Final Overall Survival Results From EORTC 1333/PEACE-3: Enzalutamide With or Without Radium-223 in Metastatic Castration-Resistant Prostate Cancer

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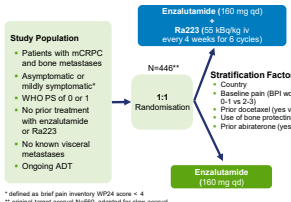
INTRODUCTION and OBJECTIVES

- Enzalutamide is a standard of care and the most frequently used treatment option for 1st line metastatic castration-resistant prostate cancer (mCRPC) (1).
- Radium-223 (Ra223), an alpha-particle emitting agent, conferred an overall survival (OS) benefit in mCRPC, as demonstrated in ALSYMPCA trial(2).
- Primary analysis of EORTC 1333/PEACE-3 (3):
  - Enzalutamide plus Ra223 showed significant improvement in radiographic progression-free survival (rPFS) compared to enzalutamide alone (primary endpoint) in patients with mCRPC.
  - Improvement in rPFS supported by a significantly improved OS (key secondary endpoint) as interim analysis.
  - Combination led to moderate increased toxicity: drug-related treatment-emergent adverse events (TEAE) ≥ grade 3 for enzalutamide alone 19% → combination 28%.

Final OS, as a key secondary endpoint, is presented here.

METHODS – STUDY DESIGN



Study Population
- Patients with mCRPC and bone metastases
- Asymptomatic or mildly symptomatic*
- WHO PS of 0 or 1
- No prior treatment with enzalutamide or Ra223
- No known visceral metastases
- Ongoing ADT

Primary Endpoint
- rPFS

Key Secondary
- Overall Survival
- Time to next treatment
- Time to pain progression
- Time to first SSE (symptomatic skeletal event)

Safety
- Treatment emergent CTCAE

Statistical Design

Primary Analysis:
- **283 rPFS event**
- Key secondary endpoints tested semi-hierarchically.
- OS tested at 1-sided α = 0.0034 due to interim testing (239 events)

Final OS analysis:
- **317 OS events** (target = 299)
- OS tested at 1-sided **α = 0.0248**
- **70% power** to detect HR=0.75

OS tested on the ITT set (ie all randomized patients) – stratified for baseline pain, prior docetaxel and use of BPA.

* defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Use of bone protecting agents (BPA) made mandatory (March 2018 after inclusion of 119 patients)

IDMC recommendation (Sep 2024): OS at primary analysis considered significant but conduct a final OS analysis to confirm the magnitude of benefit.

Baseline Characteristics	Enza+Ra223 (N=222) N (%)	Enza (N=224) N (%)
Age, Median (range) years	70.0 (43.0 - 90.0)	70.0 (47.0 - 90.0)
PSA, Median (Q25-Q75) ng/mL	24.5 (7.8-68.8) N = 190	21.2 (7.9-53.1) N = 191
WHO Performance status 0	153 (69)	154 (69)
Prior docetaxel(1)	67 (30.2)	66 (30)
Prior abiraterone(1)	4 (2)	7 (3)
Bone lesions(2)		
<10	109 (49)	105 (47)
≥10	93 (42)	99 (44)
Missing or diffuse lesions	20 (9)	20 (9)
Alkaline phosphatase		
≤ULN	127 (57)	109 (49)
>ULN	82 (37)	109 (49)
Missing	13 (6)	6 (3)
Extra-skeletal disease at baseline	77 (35)	73 (33)

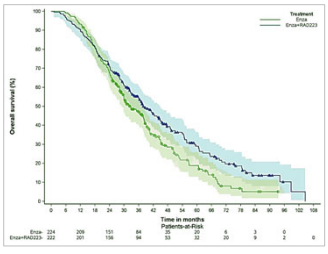
(1) Prior docetaxel or abiraterone was allowed for mHSPC
(2) Per imaging guidelines, the type of bone lesions is reported by a radiologist and classified into focal, diffuse or equivocal. Only focal bone lesions can be counted.

N = 446 patients
- Nov 2015 → Mar 2023
- 56 centres from 12 countries
- Database lock = 12 Jan 2026 (cutoff date = 1MAY2025)
- Median follow-up = 4.8 years (3.4 yrs at primary analysis)

Intergroup trial led by **EORTC (EU)**
Collaborating groups:
- **LACOG** (Brazil)
- **CTI** (Ireland)
- **CUOG** (Canada)
- **UNICANCER-GETUG** (France)

The method used (inversed censoring) censors at death. It attempts to estimate what follow-up would have been if patients had not died.

RESULTS: FINAL OS



	Enza+Ra223 (N=222) (95% CI)	Enza (N=224) (95% CI)
6 mos	96.8 (93.5-98.5%)	99.1 (96.5-99.8%)
12 mos	90.5 (85.9-93.7%)	92.9 (88.6-95.6%)
18 mos	81.1 (75.3-85.6%)	80.8 (74.9-85.3%)
24 mos	71.1 (64.7-76.6%)	67.7 (61.2-73.4%)
36 mos	54.2 (47.1-60.6%)	47.4 (40.6-54.0%)

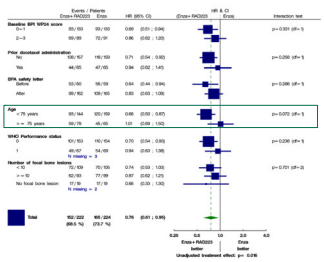
Database locked on 12 January 2026
(cut off date: 01 May 2025)

Treatment	Event/Total	Median (95%CI) (months)[1]	Hazard Ratio (95% CI)[2]	1-sided P-value
Enza	165/224	**32.62** (29.31-38.24)	**0.76** (0.60-0.96)	**Logrank: 0.0096**[3] **Permutation: 0.0105**
Enza+Ra223	152/222	**38.21** (33.08-44.75)		

[1] Kaplan-Meier method; [2] Cox model; [3] Stratified Logrank test

Preset level of significance at final analysis: <0.0248
Crossing of the curves (still) present at month 18. Only 3 patients censored < 24 months.

Final OS – Subgroup Analysis



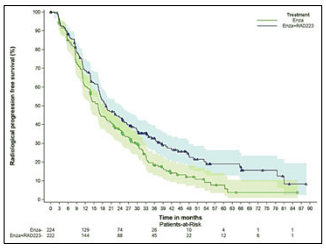
Treatment effect is reduced in older patients (≥ 75 years):
- <75 yrs: HR = 0.66
- ≥ 75 yrs: HR = 1.01

Similar but less pronounced effect for:
- Prior docetaxel administration
- WHO performance status

Reduced treatment effect may be linked with lower prognosis although small number of patients avoid a conclusion.

(1) Ravall A et al. Clin Genitourin Cancer 2025; (2) Parker C et al. N Engl J Med 2014; (3) Tombal B et al. Ann Oncol 2025.

RESULTS: Final rPFS



	Enza+Ra223 (N=222) (95% CI)	Enza (N=224) (95% CI)
6 mos	88.4 (83.3-92.0%)	84.6 (79.1-88.8%)
12 mos	68.9 (62.2-74.7%)	60.6 (53.8-66.8%)
18 mos	52.9 (45.9-59.4%)	44.5 (37.7-51.0%)
24 mos	44.1 (37.2-50.7%)	37.2 (30.7-43.7%)

Database locked on 12 January 2026
(cut off date: 01 May 2025)

Treatment	Event/ Total	Median (95%CI) (months)[1]	Hazard Ratio (95% CI)[2]
Enza	176/224	**16.43** (13.77-19.15)	176/224
Enza+Ra223	156/222	**19.19** (16.92-24.57)	**0.71 (0.57-0.89)**

[1] Kaplan-Meier method; [2] Cox model

rPFS results confirmed with longer follow-up

RESULTS: SAFETY SUMMARY

	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
Treatment-emergent AEs	218 (100%)	219 (97.8%)
Drug-related TEAEs	181 (83.0%)	160 (71.4%)
Serious TEAEs	107 (49.1%)	73 (32.6%)
Serious drug-related TEAEs	23 (10.6%)	3 (1.3%)
Grade 3-5 TEAEs	151 (69.3%)	129 (57.6%)
Grade 3-5 drug-related TEAEs	63 (28.9%)	42 (18.8%)
Death due to AE (trt emergent or post trt)	10 (4.6%)	6 (2.7%)
Treatment discontinuation due to toxicity:		
Enzalutamide	12 (5.5%)	12 (5.4%)
Ra223	7 (3.2%)	

Treatment-emergent AEs are all AEs arising from start of treatment until 28 days after last dose of any study treatment

Number of patients (%) with grade 3-5 TEAE	Enza+RAD223 (N=218) N (%)	Enza (N=224) N (%)
All	**151 (69.3%)**	**129 (57.6%)**
Hypertension	78 (35.8)	80 (35.7)
Fatigue	12 (5.5)	4 (1.8)
Fracture	12 (5.5)	3 (1.3)
Anemia	13 (6)	5 (2.2)
Neutropenia	10 (4.6)	0
Bone pain	13 (6)	12 (5.4)
Weight decreased	10 (4.6)	2 (0.9)
Spinal cord compression	7 (3.2)	8 (3.6)
Drug-related	**63 (28.9%)**	**42 (18.8%)**
Hypertension	26 (11.9)	27 (12.1)
Fatigue	9 (4.1)	3 (1.3)
Anemia	6 (2.8)	0
Neutropenia	7 (3.2)	0

Treatment-emergent AEs are all AEs arising from start of treatment until 28 days after last dose of any study drug

Side effects of special interest:
- 1 MDS
- 1 AML
- 1 CML (drug-related)

All 3 in the combination arm

- 17 osteonecrosis of the jaw:
  - 14 in the combo (5 grade 3)
  - 3 in the enza arm

No individual TEAE ≥ grade 3 has increased by more than 5% in the combination compared to the enzalutamide alone arm.

Summary

- Final OS and updated safety based on database locked on 12 January 2026. Median follow-up duration: 58 months
- Combination of enzalutamide and 6 cycles of Ra223 shows a significant improvement in OS:
  - **HR 0.76 (0.60-0.96), log-rank p-value=0.0096**
  - **Median OS increased: 32.6 → 38.2 months with the combination**
  - Crossing of the OS curves around 18 months is (still) observed.
    - Difference at month 12 = +6 deaths (16 vs 22).
    - Additional analyses are planned to further characterise the hazard ratios over time.
- Improvement in rPFS is confirmed with longer follow-up:
  - **HR 0.71 (0.57-0.89)**
  - **Median rPFS = 16.4 → 19.2 months.**
- Observed safety profile of the combination is consistent with results at primary completion: moderate increase in treatment-emergent adverse events with the combination.

CONCLUSION

- **Combination of enzalutamide and 6 cycles of Radium-223 demonstrated a significant overall survival (OS) benefit (HR=0.76).**
- **Improvement in radiographic progression-free survival was confirmed.**
- **Moderate increase in adverse events in the combination arm.**

Enzalutamide plus radium-223 (plus a bone-protecting agent) is an option in first-line treatment for mCRPC patients with bone metastases

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DOI: 10.1016/j.annonc.2026.02.009
URL: https://www.annalsofoncology.org/article/S0923-7534(26)00065-7/fulltext