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Enzalutamide + Radium-223 in mCRPC: Results of the EORTC 1333/PEACE-3 Trial

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ORIGINAL ARTICLE

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

B. Tombal[1*], A. Choudhury[2], F. Saad[3], E. Gallardo[4], A. Soares[5], Y. Loriot[6,7], R. McDermott[8], A. Rodriguez-Vida[9], P. Isaacsson Velho[10], F. Nolè[11], F. Cruz[12], T. Roumeguere[13], G. Daugaard[14], R. Yamamura[15], E. Bompas[16], P. Maroto[17], F. Gomez Veiga[18], I. Skoneczna[19], K. Martins da Trindade[20], F. Mavignier Carcano[21], F. Lecouvet[1], C. Coens[22], C. Poncet[22], B. Fournier[22] & S. Gillessen[23,24]

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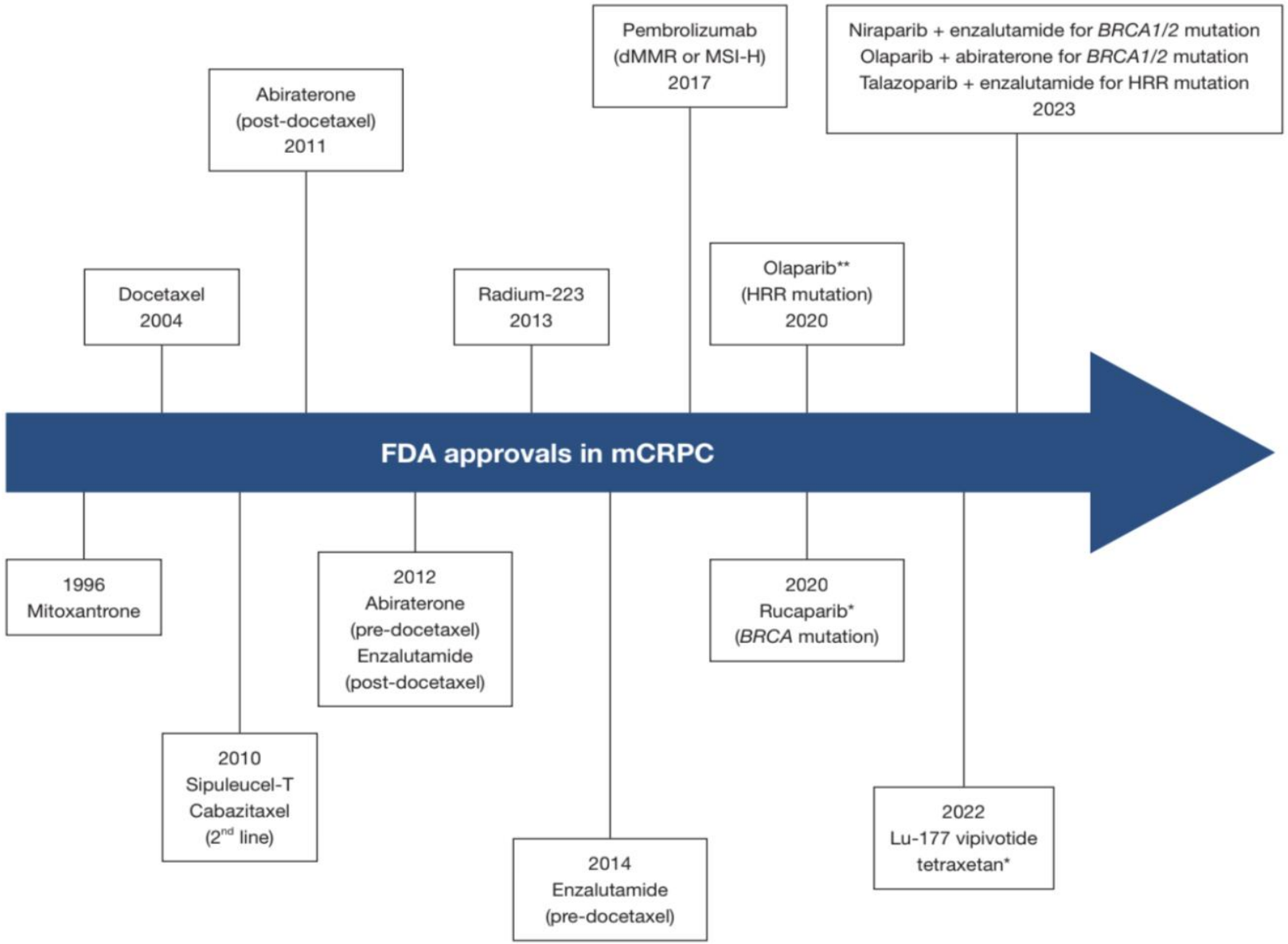
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 3.2024 — March 8, 2024

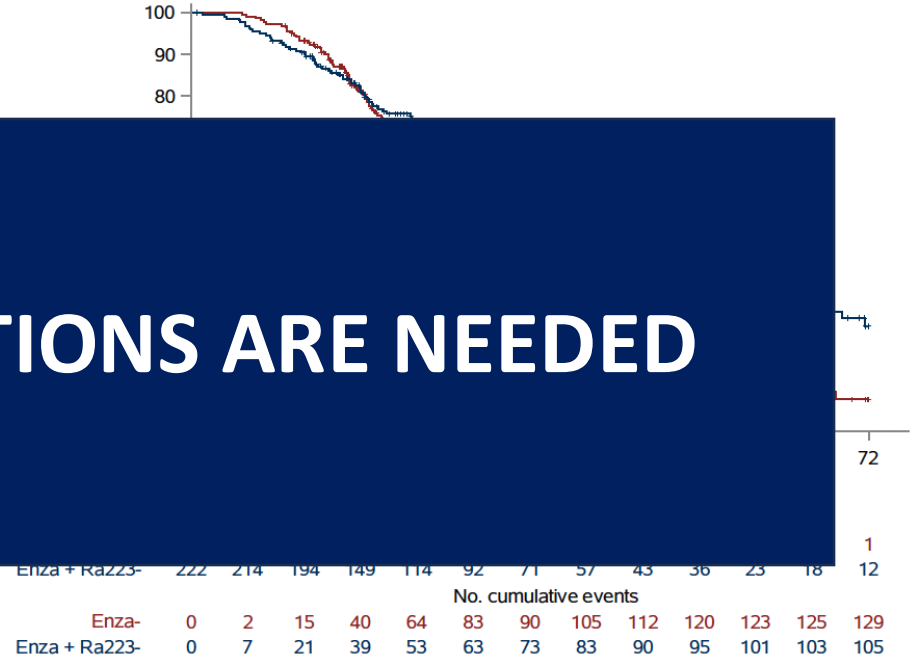


Sayyid et al. Transl Androl Urol, 2024

mCRPC – Survival Outcomes Remain Poor

- Median overall survival

ADDITIONAL AGENTS/COMBINATIONS ARE NEEDED

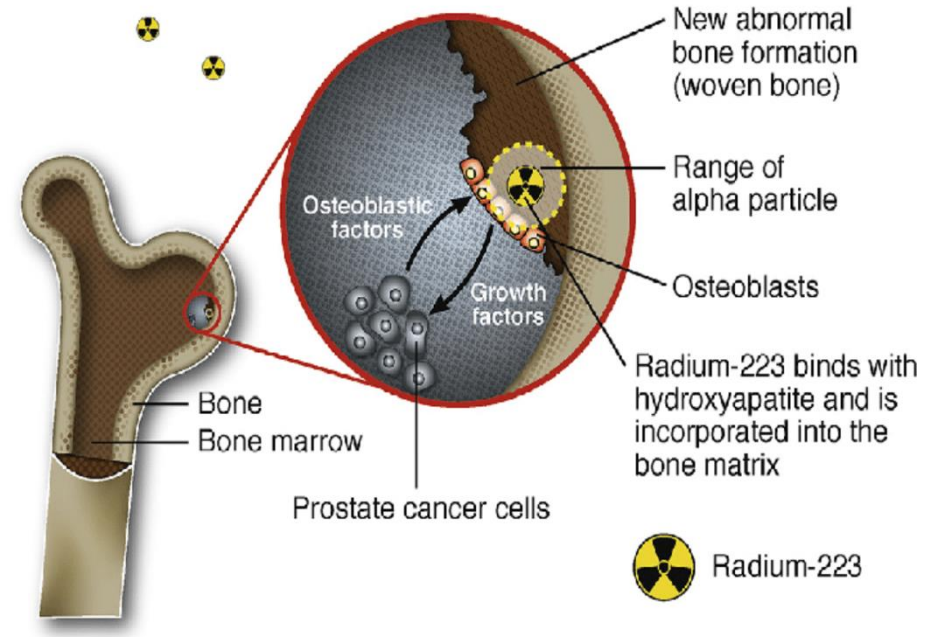


- Healthier, improved PS in RCTs
- Less likely to receive 2nd/3rd line agents

Ryan et al. NEJM, 2013.
Beer et al. Eur Urol, 2017.
George et al. CGUC, 2020.

Radium-223

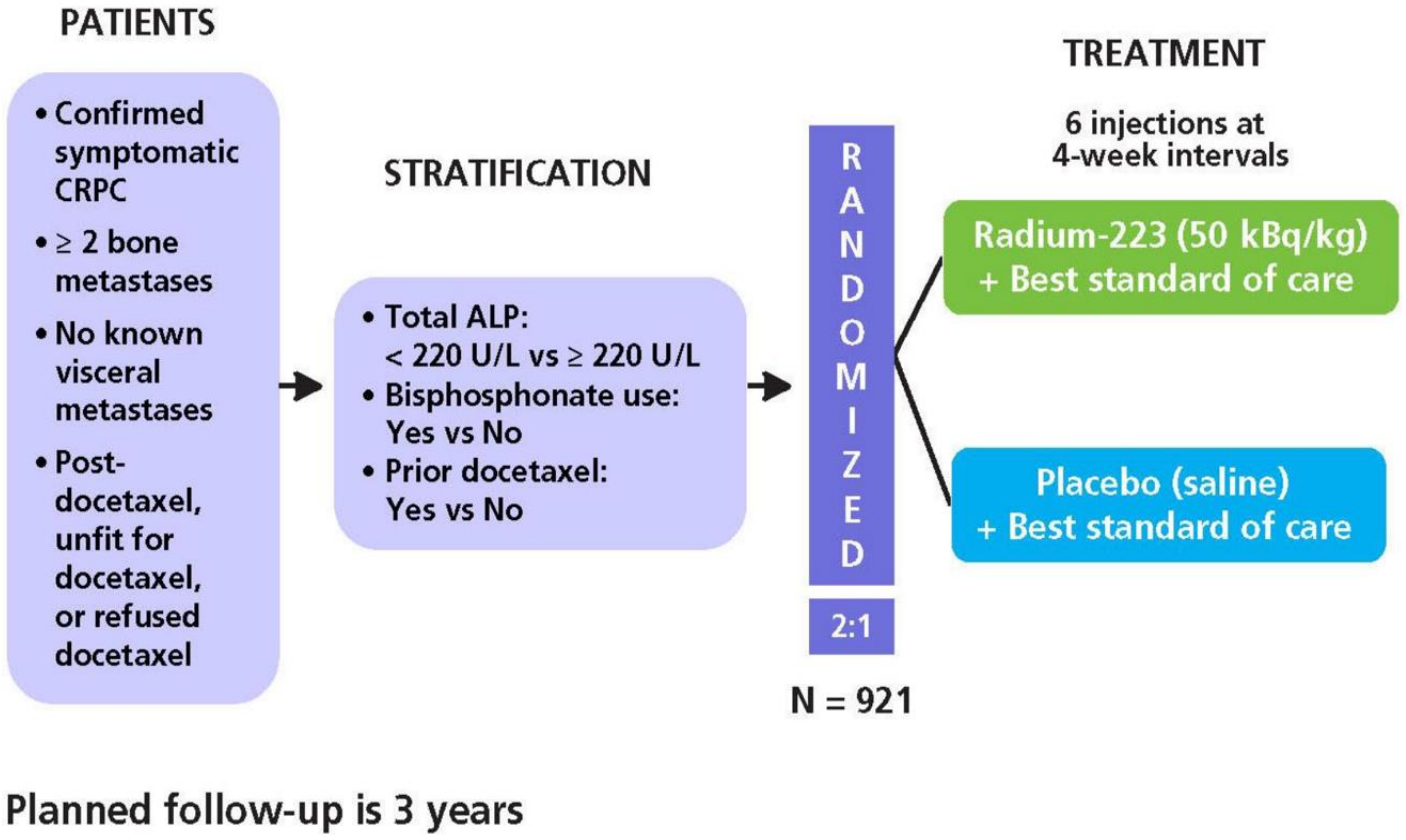
- Targeted **α-emitter:** selectively binds to areas of increased bone turnover in bone metastases
- Acts as a bone-seeking calcium mimetic, binds to new bone stroma
- Emits high energy alpha particles of short range (<100 um) → DNA double-strand breaks in nearby tumor cells, **<u>osteoblasts & osteoclasts</u>**



Mechanism of action of radium-223.

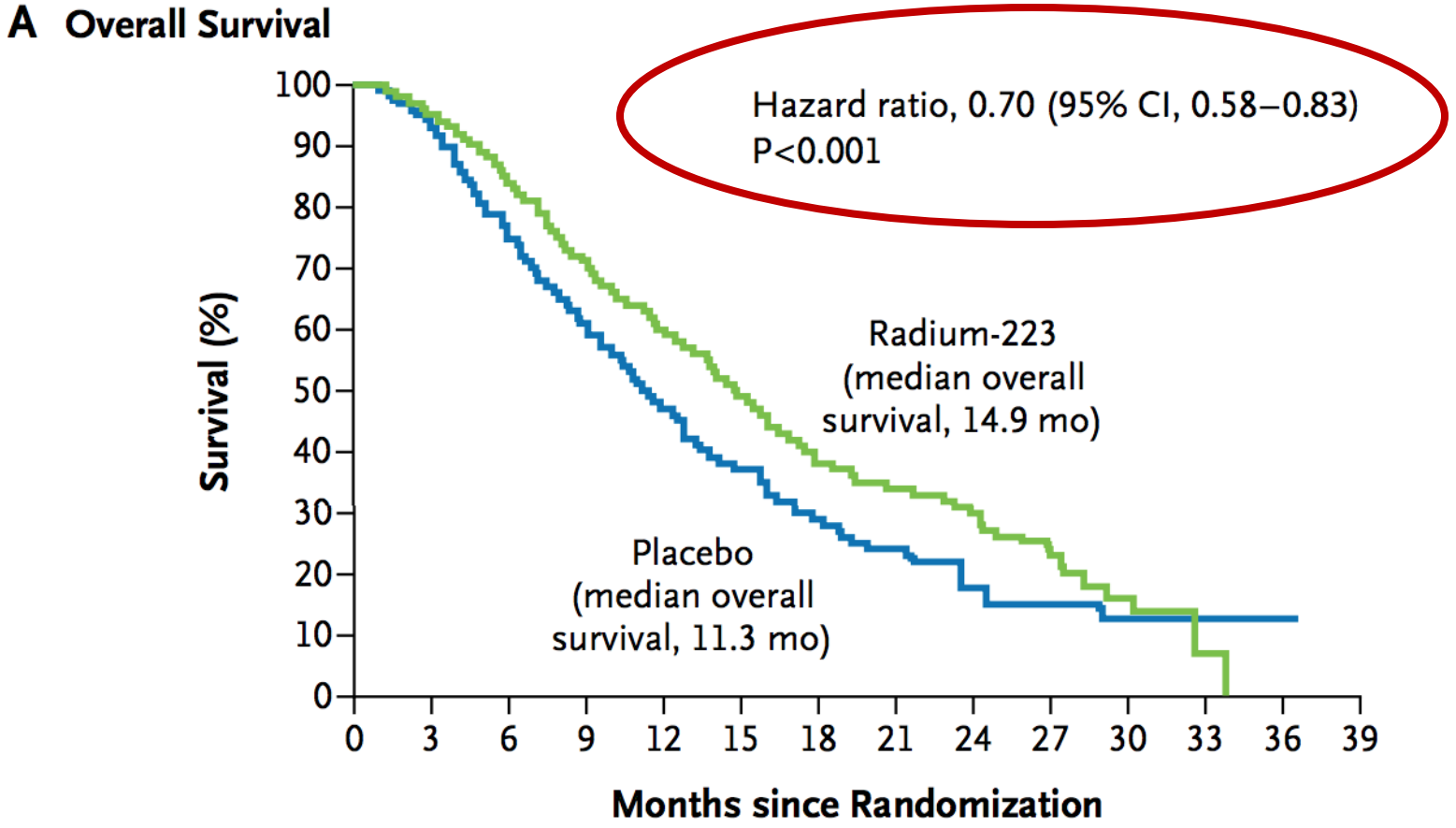
ALSYMPCA – Ra-223 in Pre-AAP/Enza Era

- Phase 3 RCT, n=921
- Symptomatic mCRPC pts with ≥2 bone mets and **no visceral mets**
- 2:1 randomization to 6 injections of Ra-223 vs placebo
- All pts received additional best SOC



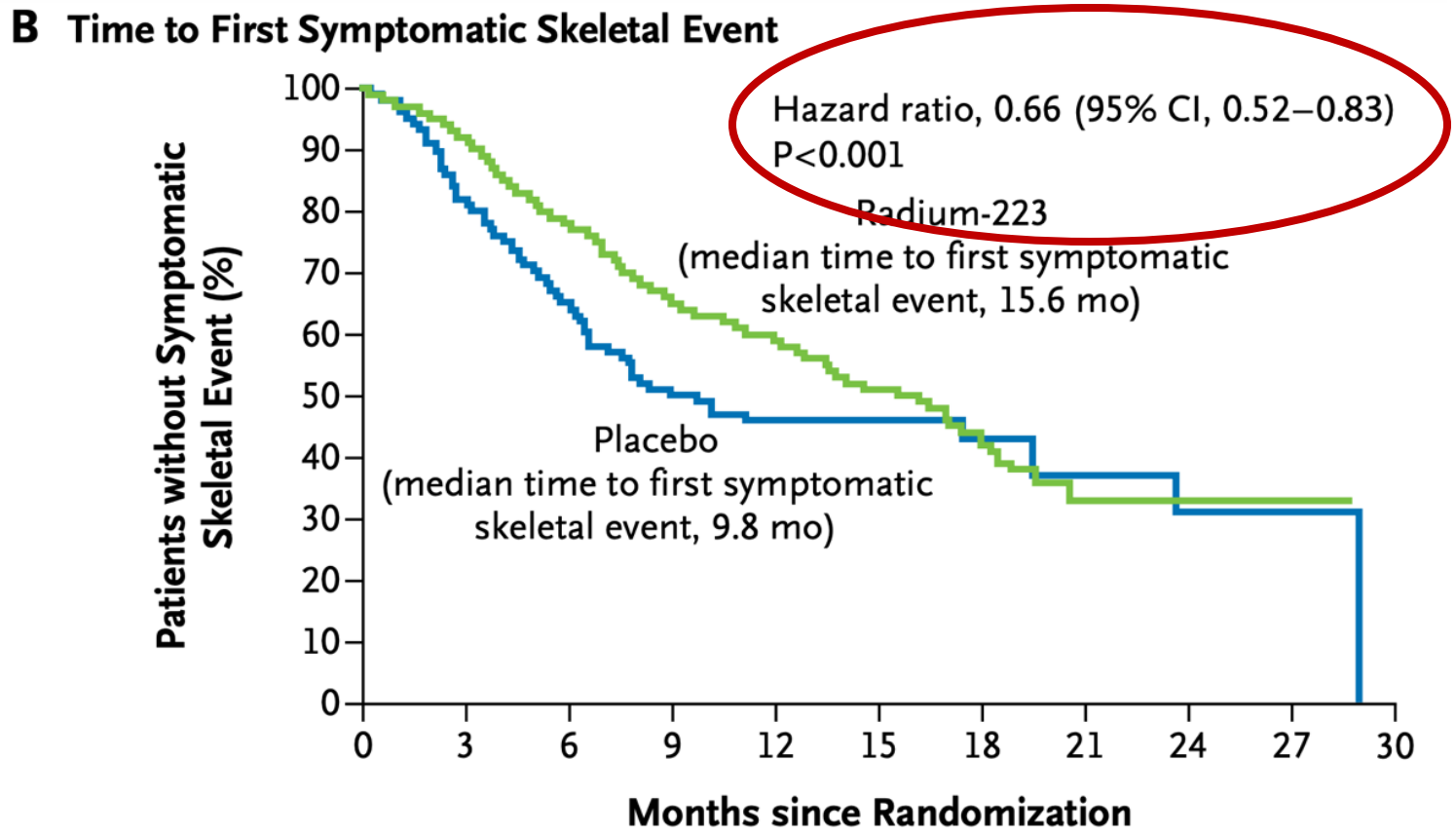
Parker et al. NEJM, 2013

ALSYMPCA – Overall Survival



Parker et al. NEJM, 2013

ALSYMPCA – Time to 1st SSE



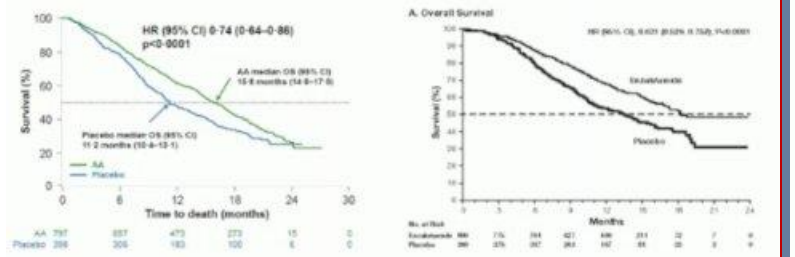
Parker et al. NEJM, 2013

Why Enzalutamide + Ra-223?

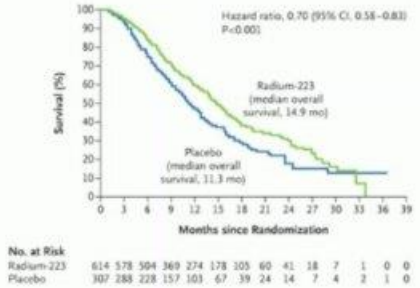
BARCELONA 2024 ESMO congress

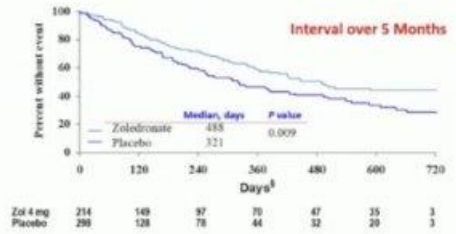
2- Standard of care for Castration-Resistant Prostate Cancer when PEACE-3 was designed

Androgen Receptor Pathway Inhibitors (Abiraterone, Enzalutamide) improve OS

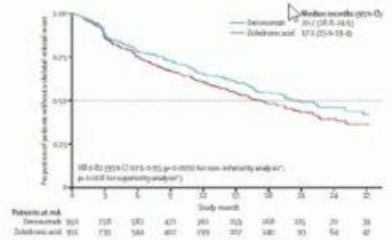


Radium-223 also improves OS (ALSYMPCA trial)





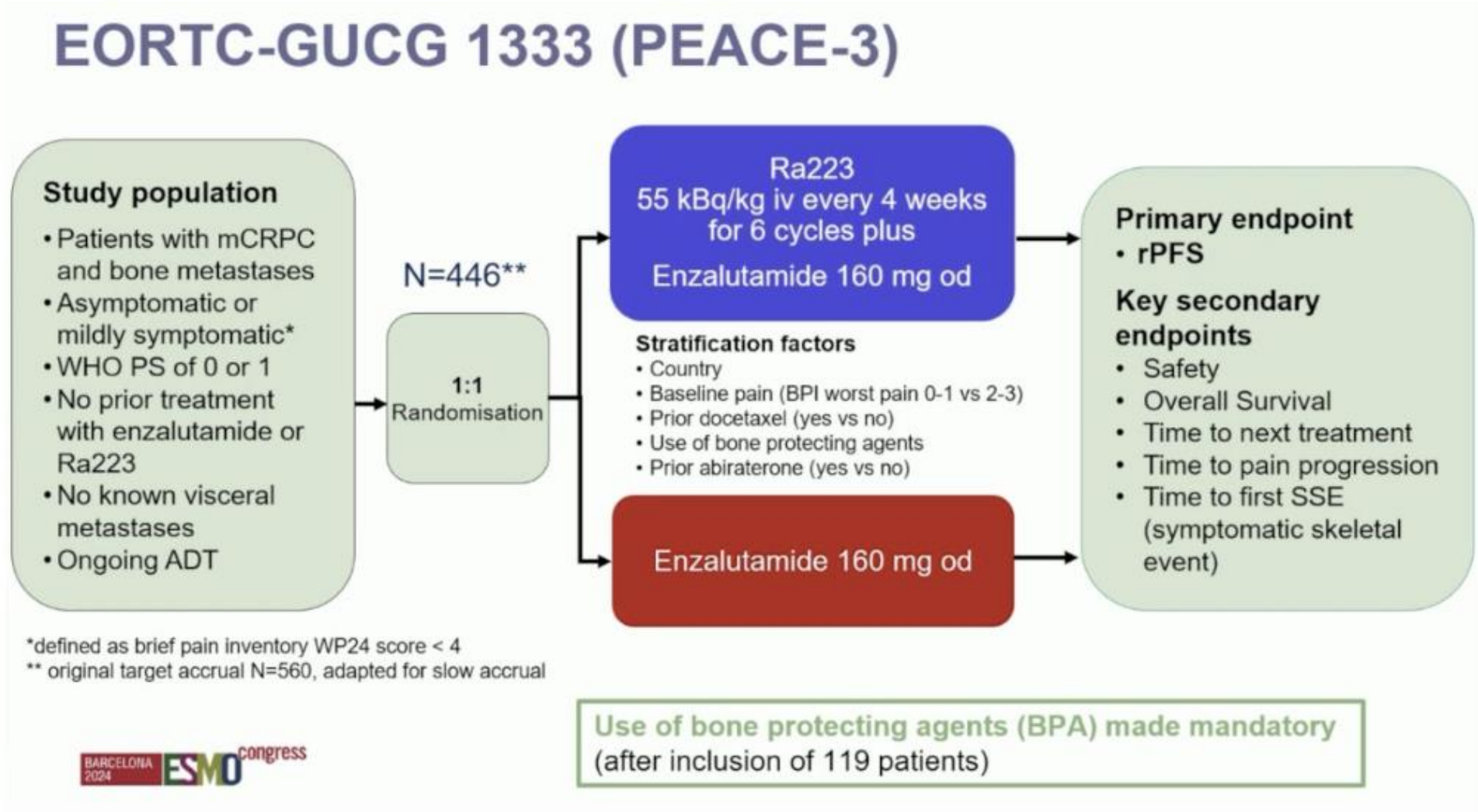
Bone-protecting agents prevent SRE (Denosumab, Zoledronate)



It made sense to combine
(cf ADT and RT synergy in localized disease)

Scher NEJM 2012, Fizazi Lancet Oncol 2012,
Parker NEJM 2013, Saad JNCI 2004, Fizazi Lancet 2011

EORTC-133/PEACE-3 Study Design



ERA 223 → Study Amendment (2018)

Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

Matthew Smith, Chris Parker, Fred Saad, Kurt Miller, Bertrand Tombal, Quan Sing Ng, Martin Boegemann, Vsevolod Matveev, Josep Maria Piulats, Luis Eduardo Zucca, Oleg Karyakin, Go Kimura, Nobuaki Matsubara, William Carlos Nahas, Franco Nolè, Eli Rosenbaum, Axel Heidenreich, Yoshiyuki Kakehi, Amily Zhang, Heiko Krissel, Michael Teufel, Junwu Shen, Volker Wagner, Celestia Higano

Smith et al. Lancet Oncol, 2019

ERA 223: AAP + Ra-223

- Phase III RCT of 806 patients randomized 1:1:
  - Ra-223 + AAP
  - Placebo + AAP
- Nov 2017: **Study unblinded – more fractures and deaths in the Ra-223 + AAP group than placebo + AAP group**
- Median SSE-free survival:
  - Ra-223 + AAP: 22.3 mo
  - Placebo + AAP: 26 mo
- Fractures:
  - Ra-223 + AAP: 29%
  - Placebo + AAP: 11%

Smith et al. Lancet Oncol, 2019

ERA-223: SSE-Free Survival by Use of Bone Protective Agents

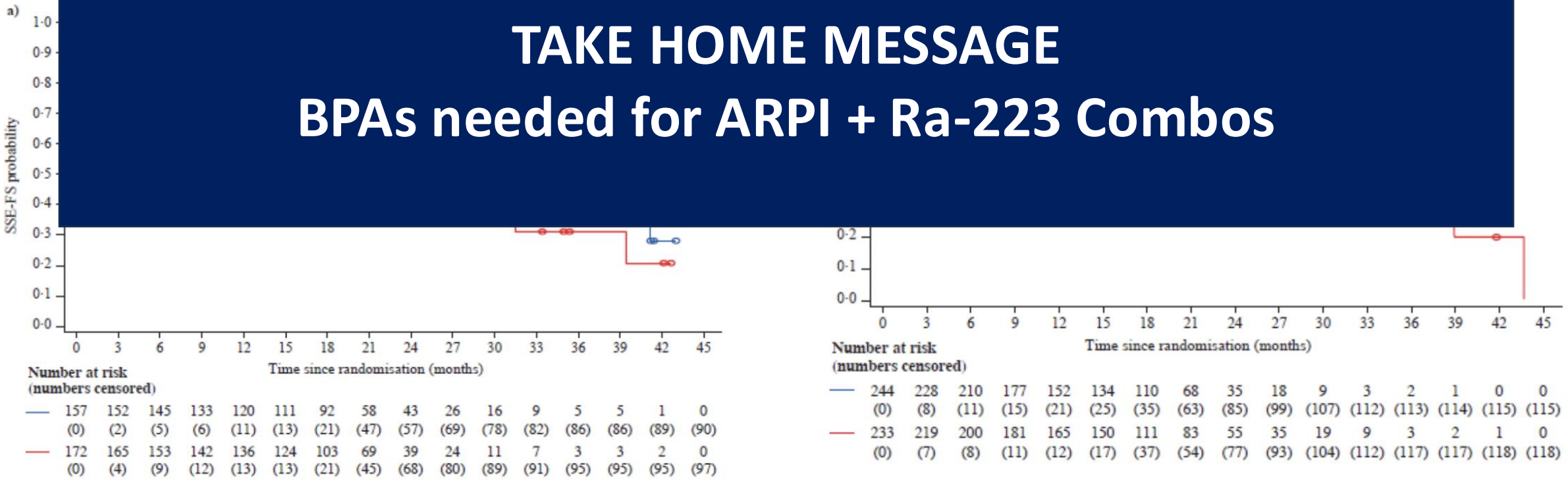
Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

Matthew Smith, Chris Parker, Fred Saad, Kurt Miller, Bertrand Tombal, Quan Sing Ng, Martin Boegemann, Vsevolod Matveev, Josep Maria Piulats, Luis Eduardo Zucca, Oleg Karyakin, Go Kimura, Nobuaki Matsubara, William Carlos Nahas, Franco Nolè, Eli Rosenbaum, Axel Heidenreich, Yoshiyuki Kakehi, Amily Zhang, Heiko Krissel, Michael Teufel, Junwu Shen, Volker Wagner, Celestia Higano

WITH Bone Protective Agents

WITHOUT Bone Protective Agents

TAKE HOME MESSAGE
BPAs needed for ARPI + Ra-223 Combos

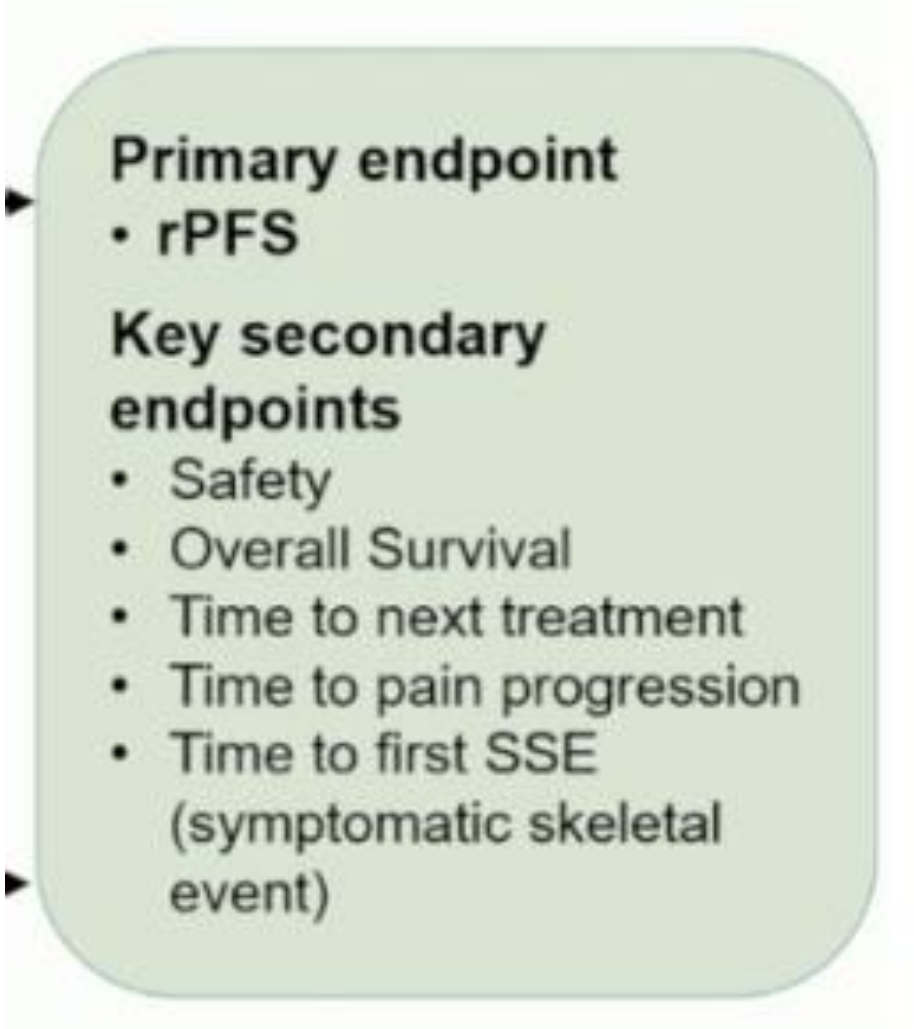


Smith et al. Lancet Oncol, 2019

PEACE-3 Study Amendment

- **March 2018:** Based on ERA 223, PEACE-III IMDC issued urgent safety letter
- **April 2018:** Mandated bone protective agents (denosumab or ZA) ≥6 weeks prior to 1st dose of Ra-223
- **July 2018:** Min # of bone mets required increased to ≥4 in Europe (Pharmacovigilance Risk Assessment Committee [PRAC] of the European Medicine Agency)

Study Endpoints



- Progression assessed using conventional imaging (bone scan + CE CT C/A/P or MRI) q12 weeks
- Secondary endpoints tested semi-hierarchically (minimize FP results)

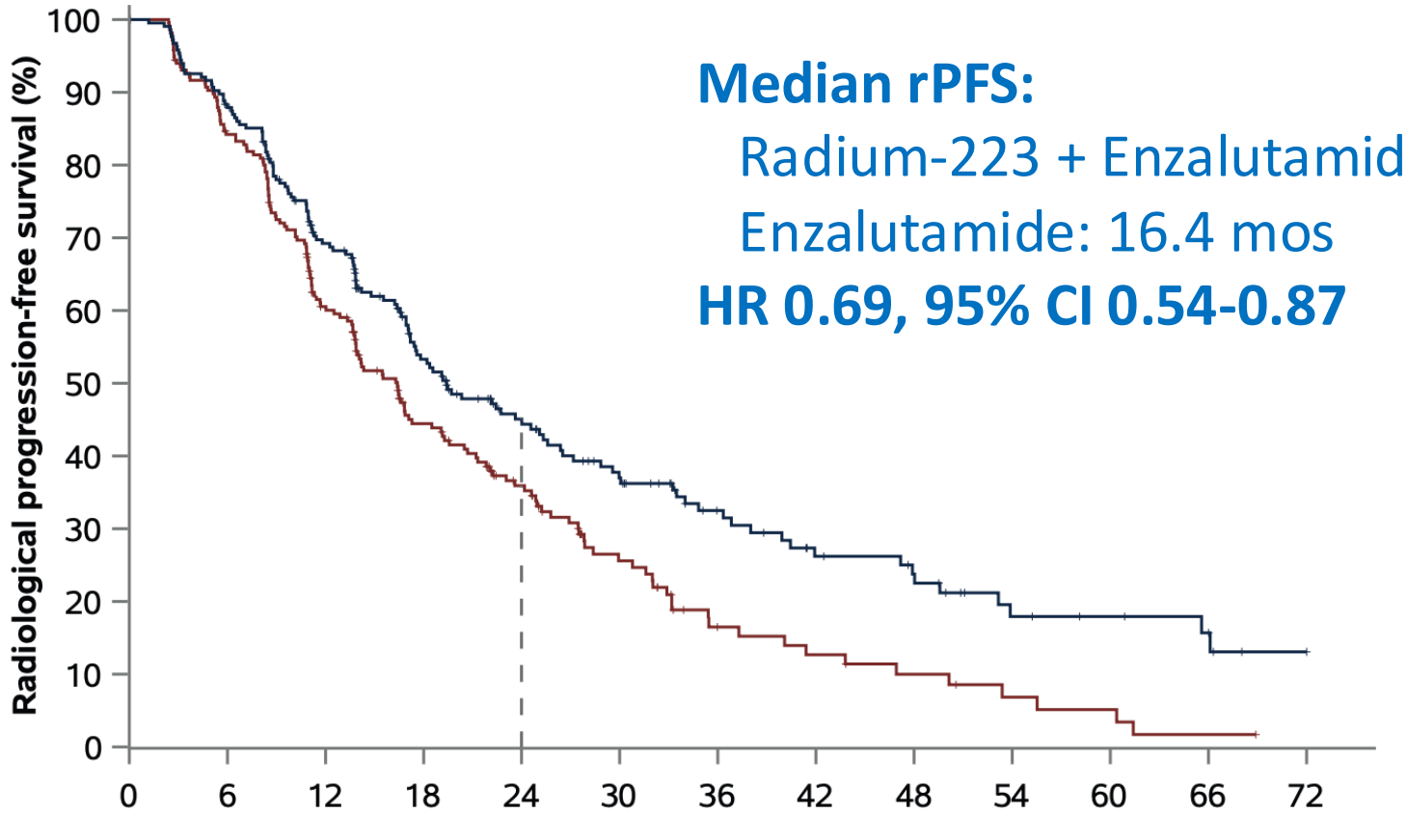
Statistical Methods

- Study powered to detect 32% rPFS benefit w/ Ra-223 + enza (HR: 0.68) at 90% power & a 1-sided type 1 error rate of 2.5%
  - 446 pts & 283 events
- Semi-hierarchical testing of 2° end points:
  - OS
  - TTNT & TTPP jointly
  - TTSSE
    - Formal testing was stopped once a formal stage was not statistically significant
- Survival analyses using KM curves, Cox PH models, & Fine-Gray competing risk analyses (TTNT, TTPP, TTSE)

Patients and Baseline 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)

rPFS (ITT Population)



Median rPFS:

Radium-223 + Enzalutamide: 19.4 mos

Enzalutamide: 16.4 mos

HR 0.69, 95% CI 0.54-0.87

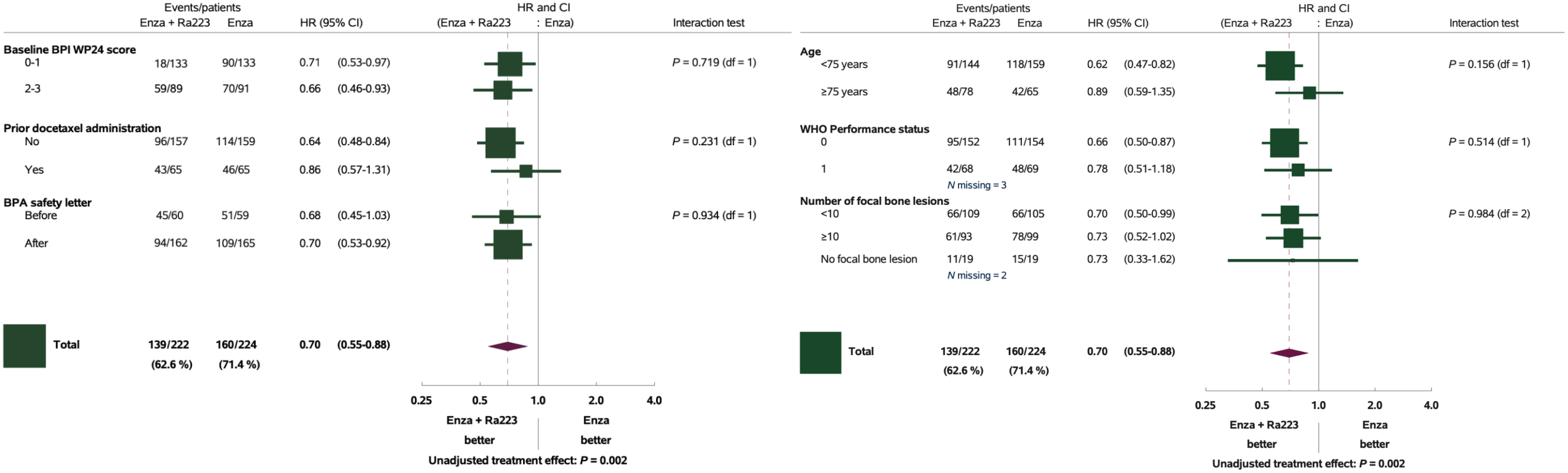
Patients at risk

Enza-	224	180	122	77	52	28	13	10	7	4	3	1	0
Enza + Ra223-	222	188	138	91	64	48	32	23	19	11	9	7	3

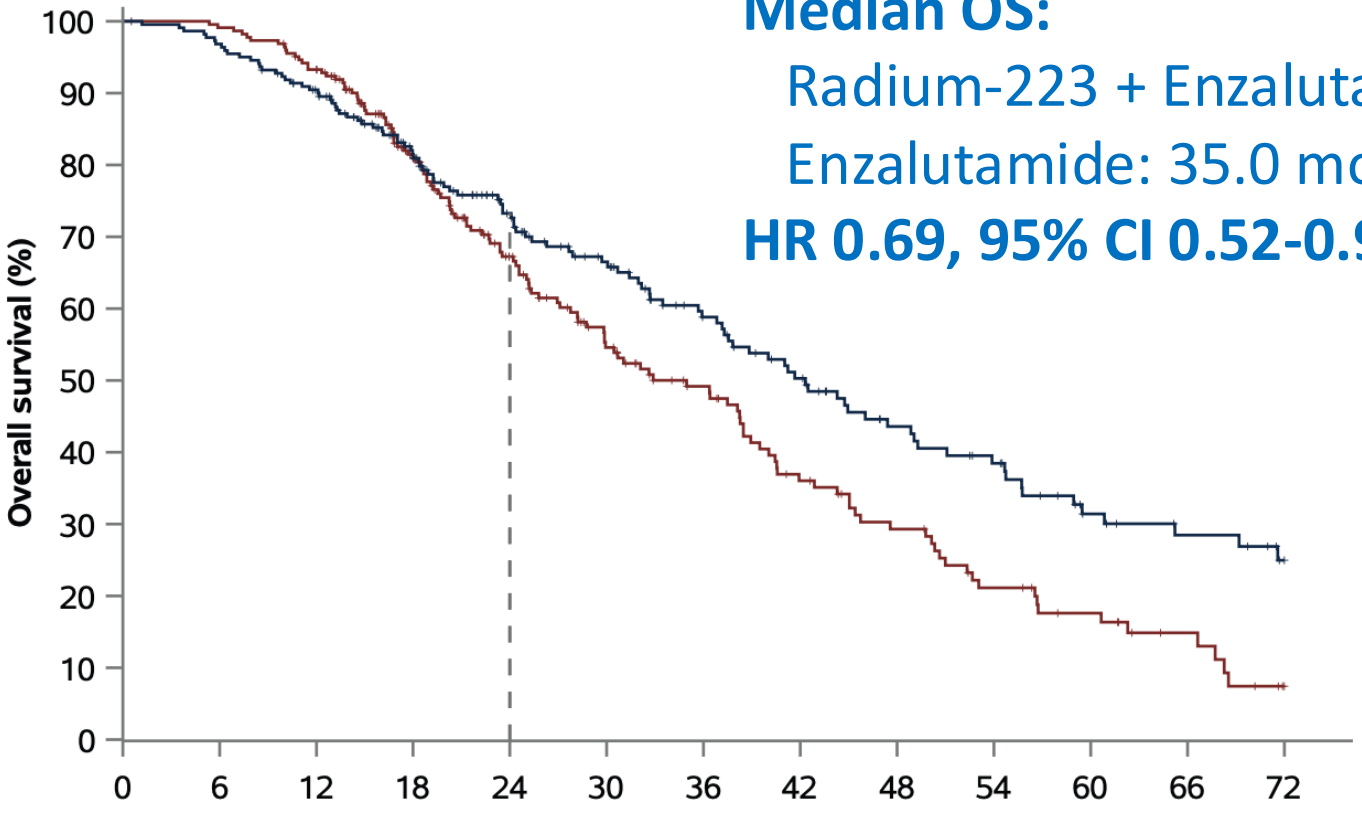
No. cumulative events

Enza-	0	34	84	114	128	141	150	153	155	157	158	160	160
Enza + Ra223-	0	26	65	94	107	118	123	129	131	135	135	136	137

rPFS Subgroup Analysis



Secondary EP: OS (ITT Population)



Median OS:

Radium-223 + Enzalutamide: 42.3 mos

Enzalutamide: 35.0 mos

HR 0.69, 95% CI 0.52-0.90

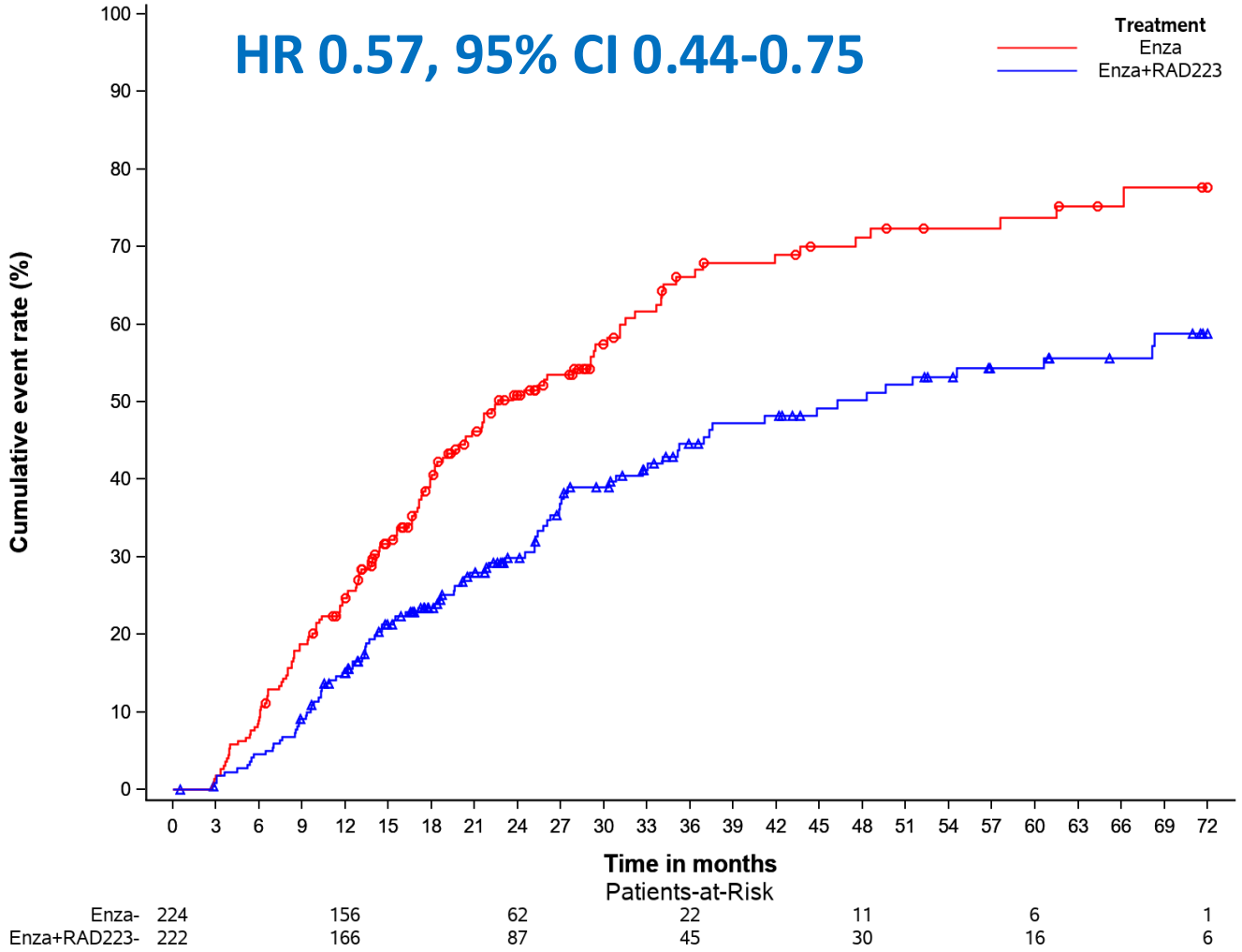
Patients at risk

Enza-	224	222	206	152	107	77	58	40	30	20	14	8	1
Enza + Ra223-	222	214	194	149	114	92	71	57	43	36	23	18	12

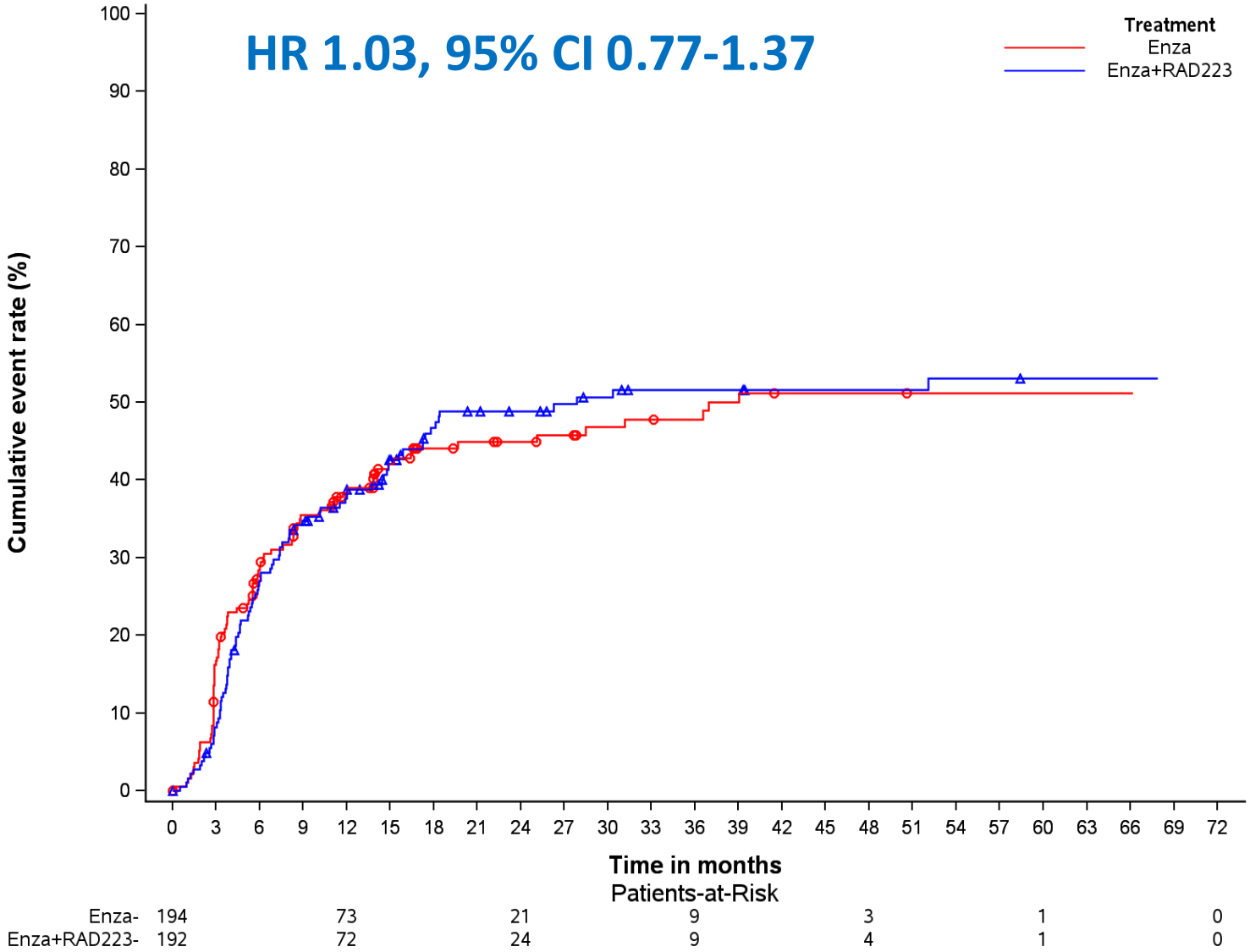
No. cumulative events

Enza-	0	2	15	40	64	83	90	105	112	120	123	125	129
Enza + Ra223-	0	7	21	39	53	63	73	83	90	95	101	103	105

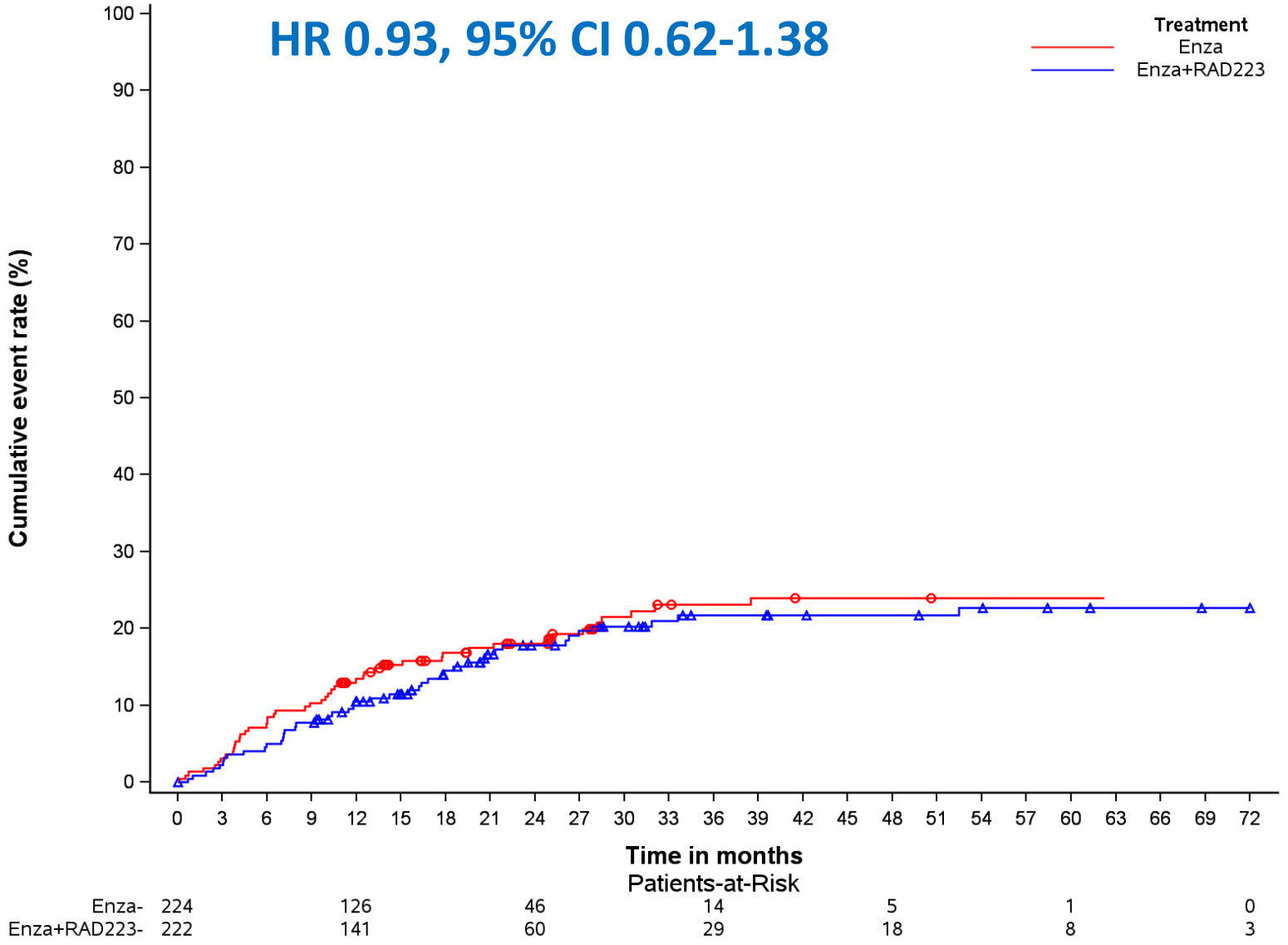
Secondary EP: Time to Next Systemic Anti-Neoplastic Treatment



Secondary EP: Time to Pain Progression



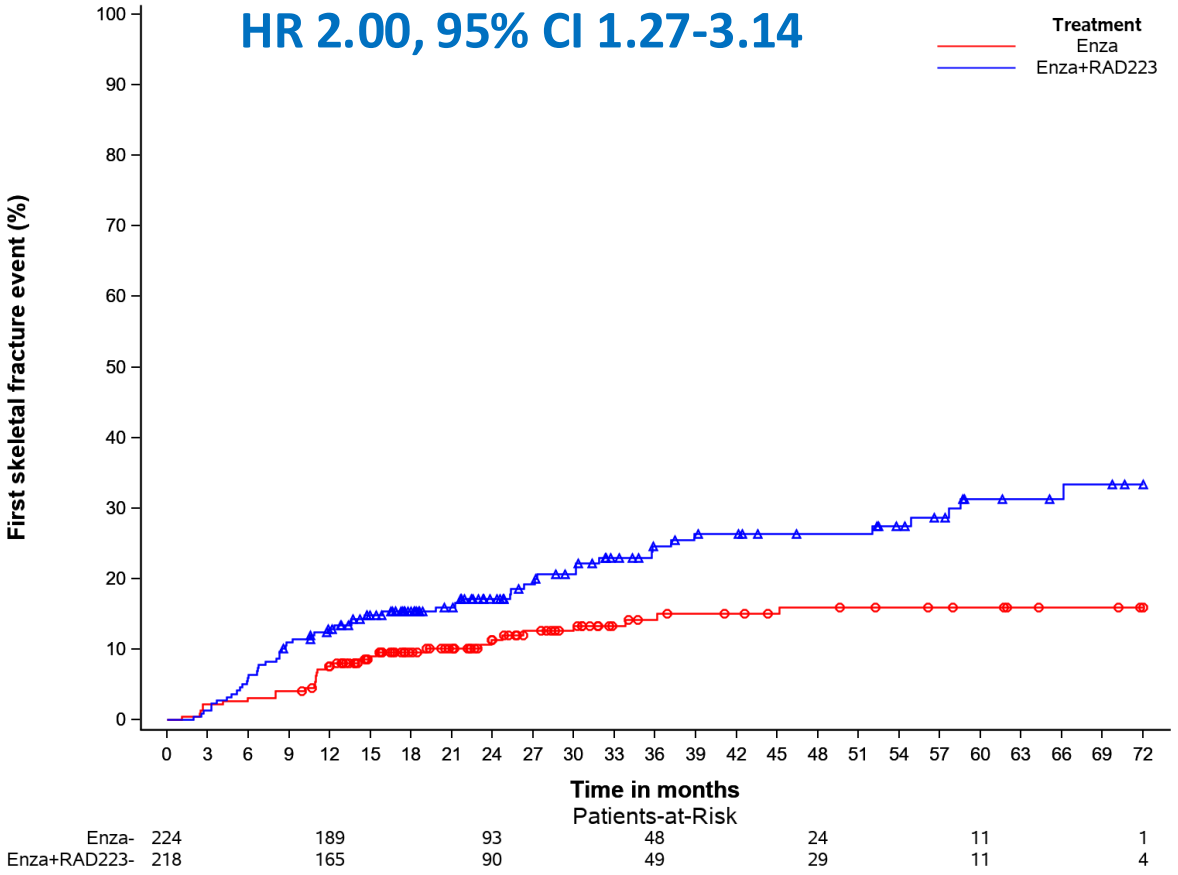
Secondary EP: Time to SSE



Treatment-Emergent Adverse Events

	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)

Fracture Characteristics



Time to First Skeletal Fracture

	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)

Discussion

- At the interim analysis with 80% OS events, PEACE-3 strongly suggested an OS benefit to 1L Ra-223 + Enza:
  1. Median OS in PEACE-3: 42.3 mos (Ra-223 + Enza) vs 35.0 mos (Enza) → OS gain - **7 mos**
  2. Median OS in Enza mono arm: congruent with PREVAIL (32.4 mos)
  3. Median OS gain in ALSYMPCA: **3.6 mos**
  4. The final analysis at 299 deaths will determine the real OS benefit of the combination

- Important considerations:
  1. Long duration of the trial (>8.5 years): hampered by the unblinding of the ERA-223 trial and regulatory agencies imposing new restrictions on Ra-223 use
  2. Only 2.5% of patients received an ARPI in the hormone sensitive setting
     - However, in developed countries, many patients still receive ADT alone for mHSPC (59%-71% in the US)

- **<u>Ideal PEACE-3 patient</u>: ADT alone prior to mCRPC, bone only metastases**

Take Home Messages

- PEACE-3 shows that adding 6 cycles of radium-223 to enzalutamide and BPA as 1L treatment for mCRPC with bone metastases increases rPFS

- An interim analysis at 80% of events suggest an OS advantage
  - Needs to be confirmed with additional follow-up

- ***Combining enzalutamide and radium-223 (<u>with a BPA</u>) is a new treatment option for patients with mCRPC***