Post-Authorisation Safety Study (PASS) Report - Study Information

Acronym/Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant **PR**ostate cancer (mCRPC) Pati**E**nts treated with Radium-223 in routine **C**linical pract**I**ce in **S**wed**E**n
Report version	v1.0
Date	14-JUN-2021
IMPACT study number	20437
Study type / Study phase	PASS ☒ PASS Joint PASS: ☐ YES ☒ NO>
EU PAS register number	EUPAS33448
Active substance	Various Therapeutic Radiopharmaceuticals (V10XX03), radium (^{223}Ra) dichloride
Medicinal product	Radium-223 (Ra-223)
Product reference	EU/1/13/873/001
Procedure number	EMEA/H/C/PSP/S/0076
Comparator / Reference therapy	Docetaxel, abiraterone, enzalutamide, cabazitaxel, and other chemotherapies that are standard of care in Sweden
Study Initiator and Funder	Bayer AG
Research question and objectives	The research questions are as follows: • Does the use of radium-223 (Ra-223) increase the risk of bone fractures compared with other treatments for metastatic castration-resistant prostate cancer (mCRPC) in routine clinical practice?

	• Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice? The primary objective of this study is to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC. The secondary objectives are to estimate the effect of Ra-223 on overall survival and prostate cancer–specific survival compared with other standard treatments for mCRPC and to estimate heterogeneity of the estimates by line of treatment (first, second, and subsequent).
Country(-ies) of study	Sweden
Author	PPD (RTI Health Solutions) PPD (Bayer Epidemiology) PPD on behalf of the Ra-223 PRECISE team

Marketing Authorisation holder	Bayer AG
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1. Abstract

Acronym/Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Report version and date **Author**	v1.0, 14 JUN 2021 PPD (RTI Health Solutions) PPD (Bayer Epidemiology) PPD on behalf of the Ra-223 PRECISE team
IMPACT study number	20437
Keywords	Radium 223; bone fracture; all-cause mortality; prostate cancer–specific mortality; castration-resistant metastatic prostate cancer
Rationale and background	Radium-223 dichloride (Ra-223) is an alpha particle–emitting radioactive agent approved in the European Union (EU) for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have symptomatic bone metastases and no known visceral metastases and who are in progression after at least 2 prior lines of systemic therapy for mCRPC (other than luteinising hormone–releasing hormone [LHRH] analogues) or are ineligible for any available systemic mCRPC treatment. The pivotal phase 3 trial ALSYMPCA (EudraCT Number 2007-006195-11) showed that Ra-223 prolonged median overall survival (OS) by 3.6 months, prolonged the time to first symptomatic skeletal event, and provided quality-of-life benefits when compared with placebo in patients with mCRPC, symptomatic bone metastases, and no visceral metastases. The safety profile was favourable, with a low incidence of myelosuppression. The later ERA 223 trial (EudraCT Number 2013-003438-33) was designed to evaluate the efficacy and safety of Ra-223 in an investigational combination with abiraterone acetate plus prednisone/prednisolone versus placebo in combination with abiraterone acetate plus prednisone/prednisolone in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant mCRPC. The trial was unblinded in November 2017 per an independent data monitoring committee's recommendation because of the observation of an imbalance of more fractures and deaths in the investigational arm treated with Ra-223 in combination with abiraterone and prednisone than in the control arm, which was treated with placebo, abiraterone, and prednisone.

	The present imposed non-interventional post-authorisation safety study PRECISE (EU PAS register number EUPAS33448) is an outcome of the referral procedure under Article 20 of Regulation (EC) No. 726/2004 that followed the findings of ERA 223 results (EMEA/H/A-20/1459/C/002653/0028).
Research question and objectives	This study addressed the following research questions: • Does the use of Ra-223 increase the risk of bone fractures compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice? • Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice? The primary objective in this study was to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC. The secondary objectives were to estimate the effect of Ra-223 on OS and prostate cancer–specific survival compared with other standard treatments for mCRPC and to estimate heterogeneity of the estimates by line of treatment (first, second, and subsequent).
Study design	Observational, non-randomised, retrospective comparative cohort study. The effect of Ra-223 was assessed in different lines of treatment for mCRPC (first, second, third/fourth). The cohort of first-line treatment included patients meeting the eligibility criteria when they started a first line of treatment for mCRPC. The cohort of second-line treatment included patients meeting the eligibility criteria when they started a second line of treatment. The same approach was used for cohorts for subsequent treatment lines. Cohorts were supposed to be analysed together when there was no evidence of effect heterogeneity. The comparator group comprised patients receiving standard of care. Patients could contribute as individuals to multiple line of treatment-specific cohorts, if eligible, and to both arms in different cohorts.
Setting	Patients receiving treatment for mCRPC recorded in the Prostate Cancer data Base Sweden (PCBaSe) during the study period, without evidence of having received Ra-223 before the study period. Patients were identified from the Patient-overview Prostate Cancer (PPC), a subregistry of the PCBaSe. The study period was from November 2013, the month of Ra-223 launch in Sweden, to December 2018, the latest date

	with full information, including cause of death available at the time of data extraction.
Subjects and study size, including dropouts	There were 1,771 patients diagnosed with mCRPC who were registered in the PPC from November 2013 through December 2018. Of these, 831 were eligible for inclusion in the first-line cohort, 591 were eligible for inclusion in the second-line cohort, 341 were eligible for inclusion in the third-line cohort, and 107 were eligible for inclusion in the fourth-line cohort; i.e., 1,870 individuals participated in the 4 treatment-line–specific cohorts, corresponding to 1,551 unique patients. The values of some baseline variables were missing for 337 individuals, and these individuals were excluded from the analysis. The size of the complete-case population was 1,434 individuals: 681 in the Ra-223 group (76.4% of the eligible population) and 753 in the comparator group (76.9% of the eligible population).
Variables and data sources	The main analysis compared the following 2 treatment strategies: A. Ra-223 initiators. Patients could stop Ra-223 after 6 cycles—or earlier—in the event of toxicity, cancer progression, or worsening of the overall health status. Patients could start other drugs for mCRPC (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) after the initiation of Ra-223, when clinically indicated, but never at the same time as Ra-223. Androgen-deprivation therapy (ADT) with first-generation antiandrogens or GnRH (gonadotropin-releasing hormone) agonists could be used at any time. B. Initiators of other standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients were 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 antiandrogens or GnRH agonists could be used at any time. Patients were assigned to the treatment strategy with which their baseline data were compatible; if they deviated from the assigned strategy during the study, follow-up was artificially censored at that time. The primary outcome was the cumulative incidence of bone fractures. Bone fractures were identified based on ICD-10 (*International Classification of Diseases, 10th Revision)* diagnosis codes in the In- and Out-Patient Register. Thus, the study captured only fractures that prompted a diagnostic work-up. The secondary outcomes were OS and prostate cancer–specific survival. The date and cause of death were identified from the Cause of Death Register. Adjustment for the following variables was performed to attain conditional exchangeability: age; calendar year of study inclusion; time

	from diagnosis to baseline; history of skeletal-related events; tumour, node, metastasis staging; tumour grade; Eastern Cooperative Oncology Group (ECOG) performance status; serum prostate-specific antigen level; serum haemoglobin level; serum alkaline phosphatase level; osteoporosis; Charlson comorbidity index; site of metastasis (visceral, bone, lymph nodes); history of spinal cord compression; use of bone-health agents and steroids; time on ADT; line of treatment for mCRPC; and type of drugs for mCRPC used in the past (taxanes, second-generation antiandrogens). This study used data from the PPC, a subregistry of the National Prostate Cancer Register (NPCR) of Sweden. In the research database Prostate Cancer data Base Sweden (PCBaSe), the NPCR has been linked with a number of other healthcare registries, including the Swedish National Cancer Register, the National In- and Out- Patient Register, the Cause of Death Register, and the Prescribed Drug Register (with filled prescriptions since July 2005). In the NPCR's primary registration, data on prostate cancer characteristics and treatment around the date of diagnosis are captured. Treatments initiated at a later stage of the disease, such as treatments for mCRPC are captured in the PPC, which contains a longitudinal registration of data on men with prostate cancer from initiation of ADT to death. Currently, the PPC contains data on approximately 12,000 men from 33 healthcare providers, some of which were incorporated to increase the number of patients for this PASS. The PPD was among the centres added most recently.
Results	In the cohort of individuals initiating a first line of treatment ("first-line cohort," N = 635), the estimated adjusted difference on the 36-month risk of **fracture** was 6.5% (95% confidence interval [CI], −7.3% to 18.4%), and the corresponding hazard ratio (HR) was 1.14 (95% CI, 0.50 to 2.15). In the cohort of individuals initiating a second line of treatment ("second-line cohort," N = 453), the estimated adjusted difference on the 36-month risk of fracture was 7.6 % (95% CI, −7.5% to 18.4%) and the corresponding HR was 1.86 (95% CI, 0.62 to 10.93). In the cohort of individuals initiating a third line of treatment ("third-line cohort," N = 262), there were 16 bone fractures in the Ra-223 group (median follow-up, 10.5 months) and 1 fracture in the comparator group (median follow-up, 6.4 months). In the cohort of individuals initiating a fourth line of treatment ("fourth-line cohort," N = 84), there were 6 fractures in the Ra-223 group (median follow-up, 11.2 months) and 0 fractures in the comparator group (median follow-up, 4.3 months). Of note, the markedly shorter follow-up and lack of fractures in the comparator group precluded an informative adjusted analysis in the third- or fourth-line cohorts. Therefore, only the unadjusted 36-month risk of fracture in the third/fourth-line cohort (third-line and fourth-line cohorts combined) were

	calculated. In both groups, patients using bone-health agents at baseline had a lower risk of fracture than those not using them. In the first-line cohort, the estimated adjusted difference on the 36-month **mortality** was 13.0% (95% CI, −3.0% to 31.2%), and the corresponding HR was 1.63 (95% CI, 1.27 to 2.16). In the second-line cohort, the estimated adjusted difference on the 36-month mortality was −7.6% (95% CI, −22.9% to 7.4%), and the corresponding HR was 0.91 (95% CI, 0.60 to 1.23). In the third/fourth-line cohort, the estimated adjusted difference on the 36-month mortality was −13.7% (95% CI, −21.4% to 15.9%), and the corresponding HR was 0.72 (95% CI, 0.41 to 1.19). The percentage of **deaths due to prostate cancer** was 91.8%; therefore, the conclusions of the prostate cancer–specific mortality analyses did not differ from the all-cause mortality analysis.
Discussion	The difference in the risk of bone fractures and of mortality associated with the use of Ra-223 compared with other standard of care for mCRPC in a Swedish study population was estimated. 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 the first line of 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. In the current study, estimations of fracture risk among Ra-223 users in a real-world setting were in line with other studies of Ra-223 as monotherapy and were markedly lower than in the ERA 223 trial (a study of Ra-223 in combination with abiraterone and corticosteroids). Estimations of fracture risk in the comparator group were lower than the risk reported by other studies and lower than expected in this patient population, especially in later lines of treatments. This needs to be taken into account when interpreting the effect estimates on the risk of fractures. The effect estimate of Ra-223 for 36-month OS, compared with other standard of care in the first line of treatment corresponded to a 13% difference in the risk of mortality, with a wide CI consistent with a slightly protective effect and with a moderately harmful effect (95% CI, −3.0% to 31.2%). The HR was 1.63 (95% CI, 1.27 to 2.16). Effect estimates for OS pointed to a decreased risk of death associated with Ra-223 in later lines of treatment. Of note, Ra-223 as monotherapy for a first line of treatment versus the standard of care in fit patients (i.e., second-generation antiandrogens or chemotherapy) does not meet the principle of equipoise and hence has not been addressed in randomised clinical trials. Ra-223 was used as a first-line treatment only in very selected patients during the study period, probably because they were not eligible for other systemic mCRPC treatments. A negative control outcome analysis using a composite cardiovascular outcome showed an increased risk of

	cardiovascular events in the first line, similar incidence in the second line, and lower incidence in the third and fourth lines comparing Ra-223 with the comparator arm. Because Ra-223 should not affect cardiovascular outcomes, these findings reflect differences in the treatment groups that remain after the statistical adjustment was implemented, i.e., residual confounding. Using real-world data, the results lead to the **conclusion** that the risk of fractures in patients receiving Ra-223 as monotherapy is similar to the risk observed in other observational studies and interventional clinical trials. The effect estimates for the risk of bone fractures do not point to a large difference and were compatible with a small, if any, increase in the risk associated with Ra-223 use versus a comparator in first and second lines of treatment. The 95% CIs around the effect estimates were consistent with no difference, and with both a small increase and with a small decrease in the 36-month fracture incidence difference. Given the apparent protection of bone-health agents on the incidence of fractures, a lower incidence of fractures in the study population may have been observed had the use of bone-health agents been more prevalent. A moderately increased risk of all-cause and prostate cancer–specific mortality associated with Ra-223 use in the first-line cohort, but a slight decrease of both outcomes in the second- and third/fourth-line cohorts, was found. The observed associations in survival need to be interpreted with caution because of the likelihood of unmeasured confounding, as suggested by the negative control analysis. The results of this study do not change the current benefit-risk profile of Ra-223. In the context of the EU referral procedure under Article 20 of Regulation (EC) No. 726/2004 (EMEA/H/A-20/1459/C/002653/0028), the PASS PRECISE study was recommended to provide further safety data in addition to the ongoing RADIANT trial, a double-blind multicentre RCT study (EudraCT Number 2019-000476-42) that will provide data to adequately characterise the safety and efficacy.
Marketing Authorisation Holder(s)	Bayer AG

2. List of abbreviations

ADT	Androgen-Deprivation Therapy
APP	Abiraterone Acetate Plus Prednisone/Prednisolone
BHA	Bone-Health Agents
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicine Agency
EU	European Union
GnRH	Gonadotropin-Releasing Hormone
HR	Hazard Ratio
ICD-10	*International Classification of Diseases, 10th Revision*
INCA	Information Network for Cancer Care
KM	Kaplan-Meier survival curves
LHRH	Luteinising Hormone–Releasing Hormone
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
NA	Not Applicable
NCT	National Clinical Trial
NPCR	National Prostate Cancer Register of Sweden
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PCBaSe	Prostate Cancer data Base Sweden
PPC	Patient-overview Prostate Cancer, a Subregistry of the PCBaSe
PRAC	Pharmacovigilance Risk Assessment Committee (of the EMA)
PSA	Prostate-Specific Antigen
Q1, Q3	first quartile, third quartile
QOL	Quality of Life
Ra-223	Radium-223 Dichloride
RCC	Regionalt Cancercentrum (in PPD
RCT	Randomised Controlled Trial
RR	Risk Ratio
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SD	Standard Deviation
WHO	World Health Organization

3. Investigators

*Please refer to the best practice document **Guidance for the supplement OS report (secondary data collection)** for further guidance and information.*

3.1 Principal investigator centre

Role:	Principal Investigator
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Role:	Lead Statistician and Analyst
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3.2 Scientific collaborating centre

Role:	Epidemiologist
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Role:	Statistician and Analyst
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4. Other responsible parties

4.1 Study team (internal or external)

Role:	OS Conduct Responsible
Name:	PPD
Email:	PPD

Role:	OS Safety Lead
Name:	PPD

Role:	OS Medical Expert
Name:	PPD

Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Role:	Regulatory Affairs responsible
Name:	PPD

Contact details of the responsible parties at Bayer AG are available upon request.

5. Milestones

Project milestones are summarised in Table 1.

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
EMA protocol endorsement		28 November 2019	Doc. Ref: EMA/PRAC/643811/2019
Start of data collection	Q1 2020	02 October 2018	
End of data collection	Q2 2020	27 November 2019	
Registration in the EU PAS Register	Following EMA endorsement and prior to start of data collection	04 February 2020	
Final report of study results	Q2 2021	22 June 2021	

EMA = European Medicines Agency; EU PAS Register = European Union electronic register of post-authorisation studies.

6. Rationale and background

In the last decade, several new treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) have been approved. Existing guidelines recommend androgen-deprivation therapy (ADT) and chemotherapy (docetaxel, cabazitaxel); novel second-generation antiandrogen agents (e.g., abiraterone acetate and enzalutamide); and alpha-emitting therapy, radium-223 dichloride (Ra-223) [1, 2].

Ra-223 is a first-in-class therapeutic alpha particle–emitting pharmaceutical with targeted antitumour effect on bone metastases, developed for the treatment of men with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease. ALSYMPCA, the pivotal phase 3, double-blind, randomised controlled trial (RCT) compared treatment with Ra-223 plus best standard of care versus placebo plus best standard of care in patients that either had received docetaxel, were not fit enough to receive docetaxel, declined to receive docetaxel, or for whom docetaxel was not available. Ra-223 prolonged median overall survival (OS) by 3.6 months (14.9 vs. 11.3 months; P <0.001) [3], regardless of previous docetaxel exposure [4], and the median time to first symptomatic skeletal event by 5.8 months (15.6 vs. 9.8 months; P <0.001) [5]. Ra-223 was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (Ra-223 vs. placebo: anaemia, 13% vs. 13%; neutropenia, 2% vs. 1%; and thrombocytopenia, 7% vs. 2%). A 3-year

follow-up of the ALSYMPCA trial confirmed a good safety profile [6]. Quality-of-life (QOL) data from the ALSYMPCA RCT demonstrated that Ra-223 provides significant QOL benefits, including a higher percentage of patients with meaningful improvement in QOL and an overall slower decline in QOL over time [7].

The ERA 223 RCT (study 15396, NCT02043678) was designed to evaluate the efficacy and safety of Ra-223 in combination with abiraterone acetate plus prednisone/prednisolone (APP) versus placebo in combination with APP in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant mCRPC. Subjects had at least 2 bone metastases, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and no known brain metastasis or visceral metastasis. The primary endpoint was symptomatic skeletal event–free survival (i.e., time from randomisation to the first of the following: use of external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgery) [8]. The trial was unblinded in November 2017, following an independent data monitoring committee's recommendation based on the observation of an unexpected increase of bone fractures and deaths in the arm with Ra-223 in combination with APP when compared with the control arm with placebo and APP [9]. Median symptomatic skeletal event–free survival was 22.3 months (95% confidence interval [CI], 20.4-27.8) in the Ra-223 group and 26.0 months (95% CI, 21.8 to 28.3) in the placebo group (hazard ratio [HR], 1.12; 95% CI, 0.92 to 1.37). Median OS was 30.7 months (95% CI, 25.8 to Not estimable) in the Ra-223 group and 33.3 months (95% CI, 30.2 to 41.1) in the placebo group (HR, 1.20; 95% CI, 0.95 to 1.51). A multivariable analysis of OS adjusting for prespecified baseline factors yielded an HR of 1.05 (95% CI, 0.83 to 1.34) [10].

On 01 December 2017, a Pharmacovigilance Risk Assessment Committee (PRAC) review under Article 20 of Regulation (EC) No. 726/2004 (EMEA/H/A-20/1459/C/002653/0028) was initiated at the request of the European Commission for Xofigo (radium-223 dichloride). As a result of this Referral procedure, the PRAC recommended that the indication of Ra-223 should be restricted to use as monotherapy or in combination with a luteinising hormone–releasing hormone (LHRH) analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases, and no known visceral metastases, in progression after at least 2 prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The PRAC further considered that Ra-223 should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone, and further warnings and precautions should be added to the product information. Other health authorities outside the EU did not impose any restrictions to the indications and adapted their labelling with the corresponding warnings.

In addition, the PRAC recommended imposing as conditions to the marketing authorisation of Xofigo (radium-223 dichloride) the conduct of a randomised controlled clinical trial, a biodistribution study, and a non-interventional post-authorisation safety study (PASS), in order to further characterise the safety and efficacy of Ra-223, including the mechanisms responsible for the increased risk of fracture and possible risk of increased mortality reported in ERA 223. The outcome was adopted with EC decision (C(2018) 6459 final) on 28 September 2018.

This document reports the results of a non-interventional PASS, intended to serve as the requested non-interventional PASS (Category 1 study, annex II condition). The protocol was endorsed by the European Medicines Agency (EMA) PRAC on 28 November 2019 (EMA/PRAC/643811/2019) and posted in the European Union electronic registry of Post-Authorisation Studies (EUPAS33448). The study uses an observational comparative cohort design to evaluate the risk of bone fractures, death,

and prostate cancer–specific death among patients treated with Ra-223 compared with other standard of care in routine clinical practice.

7. Research question and objectives

This study addresses the following research questions:

- Does the use of Ra-223 increase the risk of bone fractures compared with other treatments for mCRPC in routine clinical practice?
- Does the use of Ra-223 increase the risk of death compared with other treatments for mCRPC in routine clinical practice?
- Does the use of Ra-223 increase the risk of prostate cancer–specific death compared with other treatments for mCRPC in routine clinical practice?

7.1 Primary objective

The primary objective of this study was to estimate the effect of Ra-223 on the incidence of bone fractures compared with other standard treatments for mCRPC.

7.2 Secondary objective

The secondary objectives were as follows:

- To estimate the effect of Ra-223 on OS compared with other standard treatments for mCRPC.
- To estimate the effect of Ra-223 on prostate cancer–specific survival compared with other standard treatments for mCRPC.

8. Amendments and updates

8.1 Amendments

Not applicable.

8.2 Updates

An update was implemented in January 2020: an exclusion criterion was changed from “Patients that have participated in a Ra-223 RCT” to “Patients that have participated in an RCT (involving Ra-223 or not) in the past or at baseline, for which unblinded information on the assigned treatment is not available.” The criterion was changed because some patients had participated in RCTs that did not involve Ra-223, and information on the treatment they actually received was not available because of blinding; therefore, assigning the line of treatment was not possible.

Another update was implemented in December 2020: researchers at the Prostate Cancer data Base Sweden (PCBaSe) detected that some patients in the comparator group were granted immortal time (a form of selection bias) because of the sampling methodology, as follows. The centres where patients are treated start contributing data to the Patient-overview Prostate Cancer (PPC) on a specific calendar date; only data on patients who were alive on that date or later are collected. For those living patients, new treatments are recorded prospectively, and past treatments are reviewed and recorded retrospectively in the PPC database. Cohorts specific to the line of treatment were

constructed using both new and past treatments. Therefore, cohorts that were created using treatments received before the calendar date when the centre started contributing data to the PPC imposed a survival requirement on those patients starting that line of treatment, that is, patients must have survived until the date the centre started contributing data to the PPC. Data on the Ra-223 group was not affected by this selection bias because their sampling, driven by this PASS, did not impose any survival requirement. This selection bias was solved by using only information generated after the date when each centre started contributing data to the PCBaSe for those patients receiving a treatment other than Ra-223, effectively removing the survival requirement. This resulted in the exclusion of 1,186 individuals from the comparator group that would have contributed immortal time bias in the analyses, if included in the study.

9. Research methods

9.1 Study design

This study was an observational comparative cohort study.

Ra-223 could be administered in clinical practice in different lines of treatment during the study period (November 2013 through December 2018). A “line of treatment” was considered to be the initiation of a new mCRPC-specific drug (i.e., Ra-223, docetaxel, cabazitaxel, abiraterone, enzalutamide, and other chemotherapy combinations used in Sweden) administered because of tumour progression or intolerance (e.g., toxicity) to a previous treatment. Because the line of treatment reflects the natural evolution of the disease (i.e., patients receiving later lines of treatment are frailer, have a higher baseline risk of bone fractures, and have a worse prognosis than those receiving initial lines of treatment), cohorts specific to the line of treatment were created. For each such cohort, baseline was the time of initiation of the line of treatment that was specific for that cohort. At baseline, selection criteria were applied, baseline variables were extracted, and patients were assigned to the exposure strategy that was consistent with their baseline data [11]. In this sequence of cohorts, patients could contribute as individuals to multiple cohorts, if eligible [12-15].

A priori, there is no biological reason to expect a differential effect of Ra-223 on the risk of fracture or death by line of treatment (effect modification), although the patients’ characteristics may be very different. Therefore, the presence of heterogeneity of such effects in the first, second, and third/fourth lines of treatment were evaluated (Section 9.9.2.5). The study protocol stated that, in the absence of heterogeneity, the treatment-line–specific cohorts would be pooled, and treatment effects would be adjusted accordingly.

The main analysis estimated the effect of starting Ra-223 (with or without ADT) and continuing it until the completion of a maximum of 6 cycles, toxicity, or disease progression, without combining it with another systemic drug for mCRPC, compared with starting any other treatment for mCRPC (with or without ADT) and never receiving Ra-223. The effect corresponding to *full adherence* to the treatment strategies (i.e., the observational analogue of a per-protocol effect in an RCT), as opposed to the effect of initiating the strategy regardless of treatment received afterwards (i.e., the observational analogue of an intention-to-treat effect in an RCT), was estimated. The effect of full adherence to the treatment strategy was estimated because an intention-to-treat–like comparison may bias the effect estimate towards the null if there is lack of adherence [16]. The estimation of the per-protocol effect is very similar in an RCT [17] and in an observational cohort analysis [13] and requires artificial censoring to emulate full adherence and the use of g-methods to adjust for baseline

differences and for the potential bias introduced by the artificial censoring. The current study used inverse-probability-of-treatment weighting.

9.2 Setting

The study population comprised men with mCRPC in the PCBaSe data set during the study period. The study period started in November 2013, the month of Ra-223 approval in Sweden, and ended in December 2018, which was the latest available date of data covering full information, including cause of death, at the time of data extraction in November 2019.

Data for men on Ra-223 included a start of treatment through 31 December 2018, and follow-up was also until this date. To have a complete capture in the National Patient Register and the registry for the total population and population changes (the Census [Folkbokföringen]), a linkage with these registries was done in the fall of 2019; therefore, all events through 31 December 2018 are captured.

Besides the PCBaSe data set, alternative data sources in Europe were systematically explored but none were found to be suitable for the current PASS, mainly because of difficulties capturing Ra-223 use or incidence of fractures or comprehensively characterising patients' characteristics. Several European data sources that were considered did not capture the required exposure variables on prostate cancer therapy, including specific information on Ra-223 dispensing or administration: the System National de Données de Santé database in France, the Dutch PHARMO Database Network and associated registries, the Clinical Practice Research Datalink (CPRD) database in the United Kingdom, the German Cancer Registry, the Swiss NICER database, and the EpiChron database in Spain. Denmark's national population registries estimated that Ra-223 was scarcely used, and its identification would require primary data collection, and the databases from the Toscana and Lombardy regional health systems did not capture outpatient care. At the time of the design of this study (following a feasibility evaluation in 2018), no literature on advanced prostate cancer treatment using data from patient registries in Belgium or Norway had been published.

9.3 Subjects

Selection criteria were applied at baseline in each of the 4 cohorts (first through fourth line of treatment). The selection criteria were chosen to select a population 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 National Prostate Cancer Register (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 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, mitoxantrone.

- Docetaxel has been shown to improve survival in castration-sensitive prostate cancer [18] and was approved for that indication by the EMA on 19 September 2019, outside the study period [19]. Therefore, all docetaxel users were assumed to have had mCRPC at the time they were treated with docetaxel.
- Abiraterone was approved for the treatment of metastatic hormone-sensitive prostate cancer in 2017 [20]. To identify patients treated with abiraterone for mCRPC in the PPC in the study period, following algorithm was used:
    1. Patients treated with abiraterone during the years 2013-2016 were assumed to have mCRPC
    2. Patients starting abiraterone without any prior therapy for mCRPC, in 2017-2018:
        a. If the time from prostate cancer diagnosis to the initiation of abiraterone was ≤ 180 days, they were assumed to have hormone-sensitive prostate cancers.
        b. If the time from prostate cancer diagnosis to the initiation of abiraterone was ≥ 2 years, they were assumed to have mCRPC.
        c. 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.
    3. Patients not classified with the criteria above were classified on an individual basis after reviewing the following elements: prostate-specific antigen (PSA) curves, date of abiraterone initiation, and date of mCRPC.
- 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.
- ECOG performance status of 0-2 at treatment initiation. Patients starting any of the systemic therapies under study were assumed to have had a performance status of 0-2.
- 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 that had participated in an RCT (involving Ra-223 or not) in the past or at baseline for which unblinded information on the assigned treatment was not available.

9.4 Variables

9.4.1 Exposure definition

The following 2 groups were compared:

A. Ra-223 initiators. Patients could stop Ra-223 after 6 cycles or earlier in the event of toxicity, cancer progression, or worsening of overall health status. Patients could start other systemic drugs for mCRPC (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) after the initiation of Ra-223, when clinically indicated, but never at the same time as Ra-223. ADT with first-generation antiandrogens or GnRH (gonadotropin-releasing hormone) could be used at any time.

B. Initiators of other standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients were 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 antiandrogens or GnRH could be used at any time.

Section 9.9.2.2 describes how these 2 exposures were assigned and operationalised. Patients can contribute as individuals to both arms, if eligible (see Section 9.9.2.1)

9.4.2 Outcomes definition

The *primary outcome* was bone fractures requiring admission to a hospital [21] or treated in an outpatient setting, as recorded/captured in the PCBaSe via ICD-10 codes. Bone fractures that did not prompt a diagnostic work-up and those diagnosed only through routine imaging techniques may not have been captured in this study (detailed explanation in this limitation provided in Section 11.2).

Bone fractures are available in the PCBaSe via linkage to the National Patient Register. Bone fractures were defined as the first occurrence of any of the following [21]:

- Fracture of the cervical vertebra or other parts of the neck
- Fracture of rib(s), sternum, and thoracic spine
- Fracture of lumbar spine and pelvis
- Fracture of shoulder and upper arm
- Fracture of forearm
- Fracture at wrist and hand level
- Fracture of femur
- Fracture of lower leg, including ankle
- Fracture of foot and toe, except ankle

The *secondary outcomes* were death due to all causes and death due to prostate cancer. Date and cause of death are available in the PCBaSe via linkage to the Cause of Death Register [22]. The date of death is continuously updated (i.e., no or minimal lag to obtain the information).

9.4.3 Covariate definition

The variable “line of treatment for mCRPC” was used to define the generation of each cohort. Line of treatment for mCRPC corresponded to each of the subsequent active treatments (i.e., abiraterone,

enzalutamide, docetaxel, cabazitaxel, Ra-223, others) that were administered after progression to hormonal treatment. A patient was considered to have started a new line of treatment when the previous drug was stopped and a new mCRPC-specific drug was initiated, under the assumption that treatments were changed because of disease progression or toxicity. The Patient-overview Prostate Cancer (PPC) database records the reason for stopping a drug; therefore, allowing discrimination of line of treatment from other reasons for drug pauses, like shorter breaks due to toxicity or other reasons. Inconsistencies were reviewed by a medical oncologist.

The following variables were considered potential confounders [23] and were described and adjusted for to achieve conditional exchangeability among exposure groups.

- Baseline variables (extracted at the beginning of each cohort)
  - Age
  - Calendar year at cohort entry
  - Time from diagnosis to baseline
  - History of skeletal-related events
  - Tumour, node, metastasis staging
  - Tumour grade (Gleason score/World Health Organization [WHO] grade)
  - ECOG performance status
  - Prostate-specific antigen
  - Haemoglobin
  - Total alkaline phosphatase
  - Osteoporosis
  - Charlson Comorbidity Index
  - Site of metastasis (visceral, bone, lymph node)
  - History of spinal cord compression
  - Use of bone-health agents (zoledronate, denosumab)
  - Use of steroids
  - Time on bone-health agents
  - Time on ADT
  - Prior radiation therapy
  - Line of treatment for mCRPC
  - Types of drugs for mCRPC used in the past (taxanes, second-generation antiandrogens, others)
- Time-varying variables (updated during the follow-up within each cohort)
  - ECOG performance status

- Prostate-specific antigen
- Total alkaline phosphatase
- Haemoglobin
- Osteoporosis
- Charlson Comorbidity Index
- Site of metastasis
- Radiation therapy
- Spinal cord compression
- Use of bone-health agents (zoledronate, denosumab)
- Use of steroids
- Line of treatment for mCRPC
- Types of drugs for mCRPC used in the past (taxanes, second-generation antiandrogens, others)

9.5 Data sources and measurement

9.5.1 National Prostate Cancer Register of Sweden

Since 1998, the primary registry of the NPCR has captured >96% of all men with incident prostate cancer compared with the Swedish National Cancer Register, to which registration is mandated by law. The primary registration in the NPCR captures data around the date of diagnosis regarding cancer characteristics, diagnostic work-up, and primary treatment. This means that treatments that are initiated at a later stage of the disease, such as mCRPC treatments, are not captured in this primary registration. [22].

9.5.2 Patient-overview prostate cancer (PPC) and Prostate Cancer data Base Sweden (PCBaSe)

To overcome the lack of data of follow-up data in the primary registration of the NPCR, the PPC was created in 2014. Patient-overview prostate cancer is a longitudinal registration of treatments, laboratory values, clinical data, etc from initiation of ADT to death. Data from earlier dates is made available from retrospective inclusion of data from medical charts, back to the initiation of ADT for each patient.

In April 2021, the PPC contained data on approximately 12,000 patients from 33 healthcare providers, including among other centres PPD (including sites in PPD and PPD and, most recently, PPD Contributing centres cover almost all sites at which Ra-223 is administered in Sweden; therefore, the PPC has almost complete capture of treatment with Ra-223 in Sweden.

- To enrich the PPC with more men treated with Ra-223, these men were identified by use of (1) anonymised medication distribution information for each hospital from Bayer and (2) treatment records at the departments of nuclear medicine at these hospitals, where the personal identity numbers of the treated men were obtained. Regardless of how patients were identified, the pattern of care and follow-up does not differ by centre because of the characteristics of the Swedish health system.

All centres that register in the PPC contribute data in a standardised way through the same platform (the Information Network for Cancer Care, INCA).

In the PCBaSe, the NPCR, including the PPC, has been linked with a number of other healthcare registries by use of the unique Swedish person identity number. These registries include the Cancer Register; the Patient Register (with In- and Out-Patient Register); 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 [22].

Information on bone fractures in the PCBaSe is available by using information from the Patient Register with data from hospital admissions and outpatient visits. ICD-10 (*International Classification of Diseases, 10th Revision*) codes for all fractures and specific fractures were 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 with 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 [24]. 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 on the death certificates and determined by the committee was 96% [25].

More than 170 research manuscripts have been published based on data in the PCBaSe since its inception in 2010 (www.npcr.se/publikationer). Recently, a cohort profile paper describing the set-up of the PPC was published [26], as well as some preliminary results [27].

The Swedish healthcare system provides complete national coverage; therefore, it is safe to assume a very large proportion of fractures requiring medical care were captured in the Patient Register used in this project and that losses to follow-up were minimal.

9.6 Bias

The following potential sources of bias were considered and addressed in the design of the study:

- Measurement bias. As in all data collection platforms, errors can happen when recording information on the exposure, the outcome, or the potential confounders. To minimise the potential for this bias, data are collected via a standardised way through the same platform by trained personnel. Additionally, because the personnel recording the information in the PCBaSe were not aware of this project, it can be assumed that any measurement errors are independent and non-differential [28]. Of note, fractures requiring hospitalisation identified in the National Patient Register via ICD-10 codes (the main outcome) have been validated via medical record review and are correct up to the third digit of the code in over 90% of the cases [29].
- Confounding. Confounding was addressed by measuring all the relevant common causes of exposure assignment and the outcome and by using inverse-probability weighting to adjust for them. The analyses were adjusted for the following baseline variables: age, calendar year at cohort entry, time from prostate cancer diagnosis to baseline, history of skeletal-related events, tumour, node metastasis staging, tumour grade, ECOG performance status, PSA, haemoglobin, alkaline phosphatase, osteoporosis, Charlson Comorbidity Index, site of

metastasis (visceral, bone, lymph node), history of spinal cord compression, use of bone-health agents, use of steroids, time on bone-health agents, time on ADT, prior radiation therapy, line of treatment for mCRPC, and type of drugs for mCRPC used in the past (taxanes, second-generation antiandrogens, others). It was assumed that, within levels of these measured confounders, treatment assignment happened at random. The violation of this assumption was explored in the sensitivity analysis (see Section 9.9.4.1).

- Selection bias. The study design aligned exposure assignment, the beginning of the follow-up, and eligibility (this was used to correct the survival requirement of the selection bias described in Section 8.2). Therefore, the only source of selection bias was informative censoring during follow-up. Informative censoring can arise from losses to follow-up and from artificial censoring (Section 9.9.2.2). Because of the characteristics of the Swedish healthcare system (universal, with complete national coverage), losses to follow-up were minimal (i.e., patients leaving Sweden permanently, who are captured via the Emigration Register, as part of the Census). Patients in the comparator arm were artificially censored when they started Ra-223. Inverse-probability weighting was used to adjust for the following time-varying variables: ECOG performance status, PSA, alkaline phosphatase, haemoglobin, osteoporosis, Charlson Comorbidity Index, site of metastasis, radiation therapy, spinal cord compression, use of bone-health agents, use of steroids, line of treatment for mCRPC, and type of drugs for mCRPC used in the past (taxanes, second-generation antiandrogens, others). This created a pseudopopulation where Ra-223 initiation was independent of past history; thus, the artificial censoring was not informative. In other words, in the pseudopopulation, the censored individuals could be represented by the individuals that remained under observation.

9.7 Study size

The number of patients in each group was determined by the available data [30]. As per the estimations conducted for the study protocol, for the analysis of the first-, second-, and third/fourth-line cohorts, the expected number of patients were as shown in Table 2.

Table 2: Expected number of patients in each comparison group, by line of treatment

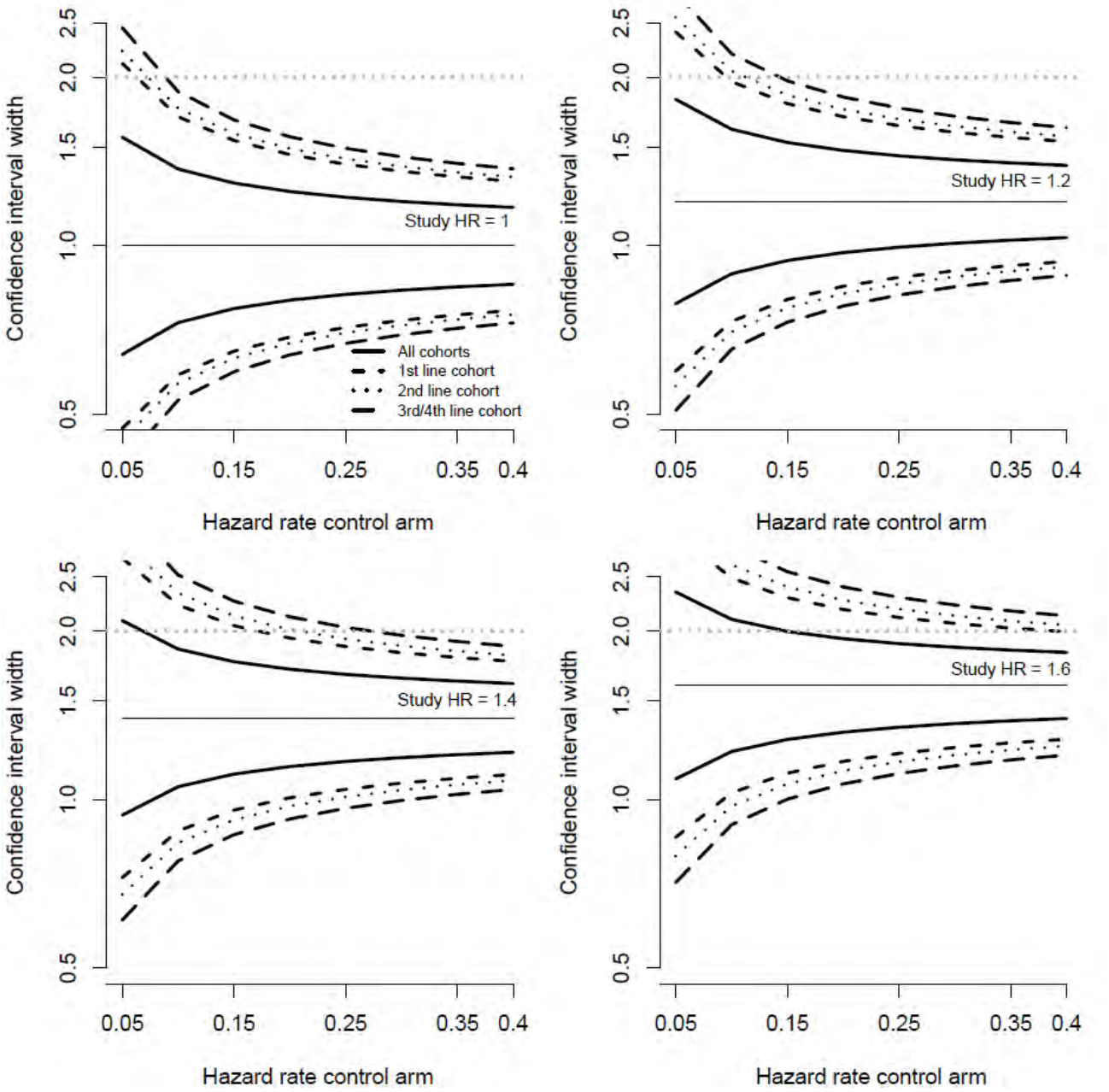
	First line	Second line	Third/fourth line	All
Ra-223	240	280	280	800
Comparator drug	1,800	750	450	3,000

Ra-223 = radium-223.

Figure 1 presents the width of the CIs [31] for different potential values of the true HR of bone fractures for the analysis of first, second, and third/fourth lines of treatment and for the pooled analysis. The incidence of bone fractures in patients recently diagnosed with prostate cancer in Sweden is approximately 5 per 100 person-years [21]. This was used as the lower bound for the expected rate of bone fractures in this study because eligible patients present more advanced stages of their disease. Therefore, the figures use a range of bone fracture incidence from 5 to 40 fractures per 100 person-years. Based on personal communication with PCBaSe researchers, 60% of the comparator group and 100% of the Ra-223 group were assumed to have had recorded bone metastases because it is the indication for the drug. Inverse-probability weighting was used to adjust for pre- and postbaseline factors. Although no methods have been previously used for power calculations of inverse probability–weighted estimates, the relative power of these estimates was estimated based on published estimates that used inverse-probability weighting. A review of some representative papers [32, 33] showed that, in settings with large amounts of time-varying

confounding, the width of the 95% CI of the inverse probability–weighted estimate is never 16% greater than that of the 95% CI of the unadjusted estimates. The standard error of these calculations was increased by 20% to account for this.

Figure 1: Confidence interval width in relation to the rate of fractures in the control group for 4 potential true hazard ratios, by line of treatment



HR = hazard ratio.
Note: Width of the confidence intervals for different effect estimates of Ra-223 (solid, thinner black line), for different hazard rates of fractures in the control group. Grey dotted line represents a harmful effect with an HR of 2. Y-axis is in a logarithmic scale.

The expected numbers during the protocol development were reduced after identifying the immortal time bias generated in the comparator group, which was solved as described in Section 8.2.

9.8 Data transformation

Data in the NPCR, including the subregistry PPC, are held at the INCA platform, which is the platform for all clinical cancer registries in Sweden. Over 500,000 cases of around 20 cancer forms are held at this platform. The INCA server is held at Umeå University at ICT Services and System Development, which develops, manages, and operates information technology systems for universities and colleges in Sweden and has several large assignments with organisations in the public sector. Maintenance and updates of the INCA platform are shared between an INCA team employed by the Federation of Regional Cancer Registers in Sweden and Sogethi, a software company.

Data from the NPCR and PPC, including the enriched data for men treated with Ra-223, were encrypted and transferred from INCA to the National Board of Health and Welfare. These data were linked by use of the person identity number to the Patient Register, the Cause of Death Register, and the Prescribed Drug Register in order to update PCBaSe 4.0. Pseudoanonymised files, one for each registry, were returned to the RCC (Regionalt Cancercentrum) in PPD in which the personal identity number has been replaced by a code, and the code key is kept at the National Board of Health and Welfare until data are checked. The National Board of Health and Welfare receives and sends out data on encrypted DVDs and/or USB flash drives.

Data source files are indexed by date of creation and stored on a secured, specifically designated server at RCC. When creating the study cohort from the data source files, scripts, documentation, and resulting data sets were stored in subfolders indexed by date of creation. A data manager ensured that the following additional supporting documentation was maintained: data dictionary representing the final data sets; for example, table names; name, label, type, and length of variables; and coding.

9.9 Statistical methods

9.9.1 Main summary measures

Data were summarised using means, standard deviations, quartiles, and minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables.

9.9.2 Main statistical methods

9.9.2.1 Creation of the treatment-line–specific cohorts

The cohort of patients receiving first-line treatment (“first-line cohort”) (see definition of line of treatment in Section 9.4.3) included patients meeting the selection criteria described in Section 9.3 when they started a first-line treatment for mCRPC (docetaxel, abiraterone, enzalutamide, cabazitaxel, Ra-223), which was considered the baseline date. The cohort of patients receiving second-line treatment (“second-line cohort”) included patients meeting the selection criteria described in Section 9.3 when they started a second line of treatment for mCRPC. Analogously, the cohort of patients receiving third- or fourth-line treatment (“third-line cohort” and “fourth-line cohort”) included patients meeting the selection criteria when they started a third or fourth line of treatment for mCRPC, respectively. In all 4 cohorts, patients were assigned to each exposure group (see Section 9.4.1) according to the drug they started taking, and the date of the start of treatment was the baseline date [14]. Under this design, patients could contribute as individuals to multiple cohorts, if eligible, and to both arms in different cohorts. Baseline variables were updated at baseline in each cohort [12]. Supplementary Figure 1 contains a summary.

9.9.2.2 Exposure assignment and follow-up

Patients were assigned to each exposure group (see Section 9.4.1) that was consistent with their observed data at the baseline date [34]:

A. Patients were assigned to the Ra-223 arm when they started Ra-223. Patients were artificially censored if and when they combined other treatment for mCRPC with Ra-223. Patients were followed from Ra-223 initiation until the artificial censoring, death, or the administrative end of follow-up, whichever occurred first.

B. Patients were assigned to the comparator group when they started a standard of care other than Ra-223 (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients were artificially censored if and/or when they started Ra-223. Patients were followed from the standard of care initiation until the artificial censoring, death, or the administrative end of follow-up, whichever was first.

Baseline characteristics are summarised by treatment strategy.

9.9.2.3 Outcome measures

For all outcomes, adjusted time-to-event curves, as well as the HR over the entire follow-up and the absolute risk difference [35] at 6-month intervals of follow-up, are presented. All effect estimates are bound with 95% CIs.

9.9.2.3.1 Bone fractures

The main outcome was cumulative incidence of bone fractures, which was estimated with a 1 − Kaplan-Meier survival curve, as well as with adjusted parametric incidence curves [36]. Time to bone fracture was defined as the time from the baseline date until the occurrence of the first bone fracture event. For patients without bone fractures, the censoring date was defined as the earlier of date of death and the end of follow-up.

9.9.2.3.2 Overall survival

Overall survival was estimated with a Kaplan-Meier survival curve, as well as with adjusted parametric survival curves [36]. Overall survival was defined as the time from the baseline date until death. For patients alive at the end of follow-up, the censoring date was defined as the last available date of follow-up.

9.9.2.3.3 Prostate cancer–specific survival

Prostate cancer–specific survival was estimated with a Kaplan-Meier survival curve, as well as with adjusted parametric survival curves [36]. Prostate cancer–specific survival was defined as the time from the baseline date until death because of prostate cancer. For patients that did not die because of prostate cancer, the censoring date was defined as the earlier of date of death (for causes other than prostate cancer) and the end of follow-up.

9.9.2.4 Adjusted analyses

The effect of the Ra-223 treatment strategy compared with the comparator treatment strategy on each of the 3 outcomes were estimated using a discrete hazards model (1 model for each outcome), approximated using a pooled logistic regression model [37, 38] that categorised time in units of 14 days and that included an indicator for the treatment strategy and a flexible function of time (cubic splines). To produce estimates of cumulative incidence (for bone fractures) and survival (for

OS and for prostate cancer–specific survival), a product term for treatment strategy and time variables was included in the pooled logistic model and used the predicted probabilities from this regression model to estimate cumulative incidence (or survival, depending on the outcome) over time. To adjust for potential baseline confounding, the outcome models were weighted using stabilised weights for the inverse-probability-of-treatment initiation at baseline. Informally, the denominator of the weights was each patient's probability of initiating his treatment strategy (Ra-223 or the comparator) conditional on the baseline variables listed in Section 9.4.3, and the numerator of the weighs was each patient's marginal probability of initiating his treatment strategy.

In the current study, the approach to estimate the treatment effect under full adherence to the treatment strategies censored individuals artificially when they deviated from the treatment strategy into which they were classified at baseline. This artificial censoring can introduce selection bias if some variables are associated with the reason for artificial censoring and any of the outcomes under study. To adjust for potential selection bias [39] introduced by the artificial censoring, each individual's contribution to the outcome model was inverse-probability weighted [40], with weights depending on predefined adjustment variables (baseline and time-varying) itemised in Section 9.4.3. Informally, the denominator of the weights was each patient's time-varying probability of following the assigned strategy, conditional on baseline and time-varying covariates, and the numerator was the probability that a patient received his observed treatment conditional only on his past treatment history and baseline prognostic factors [13]. Formal definitions of the models for the outcomes and for the weights can be found in the protocol (http://www.encepp.eu/encepp/openAttachment/fullProtocol/33477).

Because a single patient can contribute to multiple treatment-line–specific cohorts and because the use of weights induces within-subject correlation, non-parametric bootstrap resampling, based on the percentiles from 500 individual-level re-samplings, was used to obtain valid estimates of 95% CIs.

9.9.2.5 Pooling of the treatment-line–specific cohorts

The study was designed to pool the cohorts created at each line of treatment unless evidence for a heterogeneity of the effect of Ra-223 on fractures or death across lines of treatment existed. Separately for the risk of fractures and the risk of death, the homogeneity of the 12-month standardised risk difference estimates across treatment-line strata (first line, second line, and third/fourth line [combined third-line and fourth-line cohorts]) was evaluated using the I^2 statistic [41]. If the percentage of heterogeneity estimated by I^2 was high (>50%), the results are reported by line of treatment: first, second, and third/fourth lines.

9.9.3 Missing values

The study was designed to run a complete-case analysis if 10% or less of patients had missing values. Because 19% of the eligible patients had missing values, inverse-probability weighting was used to account for the missing values, as described by Toh et al. [42]. The weights used as the denominator the probability of not having missing values conditional on baseline variables that were predictive of missingness. The inverse-probability–weighted, complete-case analysis creates a pseudopopulation the size of the eligible population and estimates the effect in the entire study population under the assumption that the occurrence of missing data is not associated with the outcome, conditional on the measured confounders (i.e., data are missing at random), and that the weight models are correctly specified.

9.9.4 Sensitivity analyses

9.9.4.1 Sensitivity analysis for unmeasured confounding

Planned sensitivity analysis: As a sensitivity analysis, how strong unmeasured confounding would have had to be to explain away the association reported in the main analysis was evaluated. The value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the estimated HR of the main analysis was plotted for different values of RR_{EU} (maximum risk ratio for any specific level of the unmeasured confounders comparing those with and without treatment, with adjustment for the measured covariates) in the x-axis and RR_{UD} (the maximum risk ratio for the outcome comparing any 2 categories of the unmeasured confounders within either treatment group, conditional on the observed covariates) in the y-axis. In the plot, the "E-value," which represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates, [43] was identified. Details on its computation can be found in the protocol (http://www.encepp.eu/encepp/openAttachment/fullProtocol/33477).

Post hoc sensitivity analysis: Following the review of the originally planned analyses, additional sensitivity analyses were done for those comparisons yielding 95% CIs that were consistent with a harmful or beneficial effect of Ra-223 compared with the comparator group. A negative control outcome analysis was performed to characterise the potential unmeasured confounding [44]. 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 this population. Other than the different outcome, the analytical approach was identical to the main analysis.

9.9.4.2 Planned sensitivity analysis for the effect of information on bone metastasis

The primary analysis assumes that all patients receiving Ra-223 have bone metastasis, regardless of whether or not they are recorded. To evaluate how strong this assumption is, a sensitivity analysis that includes only patients with recorded bone metastasis (both in the Ra-223 and in the comparator group) was performed. This analysis followed the same analytical approach and evaluates the same outcomes as the main analysis.

9.9.4.3 Planned sensitivity analysis for the effect of Ra-223 alone or in combination

The main analysis estimated the effect of Ra-223 alone versus the standard of care on the incidence of bone fractures. Therefore, the main analysis did not use the person-time when Ra-223 was combined with other anticancer drug(s) (see Section 9.9.2.2). To evaluate if the exclusion of this person-time affected the conclusions of the main analysis, as a sensitivity analysis, the effect of Ra-223 alone or in combination with other treatments for mCRPC, compared with other standard of care on the incidence of bone fractures, was estimated. To operationalise this comparison, patients in the Ra-223 group were not censored when they combined other treatment for mCRPC with Ra-223.

9.9.4.4 Planned sensitivity analysis using a potential follow-up of at least 18 months

Patients who became eligible in the last months of 2018 had a short follow-up because data on follow-up was available only until 31 December 2018. The proposed time-to-event analysis

appropriately considered the time when participants were at risk and therefore this could not have been a source of bias. To evaluate if a short follow-up had any impact on the effect estimates, a sensitivity analysis where patients were eligible for the analysis only through June 2017 and thus had a potential follow-up of at least 18 months was conducted.

9.9.4.5 Post hoc sensitivity analysis letting individuals in the comparator group receive Ra-223 during the follow-up

The main analysis studied the comparator treatment strategy (Section 9.4.1) "initiate a standard of care other than Ra-223 (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) and continue with other lines of treatment when clinically indicated, with the exception of Ra-223" by censoring individuals in the comparator group when they receive Ra-223 during the follow-up. This sensitivity analysis did not censor individuals in the comparator group if they initiated Ra-223 during follow-up. The statistical approach was the same as for the main analysis, with the exception of the use of time-varying weights to adjust for artificial censoring in the comparator group. Consequently, the comparator treatment strategy being studied in this sensitivity analysis was "initiate a standard of care other than Ra-223 (docetaxel, cabazitaxel, enzalutamide, abiraterone, others) and continue with other lines of treatment when clinically indicated, including Ra-223" (i.e., akin to a clinical trial where crossing over to the experimental group is allowed).

9.9.4.6 Post hoc analysis by subgroups of bone-health agents use at baseline

This analysis described the unadjusted incidence of bone fractures by use of bone-health agents at baseline separately for the Ra-223 group and for the comparator group.

9.9.5 Amendments to the statistical analysis plan

The only amendments to the SAP were those corresponding to the post hoc subgroup analysis and post hoc sensitivity analysis described in subsections under Section 9.9.4.

9.10 Quality control

Investigators from PCBaSe programmed the analyses, and the statistician at RTI Health Solutions (RTI-HS) reviewed the programmes. The PCBaSe investigators are required to archive documents and data sets, statistical programmes, and study-relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. RTI-HS was responsible for leading development of the study protocol and study report in accordance with standard operating procedures requiring senior, editorial, and quality-control reviews. RTI-HS received results in data set format.

10. Results

10.1 Participants

There were 1,771 patients diagnosed with mCRPC who were registered in the PCBaSe at any time from November 2013 through December 2018. Of these, 831 individuals were eligible for inclusion in the first-line cohort, 591 were eligible for inclusion in the second-line cohort, 341 were eligible for inclusion in the third-line cohort, and 107 were eligible for inclusion in the fourth-line cohort; i.e., 1,870 individuals participated in the 4 treatment-line–specific cohorts, corresponding to 1,551 unique patients. In Annex 4, Table 3 through Table 6 summarise cohort attrition by exclusion criteria and line of treatment.

There were 22 patients who initiated abiraterone in 2017-2018 without having received a prior therapy for mCRPC, and thus could have been receiving it for hormone-sensitive prostate cancer or for mCRPC. All but 5 were classified as mCRPC using criterion #2 of the algorithm in Section 9.3. Using criterion #3, 3 patients were classified as having mCRPC and 2 patients were classified as having metastatic hormone-sensitive prostate cancer and were therefore excluded from the analysis.

The values of some baseline variables were missing, and the corresponding patients could not be included in the analysis. 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 performance status (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). Because haemoglobin and alkaline phosphatase are both surrogates of bone marrow infiltration in prostate cancer and to reduce the number of patients with missing values, both variables were combined into a single one containing the lowest/highest quintile of either, under the assumption that such transformation would not result in relevant residual confounding. The size of the complete-case population was 1,434 individuals: 681 in the Ra-223 group (76.4% of the eligible population) and 753 in the comparator group (76.9% of the eligible population).

In the complete-case population, 203 individuals (29.8%) initiated Ra-223 and 432 (57.4%) initiated a comparator as a first line of treatment, 239 (35.1%) initiated Ra-223 and 214 (28.4%) initiated a comparator as a second line of treatment and 239 (35.1%) initiated Ra-223 and 107 (14.2%) initiated a comparator as a third or fourth line of treatment. In Annex 7, Supplementary Figure 2 is a Sankey diagram representing the treatments received by the complete case population during the study period.

10.2 Descriptive data

In Annex 4, Table 7 contains the baseline characteristics of study individuals by treatment arm and by treatment line. Patients initiating Ra-223 did so most frequently in 2016-2017, whereas the initiation of a comparator drug was most frequent in years 2017-2018.

The following baseline prognostic variables were well balanced when considering all lines of treatment together (differences may have been present at the line-specific level): age (mean age: 74.0 years, Ra-223 group; 73.5 years, comparator group), ECOG performance status (percentage of patients with ECOG performance status 0-1: 84.3%, Ra-223; 82.1%, comparator), and Charlson Comorbidity Index score (percentage of patients with a score >1: 17.5%, Ra-223; 20.6%, comparator).

Patients receiving Ra-223 as a first line of treatment were more likely to have experienced a bone fracture before baseline (22.7%) than patients receiving a comparator (14.4%), whereas the percentage of patients experiencing a bone fracture before baseline among those receiving Ra-223 in later lines of treatment (14.6% in second line, 21.1% in third line, 23.73% in fourth line) was more similar to those receiving a comparator (17.8% in second line, 26.8% in third line, 28.0% in fourth line). Patients in the Ra-223 group had baseline characteristics compatible with a higher extent of bone metastases than those in the comparator group: the proportion of patients using bone-health agents at baseline and the duration of use was higher in the Ra-223 group (33.8%; mean duration of use, 3.5 months) than in the comparator group (17.3%; mean duration of use, 1.8 months), as well as the mean value of alkaline phosphatase (4.9 µkat/L, Ra-223; 3.6 µkat/L, comparator). Use of

steroids at baseline was more frequent in the comparator group (54.2%) than in the Ra-223 group (30.4%). A prior diagnosis of osteoporosis was very rare in both groups, and prior spinal cord compression was similar (1.6%, Ra-223; 1.3%, comparator).

The following baseline cancer-specific prognostic variables showed a distribution that favoured the comparator group compared with the Ra-223 group: metastatic disease at initial prostate cancer diagnosis (43.5%, Ra-223; 36.9%, comparator), Gleason score >7 or WHO grade 3 at diagnosis (57.7% in the Ra-223 group, 51.4% in the comparator group), and mean PSA value (268 ng/mL, Ra-223; 191 ng/mL, comparator). The distribution of some other cancer-specific prognostic variables favoured the Ra-223 group compared with the comparator group: mean time on ADT (38.4 months, Ra-223; 31.8 months, comparator), presence of visceral metastasis (4.1% in the Ra-223 group and 13.9% in the comparator group) and lymph node metastasis (25.8%, Ra-223; 42.9, comparator). T stage showed a similar distribution in both exposure groups, and N stage had been assessed in very few patients in both groups. Prior radiotherapy was received by 59.6% of the Ra-223 group and 51.0% of the comparator group. Enzalutamide was the most frequently used baseline drug in the comparator group in the first 2 lines of treatment (55.5%, first-line cohort; 37.9% second-line cohort), followed by abiraterone (27.8%, first-line cohort; 23.8%, second-line cohort). In the third and fourth lines of treatment, cabazitaxel (30.5%, third-line cohort; 32.0%, fourth-line cohort) and "others" (26.8%, third-line cohort; 48.0%, fourth-line cohort) were the main drugs and drug categories used.

In Annex 4, Table 8 contains the treatment regimens received after discontinuation of the baseline treatment regimen and their duration. Upon progression, toxicity, or end of the 6 cycles, patients in the Ra-223 group most frequently received enzalutamide (181 individuals across all lines of treatment), followed by cabazitaxel (76 patients across all lines of treatments). Patients in the comparator arm started Ra-223 most frequently as a subsequent treatment (120 individuals across all lines of treatment), followed by "others" (59 individuals across all lines of treatment) and enzalutamide (56 individuals across all lines of treatment).

10.3 Outcome data

The 681 patients in the Ra-223 group contributed a total of 9,236.6 months of follow-up, had 62 bone fractures and 437 died, 404 of whom because of prostate cancer. There were no patients artificially censored in the Ra-223 group because none combined Ra-223 with a prostate cancer–specific drug (other than first-generation ADT) during the follow-up. The 753 patients in the comparator group contributed a total of 7,462.1 months of follow-up, had 36 bone fractures and 273 died, 248 of whom because of prostate cancer. There were 120 (15.9%) patients artificially censored in the comparator group because they started Ra-223 during the follow-up.

In Annex 4, Table 9 describes the follow-up, censoring reasons, and outcomes in the overall study population and by line of treatment (first to fourth). The most frequent site of fracture in both groups was the femur (40.2% in the Ra-223 group and 33.3% in the comparator group), followed by shoulder/upper arm (14.9% in the Ra-223 group and 15.6% in the comparator group) (Annex 6, Supplementary Table 1).

10.4 Main results

The distribution of the weights used to account for exclusion of patients with missing values was mean (standard deviation [SD]), 1.30 (0.08). The distribution of the weights used to adjust for *baseline confounding* was mean (SD), 1.01 (1.4); 99th percentile, 5.69. The distribution of the weights used to adjust for *adherence to the treatment strategy* was mean (SD), 0.99 (0.10); 99th percentile, 1.52.

10.4.1 Risk of bone fractures

In the first-line cohort, there were 15 bone fractures in the Ra-223 group and 29 in the comparator group. The estimated adjusted 36-month risk of fracture (95% CI) was 18.4% (8.2% to 31.8%) in the Ra-223 group and 11.9% (6.6% to 21.7%) in the comparator group, corresponding to a difference on the 36-month risk of 6.5 % (95% CI, −7.3% to 18.4%) and an HR of 1.14 (95% CI, 0.50 to 2.15) (Annex 4, Table 10; Annex 5, Figure 2; see Annex 7, Supplementary Figure 2 and Supplementary Figure 3 for the unadjusted cumulative incidence curve).

In the second-line cohort, there were 25 bone fractures in the Ra-223 group and 6 in the comparator group. The estimated adjusted 36-month risk of fracture (95% CI) was 16.3% (9.1% to 24.4%) in the Ra-223 group and 8.7% (1.5% to 21.2%) in the comparator group, corresponding to a difference on the 36-month risk of 7.6 % (95% CI, −7.5% to 18.4%) and an HR of 1.86 (95% CI, 0.62 to 10.93) (Annex 4, Table 11; Annex 5, Figure 3; see Annex 7, Supplementary Figure 4 for the unadjusted cumulative incidence curve).

In the third-line cohort, there were 16 bone fractures in the Ra-223 group and 1 fracture in the comparator group. In the fourth-line cohort, there were 6 fractures in the Ra-223 group and no fractures in the comparator group. The lack of fractures in the comparator groups precluded an informative adjusted analysis in the third- and fourth-line cohorts combined (third/fourth-line cohorts). The unadjusted 36-month risk of fracture (95% CI) in the third/fourth-line cohorts was 21.7% (11.4% to 36.2%) in the Ra-223 group and 5.1% (0% to 24.8%) in the comparator group (Annex 4, Table 12; Annex 5, Figure 4).

The evaluation of the heterogeneity of the effect of Ra-223 versus with the comparator on the risk of fracture by line of treatment yielded an I^2 of 18.8% (Annex 4, Table 13), which was below the threshold prespecified in the protocol (>50%, although the few events in the third/fourth-line cohort may have impeded a correct estimation of heterogeneity), and the 4 cohorts were therefore pooled. When pooling the 4 treatment-line–specific cohorts, the estimated adjusted 36-month risk of fracture (95% CI) was 18.6% (12.9% to 25.7%) in the Ra-223 group and 9.9% (5.1% to 17.3%) in the comparator group, corresponding to a difference on the 36-month risk of 8.7% (95% CI, −0.1% to 17.1%) and an HR of 1.61 (95% CI, 0.96 to 3.02) (Annex 4, Table 14; Annex 5, Figure 5; see Annex 7, Supplementary Figure 5 for the unadjusted cumulative incidence curve).

10.4.2 All-cause mortality

In the first-line cohort, there were 111 deaths in the Ra-223 group and 128 deaths in the comparator group. The estimated adjusted 36-month mortality (95% CI) was 85.9% (76.1% to 94.3%) in the Ra-223 group and 72.8% (56.0% to 87.0%) in the comparator group, corresponding to a difference on the 36-month mortality of 13.0% (95% CI, −3.0% to 31.2%) and an HR of 1.63 (95% CI, 1.27 to 2.16) (Annex 4, Table 15; Annex 5, Figure 6; see Annex 7, Supplementary Figure 6 for the unadjusted mortality curve).

In the second-line cohort, there were 159 deaths in the Ra-223 group and 87 deaths in the comparator group. The estimated adjusted 36-month mortality (95% CI) was 86.7% (74.5% to 94.5%) in the Ra-223 group and 94.3% (80.4% to 100.0%) in the comparator group, corresponding to a difference on the 36-month mortality of −7.6% (95% CI, −22.9% to 7.4%) and an HR of 0.91 (95% CI, 0.60 to 1.23) (Annex 4, Table 16; Annex 5, Figure 7; see Annex 7, Supplementary Figure 7 for the unadjusted mortality curve)

In the third-line cohort, there were 120 deaths in the Ra-223 group and 43 deaths in the comparator group. In the fourth-line cohort, there were 47 deaths in the Ra-223 groups and 15 deaths in the comparator group. The estimated adjusted 36-month mortality (95% CI) for the third/fourth-line cohorts was 85.9% (77.7% to 92.3%) in the Ra-223 group and 99.7% (71.2% to 100.0%) in the comparator group, corresponding to a difference on the 36-month mortality of −13.7% (95% CI, −21.4% to 15.9%) and an HR of 0.72 (95% CI, 0.41 to 1.19) (Annex 4, Table 17, Annex 5, Figure 8; see Annex 7, Supplementary Figure 8 for the unadjusted mortality curve).

Evaluation of the heterogeneity of the effect of Ra-223 versus with the comparator on mortality by line of treatment yielded a I^2 of 62.8% (Annex 4, Table 13), which was above the threshold prespecified in the protocol (>50%). Therefore, pooling of the 4 treatment-line–specific cohorts was not appropriate to study all-cause mortality.

10.4.3 Prostate cancer–specific mortality

In the first-line cohort, there were 102 prostate cancer deaths in the Ra-223 group and 109 prostate cancer deaths in the comparator group. The estimated adjusted 36-month prostate cancer–specific mortality (95% CI) was 83.3% (72.3% to 92.9%) in the Ra-223 group and 67.9% (50.5% to 83.9%) in the comparator group, corresponding to a difference on the 36-month mortality of 15.4% (95% CI, −4.2% to 34.3%) and an HR of 1.83 (95% CI, 1.38 to 2.48) (Annex 4, Table 18; Annex 5, Figure 9; see Annex 7, Supplementary Figure 9 for the unadjusted prostate cancer–specific mortality curve)

In the second-line cohort, there were 144 prostate cancer deaths in the Ra-223 group and 82 prostate cancer deaths in the comparator group. The estimated adjusted 36-month prostate cancer–specific mortality (95% CI) was 85.0% (71.6% to 94.0%) in the Ra-223 group and 92.0% (72.8% to 100.0%) in the comparator group, corresponding to a difference on the 36-month mortality of −7.0% (95% CI, −23.5% to 13.7%) and an HR of 0.92 (95% CI, 0.59 to 1.29) (Annex 4, Table 19; Annex 5, Figure 10; see Annex 7, Supplementary Figure 10 for the unadjusted prostate cancer–specific mortality curve)

In the third-line cohort, there were 115 deaths in the Ra-223 group and 42 deaths in the comparator group. In the fourth-line cohort, there were 43 deaths in the Ra-223 group and 15 deaths in the comparator group. The estimated adjusted 36-month mortality (95% CI) for the third/fourth-line cohorts was 83.1% (74.8% to 90.7%) in the Ra-223 group and 99.6% (70.8% to 100.0%) in the comparator group, corresponding to a difference on the 36-month mortality of −16.5% (95% CI, −24.1% to 13.5%) and an HR of 0.72 (95% CI, 0.42 to 1.20) (Annex 4, Table 20; Annex 5, Figure 11; see Annex 7, Supplementary Figure 11 for the unadjusted prostate cancer–specific mortality curve)

10.5 Other analyses

10.5.1 Sensitivity analysis for unmeasured confounding

The first step for the sensitivity analysis for unmeasured confounding consisted of computing the E-value. The E-value was 1 by definition for all effect estimates on the HR scale, with the exception of all-cause mortality and prostate cancer–specific mortality in the first-line cohort, because the 95% CI included the null value [43]. In Annex 5, Figure 12 represents the value of the joint minimum strength of association on the HR scale that an unmeasured confounder must have with Ra-223 initiation and all-cause mortality to fully explain the observed treatment–outcome HR of 1.63 (95% CI, 1.27 to 2.16) in the first-line cohort. The E-value for this analysis is 3.71, i.e., the

observed HR of 1.63 for all-cause mortality could be explained away by an unmeasured confounder that was associated with both initiating Ra-223 and with death by a risk ratio of 3.71 each, above and beyond the measured confounders, but weaker confounding could not do so. In Annex 5, Figure 13 represents the value of the joint minimum strength of association on the HR scale that an unmeasured confounder must have with Ra-223 initiation and prostate cancer–specific mortality to fully explain the observed treatment–outcome HR of 1.83 (95% CI, 1.38 to 2.48) in the first-line cohort. The E-value for this analysis is 4.23, i.e., the observed HR of 1.83 for all-cause mortality could be explained away by an unmeasured confounder that was associated with both initiating Ra-223 and with prostate cancer death by a risk ratio of 4.23 each, above and beyond the measured confounders, but weaker confounding could not do so.

The second step for the sensitivity analysis for unmeasured confounding consisted of using a negative control outcome. There were 153 composite cardiovascular outcomes in the Ra-223 group, distributed as follows: 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 distributed as follows: 70 in the first-line cohort, 39 in the second-line cohort, 13 in the third-line cohort, and 3 in the fourth-line cohort. In the first-line cohort, the difference on the 36-month risk was 12.5% (95% CI, −2.3% to 25.3%) and the corresponding HR was 1.27 (95% CI, 0.80 to 1.87) (Annex 7, Supplementary Figure 12). In the second-line cohort, the difference on the 36-month risk was −5.2% (95% CI, −51.0% to 42.0%) and the corresponding HR was 1.15 (95% CI, 0.67 to 1.89) (Annex 7, Supplementary Figure 13). In the third/fourth-line cohorts, the difference on the 36-month risk was −54.1% (95% CI, −69.4% to 26.1%) and the corresponding HR was 0.56 (95% CI, 0.29 to 1.35) (Annex 7, Supplementary Figure 14).

10.5.2 Sensitivity analysis for the effect of information on bone metastasis

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 3 individuals from the Ra-223 group without recorded bone metastasis. In Annex 6, Supplementary Table 2 describes follow-up, outcomes, and censoring reasons in this population.

The estimated adjusted difference on the 36-month risk of bone fracture was 6.4% (95% CI, −6.4% to 18.1%) in the first-line cohort (Annex 6, Supplementary Table 3) and 7.7% (95% CI, −8.9% to 18.3%) in the second-line cohort (Annex 6, Supplementary Table 4). As in the main analysis, there was only 1 bone fracture in the comparator group of the third/fourth-line cohorts, precluding an informative estimation of the effect of Ra-223 versus the comparator group in this population (Annex 6, Supplementary Table 5 describes the unadjusted risks). When pooling the 4 treatment-line–specific cohorts, the estimated adjusted difference on the 36-month risk of bone fracture was 8.7% (95% CI, −8.7% to 15.7%) (Annex 6, Supplementary Table 6).

The estimated adjusted difference on the 36-month all-cause mortality was 12.9% (95% CI, −3.5% to 31.4%) in the first-line cohort (Annex 6, Supplementary Table 7), −7.6% (95% CI, −19.2% to 8.8%) in the second-line cohort (Annex 6, Supplementary Table 8), and −13.7% (95% CI, −21.7% to 17.0%) in the third/fourth-line cohorts (Annex 6, Supplementary Table 9).

The estimated adjusted difference on the 36-month prostate cancer–specific mortality was 15.4% (95% CI, −4.3% to 34.9%) in the first-line cohort (Annex 6, Supplementary Table 10), −7.0% (95% CI, −20.9% to 12.3%) in the second-line cohort (Annex 6, Supplementary Table 11), and −16.6% (95% CI, −24.2% to 16.2%) in the third/fourth-line cohorts (Annex 6, Supplementary Table 12).

10.5.3 Sensitivity analysis for the effect of Ra-223 alone or in combination

None in the study population combined Ra-223 with another treatment for mCRPC.

10.5.4 Sensitivity analysis using a potential follow-up of at least 18 months

In this sensitivity analysis, patients were eligible only through June 2017 to allow for a potential follow-up of at least 18 months. There were 454 patients in the Ra-223 group and 355 patients in the comparator group meeting this criterion. In Annex 6, Supplementary Table 13 describes the follow-up, outcomes, and censoring reasons in this population.

The estimated adjusted difference on the 36-month risk of bone fracture was 4.3% (95% CI, −13.1% to 23.6%) in the first-line cohort (Annex 6, Supplementary Table 14) and 4.7% (95% CI, −26.0% to 21.6%) in the second-line cohort (Annex 6, Supplementary Table 15). As in the main analysis, there was only 1 bone fracture in the comparator group of the third/fourth-line cohorts, precluding an informative estimation of the effect of Ra-223 versus the comparator group in this population (Annex 6, Supplementary Table 16 describes the unadjusted risks). When pooling the 4 treatment-line–specific cohorts, the estimated adjusted difference on the 36-month risk of bone fracture was 7.2% (95% CI, −4.0% to 15.7%) (Annex 6, Supplementary Table 17).

The estimated adjusted difference on the 36-month all-cause mortality was 11.1% (95% CI, −7.7% to 29.5%) in the first-line cohort (Annex 6, Supplementary Table 18), −5.5% (95% CI, −19.3% to 10.6%) in the second-line cohort (Annex 6, Supplementary Table 19), and −14.1% (95% CI, −20.4% to 14.7%) in the third/fourth line cohorts (Annex 6, Supplementary Table 20).

The estimated adjusted difference on the 36-month prostate cancer–specific mortality was 13.0% (95% CI, −8.0% to 33.6%) in the first-line cohort (Annex 6, Supplementary Table 21), −4.5% (95% CI, −18.0% to 13.4%) in the second-line cohort (Annex 6, Supplementary Table 22), and −17.0% (95% CI, −23.9% to 13.0%) in the third/fourth-line cohorts (Annex 6, Supplementary Table 23).

10.5.5 Sensitivity analysis letting individuals in the comparator group receive Ra-223 during the follow-up

There were 120 individuals in the comparator group that received Ra-223 as a subsequent line of treatment during the follow-up (69 in the first-line cohort, 36 in the second-line cohort, 12 in the third-line cohort, and 3 in the fourth-line cohort). Starting Ra-223 in the comparator group was treated as a censoring reason in the main analysis. This sensitivity analysis did not censor individuals in the comparator group if Ra-223 was initiated during the follow-up. In Annex 6, Supplementary Table 24 describes the follow-up, outcomes, and censoring reasons in this analysis.

The estimated adjusted difference on the 36-month risk of bone fracture was 4.1% (95% CI, −8.4% to 17.6%) in the first-line cohort (Annex 6, Supplementary Table 25) and 0.2% (95% CI, −31.0% to 15.3%) in the second-line cohort (Annex 6, Supplementary Table 26). As in the main analysis, there was only 1 bone fracture in the comparator group of the third/fourth-line cohorts, precluding an informative estimation of the effect of Ra-223 versus the comparator group in this population (Annex 6, Supplementary Table 27 describes the unadjusted risks). When pooling the 4 treatment-line–specific cohorts, the estimated adjusted difference on the 36-month risk of bone fracture was 7.3% (95% CI, −8.2% to 14.8%) (Annex 6, Supplementary Table 28).

The estimated adjusted difference on the 36-month all-cause mortality was 7.0% (95% CI, −7.0% to 20.8%) in the first-line cohort (Annex 6, Supplementary Table 29), −1.7% (95% CI, −17.2% to

11.0%) in the second-line cohort (Annex 6, Supplementary Table 30), and −7.8% (95% CI, −19.3 to 5.4%) in the third/fourth line cohorts (Annex 6, Supplementary Table 31).

The estimated adjusted difference on the 36-month prostate cancer–specific mortality was 8.4% (95% CI, −7.3% to 24.0%) in the first-line cohort (Annex 6, Supplementary Table 32), −1.6% (95% CI, −18.4% to 13.8%) in the second-line cohort (Annex 6, Supplementary Table 33), and −9.8% (95% CI, −21.6% to 7.6%) in the third/fourth line cohorts (Annex 6, Supplementary Table 34).

10.5.6 Analysis by subgroups of bone-health agents use at baseline

There were 230 (33.8%) individuals in the Ra-223 group (52 [25.6%] in the first-line cohort, 76 [31.8%] in the second-line cohort, 72 [40.0%] in the third-line cohort, and 30 [50.9%] in the fourth-line cohort) and 130 (17.3%) individuals in the comparator group (54 [12.5%] in the first-line cohort, 42 [19.6%] in the second-line cohort, 29 [35.4%] in the third-line cohort, and 5 [20.0%] in the fourth-line cohort) that were receiving bone-health agents at baseline (Annex 4, Table 7).

In Annex 7, Supplementary Figure 15 shows the unadjusted cumulative incidence of bone fractures by use of bone-health agents at baseline in the Ra-223 group. The unadjusted 36-month risk of fracture was 14.7% (95% CI, 6.0% to 27.5%) in those receiving bone-health agents at baseline (Annex 6, Supplementary Table 35) and 19.3% (95% CI, 13.8% to 24.9%) in those who did not (Annex 6, Supplementary Table 36).

In Annex 7, Supplementary Figure 16 shows the unadjusted cumulative incidence of bone fractures by use of bone-health agents at baseline in the comparator group. The unadjusted 36-month risk of fracture was 5.2% (95% CI, 1.1% to 10.6%) in those receiving bone-health agents at baseline (Annex 6, Supplementary Table 35) and 12.4% (95% CI, 5.9% to 24.3%) in those who did not (Annex 6, Supplementary Table 36).

10.6 Safety data (adverse events/adverse reactions)

Not applicable.

11. Discussion

11.1 Key results

The difference in the risk of bone fractures and mortality associated with the use of Ra-223 compared with other standard of care for mCRPC in a Swedish population, was estimated. Estimates obtained in the current study suggest that the difference in the risk of fractures is small, if any. A difference in the risk of mortality may be present in the first line of treatment, although it needs to be considered in the context of potential residual confounding, as suggested by the negative control outcome analysis.

In the current study, estimations of **fracture risk among Ra-223 users** in a real-world setting were in line with other studies of Ra-223 as monotherapy and markedly lower than a study of Ra-223 in combination with abiraterone and corticoids (ERA-223). In the ALSYMPCA randomised clinical trial, 8.8% of patients in the Ra-223 monotherapy arm had a bone fracture after a median follow-up of 9.1 months (Procedure No.: EMEA/H/A-20/1459/C/002653/0028. Xofigo (BAY 88-8223)/ Radium-223 dichloride Castration-Resistant Prostate Cancer Bayer Response to List of Outstanding Issues). The REASSURE study, a prospective observational cohort of patients treated with Ra-223

mostly as monotherapy (17% received concomitant enzalutamide, 15% received concomitant abiraterone, 2% received concomitant docetaxel, 1% received concomitant cabazitaxel and 1% received concomitant sipuleucel-T), reported that 5% of patients had a bone fracture after a median follow-up of 5.6 months [45]. The corresponding estimate in the current study was 9.1% after a median follow-up of 10.9 months in the pooled analysis of the 4 treatment-line–specific cohorts. In the ERA 223 trial, 26.4% of patients in the arm treated with Ra-223 and abiraterone plus prednisone/prednisolone had a bone fracture by month 12 [10]. In the current study, a 12-month risk of bone fracture of 9.9% (95% CI, 6.9% to 13.2%) was estimated in the pooled analysis of the 4 treatment-line–specific cohorts. Patients in the Ra-223 group using bone-health agents at baseline had a lower risk of fracture than those not using them. This was observed in the ERA 223 study [10], as well as in the PEACE-III study, a randomised clinical trial comparing Ra-223 plus enzalutamide versus enzalutamide alone, which mandated the use of bone-health agents after the findings of the ERA 223 study [46].

In the current study, estimations of **fracture risk in the comparator group** were lower than the risk reported in other studies. A study using SEER-Medicare linked data as a real-world data source reported, in a population of patients aged at least 65 years receiving treatment for castration-resistant prostate cancer other than Ra-223, the occurrence of incident fractures in 11.9% of the population after a mean follow-up of 10.6 months [47]. An EMA assessment report for enzalutamide reported a 10.3% risk of fractures among all patients receiving enzalutamide across 6 clinical trials. In the current study, the risk of fracture varied by line of treatment: 6.7% in the first-line cohort (median follow-up, 8.8 months), 2.8% in the second-line cohort (median follow-up, 7.5 months), 1.2% in the third-line cohort (median follow-up, 6.4 months), and 0% in the fourth-line cohort (median follow-up, 4.3 months). The observed low risk of fractures was unexpected in the comparator group, especially in later lines of treatment. The reasons behind this finding may be the short follow-up and possibly the fact that the PCBaSe captures only fractures that were diagnosed at in- or out-patient departments at hospitals and not primary care. Nevertheless, this last justification would also apply to the Ra-223 arm, where the risk estimates are in line with prior literature. To check if the data collection approach for Ra-223, which differed from the data collection for the comparator group, had any impact on the fracture risk estimates for Ra-223, an analysis was conducted that included only patients that were originally included in the PPC (i.e., without adding patients on Ra-223 by using medication distribution information from Bayer). In this analysis, 282 patients received Ra-223 as any line of treatment, and the risk of fracture was 11.4% after a median follow-up of 10.3 months. The small risk of fracture in the comparator groups needs to be taken into account when interpreting the effect estimates on the risk of fractures. As observed in the Ra-223 group, patients in the comparator group using bone-health agents at baseline had a lower risk of fracture than those not using them.

The **effect estimates** of Ra-223 on the **36-month risk of bone fractures** compared with other standard of care in the first and second lines of treatments were of small magnitude (risk difference of 6.5% in the first-line cohort and 7.6% in the second-line cohort, with 95% CIs that were consistent with no difference, and with both a slightly protective and a mildly deleterious effect: (−7.3% to 18.4% in the first-line cohort and −7.5% to 18.4% in the second-line cohort). Patients in the Ra-223 group had characteristics indicating worse bone health (prior fractures, use of bone-health agents, alkaline phosphatase), which were measured and adjusted for in analyses. Nevertheless, if any of these variables was measured with error or if there were unmeasured common causes for initiating Ra-223 and risk of fracture (e.g., the number of bone metastases, bone density), the effect estimate may not correspond to a true causal effect. Additionally, if patients in

the Ra-223 group receive more bone imaging surveillance than the comparator group, asymptomatic or paucisymptomatic fractures will be diagnosed more often. Given the apparent protection of bone-health agents on the incidence of fractures in both study groups, a lower incidence of fractures may have been observed had the use of bone-health agents been more prevalent in the study population. The occurrence of a single event in the comparator group of the third-line cohort and no events in the fourth-line cohort precluded an adjusted analysis with informative CIs for these later lines of treatment.

The effect estimates of Ra-223 on the **36-month OS** compared with other standard of care in the first line of treatment corresponded to a 13.0% difference on risk of mortality, with a CI consistent with no difference, a slightly protective effect and with a harmful effect (95% CI, −3.0% to 31.2%). On a relative scale, the HR was 1.63 (95% CI, 1.27 to 2.16). Harmful effect point estimates for OS were not found in later lines of treatment on either an absolute or a relative scale. Of note, Ra-223 as monotherapy for a first line of treatment versus the standard of care in fit patients (i.e., second-generation antiandrogens or chemotherapy) does not meet the principle of equipoise and hence has not been addressed in randomised clinical trials. Ra-223 is not used as a first-line treatment except in selected patients, probably because they are not eligible for other systemic mCRPC treatments. Yet, that is the comparison performed in this analysis. Patients who received Ra-223 monotherapy as a first-line treatment during the current study period in routine clinical practice are likely frail and have a higher bone metastatic burden than patients who receive chemotherapy or second-generation antiandrogens as a first-line treatment. An analysis of 285 patients treated with Ra-223 as standard care in the Netherlands reported that only 10% received it as a first line of treatment [48]. Although the PCBaSe has information on relevant prognostic factors like haemoglobin, alkaline phosphatase, PSA, ECOG performance status [49], and treatment line [50], we argue that these factors do not surrogate frailty with sufficient precision. To further characterise the possibility of unmeasured confounding, a negative control outcome analysis was performed. It showed an increased risk of cardiovascular events in the first line, similar incidence in the second line, and lower incidence in the third and fourth lines comparing Ra-223 with the comparator arm. Because Ra-223 is not known to affect cardiovascular outcomes, these findings reflect differences in the treatment groups that remain after the statistical adjustment was implemented, i.e., residual confounding. Because the confounders for cardiovascular events and death (e.g., smoking, overweight, blood pressure, diabetes, cholesterol, physical activity, alcohol) are likely different from those of fractures (e.g., time on ADT, steroids, history of prior fractures), this negative control outcome analysis does not inform the presence of unmeasured confounding in the bone fractures analysis.

11.2 Limitations

The pivotal trial ALSYMPCA [3] included patients that “had received docetaxel, were not healthy enough or declined to receive it, or it was not available.” Therefore, it is likely that in real practice, patients receiving Ra-223 as a first line of treatment for mCRPC (which is frequently docetaxel) are frailer than those who do not. In addition, second-generation antiandrogens, (e.g., enzalutamide and abiraterone acetate) have been introduced at the same time as Ra-223 and are considered standard of care in the first line, especially in patients with low volume and asymptomatic disease. Whereas Ra-223 is reserved for patients with symptomatic bone metastases, i.e., regular use of analgesic medication or need for treatment with external beam radiation therapy for cancer-related bone pain, Ra-223 may be preferred by patients with severe comorbidities because of its treatment schedule, which consists of up to 6 injections, and its favourable side effects profile. The PCBaSe allows for a comprehensive characterisation of patients when they start treatment (including ECOG performance

status), and the analyses were conducted by line of treatment, which is one of the main prognostic factors in this patient population [50]. Additionally, Ra-223 is a drug with a favourable safety profile, which may lead to selective prescribing to frailer patients, with the potential for residual confounding. Although an exhaustive list of potential confounders was used, results from the negative control outcome analysis suggested that some residual confounding may exist in the survival analyses. Inverse-probability-of-treatment weighting was used to adjust for baseline and postbaseline variables. This method was chosen because, based on previous observational research on prostate cancer [34], it is likely that the following 2 conditions were met: (1) there exists a time-dependent covariate that is both a risk factor for the outcome and also predicts subsequent exposure and (2) past exposure history predicts the risk factor. For example, evolution of PSA fulfils these 2 conditions. When these conditions are met, traditional regression-based approaches (e.g., time-dependent Cox proportional hazards models) are biased, as opposed to g-methods like inverse-probability-of-treatment weighting [38].

The precision of the observed effect estimates for the difference in the risk of fractures or death is not optimal, and the main reasons are the reduction in sample size in the comparator group required to avoid the immortal time bias described in Section 8.2, as well as the short follow-up observed in later lines of treatment in the comparator group. At the study design stage, the option of pooling, whenever appropriate, and the stabilisation of the weights were considered to improve precision of the analyses. The inclusion of more patients in the PPC (e.g., the PPD and other centres) was an attempt to improve precision while preserving the external validity because the added patients should not differ appreciably from those originally included in the PPC, either in the pattern of care or in the way data are collected and managed. Although the PPC does not capture all Ra-223 use in Sweden, the capture is high (60%-70%), and the NPCR and, specifically the PPC, are representative of the Swedish population of prostate cancer patients [22, 26]. The use of additional databases may have helped to improve precision, but, as described in Section 9.2, the following European data sources were systematically explored and none were considered suitable, mainly because lack of appropriate information on Ra-223 dispensing or administration: the System National de Données de Santé database in France, the Dutch PHARMO Database Network and associated registries, the CPRD database in the United Kingdom, the German Cancer Registry, the Swiss NICER database, the EpiChron database in Spain, Denmark's national population registries and the databases from the Toscana and Lombardy regional health.

This study lacks validation of the main outcome, bone fractures, in an outpatient setting. Nevertheless, bone fractures in the inpatient setting identified in the National Patient Register via ICD-10 codes have been validated and are correct up to the third digit of the code in over 90% of the cases [29]. Additionally, patients in general and in particular those with prostate cancer and symptomatic bone fractures are expected to seek medical care. Given the almost complete capture of national healthcare registries, it is safe to assume virtually all clinically relevant fractures requiring medical attention were captured in the In- and Out-Patient Register that was used in the PCBaSe. However, approximately 20% of the fractures identified during the clinical trials of Ra-223 were asymptomatic and were diagnosed through imaging for another purpose. This study was not able to capture any fracture that did not have a diagnosis recorded in the inpatient or outpatient hospital setting; thus, it is likely that none of these asymptomatic fractures were captured. Repeated diagnoses of fracture at the same site in the same patient (using the precision offered by the fourth character of the ICD-10 codes) for the same patient were reviewed, and those happening within 90 days of each other were considered a single event. This was the situation for 5 fracture diagnoses.

Cause of death is available in the PCBaSe with a reporting lag of a few months and annual updates in October for the deaths that occurred during the prior calendar year. Therefore, the study period covers the time for which available data include cause of death. Information on the site of progression (e.g., bone, visceral) is not available in the PCBaSe and cannot be analysed. Results from the ERA 223 study suggested that the risk of fractures with Ra-223, when added to abiraterone, was increased in patients with less than 6 bone metastases. Unfortunately, the number of metastases is not available in the PCBaSe, and these subgroups were not explored.

11.3 Interpretation

Despite the limitations discussed in Section 11.2, this study provides information on the risk of bone fractures associated with the use of Ra-223 compared with a standard of care comparator drug in a real-world setting. Because the risk of fracture in the comparator group was lower than expected based on prior literature, it may be argued that the results of the current study are the upper bound estimates of the effect of Ra-223 on bone fractures. The results on survival (both all-cause and prostate cancer–specific) need to be interpreted with caution in the context of the potential for residual confounding.

11.4 Generalisability

The findings of the current study apply to patient populations with access to similar healthcare systems and a similar distribution of disease characteristics.

12. Other information

Not applicable.

13. Conclusion

Using real-world data, the risk of fractures in patients receiving Ra-223 as monotherapy was similar to the risk observed in other observational studies and clinical trials.

The effect estimates for the cumulative incidence of bone fractures do not point to a large difference and were compatible with a small, if any, increase in the risk associated with Ra-223 use versus a comparator in the first and second lines of treatment. The 95% CI around the effect estimates are consistent with no difference, and with both a small increase and a small decrease in the 36-month fracture incidence difference.

A decreased risk of mortality associated with Ra-223 use was observed in the second- and third/fourth-line cohorts, where Ra-223 is predominantly used in clinical practice. A moderately increased risk of all-cause and prostate cancer–specific mortality were associated with Ra-223 use in the first-line cohort. The observed associations in survival need to be interpreted with caution because of the likelihood of unmeasured confounding.

The results of this study do not change the current benefit-risk assessment of Ra-223. In the context of the EU referral procedure under Article 20 of Regulation (EC) No. 726/2004 (EMEA/H/A-20/1459/C/002653/0028), the PASS PRECISE study was recommended to provide further safety data in addition to the ongoing RADIANT trial. This trial is a double-blind multicentre RCT study (EudraCT Number 2019-000476-42) that will provide data to adequately characterise the safety and efficacy of Ra-223.

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Appendices

Annex 1: List of stand-alone documents

None

Annex 2: Additional information

None

Annex 3: Signature pages

Signature Page – Principal Investigator

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Report version and date	v1.0, 14 JUN 2021
IMPACT study number	20437
Study type / Study phase	Observational, Phase IV PASS ☒ YES Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS33448
Medicinal product / Active substance	Xofigo®, Ra-223
Comparator / Reference therapy	Docetaxel, abiraterone, enzalutamide, cabazitaxel, and other chemotherapies that are standard of care in Sweden
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 16 June 2021. PPD

Signature Page – OS Lead Statistician and Analyst

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 2021-06-16, PPD

Signature Page – OS Conduct Responsible

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Print Name: PPD

Date, Signature: 16 June 2021, PPD

Signature Page – OS Safety Lead

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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 15.6.2021, PPD

Signature Page – OS Medical Expert

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD PPD

Date, Signature: June 15, 2021 _____

Signature Page – OS Regulatory Affairs Responsible and MAH Contact Person

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 16.6.'21, PPD

Signature Page – OS Epidemiologist

Title	PRECISE/Rates of bone fractures and survival in metastatic castration-resistant PRostate cancer (mCRPC) PatiEnts treated with Radium 223 in routine Clinical practIce in SwedEn
Report version and date	v1.0, 14 JUN 2021
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 16/June/2021, PPD

Signature Page – OS Statistician and Analyst

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Print Name: PPD

Date, Signature: 16 June 2021, PPD

Annex 4: Tables

Table 3: Cohort attrition for the patients receiving a first line of treatment for metastatic castration-resistant prostate cancer

Criterion	N
Patients diagnosed with mCRPC registered in PCBaSe at any time between November 2013 and December 2018	1,771
AND started a first line of treatment for mCRPC (baseline)	994
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
AND had bone metastasis at baseline[a]	831

mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; 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.

Table 4: Cohort attrition for the patients receiving a second line of treatment for metastatic castration-resistant prostate cancer

Criterion	N
Patients diagnosed with mCRPC registered in PCBaSe at any time between November 2013 and December 2018	1,771
AND started a second line of treatment for mCRPC (baseline)	741
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	701
AND had not received radium-223 before baseline	620
AND had bone metastasis at baseline[a]	591

mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; 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.

Table 5: Cohort attrition for the patients receiving a third line of treatment for metastatic castration-resistant prostate cancer

Criterion	N
Patients diagnosed with mCRPC registered in PCBaSe at any time between November 2013 and December 2018	1,771
AND started a third line of treatment for mCRPC (baseline)	469
And have not participated in a RCT (involving radium-223 or not, for which unblinded information on the assigned treatment is not available) in the past or at baseline	438
AND had not received radium-223 before baseline	348
AND had bone metastasis at baseline[a]	341

mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; 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.

Table 6: Cohort attrition for the patients receiving a fourth line of treatment for metastatic castration-resistant prostate cancer

Criterion	N
Patients diagnosed with mCRPC registered in PCBaSe at any time between November 2013 and December 2018	1,771
AND started a fourth line of treatment for mCRPC (baseline)	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	185
AND had not received radium-223 before baseline	113
AND had bone metastasis at baseline[a]	107

mCRPC = metastatic castration-resistant prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; 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.

Table 7: Baseline characteristics, by treatment and treatment line

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
Age, years										
Mean (SD)	74.02 (7.46)	75.08 (7.89)	74.27 (7.93)	73.28 (6.31)	71.58 (6.52)	73.50 (7.62)	74.50 (7.96)	72.68 (7.02)	71.57 (6.60)	69.59 (6.54)
Median (Q1, Q3)	PPD									
Min, Max										
<65, n (%)	79 (11.60)	24 (11.82)	27 (11.30)	18 (10.00)	10 (16.95)	105 (13.94)	51 (11.81)	30 (14.02)	15 (18.29)	9 (36.00)
65-69, n (%)	111 (16.30)	27 (13.30)	41 (17.15)	30 (16.67)	13 (22.03)	131 (17.40)	75 (17.36)	39 (18.22)	14 (17.07)	3 (12.00)
70-74, n (%)	177 (25.99)	42 (20.69)	61 (25.52)	57 (31.67)	17 (28.81)	204 (27.09)	100 (23.15)	68 (31.78)	29 (35.37)	7 (28.00)
75-80, n (%)	165 (24.23)	52 (25.62)	46 (19.25)	53 (29.44)	14 (23.73)	166 (22.05)	101 (23.38)	45 (21.03)	15 (18.29)	5 (20.00)
80+, n (%)	149 (21.88)	58 (28.57)	64 (26.78)	22 (12.22)	5 (8.47)	147 (19.52)	105 (24.31)	32 (14.95)	9 (10.98)	1 (4.00)
Calendar year at cohort entry										
Nov 2013-2014, n (%)	11 (1.62)	1 (0.49)	4 (1.67)	3 (1.67)	3 (5.08)	4 (0.53)	3 (0.69)	1 (0.47)	0 (0.00)	0 (0.00)
2015, n (%)	143 (21.00)	39 (19.21)	38 (15.90)	43 (23.89)	23 (38.98)	64 (8.50)	28 (6.48)	25 (11.68)	9 (10.98)	2 (8.00)
2016, n (%)	182 (26.73)	43 (21.18)	70 (29.29)	51 (28.33)	18 (30.51)	157 (20.85)	98 (22.69)	38 (17.76)	16 (19.51)	5 (20.00)
2017, n (%)	214 (31.42)	81 (39.90)	76 (31.80)	49 (27.22)	8 (13.56)	248 (32.93)	144 (33.33)	69 (32.24)	27 (32.93)	8 (32.00)
2018, n (%)	131 (19.24)	39 (19.21)	51 (21.34)	34 (18.89)	7 (11.86)	280 (37.18)	159 (36.81)	81 (37.85)	30 (36.59)	10 (40.00)

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
Months from prostate cancer diagnosis to baseline										
Mean (SD)	76.21 (54.85)	60.76 (55.45)	75.73 (56.34)	87.55 (48.77)	96.76 (50.32)	70.92 (53.08)	66.36 (55.65)	75.37 (50.73)	83.32 (46.72)	70.93 (37.15)
Median (Q1, Q3)	63.47 (29.93, 113.61)	38.44 (17.08, 94.88)	59.86 (29.59, 110.13)	78.41 (48.65, 116.58)	80.69 (55.66, 138.66)	55.72 (26.68, 105.30)	47.31 (20.86, 97.88)	63.51 (31.57, 108.70)	75.55 (45.81, 114.23)	56.97 (47.15, 80.79)
Min, Max	1.25, 242.69	1.25, 227.15	8.38, 242.69	11.70, 230.54	25.23, 213.65	3.71, 241.31	3.71, 241.31	8.97, 225.51	16.82, 197.36	22.83, 150.18
Skeletal-related events before baseline[a], n (%)	350 (51.40)	85 (41.87)	118 (49.37)	109 (60.56)	38 (64.41)	308 (40.90)	138 (31.94)	103 (48.13)	51 (62.20)	16 (64.00)
History of fractures, n (%)	133 (19.53)	46 (22.66)	35 (14.64)	38 (21.11)	14 (23.73)	129 (17.13)	62 (14.35)	38 (17.76)	22 (26.83)	7 (28.00)
T stage										
T1, n (%)	131 (19.24)	35 (17.24)	51 (21.34)	35 (19.44)	10 (16.95)	146 (19.39)	88 (20.37)	35 (16.36)	18 (21.95)	5 (20.00)
T2, n (%)	202 (29.66)	67 (33.00)	76 (31.80)	48 (26.67)	11 (18.64)	236 (31.34)	131 (30.32)	74 (34.58)	25 (30.49)	6 (24.00)
T3, n (%)	286 (42.00)	83 (40.89)	93 (38.91)	76 (42.22)	34 (57.63)	315 (41.83)	183 (42.36)	87 (40.65)	34 (41.46)	11 (44.00)
T4, n (%)	62 (9.10)	18 (8.87)	19 (7.95)	21 (11.67)	4 (6.78)	56 (7.44)	30 (6.94)	18 (8.41)	5 (6.10)	3 (12.00)
N stage										
N0, n (%)	155 (22.76)	55 (27.09)	55 (23.01)	34 (18.89)	11 (18.64)	161 (21.38)	101 (23.38)	46 (21.50)	12 (14.63)	2 (8.00)
N1, n (%)	91 (13.36)	29 (14.29)	30 (12.55)	29 (16.11)	3 (5.08)	142 (18.86)	73 (16.90)	41 (19.16)	17 (20.73)	11 (44.00)
NX, n (%)	435 (63.88)	119 (58.62)	154 (64.44)	117 (65.00)	45 (76.27)	450 (59.76)	258 (59.72)	127 (59.35)	53 (64.63)	12 (48.00)

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
M stage										
M0, n (%)	385 (56.53)	104 (51.23)	129 (53.97)	114 (63.33)	38 (64.41)	475 (63.08)	260 (60.19)	143 (66.82)	57 (69.51)	15 (60.00)
M1, n (%)	296 (43.47)	99 (48.77)	110 (46.03)	66 (36.67)	21 (35.59)	278 (36.92)	172 (39.81)	71 (33.18)	25 (30.49)	10 (40.00)
Gleason Grade										
Gleason ≤6/WHO grade = 1, n (%)	80 (11.75)	14 (6.90)	39 (16.32)	18 (10.00)	9 (15.25)	111 (14.74)	64 (14.81)	28 (13.08)	14 (17.07)	5 (20.00)
Gleason = 7/WHO grade = 2, n (%)	208 (30.54)	56 (27.59)	70 (29.29)	62 (34.44)	20 (33.90)	255 (33.86)	143 (33.10)	77 (35.98)	30 (36.59)	5 (20.00)
Gleason >7/WHO grade = 3, n (%)	393 (57.71)	133 (65.52)	130 (54.39)	100 (55.56)	30 (50.85)	387 (51.39)	225 (52.08)	109 (50.93)	38 (46.34)	15 (60.00)
ECOG performance status										
0, n (%)	269 (39.50)	97 (47.78)	82 (34.31)	72 (40.00)	18 (30.51)	318 (42.23)	205 (47.45)	80 (37.38)	26 (31.71)	7 (28.00)
1, n (%)	305 (44.79)	77 (37.93)	115 (48.12)	80 (44.44)	33 (55.93)	300 (39.84)	155 (35.88)	100 (46.73)	38 (46.34)	7 (28.00)
2, n (%)	100 (14.68)	25 (12.32)	41 (17.15)	26 (14.44)	8 (13.56)	124 (16.47)	69 (15.97)	29 (13.55)	16 (19.51)	10 (40.00)
3, n (%)	7 (1.03)	4 (1.97)	1 (0.42)	2 (1.11)	0 (0.00)	11 (1.46)	3 (0.69)	5 (2.34)	2 (2.44)	1 (4.00)
Prostate-specific antigen										
Mean (SD)	267.57 (828.09)	159.70 (335.77)	348.40 (1280.07)	287.93 (501.26)	249.17 (279.96)	190.56 (445.87)	159.78 (354.39)	202.89 (493.57)	266.82 (672.12)	366.71 (465.16)
Median (Q1, Q3)	91.00 (32.00, 260.00)	55.00 (20.00, 135.50)	92.00 (33.00, 297.50)	106.00 (43.00, 288.50)	153.00 (81.00, 324.00)	64.00 (22.00, 170.00)	57.05 (22.00, 144.25)	63.00 (20.18, 181.25)	110.00 (24.75, 227.50)	170.00 (63.00, 610.00)
Min, Max	0.20, 18,773.00	0.20, 3486.00	0.40, 18,773.00	0.83, 3244.00	0.41, 1707.00	0.08, 5900.00	0.52, 3082.00	0.08, 5900.00	0.10, 5700.00	8.80, 1809.00

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
Haemoglobin, g/L										
Mean (SD)	125.14 (15.46)	125.45 (15.04)	124.47 (15.45)	126.42 (16.13)	123.08 (14.99)	125.88 (15.02)	127.41 (15.22)	124.54 (14.14)	125.31 (15.29)	113.76 (11.45)
Median (Q1, Q3)	126.00 (116.00, 136.00)	126.50 (115.75, 137.00)	125.00 (115.75, 134.25)	128.00 (118.50, 137.00)	126.00 (112.00, 133.50)	127.00 (115.00, 136.00)	129.00 (118.00, 137.00)	126.00 (114.00, 135.00)	125.00 (113.75, 137.00)	112.00 (106.00, 122.00)
Min, Max	68.00, 170.00	68.00, 159.00	79.00, 170.00	78.00, 169.00	90.00, 151.00	82.00, 165.00	82.00, 165.00	93.00, 156.00	83.00, 161.00	94.00, 136.00
Alkaline phosphatase, µkat/L										
Mean (SD)	4.87 (7.27)	5.09 (6.11)	4.89 (7.63)	5.04 (8.76)	3.53 (3.31)	3.55 (4.25)	3.87 (4.83)	3.03 (3.29)	3.18 (3.18)	3.82 (3.63)
Median (Q1, Q3)	2.50 (1.50, 5.05)	2.60 (1.60, 5.90)	2.60 (1.40, 5.10)	2.30 (1.33, 4.80)	2.25 (1.60, 4.00)	2.05 (1.40, 3.70)	2.15 (1.40, 3.90)	2.00 (1.40, 3.60)	2.00 (1.30, 3.78)	2.50 (1.60, 4.20)
Min, Max	0.40, 73.00	0.80, 44.00	0.40, 70.00	0.50, 73.00	0.70, 19.10	0.60, 35.00	0.70, 35.00	0.60, 23.50	0.60, 21.00	0.80, 16.10
Osteoporosis diagnosis										
Yes, n (%)	4 (0.59)	2 (0.99)	0 (0.00)	1 (0.56)	1 (1.69)	1 (0.13)	1 (0.23)	0 (0.00)	0 (0.00)	0 (0.00)
Charlson Comorbidity Index										
0, n (%)	424 (62.26)	122 (60.10)	142 (59.41)	122 (67.78)	38 (64.41)	463 (61.49)	265 (61.34)	131 (61.21)	50 (60.98)	17 (68.00)
1, n (%)	138 (20.26)	46 (22.66)	48 (20.08)	31 (17.22)	13 (22.03)	135 (17.93)	76 (17.59)	37 (17.29)	17 (20.73)	5 (20.00)
2, n (%)	66 (9.69)	20 (9.85)	28 (11.72)	12 (6.67)	6 (10.17)	87 (11.55)	48 (11.11)	26 (12.15)	12 (14.63)	1 (4.00)
3+, n (%)	53 (7.78)	15 (7.39)	21 (8.79)	15 (8.33)	2 (3.39)	68 (9.03)	43 (9.95)	20 (9.35)	3 (3.66)	2 (8.00)
Visceral metastasis, n (%)	28 (4.11)	5 (2.46)	11 (4.60)	7 (3.89)	5 (8.47)	105 (13.94)	41 (9.49)	33 (15.42)	22 (26.83)	9 (36.00)
Lymph node metastasis, n (%)	176 (25.84)	36 (17.73)	64 (26.78)	59 (32.78)	17 (28.81)	323 (42.90)	158 (36.57)	102 (47.66)	48 (58.54)	15 (60.00)
Other site of metastasis, n (%)	22 (3.23)	3 (1.48)	12 (5.02)	5 (2.78)	2 (3.39)	43 (5.71)	18 (4.17)	15 (7.01)	8 (9.76)	2 (8.00)

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
Prior diagnosed of other cancer, n (%)	27 (3.96)	11 (5.42)	11 (4.60)	4 (2.22)	1 (1.69)	39 (5.18)	24 (5.56)	11 (5.14)	3 (3.66)	1 (4.00)
History of spinal cord compression, n (%)	11 (1.62)	2 (0.99)	3 (1.26)	4 (2.22)	2 (3.39)	10 (1.33)	4 (0.93)	6 (2.80)	0 (0.00)	0 (0.00)
Current use of bone-health agents, n (%)	230 (33.77)	52 (25.62)	76 (31.80)	72 (40.00)	30 (50.85)	130 (17.26)	54 (12.50)	42 (19.63)	29 (35.37)	5 (20.00)
Current use of steroids, n (%)	207 (30.40)	25 (12.32)	70 (29.29)	77 (42.78)	35 (59.32)	408 (54.18)	171 (39.58)	153 (71.50)	64 (78.05)	20 (80.00)
Time on bone-health agents										
Mean (SD)	3.48 (7.94)	1.47 (3.57)	3.46 (8.67)	4.96 (9.65)	5.98 (8.48)	1.77 (4.89)	1.08 (4.42)	1.86 (4.06)	4.66 (7.10)	3.62 (6.34)
Median (Q1, Q3)	0.00 (0.00, 3.91)	0.00 (0.00, 0.53)	0.00 (0.00, 3.93)	1.31 (0.00, 6.90)	1.31 (0.00, 7.33)	0.00 (0.00, 0.46)	0.00 (0.00, 0.00)	0.00 (0.00, 1.31)	1.31 (0.00, 6.90)	0.00 (0.00, 6.90)
Min, Max	0.00, 84.99	0.00, 23.95	0.00, 79.08	0.00, 84.99	0.00, 31.90	0.00, 65.15	0.00, 65.15	0.00, 24.77	0.00, 34.69	0.00, 29.93
Months on androgen-deprivation therapy b										
Mean (SD)	38.36 (29.54)	25.58 (26.58)	37.08 (26.57)	49.38 (31.24)	53.92 (25.70)	31.77 (27.63)	27.89 (28.50)	35.07 (27.32)	39.02 (21.67)	46.86 (18.39)
Median (Q1, Q3)	28.94 (16.69, 54.70)	15.84 (9.64, 29.31)	27.20 (18.97, 49.31)	39.41 (27.59, 67.15)	52.17 (34.83, 68.44)	22.74 (12.94, 40.80)	18.64 (10.15, 33.04)	27.61 (18.33, 41.13)	38.29 (22.42, 47.75)	42.97 (36.53, 53.75)
Min, Max	0.00, 147.61	0.00, 130.23	0.00, 146.63	0.00, 147.61	0.00, 109.21	0.00, 149.16	0.00, 149.16	0.00, 138.94	0.00, 101.06	19.84, 81.18
Prior radiation therapy, n (%)	406 (59.62)	96 (47.29)	142 (59.41)	125 (69.44)	43 (72.88)	384 (51.00)	171 (39.58)	135 (63.08)	57 (69.51)	21 (84.00)

Characteristic	Radium-223 arm					Comparator arm				
	All (N = 681)	**Line 1 (N = 203)**	**Line 2 (N = 239)**	**Line 3 (N = 180)**	**Line 4 (N = 59)**	**All (N = 753)**	**Line 1 (N = 432)**	**Line 2 (N = 214)**	**Line 3 (N = 82)**	**Line 4 (N = 25)**
Prior systemic therapy[c], n (%)										
Docetaxel	250 (52.30)	0 (0.00)	62 (25.94)	132 (73.33)	56 (94.92)	156 (48.60)	0 (0.00)	76 (35.51)	62 (75.61)	18 (72.00)
Cabazitaxel	60 (12.55)	0 (0.00)	1 (0.42)	20 (11.11)	39 (66.10)	22 (6.85)	0 (0.00)	2 (0.93)	7 (8.54)	13 (52.00)
Abiraterone	181 (37.87)	0 (0.00)	50 (20.92)	85 (47.22)	46 (77.97)	111 (34.58)	0 (0.00)	48 (22.43)	43 (52.44)	20 (80.00)
Enzalutamide	262 (54.81)	0 (0.00)	121 (50.63)	110 (61.11)	31 (52.54)	151 (47.04)	0 (0.00)	82 (38.32)	47 (57.32)	22 (88.00)
Others	22 (4.60)	0 (0.00)	5 (2.09)	12 (6.67)	5 (8.47)	13 (4.05)	0 (0.00)	6 (2.80)	5 (6.10)	2 (8.00)
Baseline systemic therapy, n (%)										
Docetaxel						102 (13.55)	66 (15.28)	33 (15.42)	3 (3.66)	0 (0.00)
Cabazitaxel						60 (7.97)	3 (0.69)	24 (11.21)	25 (30.49)	8 (32.00)
Abiraterone						186 (24.70)	120 (27.78)	51 (23.83)	12 (14.63)	3 (12.00)
Enzalutamide						343 (45.55)	240 (55.56)	81 (37.85)	20 (24.39)	2 (8.00)
Others						62 (8.23)	3 (0.69)	25 (11.68)	22 (26.83)	12 (48.00)

ECOG = Eastern Cooperative Oncology Group; NA = not applicable; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
[a] Includes bone fracture, spinal cord compression and bone-targeted radiotherapy.
[b] Includes both surgical and chemical castration.
[c] Percentages are computed over the number of patients starting a second, third, or fourth line of treatment.

Table 8: Cycles and duration of treatment received after baseline, by treatment and treatment line

Line of treatment	Radium-223 arm[a]		Comparator arm	
	Weeks of treatment	N	Weeks of treatment	N
All treatment lines				
Radium-223	0.00	0	0.00	120
Docetaxel	184.77	49	72.54	14
Cabazitaxel	285.93	76	145.12	46
Abiraterone	384.69	63	308.70	41
Enzalutamide	1,634.23	187	407.16	56
Others	344.64	67	314.74	59
First-line treatment				
Radium-223	0.00	0	0.00	69
Docetaxel	114.17	29	58.02	9
Cabazitaxel	57.00	17	60.32	21
Abiraterone	237.44	36	219.89	29
Enzalutamide	861.80	101	348.25	45
Others	57.43	12	65.51	16
Second-line treatment				
Radium-223	0.00	0	0.00	36
Docetaxel	54.54	17	14.52	5
Cabazitaxel	99.52	24	43.73	16
Abiraterone	118.11	19	74.81	10
Enzalutamide	513.84	53	35.09	10
Others	109.86	18	146.56	25
Third-line treatment				
Radium-223	0.00	0	0.00	12
Docetaxel	16.07	3	0.00	0
Cabazitaxel	114.76	30	19.25	8
Abiraterone	29.14	8	14.00	2
Enzalutamide	159.80	22	23.82	1
Others	121.56	26	94.03	14
Fourth-line treatment				
Radium-223	0.00	0	0.00	3
Docetaxel	0.00	0	0.00	0
Cabazitaxel	14.65	5	21.82	1
Abiraterone	0.00	0	0.00	0
Enzalutamide	98.79	11	0.00	0
Others	55.79	11	8.64	4

[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.

Table 9: Cohort follow-up, censoring reasons, and outcomes, by treatment and treatment line: complete-case analyses

Treatment line	Radium-223 arm	Comparator arm
All treatment lines		
N	681	753
Person-months of follow-up, sum	9,236.63	7,462.14
Median follow-up (Q1, Q3), months	10.87 (6.54, 18.56)	7.95 (4.14, 13.34)
Minimum, maximum follow-up, months	0.33, 47.11	0.10, 49.08
Artificially censored[a], n (%)	0 (0.00)	120 (15.94)
Censored because they were alive at the end of December 2018, n (%)	243 (35.68)	360 (47.81)
Had a bone fracture during study follow-up, n (%)	62 (9.10)	36 (4.78)
Dead because of prostate cancer, n (%)	404 (59.32)	248 (32.93)
Dead from any cause, n (%)	437 (64.17)	273 (36.25)
First-line treatment		
N	203	432
Person-months of follow-up, sum	3,016.74	4,763.37
Median follow-up (Q1, Q3), months	13.08 (7.10, 20.48)	8.77 (4.67, 15.38)
Minimum, maximum follow-up, months	0.33, 44.55	0.10, 49.08
Artificially censored[a], n (%)	0 (0.00)	69 (15.97)
Censored because they were alive at the end of December 2018, n (%)	92 (45.32)	235 (54.40)
Had a bone fracture during study follow-up, n (%)	15 (7.39)	29 (6.71)
Dead because of prostate cancer, n (%)	102 (50.25)	109 (25.23)
Dead from any cause, n (%)	111 (54.68)	128 (29.63)
Second-line treatment		
N	239	214
Person-months of follow-up, sum	3,020.32	1,929.99
Median follow-up (Q1, Q3), months	10.12 (6.14, 17.63)	7.51 (3.84, 12.34)
Minimum, maximum follow-up, months	0.36, 46.19	0.39, 45.93
Artificially censored[a], n (%)	0 (0.00)	36 (16.82)
Censored because they were alive at the end of December 2018, n (%)	80 (33.47)	91 (42.52)
Had a bone fracture during study follow-up, n (%)	25 (10.46)	6 (2.80)
Dead because of prostate cancer, n (%)	144 (60.25)	82 (38.32)
Dead from any cause, n (%)	159 (66.53)	87 (40.65)
Third-line treatment		
N	180	82
Person-months of follow-up, sum	2,353.51	638.39
Median follow-up (Q1, Q3), months	10.50 (6.36, 17.91)	6.42 (3.67, 10.02)
Minimum, maximum follow-up, months	0.36, 42.74	0.10, 32.33
Artificially censored[a], n (%)	0 (0.00)	12 (14.63)
Censored because they were alive at the end of December 2018, n (%)	60 (33.33)	27 (32.93)
Had a bone fracture during study follow-up, n (%)	16 (8.89)	1 (1.22)
Dead because of prostate cancer, n (%)	115 (63.89)	42 (51.22)
Dead from any cause, n (%)	120 (66.67)	43 (52.44)

Treatment line	Radium-223 arm	Comparator arm
Fourth-line treatment		
N	59	25
Person-months of follow-up, sum	846.06	130.40
Median follow-up (Q1, Q3), months	11.17 (6.88, 17.86)	4.27 (2.76, 6.34)
Minimum, maximum follow-up, months	1.61, 47.11	0.10, 13.11
Artificially censored[a], n (%)	0 (0.00)	3 (12.00)
Censored because they were alive at the end of December 2018, n (%)	11 (18.64)	7 (28.00)
Had a bone fracture during study follow-up, n (%)	6 (10.17)	0 (0.00)
Dead because of prostate cancer, n (%)	43 (72.88)	15 (60.00)
Dead from any cause, n (%)	47 (79.66)	15 (60.00)

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.

Table 10: Adjusted cumulative incidence of bone fractures, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	42.33 (14.56 to 80.96)	75.64 (32.01 to 132.11)	105.19 (48.16 to 183.20)	132.41 (65.71 to 221.45)	158.41 (77.23 to 261.17)	184.11 (82.00 to 317.78)	1.14 (0.50 to 2.15)
Comparator (95% CI)	45.03 (27.34 to 65.60)	71.63 (49.13 to 99.00)	89.71 (60.44 to 123.09)	102.51 (64.95 to 146.53)	111.96 (66.26 to 177.79)	119.19 (66.32 to 216.54)	
Difference (95% CI)	−2.69 (−35.82 to 40.84)	4.01 (−44.31 to 61.40)	15.48 (−49.68 to 89.99)	29.90 (−55.37 to 119.99)	46.45 (−60.76 to 149.37)	64.92 (−72.93 to 183.91)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Table 11: Adjusted cumulative incidence of bone fractures, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	57.63 (27.50 to 94.07)	120.97 (69.88 to 183.47)	154.21 (87.69 to 224.00)	162.27 (90.51 to 241.16)	163.16 (90.81 to 243.32)	163.20 (90.93 to 244.13)	1.86 (0.62 to 10.93)
Comparator (95% CI)	32.98 (3.57 to 90.33)	66.53 (10.78 to 170.33)	82.82 (14.23 to 187.75)	86.42 (14.69 to 201.41)	86.78 (14.84 to 208.44)	86.79 (14.84 to 212.36)	
Difference (95% CI)	24.65 (−44.32 to 73.33)	54.44 (−57.12 to 141.63)	71.39 (−50.78 to 172.16)	75.85 (−58.08 to 184.14)	76.38 (−69.08 to 184.10)	76.41 (−74.53 to 184.16)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Table 12: Unadjusted cumulative incidence of bone fractures, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up					
	6 months	12 months	18 months	24 months	30 months	36 months
Radium-223 (95% CI)	40.78 (17.42 to 72.93)	92.87 (51.88 to 155.09)	145.03 (90.54 to 220.61)	184.30 (110.95 to 265.35)	206.78 (114.16 to 314.73)	216.57 (114.44 to 361.53)
Comparator (95% CI)	6.14 (0.00 to 21.07)	15.86 (0.00 to 60.26)	27.95 (0.00 to 108.53)	39.17 (0.00 to 147.92)	47.00 (0.00 to 200.16)	51.09 (0.00 to 248.03)

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Table 13: Evaluation of the heterogeneity of the effect by line of treatment

Line of treatment	12-month adjusted risk difference of bone fractures (95% CI)	I^2 statistic[a]	12-month adjusted risk difference of death (95% CI)	I^2 statistic[a]
First line	4.01 (−44.31 to 61.40)	18.83	167.04 (67.34 to 273.24)	62.79
Second line	54.44 (−57.12 to 141.63)		−12.35 (−167.14 to 115.57)	
Third/fourth line	75.30 (9.89 to 140.74)		−45.27 (−281.54 to 158.58)	

CI = confidence interval.
[a] The I^2 statistic describes the percentage of variation across lines of treatments that is due to heterogeneity rather than chance

Table 14: Adjusted cumulative incidence of bone fractures, pooled analysis of all 4 treatment-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	46.52 (29.28 to 66.16)	99.42 (69.26 to 132.37)	144.02 (100.89 to 189.98)	170.74 (119.42 to 228.61)	182.16 (126.87 to 247.21)	185.63 (128.62 to 257.29)	1.61 (0.96 to 3.02)
Comparator (95% CI)	34.41 (17.81 to 51.02)	64.81 (37.70 to 92.83)	85.07 (47.95 to 124.99)	94.63 (50.33 to 150.20)	97.82 (50.62 to 162.98)	98.57 (50.71 to 173.45)	
Difference (95% CI)	12.10 (−12.48 to 37.22)	34.60 (−5.93 to 78.75)	58.95 (2.21 to 123.44)	76.11 (4.77 to 150.51)	84.34 (0.54 to 165.13)	87.06 (−1.48 to 170.64)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Table 15: Adjusted all-cause mortality, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	207.93 (145.73 to 301.80)	429.71 (343.99 to 533.65)	539.51 (452.28 to 635.04)	653.64 (582.58 to 731.09)	763.71 (685.03 to 841.74)	858.51 (760.94 to 943.10)	1.63 (1.27 to 2.16)
Comparator (95% CI)	133.13 (104.98 to 167.37)	262.67 (215.70 to 315.09)	379.71 (316.77 to 436.76)	500.28 (413.92 to 573.19)	618.81 (504.75 to 727.65)	728.39 (559.77 to 870.07)	
Difference (95% CI)	74.80 (3.85 to 168.25)	167.04 (67.34 to 273.24)	159.81 (60.41 to 268.70)	153.36 (57.12 to 257.86)	144.91 (30.50 to 269.00)	130.12 (−29.67 to 312.33)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Table 16: Adjusted all-cause mortality, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	210.18 (155.72 to 266.47)	482.39 (390.84 to 563.39)	630.04 (514.55 to 716.66)	735.93 (618.02 to 816.50)	812.03 (687.88 to 889.58)	866.57 (745.18 to 944.95)	0.91 (0.60 to 1.23)
Comparator (95% CI)	212.35 (144.63 to 311.53)	494.74 (384.19 to 606.49)	672.97 (549.57 to 777.43)	801.84 (681.28 to 892.37)	888.87 (760.48 to 983.40)	942.99 (803.80 to 999.65)	
Difference (95% CI)	−2.16 (−108.88 to 78.49)	−12.35 (−167.14 to 115.57)	−42.93 (−193.17 to 97.29)	−65.91 (−215.73 to 87.53)	−76.84 (−236.59 to 80.73)	−76.42 (−229.23 to 73.80)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Table 17: Adjusted all-cause mortality, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	179.39 (131.33 to 233.32)	498.28 (427.79 to 586.57)	671.55 (598.31 to 762.00)	767.04 (697.58 to 840.31)	823.67 (750.29 to 885.51)	859.31 (776.51 to 922.91)	0.72 (0.41 to 1.19)
Comparator (95% CI)	367.79 (210.94 to 495.96)	543.55 (348.80 to 782.46)	621.41 (406.61 to 862.44)	765.67 (579.93 to 952.03)	931.04 (693.43 to 999.99)	996.52 (711.80 to 1,000.00)	
Difference (95% CI)	−188.40 (−325.86 to −26.30)	−45.27 (−281.54 to 158.58)	50.15 (−196.14 to 305.14)	1.37 (−202.74 to 210.82)	−107.36 (−205.83 to 133.83)	−137.22 (−214.48 to 159.49)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Table 18: Adjusted prostate cancer–specific mortality, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	198.00 (136.84 to 294.28)	412.07 (325.47 to 518.74)	519.56 (432.53 to 618.30)	630.39 (550.07 to 714.78)	737.83 (646.45 to 826.33)	832.73 (723.15 to 929.01)	1.83 (1.38 to 2.48)
Comparator (95% CI)	102.77 (77.97 to 132.65)	217.81 (173.96 to 263.58)	335.36 (269.13 to 392.68)	454.44 (366.88 to 525.74)	570.57 (448.63 to 682.69)	678.71 (505.23 to 839.28)	
Difference (95% CI)	95.23 (27.82 to 185.44)	194.26 (95.08 to 301.89)	184.20 (82.37 to 289.27)	175.95 (73.35 to 286.88)	167.26 (34.13 to 312.08)	154.02 (−42.19 to 342.79)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Table 19: Adjusted prostate cancer–specific mortality, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	194.69 (139.04 to 253.70)	450.24 (358.80 to 534.45)	595.75 (477.92 to 684.86)	705.75 (584.15 to 792.17)	788.35 (658.40 to 872.58)	849.63 (716.27 to 939.93)	0.92 (0.59 to 1.29)
Comparator (95% CI)	212.27 (144.27 to 307.19)	463.59 (359.22 to 581.46)	614.61 (496.61 to 729.87)	744.55 (624.02 to 860.15)	847.18 (681.79 to 977.78)	919.53 (728.42 to 999.64)	
Difference (95% CI)	−17.58 (−125.30 to 65.19)	−13.35 (−171.71 to 116.29)	−18.86 (−182.02 to 125.29)	−38.80 (−205.02 to 116.67)	−58.83 (−234.68 to 116.08)	−69.89 (−234.68 to 137.48)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

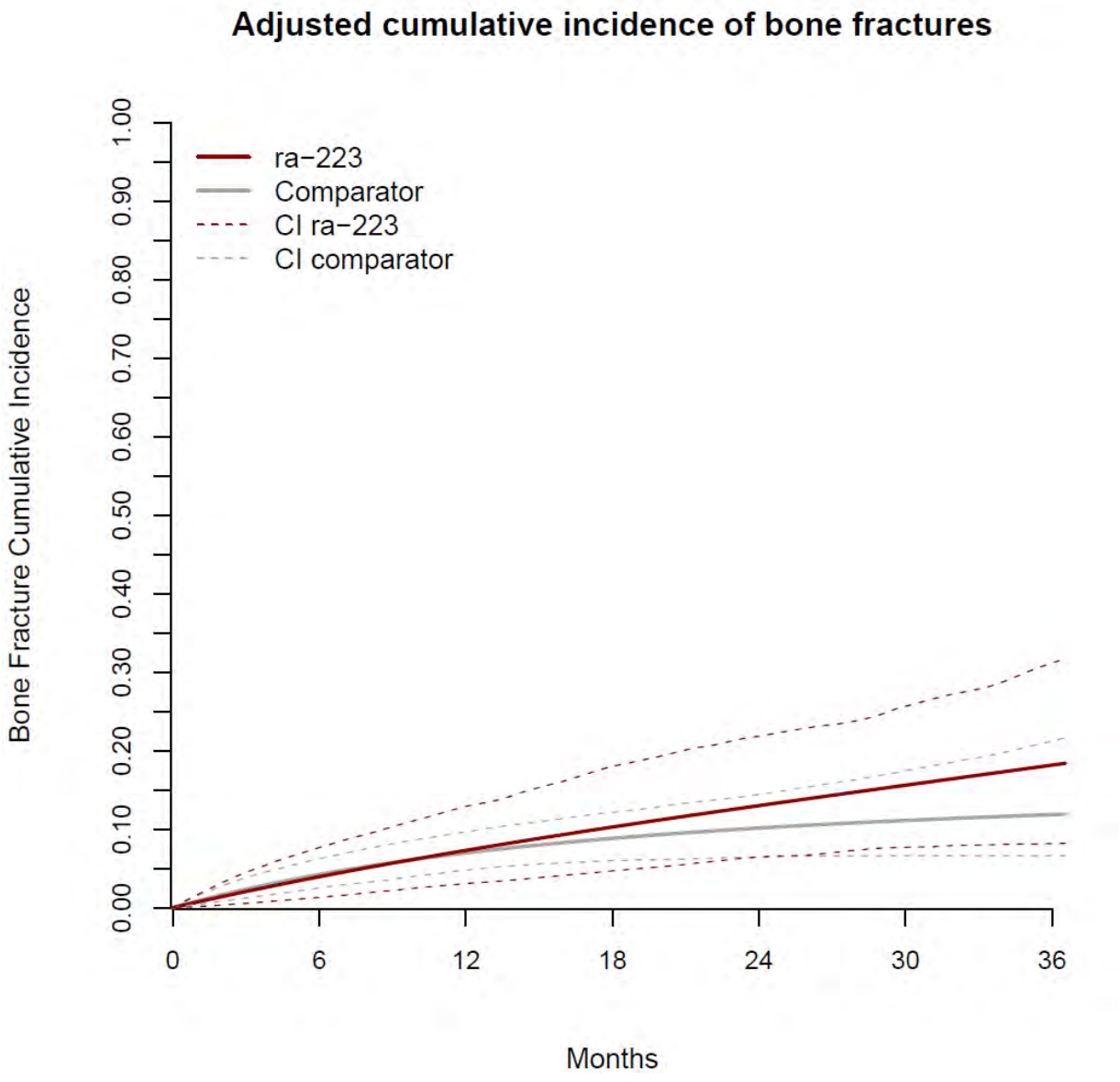
Table 20: Adjusted prostate cancer–specific mortality, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	172.46 (124.55 to 225.44)	489.12 (418.32 to 576.34)	656.04 (583.99 to 749.24)	745.70 (678.29 to 826.87)	798.06 (724.20 to 870.52)	830.62 (748.41 to 907.44)	0.72 (0.42 to 1.20)
Comparator (95% CI)	348.39 (192.86 to 471.69)	516.98 (316.98 to 761.18)	602.12 (390.70 to 859.05)	755.16 (557.62 to 946.76)	926.88 (677.35 to 999.98)	995.93 (708.37 to 1,000.00)	
Difference (95% CI)	−175.93 (−309.44 to −18.13)	−27.86 (−262.24 to 184.63)	53.92 (−203.33 to 311.09)	−9.46 (−218.48 to 211.28)	−128.82 (−230.93 to 124.69)	−165.31 (−240.87 to 134.85)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

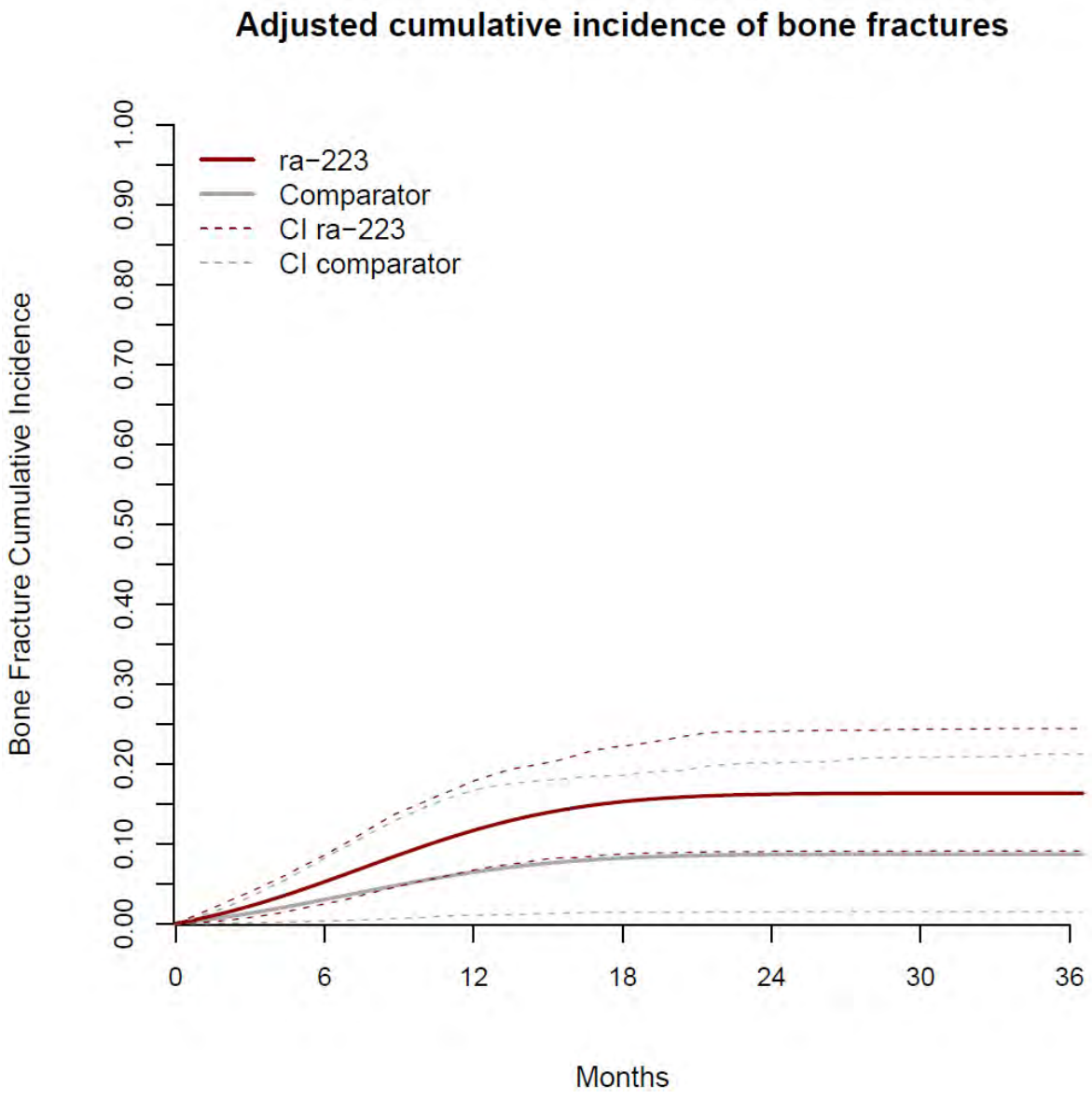
Annex 5: Figures

Figure 2: **Adjusted cumulative incidence of bone fractures, first-line cohort**



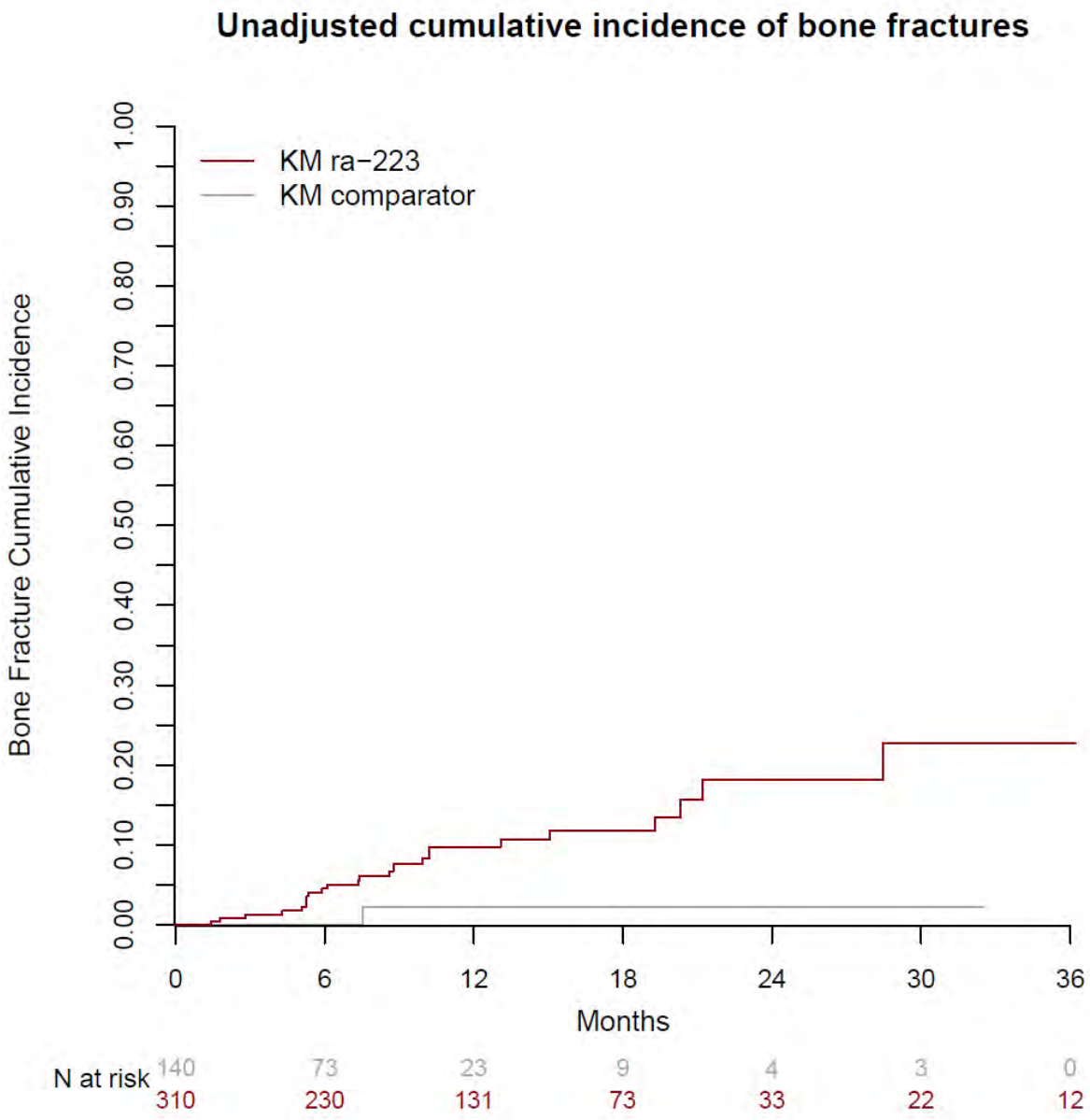
CI = confidence interval; Ra-223 = radium 223.

Figure 3: **Adjusted cumulative incidence of bone fractures, second-line cohort**



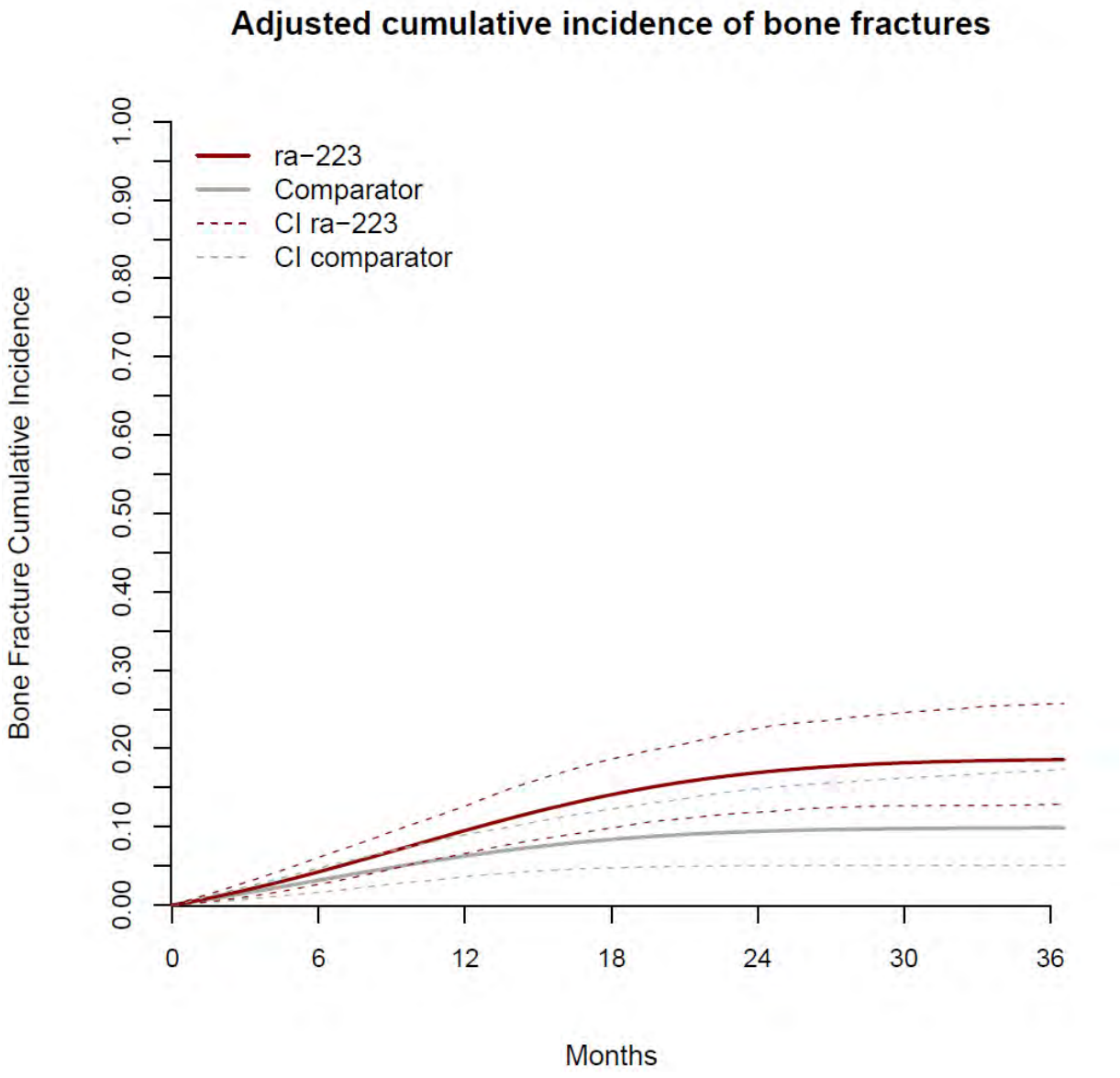
CI = confidence interval; Ra-223 = radium 223.

Figure 4: **Unadjusted cumulative incidence of bone fractures, third- and fourth-line cohorts combined**



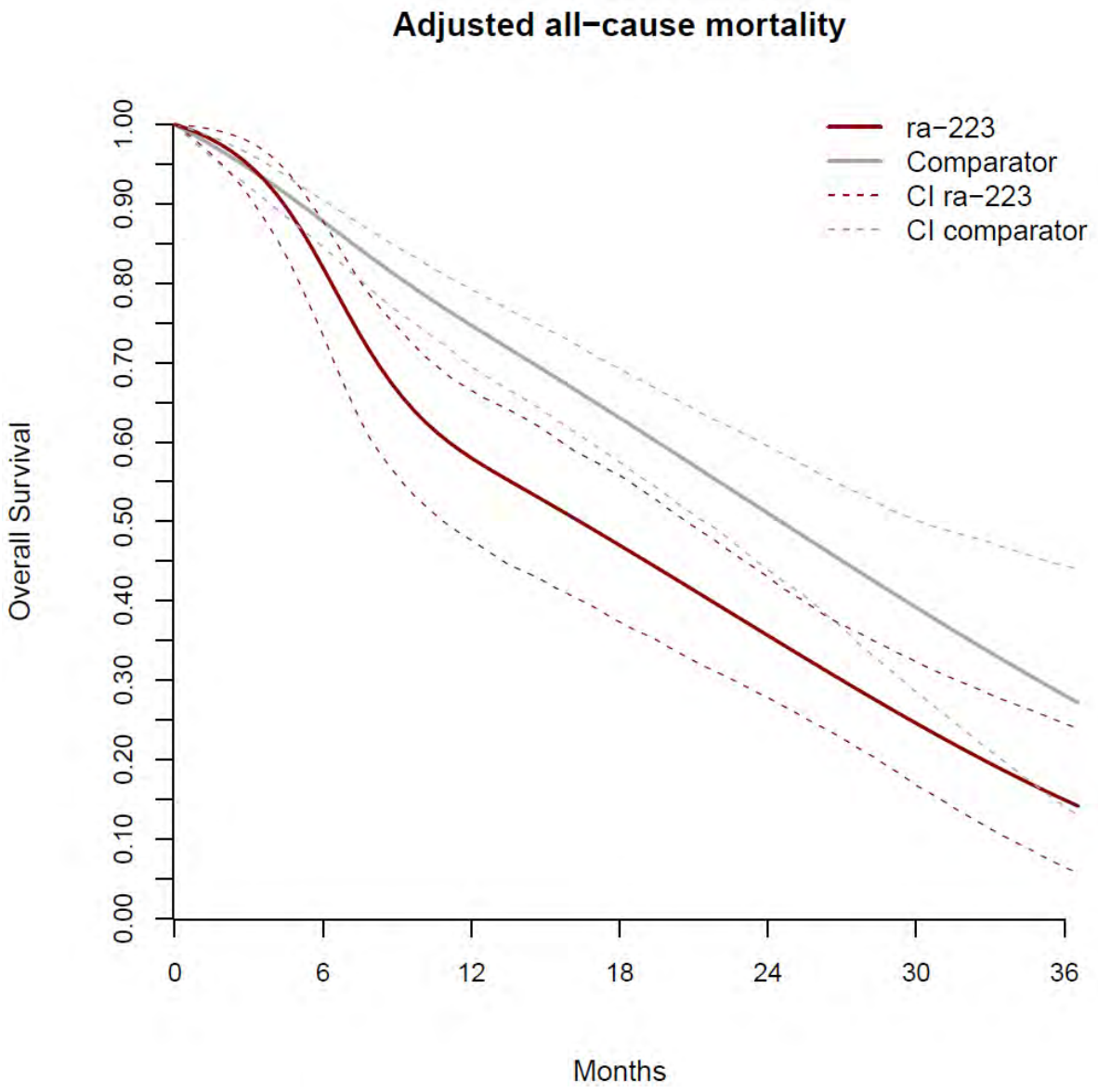
KM = Kaplan-Meier survival curves; Ra-223 = radium 223.

Figure 5: **Adjusted cumulative incidence of bone fractures, pooled analysis of all 4 treatment-line cohorts**



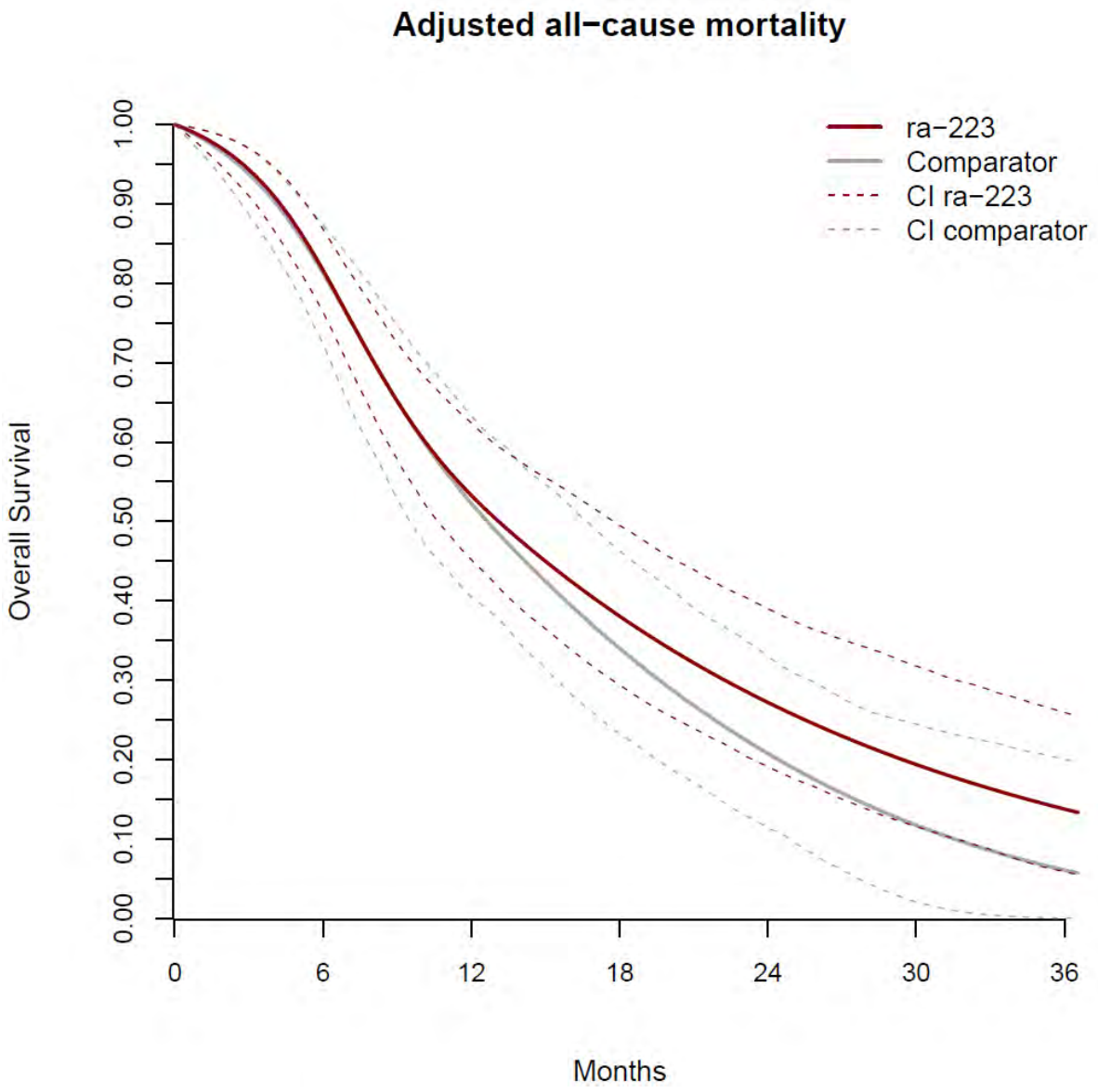
CI = confidence interval; Ra-223 = radium 223.

Figure 6: **Adjusted all-cause mortality, first-line cohort**



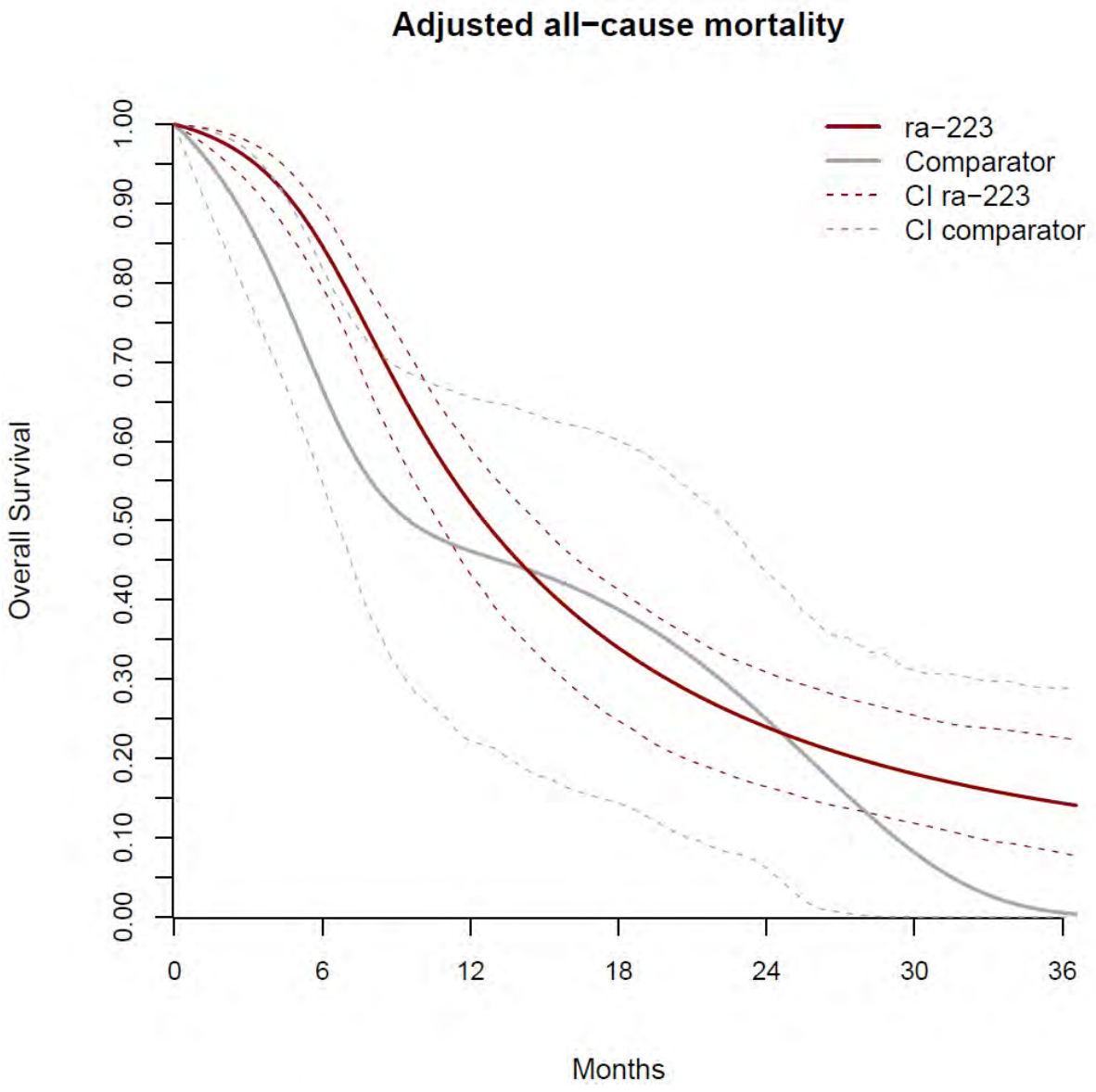
CI = confidence interval; Ra-223 = radium 223.

Figure 7: **Adjusted all-cause mortality, second-line cohort**



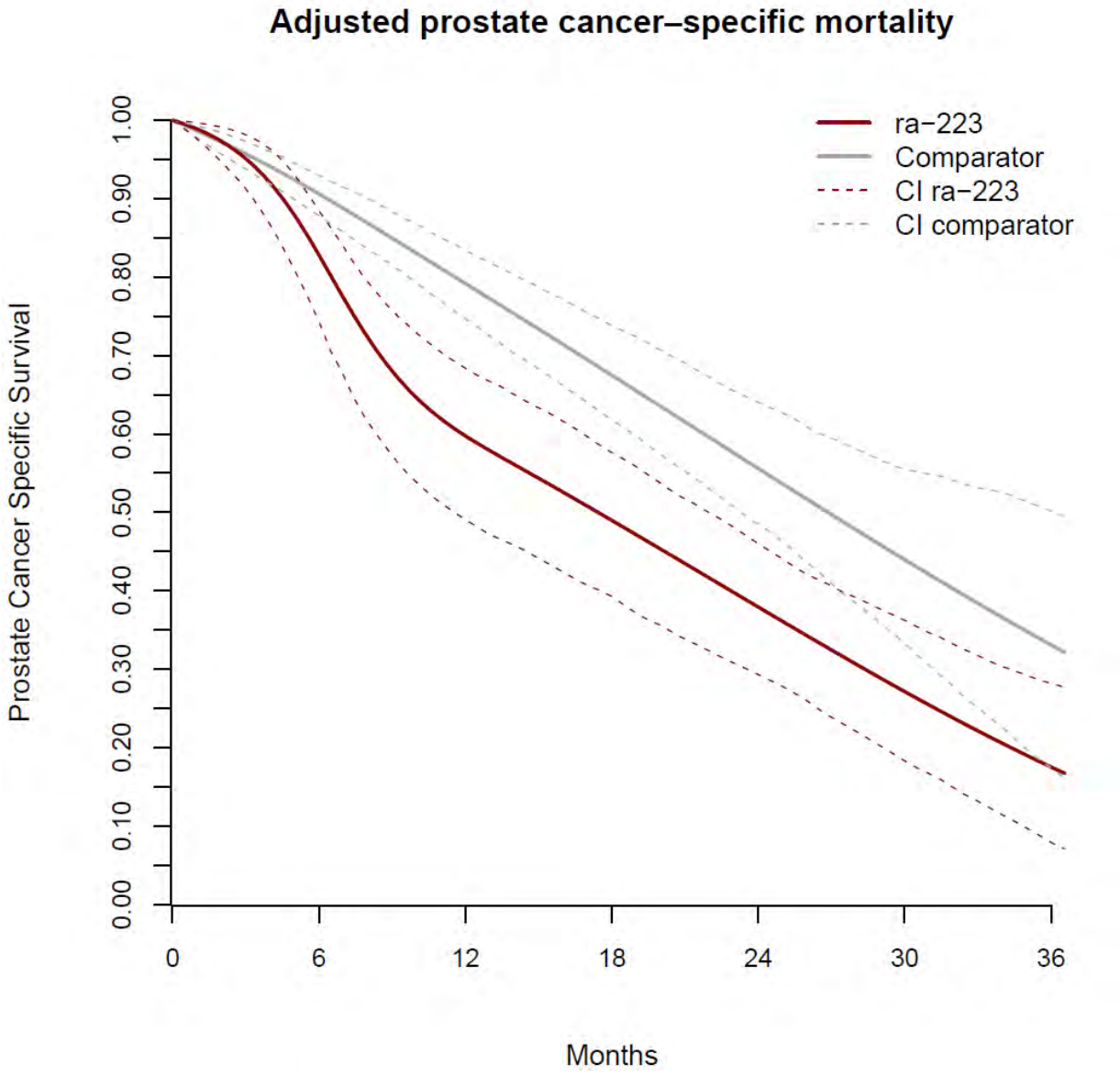
CI = confidence interval; Ra-223 = radium 223.

Figure 8: **Adjusted all-cause mortality, third- and fourth-line cohorts combined**



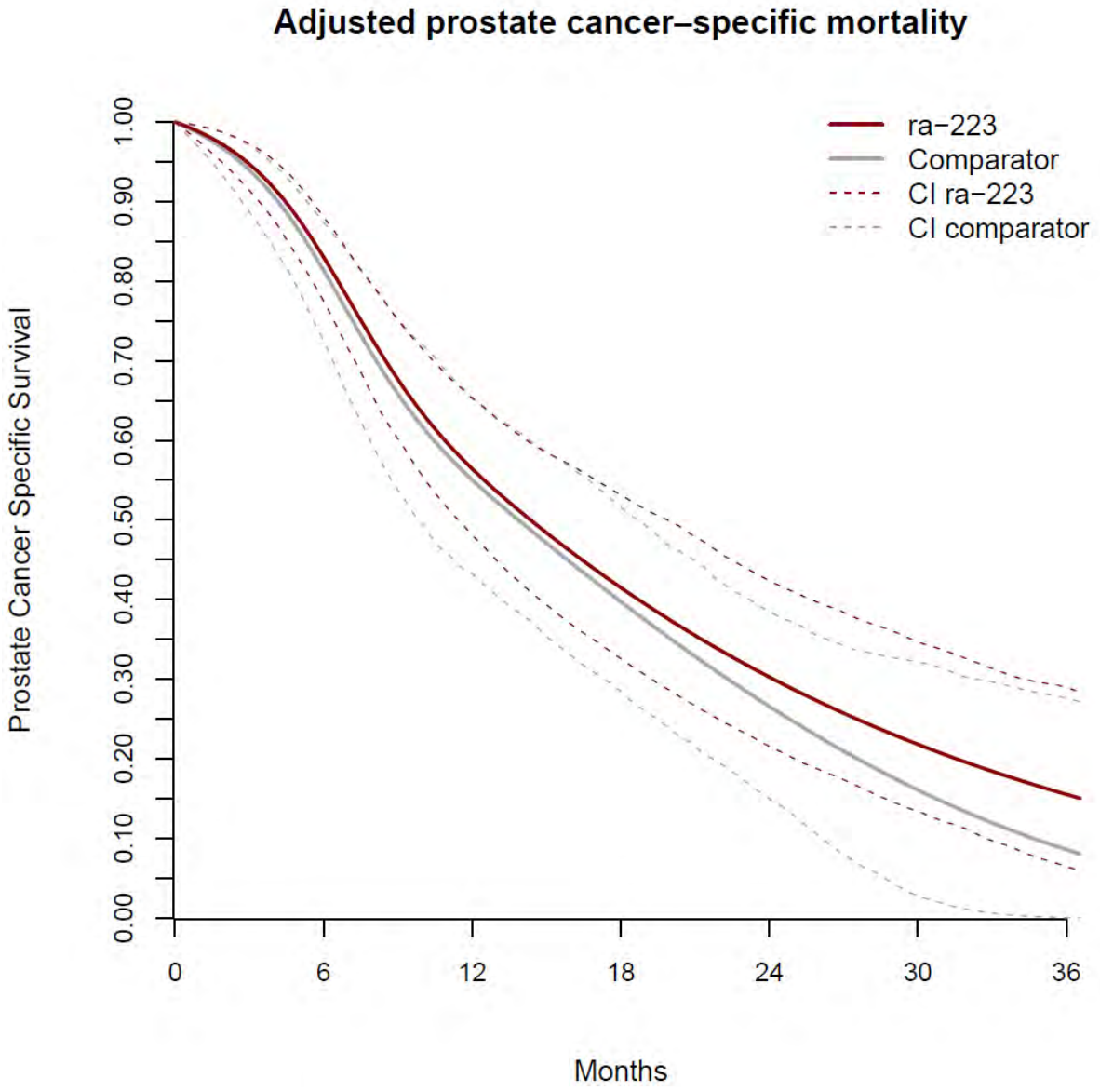
CI = confidence interval; Ra-223 = radium 223.

Figure 9: **Adjusted prostate cancer–specific mortality, first-line cohort**



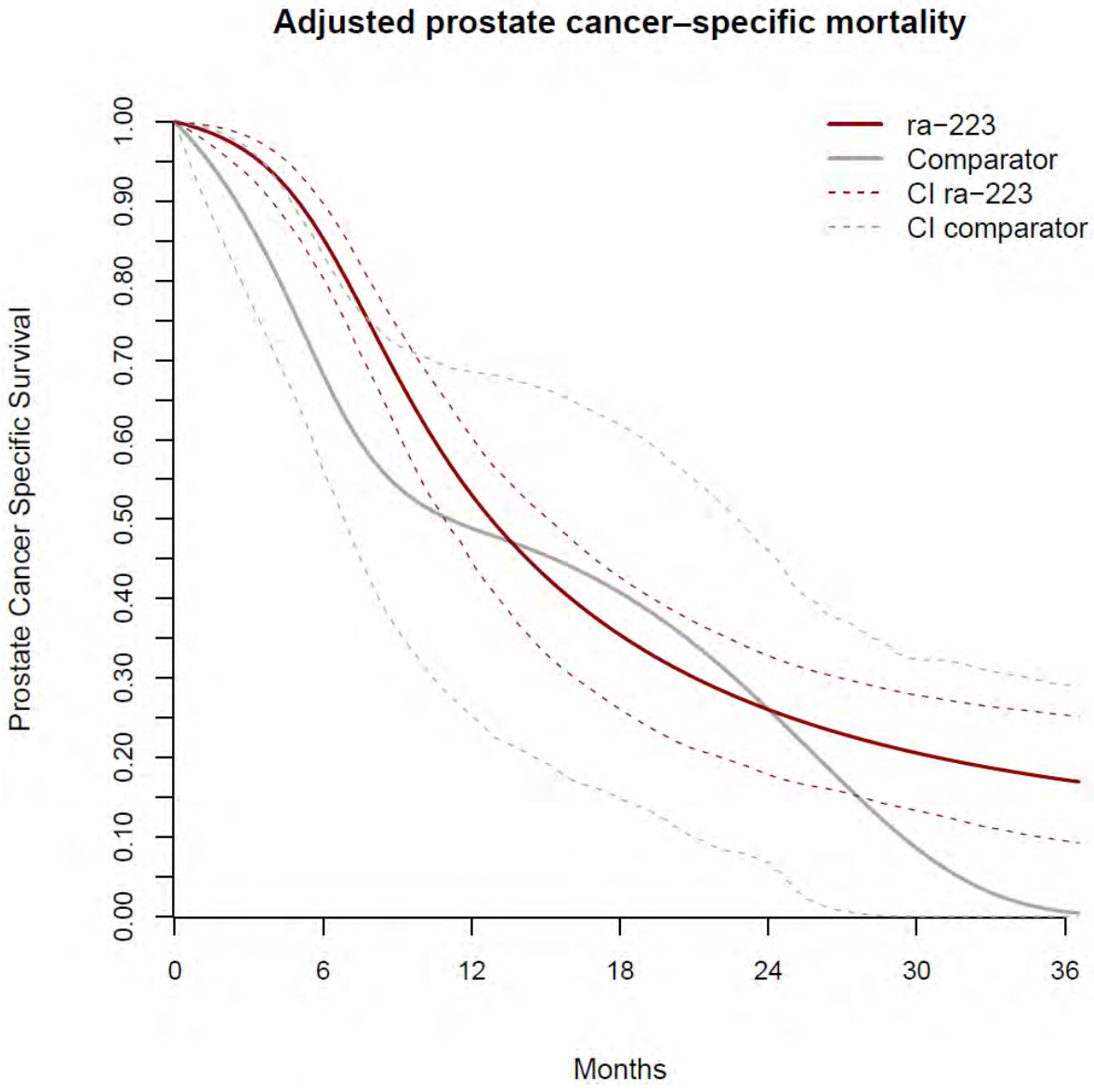
CI = confidence interval; Ra-223 = radium 223.

Figure 10: **Adjusted prostate cancer–specific mortality, second-line cohort**



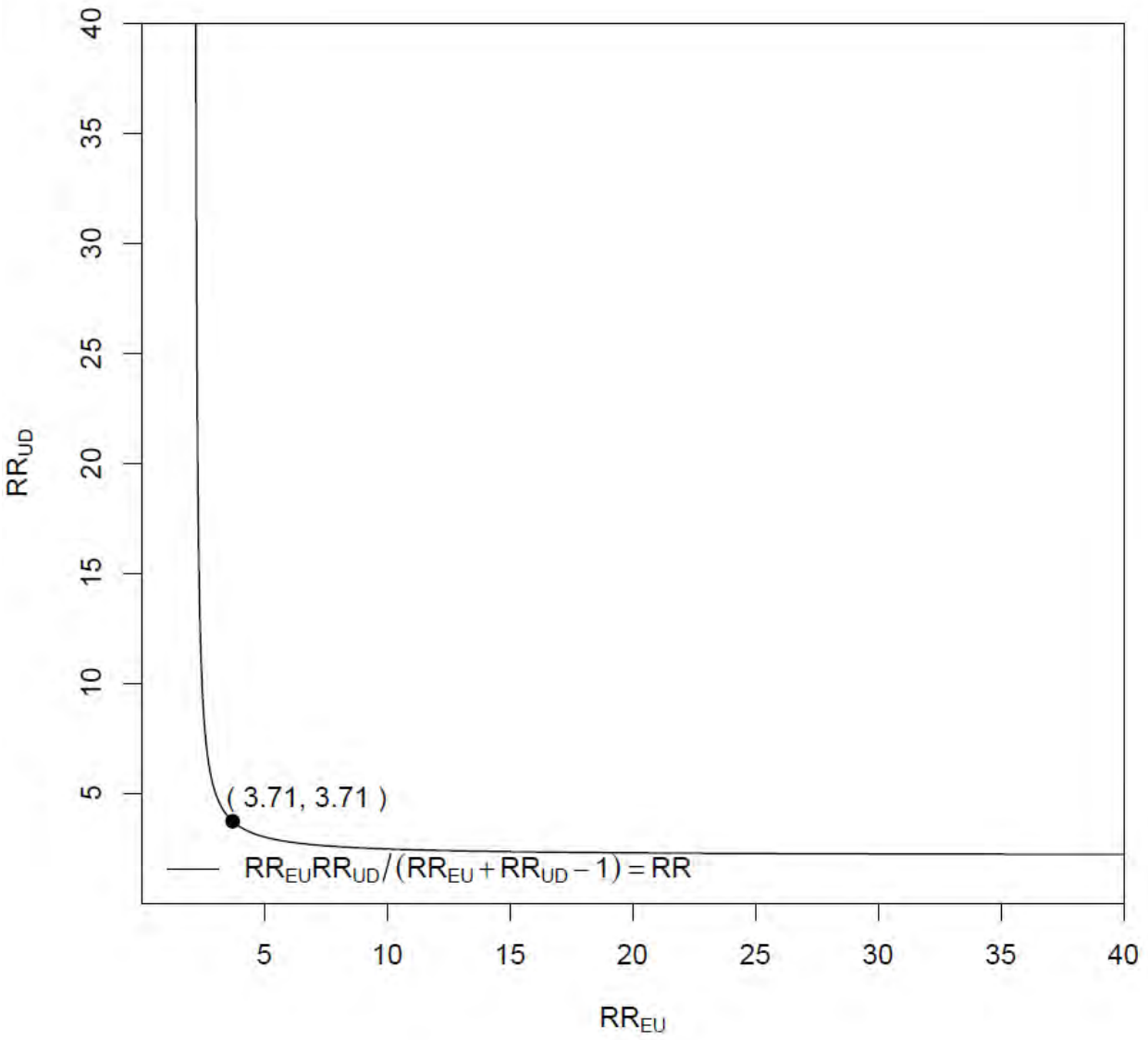
CI = confidence interval; Ra-223 = radium 223.

Figure 11: **Adjusted prostate cancer–specific mortality, third- and fourth-line cohorts combined**



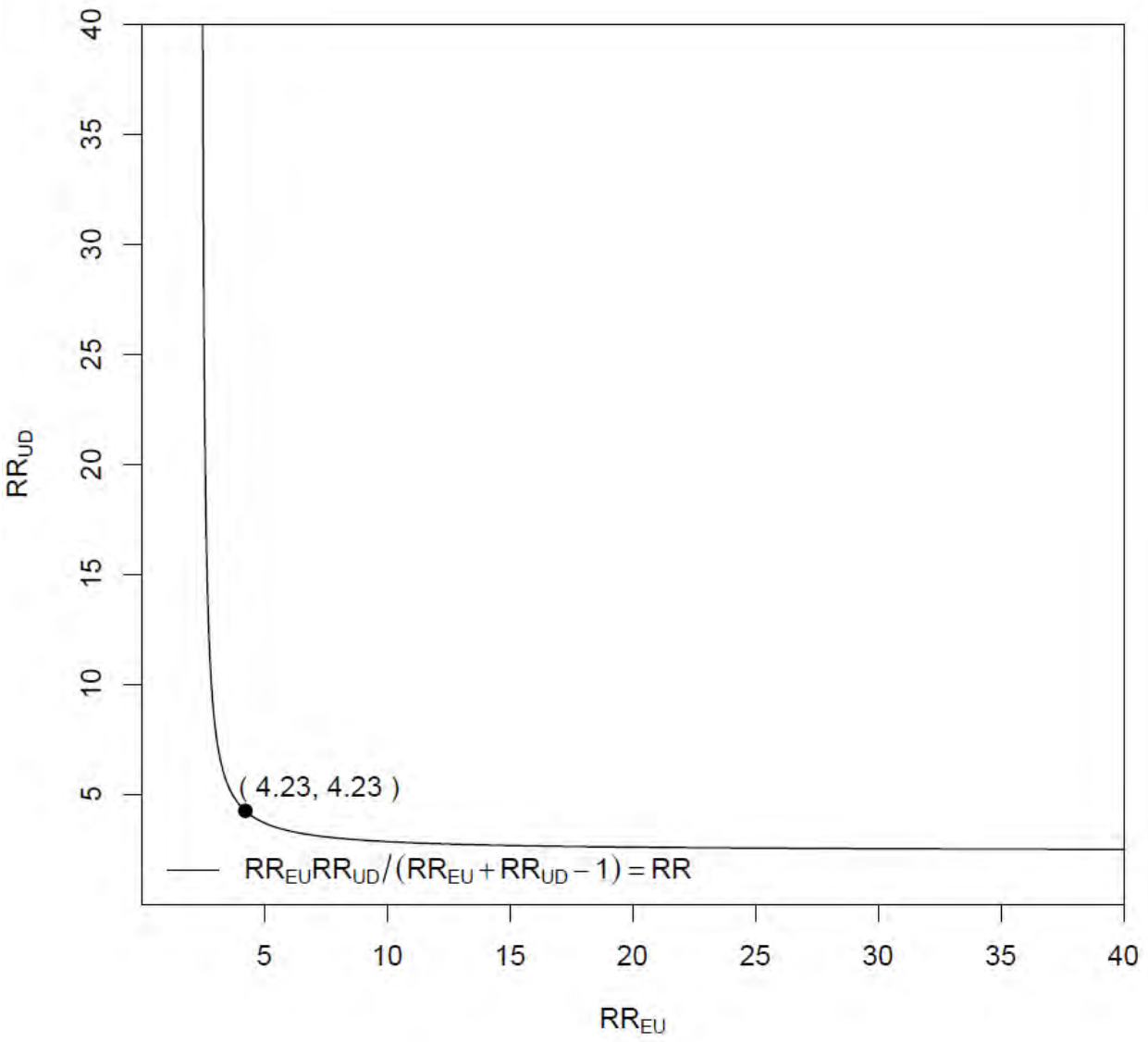
CI = confidence interval; Ra-223 = radium 223.

Figure 12: **Value of the joint minimum strength of association on the hazard ratio scale that an unmeasured confounder must have with Ra-223 initiation and all-cause mortality to fully explain the observed treatment–outcome of HR = 1.63 (95% CI, 1.27 to 2.16) in the first-line cohort (RR_{EU}: maximum risk ratio for any specific level of the unmeasured confounders comparing those with and without treatment, with adjustment for the measured covariates; RR_{UD}: maximum risk ratio for the outcome comparing any 2 categories of the unmeasured confounders within either treatment group, conditional on the observed covariates)**



CI = confidence interval; HR = hazard ratio; RR = risk ratio.

Figure 13: **Value of the joint minimum strength of association on the hazard ratio scale that an unmeasured confounder must have with Ra-223 initiation and all-cause mortality to fully explain the observed treatment–outcome HR = 1.83 (95% CI, 1.38 to 2.48) in the first-line cohort (RR_{EU}: maximum risk ratio for any specific level of the unmeasured confounders comparing those with and without treatment, with adjustment for the measured covariates; RR_{UD}: maximum risk ratio for the outcome comparing any 2 categories of the unmeasured confounders within either treatment group, conditional on the observed covariates)**



CI = confidence interval; HR = hazard ratio; RR = risk ratio.

Annex 6: Supplementary tables

Supplementary Table 1: Location of fractures, by exposure group, all treatment lines

Fractures	Radium-223 arm	Comparator arm
Total [a]	87	45
Fracture of cervical vertebra or other parts of the neck	1 (1.15)	4 (8.89)
Fracture of rib(s), sternum, and thoracic spine	4 (4.60)	4 (8.89)
Fracture of lumbar spine and pelvis	3 (3.45)	8 (17.78)
Fracture of shoulder and upper arm	13 (14.94)	7 (15.56)
Fracture of forearm	8 (9.20)	2 (4.44)
Fracture at wrist and hand level	4 (4.60)	1 (2.22)
Fracture of femur	35 (40.23)	15 (33.33)
Fracture of lower leg, including ankle	5 (5.75)	1 (2.22)
Fracture of foot and toe, except ankle	2 (2.30)	0 (0.00)
Fracture without identified location	12 (13.79)	3 (6.67)

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

Supplementary Table 2: Cohort follow-up, censoring reasons, and outcomes, by treatment and treatment line in the population with recorded bone metastases

Treatment line	Radium-223 arm	Comparator arm
All treatment lines		
N	678	753
Person-months of follow-up, sum	9,209.56	7,462.14
Median follow-up (Q1, Q3), months	10.91 (6.51, 18.59)	7.95 (4.14, 13.34)
Minimum, maximum follow-up, months	0.33, 47.11	0.10, 49.08
Artificially censored [a], n (%)	0 (0.00)	120 (15.94)
Censored because they were alive at the end of December 2018, n (%)	242 (35.69)	360 (47.81)
Had a bone fracture during study follow-up, n (%)	62 (9.14)	36 (4.78)
Dead because of prostate cancer, n (%)	403 (59.44)	248 (32.93)
Dead from any cause, n (%)	435 (64.16)	273 (36.25)
First-line treatment		
N	201	432
Person-months of follow-up, sum	2,998.51	4,763.37
Median follow-up (Q1, Q3), months	13.17 (7.06, 20.60)	8.77 (4.67, 15.38)
Minimum, maximum follow-up, months	0.33, 44.55	0.10, 49.08
Artificially censored [a], n (%)	0 (0.00)	69 (15.97)
Censored because they were alive at the end of December 2018, n (%)	91 (45.27)	235 (54.40)
Had a bone fracture during study follow-up, n (%)	15 (7.46)	29 (6.71)
Dead because of prostate cancer, n (%)	102 (50.75)	109 (25.23)
Dead from any cause, n (%)	110 (54.73)	128 (29.63)
Second-line treatment		
N	238	214
Person-months of follow-up, sum	3,011.48	1,929.99
Median follow-up (Q1, Q3), months	10.18 (6.13, 17.63)	7.51 (3.84, 12.34)
Minimum, maximum follow-up, months	0.36, 46.19	0.39, 45.93
Artificially censored [a], n (%)	0 (0.00)	36 (16.82)
Censored because they were alive at the end of December 2018, n (%)	80 (33.61)	91 (42.52)

Treatment line	Radium-223 arm	Comparator arm
Had a bone fracture during study follow-up, n (%)	25 (10.50)	6 (2.80)
Dead because of prostate cancer, n (%)	143 (60.08)	82 (38.32)
Dead from any cause, n (%)	158 (66.39)	87 (40.65)
Third-line treatment		
N	180	82
Person-months of follow-up, sum	2,353.51	638.39
Median follow-up (Q1, Q3), months	10.50 (6.36, 17.91)	6.42 (3.67, 10.02)
Minimum, maximum follow-up, months	0.36, 42.74	0.10, 32.33
Artificially censored [a], n (%)	0 (0.00)	12 (14.63)
Censored because they were alive at the end of December 2018, n (%)	60 (33.33)	27 (32.93)
Had a bone fracture during study follow-up, n (%)	16 (8.89)	1 (1.22)
Dead because of prostate cancer, n (%)	115 (63.89)	42 (51.22)
Dead from any cause, n (%)	120 (66.67)	43 (52.44)
Fourth-line treatment		
N	59	25
Person-months of follow-up, sum	846.06	130.40
Median follow-up (Q1, Q3), months	11.17 (6.88, 17.86)	4.27 (2.76, 6.34)
Minimum, maximum follow-up, months	1.61, 47.11	0.10, 13.11
Artificially censored [a], n (%)	0 (0.00)	3 (12.00)
Censored because they were alive at the end of December 2018, n (%)	11 (18.64)	7 (28.00)
Had a bone fracture during study follow-up, n (%)	6 (10.17)	0 (0.00)
Dead because of prostate cancer, n (%)	43 (72.88)	15 (60.00)
Dead from any cause, n (%)	47 (79.66)	15 (60.00)

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 3: Adjusted cumulative incidence of bone fractures in the population with recorded bone metastases, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	42.78 (16.02 to 77.52)	75.91 (34.69 to 128.39)	105.08 (52.06 to 175.54)	131.93 (65.34 to 213.86)	157.73 (77.78 to 242.38)	183.58 (85.89 to 292.13)	1.14 (0.52 to 2.15)
Comparator (95% CI)	45.14 (25.96 to 68.51)	71.67 (46.95 to 101.07)	89.75 (58.93 to 122.68)	102.67 (63.41 to 148.14)	112.36 (64.26 to 179.57)	119.95 (64.40 to 224.03)	
Difference (95% CI)	−2.35 (−37.50 to 32.65)	4.24 (−46.27 to 60.23)	15.33 (−47.42 to 93.26)	29.25 (−47.78 to 124.11)	45.37 (−50.90 to 147.76)	63.63 (−64.10 to 181.22)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 4: Adjusted cumulative incidence of bone fractures in the population with recorded bone metastases, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	57.87 (28.96 to 92.40)	121.30 (69.42 to 189.33)	154.53 (87.30 to 242.06)	162.59 (91.37 to 252.97)	163.48 (92.08 to 253.27)	163.53 (92.26 to 253.32)	1.87 (0.60 to 11.20)
Comparator (95% CI)	32.94 (2.77 to 86.02)	66.43 (11.89 to 162.08)	82.70 (15.90 to 194.48)	86.30 (17.37 to 214.01)	86.66 (17.37 to 234.43)	86.67 (17.55 to 237.66)	
Difference (95% CI)	24.93 (−34.53 to 75.37)	54.87 (−50.23 to 137.60)	71.84 (−69.31 to 179.41)	76.30 (−82.18 to 184.64)	76.83 (−89.20 to 185.63)	76.85 (−88.56 to 182.62)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 5: Unadjusted cumulative incidence of bone fractures in the population with recorded bone metastases, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up					
	6 months	12 months	18 months	24 months	30 months	36 months
Radium-223 (95% CI)	40.82 (16.51 to 90.31)	93.02 (50.49 to 179.76)	145.25 (84.98 to 249.74)	184.49 (107.11 to 292.05)	206.87 (113.81 to 335.09)	216.57 (116.09 to 381.64)
Comparator (95% CI)	6.11 (0.00 to 19.98)	15.80 (0.00 to 58.03)	27.85 (0.00 to 99.97)	39.02 (0.00 to 142.96)	46.77 (0.00 to 182.02)	50.81 (0.00 to 233.51)

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 6: Adjusted cumulative incidence of bone fractures in the population with recorded bone metastases, pooled analysis of all 4 treatment-line–specific cohorts

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	46.80 (29.09 to 63.94)	99.76 (69.91 to 135.75)	144.29 (101.98 to 192.14)	170.96 (117.27 to 224.42)	182.38 (122.00 to 241.50)	185.86 (123.01 to 249.42)	1.61 (0.93 to 2.79)
Comparator (95% CI)	34.47 (20.25 to 52.81)	64.92 (40.96 to 94.71)	85.25 (49.58 to 123.69)	94.89 (51.54 to 145.25)	98.13 (51.76 to 158.48)	98.90 (51.77 to 165.33)	
Difference (95% CI)	12.33 (−16.04 to 35.36)	34.83 (−6.93 to 75.53)	59.04 (−0.14 to 114.45)	76.06 (−0.02 to 139.45)	84.25 (−5.05 to 153.00)	86.96 (−8.65 to 157.12)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 7: Adjusted all-cause mortality in the population with recorded bone metastases, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	208.27 (143.49 to 288.32)	429.51 (333.43 to 528.31)	539.30 (458.27 to 625.86)	653.61 (582.25 to 731.80)	763.97 (686.38 to 833.74)	859.02 (760.99 to 937.29)	1.62 (1.28 to 2.16)
Comparator (95% CI)	133.68 (103.79 to 167.29)	263.14 (215.16 to 308.73)	380.18 (317.68 to 437.78)	501.03 (416.72 to 566.83)	620.02 (503.60 to 716.13)	730.09 (565.48 to 864.65)	
Difference (95% CI)	74.59 (2.73 to 159.92)	166.37 (79.08 to 270.19)	159.12 (69.14 to 263.15)	152.58 (59.24 to 256.62)	143.95 (21.07 to 277.23)	128.94 (−35.37 to 313.61)	

CI = confidence interval
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 8: Adjusted all-cause mortality in the population with recorded bone metastases, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	210.96 (157.34 to 268.02)	481.27 (402.59 to 562.89)	628.61 (532.48 to 719.56)	734.81 (640.79 to 819.71)	811.43 (704.09 to 889.10)	866.47 (747.48 to 938.70)	0.91 (0.62 to 1.27)
Comparator (95% CI)	212.25 (144.70 to 315.20)	494.85 (389.36 to 609.56)	673.21 (558.55 to 777.26)	801.96 (682.02 to 906.42)	888.82 (754.27 to 983.45)	942.83 (795.60 to 999.77)	
Difference (95% CI)	−1.29 (−112.97 to 89.86)	−13.57 (−162.30 to 110.79)	−44.60 (−191.00 to 95.65)	−67.15 (−211.94 to 73.37)	−77.39 (−204.63 to 65.56)	−76.36 (−191.57 to 88.37)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 9: Adjusted all-cause mortality in the population with recorded bone metastases, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	179.64 (130.46 to 229.92)	498.58 (422.30 to 572.92)	671.68 (594.14 to 756.26)	767.02 (688.64 to 835.48)	823.55 (746.32 to 885.94)	859.11 (780.68 to 927.31)	0.72 (0.40 to 1.23)
Comparator (95% CI)	367.49 (203.69 to 515.99)	542.92 (344.57 to 767.47)	620.74 (411.63 to 858.25)	765.06 (579.23 to 942.85)	930.74 (684.50 to 1,000.00)	996.50 (696.91 to 1,000.00)	
Difference (95% CI)	−187.85 (−357.75 to −16.60)	−44.34 (−283.57 to 164.63)	50.94 (−201.05 to 276.76)	1.97 (−201.33 to 209.42)	−107.19 (−225.17 to 162.86)	−137.39 (−217.31 to 169.53)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 10: Adjusted prostate cancer–specific mortality in the population with recorded bone metastases, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	198.93 (131.11 to 277.36)	413.63 (322.58 to 511.55)	521.03 (439.54 to 614.46)	631.94 (549.46 to 715.27)	739.52 (657.10 to 820.95)	834.48 (723.86 to 920.39)	1.83 (1.41 to 2.51)
Comparator (95% CI)	103.16 (77.06 to 132.32)	218.03 (173.73 to 264.70)	335.54 (268.92 to 396.35)	454.93 (368.80 to 528.99)	571.65 (446.85 to 677.86)	680.46 (512.55 to 841.26)	
Difference (95% CI)	95.77 (26.28 to 183.18)	195.60 (108.87 to 302.35)	185.49 (96.42 to 290.08)	177.00 (72.56 to 286.73)	167.87 (33.84 to 306.89)	154.02 (−43.42 to 348.94)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 11: Adjusted prostate cancer–specific mortality in the population with recorded bone metastases, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	195.33 (140.85 to 251.76)	448.73 (373.77 to 535.23)	593.73 (498.80 to 689.82)	704.06 (606.68 to 794.82)	787.34 (673.57 to 871.51)	849.32 (720.70 to 931.18)	0.92 (0.61 to 1.29)
Comparator (95% CI)	212.15 (144.82 to 314.25)	463.75 (352.05 to 585.09)	614.97 (496.67 to 728.50)	744.80 (627.74 to 863.67)	847.18 (705.13 to 976.20)	919.33 (727.75 to 999.80)	
Difference (95% CI)	−16.82 (−131.25 to 71.72)	−15.02 (−165.13 to 114.81)	−21.24 (−179.25 to 115.83)	−40.73 (−195.45 to 84.53)	−59.85 (−214.08 to 93.64)	−70.01 (−209.28 to 123.18)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 12: Adjusted prostate cancer–specific mortality in the population with recorded bone metastases, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	172.71 (122.74 to 216.85)	489.39 (412.03 to 562.88)	656.12 (576.07 to 742.53)	745.64 (670.84 to 817.84)	797.89 (717.91 to 867.62)	830.38 (738.88 to 902.95)	0.72 (0.40 to 1.20)
Comparator (95% CI)	348.09 (187.51 to 499.51)	516.35 (312.94 to 752.40)	601.44 (396.21 to 845.44)	754.53 (556.38 to 938.94)	926.56 (660.17 to 1,000.00)	995.90 (695.02 to 1,000.00)	
Difference (95% CI)	−175.38 (−331.22 to −13.48)	−26.95 (−266.61 to 188.23)	54.68 (−191.88 to 282.81)	−8.90 (−217.69 to 197.92)	−128.67 (−246.02 to 154.49)	−165.52 (−242.40 to 162.08)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 13: Cohort follow-up, censoring reasons, and outcomes, by treatment and treatment line in the population with at least 18 months of potential follow-up

Treatment line	Radium-223 arm	Comparator arm
All treatment lines		
N	454	355
Person-months of follow-up, sum	7,268.24	4,740.14
Median follow-up (Q1, Q3), months	13.91 (7.89, 22.37)	10.97 (6.31, 20.24)
Minimum, maximum follow-up, months	0.33, 47.11	0.36, 49.08
Artificially censored [a], n (%)	0 (0.00)	95 (26.76)
Censored because they were alive at the end of December 2018, n (%)	94 (20.70)	70 (19.72)
Had a bone fracture during study follow-up, n (%)	44 (9.69)	18 (5.07)
Dead because of prostate cancer, n (%)	333 (73.35)	171 (48.17)
Dead from any cause, n (%)	359 (79.07)	190 (53.52)
First-line treatment		
N	127	207
Person-months of follow-up, sum	2,256.30	3,168.49
Median follow-up (Q1, Q3), months	18.23 (8.28, 24.92)	14.03 (7.52, 22.29)
Minimum, maximum follow-up, months	0.33, 44.55	0.36, 49.08
Artificially censored [a], n (%)	0 (0.00)	55 (26.57)
Censored because they were alive at the end of December 2018, n (%)	37 (29.13)	60 (28.99)
Had a bone fracture during study follow-up, n (%)	8 (6.30)	14 (6.76)
Dead because of prostate cancer, n (%)	82 (64.57)	78 (37.68)
Dead from any cause, n (%)	90 (70.87)	92 (44.44)
Second-line treatment		
N	150	96
Person-months of follow-up, sum	2,290.99	1,112.34
Median follow-up (Q1, Q3), months	11.52 (6.87, 21.46)	9.40 (6.70, 15.61)
Minimum, maximum follow-up, months	0.92, 46.19	0.59, 45.93
Artificially censored [a], n (%)	0 (0.00)	27 (28.13)
Censored because they were alive at the end of December 2018, n (%)	28 (18.67)	7 (7.29)
Had a bone fracture during study follow-up, n (%)	18 (12.00)	3 (3.13)
Dead because of prostate cancer, n (%)	113 (75.33)	58 (60.42)
Dead from any cause, n (%)	122 (81.33)	62 (64.58)
Third-line treatment		
N	130	41
Person-months of follow-up, sum	1,988.86	394.02
Median follow-up (Q1, Q3), months	13.85 (8.26, 19.61)	7.20 (5.39, 11.96)
Minimum, maximum follow-up, months	0.82, 42.74	0.69, 32.33
Artificially censored [a], n (%)	0 (0.00)	10 (24.39)
Censored because they were alive at the end of December 2018, n (%)	23 (17.69)	3 (7.32)
Had a bone fracture during study follow-up, n (%)	14 (10.77)	1 (2.44)
Dead because of prostate cancer, n (%)	102 (78.46)	27 (65.85)
Dead from any cause, n (%)	107 (82.31)	28 (68.29)

Treatment line	Radium-223 arm	Comparator arm
Fourth-line treatment		
N	47	11
Person-months of follow-up, sum	732.09	65.28
Median follow-up (Q1, Q3), months	13.34 (6.88, 22.98)	5.78 (3.52, 6.88)
Minimum, maximum follow-up, months	1.61, 47.11	1.91, 13.11
Artificially censored [a], n (%)	0 (0.00)	3 (27.27)
Censored because they were alive at the end of December 2018, n (%)	6 (12.77)	0 (0.00)
Had a bone fracture during study follow-up, n (%)	4 (8.51)	0 (0.00)
Dead because of prostate cancer, n (%)	36 (76.60)	8 (72.73)
Dead from any cause, n (%)	40 (85.11)	8 (72.73)

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 14: Adjusted cumulative incidence of bone fractures in the population with at least 18 months of potential follow-up, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	25.09 (5.91 to 54.11)	51.10 (14.94 to 103.02)	78.43 (22.61 to 161.92)	105.62 (28.98 to 227.35)	131.30 (33.84 to 285.23)	154.33 (44.47 to 349.22)	1.16 (0.32 to 2.88)
Comparator (95% CI)	26.98 (7.02 to 53.12)	50.12 (19.42 to 79.88)	70.49 (36.49 to 107.36)	87.53 (46.32 to 140.16)	101.10 (49.84 to 174.43)	111.39 (50.34 to 219.24)	
Difference (95% CI)	−1.89 (−34.61 to 28.80)	0.98 (−47.95 to 56.29)	7.94 (−57.58 to 92.05)	18.10 (−73.66 to 138.34)	30.20 (−99.89 to 189.45)	42.94 (−130.89 to 236.34)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 15: Adjusted cumulative incidence of bone fractures in the population with at least 18 months of potential follow-up, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	50.17 (17.77 to 89.92)	119.79 (61.32 to 199.50)	159.24 (74.64 to 262.93)	168.24 (84.50 to 274.26)	169.05 (86.07 to 279.51)	169.08 (86.07 to 280.20)	1.25 (0.23 to 24,558,716.3)
Comparator (95% CI)	48.05 (0.00 to 204.36)	97.32 (0.00 to 377.14)	118.32 (0.00 to 403.93)	121.88 (0.00 to 408.31)	122.11 (0.00 to 408.34)	122.12 (0.00 to 408.34)	
Difference (95% CI)	2.12 (−164.80 to 76.83)	22.46 (−262.52 to 162.36)	40.92 (−263.75 to 206.31)	46.36 (−260.40 to 216.69)	46.94 (−260.32 to 216.22)	46.96 (−260.31 to 216.39)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 16: Unadjusted cumulative incidence of bone fractures in the population with at least 18 months of potential follow-up, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up					
	6 months	12 months	18 months	24 months	30 months	36 months
Radium-223 (95% CI)	37.80 (15.32 to 69.70)	87.87 (43.32 to 144.27)	140.22 (73.80 to 227.39)	181.69 (96.41 to 277.82)	206.86 (105.20 to 322.34)	218.61 (106.87 to 380.14)
Comparator (95% CI)	10.85 (0.00 to 35.06)	24.83 (0.00 to 97.23)	39.18 (0.00 to 144.85)	50.33 (0.00 to 212.93)	56.90 (0.00 to 242.91)	59.83 (0.00 to 266.08)

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 17: Adjusted cumulative incidence of bone fractures in the population with at least 18 months of potential follow-up, pooled analysis of all 4 treatment-line–specific cohorts

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	40.91 (24.03 to 59.72)	90.77 (59.44 to 130.32)	135.23 (91.10 to 189.81)	163.07 (111.05 to 224.78)	175.42 (119.50 to 239.87)	179.27 (121.38 to 246.49)	1.57 (0.76 to 3.72)
Comparator (95% CI)	29.83 (8.55 to 60.11)	61.56 (23.27 to 108.52)	86.50 (39.07 to 143.29)	100.25 (45.90 to 164.76)	105.57 (47.16 to 180.80)	107.01 (47.27 to 192.67)	
Difference (95% CI)	11.08 (−25.38 to 39.51)	29.21 (−30.51 to 85.28)	48.73 (−26.42 to 125.10)	62.83 (−26.56 to 144.13)	69.84 (−35.37 to 153.22)	72.25 (−39.82 to 157.12)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 18: Adjusted all-cause mortality in the population with at least 18 months of potential follow-up, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	163.94 (95.37 to 228.25)	421.84 (321.60 to 546.15)	559.38 (458.38 to 667.93)	670.07 (576.51 to 760.95)	758.01 (667.21 to 832.74)	826.39 (718.73 to 915.77)	1.57 (1.20 to 2.16)
Comparator (95% CI)	140.47 (98.20 to 187.37)	272.33 (213.56 to 334.04)	379.64 (308.03 to 449.60)	492.71 (409.29 to 574.03)	606.71 (492.74 to 715.78)	714.94 (553.11 to 868.84)	
Difference (95% CI)	23.46 (−48.51 to 96.51)	149.51 (45.49 to 284.25)	179.73 (57.23 to 304.53)	177.36 (61.61 to 285.10)	151.30 (19.83 to 277.30)	111.46 (−76.90 to 294.69)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 19: Adjusted all-cause mortality in the population with at least 18 months of potential follow-up, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	199.46 (147.05 to 274.69)	456.91 (376.40 to 555.65)	604.46 (506.36 to 703.30)	721.49 (622.77 to 805.10)	811.43 (705.13 to 883.55)	877.76 (763.74 to 951.57)	0.69 (0.47 to 1.09)
Comparator (95% CI)	276.27 (150.76 to 406.69)	582.54 (400.94 to 724.49)	752.65 (580.38 to 862.81)	846.14 (695.44 to 929.37)	899.97 (756.58 to 978.32)	932.30 (790.33 to 998.67)	
Difference (95% CI)	−76.80 (−223.07 to 62.76)	−125.62 (−292.77 to 70.08)	−148.19 (−293.35 to 49.85)	−124.65 (−257.66 to 41.36)	−88.54 (−224.58 to 74.37)	−54.54 (−193.05 to 106.09)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 20: Adjusted all-cause mortality in the population with at least 18 months of potential follow-up, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	185.24 (134.01 to 254.50)	503.36 (428.19 to 588.83)	668.47 (604.75 to 744.48)	763.51 (701.03 to 826.04)	821.77 (754.77 to 881.81)	859.33 (789.47 to 923.81)	0.90 (0.34 to 1.63)
Comparator (95% CI)	335.96 (145.90 to 571.87)	473.26 (223.55 to 849.86)	502.49 (238.16 to 891.60)	639.85 (373.65 to 980.39)	938.04 (684.57 to 1,000.00)	999.97 (707.35 to 1,000.00)	
Difference (95% CI)	−150.72 (−409.02 to 56.19)	30.09 (−364.61 to 297.03)	165.98 (−243.05 to 428.30)	123.66 (−224.84 to 382.94)	−116.27 (−218.22 to 165.45)	−140.64 (−204.42 to 146.80)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 21: Adjusted prostate cancer–specific mortality in the population with at least 18 months of potential follow-up, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	141.46 (79.44 to 201.05)	391.93 (299.46 to 524.47)	533.31 (423.28 to 646.82)	643.63 (542.67 to 743.19)	729.67 (631.90 to 815.90)	796.32 (686.55 to 899.93)	1.74 (1.28 to 2.48)
Comparator (95% CI)	103.58 (72.50 to 141.07)	218.28 (163.52 to 274.07)	326.26 (256.06 to 397.98)	440.10 (353.48 to 534.90)	555.50 (438.32 to 677.16)	666.64 (494.70 to 853.26)	
Difference (95% CI)	37.88 (−34.85 to 106.20)	173.65 (68.40 to 310.24)	207.05 (83.90 to 338.57)	203.53 (79.11 to 322.80)	174.17 (29.24 to 317.57)	129.68 (−80.41 to 335.56)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 22: Adjusted prostate cancer–specific mortality in the population with at least 18 months of potential follow-up, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	190.31 (137.47 to 261.86)	432.59 (354.59 to 531.64)	577.90 (476.52 to 680.14)	697.41 (594.64 to 790.10)	792.28 (678.32 to 872.57)	864.21 (745.78 to 945.98)	0.72 (0.45 to 1.18)
Comparator (95% CI)	281.43 (153.70 to 405.86)	550.69 (369.07 to 715.15)	693.05 (516.37 to 839.59)	792.59 (639.30 to 901.97)	861.64 (705.17 to 972.73)	908.91 (735.03 to 999.42)	
Difference (95% CI)	−91.12 (−238.20 to 50.78)	−118.10 (−298.89 to 72.46)	−115.15 (−270.05 to 85.08)	−95.19 (−242.65 to 82.62)	−69.36 (−215.69 to 108.62)	−44.71 (−180.22 to 133.55)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 23: Adjusted prostate cancer–specific mortality in the population with at least 18 months of potential follow-up, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	170.97 (123.76 to 223.19)	488.28 (412.42 to 566.95)	648.57 (578.74 to 725.85)	739.36 (668.66 to 808.24)	794.57 (721.28 to 864.95)	830.04 (755.84 to 906.26)	0.88 (0.34 to 1.61)
Comparator (95% CI)	319.58 (125.16 to 571.87)	450.11 (197.61 to 843.32)	481.79 (222.94 to 885.45)	626.69 (353.74 to 980.86)	934.85 (675.34 to 1,000.00)	999.97 (703.55 to 1,000.00)	
Difference (95% CI)	−148.61 (−409.93 to 41.40)	38.18 (−357.88 to 295.14)	166.78 (−248.88 to 425.23)	112.67 (−243.31 to 366.04)	−140.27 (−254.04 to 136.87)	−169.92 (−238.50 to 129.82)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 24: Cohort follow-up, censoring reasons, and outcomes, by treatment and treatment line in the analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline

Treatment line	Radium-223 arm	Comparator arm
All treatment lines		
N	681	753
Person-months of follow-up, sum	9,236.63	8,600.74
Median follow-up (Q1, Q3), months	10.87 (6.54, 18.56)	9.43 (4.50, 16.26)
Minimum, maximum follow-up, months	0.33, 47.11	0.10, 49.08
Artificially censored [a], n (%)	0 (0.00)	0 (0.00)
Censored because they were alive at the end of December 2018, n (%)	243 (35.68)	411 (54.58)
Had a bone fracture during study follow-up, n (%)	62 (9.10)	44 (5.84)
Dead because of prostate cancer, n (%)	404 (59.32)	311 (41.30)
Dead from any cause, n (%)	437 (64.17)	342 (45.42)
First-line treatment		
N	203	432
Person-months of follow-up, sum	3,016.74	5,369.23
Median follow-up (Q1, Q3), months	13.08 (7.10, 20.48)	10.30 (5.25, 18.72)
Minimum, maximum follow-up, months	0.33, 44.55	0.10, 49.08
Artificially censored [a], n (%)	0 (0.00)	0 (0.00)
Censored because they were alive at the end of December 2018, n (%)	92 (45.32)	268 (62.04)
Had a bone fracture during study follow-up, n (%)	15 (7.39)	33 (7.64)
Dead because of prostate cancer, n (%)	102 (50.25)	140 (32.41)
Dead from any cause, n (%)	111 (54.68)	164 (37.96)
Second-line treatment		
N	239	214
Person-months of follow-up, sum	3,020.32	2,281.13
Median follow-up (Q1, Q3), months	10.12 (6.14, 17.63)	9.20 (4.17, 14.41)
Minimum, maximum follow-up, months	0.36, 46.19	0.39, 46.09
Artificially censored [a], n (%)	0 (0.00)	0 (0.00)
Censored because they were alive at the end of December 2018, n (%)	80 (33.47)	106 (49.53)
Had a bone fracture during study follow-up, n (%)	25 (10.46)	10 (4.67)
Dead because of prostate cancer, n (%)	144 (60.25)	103 (48.13)
Dead from any cause, n (%)	159 (66.53)	108 (50.47)
Third-line treatment		
N	180	82
Person-months of follow-up, sum	2,353.51	772.96
Median follow-up (Q1, Q3), months	10.50 (6.36, 17.91)	7.59 (4.47, 12.44)
Minimum, maximum follow-up, months	0.36, 42.74	0.10, 40.48
Artificially censored [a], n (%)	0 (0.00)	0 (0.00)
Censored because they were alive at the end of December 2018, n (%)	60 (33.33)	30 (36.59)
Had a bone fracture during study follow-up, n (%)	16 (8.89)	1 (1.22)
Dead because of prostate cancer, n (%)	115 (63.89)	50 (60.98)
Dead from any cause, n (%)	120 (66.67)	52 (63.41)

Treatment line	Radium-223 arm	Comparator arm
Fourth-line treatment		
N	59	25
Person-months of follow-up, sum	846.06	177.41
Median follow-up (Q1, Q3), months	11.17 (6.88, 17.86)	4.90 (2.92, 8.28)
Minimum, maximum follow-up, months	1.61, 47.11	0.10, 31.28
Artificially censored [a], n (%)	0 (0.00)	0 (0.00)
Censored because they were alive at the end of December 2018, n (%)	11 (18.64)	7 (28.00)
Had a bone fracture during study follow-up, n (%)	6 (10.17)	0 (0.00)
Dead because of prostate cancer, n (%)	43 (72.88)	18 (72.00)
Dead from any cause, n (%)	47 (79.66)	18 (72.00)

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 25: Adjusted cumulative incidence of bone fractures, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	40.97 (14.59 to 80.40)	76.97 (34.25 to 133.74)	108.81 (53.23 to 189.80)	135.19 (63.11 to 225.15)	155.70 (69.52 to 258.45)	170.67 (72.34 to 306.73)	1.04 (0.45 to 2.01)
Comparator (95% CI)	47.42 (26.94 to 66.53)	79.32 (50.62 to 107.37)	101.34 (63.91 to 139.05)	115.65 (68.52 to 160.28)	124.38 (70.51 to 178.48)	129.38 (71.18 to 194.76)	
Difference (95% CI)	−6.45 (−39.01 to 31.53)	−2.35 (−52.39 to 59.80)	7.47 (−61.54 to 92.30)	19.54 (−72.64 to 122.90)	31.32 (−76.61 to 155.48)	41.28 (−83.89 to 176.38)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 26: Adjusted cumulative incidence of bone fractures, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	62.22 (31.15 to 95.58)	108.97 (63.43 to 173.06)	142.74 (82.79 to 222.92)	164.45 (93.38 to 249.41)	176.86 (102.72 to 263.87)	183.16 (105.19 to 280.69)	1.60 (0.63 to 5.60)
Comparator (95% CI)	29.32 (2.01 to 77.94)	62.97 (9.01 to 146.76)	98.92 (25.33 to 194.36)	132.64 (48.58 to 242.94)	160.53 (56.16 to 314.01)	180.95 (56.19 to 495.54)	
Difference (95% CI)	32.90 (−29.82 to 80.75)	46.01 (−43.88 to 133.63)	43.82 (−63.57 to 156.84)	31.81 (−99.74 to 155.74)	16.33 (−170.88 to 156.66)	2.21 (−310.49 to 153.31)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 27: Unadjusted cumulative incidence of bone fractures, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up					
	6 months	12 months	18 months	24 months	30 months	36 months
Radium-223 (95% CI)	40.78 (17.50 to 73.53)	92.87 (49.48 to 151.80)	145.02 (87.41 to 220.06)	184.30 (103.65 to 282.34)	206.78 (112.38 to 324.80)	216.58 (112.38 to 366.74)
Comparator (95% CI)	5.84 (0.00 to 19.40)	12.86 (0.00 to 45.96)	19.56 (0.00 to 68.32)	24.34 (0.00 to 83.10)	26.90 (0.00 to 89.46)	27.93 (0.00 to 94.33)

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 28: Adjusted cumulative incidence of bone fractures, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, pooled analysis of all 4 treatment-line–specific cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	48.19 (32.11 to 66.64)	97.01 (67.83 to 132.40)	139.53 (96.88 to 186.13)	169.65 (118.35 to 221.22)	187.08 (127.00 to 250.85)	195.30 (135.11 to 268.57)	1.53 (0.97 to 2.41)
Comparator (95% CI)	34.12 (21.03 to 51.63)	66.09 (43.75 to 95.64)	91.98 (60.03 to 128.58)	109.01 (69.45 to 156.03)	118.12 (72.82 to 171.30)	122.07 (74.84 to 186.74)	
Difference (95% CI)	14.06 (−10.96 to 36.70)	30.92 (−5.35 to 69.26)	47.55 (−0.46 to 103.74)	60.64 (0.34 to 128.45)	68.96 (−1.45 to 139.62)	73.23 (−8.20 to 148.21)	

CI = confidence interval.
Note: Cumulative incidence is expressed in number of cases per 1,000 persons.

Supplementary Table 29: Adjusted all-cause mortality, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	207.93 (138.63 to 293.05)	429.71 (340.86 to 518.69)	539.51 (453.12 to 621.13)	653.64 (573.48 to 724.00)	763.71 (688.38 to 840.54)	858.51 (760.89 to 946.01)	1.44 (1.10 to 1.89)
Comparator (95% CI)	127.20 (98.20 to 158.27)	270.91 (224.13 to 319.95)	424.82 (355.21 to 490.08)	565.36 (483.66 to 628.12)	687.68 (600.63 to 762.00)	788.49 (679.04 to 890.85)	
Difference (95% CI)	80.73 (0.84 to 168.30)	158.79 (64.28 to 264.77)	114.70 (14.02 to 230.65)	88.28 (−2.43 to 192.65)	76.03 (−33.43 to 183.97)	70.03 (−69.97 to 207.78)	

CI = confidence interval
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 30: Adjusted all-cause mortality, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	210.18 (156.97 to 263.95)	482.39 (402.16 to 561.74)	630.04 (533.25 to 716.45)	735.93 (636.68 to 819.74)	812.03 (710.55 to 891.71)	866.57 (755.08 to 945.98)	0.97 (0.68 to 1.34)
Comparator (95% CI)	204.96 (135.39 to 292.83)	476.50 (368.81 to 575.16)	649.96 (546.71 to 747.61)	761.72 (665.87 to 859.56)	835.03 (723.67 to 949.49)	883.93 (768.07 to 987.06)	
Difference (95% CI)	5.22 (−92.83 to 90.23)	5.89 (−125.28 to 123.93)	−19.92 (−162.19 to 119.94)	−25.78 (−178.75 to 102.57)	−23.00 (−175.18 to 106.00)	−17.36 (−171.66 to 109.89)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 31: Adjusted all-cause mortality, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	179.39 (131.80 to 231.59)	498.28 (424.93 to 577.42)	671.55 (594.69 to 749.59)	767.04 (695.98 to 829.06)	823.67 (754.18 to 879.75)	859.31 (784.16 to 917.71)	0.83 (0.49 to 1.27)
Comparator (95% CI)	331.36 (194.65 to 476.74)	530.92 (368.53 to 746.09)	634.24 (446.83 to 848.99)	747.71 (578.72 to 913.01)	855.56 (743.64 to 973.66)	937.31 (805.04 to 999.77)	
Difference (95% CI)	−151.97 (−300.54 to −8.50)	−32.64 (−265.81 to 151.55)	37.31 (−176.62 to 243.57)	19.33 (−171.83 to 199.77)	−31.89 (−179.09 to 112.80)	−78.00 (−193.42 to 54.29)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 32: Adjusted prostate cancer–specific mortality, analysis that allows individuals in the comparator group receiving Ra-223 as a subsequent treatment after baseline, first-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	198.00 (125.93 to 283.25)	412.07 (323.78 to 503.58)	519.56 (432.60 to 605.43)	630.39 (544.65 to 703.62)	737.83 (649.06 to 817.42)	832.73 (723.48 to 933.75)	1.63 (1.23 to 2.19)
Comparator (95% CI)	100.34 (76.24 to 126.21)	222.62 (179.34 to 267.62)	362.98 (294.46 to 426.01)	502.23 (422.53 to 563.30)	633.11 (543.65 to 713.93)	748.37 (626.81 to 863.89)	
Difference (95% CI)	97.66 (20.04 to 181.49)	189.45 (100.87 to 295.53)	156.59 (57.03 to 264.86)	128.16 (34.03 to 234.08)	104.72 (−6.87 to 227.31)	84.35 (−73.13 to 240.24)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 33: Adjusted prostate cancer–specific mortality, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, second-line cohort

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	194.69 (144.29 to 247.65)	450.24 (362.14 to 532.51)	595.75 (495.98 to 688.41)	705.75 (592.59 to 794.44)	788.35 (676.33 to 873.34)	849.63 (729.85 to 935.32)	0.96 (0.67 to 1.33)
Comparator (95% CI)	203.30 (132.19 to 293.11)	454.48 (349.46 to 559.43)	612.85 (508.72 to 704.00)	726.34 (621.21 to 835.49)	807.50 (694.23 to 931.85)	865.26 (732.82 to 983.40)	
Difference (95% CI)	−8.62 (−105.06 to 75.87)	−4.24 (−136.62 to 116.07)	−17.10 (−163.55 to 123.18)	−20.60 (−185.09 to 114.30)	−19.15 (−190.67 to 121.35)	−15.63 (−184.42 to 137.82)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 34: Adjusted prostate cancer–specific mortality, analysis that allowed individuals in the comparator group who received Ra-223 as a subsequent treatment after baseline, third- and fourth-line cohorts combined

Characteristic	Duration of follow-up						Hazard ratio over all follow-up (95% CI)
	6 months	12 months	18 months	24 months	30 months	36 months	
Radium-223 (95% CI)	172.46 (122.07 to 221.15)	489.12 (416.17 to 563.69)	656.04 (581.77 to 737.67)	745.70 (675.73 to 812.85)	798.06 (723.16 to 859.43)	830.62 (748.82 to 895.16)	0.86 (0.51 to 1.29)
Comparator (95% CI)	319.56 (173.13 to 457.12)	494.41 (332.64 to 710.55)	586.58 (397.54 to 821.04)	702.63 (531.66 to 895.46)	827.17 (685.52 to 971.14)	928.96 (768.37 to 999.82)	
Difference (95% CI)	−147.10 (−288.89 to 3.11)	−5.30 (−226.16 to 177.48)	69.46 (−165.62 to 278.69)	43.08 (−163.76 to 234.01)	−29.11 (−193.49 to 123.43)	−98.34 (−216.11 to 75.76)	

CI = confidence interval.
Note: Mortality is expressed in number of deaths per 1,000 persons.

Supplementary Table 35: Cumulative incidence of fractures among patients taking bone-health agents at baseline, by study group; all lines of treatment combined.

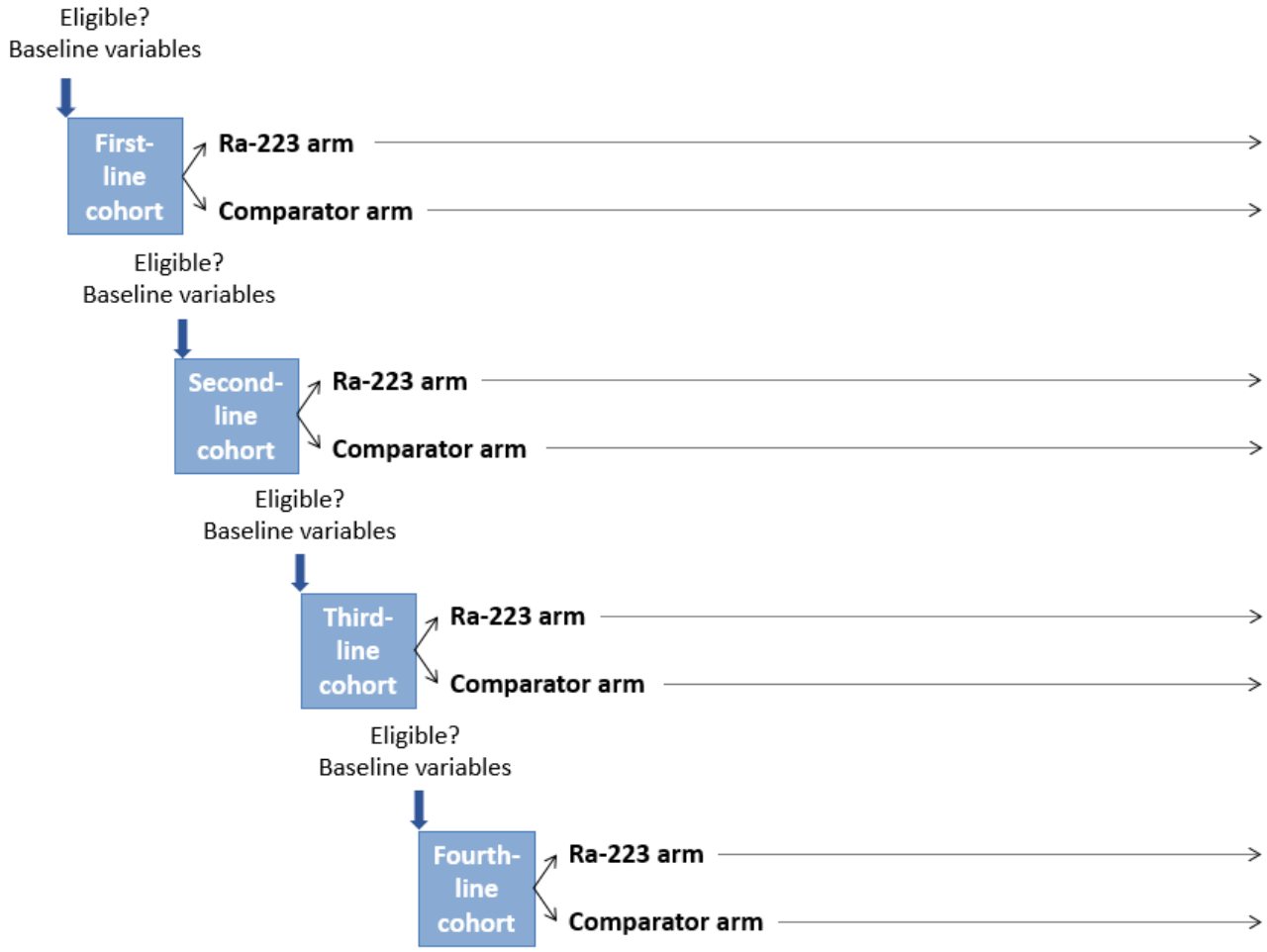
	Duration of follow-up					
Characteristic	**6 months**	**12 months**	**18 months**	**24 months**	**30 months**	**36 months**
Radium-223 (95% CI)	13.23 (1.83 to 24.86)	51.97 (21.76 to 96.41)	104.09 (50.64 to 171.29)	136.29 (58.18 to 215.14)	145.59 (60.05 to 248.65)	146.83 (60.05 to 274.71)
Comparator (95% CI)	22.41 (4.74 to 46.28)	42.15 (9.50 to 85.86)	50.63 (10.70 to 96.91)	52.30 (11.08 to 103.49)	52.45 (11.11 to 105.97)	52.46 (11.12 to 106.09)

Supplementary Table 36: Cumulative incidence of fractures among patients not taking bone-health agents at baseline, by study group; all lines of treatment combined

	Duration of follow-up					
Characteristic	**6 months**	**12 months**	**18 months**	**24 months**	**30 months**	**36 months**
Radium-223 (95% CI)	60.11(39.23 to 80.74)	107.71(78.22 to 136.92)	144.15(107.73 to 181.21)	169.22(123.65 to 216.38)	184.71(132.92 to 236.23)	193.29(137.88 to 249.49)
Comparator (95% CI)	37.60(22.36 to 54.70)	68.01(45.20 to 91.80)	91.70(56.88 to 126.41)	108.21(58.53 to 160.54)	118.49(59.41 to 197.48)	124.22(59.41 to 243.53)

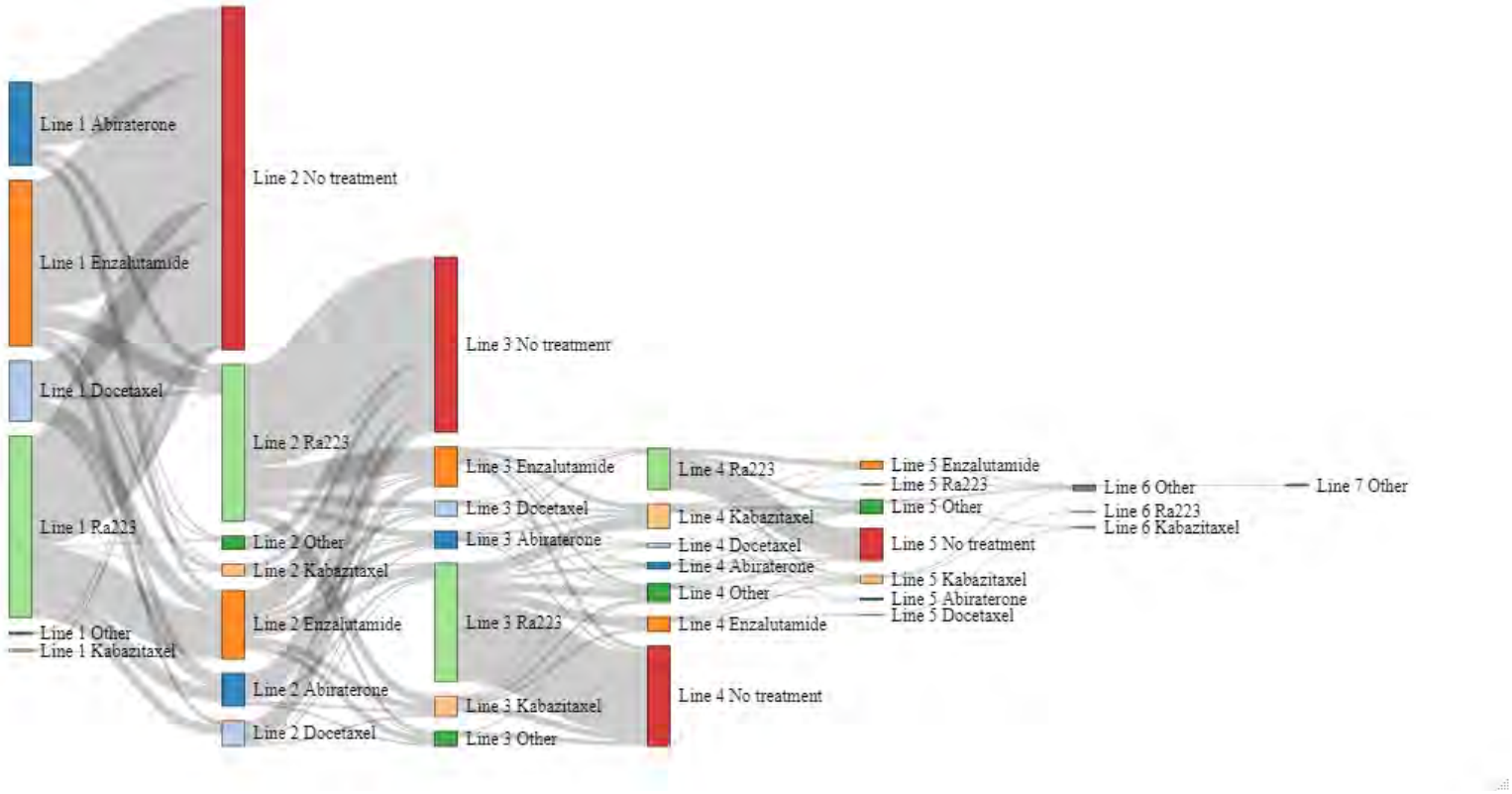
Annex 7: Supplementary figures

Supplementary Figure 1: Schematic generation of the 4 treatment-line–specific cohorts

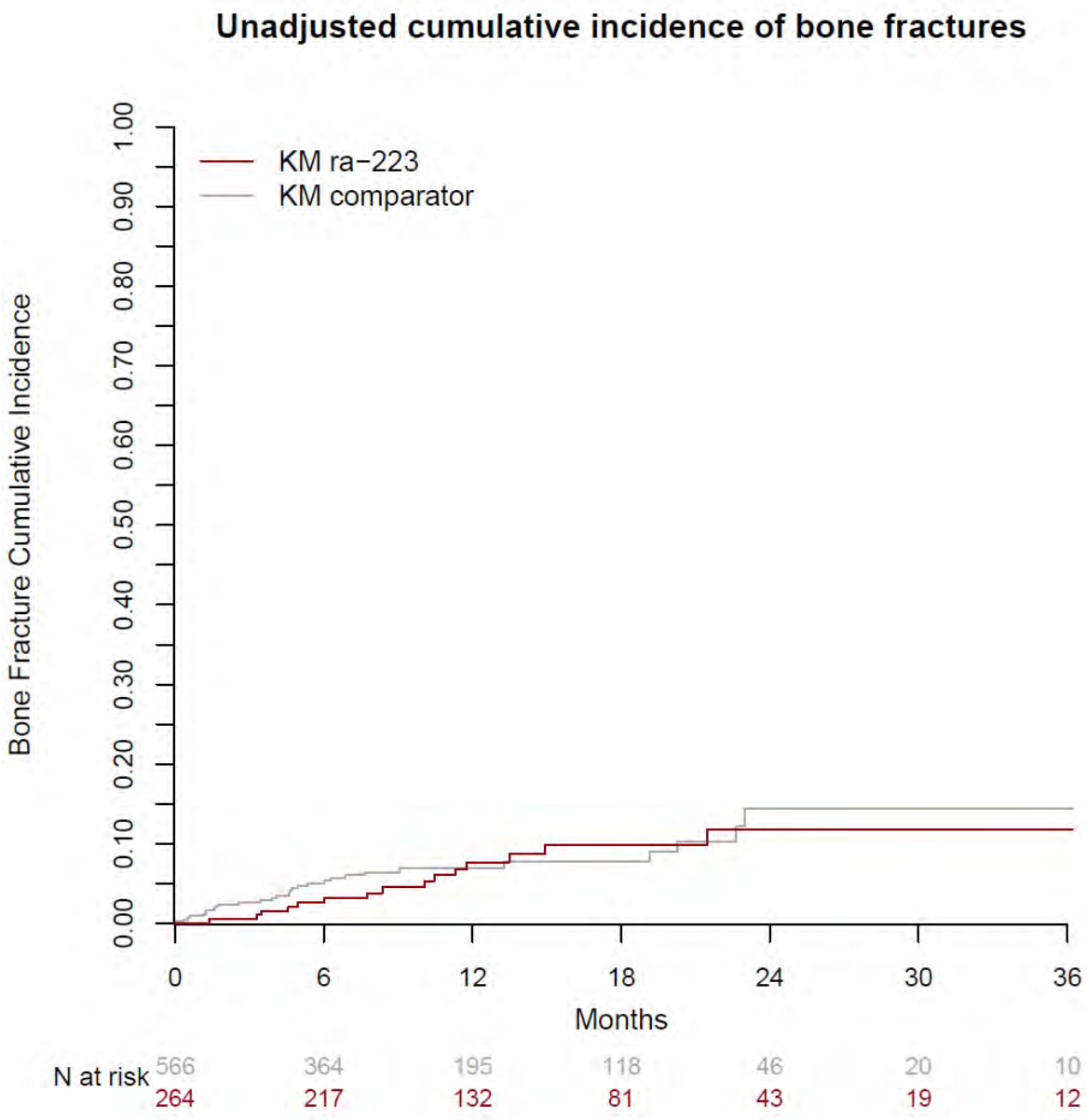


Ra-223 = radium 223.

Supplementary Figure 2: Sankey diagram of the treatments received during the study period by the complete case population

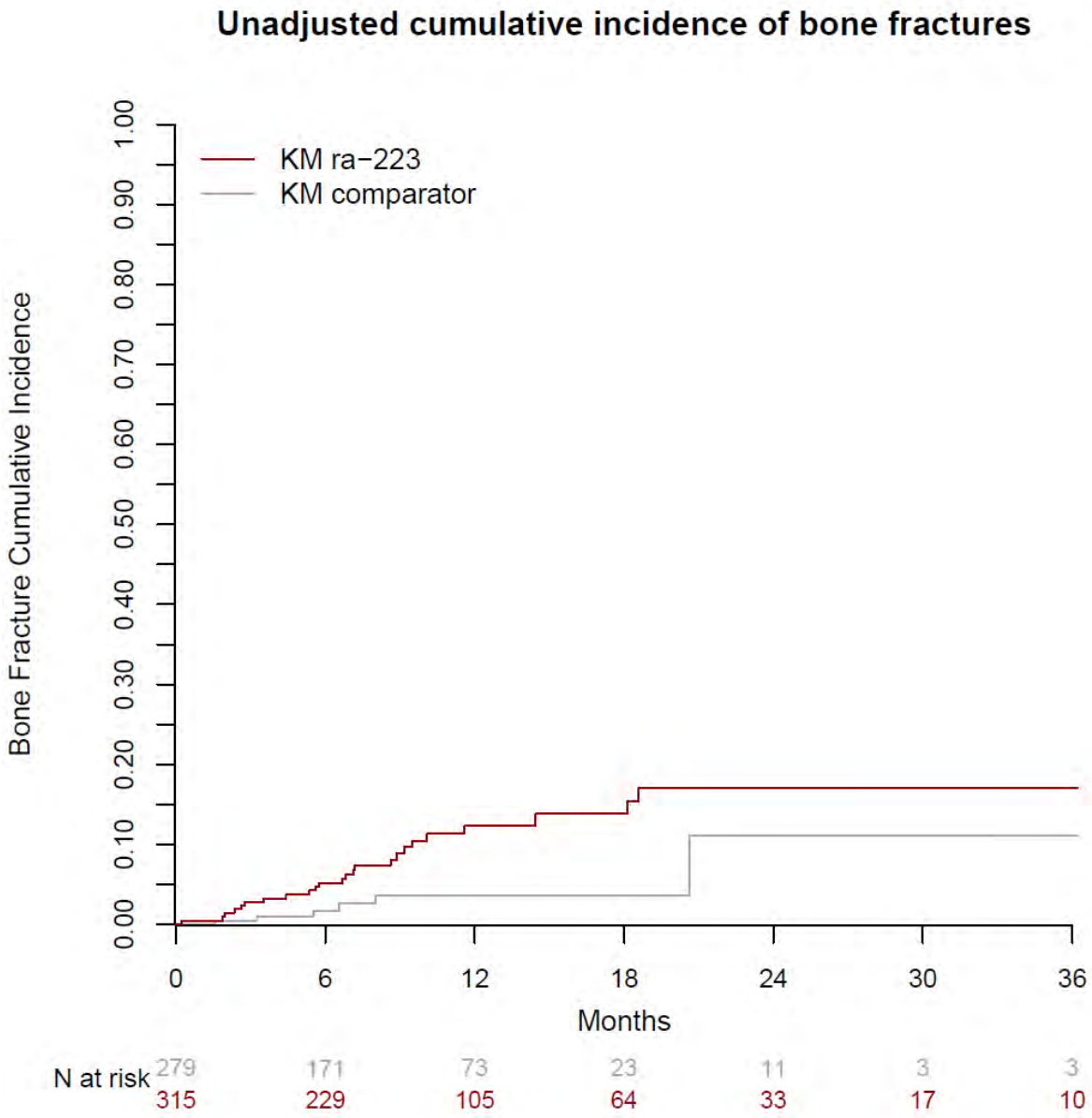


Supplementary Figure 3: Unadjusted cumulative incidence curve for bone fractures, first-line cohort



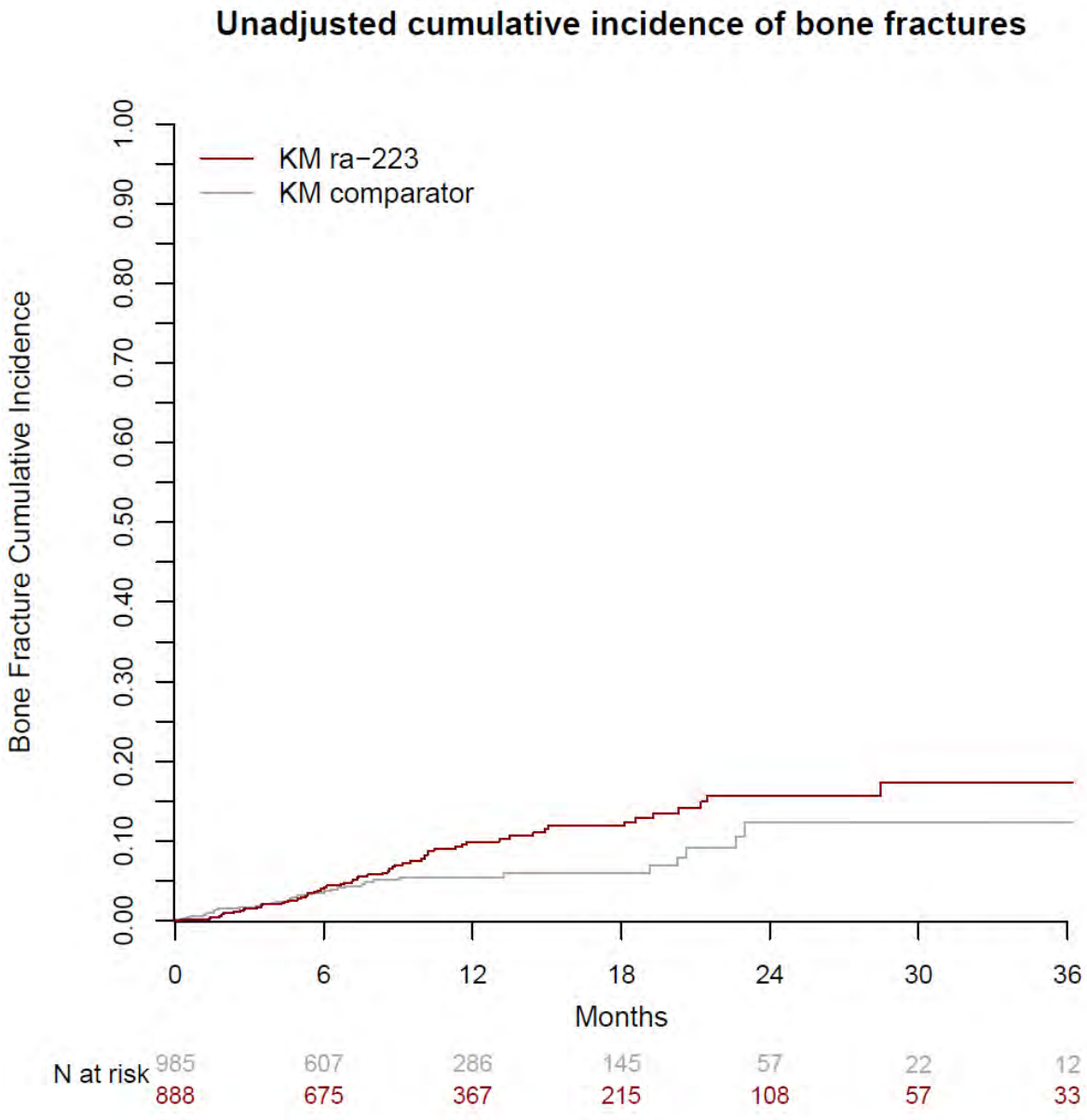
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 4: Unadjusted cumulative incidence curve for bone fractures, second-line cohort



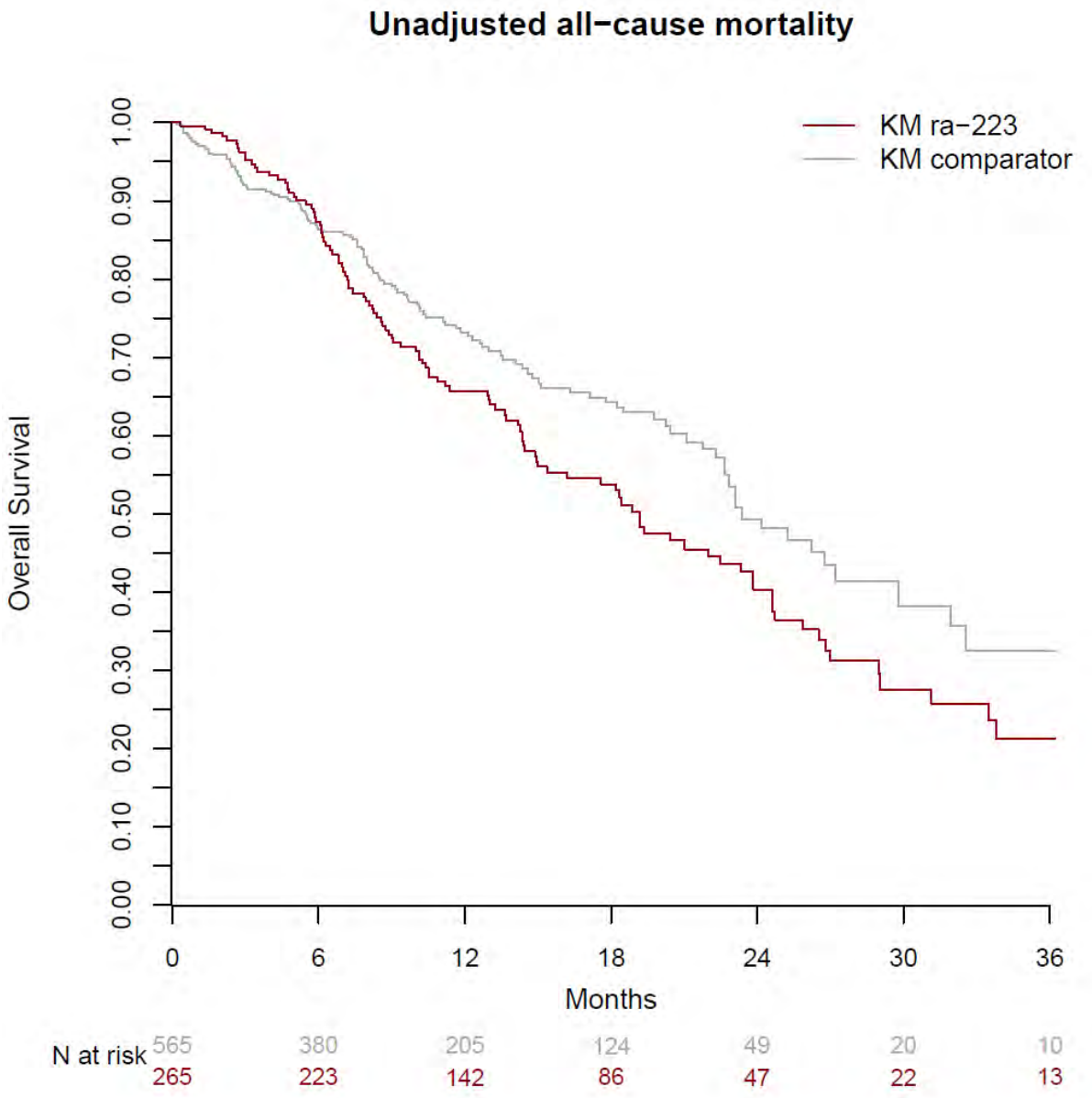
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 5: Unadjusted cumulative incidence curve for bone fractures, pooling of all 4 treatment-line–specific cohorts



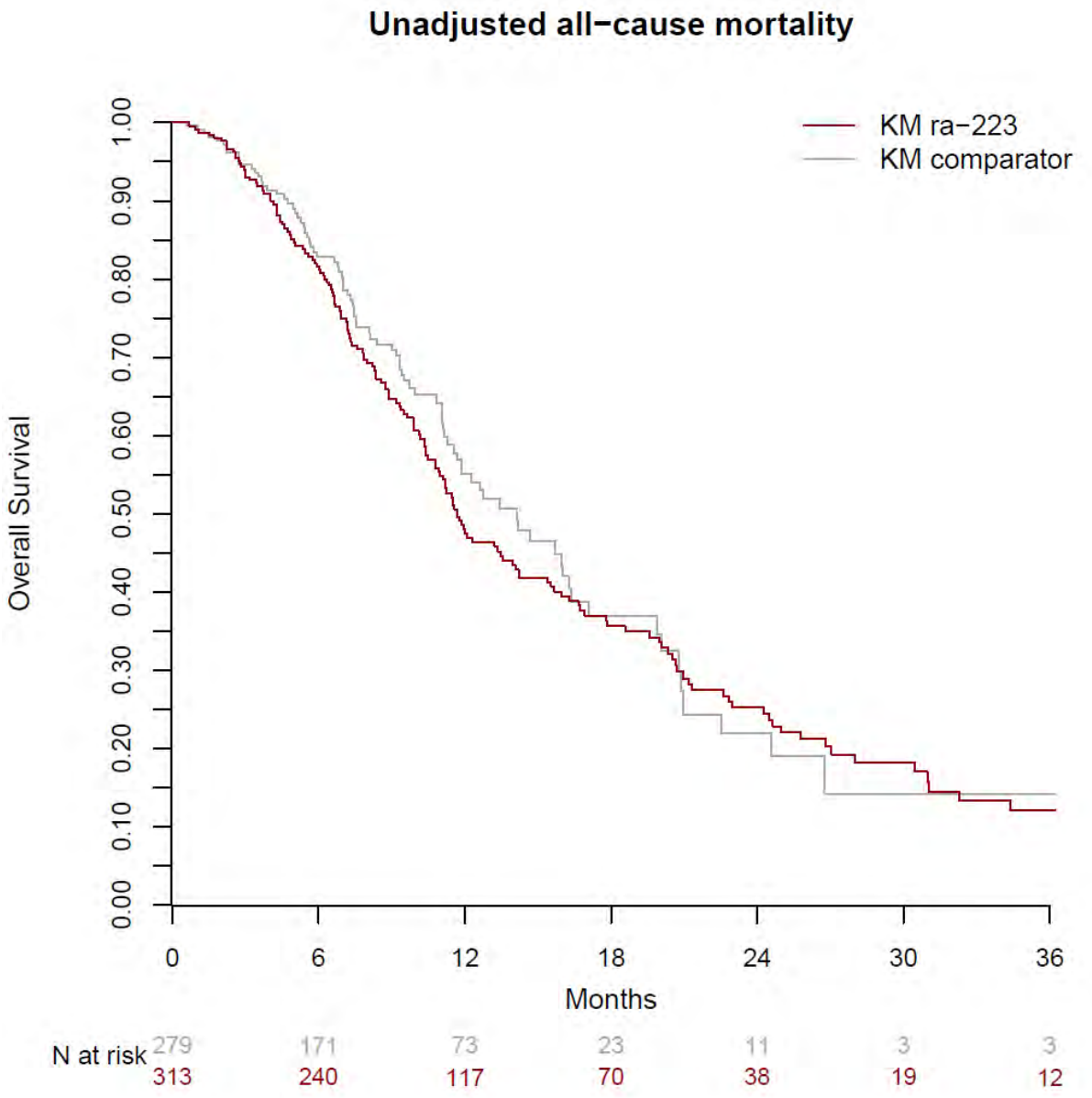
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 6: Unadjusted all-cause mortality curve, first-line cohort



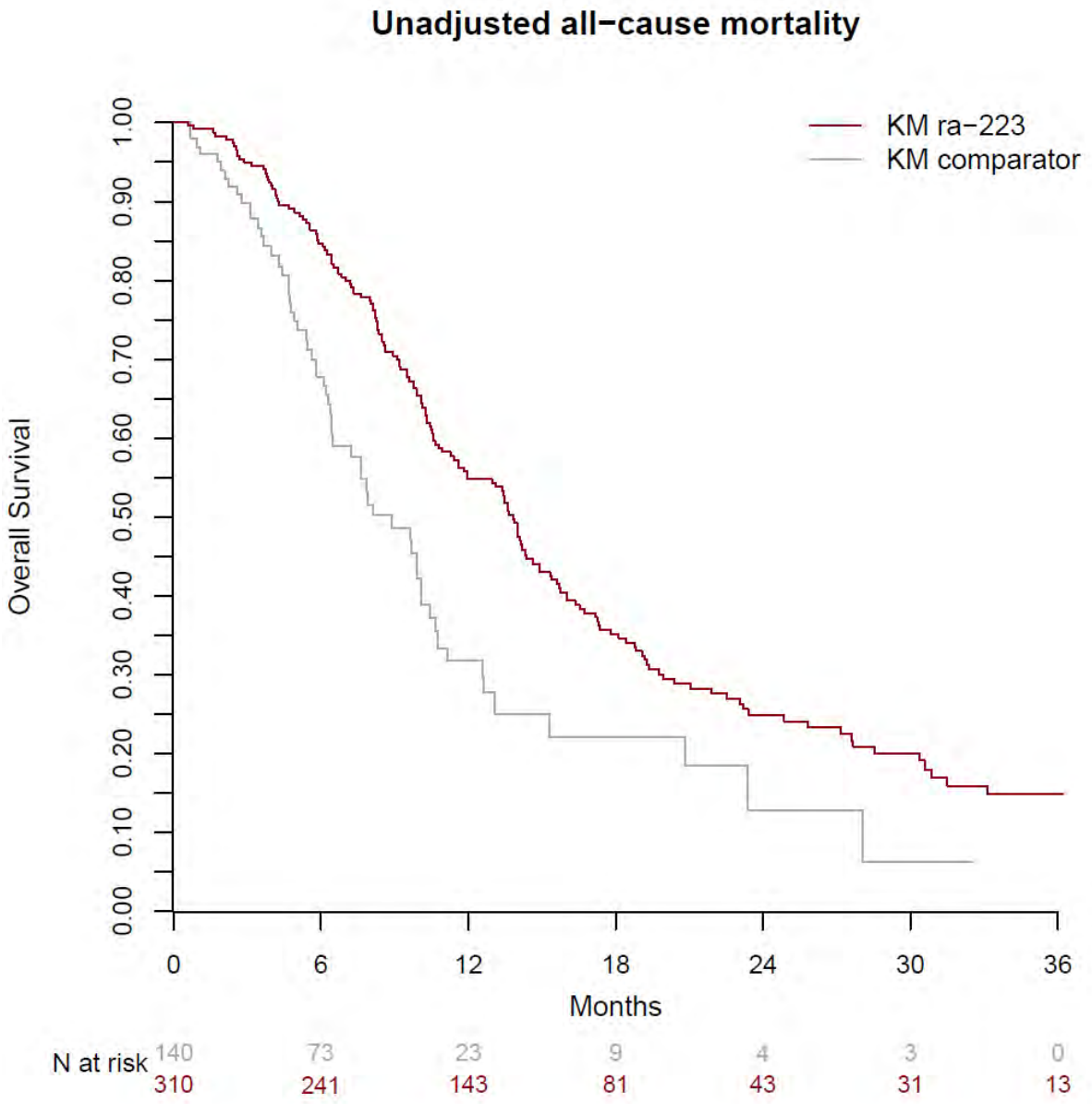
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 7: Unadjusted all-cause mortality curve, second-line cohort



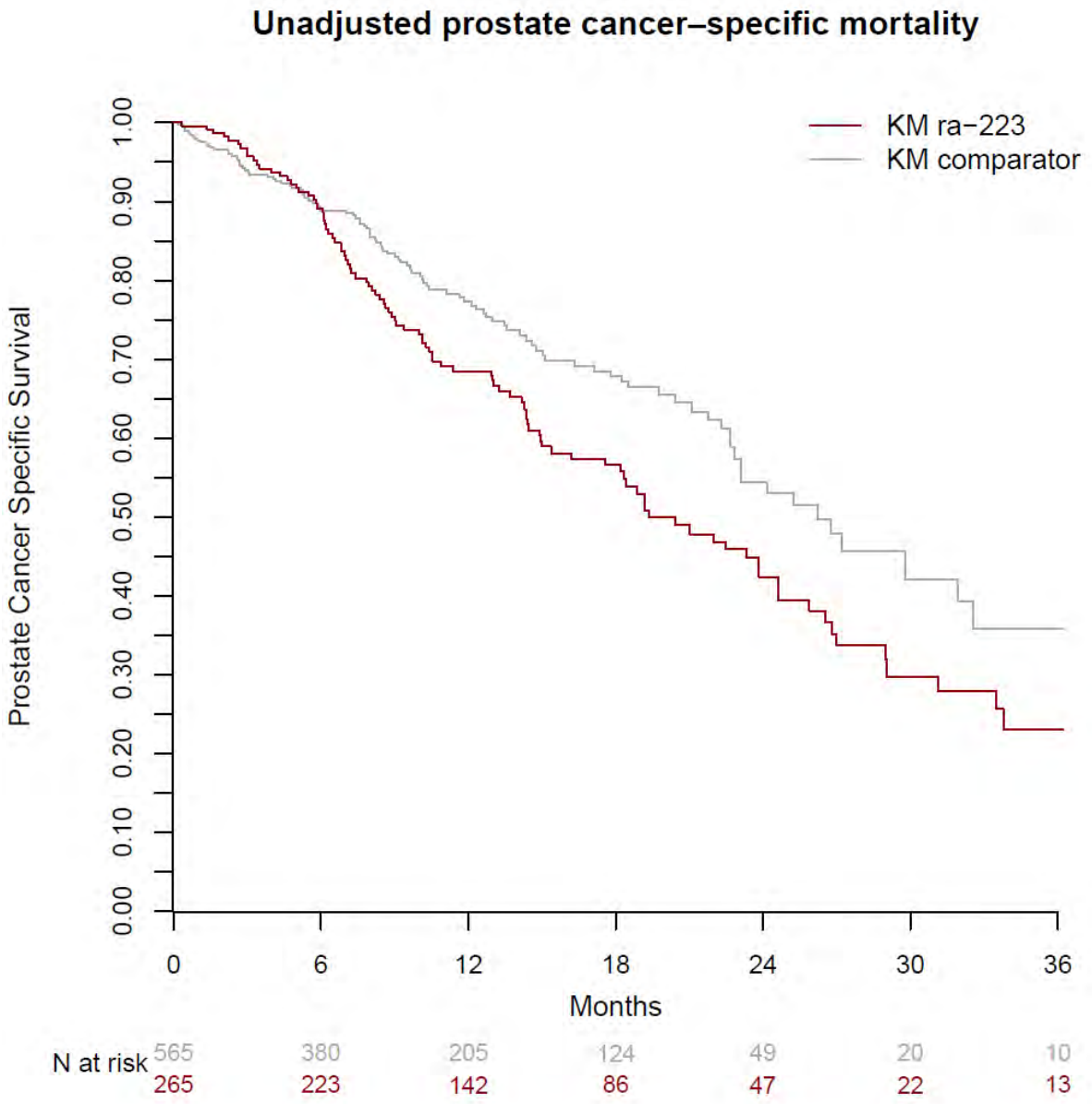
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 8: Unadjusted all-cause mortality curve, third- and fourth-line cohorts combined



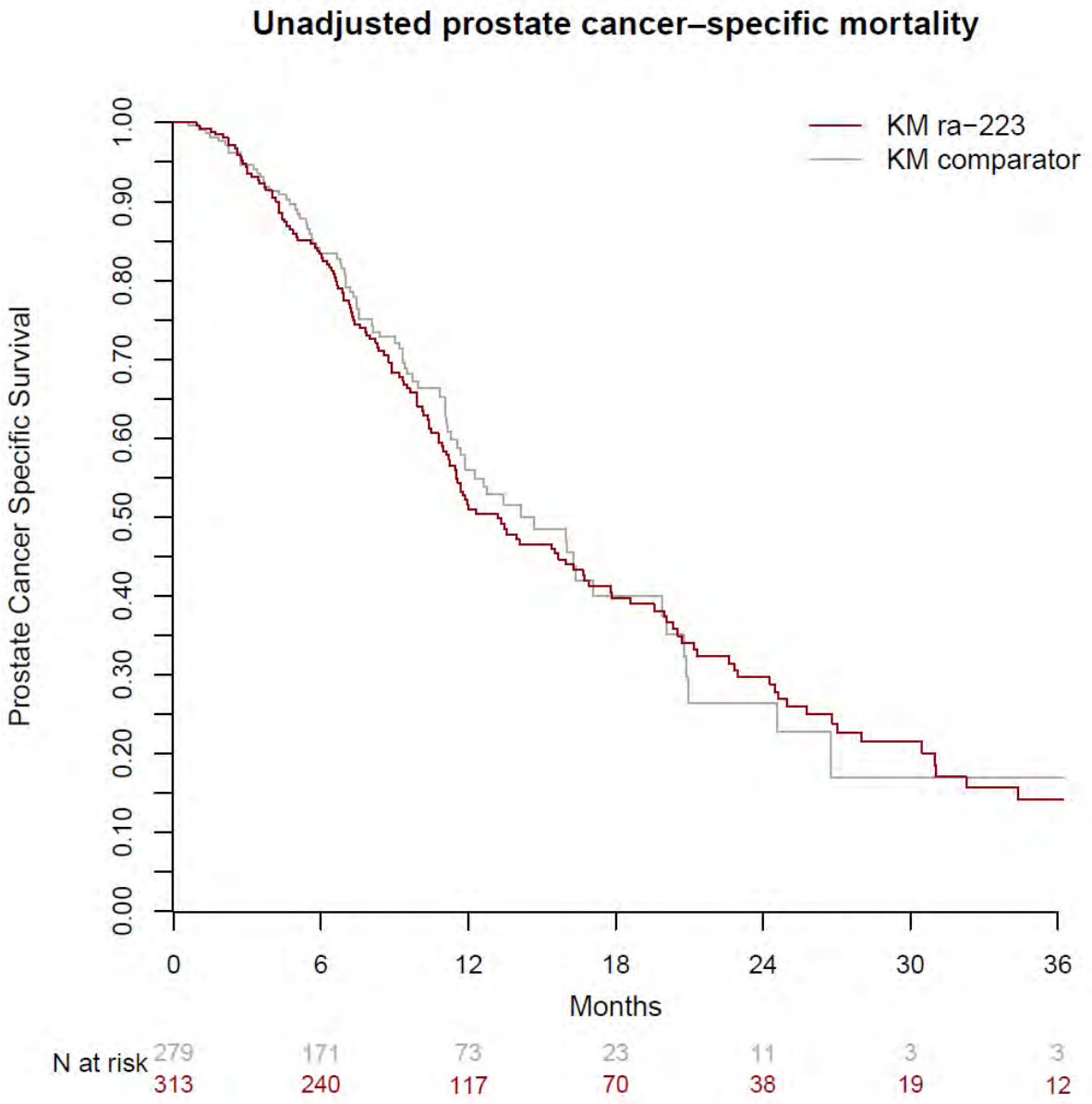
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 9: Unadjusted prostate cancer–specific mortality curve, first-line cohort



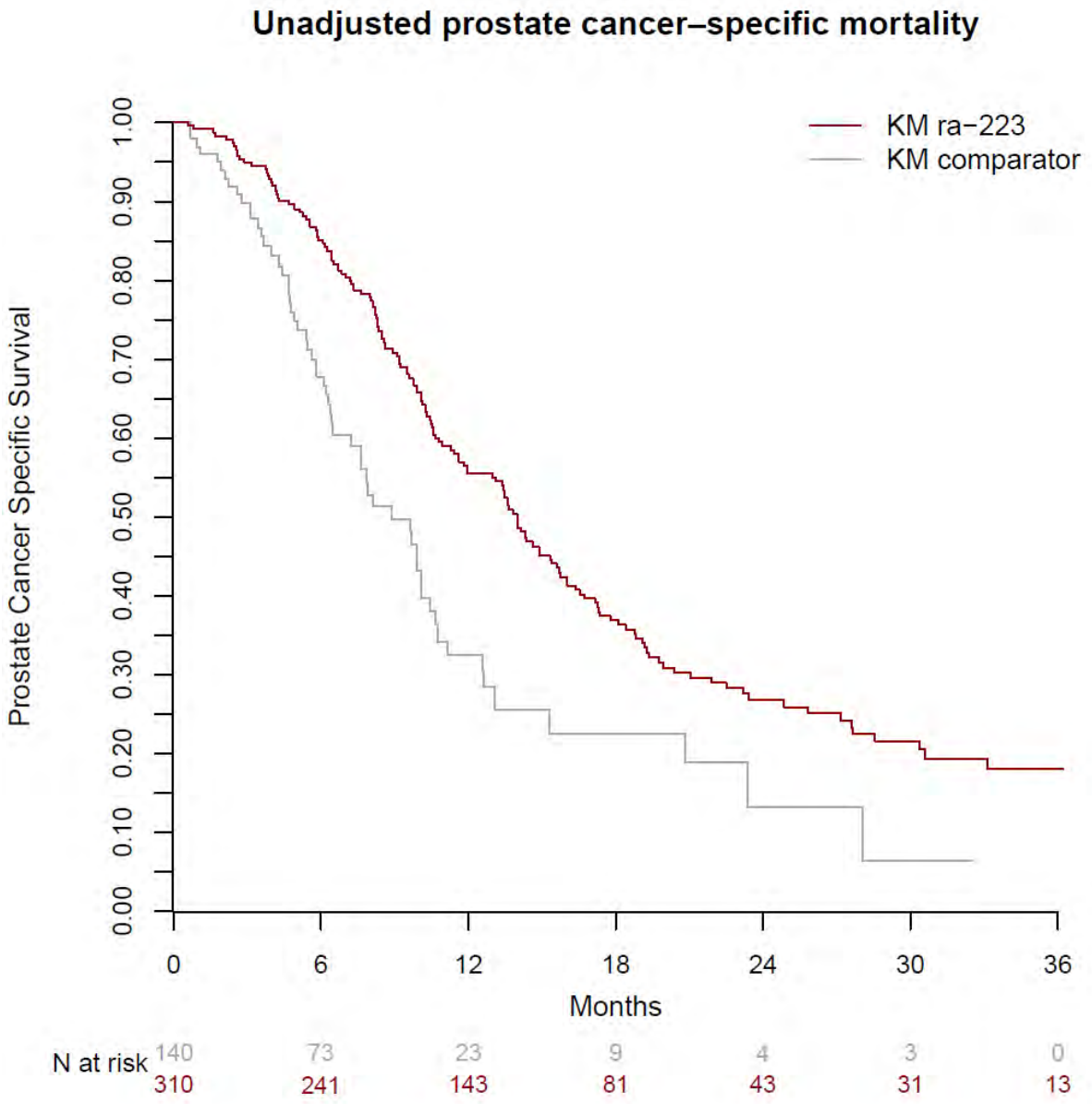
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 10: Unadjusted prostate cancer–specific mortality curve, second-line cohort



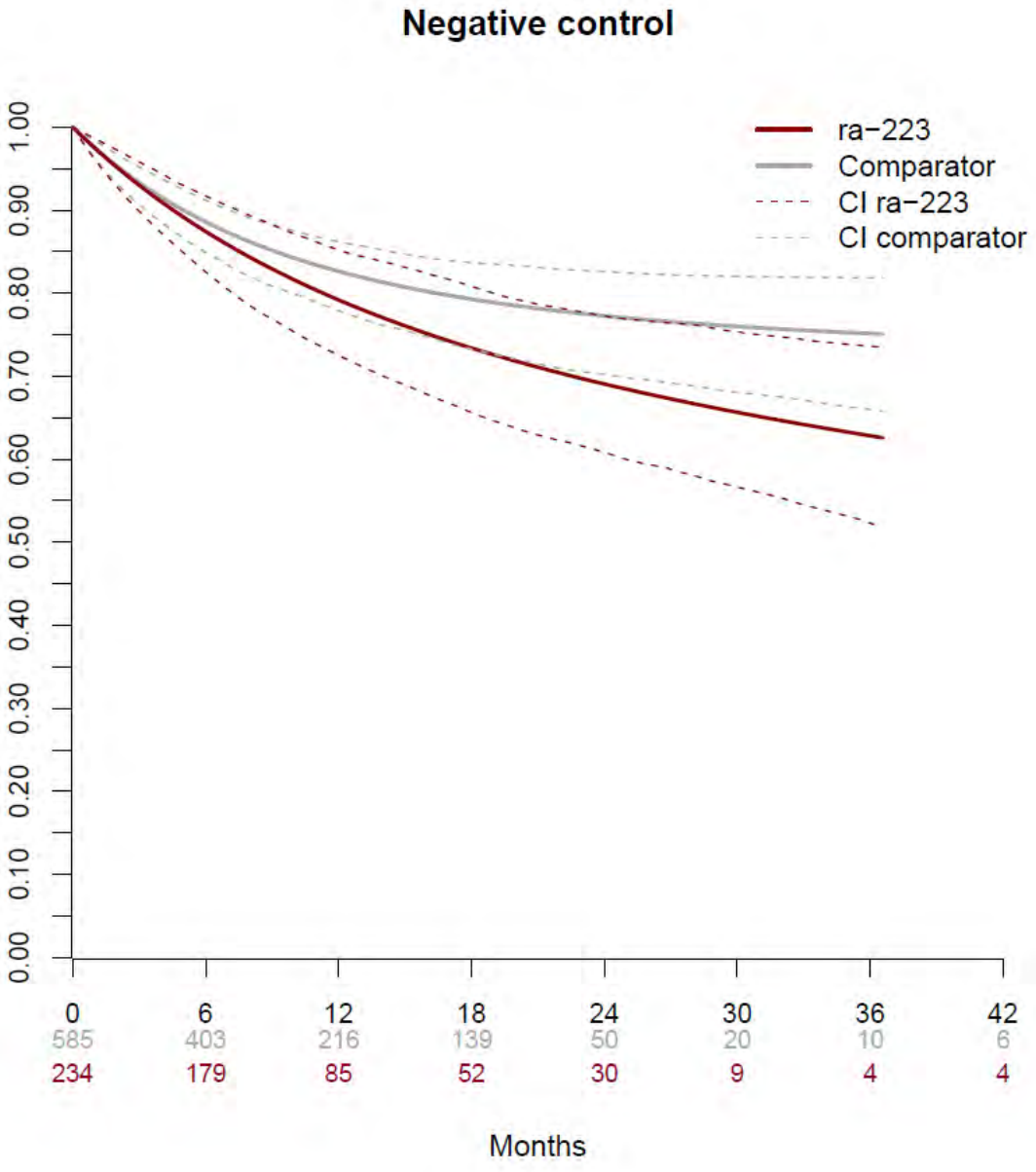
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 11: Unadjusted prostate cancer–specific mortality curve, third- and fourth-line cohorts combined



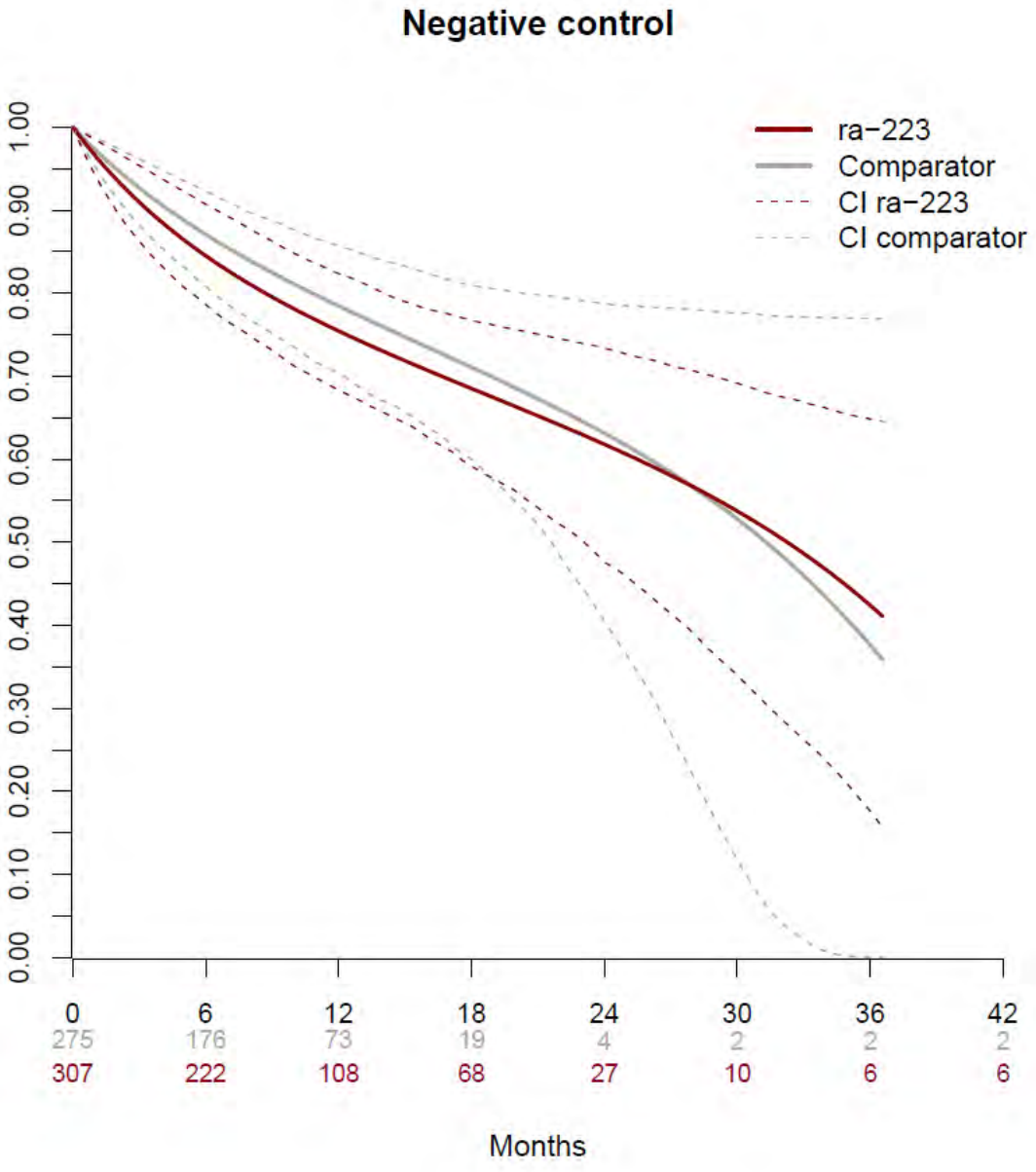
KM = Kaplan-Meier survival curves; Ra-223 = radium-223.

Supplementary Figure 12: Adjusted time to composite cardiovascular outcome, first-line cohort



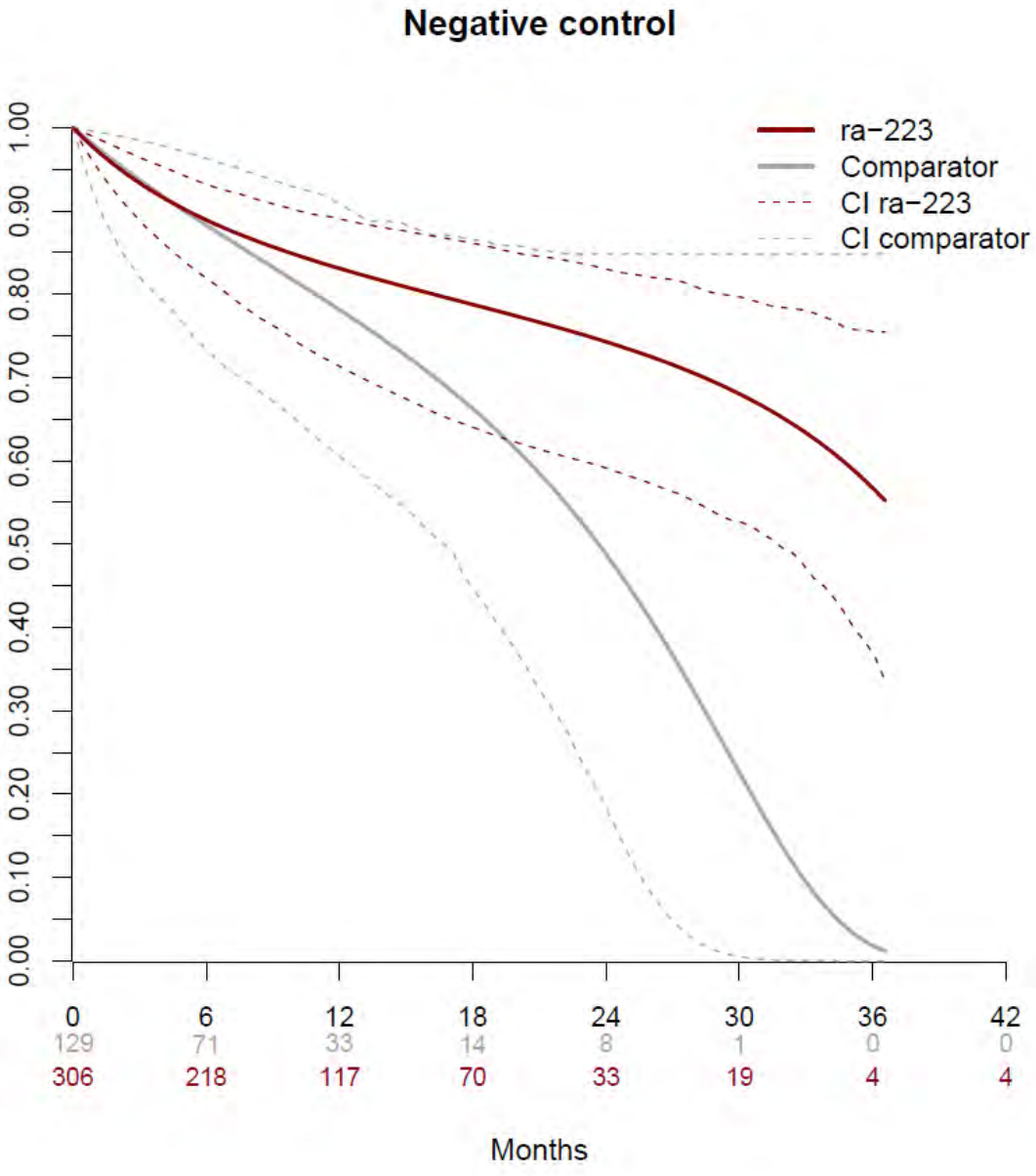
CI = confidence interval; Ra-223 = radium-223.

Supplementary Figure 13: Adjusted time to composite cardiovascular outcome, second-line cohort



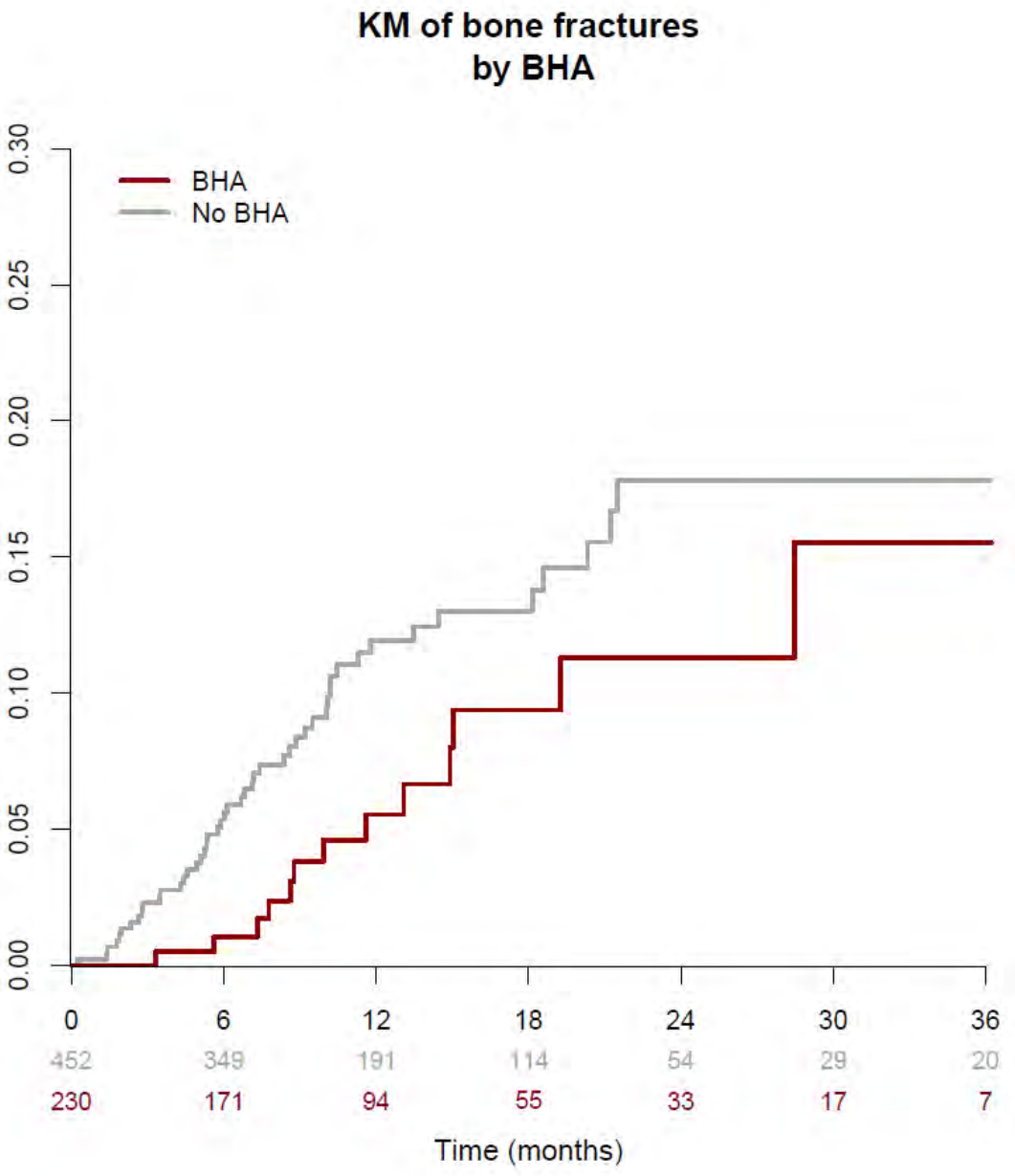
CI = confidence interval; Ra-223 = radium-223.

Supplementary Figure 14: Adjusted time to composite cardiovascular outcome, third- and fourth-line cohorts combined



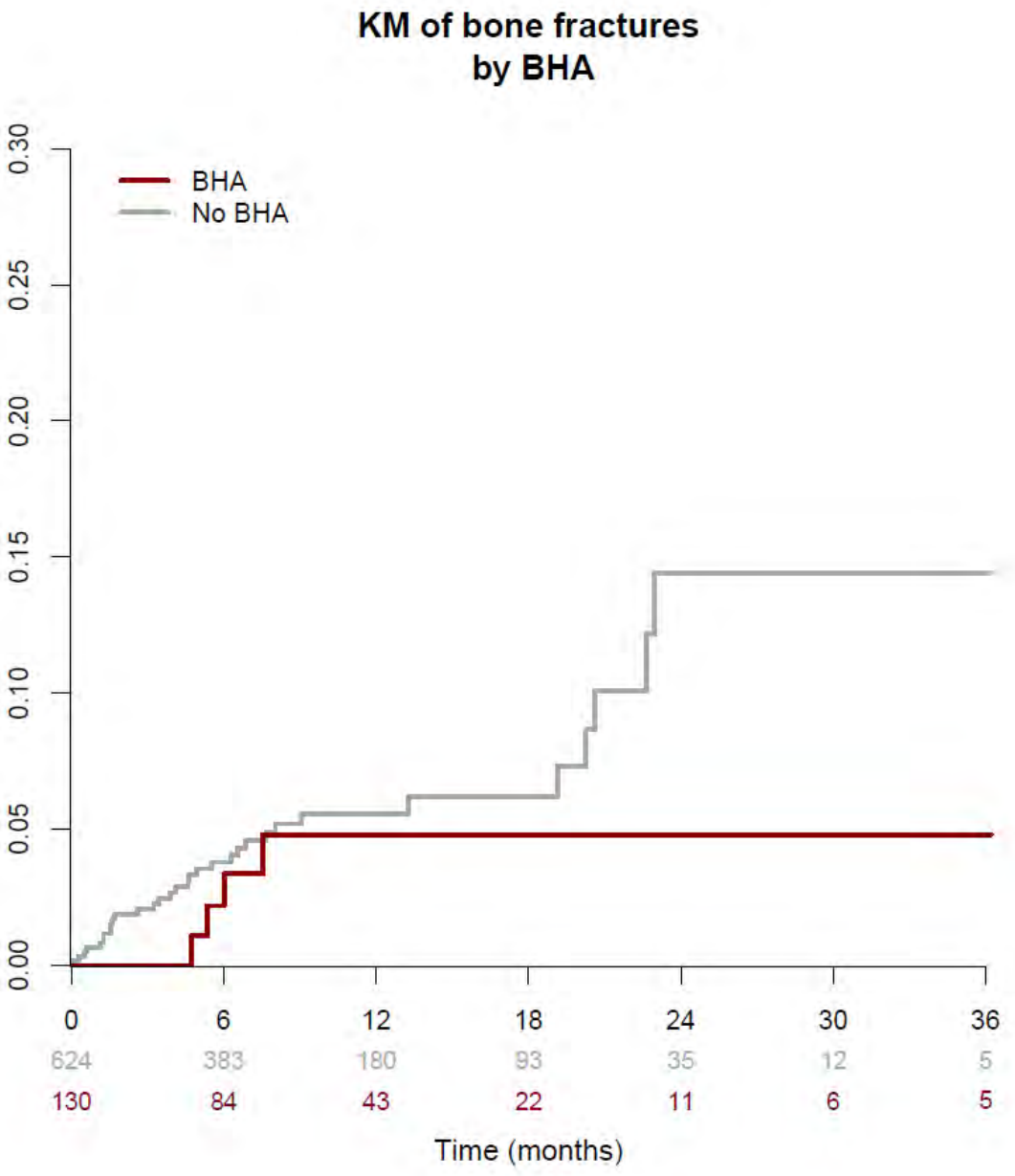
CI = confidence interval; Ra-223 = radium-223.

Supplementary Figure 15: Unadjusted cumulative incidence of bone fractures by use of bone-health agents at baseline in the Ra-223 group



BHA = use of bone-health agents; KM = Kaplan-Meier survival curves.

Supplementary Figure 16: Unadjusted cumulative incidence of bone fractures by use of bone-health agents at baseline in the comparator group



BHA = use of bone-health agents; KM = Kaplan-Meier survival curves.