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Study Need and Importance: Patients with biochemical recurrence after definitive therapy for prostate cancer and a short PSA doubling time are at high risk for metastasis and mortality. Enzalutamide, a next-generation androgen receptor pathway inhibitor, has greater potency than some earlier agents. In the phase 3 EMBARK trial, enzalutamide monotherapy demonstrated superior metastasis-free survival compared with leuprolide alone. This analysis further evaluated the efficacy and tolerability of enzalutamide monotherapy compared with leuprolide alone.

What We Found: Enzalutamide monotherapy improved several prespecified outcomes compared with leuprolide alone. Enzalutamide monotherapy demonstrated greater 5-year probabilities for remaining free from distant metastasis (86.8% vs 81.5%), free from symptomatic progression (66.6% vs 53.3%), and free from first symptomatic skeletal event (95.8% vs 91.5%; Figure). Overall survival was numerically higher with enzalutamide monotherapy (89.5% vs 87.2%), but differences were not statistically significant. Sexual health was better preserved with enzalutamide monotherapy (HR 0.76; $P = .008$). Patients who received enzalutamide monotherapy resumed hormonal therapy sooner after treatment suspension (HR 1.6; $P < .0001$). Breast-related adverse events were more common among patients who received enzalutamide monotherapy than patients who received leuprolide alone.

Limitations: The monotherapy arm was open label, which may have influenced reporting of toxicities and patient-reported outcomes. Conventional imaging was used according to the protocol and clinical standards at the time, which may underestimate the presence of metastases compared with next-generation imaging.

Interpretation for Patient Care: Enzalutamide monotherapy represents an important treatment option for patients with prostate cancer and high-risk biochemical recurrence, delaying progression and skeletal events, and better preserving sexual health compared with leuprolide alone. Clinicians should weigh these benefits against the earlier resumption of hormonal therapy after suspension and potential breast-related adverse effects. Shared decision-making should consider patient preferences, quality of life, and treatment goals.

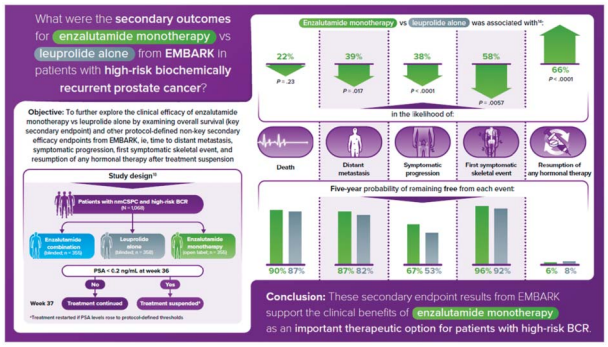

Figure. Study overview. BCR indicates biochemical recurrence; nmCSPC, nonmetastatic castration-sensitive prostate cancer.

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Enzalutamide Monotherapy for the Treatment of Prostate Cancer With High-Risk Biochemical Recurrence: EMBARK Secondary End Points

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Purpose: Primary analysis of the phase 3 EMBARK trial reported efficacy and safety outcomes for enzalutamide monotherapy in patients with high-risk biochemical recurrence. Here, we report secondary end points for enzalutamide monotherapy vs leuprolide alone.

Materials and Methods: Patients were randomized (1:1:1) to enzalutamide plus leuprolide, leuprolide alone, or enzalutamide monotherapy. Overall survival was a key secondary end point; non-key secondary end points were time to: distant metastasis, symptomatic progression, first symptomatic skeletal event, and resumption of any hormonal therapy. Sexual health was assessed using the Quality of Life Questionnaire–Prostate 25. Time-to-event end points were summarized using Kaplan-Meier methods with nominal *P* values.

Results: Five-year probability rates (95% CI) for enzalutamide monotherapy vs leuprolide alone were: overall survival, 89.5% (85.6-92.4) vs 87.2% (83.0-90.4); time to remaining free from distant metastasis, 86.8% (82.3-90.2) vs 81.5% (76.3-85.7); symptomatic progression, 66.6% (61.2-71.4) vs 53.3% (47.6-58.6); and first symptomatic skeletal event, 95.8% (92.9-97.6) vs 91.5% (87.8-94.1). After treatment suspension, the 5-year probability rate (95% CI) of remaining free from resumption of any hormonal therapy for leuprolide alone vs enzalutamide monotherapy was 7.8% (4.4-12.3) vs 5.6% (3.3-8.8). Sexual health was better preserved in patients treated with enzalutamide monotherapy than leuprolide

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alone (HR 0.76; 95% CI: 0.62-0.94; $P = .008$). After discontinuation, most patients were subsequently treated with hormonal therapies in both groups.

Conclusions: Secondary end point results support enzalutamide monotherapy as a potential option to improve efficacy and preserve sexual health vs leuprolide alone for patients with high-risk biochemical recurrence.

Trial Registration: ClinicalTrials.gov Identifier: NCT02319837

Key Words: recurrence, metastasis, enzalutamide, leuprolide acetate, prostate cancer

Approximately 20% to 50% of patients who receive primary definitive treatment for prostate cancer (PC) will relapse within 10 years, with recurrent disease characterized by rising levels of PSA.[1-3] Patients with high-risk biochemical recurrence (hrBCR) have increased risk of distant metastasis, PC-specific mortality, and overall mortality.[1,4,5]

Monotherapy with the first-generation, nonsteroidal, androgen receptor blocker, bicalutamide, has been widely used to treat advanced PC.[6] Bicalutamide has demonstrated a favorable safety profile and improvements in quality of life (QoL) but has not shown statistically significant differences in overall survival (OS) compared with androgen deprivation therapy (ADT) in patients with locally advanced PC.[7,8] Enzalutamide is a next-generation androgen receptor pathway inhibitor (ARPI) with ~10-fold higher affinity for the androgen receptor compared with bicalutamide and, moreover, lacks the partial agonist activity attributed to bicalutamide at the androgen receptor.[9-11] In phase 2 trials, enzalutamide monotherapy reduced PSA levels by $\geq$ 80% in patients with hrBCR,[12,13] which provided an impetus for further clinical studies.

In patients with hrBCR, defined as a PSA doubling time (PSADT) of $\leq$ 9 months, and who did not show evidence of distant metastatic disease on conventional imaging, the randomized, phase 3

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Conflict of Interest Disclosures: Dr Shore reports consulting for or receiving research funding from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, BMS, Dendreon, Exact Sciences, Ferring, FerGene, Johnson & Johnson Innovative Medicine (formerly Janssen), MDx Health, Merck, Nymox, Pfizer, Sanofi, Sumitomo Pharma America, Inc (formerly Myovant Sciences), and Tolmar. Dr De Giorgi reports consulting for Amgen, Astellas Pharma Inc, AstraZeneca, Bayer, Bristol Myers Squibb, Esai, Ipsen, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck KGaA, Merck Sharp & Dohme, Novartis, and Pfizer Inc; receiving travel expenses from AstraZeneca, Ipsen, and Pfizer Inc; and having other financial or non-financial interests in AstraZeneca, Roche, and Sanofi. Dr Tutrone reports being an advisory board member for Bayer; and receiving speaker honoraria from Astellas Pharma Inc, Exosome Diagnostics GmbH, Sumitomo Pharma America, Inc (formerly Myovant Sciences), and Pfizer Inc; receiving institutional research funding from Arvinas Pharm, Astellas Pharma, AstraZeneca, Bayer, BioTechne, Dendreon, ESSA Pharmaceuticals, Johnson & Johnson Innovative Medicine (formerly Janssen), Lilly, Merck, Nymox, Point Biopharma, Pfizer Inc, and Sumitomo Pharma America, Inc (formerly Myovant Sciences). Dr Bailen reports consulting and receiving honoraria from Astellas Pharma Inc, Auxilium, Bayer, Dendreon, Johnson & Johnson Innovative Medicine (formerly Janssen), and Sanofi; being on the speakers' bureau for Astellas Pharma Inc, Auxilium, Bayer, Dendreon, and Johnson & Johnson Innovative Medicine (formerly Janssen); receiving institutional research funding from Astellas Pharma Inc, Bayer, Dendreon, Johnson & Johnson Innovative Medicine (formerly Janssen), Medivation, and Takeda Oncology; and receiving travel, accommodation, and expenses from Astellas Pharma Inc, Bayer, Dendreon, and Valeant/Dendreon. Drs Roos, Kliment, and Marx report nothing to disclose. Dr Karsh reports consulting for Astellas Pharma Inc, AstraZeneca, Aurora Oncology, Bayer, Daiichi Sankyo, Dendreon, Ferring, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck, Pfizer Inc, Sanofi, Specialty Networks/UroGPO, and Vaxiion Therapeutics; being on the speakers' bureau for Astellas Pharma Inc, AstraZeneca, Bayer, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck, Sumitomo Pharma America, Inc (formerly Myovant Sciences), and Pfizer Inc; receiving institutional research funding from Astellas Pharma Inc, AstraZeneca, Bayer, BioExcel, Bristol Myers Squibb, Dendreon, Exact Sciences, Ipsen, FKD Therapies, KDX Pharma, Immunis.AI, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck, Sumitomo Pharma America, Inc (formerly Myovant Sciences), Pfizer Inc, and Tavanta Therapeutics. Dr Ramirez-Backhaus reports consulting and receiving honoraria from Astellas Pharma Inc, Bayer, and Johnson & Johnson Innovative Medicine (formerly Janssen); receiving payment for expert testimony from Johnson & Johnson Innovative Medicine (formerly Janssen); and receiving travel, accommodation, and expenses from Astellas Pharma Inc and Johnson & Johnson Innovative Medicine (formerly Janssen). Dr Uchio reports receiving institutional research funding and consulting fees from Astellas Pharma Inc, AstraZeneca, Bayer, Blue Earth Diagnostics, CG Oncology, Dendreon Pharmaceuticals LLC, Exact Sciences, Lantheus, Myriad, Johnson & Johnson Innovative Medicine (formerly Janssen) Oncology, Merck Sumitomo Pharma America, Inc (formerly Myovant Sciences), Pfizer Inc, and Seagen. Dr Supiot reports receiving honoraria from Astellas Pharma Inc, AstraZeneca, Bayer, Ferring, Ipsen, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck Sharp & Dohme, Novartis AAA, and Takeda; and receiving institutional research funding from Astellas Pharma Inc, AstraZeneca, Bayer, Boston Scientific, Johnson & Johnson Innovative Medicine (formerly Janssen), Novartis AAA, and RefleXion Medical. Dr Tang reports being an employee of and shareholder in Pfizer Inc, the study sponsor. Mr Rosbrook and Dr Tarazi report being former employees of and shareholders in Pfizer Inc, the study sponsor. Drs Haas and Rosales report being employees of Astellas Pharma Inc. Dr Zohren reports being a former employee of and shareholder in Pfizer Inc, a study sponsor; and owning stock in Allovir. Dr Freedland reports consulting for Astellas Pharma, AstraZeneca, Bayer, Dendreon, Eli Lilly, Exact Sciences, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck, Novartis, Pfizer Inc, Sanofi, and Sumitomo Pharma America, Inc (formerly Myovant Sciences).

Ethics Statement: The appropriate Institutional Review Board or independent ethics committee at participating study sites approved its design and amendments. This study received Institutional Review Board approval (IRB No. HSCMS-19-0518). The study was conducted according to principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was provided by all patients.

Author Contributions:

Conception and design: Shore, De Giorgi, Haas, Zohren, Freedland.

Collection, assembly, or interpretation of data: Shore, De Giorgi, Tutrone, Bailen, Roos, Kliment, Marx, Karsh, Ramirez-Backhaus, Uchio, Supiot, Tang, Rosbrook, Haas, Rosales, Tarazi, Freedland.

Critical revision of the manuscript for scientific and factual content: All authors.

Drafting the manuscript: All authors.

Statistical analysis: Tang, Rosbrook, Rosales, Tarazi.

Supervision: Shore, Freedland. Dr Tang had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability: Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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EMBARK trial demonstrated clinically meaningful and statistically superior metastasis-free survival (MFS) for patients who received enzalutamide plus leuprolide (enzalutamide combination) compared with leuprolide alone (HR 0.42; 95% CI: 0.30-0.61; $P < .0001$), while maintaining QoL.[14,15] A key secondary end point, MFS for patients who received enzalutamide monotherapy, was also clinically meaningful and statistically superior to leuprolide alone (HR 0.63; 95% CI: 0.46-0.87; $P = .0049$).[14] Furthermore, patients who received enzalutamide monotherapy showed significant reductions in the risk of PSA progression (HR 0.33; 95% CI: 0.23-0.49) and had prolonged time to first use of new antineoplastic therapy (HR 0.54; 95% CI: 0.41-0.71) compared with leuprolide alone ($P < .0001$ for both).[14] Based on the primary results of EMBARK, enzalutamide was approved by US and European regulatory agencies as the only ARPI for use with or without ADT for the treatment of nonmetastatic castration-sensitive PC at high risk for metastases.[16,17] Most notably, this heralds the first time that an ARPI has been approved as monotherapy for PC. Thus, EMBARK represents the first randomized phase 3 trial to evaluate an ARPI as monotherapy in patients with hrBCR, an approach that offers potential benefits over traditional castration-based approaches.[14]

To further explore the clinical efficacy of enzalutamide, we present the findings for OS (key secondary end point) and other protocol-defined non-key secondary efficacy end points for enzalutamide monotherapy. In the overall population of EMBARK, which has already been reported, enzalutamide monotherapy vs leuprolide alone demonstrated superior MFS, a composite end point that includes disease progression and mortality.[14] Here, we present MFS results in prespecified subgroups, as well as further analyses of OS and additional protocol-defined secondary end points. Secondary efficacy end points for patients who received enzalutamide combination are reported in a companion manuscript.

MATERIALS AND METHODS

Study Design and Patients

EMBARK is a global, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial.[18] The EMBARK study design and methods have been reported previously.[14,18] Patients with hrBCR (defined as a PSADT of $\leq$9 months) who did not show evidence of distant metastatic disease on conventional imaging were randomized (1:1:1) to enzalutamide combination (double blind), enzalutamide monotherapy (open label), or leuprolide alone (double blind). Randomization was stratified by the screening PSA level ($\leq$10 ng/mL vs >10 ng/mL), PSADT ($\leq$3 months vs >3 months and $\leq$9 months), and prior hormonal therapy (yes or no). If the PSA level was < 0.2 ng/mL at week 36, treatment was suspended at week 37 and restarted at protocol-defined PSA thresholds. Treatment was restarted if subsequent central laboratory PSA values increased to $\geq$ 2.0 ng/mL for patients with prior prostatectomy or $\geq$ 5.0 ng/mL for patients without prostatectomy.

Blinded independent central review using conventional CT or MRI, and whole-body radionuclide bone scans to identify bone disease were used for radiographic assessment of disease. Baseline evaluations were conducted within 4 weeks of initiation of the study treatment, and patients were assessed for progression approximately every 6 months after randomization. Patient-reported outcomes (PROs) were assessed using the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) at baseline and every 12 weeks until disease progression or the completion of data gathering.[15]

Outcomes

End points reported include interim results for OS (key secondary end point) and non-key secondary end points, including time to distant metastasis, symptomatic progression, first symptomatic skeletal event, and resumption of any hormonal therapy following treatment suspension. Given that symptomatic progression is a composite end point, we examined which of the various individual end points each patient met. As a result of differences observed between PRO end points for enzalutamide monotherapy vs leuprolide alone, we further explored any potential benefits on sexual activity in a post hoc analysis. We also report subsequent antineoplastic therapies initiated following study treatment discontinuation. In addition, we report the HRs for MFS in protocol-defined subgroups, data that have not previously been reported. Definitions of secondary efficacy and PRO end points are presented in Supplementary Table 1 (https://www.jurology.com).

Statistical Analysis

Treatment effect by HR and associated 95% CI was estimated by stratified Cox regression models for the comparisons between treatment arms, and time-to-event end points were summarized using the Kaplan–Meier method. The median, quartiles, and probabilities of an event at specific time points were estimated by the Kaplan–Meier method in each treatment arm, respectively. For all efficacy time-to-event end points, P values from a stratified log-rank test were used for treatment comparisons and considered nominal. PRO analyses using the QLQ-PR25 instrument were conducted, as previously described.[15] Analyses of non-key secondary end points reported in this manuscript were not alpha protected per study design. The prespecified sample size requirement for subgroup analyses was at least 10 events. The data cutoff was January 31, 2023.

RESULTS

Primary results of the EMBARK trial have been previously reported.[14] In brief, 1068 patients were enrolled in EMBARK between December 2014 and August 2018, and were randomized (1:1:1) to receive enzalutamide combination (n = 355), enzalutamide monotherapy (n = 355), or leuprolide alone (n = 358; Figure 1).[14]

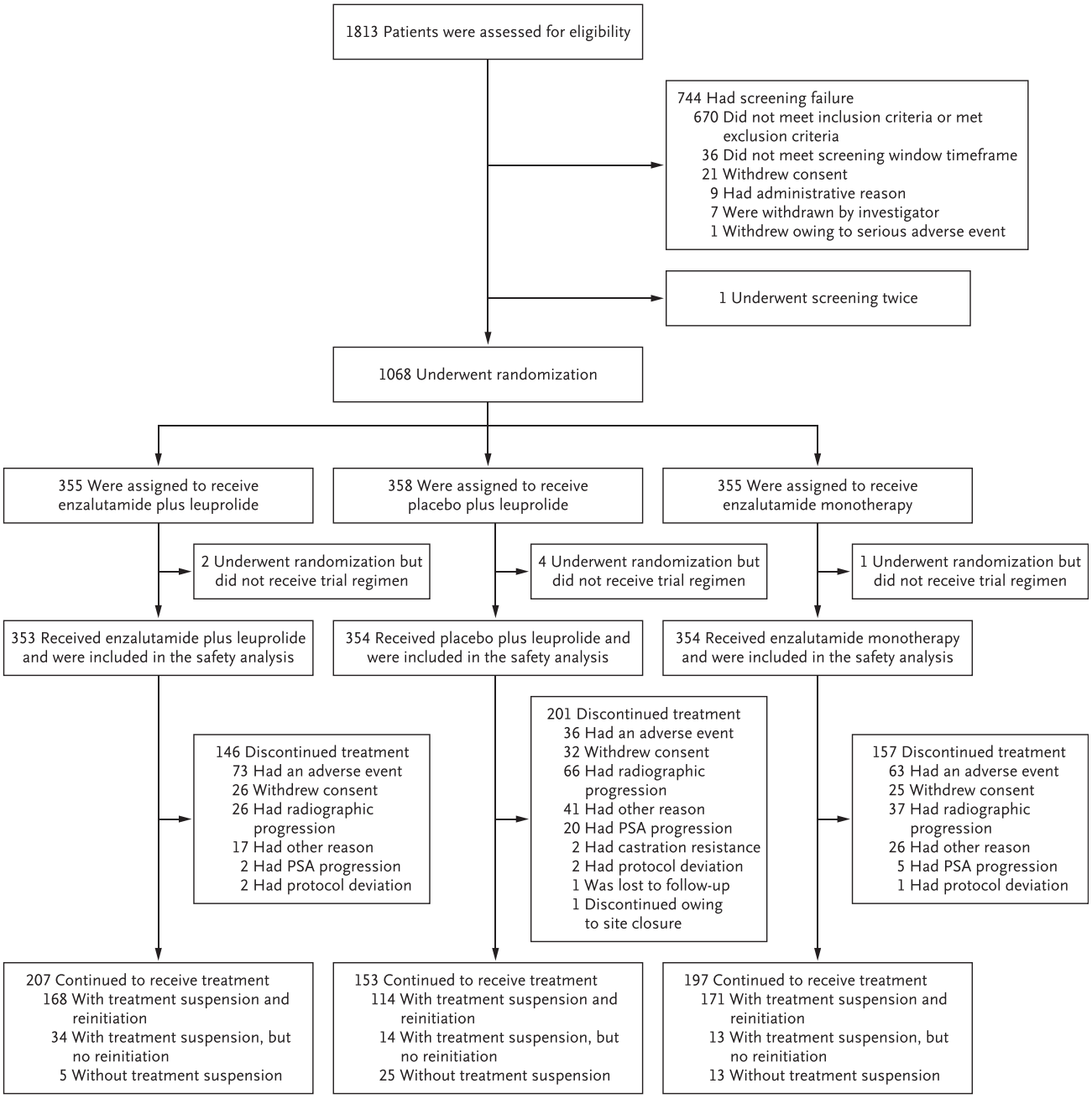

Figure 1. Trial profile. Copyright © (2023) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[19]

After treatment discontinuation, fewer patients treated with enzalutamide monotherapy (n = 84 [23.7%]) received subsequent antineoplastic therapy compared with leuprolide alone (n = 139 [38.8%]; Table 1). Hormonal therapies were the most common subsequent treatment (n = 76 [21.4%] vs n = 132 [36.9%], respectively), followed by chemotherapeutic agents (n = 18 [5.1%] vs n = 38 [10.6%], respectively; Table 1).

OS

At interim OS analysis, the median follow-up was 65 months (5 years, 5 months). As described previously, patients who received enzalutamide monotherapy trended in favor of increased OS compared with patients who received leuprolide alone.[14] However, the 5-year probability rate (95% CI) of OS was similar: 89.5% (85.6-92.4) for enzalutamide monotherapy and 87.2% (83.0-90.4) for leuprolide alone (Figure 2, A).

Time to Distant Metastasis

At the data cutoff, 40 patients treated with enzalutamide monotherapy (11.3%) and 59 patients treated with leuprolide alone (16.5%) experienced distant metastases (Table 2). Bone was the most common site

Table 1. *Subsequent Antineoplastic Therapy After Treatment Discontinuation in the Enzalutamide Monotherapy and Leuprolide Alone Groups (Intention-to-Treat Population)*

Treatments,[a] No. (%)	Enzalutamide monotherapy (n = 355)	Leuprolide alone (n = 358)
Patients taking ≥1 subsequent antineoplastic therapies, total	84 (23.7)	139 (38.8)
Chemotherapy	18 (5.1)	38 (10.6)
Docetaxel	15 (4.2)	31 (8.7)
Cabazitaxel	7 (2.0)	14 (3.9)
Cyclophosphamide	1 (0.3)	4 (1.1)
Corticosteroids	3 (0.8)	10 (2.8)
Prednisone[b]	3 (0.8)	10 (2.8)
Drugs for treatment of bone diseases	5 (1.4)	3 (0.8)
Denosumab	4 (1.1)	3 (0.8)
Hormonal therapy	76 (21.4)	132 (36.9)
Leuprorelin	44 (12.4)	79 (22.1)
Bicalutamide	20 (5.6)	18 (5.0)
Abiraterone	15 (4.2)	37 (10.3)
Triptorelin	13 (3.7)	9 (2.5)
Degarelix	12 (3.4)	6 (1.7)
Enzalutamide	11 (3.1)	44 (12.3)
Goserelin	9 (2.5)	9 (2.5)
Apalutamide	4 (1.1)	6 (1.7)
Darolutamide	3 (0.8)	15 (4.2)
Immunostimulants	5 (1.4)	11 (3.1)
Sipuleucel-T	5 (1.4)	11 (3.1)
Therapeutic radiopharmaceuticals	3 (0.8)	6 (1.7)
Radium-223 dichloride	1 (0.3)	6 (1.7)
Uncoded or blinded therapy	1 (0.3)	13 (3.6)

The data cutoff was January 31, 2023.
[a]Therapeutic class is based on WHODrug Global, version March 2022.[20]
[b]Systemic prednisone was reported for some patients with other antineoplastic therapy as a combination regimen.

of distant metastasis for both treatment groups. Soft tissue distant metastases (visceral only, nonvisceral only, or both visceral and nonvisceral) were proportionally lower with enzalutamide monotherapy (n = 15 [4.2%]) compared with leuprolide alone (n = 30 [8.4%]). The 5-year rate (95% CI) of remaining free from distant metastases was 86.8% (82.3-90.2) for enzalutamide monotherapy and 81.5% (76.3-85.7) for leuprolide alone. Patients treated with enzalutamide monotherapy had a 39% reduction in their risk of distant metastasis compared with leuprolide alone (Figure 2, B; HR 0.61; 95% CI: 0.41-0.92; $P = .017$); medians were not reached in either group.

Time to Symptomatic Progression

Following treatment with enzalutamide monotherapy and leuprolide alone, 117 (33.0%) and 169 (47.2%) patients, respectively, experienced symptomatic progression. Most patients who experienced symptomatic progression initiated a new systemic antineoplastic therapy (monotherapy, 21.7%; leuprolide alone, 32.1%). In contrast, fewer initiated opiates (monotherapy, 9.9%; leuprolide alone, 12.0%) or had a skeletal-related event (monotherapy, 1.4%; leuprolide alone, 3.1%). Notably, the percentage of patients that met any of the 3 individual end points was lower with monotherapy vs leuprolide alone (monotherapy, 33.0%; leuprolide alone, 47.2%). The 5-year rate (95% CI) of remaining free from symptomatic progression was 66.6% (61.2-71.4) for enzalutamide monotherapy and 53.3% (47.6-58.6) for leuprolide alone (Figure 2, C), with a 38% reduction in risk of symptomatic progression with enzalutamide monotherapy compared with leuprolide alone (HR 0.62; 95% CI: 0.49-0.79; $P < .0001$). The median (95% CI) time to symptomatic progression was not reached for enzalutamide monotherapy (83.6–not reached) and was 63.8 months (56.4-74.9) for leuprolide alone.

Time to First Symptomatic Skeletal Event

Fourteen patients treated with enzalutamide monotherapy (3.9%) and 32 patients treated with leuprolide alone (8.9%) experienced a symptomatic skeletal event. Most of these patients had radiation therapy to bone (monotherapy, 1.4%; leuprolide alone, 3.9%) or opiate use due to bone pain (monotherapy, 1.4%; leuprolide alone, 3.4%); the remaining cause of events (e.g., surgery to bone, pathological bone fracture, spinal cord compression) comprised < 1% of patients in both treatment groups. The 5-year rate (95% CI) of remaining free from a first symptomatic skeletal event was 95.8% (92.9-97.6) for enzalutamide monotherapy and 91.5% (87.8-94.1) for leuprolide alone (Supplementary Figure 1, https://www.jurology.com). Patients who received enzalutamide monotherapy had a 58% reduction in the risk of their first symptomatic skeletal event compared with leuprolide alone (HR 0.42; 95% CI: 0.23-0.79; $P = .0057$); medians were not reached in either group.

Time to Resumption of Any Hormonal Therapy Following Treatment Suspension

Following suspension of enzalutamide monotherapy (n = 304) or leuprolide alone (n = 240), 279 (91.8%) and 217 (90.4%) patients, respectively, resumed treatment with hormonal therapy. The 5-year rate (95% CI) of remaining free from resumption of any hormonal therapy was 5.6% (3.3-8.8) for enzalutamide monotherapy and 7.8% (4.4-12.3) for leuprolide alone (Figure 2, D). The median (95% CI) time to resumption of any hormonal therapy was shorter for enzalutamide monotherapy (10.5 months [8.9-11.5]) compared with leuprolide alone (16.8 months [14.3-17.1]). Treatment with enzalutamide monotherapy was associated with an increase in the risk of resumption of any hormonal therapy compared with treatment with leuprolide alone (HR 1.66; 95% CI: 1.38-1.98; $P < .0001$). The time to resumption of any hormonal therapy is defined as a time-to-event end point to account for 8% to 20% of patients who were censored across treatment arms at the data cutoff. This end point is summarized using the Kaplan–Meier method. This differs from the previously published duration of treatment suspension, which was summarized using descriptive statistics without considering censoring.[14] In addition, there

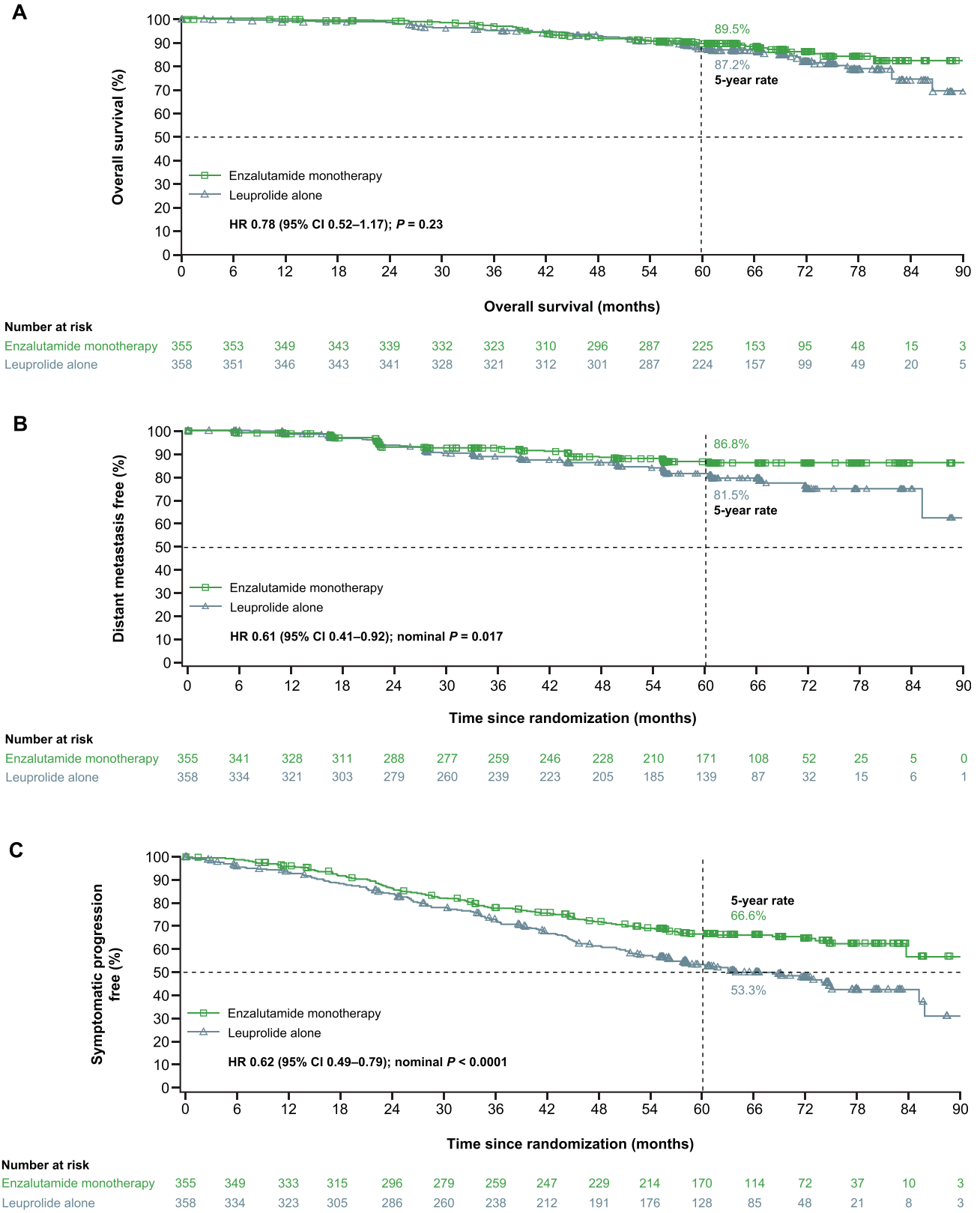

Figure 2. Kaplan-Meier estimates of (A) overall survival, (B) time to distant metastasis, (C) time to symptomatic progression, (D) time to resumption of any hormonal therapy after treatment suspension, and (E) time to first confirmed deterioration of sexual function (intention-to-treat population). The data cutoff was January 31, 2023. Treatment effects by HR and 95% CI were estimated by stratified Cox regression models, as described previously.[14] Times to distant metastasis, symptomatic progression, resumption of any hormonal therapy, and confirmed deterioration of sexual activity are presented in Supplementary Table 1 (https://www.jurology.com). Kaplan-Meier curves were truncated when there were zero patients at risk in both groups.

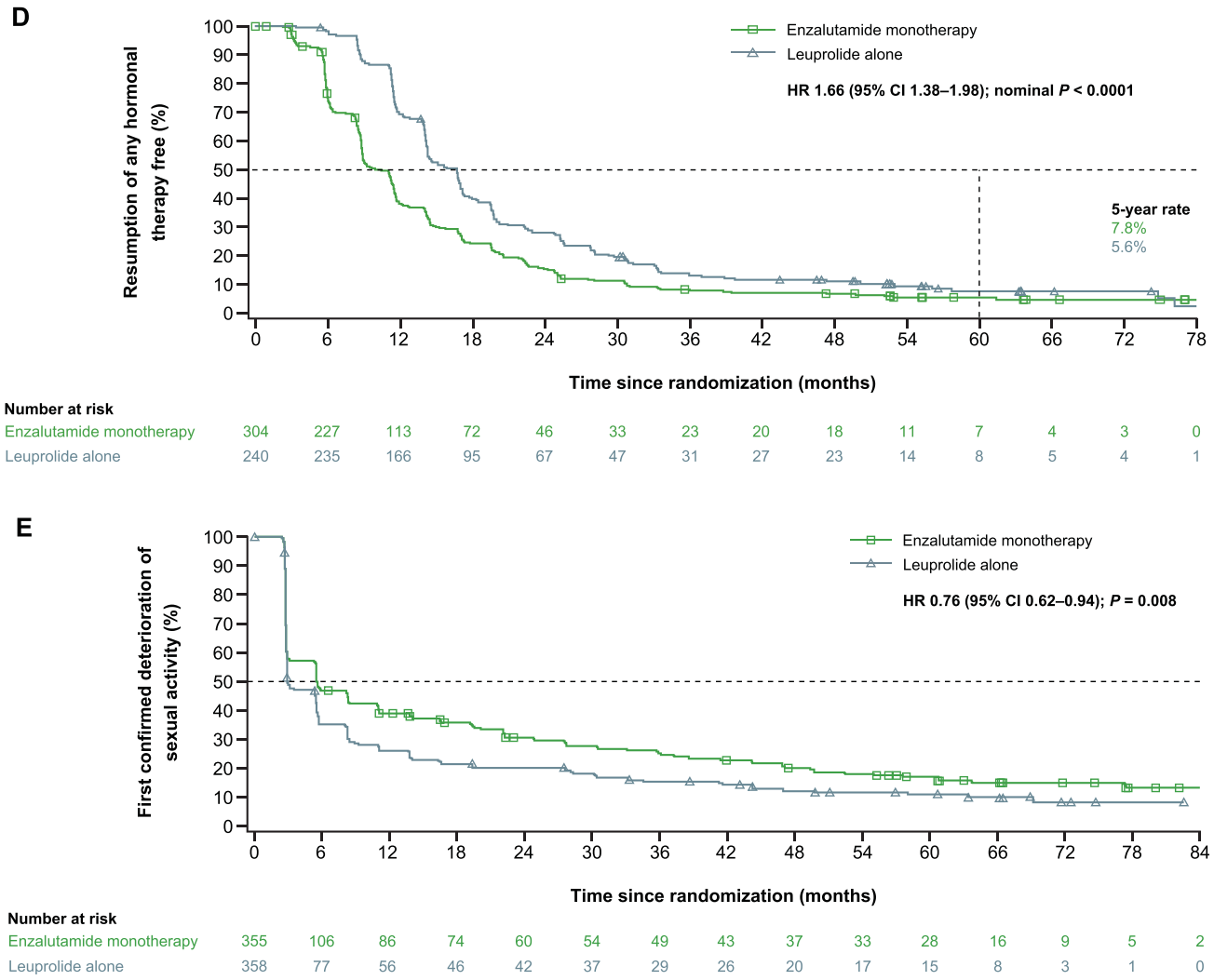

Figure 2. Continued.

were a few cases (approximately 5%) in which patients resumed hormonal therapy with treatments other than the study drug reinitiation.

Time to First Confirmed Deterioration of Sexual Activity

Enzalutamide monotherapy decreased the risk of confirmed deterioration of sexual activity compared with leuprolide alone (HR 0.76; 95% CI: 0.62-0.94; $P = .008$; Figure 2, E), but had no effect on time to first deterioration of sexual activity compared with leuprolide alone (HR 0.92; 95% CI: 0.76-1.11; $P = .38$; Supplementary Figure 2, https://www.jurology.com).

MFS in Protocol-Defined Subgroups

In all prespecified subgroups analyzed, MFS favored the enzalutamide monotherapy group compared with leuprolide alone, although this did not always reach significance (Figure 3).

DISCUSSION

EMBARK is the first phase 3 trial that demonstrated clinically meaningful outcomes for a next-generation ARPI monotherapy with the enzalutamide monotherapy group.[14] The primary analysis of EMBARK showed that enzalutamide monotherapy significantly prolonged MFS, time to PSA progression, and time to first new antineoplastic therapy.[14] Furthermore, there were no clinically meaningful differences observed in time to first deterioration of Functional Assessment of Cancer Therapy–Prostate total score between enzalutamide monotherapy and leuprolide alone, which suggests that enzalutamide monotherapy preserves patient QoL.[14] The results presented here consolidate the findings of the primary analysis. The key secondary end point of OS was numerically better with enzalutamide monotherapy vs leuprolide alone, although differences did not reach statistical

Table 2. *Location of Distant Metastasis in Enzalutamide Monotherapy and Leuprolide Alone Groups (Intention-to-Treat Population)*

Distant metastasis site,[a] no. (%)	Enzalutamide monotherapy (n = 355)	Leuprolide alone (n = 358)
Total	40(11.3)	59(16.5)
Bone	25 (7.0)	29 (8.1)
Soft tissue ± bone[b]	15 (4.2)	30 (8.4)
Visceral[c] only	4 (1.1)	7 (2.0)
Nonvisceral[d] only	9 (2.5)	21 (5.9)
Both visceral and nonvisceral	2 (0.6)	2 (0.6)

The data cutoff was January 31, 2023.
[a]Based on the earliest objective evidence of distant soft tissue metastases or metastatic bone disease by blinded independent central review.
[b]Concurrent distant soft tissue and bone metastases were detected in 1 patient from the enzalutamide monotherapy group and 3 patients from the leuprolide alone group.
[c]Visceral progression sites: adrenal gland, brain, chest wall, liver, lung, peritoneum/omentum, and pleura.
[d]Nonvisceral progression sites: lymph nodes, pelvis, and bladder.

significance, and the data had not reached maturity at the time of interim analysis. Recently published final OS data from the EMBARK trial showed no significant difference between enzalutamide monotherapy and leuprolide alone.[21] While the primary EMBARK manuscript reported interim results for OS,[14] this manuscript presents the Kaplan–Meier analysis for OS, and places OS in the context of other secondary end points, providing a more complete picture of the effect of enzalutamide monotherapy. Although significant differences in OS outcomes may take longer to appear, non-key secondary end points of time to distant metastasis, symptomatic progression, and first symptomatic skeletal event significantly favored enzalutamide monotherapy compared with leuprolide alone. The data on symptomatic progression suggest that some patients who receive enzalutamide monotherapy could stay on this treatment without modification for longer than those who receive leuprolide alone. Patients who received enzalutamide monotherapy also had better preserved sexual function compared with patients treated with leuprolide alone. These findings further suggest enzalutamide monotherapy as an important therapeutic option for patients with hrBCR.

In contrast to the other non-key secondary end points that favored enzalutamide monotherapy, time to resumption of hormonal therapy after treatment suspension favored the leuprolide alone treatment group. This is likely the result of testosterone levels remaining at castrate levels in the leuprolide alone group for several months after treatment suspension.[14] Notably, the time to testosterone recovery following treatment with ADT can vary and can take over 2 years to recover in some patients.[22] For patients treated with enzalutamide monotherapy, however, testosterone levels actually increased above baseline levels such that at the time of treatment suspension, all patients would have had noncastrate testosterone levels. Subsequently, for patients treated with enzalutamide monotherapy, PSA levels did not remain undetectable (< 0.2 ng/mL) for as long with leuprolide alone or combination therapy.[14] These data need to be considered along with the previously published PRO results[15] and adverse event profile[14] to determine the best option for each patient.

Patients considering enzalutamide monotherapy should be aware of factors affecting adverse events, sexual function, and QoL. These data should be considered alongside analyses of QLQ-PR25 in the domains of sexual activity and sexual functioning[23] and item-level analyses of sexual activity-related health-related QoL.[24] Loss of sexual function is a concern for many patients, and thus, even modest improvements may affect treatment decision-making. In addition, approximately 15% of patients treated with enzalutamide monotherapy experienced breast tenderness and nipple pain, while gynecomastia was reported by 45% of patients, which was higher than in patients treated with leuprolide alone.[14] Prophylactic radiation to the breast tissue, aromatase inhibitors, serum estrogen receptor modulators (e.g., tamoxifen), and subareolar removal of breast tissue may be appropriate treatments to prevent and/or address these adverse events reported by patients treated with enzalutamide monotherapy.[25] Prophylactic treatments were not routinely administered to patients enrolled in EMBARK but may have been effective in reducing reports of these breast-related adverse events; although these treatment options require further study.

ADT has multiple side effects including bone loss,[26] changes in body composition (e.g., sarcopenia),[27] detrimental effects on cardiovascular health,[28] and impaired sexual function.[29] While loss of sexual function is directly caused by decreased testosterone levels, increased fracture risk and hot flashes are indirectly caused by loss of estrogen, derived from the aromatization of testosterone.[30] Maintaining normal levels of testosterone may be responsible for mitigating these adverse events with enzalutamide monotherapy treatment, since testosterone levels were elevated above baseline in this group compared with enzalutamide combination.[14] Testosterone levels in patients treated with enzalutamide monotherapy may also explain some of the PROs, specifically the lesser effects on sexual health. Notably, patients treated with enzalutamide monotherapy had prolonged time to confirmed deterioration in sexual function compared with the leuprolide alone. Longitudinal analysis also showed that treatment with enzalutamide monotherapy had less deterioration in sexual activity compared

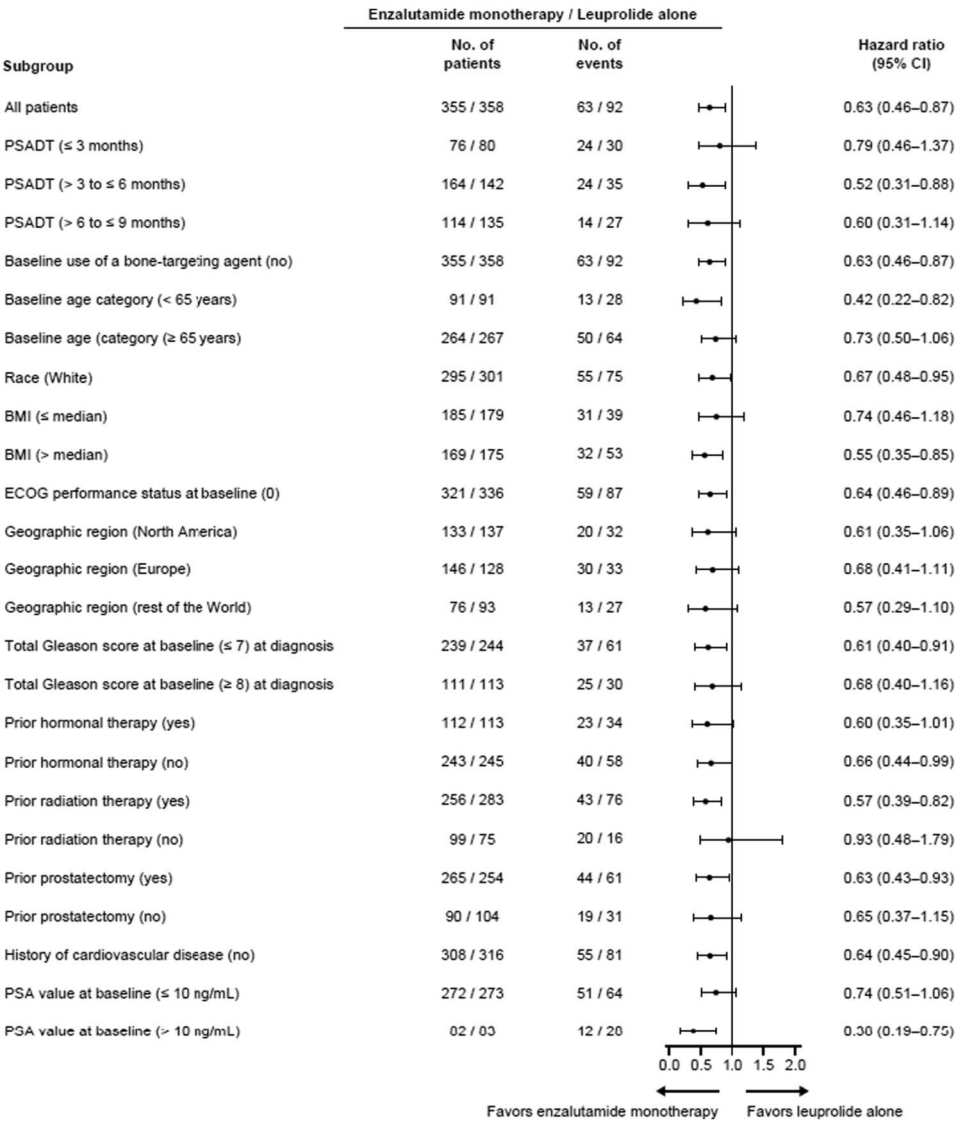

Figure 3. Metastasis-free survival for prespecified subgroups from enzalutamide monotherapy vs leuprolide alone (intention-to-treat population). The data cutoff was January 31, 2023. Treatment effects by HR and 95% CI were estimated by stratified Cox regression models, as described previously.[14] According to the statistical analysis plan, the prespecified sample size requirement was at least 10 events in a subgroup to allow meaningful comparison. ECOG indicates Eastern Cooperative Oncology Group; PSADT, PSA doubling time.

with leuprolide alone.[15] These findings of better preserved sexual function with enzalutamide monotherapy are consistent with elevated testosterone levels in patients who received enzalutamide monotherapy compared with patients who received leuprolide alone.

EMBARK represents the first phase 3 trial to compare the efficacy and safety of enzalutamide monotherapy with leuprolide alone for treating patients with hrBCR.[18] Furthermore, given that the monotherapy arm was open label, it is possible that the lack of placebo control could have influenced toxicity evaluation, reinitiation of the drug following treatment suspension, and reporting of PROs. Finally, the EMBARK trial was initiated in 2014 and used protocol-defined conventional imaging to identify metastatic PC. It is possible that next-generation imaging techniques, which are more sensitive than conventional imaging, could have identified more patients with metastases at baseline.[31] Future research is needed to investigate whether combining enzalutamide ± ADT with salvage treatments improves outcomes.

CONCLUSIONS

In patients with hrBCR, the key secondary end point of OS was numerically better with enzalutamide monotherapy compared with leuprolide alone, although differences did not reach statistical significance, and longer follow-up is needed as the data were immature at the time of publication. In all protocol-defined subgroups, MFS also favored

enzalutamide monotherapy vs leuprolide alone. Enzalutamide monotherapy demonstrated clinically meaningful delays in non-key secondary end points of time to distant metastasis, symptomatic progression, and first symptomatic skeletal event compared with leuprolide alone. After treatment suspension, enzalutamide monotherapy was associated with a shorter time to resumption of any hormonal therapy compared with leuprolide alone. Sexual health was better preserved after treatment with enzalutamide monotherapy compared with leuprolide alone. The EMBARK trial demonstrates that enzalutamide monotherapy now represents an important therapeutic option to be considered between clinicians and their patients with hrBCR during shared decision-making. Clinicians should consider potential benefits and risks for each patient, including potential financial costs, when evaluating enzalutamide monotherapy as a therapeutic option.

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