.8%) in the leuprolide-alone group, and in 300 (84.7%) in the monotherapy group (Table S3). The most common clustered adverse events of special interest that occurred in at least 10% of the patients in all the groups were fatigue, falls, fractures, hypertension, and musculoskeletal events; most were less



than grade 3 in severity. Fractures were more common in the combination group (65 patients [18.4%]) than in the leuprolide-alone group (48 patients [13.6%]) and the monotherapy group (39 patients [11.0%]). Cognitive and memory impairment occurred in 53 patients (15.0%) in the combination group, in 23 patients (6.5%) in the leuprolide-alone group, and in 50 patients (14.1%) in the monotherapy group. Seizures were reported in 4 patients (1.1%) in the combination group, in no patients in the leuprolide-alone group, and in 3 patients (0.8%) in the monotherapy group.

Figure 2 (facing page). Metastasis-free Survival (Intention-to-Treat Population).

Shown are the Kaplan–Meier curves for metastasis-free survival, defined as the time from randomization to the date of earliest evidence of imaging-based progression or death from any cause, in the combination group as compared with the leuprolide-alone group (Panel A) and in the monotherapy group as compared with the leuprolide-alone group (Panel B). To calculate the hazard ratios, we used a Cox regression model with trial group as the only covariate, with stratification according to PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. A hazard ratio of less than 1 indicated superiority to leuprolide alone. The two-sided P values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. The duration of follow-up was defined as the time from randomization to the date of data cutoff. The median follow-up was 60.7 months in the combination group, 60.6 months in the leuprolide-alone group, and 60.7 months in the monotherapy group. The squares and triangles in each panel indicate censored data. The values at the vertical dashed line in each panel represent the metastasis-free survival at 5 years. NR denotes not reached.

DISCUSSION

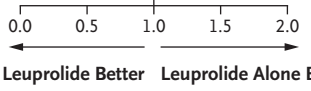
Patients who have biochemical recurrence after primary therapy for localized prostate cancer with a PSA doubling time of less than 9 months are at high risk for metastasis and death related to prostate cancer.[2,8,9] On the basis of the efficacy of enzalutamide that has been shown in metastatic hormone-sensitive prostate cancer,[11-14] we hypothesized that enzalutamide plus leuprolide or enzalutamide monotherapy could prolong metastasis-free survival among patients with high-risk biochemical recurrence. Metastasis-free survival has been shown to correlate with overall survival,[27,28] and the transition to metastatic disease has been associated with pain and disease-related morbidity.[29] After a median follow-up of 60.7 months, enzalutamide plus leuprolide and enzalutamide monotherapy significantly improved metastasis-free survival as compared with leuprolide alone, with no worsening in the time to decline in FACT-P total scores. The magnitude of risk reduction with respect to metastasis or death in this trial was consistent with the additive benefit of treatment intensification in metastatic hormone-sensitive prostate cancer[11-14] and nonmetastatic[30] and metastatic castration-resistant prostate cancer.[15,16] The data from this trial confirm findings in previous phase 3 trials,[12-16,30] in which patients treated with the androgen-receptor inhibitor enzalutamide and androgen-deprivation therapy derived clinically meaningful benefit relative to androgen-deprivation therapy alone.

Phase 2 trials of enzalutamide monotherapy have shown marked declines in PSA levels.[22-25] This phase 3 trial compared hormonal therapy with androgen-deprivation therapy in combination and alone. As compared with leuprolide alone, enzalutamide monotherapy showed a significant and clinically meaningful improvement in metastasis-free survival as well as significant improvements in other key secondary outcomes. The safety profile of enzalutamide was consistent with that shown in previous studies of enzalutamide monotherapy. Although the overall frequency of adverse events was similar in all the trial groups, the nature of the adverse events differed. Specifically, as compared with patients in the combination group and those in the leuprolide-alone group, patients who received enzalutamide monotherapy had fewer hot flashes, but gynecomastia, nipple pain, and breast tenderness were more common; most events were mild-to-moderate in severity. There was no substantial difference in the time to decline in FACT-P total scores in the combination group and the monotherapy group as compared with the leuprolide-alone group, a finding that indicates that adverse events did not affect the overall quality of life. Comprehensive results for patient-reported outcomes from the current trial have been published separately.[31]

The safety profile of enzalutamide was consistent with the known side effects in patients with advanced prostate cancer. Although patients with a history of seizure were excluded, seizures were more common in the combination group than in the leuprolide-alone group; however, the overall rate was low (1.1%; 0.3% per 100 patient-years) and was similar to that in previous trials of enzalutamide.[32] The risk of rash or hepatic disorders was not increased, unlike in some studies of newer hormonal therapies.[33,34] Rates of discontinuation due to adverse events were similar to those in previous enzalutamide studies.[32]

A Secondary End Points, Enzalutamide plus Leuprolide vs. Leuprolide Alone

End Point	Enzalutamide+ Leuprolide (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide+ Leuprolide (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival (primary end point)	355	358	45	92	0.42 (0.30–0.61)	<0.001
Overall survival	355	358	33	55	0.59 (0.38–0.91)	0.02
PSA progression	355	358	8	93	0.07 (0.03–0.14)	<0.001
First use of new antineoplastic therapy	355	358	58	140	0.36 (0.26–0.49)	<0.001
Distant metastasis	355	358	30	59	0.44 (0.28–0.69)	
Resumption of any hormonal therapy	321	240	256	217	0.69 (0.58–0.83)	
Castration resistance	355	358	14	120	0.09 (0.05–0.16)	
Symptomatic progression	355	358	104	169	0.55 (0.43–0.70)	
First symptomatic skeletal event	355	358	9	32	0.26 (0.13–0.55)	
First deterioration in FACT-P total score	355	358	257	248	1.14 (0.95–1.36)	



B Secondary End Points, Enzalutamide Monotherapy vs. Leuprolide Alone

End Point	Enzalutamide Monotherapy (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide Monotherapy (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival	355	358	63	92	0.63 (0.46–0.87)	0.005
Overall survival	355	358	42	55	0.78 (0.52–1.17)	0.23
PSA progression	355	358	37	93	0.33 (0.23–0.49)	<0.001
First use of new antineoplastic therapy	355	358	84	140	0.54 (0.41–0.71)	<0.001
Distant metastasis	355	358	40	59	0.61 (0.41–0.92)	
Resumption of any hormonal therapy	304	240	279	217	1.66 (1.38–1.98)	
Symptomatic progression	355	358	117	169	0.62 (0.49–0.79)	
First symptomatic skeletal event	355	358	14	32	0.42 (0.23–0.79)	
First deterioration in FACT-P total score	355	358	263	248	1.17 (0.98–1.39)	

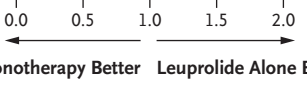


Figure 3. Secondary End Points (Intention-to-Treat Population).

The hazard ratios were calculated on the basis of a Cox regression model with trial group as the only covariate, with stratification according to PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. A hazard ratio of less than 1 indicated superiority to leuprolide alone. The two-sided P values were calculated on the basis of a log-rank test, with stratification according to PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. Metastasis-free survival in the monotherapy group, the time to PSA progression, the time to first use of new antineoplastic therapy, and overall survival were key secondary end points; the analyses of non–key secondary end points are descriptive. The duration of follow-up was defined as the time from randomization to the date of data cutoff. The median follow-up for metastasis-free survival was 60.7 months in the combination group, 60.6 months in the leuprolide-alone group, and 60.7 months in the monotherapy group. The median follow-up for overall survival was 66.0 months in the combination group, 66.2 months in the leuprolide-alone group, and 64.5 months in the monotherapy group. FACT-P denotes Functional Assessment of Cancer Therapy–Prostate.

Both short- and long-term toxic effects can affect androgen-deprivation strategies; therefore, an important consideration for this trial was a prespecified treatment suspension at week 37 if PSA levels were undetectable. Previous studies have shown that this timeframe was better for PSA nadir with hormonal treatment.[35-37] More patients in the combination group (90.9%) and the monotherapy group (85.9%) than in the leuprolide-alone group (67.8%) had treatment suspended. However, the median duration of treatment suspension in the monotherapy group was shorter than that in the combination group and the leuprolide-alone group (20.2 months in

Table 2. Adverse Events (Safety Population).*

Event	Enzalutamide + Leuprolide (N = 353)		Leuprolide Alone (N = 354)		Enzalutamide Monotherapy (N = 354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
Hot flash	243 (68.8)§	2 (0.6)	203 (57.3)§	3 (0.8)	77 (21.8)§	1 (0.3)
Fatigue	151 (42.8)§	12 (3.4)	116 (32.8)§	5 (1.4)	165 (46.6)§	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	0
Constipation	46 (13.0)	0	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	7 (2.0)	44 (12.4)	3 (0.8)	45 (12.7)	6 (1.7)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Pain in arm or leg	41 (11.6)	1 (0.3)	36 (10.2)	0	40 (11.3)	0
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	1 (0.3)	37 (10.5)	0	41 (11.6)	0
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	2 (0.6)	28 (7.9)	1 (0.3)	36 (10.2)	3 (0.8)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	1 (0.3)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	1 (0.3)
Peripheral edema	27 (7.6)	0	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	3 (0.8)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

* Patients in the safety population were evaluated according to the treatment they received. Shown are adverse events that occurred from the time of the first dose of the trial regimen through 30 days after permanent discontinuation. The median duration of treatment, excluding treatment suspension, was 32.4 months (range, 0.1 to 83.4) among patients who received enzalutamide plus leuprolide, 35.4 months (range, 0.7 to 85.7) among patients who received leuprolide alone, and 45.9 months (range, 0.4 to 88.9) among patients who received enzalutamide monotherapy. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Percentages may not total 100 because of rounding.

† Adverse events leading to death were grade 5 adverse events; none were considered by the investigator to be related to treatment.

‡ The most common adverse events include those that occurred in at least 10% of the patients.

§ These events were among the most common treatment-related adverse events (occurring in ≥30% of the patients).

the combination group, 16.8 months in the leuprolide-alone group, and 11.1 months in the monotherapy group). The shorter duration of treatment suspension with enzalutamide monotherapy was probably due to the lack of testosterone suppression; testosterone suppression with androgen-deprivation therapy may be maintained for months or years after cessation of treatment.[38] Resumption to eugonadal testosterone levels and the clinical effect of enzalutamide monotherapy are being analyzed.

Data on overall survival were immature. Underrepresentation of non-White patients (<20%) was another limitation. Although 10% of the patients enrolled in North America were Black, less than 5% of the patients in the global trial population were Black. Whether results from predominantly White patients can be extrapolated to other races is unclear, although real-world studies suggest that Black men have similar if not better responses to new hormonal therapies as compared with White men.[39,40] Moreover, the long-term consequences of prolonged exposure to enzalutamide on tolerance of subsequent treatments are unknown.

The results of this trial showed that enzalutamide had clinical benefits in patients with high-risk biochemical recurrence after definitive treatment. No new safety signals were observed. Enzalutamide plus leuprolide and enzalutamide monotherapy both resulted in significantly longer metastasis-free survival and a longer time to PSA progression and receipt of next antineoplastic therapy than leuprolide alone while maintaining overall quality of life.

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APPENDIX

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