

ORIGINAL ARTICLE

Enzalutamide and Quality of Life in Biochemically Recurrent Prostate Cancer

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Abstract

BACKGROUND EMBARK, a controlled trial reported elsewhere, showed enzalutamide plus leuprolide (combination) and enzalutamide monotherapy prolonged metastasis-free survival versus placebo plus leuprolide (alone) in patients with high-risk biochemically recurrent prostate cancer. Health-related quality of life was also analyzed but not reported.

METHODS In EMBARK, patients with biochemical recurrence (prostate-specific antigen doubling time of ≤ 9 months) were randomly assigned (1:1:1) to combination (n=355), leuprolide-alone (n=358), or enzalutamide monotherapy (n=355). In this article we provide the patient-reported outcomes (PROs) from EMBARK at baseline and every 12 weeks until metastasis or death. The key end point was time to first and confirmed clinically meaningful deterioration (TTFD/TTCD) in pain and health-related quality of life using four PRO measures and predefined thresholds.

RESULTS At baseline, all groups had high health-related quality of life. For worst pain, the median TTFD was 19.35 months with leuprolide alone, 13.93 months with combination (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.30) and 16.59 months with monotherapy (hazard ratio, 1.09; 95% CI, 0.90 to 1.31). The median TTCD was 66.27 months with leuprolide alone, 80.00 months with combination (hazard ratio, 0.82; 95% CI, 0.65 to 1.04), and 60.91 months with monotherapy (hazard ratio, 1.02; 95% CI, 0.82 to 1.28). For Functional Assessment of Cancer Therapy-Prostate total score, the median TTFD was 11.10 months with leuprolide alone, 8.31 months with combination (hazard ratio, 1.14; 95% CI, 0.95 to 1.36), and 8.38 months with monotherapy (hazard ratio, 1.17; 95% CI, 0.98 to 1.39). The median TTCD was 36.53 months with leuprolide alone, 38.77 months with combination (hazard ratio, 1.04; 95% CI, 0.85 to 1.28), and 30.55 months with monotherapy (hazard ratio, 1.16; 95% CI, 0.95 to 1.41).

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CONCLUSIONS The PROs from EMBARK show that both enzalutamide combination and monotherapy versus leuprolide alone, with oncologic benefits noted above, preserved high health-related quality of life in patients with high-risk biochemical recurrence of prostate cancer. (Funded by Pfizer and Astellas Pharma; ClinicalTrials.gov number, [NCT02319837](#).)

Introduction

Prostate cancer will approach 29% of cancer incident cases in the United States by the end of 2023.¹ After primary definitive therapies including radical prostatectomy and/or radiotherapy, about 20 to 50% of men experience biochemical recurrence, an increase in the prostate-specific antigen (PSA).²⁻⁴ Patients with biochemically recurrent, nonmetastatic, castration-sensitive prostate cancer are at increased risk of developing distant metastasis and dying of prostate cancer, especially when a PSA doubling time is less than 9 months.⁴⁻⁷

EMBARK is a clinical trial reporting the efficacy and safety of enzalutamide plus leuprolide (combination) and enzalutamide monotherapy versus placebo plus leuprolide (leuprolide alone) in patients with biochemically recurrent, nonmetastatic, castration-sensitive prostate cancer after definitive therapy.⁸ In EMBARK, enzalutamide combination and monotherapy both significantly improved the 5-year metastasis-free survival versus leuprolide alone, with combination resulting in a 57.6% lower risk of metastasis or death (hazard ratio, 0.42; 95% confidence interval [CI], 0.30 to 0.61; $P < 0.0001$) and monotherapy resulting in a 36.9% lower risk (hazard ratio, 0.63; 95% CI, 0.46 to 0.87; $P = 0.005$). The safety profile of enzalutamide was consistent with previous trials.⁸

Given the prolonged natural history of biochemically recurrent disease, management decisions are often based on concerns regarding health-related quality of life.⁹ In this report from EMBARK, we present the patient-reported outcome (PRO) data with a focus on the time to first and confirmed health-related quality-of-life deterioration and change from baseline.

Methods

TRIAL DESIGN AND PARTICIPANTS

Trial design, eligibility criteria, and protocol (available with the full text of this article at [evidence.nejm.org](#)) were described previously.^{8,10} Briefly, EMBARK is an international, phase 3, randomized trial in patients with biochemically recurrent, nonmetastatic, castration-sensitive prostate cancer progressing after radical prostatectomy, radiotherapy, or both who received no prior cytotoxic chemotherapy or hormonal therapy except for neoadjuvant/adjuvant therapy for 36 months or less in duration and 9 months or greater before random assignment or a single dose or a short course (6 months or less) of hormonal therapy for biochemical recurrence at least 9 months before random assignment. This PRO analysis was conducted on final trial data collected until January 31, 2023.

In EMBARK, patients were randomly assigned 1:1:1 to enzalutamide plus leuprolide (enzalutamide combination; double-blind), placebo plus leuprolide (leuprolide alone; double-blind), or enzalutamide monotherapy (open label). Treatment was suspended at week 37 if PSA was less than 0.2 ng/ml and reinstated if PSA increased to at least 2.0 ng/ml in patients who had been treated with radical prostatectomy or at least 5.0 ng/ml in patients who did not have radical prostatectomy. Patients with PSA at least 0.2 ng/ml at week 37 continued therapy until treatment discontinuation criteria were met (i.e., disease progression on conventional imaging). All patients provided written informed consent compliant with the Declaration of Helsinki and International Council for Harmonization Guidelines.

TRIAL OVERSIGHT

This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the Pfizer and Astellas Pharma policies on bioethics. It was designed by representatives of Pfizer and Astellas Pharma with consultation from the trial standing advisory board. Pfizer and Astellas Pharma were responsible for overseeing the collection, analysis, and interpretation of the data. All authors had full data access. The manuscript was written with medical writing assistance funded by Pfizer and Astellas Pharma, with critical review and input from the authors.

PROCEDURES AND PRO MEASURES

PROs were assessed at baseline and every 12 weeks until disease progression or completion of data gathering. For each PRO instrument, change from baseline, defined as postbaseline value minus baseline value, was calculated for each assessment of a domain. Health-related quality of life was measured using Brief Pain Inventory–Short Form (BPI-SF), Functional Assessment of Cancer Therapy–Prostate (FACT-P), Quality of Life Questionnaire–Prostate 25 (QLQ-PR25), and European Quality of Life 5-Dimensions 5-Levels health questionnaire (EQ-5D-5 L) scores.

The BPI-SF is rated on a scale of 0 to 10 with 0 representing “no pain.”¹¹ For item 3 (worst pain in the past 24 hours), BPI-SF pain severity, and BPI-SF pain interference, improvement or deterioration was classified as a decrease or an increase of 2 or more points, respectively, in the postbaseline scores (Table 1). A change of 2 or more points in the numerical BPI-SF scores was used as the primary threshold to detect clinically important improvements. The FACT-P total score ranged from 0 to 156, with a higher score indicating better health-related quality of life. For the primary threshold analysis, improvement was defined as change from baseline greater than or equal to the threshold; stabilization was defined as change from baseline between negative (–) threshold and positive (+) threshold; and deterioration was defined as change from baseline less than or equal to the threshold (Table 1).

The QLQ-PR25 has two functional domains (sexual activity and sexual functioning) and four symptom domains (urinary symptoms, incontinence aids, bowel symptoms/function, and hormonal treatment-related symptoms), with a score range of 0 to 100. A higher score for the PR25 symptom domains represents a high symptom burden, whereas a higher score in the functional domains indicates higher (“better”) level of functioning.¹² For the QLQ-PR25 instrument, the threshold obtained using the baseline distributions of QLQ-PR25 scores (i.e., a change of 1/2 baseline standard deviation or greater pooled for the two treatment groups) or change of one response category in one item, whichever is larger, was considered clinically meaningful for the primary threshold analysis (Table 1).

The score range for the EQ-5D-5 L visual analogue scale (VAS) was 0 to 100, with higher scores indicating better health.¹³ Clinically meaningful changes of 7 and 10 points in the EQ-5D-5 L VAS score were used in the primary and

sensitivity analyses, respectively. Because clinically meaningful thresholds for the EQ-5D-5 L utility index (derived using the U.S. value set) have not been reported in literature for patients with prostate cancer, a change greater than or equal to 1/2 standard deviation was considered clinically meaningful based on prior health-related quality-of-life studies.^{14,15} For the primary analysis, post-baseline scores for the EQ-5D-5 L VAS and utility index scores were classified as improved, unchanged, or deteriorated from the baseline using thresholds denoting clinically meaningful change as follows: improvement, greater than or equal to threshold points; deterioration, less than or equal to threshold points; no change, a change from baseline between – threshold and + threshold points. The primary and sensitivity thresholds for meaningful change for each PRO instrument were defined based on previous PRO studies (Table 1 and Table S1 in the Supplementary Appendix).

TRIAL OUTCOMES

The key objectives of the PRO analysis were to assess treatment differences in time to first and confirmed clinically meaningful deterioration in pain, measured by BPI-SF item 3 (worst pain in past 24 hours) and time to first and confirmed clinically meaningful deterioration in functional status, measured by the FACT-P total score. Secondary end points were time to first and confirmed clinically meaningful deterioration, longitudinal changes, and the proportion of patients with improved, stable, or deteriorated scores for the various PRO measures. Time to first and confirmed clinically meaningful deterioration were assessed for each scale of the PRO measures (Table 2).

STATISTICAL ANALYSIS

All PRO analyses were performed using the intention-to-treat principle. The adjusted completion rates were calculated as the number of patients meeting the minimum requirements for scoring of the instrument divided by the number of patients who were expected to undergo PRO assessment. Kaplan–Meier curves were used to estimate the distribution of time to first and confirmed clinically meaningful deterioration. Stratified Cox models with strata to control for randomization factors were used to estimate hazard ratios and 95% CIs. However, the widths of the CIs were not adjusted for multiplicity and therefore should not be used to interpret treatment effects.

Sensitivity analysis was conducted to assess time to event using sensitivity thresholds for clinically meaningful change

Instrument	Patient-Reported Outcomes	Primary Threshold	Interpretation	LSM Change from Baseline over 205 Weeks (95% CI)			Treatment Group with Clinically Meaningful Change
				Enzalutamide Combination	Enzalutamide Monotherapy	Leuprolide Alone	
BPI-SF	Item 3 (worst pain; past 24 hours) (range: 0–10)	Improvement: –2 Deterioration: +2	0 = “no pain” and 10 = “pain as bad as you can imagine.”	0.28 (0.10, 0.46)	0.51 (0.33, 0.69)	0.38 (0.20, 0.57)	None
	BPI-SF pain-severity score (range: 0–10)			0.22 (0.074, 0.37)	0.43 (0.28, 0.58)	0.32 (0.17, 0.46)	None
	BPI-SF pain interference score (range: 0–10)	Improvement: –1 Deterioration: +1	0 = “no interference” and 10 = “interferes completely”	0.35 (0.21, 0.50)	0.51 (0.37, 0.65)	0.42 (0.28, 0.56)	None
FACT-P	Physical well-being (range: 0–28)	Improvement: +3 Deterioration: –3	A higher score indicates better HRQoL	–2.00 (–2.29, –1.71)	–2.11 (–2.40, –1.82)	–1.27 (–1.56, –0.99)	None
	Functional well-being (range: 0–28)			–0.71 (–2.12, –1.30)	–1.65 (–2.05, –1.25)	–1.18 (–1.58, –0.78)	None
	Emotional well-being (range: 0–24)			0.31 (0.03, 0.58)	0.12 (–0.15, 0.39)	0.68 (0.41, 0.96)	None
	Social/family well-being (range: 0–28)			–0.03 (–0.41, –0.47)	–0.11 (–0.54, –0.33)	–0.24 (–0.68, –0.19)	None
	Prostate-related symptoms (range: 0–48)			–2.25 (–2.72, –1.78)	–2.53 (–3.00, –2.06)	–1.81 (–2.27, –1.35)	None
	Prostate-related symptoms pain-related score (range: 0–16)	Improvement: +2 Deterioration: –2		–0.56 (–0.81, –0.30)	–0.76 (–1.02, –0.51)	–0.67 (–0.92, –0.41)	None
	FACT-G (range: 0–108)	Improvement: +7 Deterioration: –7		–3.38 (–4.44, –2.31)	–3.79 (–4.84, –2.74)	–2.06 (–3.10, –1.01)	None
	Trial outcome index (range: 0–104)	Improvement: +9 Deterioration: –9		–6.02 (–7.01, –5.03)	–6.35 (–7.33, –5.37)	–4.30 (–5.27, –3.33)	None
	FACT advanced prostate symptom index (range: 0–32)	Improvement: +3 Deterioration: –3		–0.78 (–1.12, –0.44)	–1.22 (–1.55, –0.88)	–0.47 (–0.80, –0.13)	None
QLQ-PR25	FACT-P total score (range: 0–156)	Improvement: +10 Deterioration: –10		–5.66 (–7.06, –4.26)	–6.36 (–7.74, –4.97)	–3.88 (–5.25, –2.50)	None
	Sexual activity (range: 0–100)	Improvement: +16.67 Deterioration: –16.67	A higher score indicates higher (“better”) level of functioning	–14.20 (–16.00, –12.40)	–6.85 (–8.63, –5.07)	–12.99 (–14.76, –11.22)	None
	Sexual functioning (range: 0–100)	Improvement: +9.48 Deterioration: –9.48		Not enough participants to run the model			
	Urinary symptoms (range: 0–100)	Improvement: –7.24 Deterioration: +7.24	A higher score represents a higher (“worse”) level of symptoms	3.36 (2.05, 4.67)	3.80 (2.51, 5.10)	3.33 (2.04, 4.62)	None

(continued)

Table 1. (cont.)							
Instrument	Patient-Reported Outcomes	Primary Threshold	Interpretation	LSM Change from Baseline over 205 Weeks (95% CI)			Treatment Group with Clinically Meaningful Change
				Enzalutamide Combination	Enzalutamide Monotherapy	Leuprolide Alone	
EQ-5D-5 L	Modified urinary symptoms (range: N/A)	Improvement: −11.11 Deterioration: +11.11		4.47 (2.63, 6.30)	3.97 (2.15, 5.78)	4.35 (2.54, 6.15)	None
	Bowel symptoms/function (range: 0–100)	Improvement: −8.33 Deterioration: +8.33		1.98 (1.26, 2.71)	1.74 (1.02, 2.45)	1.83 (1.12, 2.54)	None
	Incontinence aids (range: 0–100)	Improvement: −33.33 Deterioration: +33.33		Not enough participants to run the model			
	Hormonal treatment-related symptoms (range: 0–100)	Improvement: −5.56 Deterioration: +5.56		11.44 (10.30, 12.59)	10.82 (9.69, 11.95)	9.75 (8.63, 10.88)	Enzalutamide combination, enzalutamide monotherapy, and leuprolide alone
	Visual analog scale (range: 0–100)	Improvement: +7 Deterioration: −7	100 representing the best imaginable health and 0 the worst imaginable health	−1.86 (−3.07, −0.65)	−2.35 (−3.55, −1.15)	−1.59 (−2.78, −0.40)	None
	Utility index score (range: N/A*)	Improvement: +0.059 Deterioration: −0.059	A higher index indicates better HRQoL	−0.05 (−0.06, −0.03)	−0.05 (−0.06, −0.04)	−0.04 (−0.05, −0.03)	None

* Weighted index reported as a five-digit number by combining one level from each of the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). BPI-SF denotes Brief Pain Inventory-Short Form; CI, Confidence Interval; EQ-5D-5 L, European Quality of Life 5-Dimensions 5-Levels; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRQoL, health-related quality of life; LSM, least-squares means; N/A, not applicable; PRO, patient-reported outcome; and QLQ-PR25, Quality of Life Questionnaire-Prostate 25.

Table 2. Definitions of Trial End Points, Analyses, and Variables.

Trial End Points, Analyses, and Variables	Definitions
High-risk biochemical recurrent, nonmetastatic, castration-sensitive prostate cancer	Defined as biochemical recurrence with a prostate-specific antigen doubling time ≤ 9 months and a screening prostate-specific antigen of ≥ 1 ng/ml for patients who had undergone prior radical prostatectomy (with or without radiotherapy) and ≥ 2 ng/ml above the nadir for patients who had received primary radiotherapy only
Primary objective of patient-reported outcome analysis	To assess treatment differences in time to clinically meaningful pain progression (TTFD and TTCD) as measured using the BPI-SF item 3 score and FACT-P total score
Secondary objective of patient-reported outcome analysis	To assess treatment differences in disease- and treatment-related symptoms, pain, function, and health status a) Longitudinal changes in BPI-SF, FACT-P, QLQ-PR25, and EQ-5D-5 L scores b) TTFD and TTCD in BPI-SF, FACT-P, QLQ-PR25, and EQ-5D-5 L scores c) Proportion of patients with improved/stable/deteriorated BPI-SF, FACT-P, QLQ-PR25, and EQ-5D-5 L scores
Trial time points	Patient-reported outcomes were assessed at baseline and every 12 weeks until disease progression
TTFD	Time from the date of randomization to the date of the first clinically meaningful deterioration in patient-reported outcome scores by at least one threshold unit compared with the baseline score
TTCD	Time from the date of randomization to the date of the first clinically meaningful deterioration in patient-reported outcome scores by at least one threshold unit as compared with the baseline score, which is confirmed at the next consecutive visit or followed by drop-out, resulting in monotone missing data
Domains assessed for the patient-reported outcome scores	The domain and overall scores were analyzed for BPI-SF (item 3 [worst pain in the past 24 hours], BPI-SF pain severity, and BPI-SF pain interference); FACT-P (total score, FACT-G [general] total score, trial outcome index, FACT Advanced Prostate Symptom Index, physical well-being, emotional well-being, functional well-being, social well-being, prostate cancer subscale, and prostate-related symptoms pain-related scores); QLQ-PR25 (sexual functioning, urinary symptoms, modified urinary symptoms, bowel symptoms/function, incontinence aids, and hormonal treatment-related symptoms); and EQ-5D-5 L (EQ-5D-5 L utility index value set and visual analog scale)

BPI-SF denotes Brief Pain Inventory–Short Form; EQ-5D-5 L, European Quality of Life 5-Dimensions 5-Levels; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; PRO, patient-reported outcome; QLQ-PR25, Quality of Life Questionnaire–Prostate 25; TTCD, time to first confirmed clinically meaningful deterioration; and TTFD, time to first clinically meaningful deterioration.

from baseline defined in Table S1. An additional sensitivity analysis assessed time to event where death (due to any cause) was considered as an event if the patient did not experience PRO deterioration before death and where death occurred within 13 weeks after the last available PRO assessment; disease progression was not considered a deterioration event.

Longitudinal analysis of PRO score changes from baseline was performed using a restricted maximum likelihood-based, repeated-measures approach — namely, mixed model for repeated measures. Separate models were considered for each PRO score. The primary focus was to examine treatment differences up to week 205 to minimize the impact of missing data because, after week 205, the number of men in follow-up declined. Responder analysis was performed on the intention-to-treat population to assess the proportions of patients with improved, unchanged, or deteriorated scores at each PRO assessment visit by treatment group.

The PRO statistical analysis plan was finalized on December 21, 2022, and the data cutoff for this analysis

was January 31, 2023. January 31, 2023 was also the cutoff for metastatic-free survival and interim overall survival (OS) analysis, which are not presented here. There were no prior data cuts or analyses. The final OS analysis will occur when the prespecified number of events (i.e., 271) have occurred. The PRO analysis presented here is final and there are no plans for further PRO analysis at the time of final OS analysis.

Results

From January 2015 through August 2018, 1068 patients at 244 sites in 17 countries were enrolled and randomly assigned to enzalutamide combination (n=355), leuprolide alone (n=358), or enzalutamide monotherapy (n=355).⁸ At the time of data cutoff (January 31, 2023), 33 (9%) patients in the enzalutamide combination group, 42 (12%) patients in the monotherapy group, and 55 (15%) patients in the leuprolide-alone group had died.⁸ The participants were mainly from Europe (37.8%) and North America (38.8%), with only 23.4% from other geographical locations; Table S2

shows the representativeness of the populations studied. The median follow-up time by treatment group is provided in Table S3.

PATIENT DISPOSITION AND BASELINE DEMOGRAPHICS

At baseline, adjusted PRO questionnaire completion rates were 90% or higher and comparable across groups. Adjusted completion rates remained high ($\geq 85\%$) from baseline up to week 205 across groups (Fig. S1). After week 205, completion rates declined and some differences in completion rates between the treatment groups were observed as a result of the small sample sizes in each group toward the end of the study (Fig. S1).

The number of missing responses also increased as the study progressed because more patients were not expected to have an assessment at later time points (Tables S4 and S5).

Baseline PRO scores suggested that across groups patients were generally asymptomatic with high health-related quality of life at baseline (Table 3).

KEY OUTCOMES

No differences were observed in time to first and confirmed clinically meaningful deterioration in the BPI-SF item 3 (worst pain in past 24 hours) (Fig. 1A) or in functional status measured using FACT-P total score (Fig. 1B).

OTHER OUTCOMES

No differences were observed in time to first and confirmed clinically meaningful deterioration in the BPI-SF pain severity or pain interference between the enzalutamide groups and leuprolide-alone group (Fig. 1A). Time to confirmed clinically meaningful deterioration in physical well-being score was 24.8 months with enzalutamide combination and 49.8 months with leuprolide (hazard ratio, 1.41; 95% CI, 1.15 to 1.72); for enzalutamide monotherapy the time was 27.6 months for a hazard ratio compared with leuprolide alone of 1.35; 95% CI, 1.11 to 1.65 (Fig. 1B). The time to confirmed clinically meaningful deterioration in hormonal treatment-related symptoms with enzalutamide combination was 2.86 months compared with 2.89 months for leuprolide alone (hazard ratio, 1.19; 95% CI, 1.01 to 1.40) (Fig. 1C). Although the hazard ratio of 1.19 favors the leuprolide-alone group, the quartiles (Q) of time to deterioration (enzalutamide combination: Q1 = 2.79, Q3 = 5.55; leuprolide alone: Q1 = 2.79, Q3 = 8.44) indicate that this effect is somewhat delayed and can be observed

in patients who have not experienced deterioration in hormonal treatment-related symptoms within approximately the first 3 months. Because the Cox hazard model compares the two curves at all time points compared with the median, which is an estimate that represents one aspect of the distribution, an early or a late separation in the curve can affect the hazard ratio while not affecting the median. Time to first meaningful deterioration in urinary symptoms score was 8.34 months with enzalutamide monotherapy versus 5.62 months for leuprolide alone (hazard ratio, 0.83; 95% CI, 0.70 to 0.99) (Fig. 1C). Median time to confirmed clinically meaningful deterioration in sexual-activity score was 5.55 months with enzalutamide monotherapy versus 2.99 months for leuprolide alone (hazard ratio, 0.76; 95% CI, 0.62 to 0.94) (Fig. 1C). No major differences were observed in time to first and confirmed clinically meaningful deterioration in VAS score between enzalutamide combination or enzalutamide monotherapy versus leuprolide alone (Fig. S2).

In the enzalutamide combination group, 90.9% of patients suspended treatment at week 37 for a median of 20.2 months (95% CI, 5.7 to 87.9). A total of 67.8% of the patients in the leuprolide-alone group had treatment suspended (median, 16.8 months; 95% CI, 3.4 to 83.0), whereas in the enzalutamide monotherapy group 85.9% patients had treatment suspended for a median of 11.1 months (95% CI, 2.3 to 84.9) (Fig. 2A). The mean testosterone levels were supraphysiologic until treatment suspension as compared with baseline in enzalutamide monotherapy group and remained high as the treatment was resumed. In the enzalutamide combination and the leuprolide-alone groups, testosterone levels went up slightly during treatment suspension but did not return to baseline levels. However, as treatment resumed in both groups, testosterone levels declined.

Longitudinally, no notable change in mean scores from baseline was observed up to week 205 in any group for BPI-SF item 3 (Fig. 2B) or any other BPI-SF subdomain (Fig. S3). Over the course of the trial, patients in all groups experienced decline in FACT-P subdomains to week 205; however, none of the differences in FACT-P subdomains met the a priori threshold for clinically meaningful differences, as outlined in Table 1. The clinically meaningful thresholds for FACT-P total score are 10 (improvement) and -10 (deterioration) (Table 1). The least-squares means (LSM) overall change from baseline up to week 205 for FACT-P total score for leuprolide alone was -3.88 (95% CI, -5.25 to -2.50) versus -5.66 (95% CI, -7.06 to -4.26)

Table 3. Baseline Characteristics and PRO Scores.

Baseline Characteristics	Enzalutamide Combination (n=355)	Leuprolide Alone (n=358)	Enzalutamide Monotherapy (n=355)	Total (N=1068)
Age, median (range)	69.0 (51.0, 87.0)	70.0 (50.0, 92.0)	69.0 (49.0, 93.0)	69.0 (49.0, 93.0)
Prior hormone therapy				
Yes	107 (30.1%)	113 (31.6%)	112 (31.5%)	332 (31.1%)
No	248 (69.9%)	245 (68.4%)	243 (68.5%)	736 (68.9%)
Prior prostatectomy				
Yes	269 (75.8%)	254 (70.9%)	265 (74.6%)	788 (73.8%)
No	86 (24.2%)	104 (29.1%)	90 (25.4%)	280 (26.2%)
Prior radiation therapy				
Yes	265 (74.6%)	283 (79.1%)	256 (72.1%)	804 (75.3%)
No	90 (25.4%)	75 (20.9%)	99 (27.9%)	264 (24.7%)
Prior prostatectomy and radiation				
Yes	179 (50.4%)	179 (50.0%)	166 (46.8%)	524 (49.1%)
No	176 (49.6%)	179 (50.0%)	189 (53.2%)	544 (50.9%)
Baseline PRO score, mean (SD)				
BPI-SF				
Item 3 (worst pain in past 24 hours)	1.5 (2.24)	1.3 (1.91)	1.6 (2.25)	1.5 (2.14)
Pain severity	1.2 (1.67)	1.0 (1.53)	1.2 (1.77)	1.2 (1.66)
Pain interference	0.8 (1.44)	0.6 (1.24)	0.8 (1.58)	0.7 (1.42)
FACT-P				
FACT-P total score	124.9 (16.21)	124.4 (15.79)	124.4 (15.57)	124.6 (15.84)
FACT-G total score	88.2 (11.88)	87.8 (11.88)	87.8 (11.89)	87.9 (11.87)
FACT-P trial outcome index	84.5 (11.55)	84.0 (10.51)	84.1 (10.57)	84.2 (10.88)
FACT-P advanced prostate symptom index	26.8 (3.88)	26.9 (3.77)	26.8 (3.76)	26.8 (3.80)
FACT-P physical well-being	26.0 (2.74)	26.0 (2.51)	26.1 (2.17)	26.0 (2.48)
FACT-P emotional well-being	19.5 (3.28)	19.1 (3.66)	19.3 (3.58)	19.1 (3.66)
FACT-P social well-being	20.9 (4.93)	21.2 (5.02)	21.0 (4.98)	21.0 (4.97)
FACT-P prostate-related symptoms	36.6 (5.99)	36.6 (5.22)	36.6 (5.38)	36.6 (5.53)
FACT-P prostate-related symptoms pain-related	13.1 (3.30)	13.4 (2.91)	13.0 (3.24)	13.2 (3.15)
QLQ-PR25				
Sexual activity	30.0 (24.3)	26.7 (25.0)	28.4 (25.9)	28.4 (25.1)
Sexual functioning	50.2 (19.5)	52.7 (18.2)	50.2 (19.5)	52.7 (18.2)
Urinary symptoms	17.1 (15.3)	17.5 (14.7)	16.3 (13.4)	17.0 (14.5)
Modified urinary symptoms	27.1 (22.5)	27.6 (21.9)	26.6 (20.1)	27.1 (21.5)
Bowel symptoms/function	4.9 (8.4)	4.1 (7.5)	3.8 (7.1)	4.3 (7.7)
Incontinence aids	14.4 (18.6)	19.5 (24.5)	16.3 (23.5)	16.7 (22.3)
Hormonal treatment-related symptoms	7.8 (8.9)	8.1 (8.3)	8.1 (8.3)	7.6 (8.4)
EQ-5D-5 L				
Visual analog scale	82.7 (13.88)	83.5 (12.50)	82.1 (14.05)	82.8 (13.49)

The range, sign and clinical meaning of these scores are defined in Table 1. BPI-SF denotes Brief Pain Inventory–Short Form; EQ-5D-5 L, European Quality of Life 5-Dimensions 5-Levels; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; PRO, patient-reported outcome; QLQ-PR25, Quality of Life Questionnaire–Prostate 25; and SD, standard deviation.

for enzalutamide combination (difference, -1.78 ; 95% CI, -3.54 to -0.02) and -6.36 (95% CI, -7.74 to -4.97) for enzalutamide monotherapy (difference, -2.48 ; 95% CI, -4.23 to -0.73) (Fig. 2C). The clinically meaningful

thresholds for the physical well-being subdomain are 3 (improvement) and -3 (deterioration) (Table 1). The longitudinal LSM change in scores for physical well-being subdomain were -1.27 (95% CI, -1.56 to -0.99) for leuprolide

alone versus -2.00 (95% CI, -2.29 to -1.71) enzalutamide combination (difference, -0.73 ; 95% CI, -1.09 to -0.36) and -2.11 (95% CI, -2.40 to -1.82) for enzalutamide monotherapy (difference, -0.84 ; 95% CI, -1.20 to -0.48) (Fig. 2D). The longitudinal analysis for other FACT-P subdomains favored leuprolide-alone versus enzalutamide combination and/or enzalutamide monotherapy (FACT-G total score, advanced prostate symptom index, emotional well-being, functional well-being, prostate cancer subscale score, and trial outcome index) (Fig. S4).

Longitudinally, for all QLQ-PR25 domains except bowel symptoms/function, patients experienced some deterioration over time in all treatment groups; however, these differences did not meet the a priori threshold for clinical meaningfulness. The clinically meaningful thresholds for the sexual-activity domain are 16.67 (improvement) and -16.67 (deterioration) (Table 1). The longitudinal LSM change from baseline in sexual-activity score was -6.85 (95% CI, -8.63 to -5.07) for enzalutamide monotherapy versus -12.99 (95% CI, -14.76 to -11.22) for leuprolide

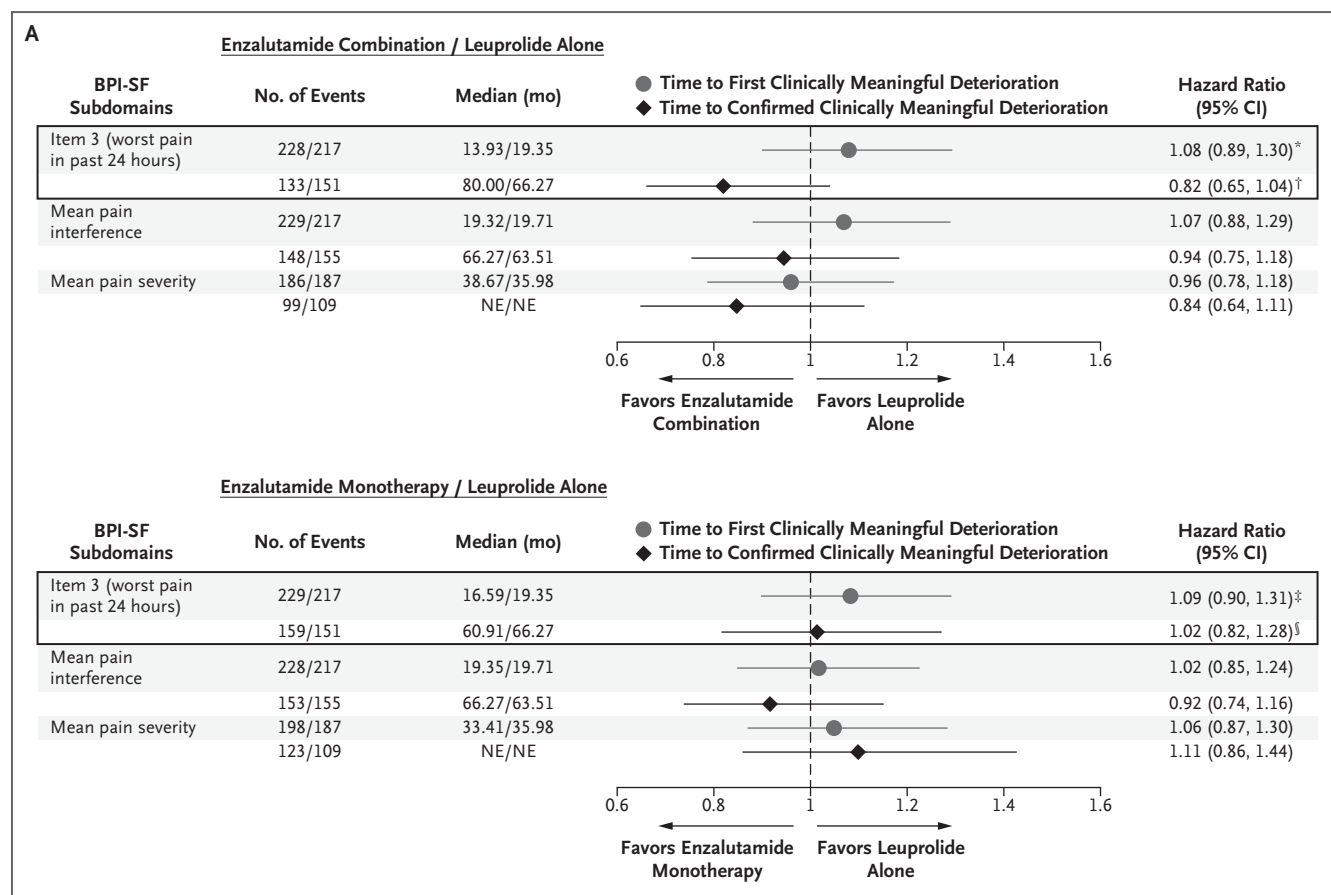


Figure 1. Time to First and Confirmed Clinical Deterioration in Patient-Reported Outcomes — Primary Threshold.

Panel A shows BPI-SF (enzalutamide combination vs. leuprolide alone on the top; enzalutamide monotherapy vs. leuprolide alone below). Panel B1 shows FACT-P (enzalutamide combination vs. leuprolide alone; Panel B2 shows enzalutamide monotherapy vs. leuprolide alone). Panel C1 shows QLQ-PR 25 (enzalutamide combination vs. leuprolide alone; Panel C2 shows enzalutamide monotherapy vs. leuprolide alone). * Parameter estimate, 0.075. † Parameter estimate, -0.193 . ‡ Parameter estimate, 0.086. § Parameter estimate, 0.114. || Parameter estimate, 0.129. ¶ Parameter estimate, 0.042. ** Parameter estimate, 0.160. †† Parameter estimate, 0.145. The widths of the 95% CIs have not been adjusted for multiplicity. Therefore, the CIs should not be used to reject or not reject treatment effects. BPI-SF denotes Brief Pain Inventory–Short Form; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-P, Functional Assessment of Cancer Therapy–Prostate; mo, months; NE, not estimable; No., number; and QLQ-PR25, Quality of Life Questionnaire–Prostate 25.

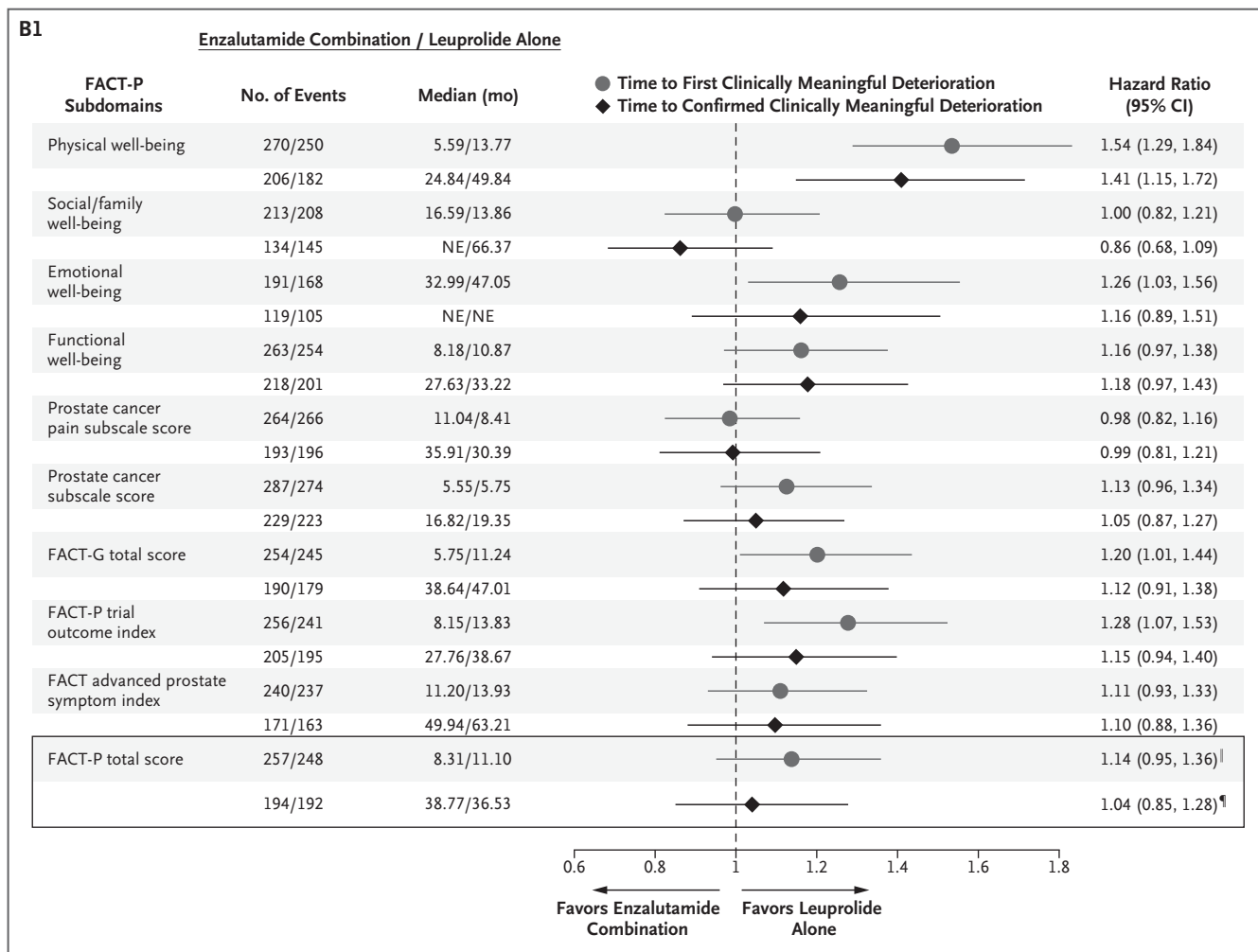


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alone (difference, 6.14; 95% CI, 3.93 to 8.35) (Fig. 2E). Clinically meaningful thresholds for hormonal treatment-related symptoms subdomain are 5.56 (deterioration) and -5.56 (improvement) (Table 1). Longitudinal LSM change from baseline in hormonal treatment-related symptoms was 9.75 (95% CI, 8.63 to 10.88) for leuprolide alone versus 11.44 (95% CI, 10.30 to 12.59) for enzalutamide monotherapy (difference, 1.69; 95% CI, 0.26 to 3.13) (Fig. 2F). These longitudinal changes met the definition for clinically meaningful in both groups. Data from the longitudinal analysis of other QLQ-PR25 subdomains are shown in Fig. S5.

Longitudinally, EQ-5D-5 L VAS scores remained stable in all groups (Fig. 2G). More than 70% of patients enrolled

were classified as stable/improved up to week 205 in item 3 (worst pain in the past 24 hours) across all groups (Fig. S6). Overall, physical well-being, prostate-related symptoms, and FACT-P total scores remained stable/improved in over 70% patients across all groups (Fig. S6). Over 40% of patients did not report deterioration in sexual-activity score, whereas most patients experienced deterioration in hormonal treatment-related symptoms in all groups (Fig. S6). The EQ-5D-5 L VAS scores did not deteriorate in over 60% of patients over time (Fig. S6).

SENSITIVITY ANALYSIS

The results of the sensitivity analyses were similar to those of the primary threshold analysis (Figs. S7 and S8).

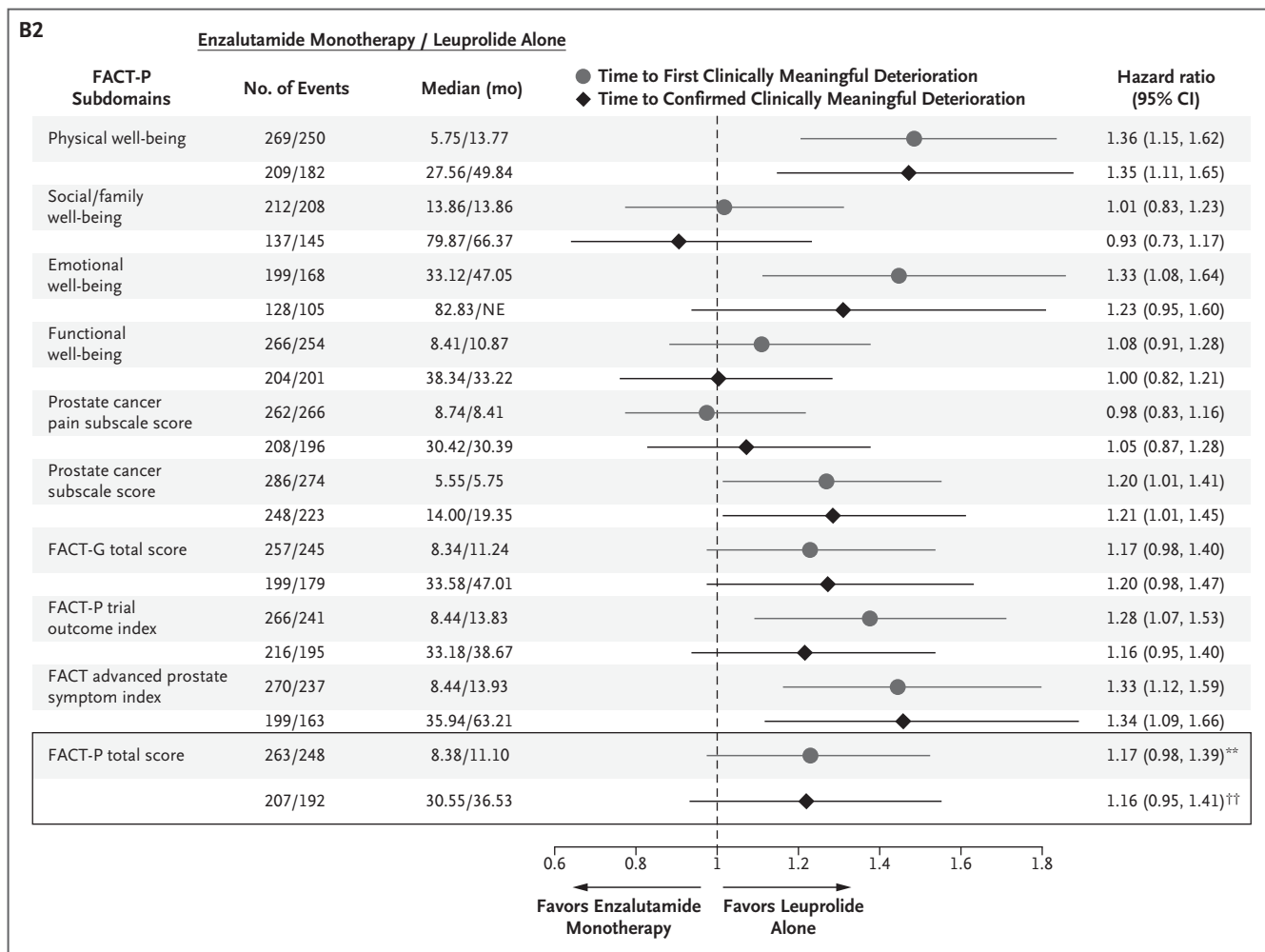


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Discussion

Prostate cancer therapies have benefits in terms of delaying disease progression but pose challenges concerning negatively affecting health-related quality of life, especially for patients with a long disease course. Preserving sexual function, a vital health-related, quality-of-life domain significantly affected by prostate cancer treatments, is pivotal in clinical decision-making because it directly affects overall health-related quality of life.¹⁶⁻¹⁹ The current PRO analysis complements the prior EMBARK data to collectively show that enzalutamide in patients with high-risk biochemical recurrence provides clinically meaningful improvements while preserving high baseline health-related quality of life.⁸

The baseline PRO scores indicated low levels of pain and high health-related quality of life, signifying that most patients were asymptomatic at baseline, consistent with previous studies involving patients with nonmetastatic prostate cancer who have not previously received hormonal therapy.²⁰ Despite high health-related quality of life at baseline, sexual-activity scores were low, likely because of previous treatments (25% primary radiotherapy, 25% prior radical prostatectomy alone, and 50% prior radical prostatectomy and radiotherapy).²¹ Very few patients reported hormonal therapy-related symptoms at baseline because most patients (69%) had not been exposed to hormone therapy, and patients who had been exposed to prior hormonal therapy had treatment at least 9 months before random assignment. The patients reported some urinary symptoms at baseline, which was

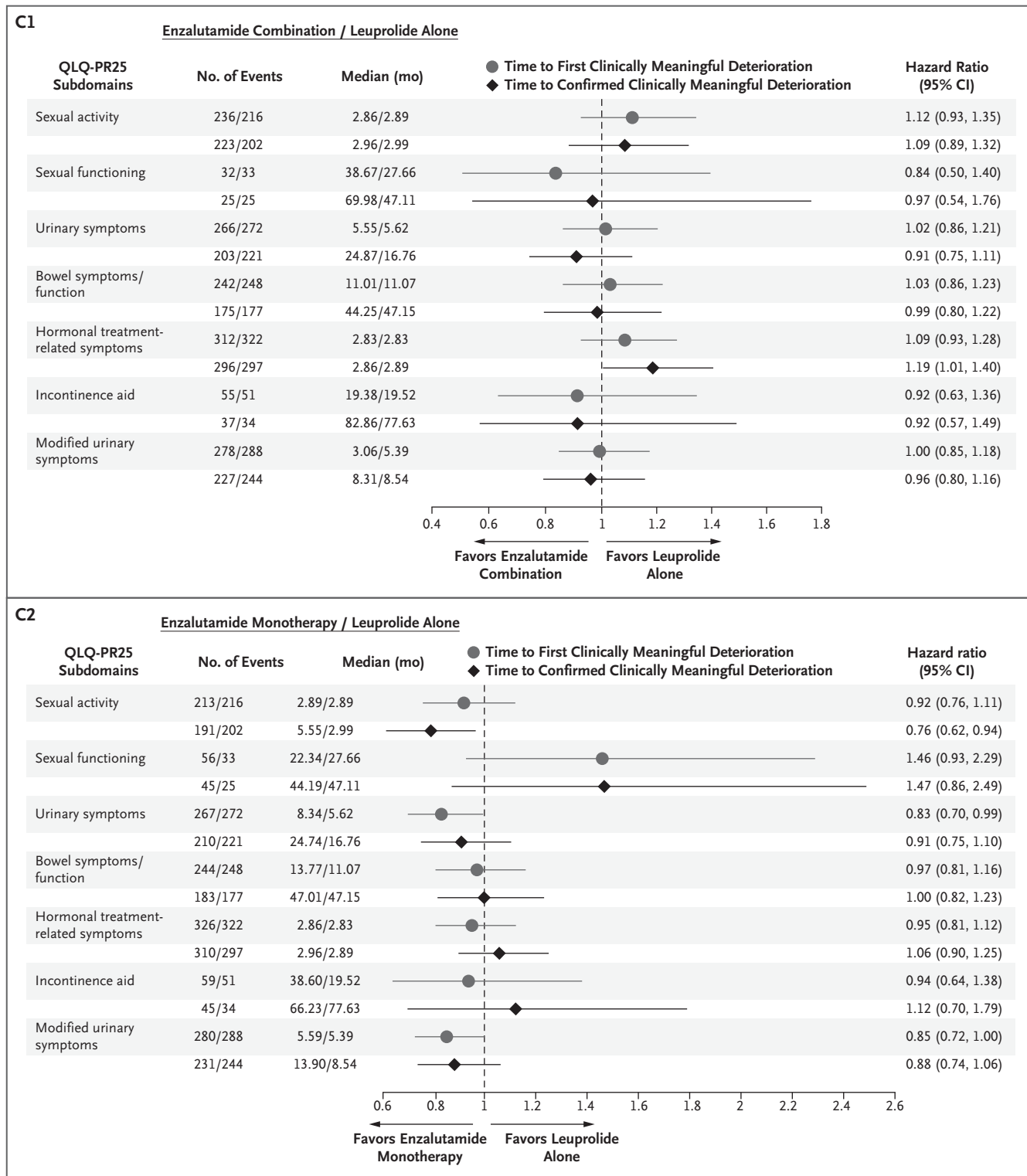


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expected given that they had previously received radical prostatectomy and/or radiotherapy.²²

The PRO scores remained stable throughout the trial for most patients in all groups, suggesting maintenance of the high baseline health-related quality of life and low baseline symptoms across all groups, with no clinically meaningful differences across groups.

Treatment was suspended in a higher proportion of patients in the enzalutamide combination group than in the monotherapy and leuprolide-alone groups. Contrastingly, the median duration of treatment suspension was shorter in the monotherapy group than in the enzalutamide combination

and leuprolide-alone groups, which can be attributed to the lack of testosterone suppression.²³ The analysis of the relationship between PROs and testosterone levels warrants further investigation.

The time to confirmed clinically meaningful deterioration in sexual-activity score was 2.56 months longer with enzalutamide monotherapy versus leuprolide alone. Longitudinal analysis also demonstrated deterioration in all groups in sexual activity, with less deterioration with enzalutamide monotherapy. Patients with localized prostate cancer who have undergone radical prostatectomy often experience sexual-dysfunction symptoms that affect health-related quality of life.²² Androgen-deprivation therapy

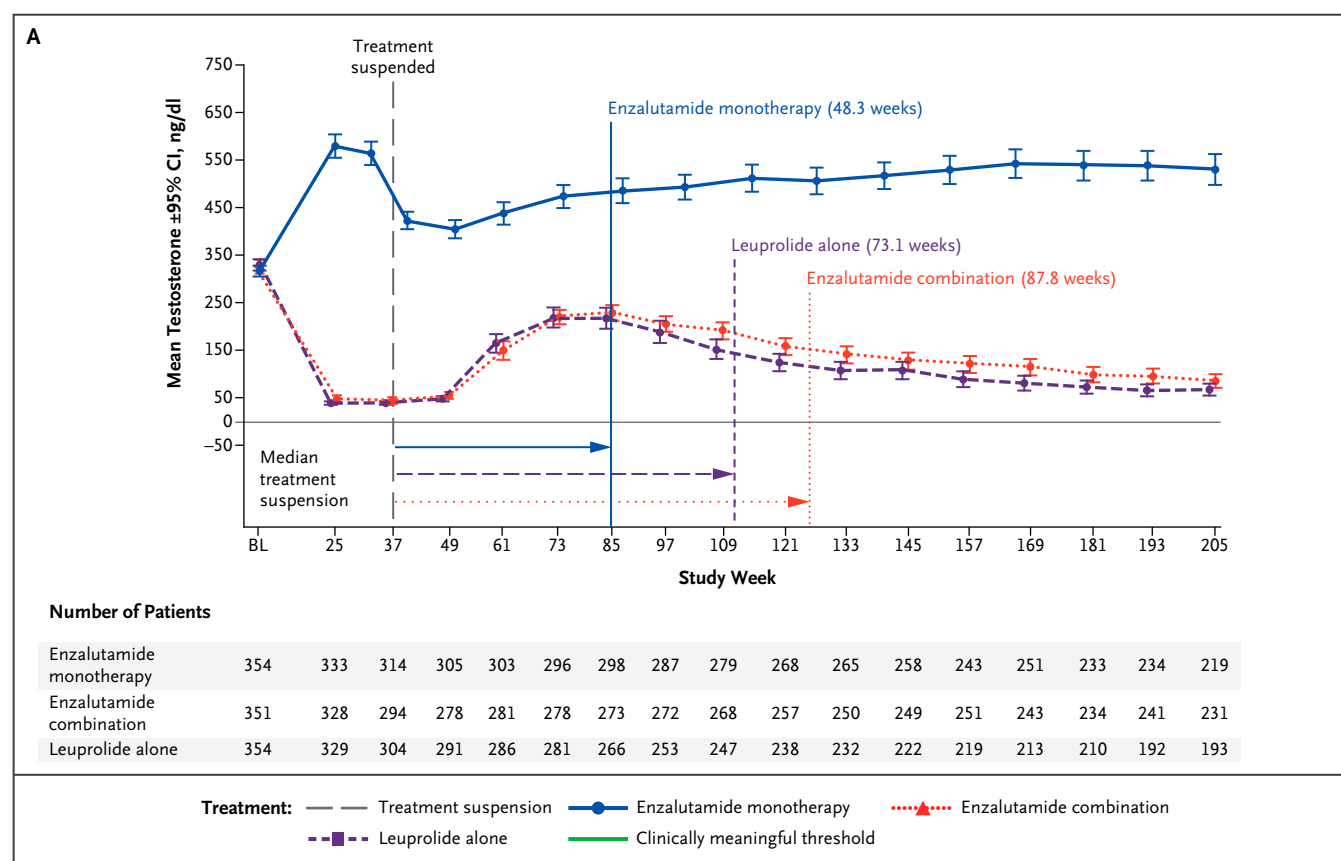


Figure 2. Longitudinal Analysis of Changes from Baseline.

Panel A shows testosterone levels. Panel B shows BPI-SF–item 3 (worst pain in past 24 hours). Panel C shows FACT-P–total score. Panel D shows FACT-P–physical well-being. Panel E shows QLQ-PR25 score–sexual activity. Panel F shows QLQ-PR25 score–hormone treatment-related symptoms. Panel G shows EQ-5D-5L visual analog scale. For Panel A, the time from suspension (after week 37) is depicted in months. For Panels B through G, the time is depicted as analysis visits, in weeks. The widths of the 95% CIs have not been adjusted for multiplicity. Therefore, the CIs should not be used to reject or not reject treatment effects. BPI-SF denotes Brief Pain Inventory–Short Form; CI, confidence interval; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels health questionnaire; FACT-P, Functional Assessment of Cancer Therapy–Prostate; LSM, least-squares means; and QLQ-PR25, Quality of Life Questionnaire–Prostate 25.

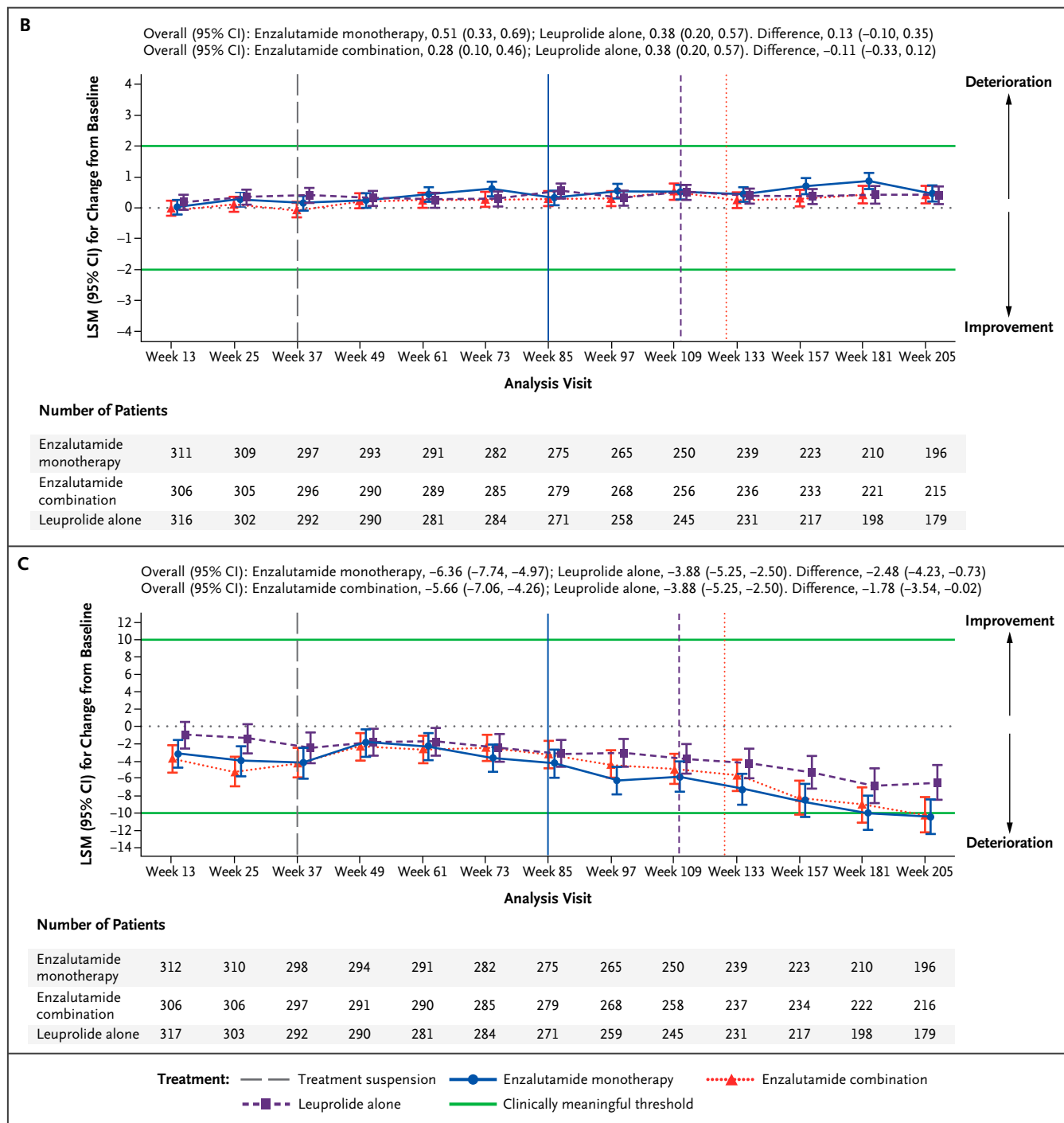


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is the recommended treatment for patients with biochemical recurrence, and sexual function is recognized as the health-related quality-of-life domain most affected by androgen-deprivation therapy for prostate cancer.¹⁶⁻¹⁹

For hormonal treatment-related symptoms, enzalutamide combination was associated with a higher hazard in time to confirmed clinically meaningful deterioration versus leuprolide alone. Longitudinal analysis also indicated

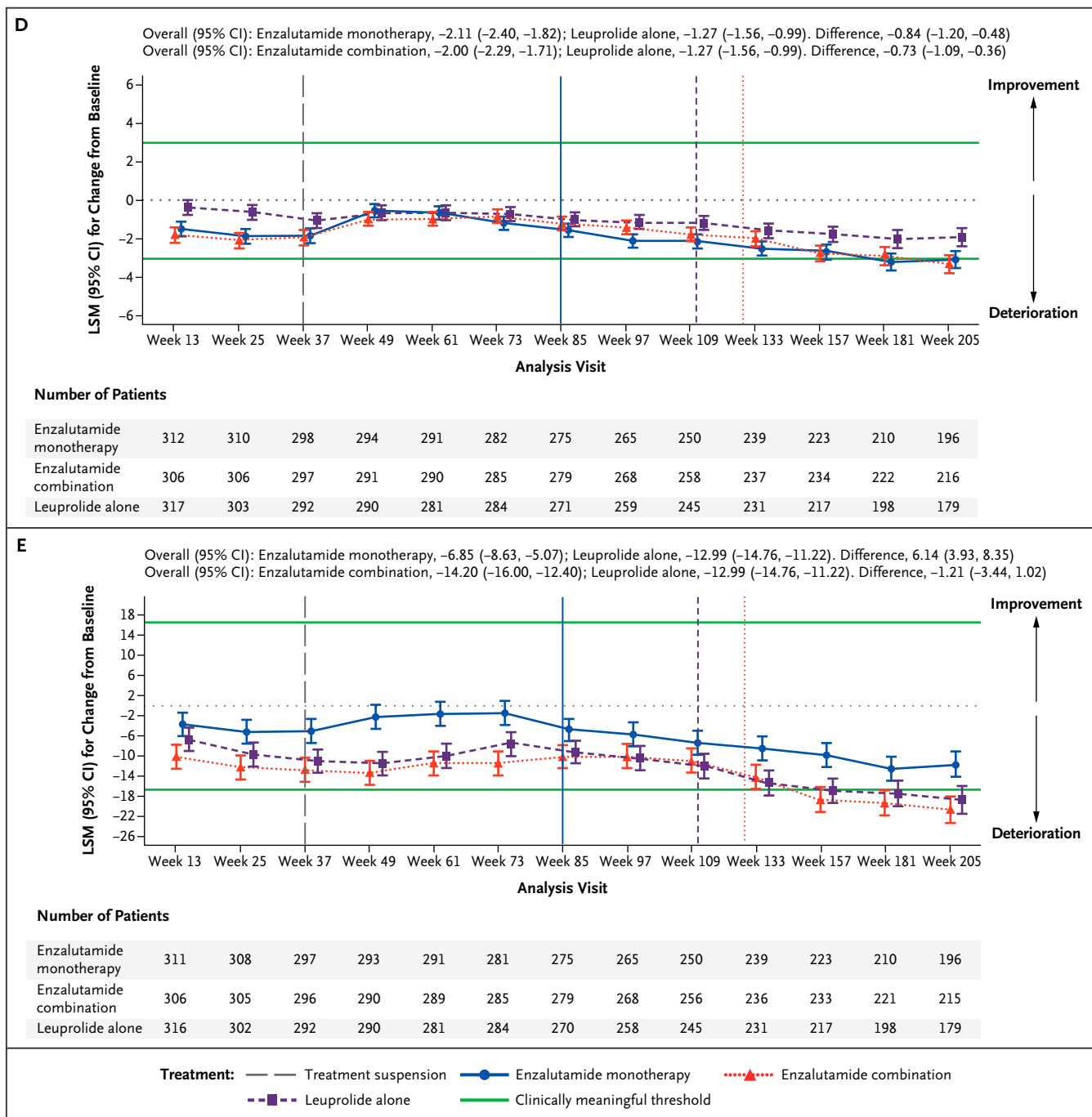


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differences in changes from baseline favoring leuprolide alone over enzalutamide combination. This aligns with expectations, because enzalutamide treatments more effectively inhibit androgen activity, evidenced by the greater declines in PSA, an androgen-regulated gene, in the primary EMBARK analysis.⁸

In physical well-being score, the time to first and confirmed deterioration was longer in the leuprolide-alone group compared with both enzalutamide groups. The longitudinal LSM change in scores for physical well-being subdomain also favored leuprolide-alone versus enzalutamide groups. The physical well-being scores were in line

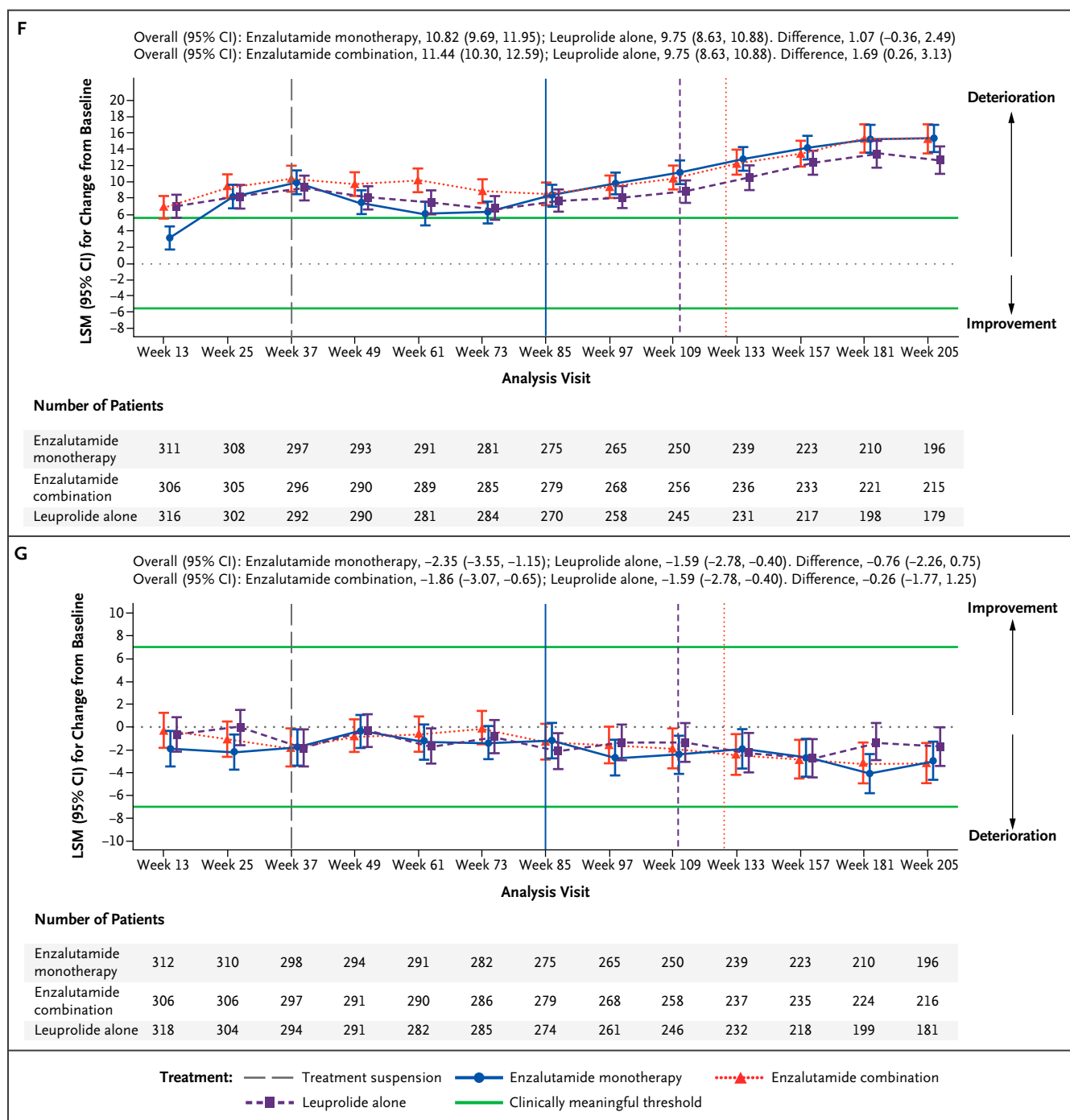


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with the higher number of patients experiencing fatigue in the enzalutamide combination (42.8%) and monotherapy (46.6%) groups, as compared with the leuprolide-alone group (32.8%) in the trial population.⁸

The EMBARK oncologic outcomes favored enzalutamide combination and monotherapy in high-risk biochemical recurrence, including improved metastasis-free survival.⁸ Notably, multiple studies in other disease settings including

nonmetastatic castration-resistant prostate cancer,²⁴ metastatic castration-resistant prostate cancer,²⁵ and metastatic hormone-sensitive prostate cancer²⁶ have shown enzalutamide combination provides clinically meaningful oncological benefits while preserving health-related quality of life. Our data show that the oncologic benefits of enzalutamide combination and monotherapy were associated with reasonably preserved health-related quality of life.

Strengths of our analysis include a substantial sample size, a study population that is representative of the typical population described in men with biochemically recurrent prostate cancer (Table S3),^{4,27-30} the use of multiple health-related quality-of-life measures, and high completion rates up to week 205 across all groups. Assessing time to confirmed clinical deterioration is also a study strength. It is possible that time to first deterioration events may be unrelated to disease progression, whereas confirmed deterioration required deterioration to be sustained until the next consecutive scheduled visit, increasing the probability that these events were related to underlying disease and disease progression.

Limitations included the unblinded monotherapy group, which confounds interpreting the PRO analysis. Regarding sexual activity, because all men received prior local prostate cancer therapy, baseline sexual-function scores show some level of dysfunction. Although sexual function was captured, there were no dedicated sexual-function questionnaires, limiting a more detailed analysis of this vital end point. The percentage of underrepresented groups was limited, which precluded us from analyzing differences by race. Finally, because we measured PROs up to approximately 4 years (205 weeks) in longitudinal analyses, some of the slight PRO declines may be explained by aging, but in the absence of a nontreated control group this effect cannot be measured. Furthermore, the quality of life should be interpreted in the setting of enzalutamide/androgen-deprivation therapy, including a one-time treatment suspension.

Conclusions

Adding enzalutamide to leuprolide and monotherapy improved metastasis-free survival versus leuprolide alone without negatively affecting overall health-related quality of life. There was no difference in time to first and

confirmed clinically meaningful deterioration in FACT-P total score. Hormonal treatment-related symptoms may occur earlier with enzalutamide combination than with leuprolide alone. Clinicians can leverage EMBARK findings for informed discussions with patients, enhancing the shared decision-making process regarding treatment options.

Disclosures

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