

Are long-term remissions possible with hormonal therapy only? Post hoc analysis of EMBARK examining sustained prostate-specific antigen <0.2 ng/mL despite testosterone recovery after treatment suspension

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Objective

- To evaluate the proportions of patients in the EMBARK trial with prostate-specific antigen (PSA) levels of <0.2 ng/mL or <0.02 ng/mL and testosterone (T) recovery to baseline, 175 ng/dL, or 250 ng/dL after treatment suspension of 12, 24, or 36 months.

Key Findings and Conclusions

- Approximately 1 in 25 patients treated with enzalutamide plus leuprolide (enza combo) for 9 months had PSA levels of <0.2 ng/mL and normal T (>250 ng/dL) 3 years post therapy, which demonstrates that long-term “remissions” are possible after only 9 months of enza combo.
- Rates with leuprolide alone and enzalutamide monotherapy (enza mono) were not zero but were much lower than with enza combo (both 1%, vs 4% with enza combo).
- Approximately 2% of patients treated with enza combo had PSA levels below the lower limit of quantification (<0.02 ng/mL) and normal T 3 years post therapy.



Plain Language Summary

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References: 1. Freedland SJ, et al. *N Engl J Med.* 2023;389(16):1453–1465. 2. Shore ND, et al. *N Engl J Med.* 2025;doi: 10.1056/NEJMoa2510310.

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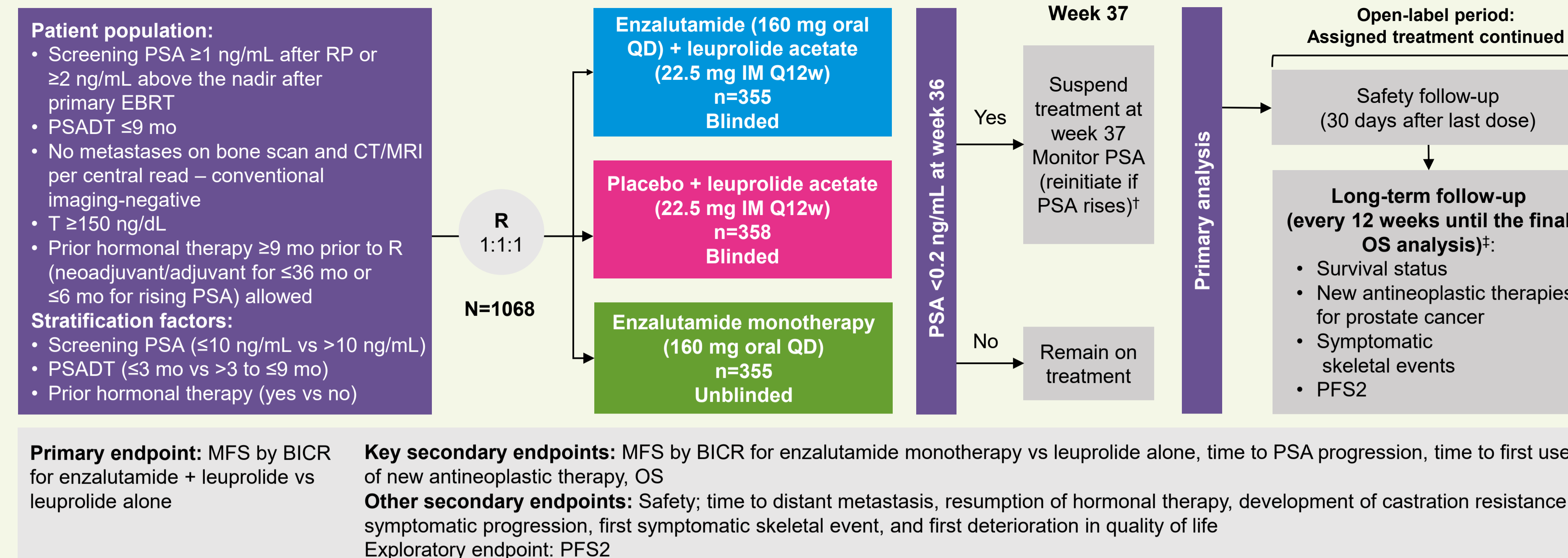
Background and Objectives

- EMBARC (NCT02319837) demonstrated significant improvements for metastasis-free survival (enza combo and enza mono) and overall survival (enza combo) in patients with prostate cancer and high-risk biochemical recurrence.¹
 - Eight-year overall survival was 78.9% (95% confidence interval [CI]: 73.9, 83.1) in the enza combo group and 69.5% (95% CI: 64.0, 74.3) in the leuprolide alone group.^{1,2}
- A key feature of EMBARK was treatment suspension after 37 weeks in patients with PSA levels of <0.2 ng/mL.¹
- The proportions of patients with sustained PSA levels of <0.2 ng/mL or <0.02 ng/mL despite T recovery were assessed.

Methods

- In EMBARK, patients were randomized 1:1:1 to receive enza combo, leuprolide alone, or enza mono for 36 weeks (**Figure 1**).
- This post hoc analysis evaluated the proportions of patients in the safety population with PSA levels of <0.2 ng/mL or <0.02 ng/mL and T recovery to 175 ng/dL, 250 ng/dL, or baseline after treatment suspension of 12, 24, or 36 months.

Figure 1. Study design

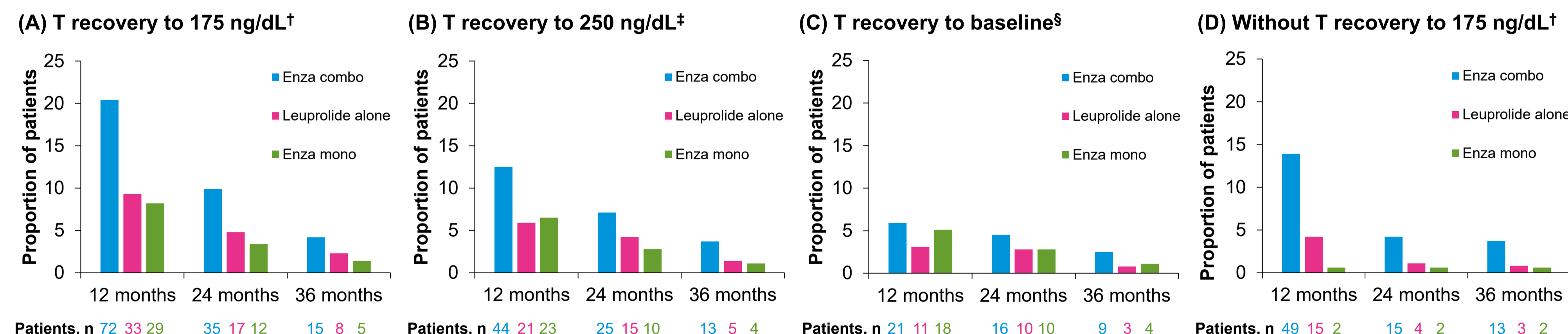


¹Study treatment was suspended once at week 37 if PSA was <0.2 ng/mL and restarted when PSA was ≥ 5.0 ng/mL without prior RP or ≥ 2 ng/mL with prior RP.
²OS was a key alpha-protected secondary endpoint. Updated results from the following endpoints were not alpha-protected and are thus considered nominal: time to first use of new antineoplastic therapy, time to first symptomatic skeletal event, and PFS2.
BICR, blinded independent central review; CT, computed tomography; D, day; EBRT, external beam radiation therapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; PSADT, PSA doubling time; Q, every; R, randomization; RP, radical prostatectomy; T, testosterone; w, weeks.
Freedland SJ, et al. *New Engl J Med.* 2023;389(16):1453–1465.

Results

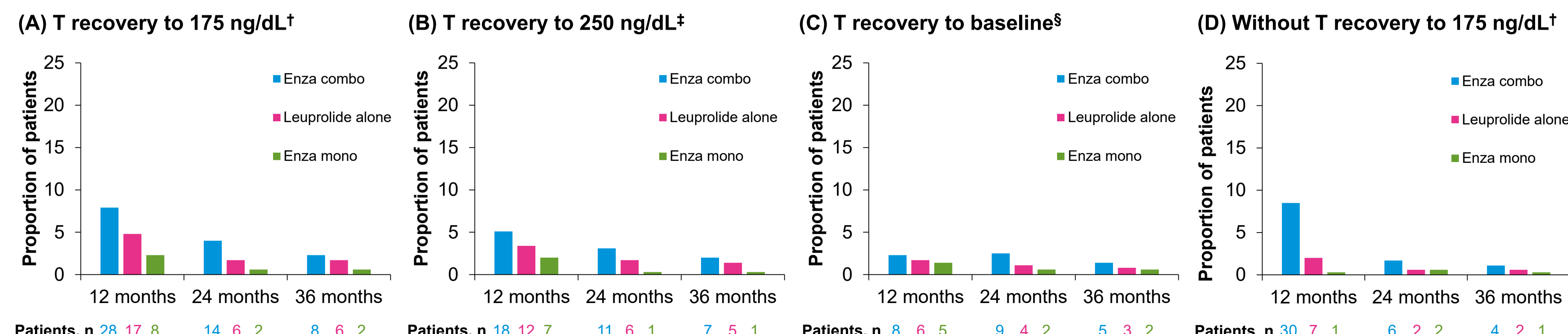
- During the entire 36 months after treatment suspension, 9.3%, 3.4%, and 2.3% of patients in the safety population in the enza combo (n=353), leuprolide alone (n=354), and enza mono groups (n=354), respectively, maintained PSA levels of <0.2 ng/mL, while 4.0%, 2.5%, and 0.8% maintained PSA levels of <0.02 ng/mL.
- The proportions of patients in the enza combo, leuprolide alone, and enza mono groups who maintained PSA levels of <0.2 ng/mL or PSA levels of <0.02 ng/mL and achieved T recovery to 175 ng/dL, 250 ng/dL, or baseline, or who did not achieve T recovery to 175 ng/dL, are shown in **Figure 2** and **Figure 3**, respectively.
 - At 36 months after treatment suspension, 3.7%, 1.4%, and 1.1% of patients in the enza combo, leuprolide alone, and enza mono groups, respectively, had maintained PSA levels of <0.2 ng/mL and achieved T recovery to 250 ng/dL (**Figure 2B**); and 2.0%, 1.4%, and 0.3%, respectively, had maintained PSA levels of <0.02 ng/mL and achieved T recovery to 250 ng/dL (**Figure 3B**).
- At 36 months post treatment suspension, 3.7% of patients treated with enza combo, 0.8% of patients in the leuprolide alone group, and 0.6% of patients in the enza mono group had maintained PSA levels of <0.2 ng/mL but had not achieved T recovery to 175 ng/dL (**Figure 2D**); and 1.1%, 0.6%, and 0.3%, respectively, had maintained PSA levels of <0.02 ng/mL but not achieved T recovery to 175 ng/dL (**Figure 3D**).

Figure 2. Patients with PSA levels of <0.2 ng/mL and T recovery to 175 ng/dL, 250 ng/dL, or baseline, or without T recovery



Data cutoff: January 31, 2023. The denominator for all percentages is the number of patients in the safety population.
[†]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to >175 ng/dL. [‡]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to >250 ng/dL. [§]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to \geq baseline T.
Enza combo, enzalutamide plus leuprolide; enza mono, enzalutamide monotherapy; PSA, prostate-specific antigen; T, testosterone.

Figure 3. Patients with PSA levels of <0.02 ng/mL and T recovery to 175 ng/dL, 250 ng/dL, or baseline, or without T recovery



Data cutoff: January 31, 2023. The denominator for all percentages is the number of patients in the safety population.
[†]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to >175 ng/dL. [‡]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to >250 ng/dL. [§]T assessment at 12, 24, or 36 months \pm 6-week window of recovery to \geq baseline T.
Enza combo, enzalutamide plus leuprolide; enza mono, enzalutamide monotherapy; PSA, prostate-specific antigen; T, testosterone.