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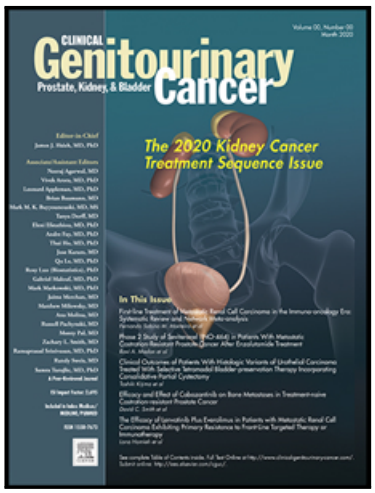

Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden

Pär Stattin , Marcus Westerberg , Ingela Franck Lissbrant , Marie Hjälm Eriksson , Anders Kjellman , Anders Ullén , Zdravko Vassilev , Per Sandstrom , Rachel Weinrib , David Martinez , Xabier Garcia-Albeniz

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Highlights

- Radium-223 is a treatment for symptomatic bone metastases in prostate cancer
- In a clinical trial, its combination with abiraterone was associated with fractures
- We used real world data from Swedish registries to evaluate the risk of fractures
- The risk of fractures associated its use as monotherapy was small, if any

Title: Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Region Uppsala has, on behalf of NPCR, made agreements on subscriptions for quarterly reports from Patient-overview Prostate Cancer with Astellas, Sanofi, Janssen, and Bayer, as well as research projects with Astellas, Bayer, and Janssen.

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ZV and PS are employees of Bayer US. They have no other financial interests or personal relationships relevant to the PRECISE study.

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ABSTRACT

Aim: Estimate the effect of Radium-223 (Ra-223) on the incidence of bone fractures, prostate cancer death, and all-cause death compared with other standard treatments for metastatic, castration-resistant prostate cancer (mCRPC).

Methods: Using a cohort design, we estimated the effect of Ra-223 on the risk of bone fractures, all-cause and prostate cancer–specific mortality across different lines of treatment for mCRPC using Prostate Cancer data Base Sweden (2013-2018). The comparator group comprised other standard treatments for mCRPC. We used 36-month risk differences and hazard ratios (HRs) as effect estimates.

Results: The number of eligible individuals was 635, 453, 262, and 84 for the first-, second-, third-, and fourth-line cohorts, respectively. When compared Ra-223 to other standard treatments, the difference in the 36-month risk of fracture was 6% (95% confidence interval [CI], −7% to 18%) in the first-line cohort (n=635) and 8% (95% CI, −7% to 18%) in the second-line cohort (n=453). The number of fractures in the third-/fourth-line cohorts was too small for an adjusted comparison. The difference in 36-month mortality was higher in the first-line cohort 13% (95% CI, −3% to 31%), but lower in the second- and third-/fourth-line cohorts−8% (95% CI, −23% to 7%) and −14% (95% CI, −21% to 16%) respectively. Most deaths were due to prostate cancer.

Conclusion: Results suggest that the difference in the risk of fractures is small, if any. A difference in the risk of mortality may be present in first-line treatment, but a decreased risk of mortality was observed in second and later lines of treatment. The results on mortality need to be considered in the context of potential unmeasured or residual confounding.

Micro-Abstract (57/max 60 words) 59

We evaluated the effect of Ra-223 on the incidence of bone fractures and mortality compared with standard of care in patients with metastatic, castration resistant prostate cancer. We used real-world data from Swedish population-based healthcare registries. The results were imprecise and compatible with both a slight benefit or harm for both fractures and mortality in all lines of treatment.

Keywords: Radium-223; fracture; metastatic castration-resistant prostate cancer

INTRODUCTION

Radium-223 (Ra-223) is a life-prolonging, systemic, targeted alpha therapy indicated for adults with metastatic castration-resistant prostate cancer (mCRPC) who have symptomatic bone metastases and no visceral metastases. In the pivotal ALSYMPCA clinical trial, Ra-223 prolonged overall survival (OS) and time to first symptomatic skeletal event, increased quality of life or delayed its decline, and had a good safety profile [1-3]. In the subsequent ERA 223 trial, Ra-223 in combination with abiraterone acetate plus prednisone/prednisolone (AAP) was found to increase the risk of bone fractures (29% of patients treated with Ra-223 plus AAP compared with 11% who received placebo plus AAP and deaths in the treatment arm, leading to unblinding [4,5]. An adjusted analysis of OS yielded a hazard ratio (HR) of 1.06 (95% confidence interval [CI], 0.84-1.35) [5].

This safety signal triggered a regulatory procedure by the European Medicines Agency (EMA) that included a change to the label in the European Union (by adding a contraindication for the combination with AAP and a restriction to patients who had progressed to at least two prior treatments for mCRPC or were ineligible for systemic mCRPC treatment). The aim of this post-authorisation safety study [6] was to estimate the effect of Ra-223 on the incidence of fractures and death compared with the standard of care in a real-world setting, which we report here. As recommended by the EMA [7], the study and its protocol and report are posted in the EU PAS register (EUPAS33448) [8].

METHODS

Study setting

We analysed data (November 2013-December 2018) from Prostate Cancer data Base Sweden (PCBaSe), a database linking the National Prostate Cancer Register of Sweden, including the Patient-overview Prostate Cancer, with other health care registries [9,10] (Supplementary Methods). This study was approved by the Research Ethics Board in Uppsala, Sweden.

Eligibility criteria

Eligibility criteria included a diagnosis of adenocarcinoma of the prostate, initiation of any systemic treatment for mCRPC after progressing to luteinising hormone-releasing hormone (LHRH) analogues (procedures to identify the use of docetaxel and abiraterone for mCRPC as opposed to their use for castration-sensitive prostate cancer are described in Supplementary Methods), and presence of bone metastasis. Patients with prior use of Ra-223 or without complete information on baseline variables were excluded (Supplementary Methods)

Study design

We designed this observational study to emulate a target trial [11] (Supplementary Table S1) that would compare two treatment strategies: (1) initiation of Ra-223 as monotherapy for ≤six cycles, with early cessation if clinically indicated, and (2) initiation of any of the following comparator drugs (docetaxel, cabazitaxel, enzalutamide, abiraterone, or others [cisplatin, cyclophosphamide, doxorubicin, estramustine, etoposide, gemcitabine, carboplatin, methotrexate, mitoxantrone]), with cessation if clinically indicated. Under both treatment strategies, patients would be allowed to receive first-generation antiandrogens/LHRH analogues and continue subsequent treatment with a different drug other than Ra-223. These

treatment strategies were operationalised by classifying patients into study groups according to their baseline data (i.e., beginning of treatment line) and by artificially censoring patients in the comparator group when they started Ra-223. Artificial censoring was not applied in the Ra-223 group because none received other mCRPC treatment concomitantly. The primary outcome was bone fractures requiring admission to a hospital or treatment in an outpatient setting. The secondary outcomes were death due to all causes and death due to prostate cancer.

Because all study drugs could be used for any treatment line for mCRPC (Supplementary Figure S1), we first emulated a trial for first-line treatment in which eligible patients were classified into treatment strategies the day they initiated a first-line treatment. They were followed until the artificial censoring, occurrence of the outcome of interest, or the administrative end of follow-up. We repeated this process for the four lines of treatment (later lines of treatment were scarcely represented in the data), creating four cohorts. Patients could contribute eligible individuals in multiple line-of-treatment–specific cohorts if they remained eligible [12-14] (Supplementary Methods). For both fractures and survival, we evaluated the homogeneity of the 12-month adjusted risk difference estimates across line-of-treatment cohorts using the I^2 statistic [15] and established a priori that if I^2 was $\leq$50%, we would pool the cohorts. Several sensitivity analyses (Supplementary Table S2) and a negative control outcome (Supplementary Methods and Supplementary Figure S2) were run.

Statistical analysis

We estimated the hazard ratios of the three outcomes for Ra-223 versus comparator drug via a weighted pooled logistic model [16,17] that included the indicator for the treatment strategy and a flexible function of time (restricted cubic splines to estimate the baseline hazard). The model was weighted using stabilised weights where the denominator indicated the probability

that a patient would initiate a treatment strategy conditional on the following baseline variables: age, calendar year, time from prostate cancer diagnosis, history of skeletal-related events, TNM (tumour [T], nodes [N], and metastases [M]) stage, tumour grade, Eastern Cooperative Oncology Group (ECOG) performance status (PS), prostate-specific antigen (PSA), haemoglobin, total alkaline phosphatase, Charlson Comorbidity Index, site of metastasis (visceral, bone, lymph node), prior spinal cord compression, bone-health agent (zoledronate, denosumab) use, steroid use, time on androgen deprivation therapy (ADT), prior radiation therapy, prior mCRPC drugs, and current treatment line. The numerator indicated the corresponding marginal probability. To adjust for the potential selection bias introduced because of the artificial censoring applied to the comparator group, we used a second set of weights that were a function of the time-varying probability of initiating Ra-223 conditional on the following time-varying variables: ECOG PS, PSA, haemoglobin, total alkaline phosphatase, Charlson Comorbidity Index, metastasis site, prior spinal cord compression, bone-health agent use, steroid use, treatment line, and prior mCRPC drugs. Missing values in baseline variables were addressed by applying weights to the complete case population [18]. Weights were truncated at percentile 99 to avoid undue influence of outliers [19,20].

To estimate cumulative incidence probabilities and survival under both strategies, we fit a weighted outcome model like the one above including product terms for treatment strategy and time. The model's predicted values were used to estimate the cumulative incidence and survival at 6-month intervals up to 36 months. We computed percentile-based 95% CIs via bootstrapping (500 resamplings).

RESULTS

There were 1,771 patients diagnosed with mCRPC registered in PCBaSe between November 2013 and December 2018. Of these, 635 individuals were eligible for the first-line cohort (Ra-223, n=203; comparator, n=432), 453 for the second-line cohort (Ra-223, n=239; comparator, n=214), 262 for the third-line cohort (Ra-223, n=180; comparator, n=82), and 84 for the fourth-line cohort (Ra-223, n=59; comparator, n=25); i.e., 1,434 individuals participated in the four treatment-line–specific cohorts (1,203 unique patients) (Supplementary Table S3).

The variables age, ECOG PS, and Charlson Comorbidity Index score were balanced, considering all lines of treatment together. Patients receiving Ra-223 as first-line treatment were more likely to have experienced a bone fracture before baseline than patients receiving a comparator. Enzalutamide was the most frequently used baseline drug in the comparator group in the first two lines of treatment and cabazitaxel in the third and fourth lines of treatment (Table 1). Supplementary Table S4 contains the treatments received after the baseline treatment strategy and Supplementary Table S5 describes the follow-up, censoring reasons, and outcomes in the overall study population and by treatment line.

Table 1. Baseline characteristics, by group and treatment line, PCBaSe, 2013-2018

Characteristic[a]	Comparator arm					Radium-223 arm				
	All (n = 753)	Line 1 (n = 432)	Line 2 n = 214)	Line 3 (n = 82)	Line 4 (n = 25)	All (n = 681)	Line 1 (n = 203)	Line 2 (n = 239)	Line 3 (n = 180)	Line 4 (n = 59)
Age, mean (SD), y	74 (8)	75 (8)	73 (7)	72 (7)	70 (7)	74 (7)	75 (8)	74 (8)	73 (6)	72 (7)
Calendar year at cohort entry, n (%)										
Nov 2013-2014	4 (1)	3 (1)	1 (0)	0	0	11 (2)	1 (0)	4 (2)	3 (2)	3 (5)
2015	64 (9)	28 (6)	25 (12)	9 (11)	2 (8)	143 (21)	39 (19)	38 (16)	43 (24)	23 (39)
2016	157 (21)	98 (23)	38 (18)	16 (20)	5 (20)	182 (27)	43 (21)	70 (29)	51 (28)	18 (31)
2017	248 (33)	144 (33)	69 (32)	27 (33)	8 (32)	214 (31)	81 (40)	76 (32)	49 (27)	8 (14)
2018	280 (37)	159 (37)	81 (38)	30 (37)	10 (40)	131 (19)	39 (19)	51 (21)	34 (19)	7 (12)
Months from prostate cancer diagnosis to baseline, mean (SD)	71 (53)	66 (56)	75 (51)	83 (47)	71 (37)	76(55)	61 (55)	76 (56)	88 (49)	97 (50)
Skeletal-related events before baseline,[b] n (%)	308 (41)	138 (32)	103 (48)	51 (62)	16 (64)	350 (51)	85 (42)	118 (49)	109 (61)	38 (64)
History of fractures, n (%)	129 (17)	62 (14)	38 (18)	22 (27)	7 (28)	133 (20)	46 (23)	35 (15)	38 (21)	14 (24)
T stage, n (%)										
T1	146 (19)	88 (20)	35 (16)	18 (22)	5 (20)	131 (19)	35 (17)	51 (21)	35 (19)	10 (17)
T2	236 (31)	131 (30)	74 (35)	25 (30)	6 (24)	202 (30)	67 (33)	76 (32)	48 (27)	11 (19)
T3	315 (42)	183 (42)	87 (41)	34 (41)	11 (44)	286 (42)	83 (41)	93 (39)	76 (42)	34 (58)
T4	56 (7)	30 (7)	18 (8)	5 (6)	3 (12)	62 (9)	18 (9)	19 (8)	21 (12)	4 (7)
N stage, n (%)										

N0	161 (21)	101 (23)	46 (22)	12 (15)	2 (8)	155 (23)	55 (27)	55 (23)	34 (19)	11 (19)
N1	142 (19)	73 (17)	41 (19)	17 (21)	11 (44)	91 (13)	29 (14)	30 (13)	29 (16)	3 (5)
NX	450 (60)	258 (60)	127 (59)	53 (65)	12 (48)	435 (64)	119 (59)	154 (64)	117 (65)	45 (76)
M stage, n (%)										
M0	475 (63)	260 (60)	143 (67)	57 (70)	15 (60)	385 (57)	104 (51)	129 (54)	114 (63)	38 (64)
M1	278 (37)	172 (40)	71 (33)	25 (30)	10 (40)	296 (43)	99 (49)	110 (46)	66 (37)	21 (36)
Grade, n (%)										
Gleason ≤6[c]	111 (15)	64 (15)	28 (13)	14 (17)	5 (20)	80 (12)	14 (7)	39 (16)	18 (10)	9 (15)
Gleason = 7[d]	255 (34)	143 (33)	77 (36)	30 (37)	5(20)	208 (31)	56 (28)	70 (29)	62 (34)	20 (34)
Gleason >7[e]	387 (51)	225 (52)	109 (51)	38 (46)	15 (60)	393 (58)	133 (66)	130 (54)	100 (56)	30 (51)
ECOG PS, n (%)										
0	318 (42)	205 (47)	80 (37)	26 (32)	7 (28)	269 (40)	97 (48)	82 (34)	72 (40)	18 (31)
1	300 (40)	155 (36)	100 (47)	38 (46)	7 (28)	305 (45)	77 (38)	115 (48)	80 (44)	33 (56)
2	124 (16)	69 (16)	29 (14)	16 (20)	10 (40)	100 (15)	25 (13)	41 (17)	26 (14)	8 (14)
3	11 (1)	3 (1)	5 (2)	2 (2)	1 (4)	7 (1)	4 (2)	1 (0)	2 (1)	0
Prostate-specific antigen, mean (SD)	191 (446)	160 (354)	203 (494)	267 (672)	367 (465)	268 (828)	160 (336)	348 (1280)	288 (501)	249 (280)
Haemoglobin, mean (SD), g/L	126 (15)	127 (15)	125 (14)	125 (15)	114 (11)	125 (15)	125 (15)	124 (15)	126 (16)	123 (15)
Alkaline phosphatase, mean (SD), µkat/L	4 (4)	4 (5)	3 (3)	3 (3)	4 (4)	5 (7)	5 (6)	5 (8)	5 (9)	4 (3)
Osteoporosis diagnosis, n (%)	1 (0)	1 (0)	0	0	0	4 (1)	2 (1)	0	1 (1)	1 (2)
Charlson Comorbidity Index, n (%)										
0	463 (61)	265 (61)	131 (61)	50 (61)	17 (68)	424 (62)	122 (60)	142 (59)	122 (68)	38 (64)
1	135 (18)	76 (18)	37 (17)	17 (21)	5 (20)	138 (20)	46 (23)	48 (20)	31 (17)	13 (22)

2	87 (12)	48 (11)	26 (12)	12 (15)	1 (4)	66 (10)	20 (10)	28 (12)	12 (7)	6 (10)
3+	68 (9)	43 (10)	20 (9)	3 (4)	2 (8)	53 (8)	15 (7)	21 (9)	15 (8)	2 (3)
Visceral metastasis, n (%)	105 (14)	41 (9)	33 (15)	22 (27)	9 (36)	28 (4)	5 (2)	11 (5)	7 (4)	5 (8)
Lymph node metastasis, n (%)	323 (43)	158 (37)	102 (48)	48 (59)	15 (60)	176 (26)	36 (18)	64 (27)	59 (33)	17 (29)
Other site of metastasis, n (%)	43 (6)	18 (4)	15 (7)	8 (10)	2 (8)	22 (3)	3 (1)	12 (5)	5 (3)	2 (3)
Prior diagnosis of other cancer, n (%)	39 (5)	24 (6)	11 (5)	3 (4)	1 (4)	27 (4)	11 (5)	11 (5)	4 (2)	1 (2)
History of spinal cord compression, n (%)	10 (1)	4 (1)	6 (3)	0	0	11 (2)	2 (1)	3 (1)	4 (2)	2 (3)
Concomitant use of bone-health agents, n (%)	130 (17)	54 (13)	42 (20)	29 (35)	5 (20)	230 (34)	52 (26)	76 (32)	72 (40)	30 (51)
Current use of steroids, n (%)	408 (54)	171 (40)	153 (72)	64 (78)	20 (80)	207 (30)	25 (12)	70 (29)	77 (43)	35 (59)
Months on androgen deprivation therapy[f]										
Mean (SD)	32 (28)	28 (29)	35 (27)	39 (22)	47 (18)	38 (30)	26 (27)	37 (27)	49 (32)	54 (26)
Prior radiation therapy, n (%)	384 (51)	171 (40)	135 (63)	57 (70)	21 (84)	406 (60)	96 (47)	142 (59)	125 (69)	43 (73)
Prior systemic therapy[g], n (%)										
Docetaxel	156 (49)	0	76 (36)	62 (76)	18 (72)	250 (52)	0	62 (26)	132 (73)	56 (95)
Cabazitaxel	22 (7)	0	2 (1)	7 (9)	13 (52)	60 (13)	0	1 (0)	20 (11)	39 (66)
Abiraterone	111 (35)	0	48 (22)	43 (52)	20 (80)	181 (38)	0	50 (21)	85 (47)	46 (78)
Enzalutamide	151 (47)	0	82 (38)	47 (57)	22 (88)	262 (55)	0	121 (51)	110 (61)	31 (53)
Others	13 (4)	0	6 (3)	5 (6)	2 (8)	22 (5)	0	5 (2)	12 (7)	5 (8)
Baseline systemic therapy, n (%)										
Docetaxel	102 (14)	66 (15)	33 (15)	3 (4)	0					

Cabazitaxel	60 (8)	3 (1)	24 (11)	25 (30)	8 (32)					
Abiraterone	186 (25)	120 (28)	51 (24)	12 (15)	3 (12)					
Enzalutamide	343 (46)	240 (56)	81 (38)	20 (24)	2 (8)					
Others	62 (8)	3 (1)	25 (12)	22 (27)	12 (48)					

ECOG = Eastern Cooperative Oncology Group; NA = not applicable; PCBaSe = Prostate Cancer data Base Sweden; PS = performance status; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHO = World Health Organization.

[a] Each individual may contribute to more than one line of treatment.

[b] Includes bone fracture, spinal cord compression and bone-targeted radiotherapy.

[c] Gleason score 6 included 6 (3%) cancers graded as WHO grade I

[d] Gleason score 7 included 18 (4%) cancers graded as WHO grade II

[e] Gleason score >7 included 15 (2%) cancers graded as WHO grade III

[f] Includes both surgical and chemical castration.

[g] Percentages are computed over the number of patients starting a second, third, or fourth line of treatment.

Risk of bone fractures

Overall, 62 fractures (9%) occurred in the Ra-223 group and 36 (5%) in the comparator group. The most common fractures were factures of the femoral neck and pertrochanteric and subtrochanteric femur (Supplementary Table S6). In the first-line cohort, the estimated adjusted 36-month risk of fracture (95% CI) was 18% (8%-32%) in the Ra-223 group and 12% (7%-22%) in the comparator group, corresponding to a difference in 36-month risk of 6 % (95% CI, −7% to 18%). In the second-line cohort, the estimated adjusted 36-month risk of fracture was 16% (9%-24%) in the Ra-223 group and 9% (1%-21%) in the comparator group, corresponding to a difference in 36-month risk of 8 % (95% CI, −7% to 18%). Table 2 indicates the corresponding HRs. In the third and fourth lines of treatment cohorts, there was only one fracture in the comparator groups, precluding an informative adjusted analysis.

Table 2. Bone fractures and survival analyses for Ra-223 versus comparator drug, by group and treatment line in the Prostate Cancer data Base Sweden, 2013-2018 [a]

	First line		Second line		Third/fourth line		Pooled	
	Comparator	**Ra-223**	**Comparator**	**Ra-223**	**Comparator**	**Ra-223**	**Comparator**	**Ra-223**
Fractures								
36-month risk (95% CI)	12 (7 to 22)	18 (8 to 32)	9 (1 to 21)	16 (9 to 24)	NE	NE	10 (5 to 17)	19 (13 to 26)
Difference in 36-month risk (95% CI)	Ref.	6 (−7 to 18)	Ref.	8 (−7 to 18)	Ref.	NE	Ref.	9 (0 to 17)
Hazard ratio (95% CI)	Ref.	1.14 (0.50 to 2.15)	Ref.	1.86 (0.62 to 10.93)	Ref.	NE	Ref.	1.61 (0.96 to 3.02)
Death								
36-month risk (95% CI)	73 (56 to 87)	86 (76 to 94)	94 (80 to 100)	87 (75 to 94)	100 (71 to 100)	86 (78 to 92)	NE	NE
Difference in 36-month risk (95% CI)	Ref.	13 (−3 to 31)	Ref.	−8 (−23 to 7)	Ref.	−14 (−21 to 16)	Ref.	NE
Hazard ratio (95% CI)	Ref.	1.63 (1.27 to 2.16)	Ref.	0.91 (0.60 to 1.23)	Ref.	0.72 (0.41 to 1.19)	Ref.	NE
Prostate cancer death								
36-month risk (95% CI)	68 (51 to 84)	83 (72 to 93)	92 (73 to 100)	85 (72 to 94)	100 (71 to 100)	83 (75 to 91)	NE	NE
Difference in 36-month risk (95% CI)	Ref.	15 (−4 to 34)	Ref.	−7 (−23 to 14)	Ref.	−17 (−24 to 13)	Ref.	NE
Hazard ratio (95%	Ref.	1.83 (1.38 to	Ref.	0.92 (0.59 to	Ref.	0.72 (0.42 to	Ref.	NE

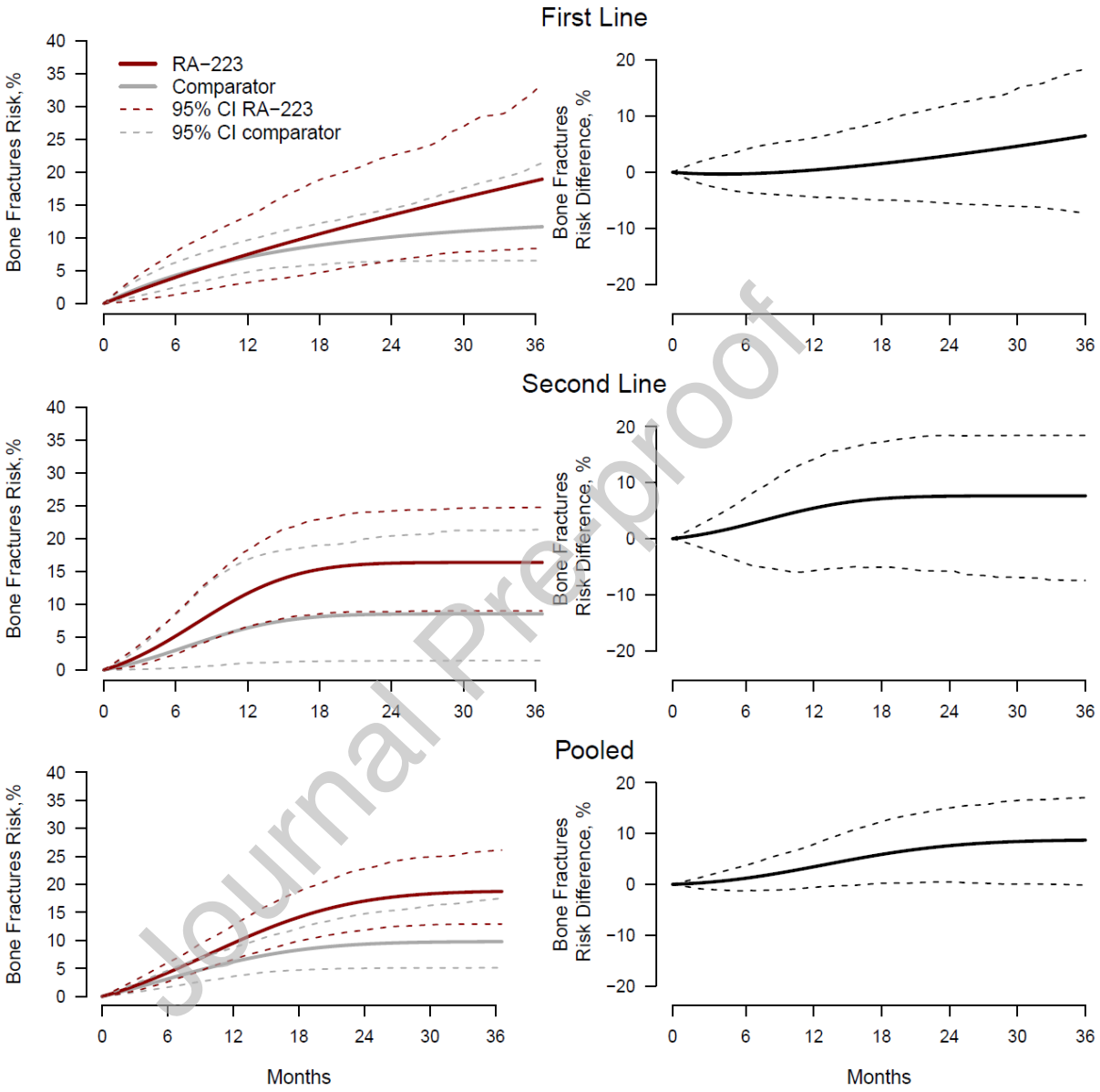
CI)		2.48)		1.29)		1.20)		

CI = confidence interval; NE = not estimable; Ref. = reference.

[a] Risk is expressed in number of cases per 100 persons.

The evaluation of the heterogeneity of the effect of Ra-223 versus the comparator on the risk of fracture by treatment line yielded an I^2 of 19% (although the few events in the third-/fourth-line cohorts may have impeded a correct estimation of heterogeneity), and the four cohorts were therefore pooled. When pooling the four treatment-line–specific cohorts, the estimated adjusted 36-month risk of fracture (95% CI) was 19% (13%-26%) in the Ra-223 group and 10% (5%-17%) in the comparator group, corresponding to a difference in 36-month risk of 9% (95% CI, 0%-17%) (Figure 1).

Figure 1. Standardised cumulative incidence curves for bone fractures, by treatment group, first and second lines, and all lines of treatment-specific cohorts



CI = confidence interval; Ra-223 = radium-223.

All-cause mortality

In the first-line treatment cohort, the 36-month mortality (95% CI) was 86% (76%-94%) in the Ra-223 group and 73% (56%-87%) in the comparator group; the risk difference was 13% (−3% to 31%). In the second-line treatment cohort, the 36-month mortality was 87% (75%-

94%) in the Ra-223 group and 94% (80%-100%) in the comparator group; the risk difference was −8% (−23% to 7%). In the third-/fourth-line treatment cohorts, the 36-month mortality was 86% (78%-92%) in the Ra-223 group and 100% (71%-100%) in the comparator group; the risk difference was −14% (−21% to 16%) (Table 2). The I^2 was 63%, and thus pooling was not considered appropriate.

Prostate cancer–specific mortality

In the first-line treatment cohort, the 36-month prostate cancer mortality (95% CI) was 83% (72%-93%) in the Ra-223 group and 68% (51%-84%) in the comparator group; the risk difference was 15% (−4% to 34%). In the second-line treatment cohort, the 36-month mortality was 85% (72%-94%) in the Ra-223 group and 92% (73%-100%) in the comparator group; the risk difference was −7% (−23% to 14%). In the third-/fourth-line treatment cohorts, the 36-month mortality was 83% (75%-91%) in the Ra-223 group and 100% (71%-100%) in the comparator group; the risk difference was −17% (−24% to 13%) (Table 2).

Sensitivity analyses that analysed patients with recorded bone metastasis, those that included a potential follow-up of 18 months, and those that that did not censor patients in the comparator group when they started Ra-223 during the follow-up yielded consistent results (Supplementary Table S6).

Bone-health agents use at baseline

There were 230 (34%) individuals in the Ra-223 group and 130 (17%) individuals in the comparator group receiving bone-health agents at baseline (Table 1). In the Ra-223 group, the unadjusted 36-month risk of fracture was 15% (95% CI, 6%-27%) in those receiving bone-health agents at baseline and 19% (95% CI, 14%-25%) in those who did not. In the comparator group, the unadjusted 36-month risk of fracture was 5% (95% CI, 1%-11%) in

those receiving bone-health agents at baseline and 12% (95% CI, 6%-24%) in those who did not.

DISCUSSION

The effect estimates of Ra-223 on the 36-month risk of bone fractures compared with other standard of care in first- and second-line treatments were of small magnitude, with 95% CIs that were compatible with both a slightly protective and a mildly deleterious effect.

Our estimations of fracture risk among Ra-223 users were in line with other studies of Ra-223 monotherapy: 9% after 9-month median follow-up in ALSYMPCA (Procedure No.: EMEA/H/A-20/1459/C/002653/0028. Xofigo [BAY 88–8223)]/Radium-223 dichloride Castration-Resistant Prostate Cancer [CRPC] Bayer Response to List of Outstanding Issues), 5% after 6-month median follow-up in REASSURE [21], and a substantially lower percentage than in ERA 223 (26% after 21-month median follow-up [5]). We found that patients in the Ra-223 group using bone-health agents at baseline had a lower risk of fracture than those not using them, a finding previously reported by ERA 223 [5] and PEACE-III [22]. In contrast, our estimations of fracture risk in the comparator group were lower than the risk reported in a study using SEER-Medicare data, which reported a 12% risk of fractures in patients treated with drugs other than Ra-223 for mCRPC after a mean follow-up of 11 months [23], and lower than the risk of fractures for the control group in PEACE-III (enzalutamide without bone-health agents), which was reported to be 16% after 12-month follow-up [22].

Patients in the Ra-223 group had characteristics indicating worse bone health (prior fractures, bone-health agent use, high alkaline phosphatase levels) than the comparator group, which were measured and adjusted for via inverse-probability weighting for both baseline and time-

varying confounding. Nevertheless, if these variables were mismeasured (e.g., capture of bone-health agents may be differential between study groups because reporting their use was mandatory only for patients receiving Ra-223, and zoledronate administration is not captured in PCBaSe if administered in hospital), if the models used were misspecified, if unmeasured confounders existed (e.g., the number of bone metastases, metastatic volume, bone density), or if patients in the Ra-223 group received more imaging surveillance, the estimates may not correspond to the true causal effect. In the Swedish National Patient Register, fractures have been validated in the inpatient [24] but not in the outpatient setting. Given the almost complete coverage of national healthcare registries, it is safe to assume that all symptomatic fractures requiring medical care were captured. These limitations and the small risk of fracture in the comparator groups need to be considered when interpreting the results.

The effect estimates of Ra-223 on the 36-month OS compared with other standard of care in first-line treatment corresponded to a 13% difference in risk, with a 95% CI compatible with both a slightly protective effect and a harmful effect (−3% to 31%). The corresponding HR was 1.63 (95% CI, 1.27-2.16). Decreases in overall survival associated with Ra-223 use were not found in later lines of treatment. Ra-223 as monotherapy for first line versus standard of care in fit patients has not been addressed in clinical trials, probably because it is not considered to meet equipoise. In clinical practice during the study period, Ra-223 as first-line monotherapy was probably used in patients not eligible for other systemic mCRPC treatments, maybe because of frailty (unmeasured in our study setting). A real-world analysis of 285 patients treated with Ra-223 in the Netherlands reported that 10% received it as a first-line monotherapy [25]. Although the PCBaSe has information on relevant prognostic factors (e.g., haemoglobin, alkaline phosphatase, PSA, ECOG PS [26], and treatment line [27]), these factors may not sufficiently surrogate frailty. To characterise the presence of unmeasured confounding, an analysis of a composite cardiovascular outcome as a negative

control was performed, which mapped the results of survival (Supplementary Methods and Supplementary Figure S2), thus supporting the presence of residual confounding. Because the confounders for cardiovascular events and death (e.g., overweight, hypertension, hyperlipidaemia) are likely different from those for fractures (e.g., time on ADT, steroids, history of prior fractures), this negative control outcome analysis does not inform the bone fractures results. Drugs used in this study for mCRPC (docetaxel, abiraterone, enzalutamide) have subsequently been approved for treatment of castration-sensitive prostate cancer in recent years, meaning that in the future, a larger proportion of men treated for mCRPC (either with Ra-223 or with other drugs) will have received them earlier than the men in our study. Therefore, this rapidly changing treatment landscape needs to be considered when interpreting the results. We provide results for patients receiving second and later lines of treatment for mCRPC, although admittedly these estimates were imprecise.

In conclusion, real-world data indicated that the risk of fractures in patients receiving Ra-223 was similar to that in previous observational studies and clinical trials, and the effect estimates for fractures do not point to a large increase and were compatible with a small, if any, increase in the risk associated with Ra-223 use versus a comparator in first- and second-line treatment. In the first-line cohort, Ra-223 use was associated with moderately increased risks of all-cause and prostate cancer–specific mortality. In the second- and third-/fourth-line cohorts, i.e., in the lines during which Ra-223 was predominantly used in clinical practice, Ra-223 use was associated with a decreased risk of mortality. The observed associations in survival need to be interpreted with caution because of the likelihood of unmeasured confounding.

Clinical Practice Points (245/max 250 words)

In the ALSYMPCA trial, Ra-223 for the treatment of metastatic castration-resistant prostate cancer (mCRPC) demonstrated prolonged overall survival and time to first symptomatic

skeletal event, as well as improvements to quality of life. However, in the subsequent ERA 223 trial Ra-223 combined with abiraterone acetate plus prednisone/prednisolone (APP) increased the risk of bone fractures compared to placebo plus APP. This report caused the European Medicines Agency to issue a label contraindication against the combination of Ra-223 with APP and a restriction for Ra-223 to patients who had progressed after two or more prior treatments for mCRPC or who were ineligible for other mCRPC treatment.

The aim of this real-world study was to estimate the effect of Ra-223 on the incidence of fractures and death compared with standard of care. Data on 1,434 men who underwent treatment for mCRPC from Swedish registries were analysed.

Our findings on bone fractures were imprecise and compatible with both a slightly protective and a mildly deleterious effect of Ra-223 both as first- and as second-line treatment. Patients in the Ra-223 group using concomitant bone-health agents had a lower risk of fracture than those not using them. Our study found moderately increased mortality risk in patients treated with Ra-223 in the first line, which was not observed in later lines of treatment. This result should be interpreted with caution since residual confounding is plausible, e.g. patients receiving Ra-223 as first-line monotherapy were likely ineligible for other treatments, possibly due to frailty.

PRECISE Manuscript CRediT Author Statement

Pär Stattin: Data collection, Supervision, Writing - Review & Editing
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SUPPLEMENTARY METHODS

Description of the Prostate Cancer data Base and Patient-overview

Prostate Cancer

By use of the unique Swedish person identity number, the National Prostate Cancer Register of Sweden (NPCR) has been linked with a number of other health care registers, including the Swedish National Cancer Register, the National Patient Register (with hospital and outpatient hospital clinic diagnoses), the Cause of Death Register, the Prescribed Drug Register with filled prescriptions since July 2005, the Multi Generation Register, and the LISA database, a socioeconomic database with information on the educational level, income, and marital status of patients [9]. Since 1998, the primary register of the NPCR of Sweden has captured 98% of all men with incident prostate cancer compared with the National Cancer Registry to which registration is mandated by law. Comprehensive data on cancer characteristics, workup, and primary treatment are registered by staff at each respective department in Sweden where men with prostate cancer are treated [9]. The Prostate Cancer data Base (PCBaSe) 4.0 was created with patients diagnosed with prostate cancer from 01 January 1998 through 31 December 2016.

Information on bone fractures in the PCBaSe is available by using information from the Patient Registry with data from hospital admissions and outpatient visits. *International Classification of Diseases, Tenth Revision* (ICD-10) codes for all fractures and specific fractures are used to characterise fractures (e.g., location) and to ascertain comorbidities or conditions of interest (e.g., osteoporosis).

Information on the cause of death in the PCBaSe is available through the Cause of Death Register. The validity of prostate cancer as a cause of death has been found to be high. In a

comparison of the cause of death in the Cause of Death Register and cause of death as assessed by a chart review of medical records, there was an 86% overall agreement [28]. In another study, an independent cause-of-death committee reviewed medical data including death certificates according to a standardised algorithm. The overall agreement between cause of death recorded in the death certificates and determined by the committee was 96% [29].

A pilot study on the use of enzalutamide and abiraterone based on data in the Prescribed Drug Registry was recently published [30]. Information on the drug of interest is considered highly valid due to implementation of the Patient-overview Prostate Cancer (PPC), a longitudinal subregister in the NPCR.

The NPCR captures data around date of diagnosis regarding information such as cancer characteristics, workup, primary treatment. However, treatments that are initiated at a later stage of the disease, such as treatments for metastatic castration-resistant prostate cancer (mCRPC), are not captured in the primary registration of NPCR. Instead, this information is captured in a subregister of the NPCR, the PPC, which is a longitudinal register that provides the treating clinician with an overview of information, such as previous treatments, laboratory values, and clinical data. The PPC collects data on men from diagnosis to death and has collected data since 2014. Data from earlier dates are made available from retrospective inclusion of data from medical charts, back to the initiation of androgen deprivation therapy for each patient.

Currently, the PPC contains data on approximately 17,000 men from 33 health care providers, including Sahlgrenska University Hospital (Göteborg), Uppsala University Hospital, Södersjukhuset (Stockholm), Umeå University Hospital, Skåne university Hospitals (Lund and Malmö), and, most recently, Karolinska University Hospital (Stockholm).

Contributing centres cover almost all the sites licensed to administer Ra-223 in Sweden; therefore, the PPC has almost complete coverage for the treatment with Ra-223 in Sweden today. In order to enrich the PPC with more men treated with Ra-223, PCBaSe researchers identified these men by (1) medication distribution information for each hospital from Bayer and (2) treatment records at the departments of nuclear medicine at these hospitals, where the person identity numbers of the treated men were obtained. Regardless of how patients were identified, the pattern of care and follow-up should not differ by centre because of the characteristics of the Swedish health care system. All centres connected to the PPC contribute data in a standardised way through the same platform (the Information Network for Cancer care). The Swedish health system provides complete national coverage, and therefore it is safe to assume that most, if not all, fractures requiring medical attention will be captured in the Swedish databases used in this project, and there will not be losses to follow-up.

Eligibility criteria

The selection criteria were chosen so that the population selected would be as similar as possible to the one included in the ALSYMPCA and ERA 223 trials.

- Inclusion criteria (*all* of the following must have been present):
  - Histologically confirmed adenocarcinoma of the prostate, i.e., the patient was registered in the NPCR of Sweden (tumours with histology other than adenocarcinomas are not registered in the NPCR, and if they are, they are very rare; occasionally the diagnosis is based on clinical symptoms and signs, including extremely high serum levels of prostate-specific antigen (PSA), in men who are assessed to be too frail to undergo prostate biopsy, i.e., men who were very old and had severe comorbidity).

- Start of any systemic treatment for mCRPC as an *n*th line of treatment, during the study period, where *n* goes from 1 to 4. The following were considered systemic treatment for mCRPC: Ra-223, docetaxel, cabazitaxel, enzalutamide, abiraterone, and the following group of less commonly used drugs in Sweden, which were labelled as "others"—cisplatin, cyclophosphamide, doxorubicin, estramustine, etoposide, gemcitabine, carboplatin, methotrexate, and mitoxantrone.

- Docetaxel has been shown to improve survival in castration-sensitive prostate cancer [31] and was approved for that indication by the European Medicines Agency on 19 September 2019, outside the study period [32]. However, docetaxel had been used off-label for castration-sensitive prostate cancer since 2016 in Sweden. Therefore, docetaxel, which was initiated prior to any other treatment, was considered as line 1 treatment for mCRPC if the subject had mCRPC and metastases prior to docetaxel initiation.

- Abiraterone was approved for the treatment of metastatic hormone-sensitive prostate cancer in 2017, and subsidized use was approved in June 2018 [33]. To identify patients treated with abiraterone for mCRPC in the PPC during the study period, the following algorithm was used:
  - Patients treated with abiraterone during the years 2013-2016 were assumed to have mCRPC
  - Patients starting abiraterone without any prior therapy for mCRPC, in 2017-2018:
    - If the time from prostate cancer diagnosis to the initiation of abiraterone was ≤ 180 days, they were assumed to have hormone-sensitive prostate cancers

- If the time from prostate cancer diagnosis to the initiation of abiraterone was ≥ 2 years, they were assumed to have mCRPC
- If there were confirmed metastasis and a recorded date of mCRPC diagnosis that was earlier than the date of abiraterone initiation plus 60 days, they were assumed to have mCRPC

- Patients not classified with the criteria above were classified on an individual basis after reviewing the following elements: PSA curves, date of abiraterone initiation, and date of mCRPC. Marcus Westerberg, our study statistician performed this assessment after consultation with the study oncologists (I.F.L.; M.H.E.)

- Prostate cancer progression to ADT or subsequent lines of therapy. Prostate cancer progression was surrogated by the initiation of a drug specific for mCRPC in the first or later lines of treatment.
- Eastern Cooperative Oncology Group performance status appropriate to start systemic treatment (e.g., 0-2). Patients starting any of the systemic therapies under study were assumed to have an appropriate performance status.
- Presence of bone metastasis. All patients receiving Ra-223 were assumed to have had bone metastasis, and those with recorded bone metastasis initiating a comparator drug were selected for the comparator group.

- Exclusion criteria (either of the following):
  - Prior use of Ra-223
  - Patients who had participated in a randomised controlled trial (involving Ra-223 or not) in the past or at baseline for which unblinded information on the assigned treatment was not available

Creation of line-of-treatment–specific cohorts

The cohort of first-line treatment included patients meeting the eligibility criteria when they started a first-line treatment for mCRPC (docetaxel, abiraterone, enzalutamide, cabazitaxel, Ra-223, others), which was considered the baseline date for this cohort. Analogously, the cohort of second-line treatment included patients meeting the eligibility criteria when they started a second line of treatment for mCRPC, which was the baseline date for this cohort. The same approach was used for third- and fourth-line treatment cohorts [13]. Patients were assigned to each exposure group according to the drug they started taking at the baseline date, which was variable based on the cohort and line of treatment. Under this design, patients can contribute to several cohorts, if eligible, and to both arms in different cohorts [12]. Baseline variables are updated at baseline in each cohort. The following is a hypothetical example of the cohort-generation process explained above. This table represents three mock patients, the treatments they receive over time (times when the line of treatment starts are arbitrary and synced for simplicity), and their eligibility status.

Hypothetical example of observed treatments

		Time interval when line of treatment starts			
		1	**5**	**10**	**15**
Patient 1	Treatment	Ra-223	Docetaxel	Abiraterone	No treatment
	Eligible?	Yes	No	No	No
	Time-varying characteristic (e.g., performance status)	0	0	1	4
Patient 2	Treatment	Docetaxel	Abiraterone	Enzalutamide	Ra-223
	Eligible?	Yes	Yes	Yes	Yes
	Time-varying characteristic (e.g., performance status)	0	1	2	2
Patient 3	Treatment	Docetaxel	Abiraterone	Abiraterone + Ra-223	Enzalutamide

	Time interval when line of treatment starts			
	1	**5**	**10**	**15**
Eligible?	Yes	Yes	No	No
Time-varying characteristic (e.g., performance status)	1	1	1	1

The panel below represents the database created after the generation of the cohorts:

- Patient 1 contributes only to the first-line cohort as part of the Ra-223 group because having received Ra-223 in the past is an exclusion criterion for subsequent cohorts. The patient is followed until the outcome of interest, death, or administrative end of follow-up because subsequent standard of care is allowed after Ra-223.
- Patient 2 contributes to the first-, second-, and third-line cohorts as part of the comparator group and to the fourth-line cohort as part of the Ra-223 group. The patient is followed until time interval 15 in the first three cohorts and until the outcome of interest, death, or administrative end of follow-up in the fourth-line cohort. The patient's value of the baseline variable (e.g., performance status) is updated in each cohort.
- Patient 3 contributes to the first- and second-line treatment cohorts and is not followed beyond time interval 10 because starting Ra-223 is a censoring event for the comparator group. The patient's value for the baseline variable (e.g., performance status) is updated in each cohort. A more detailed technical explanation can be found elsewhere [12,34,35].

Hypothetical example of cohort generation and treatment strategy assignment

Patient ID	Cohort	Treatment Arm	Baseline (start of follow-up)	End of follow-up	Baseline variable (e.g., performance status)
1	First line	Ra-223	1	Outcome of interest, death, or AEFUP	0
2	First line	Comparator	1	15	0
3	First line	Comparator	1	10	1
2	Second line	Comparator	5	15	1
3	Second line	Comparator	5	10	1
2	Third line	Comparator	10	15	2
2	Fourth line	Ra-223	15	Outcome of interest, death, or AEFUP	2

AEFUP = administrative end of follow-up.

Negative control outcome analysis

A negative control outcome analysis was performed to characterise the potential unmeasured confounding [36]. The purpose of using a negative control outcome is to reproduce a condition that cannot involve a causal mechanism of Ra-223 but is very likely to involve the same sources of bias that may be present in the main analysis. A composite cardiovascular outcome (arrythmia, acute myocardial infraction, stroke, and heart failure) was chosen because Ra-223 should not have any cardiovascular effect and because the common causes of Ra-223 and mortality were assumed to be similar to the common causes of Ra-223 and cardiovascular outcomes in the study population. Other than the different outcome, the analytical approach was identical to the main analysis. In the absence of unmeasured confounding, there should not be any association between Ra-223 use and the negative control outcome (composite cardiovascular outcome).

Supplementary Table S1. Specification and emulation of a target trial of Ra-223 therapy and risk of fractures using the PCBaSe observational data

Protocol component	Target trial specification	Target trial emulation using PCBaSe
Aim	To estimate the effect of Ra-223 on the incidence of bone fractures, prostate cancer mortality and all-cause mortality compared with other standard treatments for mCRPC.	Same as for the target trial
Eligibility criteria	▪ Histologically confirmed adenocarcinoma of the prostate ▪ Tumour is castration-resistant, i.e., has progressed to ADT ▪ Initiation of a systemic therapy for mCRPC as an *n*th line of treatment, where n goes from 1 to 4 ▪ ECOG PS 0-2 ▪ Presence of bone metastases ▪ No prior use of Ra-223 ▪ No prior participation in a RCT for with unblinded information is not available	Same as for the target trial The initiation of a systemic therapy for mCRPC was used as surrogate for castration resistance and for ECOG PS 0-2 We assumed all patients initiating Ra-223 have bone metastasis, only patients with recorded bone metastasis were chosen for the comparator
Treatment strategies	**Group 1: Initiate Ra-223**. Patients can stop Ra-223 after 6 cycles or earlier in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other systemic drugs for mCRPC after the initiation of Ra-223, when clinically indicated, but they can never be used while taking Ra-223. ADT with first-generation antiandrogens can be used at any time **Group 2: Initiate other standard of care** (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated. ADT with first-generation	Same as for the target trial

Protocol component	Target trial specification	Target trial emulation using PCBaSe
	antiandrogens can be used at any time.	
Treatment assignment	Individuals will be randomly assigned to a strategy at baseline and will be aware of the strategy to which they have been assigned	Individuals were classified according to the strategy that their data were compatible with at baseline. Randomisation was emulated by adjusting for baseline confounders
Outcomes	▪ Fractures ▪ Death ▪ Prostate cancer–specific death	Same as for the target trial
Follow-up	Starts at baseline and ends at the time of fracture, death, lost to follow-up, 36 months after baseline, or administrative end of follow-up	Same as for the target trial
Causal contrast	Per protocol effect	Observational analogue of the per protocol effect
Statistical analysis	Censor participants if and when they deviate from their assigned treatment strategy and apply inverse probability weights to adjust for prebaseline and postbaseline prognostic factors associated with adherence	Same per protocol analysis with sequential emulation and additional adjustment for baseline covariates

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; PS = performance status; Ra-223 = radium-223; RCT = randomised controlled trial.

Supplementary Table S2. Sensitivity analyses

Effect estimate	Analysis of patients with recorded bone metastasis[a]	Analysis of patients with a potential follow-up of 18 months[b]	Analysis letting men in the comparator group receive Ra-223 after baseline[c]
Difference in 36-month risk of bone fracture (95% CI)[d]			
First-line cohort	6% (−6% to 18%)	4% (−13% to 24%)	4% (−8% to 18%)
Second-line cohort	8% (−9% to 18%)	5% (−26% to 22%)	0% (−31% to 15%)
Third-/fourth-line cohort	NE	NE	NE
Difference in 36-month mortality (95% CI)[d]			
First-line cohort	13% (−4% to 31%)	11% (−8% to 29%)	7% (−7% to 21%)
Second-line cohort	−8% (−19% to 9%)	−5% (−19% to 11%)	−2% (−17% to 11%)
Third-/fourth-line cohort	−14% (−22% to 17%)	−14% (−20% to 15%)	−8% (−19 to 5%)
Difference in 36-month prostate cancer mortality (95% CI)[d]			
First-line cohort	15% (−4% to 35%)	13% (−8% to 34%)	8% (−7% to 24%)
Second-line cohort	−7% (−21% to 12%)	−4% (−18 to 13%)	−2% (−18% to 14%)
Third-/fourth-line cohort	−17% (−24% to 16%)	−17% (−24% to 13%)	−10% (−22% to 8%)

CI = confidence interval; NE = not estimable.

[a] The main analysis assumed that all individuals in the Ra-223 group had bone metastasis and selected for the comparator groups only those with recorded bone metastasis. This sensitivity analysis excluded three individuals from the Ra-223 group without recorded bone metastasis.

[b] In this sensitivity analysis, patients were eligible only through June 2017 to allow for a potential follow-up of at least 18 months.

[c] This sensitivity analysis did not censor individuals in the comparator group if Ra-223 was initiated during the follow-up (69 in the first-line cohort, 36 in the second-line cohort, 12 in the third-line cohort, and three in the fourth-line cohort).

[d] The comparator arm is the reference.

Supplementary Table S3. Attrition of the line-of-treatment–specific cohorts, PCBaSe 2013-2018

Criterion	First line, n	Second line, n	Third line, n	Fourth line, n
Patients diagnosed with mCRPC registered in PCBaSe at any time between November 2013 and December 2018	1,771	1,771	1,771	1,771
AND started a first line of treatment for mCRPC (baseline)	994	NA	NA	NA
AND started a second line of treatment for mCRPC (baseline)	NA	741	NA	NA
AND started a third line of treatment for mCRPC (baseline)	NA	NA	469	NA
AND started a fourth line of treatment for mCRPC (baseline)	NA	NA	NA	210
And have not participated in an RCT (involving radium-223 or not, for which unblinded information on the assigned treatment is not available) in the past or at baseline	958	701	438	185
AND had not received radium-223 before baseline	NA	620	348	113
AND had bone metastasis at baseline[a]	831	591	341	107
AND had complete information on baseline variables[b]	635	453	262	84

ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; NA: not applicable; PCBaSe = Prostate Cancer data Base Sweden; PS = performance status; PSA = prostate-specific antigen; RCT = randomised controlled trial.

[a]The main analysis assumed that all patients receiving radium-223 had bone metastasis; patients with recorded bone metastasis were selected for the comparator group.

[b]The baseline variables that had missing values were T stage (2.5% in the Ra-223 group, 2.2% in the comparator group), Gleason score/WHO grade (3.1% in the Ra-223 group, 3.3% in the comparator group), ECOG PS (15.2% in the Ra-223 group, 11.9% in the comparator group), PSA (4.7% in the Ra-223 group, 1.7% in the comparator group), haemoglobin (12.5% in the Ra-223 group, 14.3% in the comparator group) and alkaline phosphatase (9.4% in the Ra-223 group, 10.6% in the comparator group).

Supplementary Table S4. Treatments and duration of treatment received subsequently to the baseline treatment, by treatment line

	Comparator arm		Radium-223 arm	
Line of treatment	**Weeks of treatment**	**n**	**Weeks of treatment**	**n**
First-line treatment				
Radium-223	0[a]	69	0	0
Docetaxel	58	9	114	29
Cabazitaxel	60	21	57	17
Abiraterone	220	29	237	36
Enzalutamide	348	45	862	101
Others	66	16	57	12
Second-line treatment				
Radium-223	0[a]	36	0	0
Docetaxel	15	5	55	17
Cabazitaxel	44	16	100	24
Abiraterone	75	10	118	19
Enzalutamide	35	10	514	53
Others	147	25	110	18
Third-line treatment				
Radium-223	0[a]	12	0	0
Docetaxel	0	0	16	3
Cabazitaxel	19	8	115	30
Abiraterone	14	2	29	8
Enzalutamide	24	1	160	22
Others	94	14	122	26
Fourth-line treatment				
Radium-223	0[a]	3	0	0
Docetaxel	0	0	0	0
Cabazitaxel	22	1	15	5
Abiraterone	0	0	0	0
Enzalutamide	0	0	99	11
Others	9	4	56	11

[a]Patients in the comparator arm were censored if and when they started radium-223.

Supplementary Table S5. Cohort follow-up, censoring reasons, and outcomes, by treatment and treatment line

Treatment line	Comparator arm	Radium-223 arm
First-line treatment		
n	432	203
Person-months of follow-up, sum	4,763	3,017
Median follow-up (Q1, Q3), months	9 (5, 15)	13 (7, 20)
Minimum, maximum follow-up, months	0, 49	0, 45
Artificially censored[a], n (%)	69 (16)	0
Censored because they were alive at the end of December 2018, n (%)	235 (54)	92 (45)
Had a bone fracture during study follow-up, n (%)	29 (7)	15 (7)
Dead because of prostate cancer, n (%)	109 (25)	102 (50)
Dead from any cause, n (%)	128 (30)	111 (55)
Second-line treatment		
n	214	239
Person-months of follow-up, sum	1,930	3,020
Median follow-up (Q1, Q3), months	8 (4, 12)	10 (6, 18)
Minimum, maximum follow-up, months	0, 46	0, 46
Artificially censored,[a] n (%)	36 (17)	0
Censored because they were alive at the end of December 2018, n (%)	91 (43)	80 (33)
Had a bone fracture during study follow-up, n (%)	6 (3)	25 (10)
Dead because of prostate cancer, n (%)	82 (38)	144 (60)
Dead from any cause, n (%)	87 (41)	159 (67)
Third-line treatment		
n	82	180
Person-months of follow-up, sum	639	2,354
Median follow-up (Q1, Q3), months	6 (4, 10)	11 (6, 18)
Minimum, maximum follow-up, months	0, 32	0, 43
Artificially censored,[a] n (%)	12 (15)	0
Censored because they were alive at the end of December 2018, n (%)	27 (33)	60 (33)
Had a bone fracture during study follow-up, n (%)	1 (1)	16 (9)
Dead because of prostate cancer, n (%)	42 (51)	115 (64)
Dead from any cause, n (%)	43 (52)	120 (67)
Fourth-line treatment		
n	25	59

Treatment line	Comparator arm	Radium-223 arm
Person-months of follow-up, sum	130	846
Median follow-up (Q1, Q3), months	4 (3, 6)	11 (7, 18)
Minimum, maximum follow-up, months	0, 13	2, 47
Artificially censored,[a] n (%)	3 (12)	0
Censored because they were alive at the end of December 2018, n (%)	7 (28)	11 (19)
Had a bone fracture during study follow-up, n (%)	0	6 (10)
Dead because of prostate cancer, n (%)	15 (60)	43 (73)
Dead from any cause, n (%)	15 (60)	47 (80)

Q1 = first quartile; Q3 = third quartile.

[a]Patients in the radium-223 arm were censored if and when they combined other treatment for metastatic castration-resistant prostate cancer with radium-223. Patients in the comparator arm were censored if and when they started radium-223.

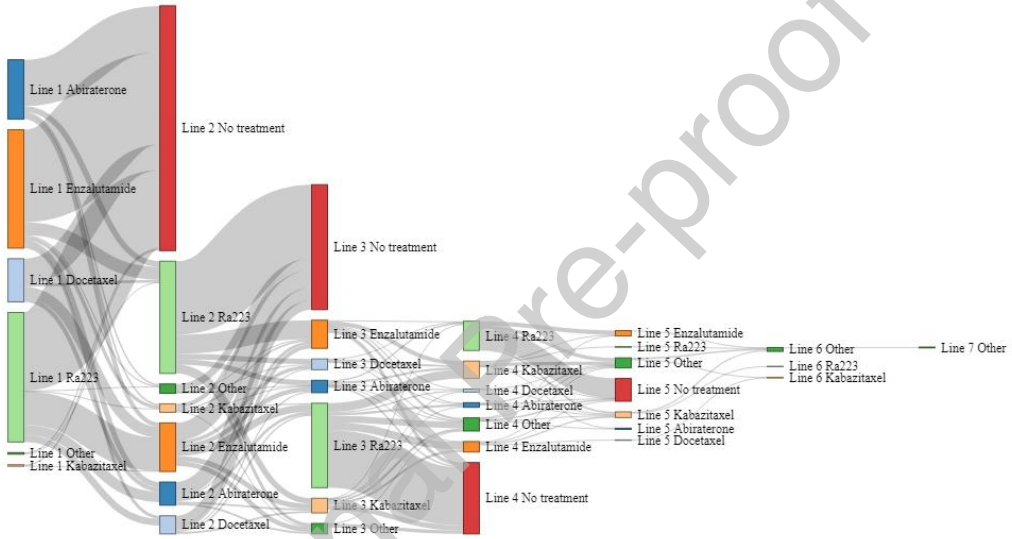
Supplementary Table S6. Location of fractures, by exposure group, all treatment lines

Location of fracture	Comparator arm, n (%)	Radium-223 arm, n (%)
Total [a]	45	87
Fracture of cervical vertebra or other parts of the neck	4 (9)	1 (1)
Fracture of rib(s), sternum, and thoracic spine	4 (9)	4 (5)
Fracture of lumbar spine and pelvis	8 (18)	3 (3)
Fracture of shoulder and upper arm	7 (16)	13 (15)
Fracture of forearm	2 (4)	8 (9)
Fracture at wrist and hand level	1 (2)	4 (5)
Fracture of femur	15 (33)	35 (40)
Fracture of head and neck of the femur	10 (67*)	17 (49*)
Pertrochanteric fracture	2 (13*)	8 (23*)
Subtrochanteric fracture	6 (40*)	3 (9*)
Fracture of shaft of femur	0	6 (17*)
Fracture of lower end of femur	0	1 (3*)
Other fracture of femur	0	2 (6*)
Unspecified fracture of femur	0	1 (3*)
Fracture of lower leg, including ankle	1 (2)	5 (6)
Fracture of foot and toe, except ankle	0	2 (2)
Fracture without identified location	3 (7)	12 (14)

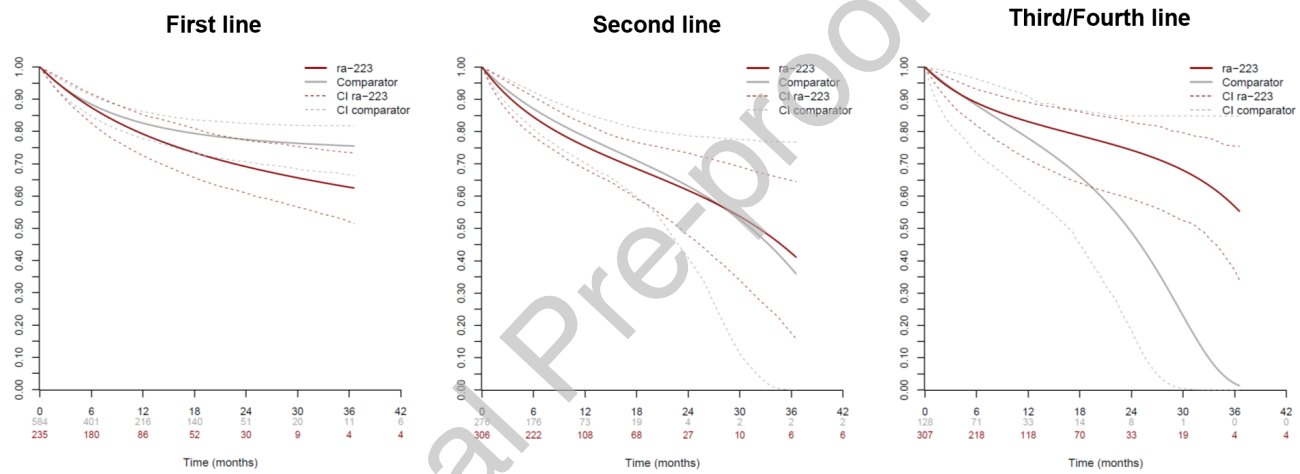
[a] A single individual can have fractures in more than one location and can contribute a fracture to more than one line of treatment.

* Percentages are over the number of fractures of the femur.

Supplementary Figure S1. Sankey diagram of the treatments received during the study period by the study population



Supplementary Figure S2. Adjusted time to composite cardiovascular outcome (negative control outcome[a]), by treatment line and by study group



[a]There were 153 composite cardiovascular outcomes in the Ra-223 group (51 in the first-line cohort, 59 in the second-line cohort, 32 in the third-line cohort, and 11 in the fourth-line cohort). There were 125 composite cardiovascular outcomes in the comparator group (70 in the first-line cohort, 39 in the second-line cohort, 13 in the third-line cohort, and three in the fourth-line cohort). In the first-line cohort, the difference in 36-month risk was 12% (95% CI, −2% to 25.3%) and the corresponding HR was 1.27 (95% CI, 0.80 to 1.87). In the second-line cohort, the difference in 36-month risk was −5% (95% CI, −51% to 42%) and the corresponding HR was 1.15 (95% CI, 0.67 to 1.89). In the third-/fourth-line cohorts, the difference in 36-month risk was −54% (95% CI, −69% to 26%) and the corresponding HR was 0.56 (95% CI, 0.29 to 1.35).