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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial

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Background: The EORTC 1333 'PEACE-3' study investigated the combination of enzalutamide and 6 monthly injections of radium-223 (Ra223) in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases.

Materials and methods: From November 2015 to March 2023, 446 patients, including 11 who received abiraterone, were randomized to enzalutamide (without placebo) or enzalutamide combined with six cycles of Ra223. As of March 2018, the co-administration of zoledronic acid or denosumab was mandatory. The primary endpoint was radiological progression-free survival (rPFS) by investigator assessment. Key secondary endpoints included overall survival (OS), time to subsequent systemic treatment, pain progression, and symptomatic skeletal event.

Results: The hazard ratio (HR) for rPFS was 0.69 [95% confidence interval (CI) 0.54-0.87, $P = 0.0009$], with a median rPFS of 16.4 months (95% CI 13.8-19.2 months) in the enzalutamide arm and 19.4 months (95% CI 17.1-25.3 months) in the combination arm. At the preplanned interim analysis conducted at 80% of the OS events, the HR for OS was 0.69 (95% CI 0.52-0.90, $P = 0.0031$), with a median OS of 35.0 months (95% CI 28.8-38.9 months) in the enzalutamide arm and 42.3 months (95% CI 36.8-49.1 months) in the combination arm. Due to non-proportional hazards, this will be tested further at the final OS analysis. Treatment-emergent adverse events (TEAEs) $\geq$ grade 3 were recorded in 55.8% and 65.6% of the patients in the enzalutamide and combination arms, respectively. The most frequent grade $\geq$3 TEAEs in the combination arm were hypertension (34%), fatigue (6%), fracture (5%), anemia (5%), and neutropenia (5%). Fractures [either treatment-emergent or post-treatment, symptomatic or pathologic, or with or without bone-protecting agent (BPA) use] were reported in 30 (13.4%) patients in the enzalutamide arm and 53 patients (24.3%) in the combination arm.

Conclusion: PEACE-3 demonstrates that combining enzalutamide with Ra223 as first-line therapy for mCRPC significantly improves rPFS. Although statistically significant at the OS interim boundary, the study will continue to the final OS analysis.

Key words: metastatic castration-resistant prostate cancer, bone metastases, radium-223, enzalutamide

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease for most patients.[1] Over the years, several first-line treatments for mCRPC were shown to increase the radiographic progression-free survival (rPFS) or overall survival (OS) of patients whose cancer had progressed on androgen deprivation therapy (ADT): docetaxel, radium-223 dichloride (Ra223), abiraterone/

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prednisone, enzalutamide alone or in combination with talazoparib or lutetium Lu 177 vipivotide tetraxetan.[2]

Ra223 is an alpha particle-emitting calcium mimetic that incorporates into newly formed bone matrix within osteoblastic metastatic lesions and induces DNA double-strand breaks in nearby exposed tumor cells, osteoblasts, and osteoclasts.[3] The ALSYMPCA trial randomized 921 symptomatic mCRPC patients progressing on ADT, before or after docetaxel, to receive the standard of care plus six cycles of Ra223 or placebo.[4] Ra223 significantly improved OS, time to symptomatic skeletal events, and quality of life (QoL) compared with placebo [hazard ratio (HR) 0.70].[4,5]

Following the COU-AA-302 and PREVAIL trials, abiraterone acetate and enzalutamide became the reference treatments for most patients with asymptomatic or early symptomatic mCRPC who progressed on ADT.[6,7] These oral drugs also improved OS, QoL, prostate-specific antigen response, and rPFS. In most countries, monotherapy Ra223 has been considered a second- or third-line treatment option following androgen-receptor pathway inhibitor (ARPI).[8]

Two trials were designed to assess the safety and efficacy of Ra223 in combination with this novel class of therapies in a contemporary environment. The ERA 223 trial (NCT02043678) investigated the addition of six cycles of Ra223 or placebo to abiraterone and prednisone in patients with mCRPC and bone metastases.[9] The primary endpoint of symptomatic skeletal event-free survival was not met. The study had been unblinded prematurely on 17 November 2017, after more fractures and deaths had been observed in the Ra223 group than in the placebo group.[9]

In this article, we report on the phase III trial, EORTC GUCG 1333, or PEACE-3 (NCT02194842/EudraCT2014-001787-36), which investigated the use of six cycles of Ra223 in combination with enzalutamide in patients with bone mCRPC.

MATERIALS AND METHODS

Trial design and oversight

The EORTC GUCG-1333 (PEACE-3) trial is an international, randomized, academic, open-label, phase III trial run in collaboration with Clinical Trial Ireland (CTI), the Canadian Urological Oncology Group (CUOG), the Latin American Cooperative Oncology Group (LACOG), and the French group GETUG/UNICANCER. Patients with mCRPC and bone metastases were randomly assigned 1 : 1 to oral enzalutamide 160 mg daily monotherapy (enzalutamide arm) or combined with six intravenous injections of 55 kBq/kg Ra223 monthly (combination arm). Treatment allocation occurred centrally using a minimization technique (variance method) with stratification factors: country, baseline pain score [worst pain in the last 24 h as measured by the Brief Pain Inventory (WP24-BPI 0-1 versus 2-3)], prior docetaxel (yes versus no), use of bone-protecting agents (BPAs) for no use or $\leq$4 versus >4 weeks, and prior abiraterone (yes versus no).[10,11] A local institutional review board or independent ethics committee approved the trial. The trial was conducted according to the requirements of each country's regulatory authorities and by the Declaration of Helsinki and the good clinical practice guidelines of the International Council for Harmonisation. All patients provided written informed consent.

Patients and treatment

Patients were eligible if they had progressive mCRPC, according to the Prostate Cancer Working Group 3.[12] Patients were asymptomatic or mildly symptomatic (defined as WP24-BPI score < 4) with two or more bone metastases with or without additional lymph node metastases. Patients with visceral metastases were excluded. Further inclusion and exclusion criteria are provided in the trial protocol.

The protocol was amended in April 2018 following the release of the ERA 223 results.[9] Patients were required to start a BPA, zoledronic acid, or denosumab, at their monthly dose at enzalutamide initiation in both arms and 6 weeks before the first dose of Ra223.[13] Following the July 2018 recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency, the minimum number of bone metastases was increased to four in Europe.[14] Enzalutamide could be continued for up to 3 months after the first progression or until initiation of a second-line treatment, whichever came first. The use of docetaxel and, from 2021, abiraterone was allowed if given in the metastatic hormone-sensitive setting. The protocol and a summary of all amendments are available in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.05.011.

Endpoints

Endpoints are detailed in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.05.011. The primary endpoint was rPFS by investigator assessment according to modified Prostate Cancer Clinical Trials Working Group 3 criteria (see protocol for detail).[12] Progression was assessed using bone scintigraphy and contrast-enhanced computed tomography or magnetic resonance imaging of the thorax, abdomen, and pelvis. Imaging was scheduled at baseline and every 12 weeks until the first progression. Key secondary endpoints that were semi hierarchically tested are OS, time to next systemic treatment (TTNT), time to pain progression (TTPP) jointly, and time to symptomatic skeletal event [SSE; first event of new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or the first use of external-beam radiotherapy to relieve skeletal symptoms, tumor-related orthopedic surgical intervention; time to the first symptomatic skeletal event (TTSSE)]. Pain progression was defined as an increase of $\geq$2 points in the BPI-WP24 score from baseline observed at two consecutive evaluations $\geq$4 weeks apart or initiation of opioid use. The safety population comprises all randomized patients who have received at least one dose of at least one of the study drugs. Safety was assessed through clinical laboratory tests, vital sign measurements, and reporting of adverse events (AEs), according to the National Cancer Institute Common Terminology Criteria for Adverse

Events (CTCAE, version 4.03). AE preferred terms were coded according to the MedRA dictionary. An AE is considered a treatment-emergent AE (TEAE) if it occurred or worsened during the on-treatment period (between the first dose and up to 28 days after the last dose of any study treatment). After April 2018, all treatment-emergent fractures were recorded as serious AEs, and baseline fractures and occurrences of fractures were recorded throughout the study. Due to the ERA 223 results, the continuous administration of a BPA at the dose registered to reduce the incidence of skeletal related events was implemented in March 2018 through an urgent safety letter and formalized in protocol version 4.0.[13]

Statistics

The trial aimed to demonstrate that combining enzalutamide and Ra223 improves rPFS with 90% power to detect a HR of 0.68 at a one-sided 0.025 significance level. This required 283 events to be observed in 446 patients, who were projected to be recruited over 78 months. The two-stage OS design assumed an increase in OS equal to a HR of 0.75. With a one-sided significance = 0.025 and 70% power, the required number of OS events at the final analysis was 299. The interim analysis of OS at the time of the primary analysis used a one-sided significance according to a gamma-family alpha-spending function. Key secondary endpoints were tested following a semi-hierarchical testing procedure subject to a family-wise error rate controlling gatekeeping strategy. They were tested in the following order: OS, then jointly TTNT and TTPP, and finally TTSSE; both TTNT and TTPP results were significant. Further formal testing was stopped once a formal stage was not statistically significant. All formal tests were repeated using a permutation-based appropriate test to account for the allocation mechanism.[15] Additional details can be found in the statistical analysis plan provided in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.05.011.

For all randomized patients, rPFS and OS were analyzed using a Cox proportional hazards survival model stratified by baseline pain score, prior docetaxel, and BPA use reported at randomization and graphically presented using Kaplan–Meier curves by treatment arm, 95% confidence interval (CI), and summary statistics, and a stratified log-rank test with the same stratification factors. The supremum test was used to determine the proportionality of hazard.[16] TTNT, TTPP, and TTSSE were assessed with a semi-parametric Fine and Gray regression model to account for competing risks. Efficacy analyses included all randomized participants according to allocated treatment, i.e. intent-to-treat (ITT), except for the analysis of TTPP endpoint carried out in the pain-assessable population, which excluded patients on opioids at baseline and patients with BPI-WPS24 scores either missing or $\geq$9 at trial entry. Censoring and event rules for the time-to-event endpoints can be found in the statistical analysis plan provided in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.05.011. Safety analyses included all patients who received at least one dose of at least one of the study drugs.

The database for this analysis was locked on 28 June 2024 and truncated at the clinical cut-off date of 19 February 2024.

RESULTS

Patients

From November 2015 to March 2023 (88 months), 446 patients had been enrolled from 56 centers in 12 countries; 224 had been randomized in the enzalutamide arm and 222 in the combination arm. (Supplementary Table S2 and CONSORT Diagram, available at https://doi.org/10.1016/j.annonc.2025.05.011). In the enzalutamide arm, 224 (100%) patients received at least one treatment dose. In the combination arm, 215 out of the 222 patients (96.8%) received both enzalutamide and Ra223, 3 (1.3%) patients received only enzalutamide, no patient received only Ra223, and 4 (1.8%) patients received neither enzalutamide nor Ra223. The baseline patient characteristics are reported in Table 1. The median (range) duration of exposure to enzalutamide was 14 months (0.2-71 months) in the enzalutamide arm and 17 months (1-83 months) in the combination arm. At the time of this analysis, enzalutamide treatment had been ongoing in 44 (19.6%) and 56 (25.7%) patients in the enzalutamide and combination arms, respectively. The number of administered cycles of Ra223 was 6 in 189 (87.9%) patients, 5 in 4 (1.9%), and $<$5 in 21 (9.7%).

Efficacy

The median duration of follow-up in the ITT population was 41.1 months (95% CI 31.8-55.8 months) in the enzalutamide arm and 42.3 months (95% CI 32.8-54.4 months) in the combination arm.

The primary endpoint (rPFS) analysis required 283 events, while 299 (=106%) events were observed at database lock (28 June 2024). rPFS events were recorded by the investigator in 160 (71.4%) and 139 (62.6%) patients in the enzalutamide and combination arms, respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.05.011). The HR for rPFS was 0.69 (95% CI 0.54-0.87, $P = 0.0009$), with a median rPFS of 16.4 months (95% CI 13.8-19.2 months) in the enzalutamide arm and 19.4 months (96% CI 17.1-25.3 months) in the combination arm (Figure 1). The 12- and 24-month rPFS estimates were 60.5% (95% CI 53.6% to 66.8%) and 35.9% (95% CI 29.1% to 42.8%), respectively, in the enzalutamide arm and 69.2% (95% CI 62.5% to 75.0%) and 45.1% (95% CI 37.7% to 52.1%), respectively, in the combination arm. The assumption of proportional hazard held (supremum test P value = 0.5827). The treatment effect on rPFS was consistent across all the analyzed subgroups (Figure 2A and B). No significant interaction was found.

An interim analysis of the key secondary endpoint OS was planned to coincide with the primary analysis of rPFS. At that time, 239 events were observed, corresponding to 80% of the 299 events foreseen for the final OS analysis. At the interim analysis, 129/224 (57.6%) patients had died in the

Table 1. Patients and baseline disease characteristics

	Treatment		Total (N = 446)
	Enza (n = 224)	Enza + RaA223 (n = 222)	
	n (%)	n (%)	N (%)
Age, median (range), years	70.0 (47.0-90.0)	70.0 (43.0-90.0)	70.0 (43.0-90.0)
Time since initial diagnosis, median (range), years	2.9 (0.5-28.1)	3.4 (0.0-22.4)	3.3 (0.0-28.1)
Time since diagnosis of M1 prostate cancer, median (range), years	1.5 (0.0-28.1)	1.5 (0.0-18.1)	1.5 (0.0-28.1)
Time since initiation of ADT, median (range), years	1.9 (0.0-14.4)	1.9 (0.0-19.6)	1.8 (0.0-19.6)
Baseline pain			
Worst pain BPI 0-1	121 (54.0)	122 (55.0)	243 (54.5)
Worst pain BPI 2-3	89 (39.7)	79 (35.6)	168 (37.7)
Worst pain BPI >3	10 (4.5)	9 (4.1)	19 (4.3)
Missing	4 (1.8)	12 (5.4)	16 (3.6)
Use of denosumab or bisphosphonates for > 4 weeks before randomization	77 (34.4)	77 (34.7)	154 (34.5)
Prior docetaxel[a]	66 (29.5)	67 (30.2)	133 (29.8)
Prior abiraterone[a]	7 (3.1)	4 (1.8)	11 (2.5)
WHO performance status 0	154 (68.8)	152 (68.5)	306 (68.6)
Gleason score			
<8	73 (32.6)	82 (36.9)	155 (34.8)
≥8	147 (65.6)	138 (62.2)	285 (63.9)
Missing	4 (1.8)	2 (0.9)	6 (1.3)
N1 stage at randomization	52 (23.2)	57 (25.7)	109 (24.4)
M1b stage at randomization	223 (99.6)	220 (99.1)	443 (99.3)
Focal bone lesions,[b]			
0 (i.e. no focal lesion)	19 (8.5)	19 (8.6)	38 (8.5)
<10	105 (46.9)	109 (49.1)	214 (48.0)
≥10	99 (44.2)	93 (41.9)	192 (43.0)
Missing	1 (0.4)	1 (0.5)	2 (0.4)
M1c stage at the time of the randomization	1 (0.4)	2 (0.9)	3 (0.7)
Extra-skeletal disease at baseline	73 (32.6)	77 (34.7)	150 (33.6)
PSA, median (Q1-Q3), ng/ml	n = 192 21.4 (8.0-57.6)	n = 189 24.0 (7.8-68.8)	N = 381 22.4 (7.9-62.0)
Alkaline phosphatase, median (Q1-Q3), IU/l	n = 218 124.5 (85.0-216.0)	n = 207 106.0 (78.0-183.0)	N = 425 119.0 (81.0-203.0)

ADT, androgen deprivation therapy; BPI, Brief Pain Inventory; Enza, enzalutamide; PSA, prostate-specific antigen; Ra223, radium-223; WHO, World Health Organization.
[a]Prior docetaxel or abiraterone was allowed in combination with ADT for the treatment of metastatic hormone-sensitive prostate cancer.
[b]Per imaging guidelines, the type of bone lesions is reported on bone scans reports by the radiologist and classified into focal, diffuse, or equivocal. Only focal bone lesions can be counted as they are identifiable on the scans.

enzalutamide arm and 110/222 (49.5%) in the combination arm (Table 2). Prostate cancer was the cause of death in 75.2% and 77.3% of the deaths in the enzalutamide and combination arms, respectively. The HR for OS was 0.69 (95% CI 0.52-0.90, P = 0.0031) with a median OS of 35.0 months (95% CI 28.8-38.9 months) in the enzalutamide arm and 42.3 months (95% CI 36.8-49.1 months) in the combination arm (Figure 3). The 12- and 24-month OS estimates were 93.3% (95% CI 89.1% to 95.9%) and 67.2% (95% CI 60.1% to 73.4%), respectively, in the enzalutamide arm and 90.5% (95% CI 85.7% to 93.7%) and 73.3% (95% CI 66.4% to 79.0%), respectively, in the combination arm. The actual interim boundary resulted in a statistically significant level of 0.0034. A visual inspection of the Kaplan–Meier plots suggested an enzalutamide arm initially above the combination arm, followed by declining HR, crossing around 18 months. The initial increased risk of death in the combination arm results from six more deaths at 12 months, including three more deaths due to progression and two due to cardiovascular disease. OS events and censoring before and after month 18 are reported in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.05.011. The assumption of proportional hazard was violated (supremum test P value = 0.0351). Sensitivity analyses with the unstratified restricted mean survival test (RMST) at 15% and 7.5% of the at-risk patients led to respective P values of 0.076 and 0.024 (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.05.011). Together with the short gap between the end of randomization and the interim cut-off, this suggested the possibility that the evidence of efficacy will increase with further follow-up. An independent Data Monitoring Committee (IDMC) evaluation was conducted on 27 August 2024 and confirmed that the study will continue to its final OS analysis with 100% of the planned events to confirm and further characterize the results. The IDMC authorized formal testing of the other key secondary endpoints to be continued as per the pre-defined semi-hierarchical testing procedure.

At the time of the rPFS analysis, 133 (59.4%) patients in the enzalutamide arm and 94 (42.3%) patients in the combination arm had received a subsequent systemic antineoplastic agent (Table 2). In patients who progressed, in the enzalutamide arm, the first treatment was chemotherapy (with or without other treatments) in 99 (70.7%) patients, a second line of hormone therapy in 18 (12.9%), a poly (ADP-ribose) polymerase (PARP) inhibitor in 3 (2.1%), and an 'other' treatment in 13 (9.3%) patients. In the

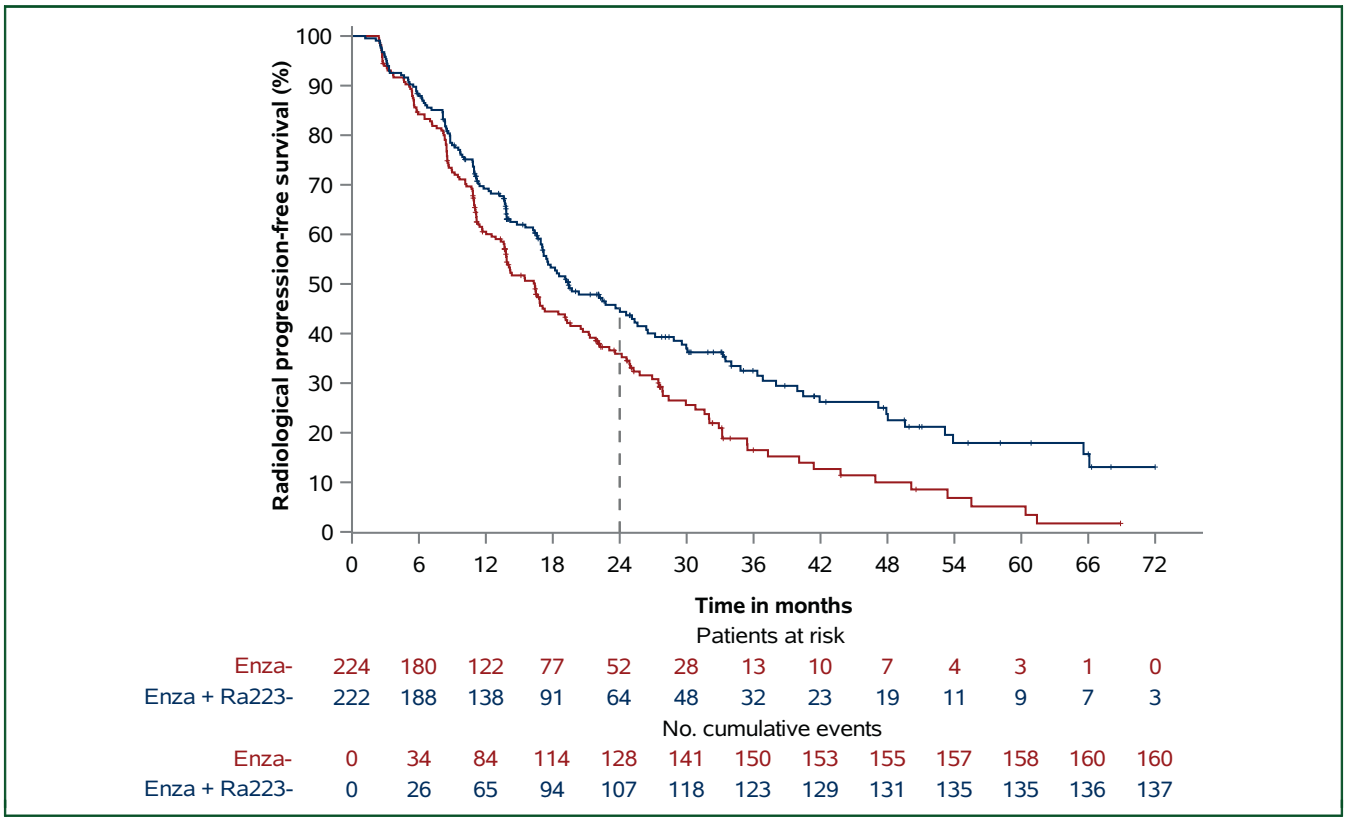

Figure 1. Radiological progression-free survival was assessed by the local investigator in the ITT population. The hazard ratio (HR) and 95% confidence interval (95% CI) for all patients are based on a Cox model stratified by baseline pain score, prior docetaxel, and bone-protecting agent use at randomization.
Enza, enzalutamide; ITT, intent-to-treat; Ra223, radium-223.

combination arm, the first treatment was chemotherapy in 73 (75.3%) patients, a second line of hormone therapy in 15 (15.5%), a PARP inhibitor in 2 (2.1%), and an 'other' treatment in 2 (2.1%) patients. Adding Ra223 to enzalutamide significantly increased the TTNT. The HR for TTNT was 0.57 (95% CI 0.44-0.75, $P \leq 0.0001$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.05.011). The 12- and 24-month cumulative incidence estimates of next treatment were 24.7% (95% CI 19.2% to 30.5%) and 50.9% (95% CI 43.6% to 57.6%), respectively, in the enzalutamide arm and 15.1% (95% CI 10.7% to 20.2%) and 29.9% (95% CI 23.6% to 36.4%), respectively, in the combination arm. At the time of this analysis, the combination was not beneficial for the TTPP and TTSSE (Table 2 and Supplementary Figures S2 and S3, available at https://doi.org/10.1016/j.annonc.2025.05.011).

Safety

A summary of relevant TEAEs is shown in Table 3. A detailed description of TEAEs can be found in Supplementary Tables S6 and S7, available at https://doi.org/10.1016/j.annonc.2025.05.011. TEAEs $\geq$ grade 1 were reported in 96.4% and 100%, and $\geq$ grade 3 in 55.8% and 65.6% of the patients in the enzalutamide and combinations arms, respectively. Grade $\geq$3 TEAEs reported in >3% of patients in the enzalutamide arm included hypertension (34.4%), bone pain (4.9%), spinal cord compression (3.6%), and weight decreased (3.2%). Grade $\geq$3 TEAEs reported in >3% of patients in the combination arm included hypertension (33.5%), fatigue (5.5%), fractures (5.0%), anemia (4.6%), neutropenia (4.6%), and bone pain (4.1%). Grade $\geq$1 osteonecrosis of the jaw was reported in 13 patients: 3 (1.3%) in the enzalutamide arm and 10 (4.6%) in the combination arm. Of these, 3 occurred in the 115 patients enrolled before and 10 in the 327 patients enrolled after the urgent safety letter that mandated BPA use. No individual TEAE $\geq$ grade 3 had increased by >5% in the combination arm compared with the enzalutamide arm. Definitive treatment discontinuations due to AEs were similar in both study arms.

Fractures (regardless of their symptomatic or pathologic nature) were reported in 30 (13.4%) patients in the enzalutamide arm and 53 (24.3%) patients in the combination arm. The characteristics of the fractures are detailed in Table 4. In the combination arm, fractures occurred in 53.6% of patients enrolled before the urgent safety letter and only in 14.2% of patients enrolled afterwards. In the enzalutamide arm, fracture incidence dropped from 20.3% before the urgent safety letter to 10.9% afterwards. The HR between the two treatment arms for the time to first fracture was 2.00 (95% CI 1.27-3.14) (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.05.011). The 12- and 24-month estimates of the

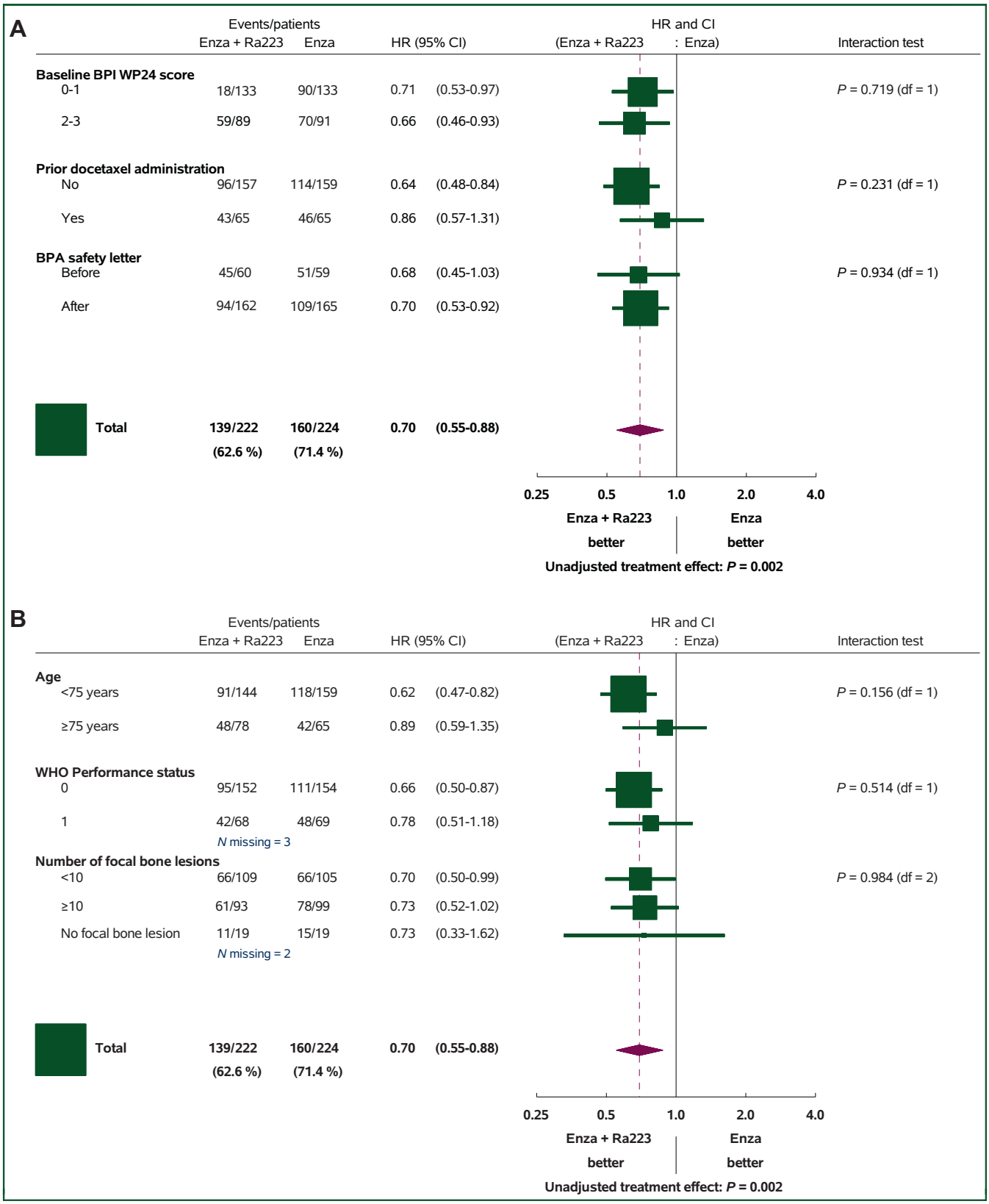

Figure 2. Subgroup analysis of radiological progression-free survival as assessed by the local investigator. (A) Analysis for stratification factor as entered at randomization. (B) Analysis for additional subgroups of interest. The treatment effect is unstratified, thus not reflecting the primary analysis but a sensitivity one. BPA, bone protecting agent; CI, confidence interval; Enza, enzalutamide; HR, hazard ratio; Ra223, radium-223.

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Table 2. Key secondary endpoints

Secondary endpoint	Enzalutamide	Enzalutamide + Ra223	HR	*P* value
	n event/*N* total			
Overall survival	129/224	110/222	0.69 (0.52-0.90)	0.0031[a] (0.0035[b])
Time to next treatment	133/224	94/222	0.57 (0.44-0.75)	<0.0001[c] (<0.0001[d])
Time to pain progression	88/194[e]	89/192[e]	1.03 (0.77-1.37)	0.5737[c] (0.5700[d])
Time to first symptomatic skeletal event	47/224	44/222	0.93 (0.62-1.38)	

BPI-SF, Brief Pain Inventory-Short Form; HR, hazard ratio; Ra223, radium-223.
[a]Stratified log-rank test one-sided *P* value.
[b]Permutation-based log-rank test one-sided *P* value.
[c]Fine and Gray test one-sided *P* value.
[d]Permutation-based Fine and Gray test one-sided *P* value.
[e]Pain-assessable population: all intent-to-treat patients who were opioid free at baseline and had baseline BPI-SF worst pain in the last 24-h score available and <9.

cumulative incidence of skeletal fracture were 7.6% (95% CI 4.6% to 11.6%) and 11.3% (95% CI 7.5% to 16.0%), respectively, in the enzalutamide arm and 12.9% (95% CI 8.8% to 17.7%) and 17.1% (95% CI 12.4% to 22.6%), respectively, in the combination arm.

DISCUSSION

The EORTC 1333 PEACE-3 trial was an academic trial designed to test the combination of enzalutamide with Ra223. Initially intended as a companion trial to ERA 223, it used rPFS as a primary endpoint, with 60% power to detect an OS HR of 0.75. Initially, using a BPA had been left to the investigator, but the study was amended to mandate their use after the ERA 223 findings.[13] The median rPFS in PEACE-3 increased from 16.4 months in the enzalutamide group to 19.4 months in the combination group. This is the first study to show that Ra223 delays radiological progression. It can be argued that the study was not blinded. The absolute difference in median rPFS is half the difference in OS when the opposite is usually observed. This suggests a non-cytotoxic effect of Ra223. Such observation is common in immunotherapy trials. Indeed, unlike other therapies where a significant benefit in rPFS may not translate to OS, treatment effect sizes in randomized controlled trials of programmed cell death protein 1 inhibitors can be more pronounced for OS than rPFS.[17] Hence, the OS benefits are poorly captured by rPFS. In immunotherapy trials, an OS

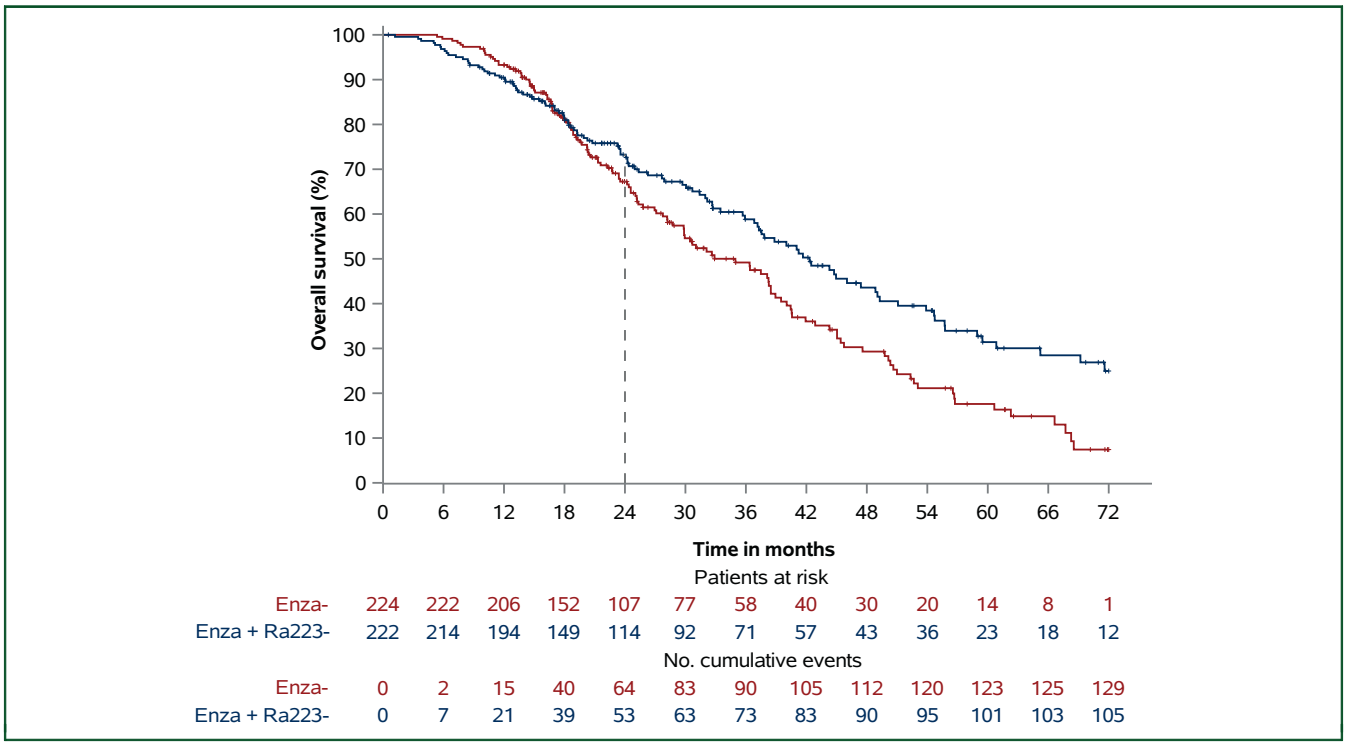

Figure 3. Overall survival in the ITT population. The hazard ratio (HR) and 95% confidence interval (95% CI) for all patients are based on a Cox model stratified by baseline pain score, prior docetaxel, and bone protecting agent at randomization.
Enza, enzalutamide; ITT, intent-to-treat; Ra223, radium-223.

Table 3. Treatment-emergent Adverse Events (TEAE)[a]

	Enzalutamide $n = 224$		Enzalutamide + Ra223 $n = 218$	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AEs, *n* (%)	216 (96.4)	125 (55.8)	218 (100)	143 (65.6)
Serious AEs, *n* (%)	66 (29.5)	41 (18.3)	93 (42.7)	62 (28.4)
Fatal AEs,[b] *n* (%)	4 (1.8)	4 (1.8)	7 (3.2)	7 (3.2)
Percentage of definitive treatment interruption for an adverse event, *n* (%)	12 (6.7)		13 (8.0)	
AEs that occurred in >10% of the patients in either arm, *n* (%)[c]				
Hypertension	133 (59.4)	77 (34.4)	118 (54.1)	73 (33.5)
Anemia	23 (10.3)	5 (2.2)	46 (21.1)	10 (4.6)
Neutropenia	1 (0.4)	0 (0.0)	23 (10.6)	10 (4.6)
Constipation	25 (11.2)	0 (0.0)	31 (14.2)	0 (0.0)
Diarrhea	20 (8.9)	2 (0.9)	46 (21.1)	1 (0.5)
Nausea	17 (7.6)	3 (1.3)	60 (27.5)	1 (0.5)
Asthenia	24 (10.7)	4 (1.8)	38 (17.4)	3 (1.4)
Fatigue	87 (38.8)	4 (1.8)	83 (38.1)	12 (5.5)
Weight loss	63 (28.1)	1 (0.4)	84 (38.5)	7 (3.2)
Weight gain	23 (10.3)	0 (0.0)	23 (10.6)	0 (0.0)
Decreased appetite	31 (13.8)	2 (0.9)	44 (20.2)	0 (0.0)
Arthralgia	25 (11.2)	1 (0.4)	34 (15.6)	0 (0.0)
Back pain	41 (18.3)	2 (0.9)	49 (22.5)	4 (1.8)
Bone pain	81 (36.2)	11 (4.9)	56 (25.7)	9 (4.1)
Hot flush	30 (13.4)	0 (0.0)	20 (9.2)	0 (0.0)

AE, adverse event; Ra223, radium-223.
[a]Shown are the number of patients with an AE, rather than the number of AEs.
[b]Fatal AEs are grade 5 by definition.
[c]The complete AE tables can be found in the Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.05.011.

benefit with this pattern has been generally accepted as a genuine, clinically meaningful treatment in immunotherapy effect.[18]

At the interim analysis with 80% of events, PEACE-3 strongly suggests that adding Ra223 to enzalutamide as first-line mCRPC treatment improves OS. In ALSYMPCA, the HR for death was 0.70 (95% CI 0.55-0.88), with a *P* value of 0.002. In the present trial, the HR was 0.69, with a *P* value of 0.0031. The median OS in PEACE-3 was 42.3 months in the combination arm and 35.0 months in the enzalutamide arm, resulting in a difference of over 7 months. The median survival in the enzalutamide monotherapy arm was congruent with the median OS seen in the enzalutamide arm of the PREVAIL study (32.4 months). In ALSYMPCA, the median OS gain was 3.6 months; in PEACE-3, the OS gain appears to be over 7 months. Because of the indication of non-proportional hazard, further RMST analyses were carried out, under the SAP. The final analysis at 299 deaths will determine the real OS benefit of the combination. Longer follow-up may strengthen the curve's tail, given that the excess mortality at the beginning of the curve is small in absolute numbers and one-third of censoring occurs before 18 months (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.05.011).

Table 4. Fracture characteristics

	Enzalutamide ($n = 224$)	Enzalutamide + Ra223 ($n = 218$)
	n (%)	*n* (%)
Patients with at least one fracture event[a]	**30 (13.4)**	**53 (24.3)**
Enrolled before urgent safety letter (14 March 2018)	12 (20.3% of 59 patients)	30 (53.6% of 56 patients)
Enrolled after urgent safety letter (14 March 2018)	18 (10.9% of 165 patients)	23 (14.2% of 162 patients)
Bone-protecting agents (denosumab or biphosphonates) during treatment (excluding use for fracture)		
No	13 (43.3)	24 (45.3)
Yes	17 (56.7)	29 (54.7)
Timing of the first fracture		
As a treatment-emergent event	24 (80.0)	45 (84.9)
As a post-treatment event	6 (20.0)	8 (15.1)

All fractures that occurred during or after protocol treatment are considered regardless being symptomatic or pathological in nature.
Ra223, radium-223.
[a]Patients with multiple fractures are counted once.

This peculiar ratio between rPFS and OS may reflect the mechanism of action of Ra223, which is not fully understood. Specifically, it remains unclear whether it has a direct cytotoxic effect on cancer cells or if it creates a less favorable environment in the bone for the growth of metastases.[19] Preclinical studies have demonstrated that Ra223 is incorporated into the bone matrix, inhibiting the proliferation of cancer cells and the differentiation of osteoblasts and osteoclasts. The binding of Ra223 to bone tissue occurs due to active incorporation by osteoblasts and passive binding as a calcium mimetic to hydroxyapatite. Consequently, calcium disrupts the vicious cycle of bone metastasis. Ra223 has also been found deposited within prostate cancer cells in mice xenograft models, suggesting a direct effect on tumor metastasis. However, the extent and nature of co-localization with tumor cells remain to be elucidated. Preclinical data indicate that Ra223 may need to be combined with other agents to target larger areas of bone metastases, especially in bone metastases with weaker osteoblastic reactions.[20]

The safety profiles of enzalutamide and Ra223 are consistent with earlier monotherapy trials, except for hypertension, recorded in over 50% of patients, with 34.4% and 33.5% grade $\geq$3 in the enzalutamide and combination groups, respectively. In the PREVAIL trial, 13% and 7% of the patients receiving enzalutamide had all-grade and grade >3 hypertension, respectively.[21] The reason for the higher hypertension rate in our trial was unclear. As an academic trial, it included a broader spectrum of patients with medical history findings or additional comorbidities. Hypertension is a well-established side-effect of hormone therapies.[22] In a recent systematic analysis of 24 studies conducted on patients with advanced prostate cancer, the risk for grade $\geq$3 hypertension was 25% (95% CI 1.74% to 2.90%, $P < 0.001$).[23]

A limitation of our study is its long duration, taking >8.5 years from the first patient enrolled until the database lock. The main reason was the unblinding of the ERA 223 trial. As a result of those safety concerns, regulatory agencies imposed new restrictions on Ra223 use.[14] Specifically, Ra223 has been contraindicated in combination with abiraterone acetate and prednisone/prednisolone. In Europe, its use has been restricted for patients with mCRPC who have symptomatic bone metastases, no known visceral metastases, and who have received at least two prior systemic treatments or are ineligible for other systemic therapies.[14] The safety concerns and ensuing restrictions have resulted in a decline in its use as clinicians have exercised increased caution and adhered to the updated guidelines.[24] This significantly impacted the trial. Due to its long duration, the trial required several amendments to reflect the evolving clinical landscape, which may affect the generalizability of the results. It is now recommended to add an ARPI to ADT for patients with hormone-sensitive metastatic disease, leading to patients entering the mCRPC stage already having received an ARPI.[2] In PEACE-3, only 11 (2.5%) patients had received an ARPI in the hormone-sensitive setting, while 133 (29.8%) had received docetaxel. However, in most countries, even with ARPIs available and reimbursed, a significant proportion of patients with hormone-sensitive metastatic prostate cancer still receive ADT alone. Moreover, patients with mCRPC may also originate from a population treated with ADT only for non-metastatic prostate cancer. For instance, in the SPARTAN trial that evaluated the role of apalutamide in the non-metastatic CRPC stage, metastases were diagnosed in 517 (24%) of the 2132 patients evaluated for eligibility. In a recently published community-based study in the United States involving 6301 patients diagnosed between 2018 and 2022, 71% of patients remained ARPI-naïve at the time of diagnosis of mCRPC. Another similar survey conducted on 609 men diagnosed between 2020 and 2023 indicates that ADT alone was administered to 59% of the metastatic hormone-sensitive prostate cancer patients. Therefore, this combination treatment continues to be of interest. It is noteworthy that other recently published trials have faced similar limitations. In the PROpel trial, which evaluated abiraterone and olaparib, only one patient had been treated with a prior ARPI. In the TALAPRO-2 trial, which assessed the combination of enzalutamide and talazoparib, only 5% had received prior abiraterone.

The study does not demonstrate any benefit regarding TTPP and TTSSE. This confirms the results of the ERA 223 trial, which failed to show a benefit on TTSSE, its primary endpoint.[9] At 2 years, 18% and 17.8% of the patients in the enzalutamide and combination arms experienced an SSE, respectively. In a recent series of 532 Australian patients with CRPC and bone metastases, SSEs occurred in 28%. The lower incidence recorded in PEACE-3 may reflect the mandatory use of BPA.

Skeletal fractures have emerged as a safety concern with hormonal treatment use and, most importantly, when combining ARPI with Ra223.[25,26] In November 2017, the ERA 223 trial was unblinded for a significant increase in fractures from 11% in the abiraterone plus placebo group to 29% in the abiraterone plus Ra223 group. Upon review, most of those fractures appeared to have been osteoporotic.[9] After having already randomized 115 patients, EORTC 1333 was amended to make the co-administration of zoledronic acid or denosumab obligatory. The details of that amendment and the impact on the short-term fracture risk had been reported elsewhere.[13] PEACE-3 confirms the importance of bone-targeted agents for CRPC patients with bone metastases receiving enzalutamide with or without Ra223. Although the combination with Ra223 increased the risk of fractures, both groups benefited from adding a BPA.[13]

In conclusion, PEACE-3 shows that adding six cycles of Ra223 to enzalutamide and a BPA as first-line treatment for mCRPC with bone metastases increases rPFS. An interim analysis at 80% of events suggests an OS advantage for combining enzalutamide and Ra223, which need to be further confirmed. As expected, toxicity had been moderate. Hence, combining enzalutamide and Ra223 is a new treatment option for patients with mCRPC.

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DISCLOSURE

The following authors have reported consulting fees or payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events. BT: Accord, Amgen, Astellas, Bayer, Myovant, MSD, Ferring, Pfizer. AC: Bayer, Pfizer, AstraZeneca, Merck, Roche, Janssen. FS: Janssen, Merck, Pfizer, BMS, Novartis, Sanofi, AstraZeneca. EG: Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Johnson & Johnson, Merck, MSD, Pfizer, Recordati, Roche. AS: Novartis, AstraZeneca, Janssen, MSD, Pfizer, Bayer. YL: Amgen, Sanofi, Astellas, Pfizer, Merck KGaA, Janssen, Exelexis, BMS, Roche, MSD, Tahio, Orion, Incyte, Gilead, Tyra, Lilly, AstraZeneca. RM: Astellas, Bristol Myers Squibb, MSD, Ipsen, Novartis, Pfizer, Bayer. ARV: Pfizer, MSD, Astellas, Merck, BMS, Janssen, AstraZeneca, Bayer, and Ipsen. PIV: Bayer, Janssen, Bristol Myers Squibb, MSD, Merck, Astellas, Novartis, AstraZeneca. FN: Astellas, Janssen, Novartis, AstraZeneca, Bayer. PM: Bayer, Pfizer, Novartis, AstraZeneca. SG: Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Innomedica, Ipsen, Macrogenics, MSD, Novartis. GV: Astellas, Janssen, Novartis, AstraZeneca, Bayer, MSD, Ipsen, Bayer, Sanofi, Pfizer, Gilead, Recordati, Ferring, Amgen, GE, Abex, Dormier. KMdT: Astellas, Pfizer, Merck, Johnson & Johnson, BMS, MSD, AstraZeneca, Novartis, Bayer. All other authors have declared no conflicts of interest.

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