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Annual Congress of the European Association of Nuclear Medicine
BARCELONA
OCTOBER 4-8, 2025
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Fracture Risk and Treatments at Progression in EORTC-1333 PEACE-3 study evaluating the addition of Radium223 in metastatic castration-resistant prostate cancer starting enzalutamide.

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Disclosures of Interest

Dr. A. Rodriguez-Vida reports serving in an advisory role for Pfizer, Bristol Myers Squibb, Merck Serono, MSD, Astellas, Johnson&Johnson, Astra Zeneca, Bayer, Novartis and Ipsen; receiving honoraria or travel expenses from Pfizer, MSD, Astellas, Merck Serono, Bristol Myers Squibb, Johnson&Johnson, Astra Zeneca, Bayer, Novartis and Ipsen.

PEACE-3 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

N=446**

1:1
Randomization

- **Ra223**: 55 kBq/kg iv every 4 weeks for 6 cycles plus
- **Enzalutamide:** 160 mg od

Stratification Factors
- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone protecting agents
- Prior abiraterone (yes vs no)

- **Enzalutamide**: 160 mg od

Primary Endpoint

- **rPFS**[+]

Key Secondary Endpoints

- Safety (CTCAE v4)
- Overall Survival (OS)
- Time to subsequent treatment (TST)
- Time to pain progression
- Time to first SSE (symptomatic skeletal event)

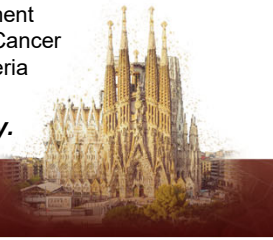
*Defined as brief pain inventory WP24 score < 4

** Original target accrual N=560, adapted for slow accrual

*** Of these 119, four patients did not start protocol treatment

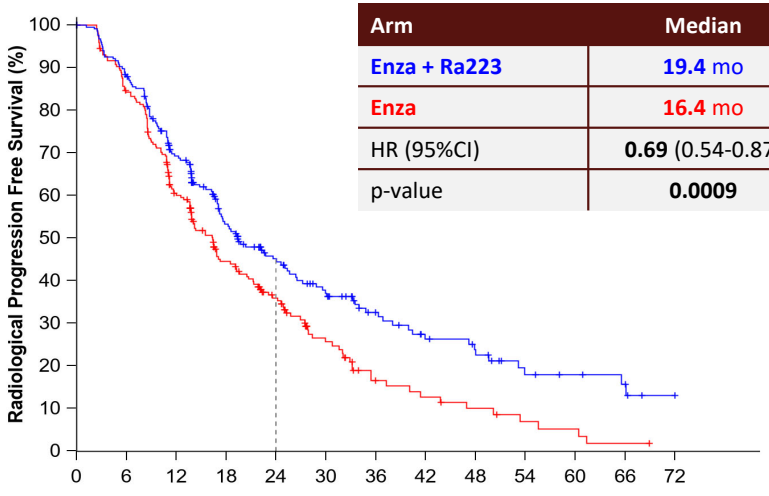
[+]rPFS = radiological progression free survival by investigator assessment according to modified Prostate Cancer Working Group 3 (PCWG3) criteria

On 18 MAR 2018, with 119 = 27% of 446 patients enrolled, an urgent safety letter (USL) made co-administration of zoledronic acid or denosumab obligatory.***



Topline Results

Primary Endpoint: rPFS

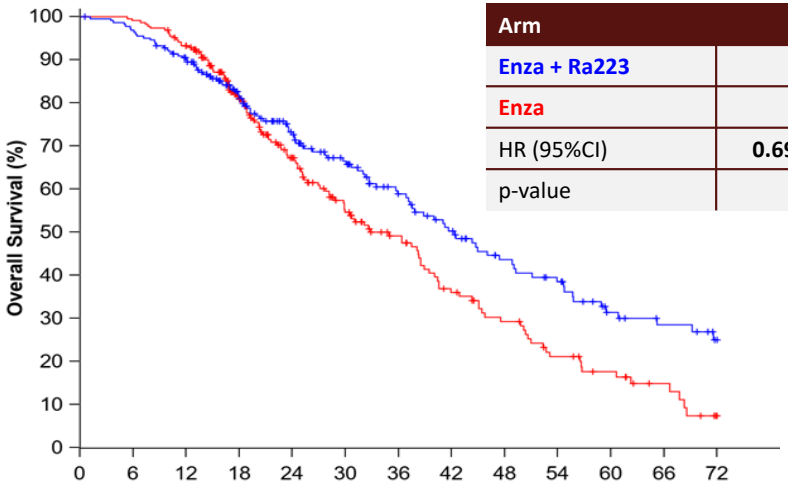


Arm	Median
Enza + Ra223	**19.4** mo
Enza	**16.4** mo
HR (95%CI)	**0.69** (0.54-0.87)
p-value	**0.0009**

Patients-at-Risk (No. Cumulative Events)

Enza-	224 (0)	122 (84)	52 (128)	13 (150)	7 (155)	3 (158)	0 (160)
Enza+Ra223-	222 (0)	138 (65)	64 (107)	32 (123)	19 (131)	9 (135)	3 (137)

Secondary Endpoint: OS
(Interim Analysis at 80% of Events)



Arm	Median
Enza + Ra223	**42.3** mo
Enza	**35.0** mo
HR (95%CI)	**0.69** (0.52-0.90)
p-value	**0.0031**

Patients-at-Risk (No. Cumulative Events)

Enza-	224 (0)	206 (15)	107 (64)	58 (90)	30 (112)	14 (123)	1 (129)
Enza+Ra223-	222 (0)	194 (21)	114 (53)	71 (73)	43 (90)	23 (101)	12 (105)

Impact of USL on BPA Adoption and Fracture Risk, 2021 Interim Safety Analysis

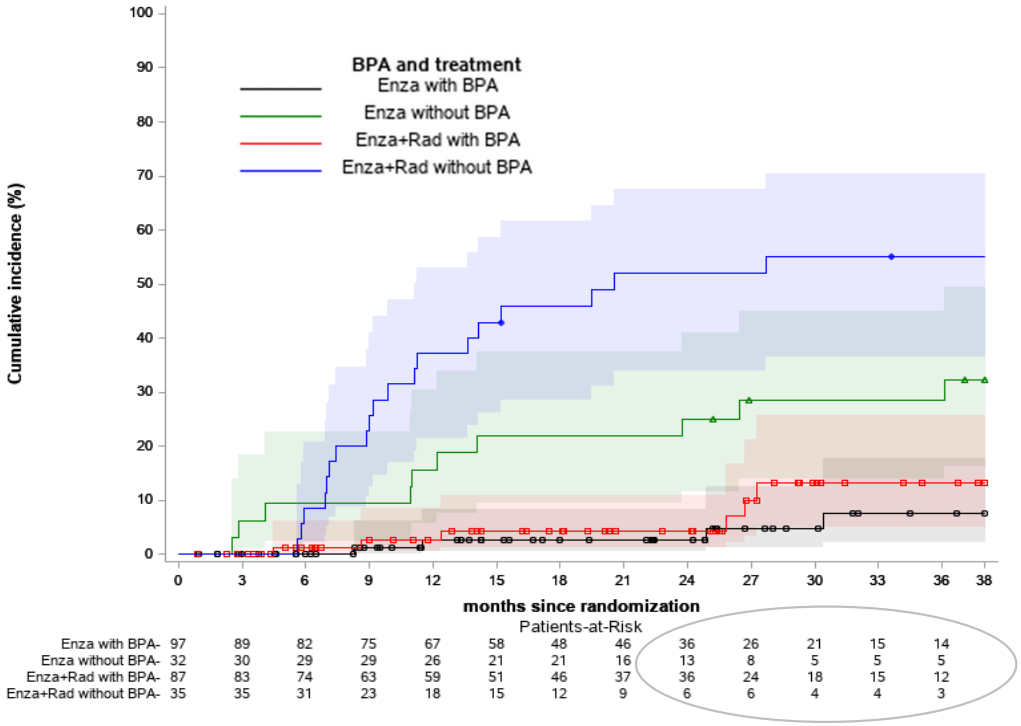
BPA (Denosumab or Biphosphonates)	Randomized		Total (N=251)
	Before Urgent Safety Letter (N=115)	After Urgent Safety Letter (N=136)	
	N (%)	N (%)	N (%)
No Use	**52 (45.2%)**	**4 (2.9%)***	56 (22.3%)
Use at Registration, But Stopped Before Protocol Treatment	2 (1.7%)	-	2 (0.8%)
Use After Bone Fracture	8 (7.0%)	1 (0.7%)*	9 (3.6%)
Use at Registration and Continued	19 (16.5%)	120 (88.2%)	139 (55.4%)
No Use at Registration, But Started During Protocol Treatment	34 (29.6%)	11 (8.1%)	45 (17.9%)
Total number with bone protection during treatment	**63 (54.8%)**	**131 (96.3%)**	**184 (73.3%)**

* 3 patients: misunderstanding at site, 2 patients: medical decision - dental issues

Gillesen et al. Eur Urol. . 2025 Mar;87(3):285-288.

Impact of USL on BPA Adoption and Fracture Risk, 2021 Interim Safety Analysis

Cumulative Incidence of Fractures By Treatment Arm and Use of BPA



Patients-at-Risk

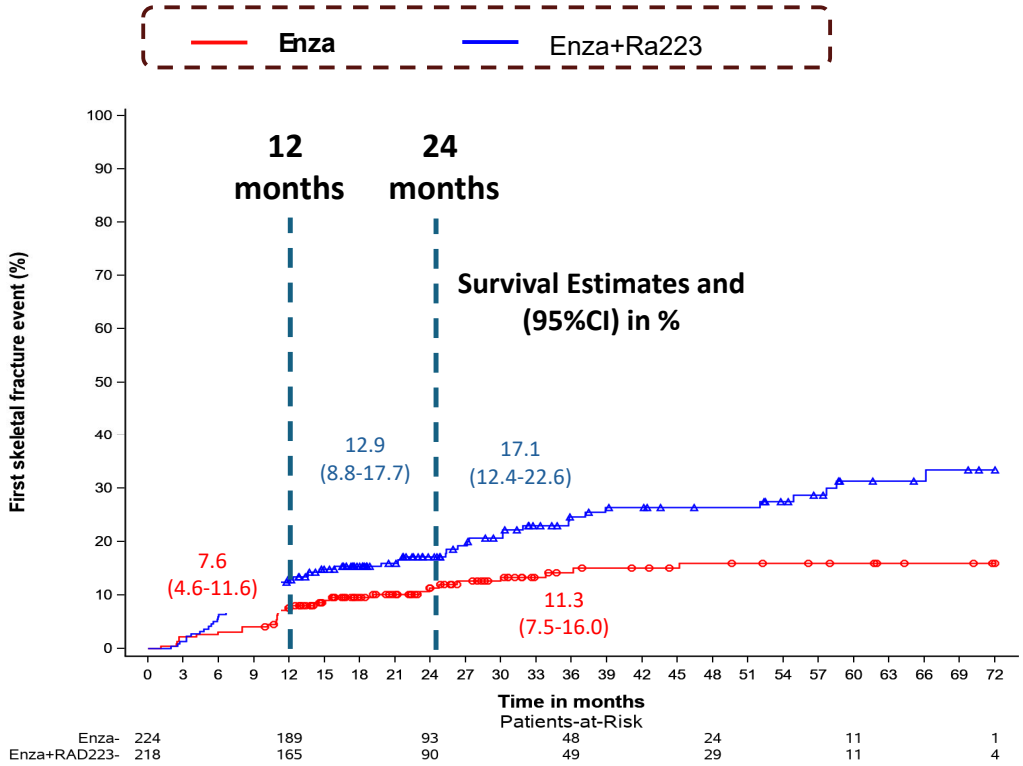
Enza with BPA-	97	89	82	75	67	58	48	46	36	26	21	15	14
Enza without BPA-	32	30	29	29	26	21	21	16	13	8	5	5	5
Enza+Rad with BPA-	87	83	74	63	59	51	46	37	36	24	18	15	12
Enza+Rad without BPA-	35	35	31	23	18	15	12	9	6	6	4	4	3

At 12 months:

- **without bone protecting agent**, there is a **15.6%** cumulative **risk of fracture** with enzalutamide increasing to **37.1%** when Ra223 is added.

- **with continuous administration of a bone-protecting agent** starting at least 6 weeks before the first injection of Ra223, the cumulative risk was **2.6%** on enzalutamide alone and **2.7%** with the combination.

Time to First Skeletal Fractures - Cumulative Incidence



Treatment	Event/Total (%)	Hazard Ratio (95% CI)[1]
Enza	30/224 **13.4%**	Reference
Enza+Ra223	53/218 **24.3%**	2.00 (1.27-3.14)

[1]Cox model

[1]Cumulative incidence method

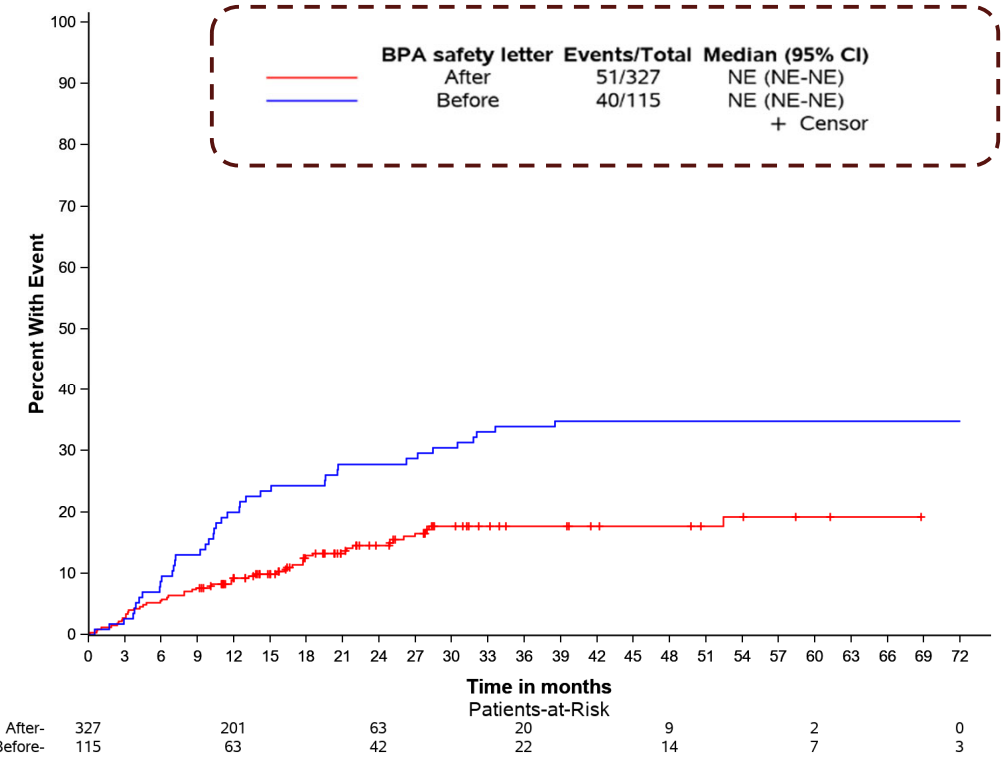
Fracture Characteristics

	Enzalutamide (N=224)	Enzalutamide/Ra223 (N=218)
	N (%)	N (%)
Patients with at Least One Fracture Event*	30 (13.4%)	53 (24.3%)
Enrolled Before Urgent Safety Letter (14 March 2018)	12 (20.3% of 59 Pts)	30 (53.6% of 56 Pts)
Enrolled After Urgent Safety Letter (14 March 2018)	18 (10.9% of 165 Pts)	23 (14.2% of 162 Pts)
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%)

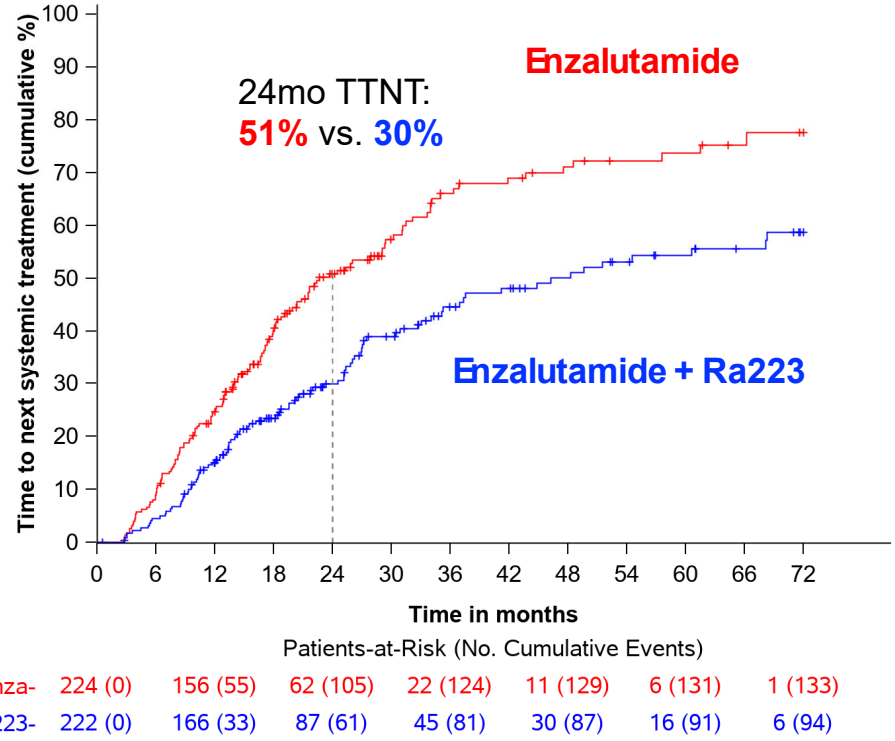
*Patients with multiple fractures are counted once

All fractures that occurred during or after protocol treatment are considered regardless whether symptomatic or pathological in nature.

Fracture Rate Before and After Urgent Safety Letter (USL)



Time to the Next Systemic Treatment



Patients-at-Risk (No. Cumulative Events)

Enza-	224 (0)	156 (55)	62 (105)	22 (124)	11 (129)	6 (131)	1 (133)
Enza+Ra223-	222 (0)	166 (33)	87 (61)	45 (81)	30 (87)	16 (91)	6 (94)

Hazard Ratio	Fine&Gray p-value
0.57 (0.44-0.75)	**<0.0001**

Estimate of Proportion Started Next Systemic Treatment	Enza+Ra223 (N=222)	Enza (N=224)
	% (95% CI)	
At 24 months	**29.9%** (23.6-36.4)	**50.9%** (43.6-57.6)

Gillessen et al. Annals of Oncology (2024) 35 (suppl_2): 1-72. 10.1016/annonc/annonc1623

Next Systemic Treatment at Progression

Type of Next systemic anti-neoplastic therapy	Treatment		Total (N=227)
	Enza+Ra223 (N=94)	Enza (N=133)	
	N (%)	N (%)	N (%)
Chemotherapy	79 (84.0%)	105 (78.9%)	184 (81.1%)
Hormonotherapy	10 (10.6%)	10 (7.5%)	20 (8.8%)
Targeted agents	2 (2.1%)	8 (6.0%)	10 (4.4%)
Other	3 (3.2%)	10 (7.5%)	13 (5.7%)

At the time of the rPFS analysis, **133 (59.4%) patients in the enzalutamide group** and **94 (42.3%) patients in the combination group** have received a subsequent systemic anti-neoplastic agent.

Conclusions

- The combination of Ra223 and enzalutamide increases the risk of fracture. However, that risk is mitigated by proper use of bone protective agents.
- Chemotherapy was the first treatment administered at progression in most patients.
- Time to next systemic treatment was significantly prolonged with the combination of Ra223 and enzalutamide.

Acknowledgements

- The patients and their families
- The team at EORTC HQ
- The EORTC IDMC
- CTI/CUOG/LACOG/UNICANCER
- Astellas Pharma Europe
- Bayer Healthcare Pharmaceuticals

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