Original Study

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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

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Keywords: Fracture, Safety, Lines of treatment, Observational study

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Abstract

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.

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.

Clinical Genitourinary Cancer, Vol. 21, No. 1, 107.e1–107.e9

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Submitted: Jun 21, 2022; Revised: Sep 2, 2022; Accepted: Sep 3, 2022; Epub: 9 September 2022

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1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2022.09.002

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 and/or 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 less than or equal to 6 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 and/or 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 (ie, 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 1771 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); ie, 1434 individuals participated in the four treatment-line–specific cohorts (1203 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.

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.

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).

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.

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)

(*continued on next page*)

Table 1 (*continued*)

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)
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)					

Abbreviations: 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.

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% CI)	Ref.	1.83 (1.38 to 2.48)	Ref.	0.92 (0.59 to 1.29)	Ref.	0.72 (0.42 to 1.20)	Ref.	NE

Abbreviations: CI = confidence interval; NE = not estimable; Ref. = reference.
[a] Risk is expressed in number of cases per 100 persons.

Discussion

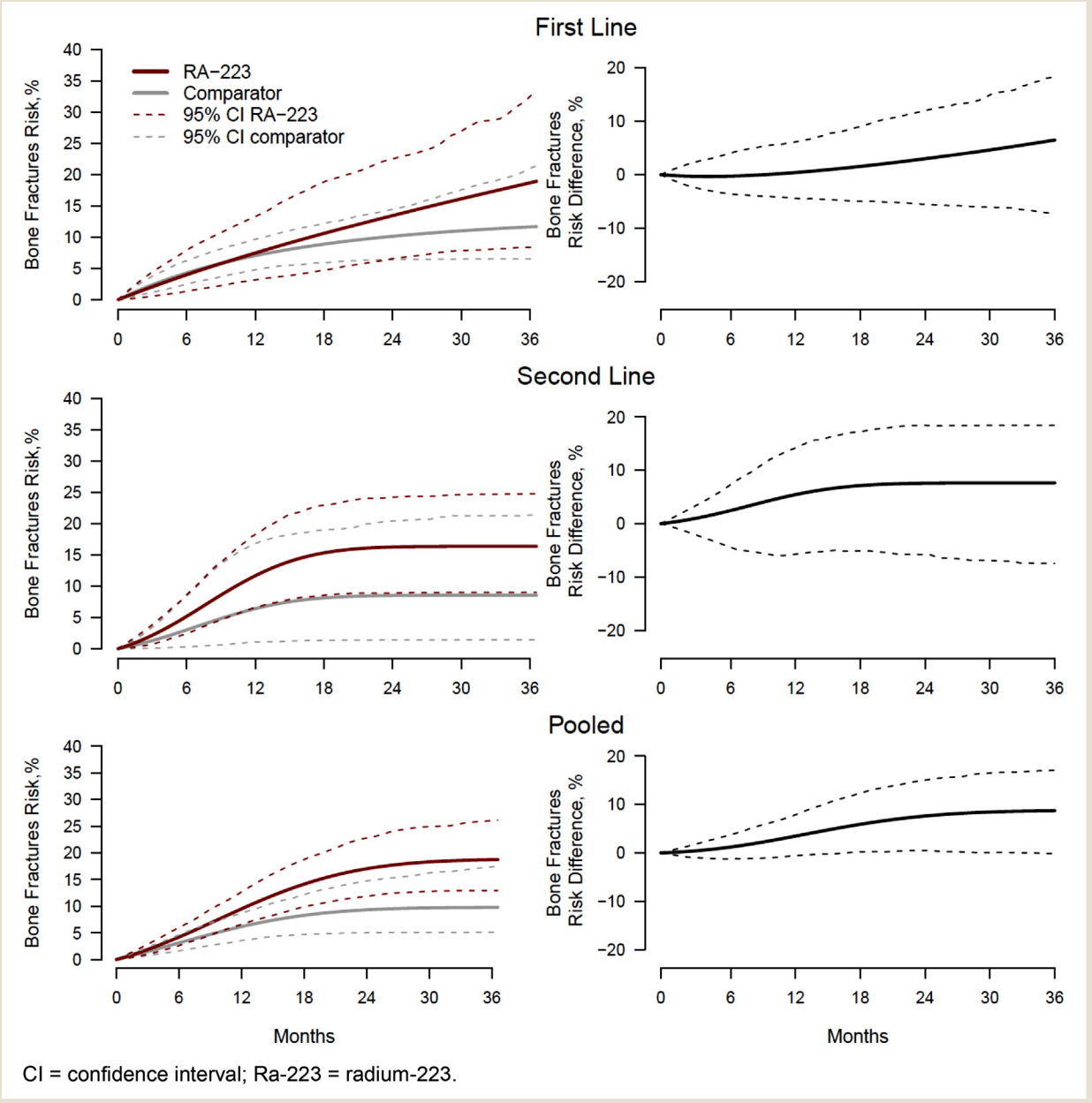
The effect estimates of Ra-223 on the 36-month risk of bone fractures compared with other standard of care in first- and second-line treatments were of small magnitude, with 95% CIs that were compatible with both a slightly protective and a mildly deleterious effect.

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 (eg, 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 (eg, 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

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.



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 (eg, 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 (eg, overweight, hypertension, hyperlipidaemia) are likely different from those for fractures (eg, 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, ie, 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

- 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 and/or 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 1434 men who underwent treatment for mCRPC from Swedish registries were analyzed.
- 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, eg, patients receiving Ra-223 as first-line monotherapy were likely ineligible for other treatments, possibly due to frailty.

Funding

Bayer US contributed to the study design, interpretation of the results and writing of the report. Bayer US was not involved in the collection, analysis of the data, or in the decision to submit the article for publication.

Disclosure

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. IFL has received speaker's honoraria from Astra Zeneca. AU received a grant from Bayer in 2016 for IIR to support the study; Retrospective evaluation of ALP kinetics as a pharmacodynamic marker in radium-223 treated mCRPC patients – A 10-year single center experience of Radium-223 treatment in 100+ patients. ZV and PS are employees of Bayer US. They have no other financial interests or personal relationships relevant to the PRECISE study. RW, DM, and XGA are employees of RTI Health Solutions, which was contracted to perform work on the study and manuscript, funded by Bayer AG.

Acknowledgments

This project was made possible by the continuous work of the National Prostate Cancer Register of Sweden (NPCR) steering group: Pär Stattin (chairman), Ingela Franck Lissbrant (co-chair), Camilla Thellenberg-Karlsson, Johan Styrke, Hampus Nugin, Eva Johansson, Magnus Törnblom, Stefan Carlsson, David Robinson, Mats Andén, Olof Ståhl, Thomas Jiborn, Hans Joelsson, Gert Malmberg, Olof Akre, Johan Stranne, Jonas Hugosson, Maria Nyberg, Per Fransson, Fredrik Jäderling, Fredrik Sandin and Karin Hellström. Susana Perez-Gutthann (RTI Health Solutions) provided scientific input and senior advising to the study and manuscript. We thank John Forbes at RTI Health Solutions for providing editorial assistance.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.09.002.

CRediT authorship contribution statement

Pär Stattin: Data curation, Supervision, Writing – review & editing. **Marcus Westerberg:** Writing – review & editing, Formal analysis, Data curation. **Ingela Franck Lissbrant:** Data curation, Writing – review & editing. **Marie Hjälm Eriksson:** Data curation, Writing – review & editing. **Anders Kjellman:** Data curation, Writing – review & editing. **Anders Ullén:** Data curation, Writing – review & editing. **Zdravko Vassilev:** Writing – review & editing. **Per Sandstrom:** Writing – review & editing. **Rachel Weinrib:** Writing – review & editing, Project administration. **David Martinez:** Writing – review & editing, Methodology. **Xabier Garcia-Albeniz:** Writing – original draft, Methodology, Conceptualization.

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