Post Authorization Safety Study (PASS) Report – Study Information

Acronym/Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Report version and date	v 1.0, 07 APR 2025
GEMSTONE study number	16913
Study type/Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS7187
Active substance	Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001; NDA 203971
Procedure number	Not applicable
Comparator/Reference therapy	Not applicable
Study Initiator and Funder	Ex-USA: Bayer AG, 51368 Leverkusen, Germany USA: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA
Research question and objectives	This study evaluated the short- and long-term safety profile of radium-223 and assessed the incidence of second primary malignancies among patients with metastatic castration-resistant prostate cancer receiving radium-223 in the routine clinical practice setting. In addition, safety, pain, and overall survival were assessed.
Countries of study	Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy,

	Luxembourg, Mexico, the Netherlands, Portugal, Spain, Sweden, United Kingdom, United States of America
Author	PPD Global Medical and Evidence Targeted Radionuclide Therapies and Xofigo Bayer U.S PPD

Marketing authorization holder

Marketing authorization holder(s)	Ex-USA: Bayer AG, Kaiser-Wilhelm-Allee 1 51373 Leverkusen Germany USA: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA
MAH contact person	PPD Global Regulatory Affairs, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

Table of contents

1. Abstract

Acronym/Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Report version and date **Author**	v 1.0, 07 APR 2025 PPD Global Medical and Evidence Targeted Radionuclide Therapies and Xofigo Bayer U.S
GEMSTONE study number	16913
Keywords	Radium-223, alpha emitter radionuclide therapy, mCRPC, bone-predominant prostate cancer
Rationale and background	Prostate cancer is the most common non-cutaneous malignancy in men worldwide. Once prostate cancer becomes metastatic, survival depends on extent of disease and site of metastases. Patients with metastatic castration-resistant prostate cancer (mCRPC) usually suffer from painful bone metastases and complications from other skeletal events. With survival extension, cumulative toxicity may be observed. This study collected and reviewed safety and effectiveness data in the clinical setting.
Research question and objectives	This study aimed to evaluate short- and long-term safety profile of radium-223, which selectively targets bone metastases with high-energy, short-range alpha-particles. Primary objectives : • Assess incidence of all second primary malignancies (SPMs) • Assess incidence of treatment-emergent serious adverse events (SAEs), drug-related adverse events (AEs), and drug-related SAEs • Assess bone marrow suppression Secondary objectives: • Determine overall survival (OS) • Evaluate pain over time using the “Brief pain inventory short form” (BPI-SF) questionnaire

	• Assess incidence of bone fractures and bone-associated events
Study design	International, multicenter, observational, prospective, single-arm cohort study conducted in routine clinical practice settings.
Setting	Sites in Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Mexico, Netherlands, Portugal, Spain, Sweden, United Kingdom, United States of America. Patients were enrolled from 2014 to end of 2017. Observation period was time from start of radium-223 therapy to death, withdrawal of consent, loss to follow-up, or end of study (maximum of 7 years after last radium-223 administration).
Subjects and study size, including dropouts	The study enrolled CRPC patients with bone metastasis treated with radium-223. To achieve 1200 evaluable patients, approximately 1334 patients were to be enrolled (expected drop-out rate: around 10%).
Variables and data sources	Data were collected from medical records, routine measurements, other physicians, and patient questionnaires. Primary variables: SPMs, treatment-emergent SAEs, drug-related treatment-emergent AEs, drug-related SAEs, therapeutic/prevention measures for bone marrow suppression, white blood cell count, febrile neutropenia, haemorrhage Secondary variables: OS, worst pain/pain interference/pain severity score on BPI-SF, bone fractures, bone-associated events
Results	Of the 1550 screened patients, 1473 patients (95.0%) were enrolled and 1472 patients were included in the safety analysis set (SAF; i.e., patients who received at least one dose of radium-223). Median time from start of radium-223 to either death or last-known-alive date (LKAD) was 13.97 months. <u>Primary objectives</u> Overall, 24 patients in the SAF (1.6%) experienced 25 **SPMs** (including skin cancer, lung-related SPMs, and gastrointestinal SPMs in 5 patients each, urinary related

	SPMs in 3 patients, and neuroendocrine and hematologic SPMs in 2 patients each). Two (2) SPMs were assessed as related to radium-223 by the investigator, and 7 SPMs were fatal. To contextualize SPM incidence data, three population-based, retrospective cohort studies from Germany, Sweden, and the US were used as reference. The expected number of patients with SPMs in REASSURE as derived from the reference data was 192.176 for the German cohort, 98.881 for the US cohort, and 148.043 for the Swedish cohort. The corresponding Standardized Morbidity Ratios (SMRs) were 0.099, 0.192, and 0.128, respectively, showing that the incidence of SPMs observed over the course of the study was below the incidences in the external references. Regarding **treatment-emergent SAEs**, **treatment-emergent drug-related AEs**, and **drug-related SAEs**, the preferred term (PT) anaemia was among the most common events, across all three types of AEs/SAEs. Anaemia was also commonly reported as prior disease (6.8%) and concomitant disease (6.5%). Treatment-emergent SAEs were reported for 325 patients (22.1%), the most common PTs being anaemia (1.8%), worsening of prostate cancer (PT: prostate cancer; 1.1%), general physical health deterioration (1.0%), pneumonia (1.0%), and spinal cord compression (0.9%). Treatment-emergent drug-related AEs were reported for 537 patients (36.5%), the most common PT being diarrhoea (10.9%), followed by nausea (9.2%), anaemia (8.8%), and fatigue (7.5%). Drug-related SAEs were reported for 88 patients (6.0%), the most common PTs being anaemia (1.6%), thrombocytopenia (0.8%), and platelet count decreased (0.7%). **Bone marrow suppression** relevant treatments up to 6 months after last administration of radium-223 were reported for 339 patients (23.0%). These were blood transfusions (21.5%), erythropoiesis stimulating drugs (1.6%), and colony stimulating factors (1.6%). Post-radium-223 grade 3 or 4 bone marrow suppression relevant events (up to 6 months from last radium-223 administration) were reported for 227 patients (15.42%). The most common reported category was anaemia, defined as Standardized MedDRA Query (SMQ) 'haematopoietic erythropenia (SMQ)' (12.64%), followed by MedDRA Labelling Groupings (MLG): 'thrombocytopenia' (3.87%).

	<u>Secondary objectives</u> Of the 1472 patients in the SAF, 1308 patients (88.9%) died and 164 patients (11.1%) were censored. The median **OS** (from start of radium-223 to death due to any cause) was 15.6 months. The pain severity score of the **BPI-SF** questionnaire was consistently lower on treatment and during follow-up than at baseline. The mean pain severity score was 3.003 at baseline and ranged from 2.760 at treatment 2 to 2.261 at treatment 5. The pain interference score showed similar trends, mean score being 3.283 at baseline and ranging from 2.965 at treatment 2 to 2.358 at treatment 5. Both scores increased slightly at follow-up visits in comparison to post-baseline treatment measurements but remained below the baseline values. The proportion of patients with a clinically meaningful pain response in worst pain item in the SAF increased slightly over treatment time points, ranging from 28.0% at treatment 2 to 34.7% at treatment 5. In a post-hoc analysis restricted to patients with a baseline worst pain score ≥2, the proportion of patients with a clinically meaningful pain response in worst pain item was constantly higher than in the overall SAF. A total of 247 patients (16.8%; Exposure Adjusted Incidence Rate per year: 0.36) had at least one **bone fracture or bone-associated event**. Bone disorders (excl congenital and fractures) occurred in 8.5% and Fractures in 9.7% of patients. In patients with **concomitant bone health agent therapy**, the incidence of bone fractures or bone-associated events was slightly lower than in patients without such therapy (13.9% versus 18.8%).
Discussion	The study provides a robust dataset which demonstrates a low incidence of SPMs and observation of manageable treatment-emergent AEs. Generalizability is supported by the diverse patient population across multiple countries, reflecting real-world clinical settings. Therefore, the study confirms that radium-223 maintains a favorable benefit-risk profile in treatment of mCRPC, reinforcing its role as therapeutic option for patients with bone metastases. No immediate further evidence is deemed necessary to confirm the safety profile. The results do not warrant changes to the known benefit-risk of radium-223 in the authorized indication.

Marketing Authorization Holder(s)	Ex-USA: Bayer AG, 51368 Leverkusen Germany USA: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981, USA
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating and/or all investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1).

2. List of abbreviations

AE	Adverse Event
AG	Aktiengesellschaft
AJCC	American Joint Committee on Cancer
ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer
AML	Acute Myeloid Leukaemia
ATC	Anatomical Therapeutic Chemical (Classification System)
BHA	Bone Health Agent
BPI-SF	Brief pain inventory short form
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
EAIR	Exposure Adjusted Incidence Rate
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
EMA	European Medicine Agency
EOD	Extent of Disease
EOO	End of Observation
EU	European Union
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
ICD	International Classification of Diseases
ID	Identifier
IEC	Independent Ethics Committee
KM	Kaplan-Meier
LKAD	Last-Known-Alive Date
MAH	Marketing Authorization Holder
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA Labelling Groupings
MRP	Medical Review Plan
OS	Overall Survival
OS Report	Observational Study Report
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PCBaSe	Prostate Cancer Data Base Sweden
PET	Positron Emission Tomography
PSA	Prostate Specific Antigen Level
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible For Pharmacovigilance
ROW	Rest of the World
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SEER	US Surveillance, Epidemiology and End Results
SMQ	Standardized MedDRA Query
SMR	Standardized Morbidity Ratio
SOC	System Organ Class
SOP	Standard Operating Procedure
SSE	Symptomatic Skeletal Event
SPM	Second Primary Malignancy
TLF	Tables, Listings, and Figures
TTP	Time to Progression
UK	United Kingdom
US(A)	United States (of America)
VDR	Validity Review and Data Decision Report
WBC	White Blood Cell Count
WHO-DD	World Health Organization Drug Dictionary

3. Investigators

Contact details of the principal and/or coordinating investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Annex 1).

4. Other responsible parties

Administrative changes of responsible persons and/or the composition of the committees were documented by updating the respective lists but did not require formal protocol amendments.

4.1 Sponsor contact names

Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD
Role	PPD
Name	PPD

Role	PPD
Name	PPD

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

4.2 Contract research organization

Contract Research Organization (CRO) contact details:

Oracle Life Sciences

Riesstr. 25, 80992 Munich, Germany

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (first patient first visit)	Q3 2014	20 AUG 2014	None
End of data collection (last patient last visit)	DEC 2023	02 AUG 2024	Recruitment prolonged until DEC 2017 to allow for continued enrollment in Latin America (regulatory obligation)
Registration in the EU PAS register	06 AUG 2014	06 AUG 2014	
Interim report 1	SEP 2017	11 MAY 2017 (data cut-off 22 SEP 2016)	Amended on 20 APR 2018
Interim report 2	SEP 2019	16 SEP 2019 (data cut-off 20 MAR 2019)	None
IEC or IRB approval – Study protocol version 3.0[a, b]	None	First approval: 03 JUN 2014 Last approval: 05 SEP 2016	None
IEC or IRB approval – Study protocol version 4.0[a]	None	First approval: 12 FEB 2015 Last approval: 27 APR 2018	None
IEC or IRB approval – Study protocol version 5.0[a]	None	First approval: 10 SEP 2018 Last approval: 22 DEC 2021	None
Database Clean	24 OCT 2024	24 OCT 2024	
Final report of study results	SEP 2024	07 APR 2025	Delayed due to longer recruitment period

Abbreviations: EU PAS: European Union Post Authorization Studies, IEC: independent ethics committee, IRB: independent review board, N/A: not applicable, PAS: post-approval study, Q3/Q4: 3rd/4th quarter

a: A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1).

b: Protocol version 3.0 was the first version that was rolled out in countries.

6. Rationale and background

Prostate cancer is the most common non-skin cancer and the second-leading cause of cancer-related death among men in the United States of America (USA). According to recent national estimates, 268,490 new cases of prostate cancer were estimated to be diagnosed in the USA in 2022, and 34,500 deaths from prostate cancer were estimated to occur. Approximately 8% of prostate cancer cases are diagnosed with distant (metastatic) stage [Siegel 2025]. Aggressive or advanced forms of prostate cancer may require surgical or hormonal castration. Castration-resistant prostate cancer (CRPC), which is characterized by disease progression after such castration therapy, has a poor prognosis. Approximately 10 to 20% of prostate cancer patients develop CRPC within 5 years of primary therapy, and a large proportion of them have bone metastases at the diagnosis of CRPC, including spreads in the vertebral column, skull, ribs, and bones [Bubendorf 2000, Kirby 2011] . Metastatic CRPC (mCRPC) is associated with poor prognostic outcomes including significantly lower survival compared to local or regional prostate cancer [Kirby 2011, Siegel 2022].

Bone metastases commonly cause bone pain and lead to bone complications with skeletal-related events (SREs), such as fractures and spinal cord compression, and hematological consequences of bone marrow involvement, thus impairing the patient's quality of life (QoL). Bone metastases and/or SREs are associated with significantly lower survival in men with mCRPC [Broder 2015, Tablazon 2019].

Control of bone metastases is expected to lead to improved symptoms and QoL as well as prolonged overall survival (OS).

There is little or limited information on the timing of progression and management of progression in the clinical setting for this patient population. Time to progression has been and continues to be of interest as a potential surrogate marker in other solid tumors [Buyse 2007, Korn 2013, Soloway 1988].

Available treatment options differ in terms of mode of actions and/or safety profile. With survival extension, cumulative toxicity may be observed [Carroll 2018].

The active moiety of Xofigo is the isotope radium-223, which as a calcium-mimetic, is taken up into areas of high bone turnover. The decay deposits high-energy, short-range alpha-particles selectively into bone metastases.

The Phase III, double-blind, randomized, BC1-06, ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial was started in 2008 [Parker 2013]. A total of 921 patients with CRPC and symptomatic bone metastases who had received, were unfit for or declined docetaxel were randomized (2:1) to receive 6 injections of radium-223 (55 kBq/kg intravenous [IV]) with standard of care or matching placebo with standard of care every 4 weeks. The primary endpoint was OS. Radium-223 significantly improved OS compared to placebo (median OS 14.9 vs. 11.3 months, respectively; p=0.00007; hazard ratio=0.695) and also preserved QoL better than placebo [Parker 2012]. Additional key secondary endpoints were reached, including time to symptomatic skeletal event (median time to symptomatic skeletal event 15.6 months vs. 9.8 months, respectively; hazard ratio=0.66, 95% confidence interval [CI]: [0.52, 0.83]; P<0.001). Post-hoc analyses of pain parameters and pain-related QoL revealed that radium-223 reduced pain and opioids use.

Since efficacy of radium-223 solution for injection is achieved by deposition of alpha-particle radiation into active bone lesions, long-term radiation effects to adjacent bone marrow and normal bone tissue was specifically evaluated during the follow-up period. The safety and

tolerability of radium-223 did not show new or unexpected changes in the safety profile in ALSYMPCA [Bayer 2015].

Data from the Surveillance, Epidemiology and End Results (SEER) Program cancer registry (1973-1993) [Brenner 2000] indicated that of a total of 51,584 men with prostate cancer who had received radiotherapy, 3549, i.e., 6.9% developed a second malignancy. Most (3171) had solid tumors. Skin cancers were not included in the analysis. The follow-up period for these patients was up to more than 10 years (between 1973 and 1993).

The proposed 7-year follow-up of REASSURE is based on the finding from the "Spiess study" that follows the health of 899 persons who received multiple injections of another short-lived alpha-particle emitter radium-224 mainly between 1945 and 1955 for the treatment of tuberculosis, ankylosing spondylitis, and some other diseases. In December 2007, 124 persons were still alive. The most striking health effect, observed shortly after radium-224 injections, was a temporal wave of 57 malignant bone tumors. During the two most recent decades of observation, a significant excess of non-skeletal malignant diseases has become evident. Up to the end of December 2007, the total number of observed malignant non-skeletal diseases was 270 (248 specified cases of non-skeletal solid cancers and 22 other malignant diseases, among these 16 malignant neoplasms of lymphatic and hematopoietic tissue, 6 without specification of site) compared to 192 expected cases. The peak of development of secondary tumors was observed between 7 and 8 years [Nekolla 2010].

At the request of regulatory authorities, the safety of radium-223 was further assessed through the conduct of an international, prospective, observational single-arm cohort study to evaluate the occurrence of second primary malignancies (SPMs) among other key safety endpoints in patients treated with radium-223: the REASSURE study.

7. Research question and objectives

The purpose of this observational study was to evaluate the short- and long-term safety profile of radium-223, with a particular interest in the risk of developing SPMs, bone marrow toxicity, and fractures or other bone-associated events among CRPC patients receiving radium-223 in the routine clinical practice setting.

The primary objectives of this study were:

- To assess the incidence of all SPMs (including myelodysplastic syndrome [MDS]/acute myeloic leukaemia [AML] and osteosarcoma) in mCRPC patients treated with radium-223 in the routine clinical practice setting
- To assess the incidence of treatment-emergent serious adverse events (SAEs) (collected up to 30 days after last administration), drug-related adverse events (AEs) (collected up to 30 days after last administration), and drug-related SAEs (up to 7 years after the last administration of radium-223)
- To assess bone marrow suppression

The secondary objectives of this study were:

- To determine the OS in patients treated with radium-223
- To evaluate pain over time using the "Brief pain inventory short form" (BPI-SF) questionnaire
- To assess the incidence of bone fractures and bone-associated events (e.g., osteoporosis)

8. Amendments and updates

Table 2: Amendments

No.	Date	Section of study protocol	Amendment/Update	Reason
AM01	18 JAN 2016	Throughout document	Milestones were adapted: end of recruitment was updated and date of EU PAS registration was added.	Enrollment took longer than anticipated. Thus, the purpose of this amendment was to extend the enrollment period to allow for sufficient patient recruitment. An additional purpose was the introduction of patterns of progression.
		Section 7 and 13	Added reference to rationale.	
		Section 9.3.2	Added that completion of BPI-SF questionnaire is voluntary.	
		Section 9.3.5 and 9.3.6	Added clarification of study start.	
		Section 9.3, 9.3.9.1, 9.3.9.2, and 9.3.9.3	Reordered text for clarity and ensured all variables being assessed were captured and consistent.	
		Sections 9.3.9.2, 9.3.9.3, 9.3.11, 9.7.8, and 11	Added that data on progression will be collected and analyzed.	
		Section 9.7.11	Deleted text no longer applicable.	
		Section 9.8.1	Added text for MRP.	
		Throughout document	Administrative and formal changes were implemented in several sections.	

No.	Date	Section of study protocol	Amendment/Update	Reason
AM02	20 AUG 2018	Sections 8.2, 9.1.2, 9.7.5, 11.2 Section 9.1 and throughout document Throughout document	Assessment of the incidence of bone fractures and bone-associated events (e.g., osteoporosis) was added to the secondary objectives. Radium-223 dichloride should not be given concurrently with abiraterone plus prednisone/prednisolone. A general change was implemented that the option of starting a bone health agent should be considered, taking into consideration applicable guidelines. The study milestone for global last patient first visit was changed to 31 Dec 2017 to allow for continued enrollment in Latin America (regulatory obligation). The protocol was adapted to most current template. Administrative and formal changes were implemented in several sections.	The ERA-223 study was unblinded based on the IDMC recommendation following an ad hoc independent analysis where more treatment-emergent fractures were observed in the active treatment arm compared to the placebo arm. Additionally, bone health agents appeared to decrease the fracture rate in both treatment arms. Therefore, after the agreement with several health authorities, the protocol was amended to better assess the fracture risk in the routine practice in the approved indication.

Abbreviations: AM: Amendment, BPI-SF: Brief pain inventory short form, EU PAS: European Union Post Authorization Studies, IDMC: Independent Data Monitoring Committee, MRP: Medical Review Plan

9. Research methods

9.1 Study design

REASSURE was an observational, prospective, single-arm cohort study, conducted in routine clinical practice settings. Enrollment of 1334 patients was planned in order to achieve 1200 evaluable patients. The decision to treat with radium-223 was to be made independent from and before patient enrollment in the study. Treatment with radium-223 was to follow the approved local product information.

Based on the protocol amendment from August 2018, radium-223 dichloride was not to be given concurrently with abiraterone plus prednisone/prednisolone. The option of starting a bone health agent including bisphosphonates or denosumab was to be considered, taking into account applicable guidelines.

To contextualize findings from the REASSURE study, SPM incidence data from external secondary data sources was generated and used as reference. SPM incidence rates in mCRPC patients enrolled in the REASSURE study were indirectly compared with the corresponding reference information on SPM in mCRPC patients from external secondary data source(s) (see Section 9.9.2.5).

9.1.1 Primary endpoints

- The incidence of developing SPMs
- AEs/SAEs
  - Incidence of treatment-emergent SAEs (up to 30 days after last administration)
  - Incidence of drug-related treatment-emergent AEs (up to 30 days after last administration)
  - Incidence of drug-related SAEs (up to 7 years after last administration)
- Bone marrow suppression

9.1.2 Secondary endpoints

- The OS in mCRPC patients treated with radium-223 in the routine clinical setting
- The worst pain score and pain interference score over time as determined by patient responses on the BPI-SF questionnaire
- Bone fractures and bone-associated events (e.g., osteoporosis), regardless of investigator assessment of causality, based on AEs

9.1.3 Strengths of the study design

REASSURE was an international, prospective, observational, cohort study of CRPC patients with bone metastasis who received radium-223 in routine clinical practice settings. The study included patients from a more diversified and less selected patient population than in clinical trial setting, using fewer eligibility criteria to be as representative to the general CRPC patients with bone metastasis as possible.

9.2 Setting

The study was initiated in the USA, Canada, Israel, European Union (EU; Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Luxembourg, Netherlands,

Portugal, Spain, Sweden), the United Kingdom (UK), and Latin America (Argentina, Colombia, Mexico) according to health authority approval timelines. Enrollment started in 2014 and recruitment was completed at the end of 2017. The observation period for each patient enrolled in this study was the time from start of therapy with radium-223 to death, withdrawal of consent, loss to follow-up, or end of study (maximum of 7 years after last radium-223 administration) for each individual patient, whichever came first.

After the patient and treating physician had agreed on a treatment decision, the patient was to be informed about the study and had to sign an informed consent in order to participate in this study.

Baseline information was to be recorded with the status before the first radium-223 administration during the patient visit. For each treatment cycle, information from patient medical records was to be documented and entered into the electronic data capture system (EDC) by the physician or a designated person within the treatment team. Pain assessment questionnaires were to be collected at each treatment cycle and to be entered into the database by the CRO.

After end of treatment, the patient information regarding the outcomes of interest (SPM, other safety information, OS, and progression) was to be gathered at intervals of approximately 3, 6 and 12 months and thereafter yearly for a maximum of 7 years after last administration of radium-223 according to local clinical practice. Information was to be collected from patient's record or during follow-up visits by the recruiting physician or a designated person within the treatment team. The visit frequency was determined by the local standard of care at the local site.

9.3 Subjects

The study population consisted of CRPC patients with bone metastasis treated with radium-223.

9.3.1 Inclusion criteria

- The treatment decision to radium-223 had to be made independent from and before patient enrollment in the study
- Patients with histologically or cytologically confirmed castration-resistant adenocarcinoma of the prostate with bone metastases
- Signed informed consent

9.3.2 Exclusion criteria

- Patients previously treated with radium-223 for any reason
- Patients currently treated in clinical trials including other radium-223 studies
- Patients planned for the systemic concomitant use of other radiopharmaceuticals for treatment of prostate cancer or for other use

Inclusion and exclusion criteria were to follow the locally approved radium-223 product information.

Eligibility criteria for external secondary data sources are described in Section 9.9.2.5.

9.4 Variables

At baseline, patients' demographic variables and information about disease characteristics were collected from the treating physician (including date of diagnosis, prior treatment, tumor staging information, co-morbidities, prior medication, and concomitant medication).

Treatment information and potential outcomes (SPM, other safety information, OS, and progression [defined as first progression after initial treatment with radium-223]) were recorded in an EDC by the treating physician, radium-223 administering physician, or a designated person within the treatment team. Pain measurements were recorded starting before the first injection of radium-223 until 6 months after last injection of radium-223.

The follow-up took place at approximately 3 months (M), 6M, 12M, 24M, 36M, 48M, 60M, 72M, and 84M after the last administration to collect information regarding the outcomes of interest (SPM, other safety information, OS, and progression). The visit frequency was driven by the local standard of care at the local site.

An overview of the variables collected during the study is given in Table 3. Detailed information regarding all variables is provided in the observational study protocol (see Annex 1; available on request).

Table 3: Tabulated overview on variables collected during the study

	Baseline	Treatment (until 30 days post last dose)	6 Months follow-up post last dose	Long-term follow-up
Demography	X			
Vital Signs	X			
Prostate cancer history (classification, risk factors, ECOG, procedures)	X			
Medical history/concomitant disease	X			
Medication (prior, concomitant, subsequent)	X	X	X[a]	X[a]
Anti-cancer therapies (prior, concomitant, subsequent)[b]	X	X	X	X
Exposure treatment (radium-223)		X		
AEs[c]		X	X	X
Laboratory parameters	X	X	X[d]	X[d]
Progression[e]		X	X	X
Pain measurements (BPI-SF)	X	X	X	

	Baseline	Treatment (until 30 days post last dose)	6 Months follow-up post last dose	Long-term follow-up

a: Medications taken for treatment of drug-related SAEs/SPM. Therapeutic, prevention measures, and treatment modalities for bone marrow suppression were collected up to 6 months after the last dose administration.
b: Anti-cancer therapy includes antihormonals, chemotherapy, radiotherapy, immunotherapy, bone health agents (e.g., bisphosphonates/denosumab), and/or re-treatment with radium-223.
c: Collection periods for events:
- SAEs and drug-related AEs: during treatment and up to 30 days after last administration of radium-223
- Drug-related SAEs: up to 7 years after last administration of radium-223
- SAEs of SPM: up to 7 years after last administration of radium-223
- AEs of bone fractures and bone associated events: up to 7 years after last administration of radium-223
- Post-radium-223 treatment grade 3/4 hematological toxicities: up to 6 months after last administration of radium-223
- AEs/SAEs of febrile neutropenia and hemorrhage (for patients receiving subsequent chemotherapy): up to 6 months after last administration of chemotherapy

d: Patients with a platelet or white blood cell count less than the lower limit of normal at 6 months post last dose of radium-223 were followed until resolution at a frequency based on local clinical practice.
e: Only the first progression post-radium-223 treatment had to be collected.
AE: adverse event, BHA: bone health agent, BPI-SF: Brief pain inventory short form, ECOG: Eastern Cooperative Oncology Group, SPM: second primary malignancies

9.4.1 Primary variables

- SPMs (reported as SAEs)
  SPMs were defined as new malignancies unrelated to prostate cancer or unrelated to progression of prostate cancer. All SPMs were to be collected irrespectively of their relationship to radium-223. Patients were followed up until death, withdrawal of consent, loss to follow-up, or end of the study, whichever occurred first. All types of malignancies including MDS/AML and osteosarcoma (which had been reported with the use of radiation) and all other malignancies (including skin cancers) were to be documented. Detailed information was collected as an SAE as follows:
  - Description of the event (including location and type)
  - Start date
  - Stop date
  - Treatment prior to the event (particularly any cancer-related treatment and radiotherapy)
  - Relationship to radium-223
  - Toxicity grade
  - Outcome
- Treatment-emergent SAEs (data were collected up to 30 days after last administration)
- Drug-related[1] treatment-emergent AEs (data were to be collected up to 30 days after last administration)
- Drug-related[1] SAEs (data were to be collected up to 7 years after last administration)

[1] A drug-related AE is any AE judged by the treating physician or radium-223-administering physician (if applicable) as having a reasonable suspected causal relationship to radium-223. In this report, AE relatedness to study drug (causality assessment) reflects the opinion provided by the reporting investigator.

- Bone marrow suppression; the following was to be assessed:
  - Therapeutic or prevention measures, treatment modalities (e.g., blood transfusion/erythropoietin/colony growth stimulating factors) (up to 6 months after last administration of radium-223)
  - All post-radium-223 treatment grade 3/4 hematological toxicities (up to 6 months after last administration of radium-223 as AEs/SAEs)
    - Description of the event
    - Start date
    - Stop date
    - Therapeutic or prevention measures, treatment modalities
    - Toxicity grade
    - Outcome
    - Relationship to radium-223
  - Patients with a platelet count or white blood cell count (WBC) less than the lower limit of normal at 6 months post last dose of radium-223 were to be followed until resolution at a frequency based on local clinical practice.
  - Patients who received subsequent cytotoxic chemotherapy were to be followed for the development of febrile neutropenia and hemorrhage up to 6 months after the last administration of chemotherapy at a frequency based on local clinical practice.

9.4.2 Secondary variables

- OS, defined as the time interval from the start of radium-223 therapy to death due to any cause
- Worst pain score based the BPI-SF assessments
- Pain interference score and pain severity score based on the BPI-SF assessments
- Bone fractures and bone-associated events (e.g., osteoporosis), regardless of investigator assessment of causality, reported as AEs[2]

9.5 Data sources and measurement

Treating physicians or designated persons within the treatment team collected historic and on-study data from medical records, routine measurements (e.g., tumor assessment), radium-223 administering physicians (if applicable), and other physicians. They used the EDC to enter the data. Patient questionnaires were collected via paper forms, which were then entered into the study database.

Quality control of entered data included range, coding, missing, and date checks as well as cross-reference (consistency) checks between variables. Accuracy of data transcription from source to the EDC was confirmed by source data verification.

[2] Bone fractures and bone-associated events were added as a secondary variable in the protocol amendment from 20 AUG 2018. All events that were reported prior to the amendment were included retrospectively.

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the Data Management Plan (DMP). The DMP also specifies measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Annex 1).

For the external reference group(s), appropriate secondary data source(s) were evaluated and identified (see Section 9.9.2.5).

9.6 Bias

Due to the non-interventional study design and limitations inherent to observational studies, careful attention should be paid to describing the patient population and caution should be applied to the interpretation of results, especially when making comparisons to previous studies, and/or making comparisons across subgroups, as there may be confounding factors, measured or unmeasured.

The full collection of bone fracture data was implemented at the time when most patients were already enrolled, meaning that estimates for incidence rates of fractures might be underestimated due to this partially retrospective data collection.

In addition, as a result of the relatively long follow-up time and challenges to evaluation and documentation of SPM occurrence, some patients may not have completed follow-up and/or the time to development of SPMs may not be completely known. Therefore, careful attention should be applied to the interpretation of the summary measures to be estimated, including incidence proportion and EAIR.

9.7 Study size

The goal of the study was to have 1200 evaluable patients. As a drop-out rate of around 10% was expected, approximately 1334 patients were to be enrolled.

Based on the data from the Phase III study ALSYMPCA and SEER program data [Brenner 2000], the incidence proportion of SPM is approximately in the range of 1.1% to 6.9%. The follow-up periods for the patients varied from approximately 3 years (ALSYMPCA) to >10 years for SEER data.

With 1200 patients, if the observed incidence proportion were between 1.1% and 6.9%, the width of a 95% CI for the rate of SPM (based on the exact binomial distribution) would be approximately 0.0131 (i.e., approximately 1.3%) to 0.0296 (i.e., approximately 3%).

9.8 Data transformation

9.8.1 Data rules

Therapies were coded using the World Health Organization – Drug Dictionary (WHO-DD) version 03/2024. Medical history, diseases, and AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0, and the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Unless otherwise specified, baseline value was defined as last non-missing value on or prior to date of first injection of radium-223. If more than one value was reported at the same date prior to first radium-223 injection, baseline value was derived as the worst of these values.

Radium-223 dosage was converted to standard units (KBq/kg).

Calculation of durations: days = Day of last dose - day of first dose + 1.

Calculation of months was derived according to Bayer Xofigo standard:
months = (days/365)*12.

Ideal body weight normalized doses = 50 + [0.89 x (height[cm] – 152.4)].

9.8.2 Derived variables

Derived variables required for analyses are specified in the corresponding analysis section (Section 9.9.2).

Last-know-alive date

Last-known-alive date (LKAD) in the study was calculated based on documented dates indicating that the patient was alive. For this derivation only, the date was imputed as earliest possible date in case of partially documented dates.

Prior, concomitant and post-radium-223 medication

Medications, including systemic anti-cancer medications, were classified based on medication administration dates in relation to radium-223 injections:

- Any prior medication: all medications taken before first radium-223 injection
    - Prior completed medication: all prior medications with stop date prior to first radium-223 injection
- Concomitant medication: all medications taken in addition to radium-223
- Post-radium-223 medication: all medications taken after the last radium-223 injection
    - Subsequent medication: all post-radium-223 treatment medications starting after last injection of radium-223

Systemic anti-cancer therapies were identified by the medical expert.

Prior, concomitant, and subsequent opioid use (identified by Anatomical Therapeutic Chemical [ATC] groups N02A, N01AH, N02AG, R05DA, R05FA, A07DA) was summarized by ATC levels 3 and 4.

Other medications than for anti-cancer or opioids were separately summarized by ATC levels 2 and 4.

Prior, concomitant, and post-radium-223 treatment blood transfusions and radiotherapies were handled in the same way as prior, concomitant, and post-radium-223 medications.

A patient could have multiple therapies and/or fall into multiple medication categories.

9.9 Statistical methods

The statistical analysis was performed using the software package SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), except when noted otherwise. It is described in detail in the statistical analysis plan (SAP, version 3.0, 23-OCT-2024), which is available on request (see Annex 1).

All variables were analyzed by descriptive statistical methods.

For specific variables, subgroups of interest were region (Europe, North America, Rest of the World [ROW]) and chemotherapy (prior chemotherapy, subsequent chemotherapy). Chemotherapies were identified by the medical expert.

9.9.1 Main summary measures

Descriptive analysis was performed using summary statistics for categorical and quantitative (continuous) data. Continuous data were described by the number of non-missing values, median, mean, standard deviation, minimum, and maximum as well as lower and upper quartiles. Frequency tables were generated for categorical data. Selected continuous variables were categorized in a clinically meaningful way.

9.9.2 Main statistical methods

9.9.2.1 Analysis sets

Patients who received at least one dose of radium-223 were included in the safety analysis set[3] (SAF).

9.9.2.2 Population characteristics

Descriptive summaries were provided for patient disposition and demographic and baseline characteristics. Demographic and baseline characteristics were provided overall and by region.

Details on the respective variables are provided in Table 9-1 of the SAP.

9.9.2.3 Analysis of primary outcome variables

Second primary malignancies

All reported SPMs were summarized as assessed by the physician.

SPMs were summarized using incidence proportion and exposure adjusted incidence rate (EAIR). For both, the incidence proportion and the EAIR, the corresponding exact 95% CIs [Clopper 1934] are provided.

The EAIR was defined as the number of patients with a specific event divided by the total follow-up time from first dose of study drug. For patients with an event, the follow-up time was truncated at the time when the first event was reported. For patients without an event, LKAD was used to derive follow-up time.

The incidence rate per year, defined as number of SPM events within the x^{th} year divided by the number of patients at risk at beginning of year x, was generated. In addition, the median time to follow-up is presented.

Because of the low incidence of SPMs, the cumulative incidence rate taking into account the competing risk of death was not calculated. Instead, as specified in the SAP, incidences of patients with SPMs and patient listings were provided for patients who developed SPMs. Time to SPM was estimated using descriptive statistics (e.g., median, mean, standard deviation, minimum, and maximum as well as lower and upper quartiles). For further details refer to the SAP (see Annex 1).

In addition, descriptive summaries of Kaplan-Meier (KM) estimates (including number failed, number censored; 25^{th}/75^{th} percentiles and median, all with respective 95% CIs using loglog-transformation) and KM curves were presented for time from first radium-223 injection to

[3] The protocol referred to the full analysis set instead of the SAF: "Patients who receive at least one dose of Radium-223 will be considered valid for safety and included in the full analysis set."
As per the SAP, the analysis set used is the SAF.

development of SPM. Patients who started other radiopharmaceuticals or enrolled into other trials were censored at initiation of the respective radiopharmaceuticals. Patients without an SPM until data cut off were censored at LKAD.

Section 9.9.2.5 describes how data from external reference secondary data sources was used to put SPMs from REASSURE into perspective.

AEs/SAEs

Incidence proportion and EAIR for the following AEs were summarized, along with the exact 95% CIs:

- Treatment-emergent SAEs (up to 30 days after last administration of radium-223)
- Drug-related treatment-emergent AEs (up to 30 days after last administration)
- Drug-related SAEs (up to 7 years after last administration)
    - Drug-related treatment-emergent SAEs (up to 30 days after last administration)
    - Drug-related SAEs after the treatment-emergent period (> 30 days after last administration)
- Post-radium-223 treatment grade 3/4 hematological toxicities were summarized up to 6 months after last administration of radium-223
- For patients receiving subsequent chemotherapy, all AEs/SAEs of febrile neutropenia and hemorrhage were summarized up to 6 months after the last administration of chemotherapy

AEs were summarized using the MedDRA coding system. They were categorized and summarized according to relation, seriousness, CTCAE grade, discontinuation of therapy, action taken (permanent discontinuation, interruption, or dose modification) and outcome (patient hospitalization or prolongation of hospitalization, death).

AEs during treatment with radium-223, i.e., treatment-emergent AEs, were defined as any event arising or worsening on the day of start or after the start of radium-223 treatment until 30 days after last radium-223 injection.

AE tables were summarized according to protocol reporting definitions (e.g., treatment-emergence for SAEs and related AEs, 6 months after last dose for grade 3/4 hematological AEs). Summaries are provided for all entered grade 3/4 hematological AEs and separately for such AEs occurring within 6 months (183 days) after last dose of radium-223. Summaries were provided for all entered AEs of febrile neutropenia and hemorrhage and separately for such AEs occurring within 6 months (183 days) after last dose of chemotherapy.

In addition, all AEs were listed.

Bone marrow suppression

Incidence of post-radium-223 treatment grade 3/4 hematological toxicities was provided by worst grade, along with the exact 95% CI. Bone marrow suppression risk search criteria were covered by the MedDRA Labelling Groupings (MLGs) “MLG Thrombocytopenia”, “MLG Neutropenia”, “MLG Leukopenia not further specified”, “Pancytopenia”, and by the Standardized MedDRA Query (SMQ) “Haematopoietic erythropenia (SMQ)”.

The proportions of patients taking therapeutic or prevention measures, treatment modalities (e.g., blood transfusion, erythropoietin [defined by standardized drug grouping

'Erythropoiesis stimulating drugs' according to WHO-DD], colony growth stimulating factors [defined based on ATC code L03AA]) were also provided. Incidences of abnormal platelet count or WBC were summarized by period (initiation of radium-223 to 30 days after last administration and after 30 days after last administration to 6 months after last administration) and worst grade. For patients who received subsequent chemotherapy, incidences of febrile neutropenia (defined by preferred term [PT]: 'Febrile neutropenia') and hemorrhage (defined based on the most recent SMQ: 'Haemorrhage terms [excluding laboratory terms]') after start of first subsequent chemotherapy were summarized.

Summaries were provided for treatments as specified above and separately for these treatments within 6 months (183 days) after last dose of radium.

Listings including all search terms and corresponding version numbers were generated.

9.9.2.4 Analysis of secondary outcome variables

Overall survival

Descriptive summaries of KM estimates and KM curves were presented for OS. OS was defined as the time from the first injection date to death due to any cause in months. Patients who were alive (or patients whose death was not confirmed) at the time of data cut-off were censored at LKAD.

Patient listings were provided for deceased patients.

Pain

Pain over time was assessed using the BPI-SF questionnaire. Completion of the BPI-SF was voluntary. The pain severity score and the pain interference score were defined according to the BPI-SF guideline.

The pain severity score and the pain interference score were calculated per visit with means of value at visit and change from baseline. Baseline was defined as last observation prior to first administration of radium-223. When there was only one follow-up (i.e., post-radium-223 treatment) pain measurement available, the patient was counted in the first as well as in the last available follow-up measurement.

The pain severity score was defined as the mean of the following items: 3: pain at its worst, 4: pain at its least, 5: pain on average, 6: pain right now. Each item had possible entries from 0 (no pain) to 10 (pain as bad as you can imagine). When a patient had one or more missing items out of the 4 items at one visit, the corresponding pain severity score was set to missing.

The pain interference score was defined as mean of the following items: 9A: general activity, 9B: mood, 9C: walking ability, 9D: normal work, 9E relations with other people, 9F: sleep, 9G: enjoyment of life. Each item had possible entries from 0 (does not interfere) to 10 (completely interferes). When a patient had more than 3 missing items out of the 7 items at one visit, the corresponding pain interference score was set to missing.

A clinically meaningful pain response was determined by the worst pain item on the BPI-SF and was defined as an improvement of 2 points (or more) from the baseline worst pain score.

In a post-hoc analysis, calculation of the proportion of patients with a clinically meaningful pain response was restricted to evaluable patients, i.e., patients with a baseline worst pain score ≥ 2, since patients with a baseline value <2 can by definition not have a clinically meaningful response.

Bone-associated events

Bone fractures and bone-associated events (reported as AEs) were summarized via incidence proportion and EAIR, regardless of investigator assessment of causality. Events were identified by MedDRA high-level group terms (HLGTs) “Fractures” and “Bone disorders (excl congenital and fractures)”.

In addition, the number and proportion of patients with bone fractures and bone-associated events were summarized by bone health agents (defined as denosumab: ATC code M05BX; bisphosphonates: ATC code M05BA, M05BB or MB05BC).

9.9.2.5 Analysis of external reference secondary data sources

Three population-based, retrospective cohort studies assessing the overall and site-specific incidence of SPMs were conducted in Germany, Sweden, and the USA.

The US study used combined registry-claims data from the US Surveillance, Epidemiology and End Result (SEER)-Medicare linked database. It is a comprehensive representation of the US general population aged ≥65 years, covering approximately 94% of this population [Vassilev 2020].

The German study used data from the German Pharmacoepidemiological Research Database (GePaRD), covering approximately 20% of the German general population and with representative data in terms of age, sex, and region of residence [Vassilev 2020].

The Swedish study used data from the Prostate Cancer Data Base Sweden (PCBaSe). This database includes data from the National Prostate Cancer Register of Sweden linked with other national health registers, altogether covering 98% of all newly diagnosed cases of prostate cancer in Sweden and is therefore representative of all men diagnosed with prostate cancer in Sweden [Vassilev 2020].

Table 4 shows the methods used for the three cohort studies and the REASSURE study.

Table 4: Summary of study methods (German, Swedish, US cohorts; REASSURE)

	German cohort (GePaRD)	Swedish cohort (PCBaSe)	US cohort (SEER-Medicare)	REASSURE
Enrollment period (end of follow up)				
	01 JAN 2004 to 31 DEC 2011 (31 DEC 2013)	01 JAN 2006 to 31 DEC 2011[a] (31 DEC 2013)	01 JAN 2000 to 31 DEC 2011 (31 DEC 2013[b])	20 AUG 2014 to end of 2017 (02 AUG 2024)
Cohort/study entry date				
	First observed bone metastasis	First observed bone metastasis	First 2nd-line systemic treatment for PC after ADT	Date of informed consent
End-of-follow-up date				
	Occurrence of SPM, end of study period, lapse of registry-tracked insurance coverage[c]			Death, withdrawal of consent, loss to follow-up, or end of study
Primary objective (related to SPM)				
	Estimate the incidence of any SPM among men with mCRPC			Assess incidence of all SPMs mCRPC patients treated with radium-223 in the routine clinical practice setting
Main inclusion criteria				
	Primary diagnosis of PC		Primary diagnosis of PC	Patients with histologically or cytologically confirmed castration-resistant adenocarcinoma of the prostate with bone metastases
	History of bone metastases		Initiation of second-line systemic therapy after ADT[d]	
	Had surgical castration or medical ADT after PC diagnosis and had evidence that PC was resistant to surgical castration or ADT. Resistant disease was indicated by starting one of the following second-line systemic therapies:			
	Abiraterone, cabazitaxel, docetaxel, enzalutamide, estramustine, ketoconazole, mitoxantrone, sipuleucel-T	Abiraterone, cabazitaxel, docetaxel, enzalutamide, ketoconazole, mitoxantrone, sipuleucel-T	Abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, sipuleucel-T	

German cohort (GePaRD)	Swedish cohort (PCBaSe)	US cohort (SEER-Medicare)	REASSURE
Resistant disease was also defined as initiation of ADT treatment, chemotherapy or mitoxantrone ≥1 month after surgical castration; discontinuation of ADT; or change of ADT agent or modality		--	see above
Identification of resistant disease any time before or within 30 days after diagnosis of bone metastases		--	see above
Data available for ≥1 year before first diagnosis of bone metastases		--	--
--	--	Enrollment in both Medicare Parts A and B for ≥1 year before entry and continuously between initial diagnosis of PC and entry	--
--	--	--	Treatment decision to radium-223 to be independent from and before enrollment in the study
Main exclusion criteria			
First PC diagnosis > 2 months after diagnosis of bone metastases		--	--
Use of any radiopharmaceutical for bone metastases (e.g., samarium, strontium, rhenium, or radium)		--	Patients previously treated with radium-223 for any reason or currently treated in clinical trials incl. other radium-223 studies or planned for systemic concomitant use of other radiopharmaceuticals
--	--	Enrollment in health maintenance organization during the year before cohort entry	--
--	--	Diagnosis of any other cancer (except nonmelanoma skin cancer) on or before cohort entry	--

	German cohort (GePaRD)	Swedish cohort (PCBaSe)	US cohort (SEER-Medicare)	REASSURE
	--	--	Any diagnostic code for metastases (other than bone or lymph node metastases) on or before cohort entry	--
Outcomes				
	Events of SPM were defined as diagnoses of incident malignancies after cohort entry			New malignancies unrelated to PC or progression of PC
	SPMs considered incident if respective ICD-10 code (C00-C76, C81-C96, excluding C61) had not occurred before cohort entry		SPMs were defined as[b]: • SEER: diagnosis of nonprostate primary cancer after cohort entry or • Medicare: ICD-9-CM code for primary malignancy (other than PC or nonmelanoma skin cancer) associated with 1 hospitalization or 2 hospital outpatient visits or 2 physician visits after cohort entry	SPMs were collected from first treatment with radium-223 onwards
	Sites of SPM included: bladder, colon, lung, rectum, leukaemia; In situ neoplasms and neoplasms of uncertain or unknown behavior were excluded (ICD-10 codes: D00-D09, D37-D48)		Analyzed cancer categories: urinary bladder; lung/bronchus; nonprostate, nonbladder GU tract (incl. kidney, ureters, urethra, testis); non-Hodgkin lymphoma and myeloma; colon/ rectum; noncolorectal GI tract (incl. esophagus, stomach, biliary tract, small intestine, liver, pancreas); brain; melanoma, breast, nipple; meningeal, head, neck, endocrine; and miscellaneous or unspecified	All types of SPMs

	German cohort (GePaRD)	Swedish cohort (PCBaSe)	US cohort (SEER-Medicare)	REASSURE
	Date of diagnosis = hospital admission date for inpatient diagnoses or first coded diagnostic or therapeutic procedure in quarter of outpatient diagnosis; outpatient diagnosis to be confirmed by inpatient or second outpatient diagnosis within 183 days	--	--	--

a: The period of 01 JAN 1998 to 31 DEC 2011 was used to identify men with prostate cancer. Because information on drug purchases in Sweden was only available from 01 JAN 2006 onward, only data from 01 JAN 2007 onwards were used in identifying mCRPC patients. This approach ensured ≥1 year of history before enrollment and ≥2 years of potential follow-up time.
b: Follow up was based on linked Medicare data.
c: I.e., for emigration, death, or discontinuation of Medicare Parts A or B coverage (US cohort) or when insurance coverage ended due to any reason including death (German cohort).
d: History of bone metastases was not an explicit inclusion criterion and metastases were less likely to be completely captured and accurately coded. It nevertheless was found that 84.5% of the men in the US study had either a history of bone metastases recorded in their claims data or were prescribed second-line, bone-targeting therapy (a proxy for bone metastases), or both[Saltus 2019] [Vassilev 2020].

ADT: androgen deprivation therapy, GePaRD: German Pharmacoepidemiological Research Database, GI: gastrointestinal, GU: genitourinary, mCRPC: metastatic castration-resistant prostate cancer, PC: prostate cancer, PCBaSe: Prostate Cancer Data Base Sweden, SEER: US Surveillance, Epidemiology and End Results

Source for the three cohort studies: [Vassilev 2020]

The primary objective in the three cohort studies was to estimate the incidence of any SPM among men with mCRPC using large populations reflective of real-world practice with non-radium-223. The incidence was operationalized as incidence rate per 1000 person-years, i.e., by number of incident cases divided by the accumulated person-time per 1000 person-years in the cohort (until SPM occurred or until cohort exit, whichever came first). The corresponding 95% CIs were also reported, based on the substitution method assuming a Poisson distribution of the cases.

Overall incidence rates of cancer diagnoses were analyzed by comparing the observed number of cases for SPMs in the REASSURE cohort with the corresponding expected numbers based on cancer incidence rates derived from the external reference secondary data sources. Age (by 5-year age groups) was accounted for in the analysis. Since the necessary site-specific data by age range was not available for the US and Swedish cohort studies, only the overall incidence rates of cancer diagnoses were analyzed.

The ratio of the observed and expected number of cases by means of standardized morbidity ratio (SMR) was used as the measure of the increased or decreased incidence rates, accompanied by an exact 95% CI assuming the observed number of SPM cases.

The SMR is the number of observed SPMs divided by the number of expected SPMs. The incidence rate was calculated per x years (e.g., 1000 years).

95% CI = 1.96 x (square root [observed SPMs]/expected SPMs)[4]

Summaries of SPMs were provided by age groups. Alignment between REASSURE and external reference data was performed via medical review. External data did not include all sites in the reference analysis.

9.9.2.6 Safety analysis

All safety variables are indicated as primary and secondary outcomes (see Section 9.9.2.3 and Section 9.9.2.4).

Laboratory measurements at baseline were summarized. Post-baseline measurements were summarized as measurement closest to the treatment or follow-up date. In case of ties the earlier measurement will be summarized.

9.9.2.7 Analysis of other data

Descriptive summaries of KM estimates and KM curves were presented for time to progression (TTP). The $25^{th}/75^{th}$ percentiles and median, all with respective 95% CIs using loglog-transformation and KM curves were presented. Progression was defined as first progression after initial treatment with radium-223. The type of progression (as assessed by the physician) could include any of the following:

- Symptomatic Skeletal Events (SSEs)
  Progression defined as SSE included any of the following: use of external beam radiation therapy to relieve skeletal symptoms, new pathological bone fractures (vertebral or non-vertebral), occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention

[4] The formula in the SAP mistakenly included multiplication by 100:
95% CI = 1.96 x (square root [observed SPMs]/expected SPMs) * 100
This was corrected in the actual analyses.

- Prostate Specific Antigen Level (PSA)
  Progression defined as increase of PSA level and/or radiological progression was solely based on physician's assessment
- Radiological imaging
- Unequivocal clinical progression

Progression did not include SPMs, tumor-related death, or death from any cause.

Patients who did not have a progression at the end of the study were censored at the LKAD.

9.9.3 Missing values

Missing values were not imputed or carried forward unless otherwise specified.

Imputation rules for incomplete dates of medication administration, blood transfusions and radiotherapies can be found in the Xofigo BPP-CM, version 1.0 (see Annex 1).

In addition, all end dates imputed after date of death were set to date of death.

For partially documented death dates (i.e., day), the missing day was imputed by day 15. In case the imputed date was after end-of-observation (EOO) date, date of EOO was used.

When the AE (including primary malignancy) start date was completely or partially missing, it was assumed that the start date occurred at the earliest possible time point (Day 1 if day of the month was missing, January if month was missing). If this date was prior to radium-223 treatment start, the date of first radium-223 treatment was taken instead.

In case of missing dates, the respective AE was considered as 'treatment emergent' as a worst-case assumption.

9.9.4 Sensitivity analyses

Not applicable

9.9.5 Amendments to the statistical analysis plan

A separate SAP was written for each of the interim analyses and for the final analysis. The SAP for the final analysis was version 3.0, dated 23 OCT 2024 (Annex 1; available on request). There was no amendment to this SAP.

Post-hoc analyses are mentioned in the respective methods sections above.

9.10 Quality control

Before study start at the sites, all physicians participating in the study were sufficiently trained by Bayer or the designated CRO on the background and objectives of the study and ethical as well as regulatory obligations. Treating physicians and radium-223 administering physicians (if applicable) had the chance to discuss and develop a common understanding of the study protocol and the case report form (CRF).

A CRO was assigned for EDC development, quality assurance, verification of the data collection, data analysis, and data transfer to Bayer.

Prior to submission of the electronic CRF, all pages were to be filled out completely. A check for plausibility was performed while data was being entered. Missing or implausible data were directly queried online. Data from the CRF had to be verifiable against source

documents. Data from patient questionnaires were entered in the study database. Checks for multiple documented patients was done. All details of the above analyses are described in detail in the DMP (see Annex 1; available on request).

For quality purposes, a three-step quality review was used. In the first step, 41 sites were interviewed over the telephone. In general, they were well informed about the study and study-related processes. In the second step, on-site visits took place at 15 randomly selected sites to review the documented data for completeness and plausibility, adherence to the study protocol, and consistency with source documents. As the overall h rate of 2.4% was in the accepted range of ≤ 5%, no further escalation was needed.

The third step consisted of for-cause on-site reviews. In Wave a, on-site reviews were performed at 7 sites that had been identified in a risk-based approach. The error rate for Wave a was 4.2%. After an authority inspection, extensive source data verification was done at two sites (Wave b). Additional source data verification took place at 15 high-enrolling sites and 19 low-enrolling sites (Wave c). The error rate for Wave c was 5.26% for high-enrolling sites and 9.69% for low-enrolling sites. Detailed information on the quality review process and its outcome are provided in the Quality Review Plan and the Final Quality Review Report, which are available on request (see Annex 1).

AEs and SAEs were handled in the same way as other data reported in the CRF. However, in addition, SAEs were entered into the safety database for coding, medical assessment, and for reporting to authorities according to national regulatory requirements. Coding of AEs, medical history, and signs and symptoms was performed according to MedDRA, and coding of concomitant medications, prior anti-cancer therapy, and further therapy was performed according to WHO-DD version 03/2024.

Detailed information on checks for completeness, accuracy, plausibility, validity, measures for handling of missing data, and permissible clarifications are given in the DMP (see Annex 1).

Medical Review of the data was performed according to the Medical Review Plan (see Annex 1). The purpose of the Medical Review was to verify the data from a medical perspective for plausibility, consistency, and completeness, and to identify potential issues that could affect the robustness of the collected study data or the progress of the study.

Clean database was declared on 24 OCT 2024, after all data had been entered, verified, and validated, and after the final SAE reconciliation had taken place.

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for patient documentation were validated according to 21 Code of Federal Regulations (CFR) Part 11 (Food and Drug Administration) [Food and Drug Administration].

10. Results

This report presents the results of the final analysis. The results Tables, Listings, and Figures (TLF) can be found in the TLF dated 27 FEB 2025 and are available on request (see Annex 1).

10.1 Participants

A Validity Review and Data Decision Report (VDR) identifying the patient population valid for analyses was prepared prior to clean database (see Annex 1). Of the 70 patients who enrolled in the study but decided to terminate study participation (withdrew consent), 17 patients refused further use of their data. The data of these patients are not included in the analysis and are not reflected in the numbers on patient screening and enrollment presented below. This explains why the screening and enrollment numbers in interim report 2 are higher than in the final report. A summary of patient enrollment is given in Table 5.

Table 5: Patient enrollment (screened patients; N=1550)

	n	(%)
Total patients screened	1550	(100.0)
Number of patients included in the study	1473	(95.0)
Number of patients not included in the study	77	(5.0)
Primary reason		
Inclusion criteria not met/exclusion criteria met	35	(2.3)
Medical reason, unable to participate	19	(1.2)
Patient's decision	12	(0.8)
Death	6	(0.4)
Administrative reason	5	(0.3)

N: number of screened patients, n: number of patients
Source: Table 14.1.1/1

Of the 1550 patients who were screened, 1473 patients (95.0%) were included in this study. The main reasons for patients not being included were "inclusion criteria not met/exclusion criteria met" (2.3%), followed by "medical reason, unable to participate" (1.2%), "patient's decision" (0.8%), "death" (0.4%), and "administrative reason" (0.3%). Detailed information on inclusion criteria not met and exclusion criteria met can be found in Table 14.1.1/2.

Over the course of the study, 113 patients were identified for whom no signed informed consent form was available on site. The process that was followed was described in the VDR (see Annex 1; available on request):

- If informed consent was missing but source data confirmed that the patient signed the informed consent form, the patient data was to remain in the database and could be used for analysis.
- If informed consent was missing and source data did not confirm that the patient signed the informed consent form, the patient data was to be deleted from the database and to be moved into an archived database.

A total of 107 patients with missing signed informed consent form were moved to an archived database and excluded from the analysis, since there was no evidence on informed consent in the source data. The data of the remaining 6 patients with missing signed informed consent form were retained in the EDC system and included in the study analysis, since the source data confirmed that the patients had signed the informed consent form.

Of the 1473 patients included in the study, 1 patient withdrew consent before initiation of study treatment and was therefore excluded from the SAF (see Section 9.9.2 and VDR in Annex 1, available on request). Two (2) patients retrospectively violated an inclusion criterion (Patient with histologically or cytologically confirmed castration resistant adenocarcinoma of the prostate with bone metastases) or an exclusion criterion (Patient previously treated with radium-223 for any reason). Since both patients had received study medication, they were considered valid for the SAF. Thus, 1472 patients were included in the SAF. The patient disposition is given in Table 6.

Table 6: Disposition of patients (SAF[a])

	Europe N=903		North America N=530		ROW N=39		Total N=1472	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of patients who completed 6 radium-223 injections	525	(58.1)	330	(62.3)	23	(59.0)	878	(59.6)
End of treatment documented	525	(58.1)	330	(62.3)	23	(59.0)	878	(59.6)
No end of treatment documented so far	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients who had less than 6 radium-223 injections	378	(41.9)	200	(37.7)	16	(41.0)	594	(40.4)
End of treatment documented	378	(41.9)	200	(37.7)	16	(41.0)	594	(40.4)
No end of treatment documented so far	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients with documented of end of treatment	903	(100)	530	(100)	39	(100)	1472	(100)
Primary reason								
Completed[b]	526	(58.3)	330	(62.3)	23	(59.0)	879	(59.7)
Progressive disease	201	(22.3)	78	(14.7)	6	(15.4)	285	(19.4)
AE	101	(11.2)	48	(9.1)	1	(2.6)	150	(10.2)
Death	32	(3.5)	27	(5.1)	4	(10.3)	63	(4.3)
Patient's decision to end treatment	26	(2.9)	33	(6.2)	2	(5.1)	61	(4.1)
Non-AE related medical reason (physician's decision)	13	(1.4)	8	(1.5)	1	(2.6)	22	(1.5)
Lost to follow-up	3	(0.3)	1	(0.2)	1	(2.6)	5	(0.3)
Cost/Reimbursement issues	0	(0.0)	2	(0.4)	1	(2.6)	3	(0.2)
Patient withdrew consent (treatment ongoing)	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.1)
Inclusion criteria not met/exclusion criteria met	1	(0.1)	0	(0.0)	0	(0.0)	1	(<0.1)
Unknown	0	(0.0)	1	(0.2)	0	(0.0)	1	(<0.1)
Number of patients with at least one documented follow-up visit	730	(80.8)	391	(73.8)	26	(66.7)	1147	(77.9)
Number of patients with documented end of observation[c]	900	(99.7)	528	(99.6)	39	(100)	1467	(99.7)
Primary reason								
Death	805	(89.1)	469	(88.5)	34	(87.2)	1308	(88.9)
Lost to follow-up	64	(7.1)	17	(3.2)	3	(7.7)	84	(5.7)
Withdrawal by patient	21	(2.3)	30	(5.7)	1	(2.6)	52	(3.5)
Completed	9	(1.0)	12	(2.3)	1	(2.6)	22	(1.5)
Physician decision	1	(0.1)	0	(0.0)	0	(0.0)	1	(<0.1)

a: Patients with no documentation of radium-223 were excluded from the SAF; details are listed in the VDR.
b: Primary reason for end of treatment "completed" was documented by the physician and may include patients with < 6 radium-223 injections.
c: The table includes 5 patients without documented end of observation due to premature site closure.
AE: adverse event, N: number of patients in analysis set, n: number of patients, ROW: rest of world, SAF: safety analysis set, VDR: Validity Review and Data Decision Report
Source: Table 14.1.2/1

More than half of the patients in the SAF (59.6%) completed all 6 radium-223 injections, while 40.4% had less than 6 injections. The most common primary reason for end of treatment was treatment completion (59.7%), followed by progressive disease (19.4%) and AE (10.2%).

About three quarters of the patients in the SAF (77.9%) had at least one documented follow-up visit and 99.7% had end of observation documented. The most common primary reason for end of observation was death (88.9%), followed by lost to follow-up (5.7%) and withdrawal of consent (3.5%). Only few patients (1.5%) completed the full observation period.

When analyzed by region, the proportion of patients who ended the treatment because of progressive disease was slightly higher in Europe (22.3%) than in North America (14.7%) and ROW (15.4%). More patients had at least one documented follow-up visit in Europe (80.8%) than in North America (73.8%) and ROW (66.7%). Other results were comparable between the regions.

The median (Q1; Q3) time for patients in the SAF from start of radium-223 to either death or LKAD was 13.97 (7.23; 25.45) months (Table 14.1.2/2). For the 1467 patients with documented end of observation, the median (Q1; Q3) time from start of radium-223 to end of observation was 17.03 (8.28; 32.45) months. The end of observation date was the administrative date of last information collection and therefore there are limitations to the interpretation as it relates to outcomes. No large differences between the regions were seen in the stratified analysis.

10.2 Descriptive data

10.2.1 Demographics and baseline disease characteristics

10.2.1.1 Demographic characteristics

The countries and regions from which the patients of this interim analysis originated are given in Table 7.

Table 7: Countries and regions, SAF (N=1472)

	n	(%)
Region[a]		
Europe[b]	903	(61.3)
North America[b]	530	(36.0)
ROW[b]	39	(2.6)
Country		
USA	498	(33.8)
Italy	200	(13.6)
United Kingdom	167	(11.3)
Germany	124	(8.4)
Belgium	95	(6.5)
Spain	75	(5.1)
Austria	43	(2.9)
Netherlands	37	(2.5)
France	36	(2.4)
Canada	32	(2.2)
Sweden	31	(2.1)
Israel	30	(2.0)
Denmark	20	(1.4)
Argentina	20	(1.4)

	n	(%)
Luxembourg	19	(1.3)
Czech Republic	15	(1.0)
Mexico	10	(0.7)
Colombia	9	(0.6)
Portugal	6	(0.4)
Greece	5	(0.3)

a: The regional values as percentages of the SAF are not presented in the TLF and were calculated separately for this table.
b: Europe: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, United Kingdom
North America: Canada, USA
ROW: Argentina, Colombia, Mexico
N: number of patients in analysis set, n: number of patients, ROW: rest of the world, SAF: safety analysis set, TLF: tables, listings, and figures, USA: United States of America
Source: Table 14.1.2/3

In the SAF, 61.3% of patients originated from Europe and 36.0% from North America. On a by country level, most patients originated from the USA (33.8%), followed by Italy (13.6%), the UK (11.3%) and Germany (8.4%).

A summary of the demographic characteristics and vital signs for this study is given in Table 8.

Table 8: Demographic characteristics and vital signs, SAF (N=1472)

Ethnicity, n (%)		
Not Hispanic or Latino	1159	(78.7%)
Hispanic or Latino	170	(11.5%)
Not reported	143	(9.7%)
Race, n (%)		
White	1295	(88.0%)
Black or African American	63	(4.3%)
Asian	16	(1.1%)
Multiple	2	(0.1%)
American Indian or Alaska Native	1	(<0.1%)
Not reported	95	(6.5%)
Age calculated at date of informed consent, years		
Median (min, max)	73.0	(44, 94)
Age category, n (%)		
<65 years	236	(16.0%)
≥65 to <70 years	257	(17.5%)
≥70 to <75 years	328	(22.3%)
≥75 to <80 years	319	(21.7%)
≥80 to <85 years	215	(14.6%)
≥85 years	117	(7.9%)
Weight at baseline, kg		
Not reported, n	90	
Median (min, max)	82.10	(42.7, 167.8)
Height at baseline, cm		
Not reported, n	259	
Median (min, max)	175.00	(149.9, 210.8)
BMI at baseline, kg/m^2		
Not reported, n	270	
Median (min, max)	26.95	(15.1, 54.6)
Ideal body weight at baseline[a], kg		
Not reported, n	259	
Median (min, max)	70.11	(47.8, 102.0)

a: Ideal body weight was defined as 50+[0.89 x (height[cm]-152.4)].
BMI: Body Mass Index, max: maximum, min: minimum, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set.
Source: Table 14.1.2/3 and Table 14.1.2/4

In the SAF, the vast majority of patients (88.0%) were White, 4.3% were Black or African American, 1.1% were Asian, 0.1% were Multiple and <0.1% were American Indian or Alaska Native. For 6.5% of patients race was not reported, i.e., the field "not reported" was ticked in the CRF. At informed consent, patients had a calculated median age of 73.0 years (range: 44-94 years). The most common age categories were ≥70 to <75 years (22.3%), and ≥75 to <80 years (21.7%). The patients' median weight was 82.10 kg (range: 42.7-167.8 kg), their median height was 175.00 cm (range: 149.9-210.8 cm), and their median Body Mass Index (BMI) was 26.95 kg/m^2 (range: 15.1-54.6 kg/m^2). The patients' median ideal body weight was 70.11 kg (range: 47.8-102.0 kg).

The demographic characteristics and vital signs stratified by region are presented in Table 14.1.2/3 and Table 14.1.2/4. As expected, more patients in North America (58 patients, 10.9%) than in Europe (4 patients, 0.4%) were Black or African American. No other major differences were observed.

Risk factors for cancer for patients in the SAF are summarized in Table 9.

Table 9: Risk factors for cancer, SAF (N=1472)

	n	(%)
Smoking status		
Never	647	(44.0)
Former	614	(41.7)
Current	131	(8.9)
Missing	80	(5.4)
Alcohol use		
Abstinent	507	(34.4)
Light	567	(38.5)
Moderate	93	(6.3)
Heavy	13	(0.9)
Unknown	283	(19.2)
Missing	9	(0.6)
Family history of cancer		
No	765	(52.0)
Yes	707	(48.0)
Other risk factors for cancer[a]		
No	1390	(94.4)
Yes	82	(5.6)

a: The most common other risk factors were tobacco user, obesity, polyp, ex-tobacco user, exposure to chemical pollution, exposure to toxic agent, and hypertension.
N: number of patients in analysis set, n: number of patients, SAF: safety analysis set
Source: Table 14.1.2/5, Table 14.1.2/6

The percentages of never smokers (44.0%) and former smokers (41.7%) were similar. Current smokers accounted for 8.9% of patients. For 5.4% of patients, information on smoking status was missing.

Concerning alcohol use, almost three quarters of patients were either abstinent (34.4%) or reported light alcohol use (38.5%). Moderate and heavy alcohol use was reported for 6.3% and 0.9% of patients, respectively. For 19.2% of patients, the alcohol use was unknown, i.e., the field "unknown" in the CRF was ticked, and for 0.6% of patients, information on alcohol use was missing.

Family history of cancer was documented for 707 patients (48.0%). A first degree relative (parent, sibling, offspring) was concerned for 634 patients (43.1%), while for 148 patients (10.1%) a second degree relative (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) was concerned (Table 14.1.2/5).

Among the minority (5.6%) of patients that reported other risk factors for cancer, the most common PTs were tobacco user (0.8%), obesity (0.7%), polyp and ex-tobacco user (0.5% each), exposure to chemical pollution and exposure to toxic agent (0.4% each), and hypertension (0.3%) (Table 14.1.2/6).

The risk factors for cancer stratified by region are presented in Table 14.1.2/5. More North American than European patients were former smokers (North America: 50.9% versus Europe: 36.7%). It is notable that the number of patients that abstain from alcohol was higher in North America than in Europe (44.3% versus 28.9%); however, the relatively high number of missing or unknown values for Europe (25.8%) makes it difficult to draw conclusions from this comparison. In North America, more patients reported a family history of cancer (61.7%) than in Europe (40.2%).

10.2.1.2 Baseline characteristics of prostate cancer

A summary of the baseline characteristics of prostate cancer for patients in the SAF is given in Table 10.

Table 10 Baseline characteristics of prostate cancer, SAF (N=1472)

Characteristic		
Status of primary tumor at study entry, n (%)		
Unresected	946	(64.3%)
Resected. Status of residual tumor unknown	239	(16.2%)
R0 complete tumor resection with all margins histologically negative	149	(10.1%)
R1 incomplete tumor resection with microscopic surgical resection margin involvement	87	(5.9%)
R2 incomplete tumor resection with gross residual tumor that was not resected	22	(1.5%)
Missing	29	(2.0%)
Stage at initial diagnosis (according to AJCC), n (%)		
Stage I	118	(8.0%)
Stage IIA	143	(9.7%)
Stage IIB	145	(9.9%)
Stage III	289	(19.6%)
Stage IV	551	(37.4%)
Missing	226	(15.4%)
Gleason score at initial diagnosis, n (%)		
≤6	189	(12.8%)
7	364	(24.7%)
8-10	710	(48.2%)
Unknown	195	(13.2%)
Missing	14	(1.0%)
Time since initial diagnosis of prostate cancer to castration-resistant cancer, months		
Missing, n	849	
Median (min, max)	30.02	(0.0, 296.9)
Time since bone metastases to study entry, months		
Missing, n	458	
Median (min, max)	23.15	(0.0, 235.7)

Characteristic		
Time since castration-resistant cancer to study entry, months		
Missing, n	716	
Median (min, max)	12.67	(0.0, 146.9)
Time since first progression to most recent progression, months		
Missing, n	850	
Median (min, max)	17.52	(0.0, 265.6)
Extent of disease at baseline (bone scan), n (%)		
N*	1388	(100.0%)
EOD 0	23	(1.7%)
EOD 1	258	(18.6%)
EOD 2	662	(47.7%)
EOD 3	278	(20.0%)
EOD 4	79	(5.7%)
Missing	88	(6.3%)
Metastases at study entry, n (%)		
Bone metastases only	1196	(81.3%)
Bone metastases plus lymph nodes	186	(12.6%)
Bone metastases plus other metastases[a] excl. lymph nodes	61	(4.1%)
Bone metastases plus lymph nodes plus other metastases[a]	29	(2.0%)
ECOG performance status at study entry, n (%)		
0	442	(30.0%)
1	729	(49.5%)
2	181	(12.3%)
3	40	(2.7%)
Missing	80	(5.4%)
Laboratory values at baseline, n (%)		
Alkaline phosphatase		
<140 U/L	557	(37.8%)
≥140 U/L	512	(34.8%)
<220 U/L	749	(50.9%)
≥220 U/L	320	(21.7%)
Missing	403	(27.4%)
Lactate dehydrogenase		
<250 U/L	259	(17.6%)
≥250 U/L	315	(21.4%)
Missing	898	(61.0%)
Prostate specific antigen		
0 - 4 ng/mL	112	(7.6%)
>4 - 100 ng/mL	550	(37.4%)
>100 ng/mL	443	(30.1%)
Missing	367	(24.9%)
Neutrophils		
$<1.5 \times 10^9$/L	49	(3.3%)
$\geq 1.5 \times 10^9$/L	745	(50.6%)
Missing	678	(46.1%)
Platelets		
$<100 \times 10^9$/L	14	(1.0%)
$\geq 100 \times 10^9$/L	1326	(90.1%)
Missing	132	(9.0%)
Hemoglobin		
<10 g/dL	113	(7.7%)
≥10 g/dL	1238	(84.1%)
Missing	121	(8.2%)

Characteristic

a: Other metastases are specified in the CRF and included metastases in the following anatomical locations: ureter, bladder, urethra, rectal, lung, liver, brain, and "other, please specify".
Study entry was indicated by date of informed consent.
Baseline value was defined according to the SAP.
Patients could have multiple metastases at study entry and could be assigned to more than one of the following categories:
EOD 0 = normal or abnormal because of benign bone disease; EOD 1 = fewer than six metastatic sites; EOD 2 = 6 to 20 metastatic sites; EOD 3 = more than 20 lesions but not a superscan; EOD 4 = superscan
ECOG: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % waking hours; 3 = capable of only limited self-care, confined to bed or chair, more than 50 % waking hours; 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair
Gleason ≤ 6 = Well differentiated (slight anaplasia); Gleason 7 = Moderately differentiated (moderate anaplasia); Gleason 8-10 = Poorly differentiated/undifferentiated (marked anaplasia)
AJCC: American Joint Committee on Cancer, CRF: case report form, ECOG: Eastern Cooperative Oncology Group, EOD: extent of disease, max: maximum, min: minimum, N: number of patients in analysis set, N*: number of patients for whom bone scan was documented at baseline, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan
Source: Table 14.1.2/7, Table 14.1.2/8, Table 14.1.2/10 and Table 14.1.6/1

The status of the primary tumor at study entry was most commonly reported as unresected (64.3%). In 16.2% of patients the status of residual tumor was unknown, and R0 complete tumor resection with all margins histologically negative was present in 10.1% of patients. When interpreting this, it should be highlighted that 63.1% of patients received prior radiotherapy, the majority (72.3%) of whom received treatment for prostate cancer (see Table 14).

Tumor stage at initial diagnosis according to American Joint Committee on Cancer (AJCC) most frequently was Stage IV (37.4%), followed by Stage III (19.6%), Stage II B (9.9%), Stage II A (9.7%), and Stage I (8.0%). For 15.4% of patients the information on the stage was missing.

At initial diagnosis, almost half of the patients (48.2%) had a Gleason score of 8-10, about a quarter of patients (24.7%) had a Gleason score of 7, and 12.8% of patients had a Gleason score of ≤6. For 13.2% of patients the Gleason score was unknown, i.e., "unknown" was ticked in the CRF, and for 1.0%, Gleason score was missing.

The median time since initial diagnosis of prostate cancer to castration-resistant cancer was 30.02 months (range: 0.0-296.9 months), and the median time from castration-resistant cancer to study entry was 12.67 months (range: 0.0-146.9 months). A median time of 23.15 months (range: 0.0-235.7 months) had passed from the time of bone metastases to study entry. A median time of 17.52 months (range: 0.0-265.6 months) had passed from the time of first progression to the most recent progression.

Extent of disease (EOD) was determined using the baseline bone scan, i.e., the last available bone scan before first radium-223 injection. Patients could have more than one bone scan, with different imaging methods (see Section 10.2.3.1), thereby leading to differing results. For EOD, only the last scan was used, irrespective of results from previous scans, which might potentially underestimate the presence of bone metastases. For 1.7% of patients, the baseline bone scan was normal or abnormal because of benign bone disease (EOD 0); 18.6% of patients had fewer than 6 metastatic sites (EOD 1), 47.7% of patients had 6 to 20 metastatic sites (EOD 2), 20.0% of patients had more than 20 lesions but not a superscan (EOD 3), and 5.7% of patients had a superscan (EOD 4).

In the SAF, 81.3% of patients had bone metastases only. Bone metastases plus lymph node metastases were recorded in 12.6% of patients, and bone metastases plus other metastases excluding lymph nodes were recorded in 4.1% of patients. In 2.0% of patients, bone metastases plus lymph node metastases plus other metastases were recorded.

A total of 276 patients (18.8%) had metastases other than of the bone. Lymph node metastases were reported in 215 patients (14.6%) and included both regional (e.g., pelvic, iliac) and distant (e.g., retroperitoneal, axillary) lymph node metastases. Non-lymph node metastases were reported in 90 patients (6.1%), with the most common being lung in 36 patients (2.4%), bladder in 18 patients (1.2%), visceral[5] in 18 patients (1.2%), and liver in 16 patients (1.1%) (Table 14.1.2/9).

The Eastern Cooperative Oncology Group (ECOG) performance status at study entry was either 0 (30.0%) or 1 (49.5%) in the majority of patients, while this information was missing for 80 patients (5.4%).

Concerning prostate specific antigen at baseline, most patients had values of >4-100 ng/mL (37.4%) or >100 ng/mL (30.1%). Information on values was missing for 24.9% of patients. The remaining 7.6% of patients had prostate specific antigen values of 0 – 4 ng/mL.

A total of 37.8% of patients had a normal alkaline phosphatase level of <140 U/L. A similar proportion of patients (34.8%) had an elevated alkaline phosphatase level ≥140 U/L. When further examining the patients with elevated alkaline phosphatase levels, 21.7% had values ≥220 U/L. Alkaline phosphatase values were missing for 27.4% of patients.

Just over half of patients had neutrophil values of ≥1.5 x 10^9/L (50.6%), with values missing for 46.1%. The majority of patients had platelet values of ≥100 x 10^9/L (90.1%) and hemoglobin values of ≥10 g/dL (84.1%). Lactate dehydrogenase values were missing for the majority of patients (61.0%).

In the analyses by region, though some variability was observable between the groups, there were few clinically significant differences (Table 14.1.2/7, Table 14.1.2/8, Table 14.1.2/9, Table 14.1.2/10). Additionally, since few patients were enrolled from ROW, any differences are inherently biased. One exception is the time since initial diagnosis of prostate cancer to CRPC, which was nearly 6 months longer in North America than Europe (median time: 32.68 months vs 27.14 months, respectively).

10.2.2 Prior and concomitant diseases

Investigators were asked to document all medical findings (excluding mCRPC) from the last 10 years in the CRF, independent of whether they were still ongoing at study entry.

Prior and concomitant diseases were categorized by indication according to the MedDRA coding system (version 27.0) using system organ class (SOCs) and PTs.

10.2.2.1 Prior diseases

In the analyses, prior diseases were indicated as medical findings from the last 10 years prior to inclusion and include conditions ongoing at study entry and conditions stopped before study entry. Table 11 shows presents the most common (≥3% of patients) prior diseases overall at the SOC and PT level. All SOCs/PTs without cut-off are presented in the TLF (Table 14.1.2/11; see Annex 1).

[5] The category “visceral” does not include other listed categories, such as brain, liver, and lung.

Table 11: Most common medical history findings (≥3% of patients; SAF)

MedDRA v27.0 SOC/PT	Total N=1472 n (%)
Patients with at least one prior disease	1212 (82.3)
Blood and lymphatic system disorders	129 (8.8)
Anaemia	100 (6.8)
Cardiac disorders	309 (21.0)
Atrial fibrillation	106 (7.2)
Coronary artery disease	72 (4.9)
Ear and labyrinth disorders	48 (3.3)
Endocrine disorders	65 (4.4)
Eye disorders	98 (6.7)
Gastrointestinal disorders	318 (21.6)
Constipation	83 (5.6)
Gastrooesophageal reflux disease	102 (6.9)
Nausea	44 (3.0)
General disorders and administration site conditions	207 (14.1)
Fatigue	122 (8.3)
Infections and infestations	136 (9.2)
Injury, poisoning and procedural complications	74 (5.0)
Investigations	110 (7.5)
Metabolism and nutrition disorders	536 (36.4)
Diabetes mellitus	142 (9.6)
Dyslipidaemia	49 (3.3)
Hypercholesterolaemia	165 (11.2)
Hyperlipidaemia	85 (5.8)
Type 2 diabetes mellitus	81 (5.5)
Musculoskeletal and connective tissue disorders	497 (33.8)
Arthralgia	103 (7.0)
Arthritis	62 (4.2)
Back pain	164 (11.1)
Bone pain	102 (6.9)
Osteoarthritis	58 (3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	168 (11.4)
Nervous system disorders	211 (14.3)
Psychiatric disorders	155 (10.5)
Depression	72 (4.9)
Insomnia	56 (3.8)
Renal and urinary disorders	279 (19.0)
Nocturia	59 (4.0)
Pollakiuria	51 (3.5)
Urinary retention	52 (3.5)
Reproductive system and breast disorders	128 (8.7)
Benign prostatic hyperplasia	64 (4.3)
Erectile dysfunction	54 (3.7)
Respiratory, thoracic and mediastinal disorders	205 (13.9)
Chronic obstructive pulmonary disease	65 (4.4)
Skin and subcutaneous tissue disorders	57 (3.9)
Surgical and medical procedures	244 (16.6)
Vascular disorders	723 (49.1)
Hot flush	59 (4.0)
Hypertension	654 (44.4)

MedDRA v27.0 SOC/PT	Total N=1472 n (%)

According to protocol, medical findings from the last 10 years prior to inclusion were collected.
The table contains conditions ongoing at study entry and conditions stopped before entry.
A subject was counted only once within each category (e.g., primary SOC).
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients, PT: preferred term, SAF: safety analysis set, SOC: system organ class
Source: Table 14.1.2/11

Most of the patients in the SAF (82.3%) had at least one prior disease, the most frequent at SOC level being Vascular disorders (49.1%), Metabolism and nutrition disorders (36.4%), and Musculoskeletal and connective tissue disorders (33.8%). At PT level, the most frequent prior disease was hypertension (44.4%), followed by hypercholesterolaemia (11.2%) and back pain (11.1%).

The analysis by region showed some differences between the groups. Since the category ROW only consisted of 39 patients (2.6% of patients in the SAF, see Table 7), it was not considered for the comparison. The proportion of patients with at least one prior disease was higher in North America (97.2%) than in Europe (75.3%), which was reflected by higher proportions in North America at SOC and PT level. The main drivers for the difference were the SOCs Gastrointestinal disorders (North America: 40.0% versus Europe: 11.6%), General disorders and administration site conditions (26.6% versus 7.3%), Musculoskeletal and connective tissue disorders (54.3% versus 23.1%), Psychiatric disorders (22.5% versus 4.0%), Renal and urinary disorders (35.7% versus 9.7%), and Vascular disorders (67.2% versus 39.3%). At PT level, the observation was most pronounced for hypertension (61.3% versus 35.1%), back pain (22.1% versus 5.2%), fatigue (18.9% versus 2.4%), and gastrooesophageal reflux disease (16.8% versus 1.4%) (Table 14.1.2/11). The difference between North America and Europe might be related to the pay structure for comorbid conditions in the USA or to cultural differences in sensitivity for reporting certain conditions, such as psychiatric disorders.

Certain prior diseases were of specific interest based on the primary and secondary objectives. These included prior malignancies (other than prostate cancer), bone fractures, and bone-associated conditions. Relevant PTs for bone fractures and bone-associated conditions are defined in Listing 14.5/3 (see Annex 1). Table 12 summarizes the most frequently reported (≥3 patients) of these conditions at PT level.

Table 12: Most common prior malignancies, bone fractures, and bone-associated conditions at PT level (≥3 patients; SAF)

MedDRA v27.0 PT	Total N=1472 n (%)
Prior malignancies	
Basal cell carcinoma	20 (1.4)
Bladder cancer	18 (1.2)
Cancer pain	11 (0.7)
Chronic lymphocytic leukaemia	4 (0.3)
Colon cancer	4 (0.3)
Colorectal adenoma	3 (0.2)
Malignant melanoma	5 (0.3)
Meningioma	3 (0.2)
Metastases to bone	5 (0.3)
Monoclonal gammopathy	3 (0.2)
Plasma cell myeloma	4 (0.3)
Renal cell carcinoma	3 (0.2)

MedDRA v27.0 PT	Total N=1472 n (%)
Skin cancer	10 (0.7)
Squamous cell carcinoma	4 (0.3)
Squamous cell carcinoma of skin	5 (0.3)
Transitional cell carcinoma	3 (0.2)
Prior bone fractures	
Ankle fracture	3 (0.2)
Femur fracture	4 (0.3)
Pathological fracture	6 (0.4)
Rib fracture	6 (0.4)
Prior bone-associated conditions	
Bone pain	102 (6.9)
Osteomyelitis	4 (0.3)
Osteonecrosis	3 (0.2)
Osteonecrosis of jaw	14 (1.0)
Osteopenia	19 (1.3)
Osteoporosis	20 (1.4)
Spinal pain	17 (1.2)

According to protocol, medical findings from the last 10 years prior to inclusion were collected.
The table contains conditions ongoing at study entry and conditions stopped before entry.
A subject was counted only once within each PT.
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients, PT: preferred term, SAF: safety analysis set
Source: Table 14.1.2/11

The most frequent prior malignancies were basal cell carcinoma (1.4% of patients in the SAF), bladder cancer (1.2%), and cancer pain and skin cancer (0.7% each). The most frequent prior bone fractures were pathological fracture and rib fracture (0.4% each), and the most frequent prior bone-associated conditions were bone pain (6.9%), osteoporosis (1.4%), osteopenia (1.3%), spinal pain (1.2%), and osteonecrosis of jaw (1.0%). The analysis by region showed a tendency for higher prevalence of such prior diseases in North America compared to Europe, albeit the number of patients with a certain prior disease was in general too small for meaningful comparisons.

10.2.2.2 Concomitant diseases

In the analyses, concomitant diseases were indicated as conditions that were ongoing at study entry. Table 13 shows the most common (≥3% of patients) concomitant diseases at the SOC and PT level.

Table 13: Most common ongoing conditions (≥3% of patients; SAF)

MedDRA v27.0 SOC/PT	Total N=1472 n (%)
Patients with at least one concomitant disease	1125 (76.4)
Blood and lymphatic system disorders	121 (8.2)
Anaemia	96 (6.5)
Cardiac disorders	257 (17.5)
Atrial fibrillation	92 (6.3)
Coronary artery disease	69 (4.7)
Ear and labyrinth disorders	45 (3.1)
Endocrine disorders	62 (4.2)
Eye disorders	67 (4.6)

MedDRA v27.0 SOC/PT	Total N=1472 n (%)
Gastrointestinal disorders	274 (18.6)
Constipation	79 (5.4)
Gastrooesophageal reflux disease	98 (6.7)
Nausea	43 (2.9)
General disorders and administration site conditions	191 (13.0)
Fatigue	116 (7.9)
Infections and infestations	75 (5.1)
Investigations	85 (5.8)
Metabolism and nutrition disorders	515 (35.0)
Diabetes mellitus	139 (9.4)
Dyslipidaemia	49 (3.3)
Hypercholesterolaemia	164 (11.1)
Hyperlipidaemia	78 (5.3)
Type 2 diabetes mellitus	80 (5.4)
Musculoskeletal and connective tissue disorders	470 (31.9)
Arthralgia	96 (6.5)
Arthritis	62 (4.2)
Back pain	159 (10.8)
Bone pain	99 (6.7)
Osteoarthritis	57 (3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	84 (5.7)
Nervous system disorders	160 (10.9)
Neuropathy peripheral	29 (2.0)
Psychiatric disorders	149 (10.1)
Anxiety	40 (2.7)
Depression	69 (4.7)
Insomnia	54 (3.7)
Renal and urinary disorders	228 (15.5)
Nocturia	52 (3.5)
Pollakiuria	50 (3.4)
Urinary retention	39 (2.6)
Reproductive system and breast disorders	116 (7.9)
Benign prostatic hyperplasia	58 (3.9)
Erectile dysfunction	52 (3.5)
Respiratory, thoracic and mediastinal disorders	170 (11.5)
Chronic obstructive pulmonary disease	65 (4.4)
Surgical and medical procedures	62 (4.2)
Vascular disorders	689 (46.8)
Hot flush	55 (3.7)
Hypertension	637 (43.3)

The table contains conditions ongoing at study entry.
A subject was counted only once within each category (e.g., primary SOC).
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients, PT: preferred term, SAF: safety analysis set, SOC: system organ class
Source: 14.1.2/12

Most of the patients in the SAF (76.4%) had at least one concomitant disease, the most frequent at SOC level being Vascular disorders (46.8%), Metabolism and nutrition disorders (35.0%), and Musculoskeletal and connective tissue disorders (31.9%). At PT level, the most frequent concomitant disease was hypertension (43.3%), followed by hypercholesterolaemia (11.1%) and back pain (10.8%).

The analysis by region showed some differences between the groups. Since the category ROW only consisted of 39 patients (2.6% of patients in the SAF, see Table 7), it was not considered for the comparison. The proportion of patients with at least one concomitant disease was higher in North America (93.8%) than in Europe (67.7%), which was reflected by

higher proportions in North America at SOC and PT level (Table 14.1.2/12). The main drivers for the difference were the SOCs Gastrointestinal disorders (North America: 36.6% versus Europe: 8.7%), Musculoskeletal and connective tissue disorders (53.0% versus 20.9%), and Vascular disorders (63.8% versus 37.5%). At PT level, the observation was most pronounced for hypertension (59.2% versus 34.4%), back pain (21.5% versus 5.0%), fatigue (17.9% versus 2.3%), and gastrooesophageal reflux disease (16.4% versus 1.2%) (Table 14.1.2/12). The difference between North America and Europe might be related to the pay structure for comorbid conditions in the USA or to cultural differences in sensitivity for reporting certain conditions, such as psychiatric disorders.

Certain concomitant diseases were of specific interest based on the primary and secondary objectives (for more details, see Section 10.2.2.1. These included concomitant malignancies (other than prostate cancer), bone fractures, and bone-associated conditions. The most frequent concomitant malignancies were cancer pain (11 patients, 0.7%), bladder cancer (8 patients, 0.5%), basal cell carcinoma and metastases to bone (5 patients each, 0.3%), and chronic lymphocytic leukaemia and plasma cell myeloma (4 patients each, 0.3%). The most frequent concomitant bone-associated conditions were bone pain (99 patients, 6.7%), osteoporosis (19 patients, 1.3%), osteopenia (18 patients, 1.2%), spinal pain (17 patients, 1.2%), and osteonecrosis of jaw (7 patients, 0.5%). Concomitant bone fractures were reported for 2 patients or less per PT (Table 14.1.2/12). The analysis by region showed a tendency for higher prevalence of such concomitant diseases in North America compared to Europe, albeit the number of patients with a certain concomitant disease was in general too small for meaningful comparisons.

10.2.3 Prior, concomitant, and post-radium-223 therapy and prior diagnostic and therapeutic procedures for prostate cancer

All medications taken before first radium-223 injection are categorized as prior medications. Prior completed medications, i.e., all prior medications with a stop date prior to first radium-223 injection, are a subset of prior medications.

All medications taken in addition to radium-223 are categorized as concomitant medication.

All medications taken after the last radium-223 injection are categorized as post-radium-223 medication. Subsequent medications, i.e., all post-radium-223 medications starting after the last injection of radium-223, are a subset of post-radium-223 medications.

For details, see Section 9.8.2.

10.2.3.1 Prior anti-cancer therapy and prior diagnostic and therapeutic procedures for prostate cancer

A summary of prior anti-cancer therapy and of prior diagnostic and therapeutic procedures for prostate cancer for the SAF is shown in Table 14. It includes a list of the most common prior and prior completed systemic anti-cancer therapies (>5% of patients). All prior and prior completed systemic anti-cancer therapies without cut-off are presented in the TLF (Table 14.1.3/4 and Table 14.1.3/7; see Annex 1). Information on bone scans is presented in Section 10.2.4.

Table 14: Prior anti-cancer therapy and prior diagnostic and therapeutic procedures for prostate cancer, SAF (N=1472)

Procedure	n	(%)
Any prior systemic anti-cancer therapy		
No	19	(1.3)
Yes	1453	(98.7)
Most common prior systemic anti-cancer therapies[a]		
Leuprorelin	832	(56.5)
Bicalutamide	820	(55.7)
Abiraterone	700	(47.6)
Docetaxel	579	(39.3)
Enzalutamide	576	(39.1)
Denosumab	457	(31.0)
Zoledronic acid	298	(20.2)
Goserelin	261	(17.7)
Degarelix	196	(13.3)
Triptorelin	195	(13.2)
Cabazitaxel	138	(9.4)
Sipuleucel-T	126	(8.6)
Any prior completed systemic anti-cancer therapy		
Yes[b]	1243	(84.4)
Most common prior completed systemic anti-cancer therapies[a]		
Bicalutamide	678	(46.1)
Docetaxel	556	(37.8)
Abiraterone	517	(35.1)
Enzalutamide	364	(24.7)
Leuprorelin	300	(20.4)
Zoledronic acid	137	(9.3)
Cabazitaxel	131	(8.9)
Degarelix	116	(7.9)
Sipuleucel-T	117	(7.9)
Goserelin	91	(6.2)
Denosumab	90	(6.1)
Triptorelin	75	(5.1)
Any prior radiotherapy		
No	543	(36.9)
Yes	929	(63.1)
Indication of prior radiotherapy		
n	929	(100.0)
Prostate cancer	672	(72.3)
Other	359	(38.6)
Missing	3	(0.3)
Type of prior radiotherapy		
n	929	(100.0)
External beam	754	(81.2)
Brachytherapy	80	(8.6)
Gamma knife	30	(3.2)
Stereotactic	30	(3.2)
Radio-frequency ablation	18	(1.9)
Proton therapy	4	(0.4)
Brachytherapy + External beam	2	(0.2)
Greenlight + Photovaporization	2	(0.2)
Thermal ablation	1	(0.1)
Unknown	71	(7.6)

Procedure	n	(%)
Prior diagnostic and therapeutic procedures		
Biopsy	994	(67.5)
CT scan	622	(42.3)
Prostatectomy	407	(27.6)
	316	(21.5)
Surgery	75	(5.1)
Orchiectomy	48	(3.3)
Transurethral resection	42	(2.9)
Other	19	(1.3)
Any prior blood transfusions		
No	1356	(92.1)
Yes	116	(7.9)

a: Including anti-cancer therapy undertaken by >5% subjects; patients could have more than one entry.
b: The remaining patients could be considered as having no prior completed systemic anti-cancer therapy, though this number is not presented in the TLF.
Systemic anti-cancer therapies were identified by the medical experts as specified in appendix of the SAP.
Prior therapies were therapies before first radium-223 injection and are defined in the SAP.
Prior completed therapies were defined as therapy with stop date prior to first radium-223 injection and are defined in the SAP.
For start and end dates imputation rules were applied as defined in the SAP.
Since patients could have multiple prior procedures, table includes incidences per patient.
CT: computed tomography, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan, TLF: tables, listings, and figures
Source: Table 14.1.3/1, Table 14.1.3/3, Table 14.1.3/4 and Table 14.1.3/7

As expected in a patient population exposed to prior castration, at least one prior systemic anti-cancer therapy was reported in almost all patients (98.7%), with the most common therapy being leuprorelin (56.5%), followed by bicalutamide (55.7%) and abiraterone (47.6%).

Prior radiotherapy was reported in 63.1% of patients. The type of prior radiotherapy was external beam in most cases (81.2% of patients with prior radiotherapy), followed by brachytherapy (8.6%). The remaining types were used in less than 5% of patients. In the majority of patients with prior radiotherapy (72.3%), the indication for radiotherapy was prostate cancer. In 38.6% of patients the indication was other and for 0.3% of patients this information on the indication was missing.

The most common prior diagnostic and therapeutic procedures for prostate cancer included biopsy (67.5% of patients in the SAF), computed tomography (CT, 42.3%), prostatectomy (27.6%), and imaging (21.5%).

Several imaging methods were used to evaluate tumor stage prior to baseline, including CT in 622 patients. CT scan was most commonly performed on the abdomen (91.2% of patients with CT scan), followed by pelvis (69.9%), and the chest (65.3%). Other imaging methods were used on 316 patients, mainly performed on ‘other’ body regions (48.7%) followed by the vertebral column (35.8%), and the pelvis (27.8%). Further details on prior diagnostic and therapeutic procedures for prostate cancer are given in Table 14.1.3/2.

Prior blood transfusions were reported for 7.9% of patients.

Information on patients with prior bone health agents is presented in Table 33.

10.2.3.2 Prior medications

Nearly half (47.7%) of patients in the SAF reported prior use of opioids. The most common opioids at ATC level 3 were Opioids (47.1%), followed by Anesthetics, general (8.7%). The remaining classes of opioids at ATC level 3 were reported by <5.0% of patients each (Table 14.1.3/5). Any prior completed use of opioids for patients in the SAF is summarized in Table 14.1.3/8.

At least one other prior medication (other than systemic anti-cancer therapies and opioids) was recorded for 92.7% of patients in the SAF. Further information on other prior medication and other prior completed medication is presented in Table 14.1.3/6 and Table 4.1.3/9 respectively.

10.2.3.3 Concomitant anti-cancer therapy and medications

Table 15 summarizes the incidence of concomitant anti-cancer therapies. It includes a list of the most common concomitant systemic anti-cancer therapies (>5% of patients). All concomitant systemic anti-cancer therapies without cut-off are presented in the TLF (Table 14.1.4/2; see Annex 1).

Table 15: Incidence of concomitant anti-cancer therapies, SAF (N=1472)

Procedure	n	(%)
Any concomitant systemic anti-cancer therapy		
Yes[a]	1270	(86.3)
Most common concomitant systemic anti-cancer therapies[b]		
Leuprorelin	663	(45.0)
Denosumab	411	(27.9)
Enzalutamide	259	(17.6)
Abiraterone	219	(14.9)
Goserelin	187	(12.7)
Zoledronic acid	186	(12.6)
Bicalutamide	181	(12.3)
Triptorelin	138	(9.4)
Degarelix	92	(6.3)
Any concomitant radiotherapy		
No	1318	(89.5)
Yes	154	(10.5)
Indication of concomitant radiotherapy		
n	154	(100.0)
Prostate cancer	129	(83.8)
Other	29	(18.8)
Type of concomitant radiotherapy		
n	154	(100.0)
External beam	110	(71.4)
Brachytherapy	12	(7.8)
Stereotactic	8	(5.2)
Gamma knife	8	(5.2)
Proton therapy	1	(0.6)
Radio-frequency ablation	1	(0.6)
Unknown	19	(12.3)
Any concomitant blood transfusions		
No	1349	(91.6)
Yes	123	(8.4)

a: The remaining patients could be considered as having no concomitant systemic anti-cancer therapy, though this number is not presented in the TLF.
b: Including anti-cancer therapy undertaken by >5% subjects; subjects may have had more than one entry.
Concomitant therapy was defined as therapy in addition to radium-223.
For start and end dates imputation rules were applied as defined in the SAP.
Since patients could have multiple therapies, table includes incidences per patient.
N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan, TLF: tables, listings, and figures
Source: Table 14.1.4/1 and Table 14.1.4/2

At least one concomitant systemic anti-cancer therapy, defined as therapy in addition to radium-223, was reported in 86.3% of patients. The most common category of concomitant anti-cancer therapy was androgen deprivation (leuprorelin in 45.0% of patients, goserelin in 12.7% of patients), followed by the use of bone health agents (denosumab in 27.9% of

patients, zoledronic acid in 12.6% of patients). Other concomitant systemic therapies to treat prostate cancer included enzalutamide reported in 17.6% of patients, abiraterone in 14.9% of patients, and bicalutamide in 12.3% of patients.

Concomitant radiotherapy was reported in 10.5% of patients, including mostly external beam radiation (71.4% of the patients with concomitant radiotherapy).

Concomitant blood transfusions were reported for 8.4% of patients.

Concomitant use of opioids was reported for 55.7% of patients in the SAF. Information on concomitant use of opioids by ATC level 3 and 4 is provided in Table 14.1.4 /3. Information on other concomitant medication use by ATC level 2 and 4 is provided in Table 14.1.4 /4.

10.2.3.4 Post-radium-223 therapy and medications during follow-up

The incidence of post-radium-223 therapies during follow-up, defined as all therapies that continued or started after the last dose of radium-223, is provided in Table 14.1.5/1 to Table 14.1.5/7.

At least one post-radium-223 systemic anti-cancer therapy was reported by 90.2% of patients in the SAF. The most common category of post-radium-223 systemic anti-cancer therapy was androgen deprivation (leuprorelin in 44.7% of patients, goserelin in 12.9% of patients), followed by bone health agents (denosumab in 28.9% of patients, zoledronic acid in 13.8% of patients, bisphosphonates in 0.4% of patients). Other post-radium-223 systemic anti-cancer therapies to treat prostate cancer included enzalutamide reported in 28.6% of patients, abiraterone in 22.5% of patients, docetaxel in 19.1% of patients, bicalutamide in 12.0% of patients, and cabazitaxel in 11.7% of patients (Table 14.1.5/2).

Post-radium-223 radiotherapy was reported for 29.5% of the patients who entered follow-up. The most common type of radiotherapy during follow-up was external beam radiation (81.8% of patients with post-radium-223 radiotherapy). Post-radium-223 blood transfusions during follow-up were reported for 24.6% of patients (Table 14.1.5/1).

Post-radium-223 use of opioids was reported for 59.8% of patients in the SAF. The most common opioids at ATC level 3 were Opioids (58.2%), followed by Anesthetics, general (13.0%). The remaining classes of opioids at ATC level 3 were reported by <5.0% of patients each (Table 14.1.5/3). Information on other post-radium-223 medication use is summarized in Table 14.1.5/4.

At least one subsequent systemic anti-cancer therapy, defined as therapy starting after the last dose of radium-223, was reported for 44.5% of patients. The most common subsequent systemic anti-cancer therapies were docetaxel in 17.7% of patients, enzalutamide in 14.8% of patients, cabazitaxel in 11.1% of patients, and abiraterone in 11.0% of patients (Table 14.1.5/5).

At least one subsequent use of opioids was reported for 17.1% of patients. The most common opioids at ATC level 3 were Opioids (16.6%), followed by Anesthetics, general (4.8%). The remaining classes of opioids at ATC level 3 were reported by <1.0% of patients each (Table 14.1.5/6). Information on other subsequent medication use is summarized in Table 14.1.5/7.

10.2.4 Bone scan

At baseline 1388 of the 1472 patients in the SAF had a bone scan, baseline being defined as last assessment before initiation of radium-223. For other tumor evaluation imaging techniques, please refer to Table 14. The most common method of bone assessment at baseline was scintigraphy (91.5% of patients with baseline bone scan), followed by sodium fluoride positron emission tomography (NaF PET)/CT scan (2.7%) and cholin PET/CT scan (1.6%) (Table 14.1.6/1). Information on the method of assessment for bone scans resulting in EOD is provided in Table 14.1.6/2.

Since imaging assessments were done according to local standard of care, the number of reported bone scans varies during the treatment and follow-up periods. While fewer bone scans were reported during the treatment period (from 16 patients at treatment 2 to 137 at treatment 4), more bone scans were reported during follow-up, with bone scans available for 433 patients at follow-up 1. At all visits, the most common method of assessment was scintigraphy.

The most commonly observed EOD among patients was 6 to 20 metastatic sites (EOD 2) across all treatment and follow-up visits, ranging from 35.0% to 52.5%, not considering the later follow-up visits due to the rapidly declining available bone scans (Table 14.1.6/1).

Baseline results of bone scan are presented in Table 10.

10.2.5 Extent of exposure

The extent of exposure for patients in the SAF is summarized in Table 16.

Table 16: Extent of exposure, SAF (N=1472)

Exposure parameter		
Number of injections		
Mean (SD)	4.8	(1.6)
Median (min, max)	6.0	(1, 6)
Number of injections, n (%)		
1 injection	90	(6.1%)
2 injections	103	(7.0%)
3 injections	156	(10.6%)
4 injections	136	(9.2%)
5 injections	109	(7.4%)
6 injections	878	(59.6%)
Radium-223 treatment duration[a] (weeks)		
Mean (SD)	16.735	(7.277)
Median (min, max)	20.143	(0.14, 47.14)
Total radioactivity injected per patient[b] (kBq)		
Mean (SD)	21352.64	(8901.62)
Median (min, max)	22805.00	(8.3, 52091.6)

a: Duration of treatment is derived as defined in the SAP. Missing start and stop dates of radium-223 were not imputed.
b: Total radioactivity injected was calculated per 55kBq.
kBq: kilo Becquerel, max: maximum, min: minimum, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan, SD: standard deviation
Source: Table 14.1.8/1

Patients received a mean number of 4.8±1.6 injections (median: 6.0 injections), with the majority of patients receiving 6 injections (59.6%). A further 7.4% of patients received 5 injections, and the remaining patients received 1 to 4 injections.

The radium-223 treatment had a mean duration of 16.735±7.277 weeks (median: 20.143 weeks). The mean total radioactivity injected was 21.352.64±8901.62 kBq (median: 22.805.00 kBq).

10.3 Outcome data

The number of documented patients across the categories of the main outcomes are provided in Section 10.2 for demographic and disease characteristics, prior and concomitant diseases, prior and concomitant medications, bone scans, and extent of exposure, in Section 10.4.1 for the primary outcome variables and in Section 10.4.2 for the secondary outcome variables (including safety parameters).

10.4 Main results

10.4.1 Analysis of primary outcome variables

The primary objectives of this study were:

- To assess the incidence of all SPMs
- To assess the incidence of treatment-emergent SAEs, drug-related AEs, and drug-related SAEs
- To assess bone marrow suppression

For details, refer to Section 7.

10.4.1.1 Second primary malignancies

10.4.1.1.1 Summary of second primary malignancies

Table 17 presents incidences of patients with SPM, overall and by time interval.

Table 17: Incidences of patients with SPM, overall and by time interval, SAF (N=1472)

Time interval[a]	SPMs	Patients with SPM	
	n	n	(%)
Overall	25	24	(1.6) 95% CI: [1.0, 2.4]
First Ra-223 injection to last Ra-223 injection	2	2	(0.1)
Last Ra-223 injection to 6 months afterwards	8	8	(0.5)
6 to 12 months after last Ra-223 injection	1	1	(<0.1)
12 to 18 months after last Ra-223 injection	7	7	(0.5)
18 to 24 months after last Ra-223 injection	4	4	(0.3)
After 24 months	3	3	(0.2)

a: For calculation of time intervals, months are derived as 30 days.
CI: confidence interval, N: number of patients in analysis set, n: number of events or patients, Ra-223: radium-223, SAE: serious adverse event, SAF: safety analysis set, SPM: second primary malignancy
Source: Table 14.2.1/1, Table 14.2.1/10

Overall, 25 SPMs were reported for 24 patients (1.6% of all patients in the SAF; 95% CI: [1.0, 2.4]), with an EAIR of 10.4 per 1000 years (95% CI: [6.7, 15.5]) (Table 14.2.1/10). Most SPMs were diagnosed in the period from last radium-223 injection to 6 months afterwards (0.5% of patients), followed by 12 to 18 months (0.5%), then 18 to 24 months after the last

radium-223 injection (0.3%). When looking at the corresponding PTs, no obvious trend or pattern was found (Table 14.2.1/11). Incidences of SPMs by worst grade are presented in Table 14.2.1/10.

The mean (SD) time to SPM (i.e., the time from first radium-223 to first SPM) was 16.66 (14.96) months, with a median (Q1, Q3) of 17.03 (4.47, 20.81) months and a range of 0.3 to 57.8 months (Table 14.2.1/12).

Figure 1 shows the KM curve of time to SPM.

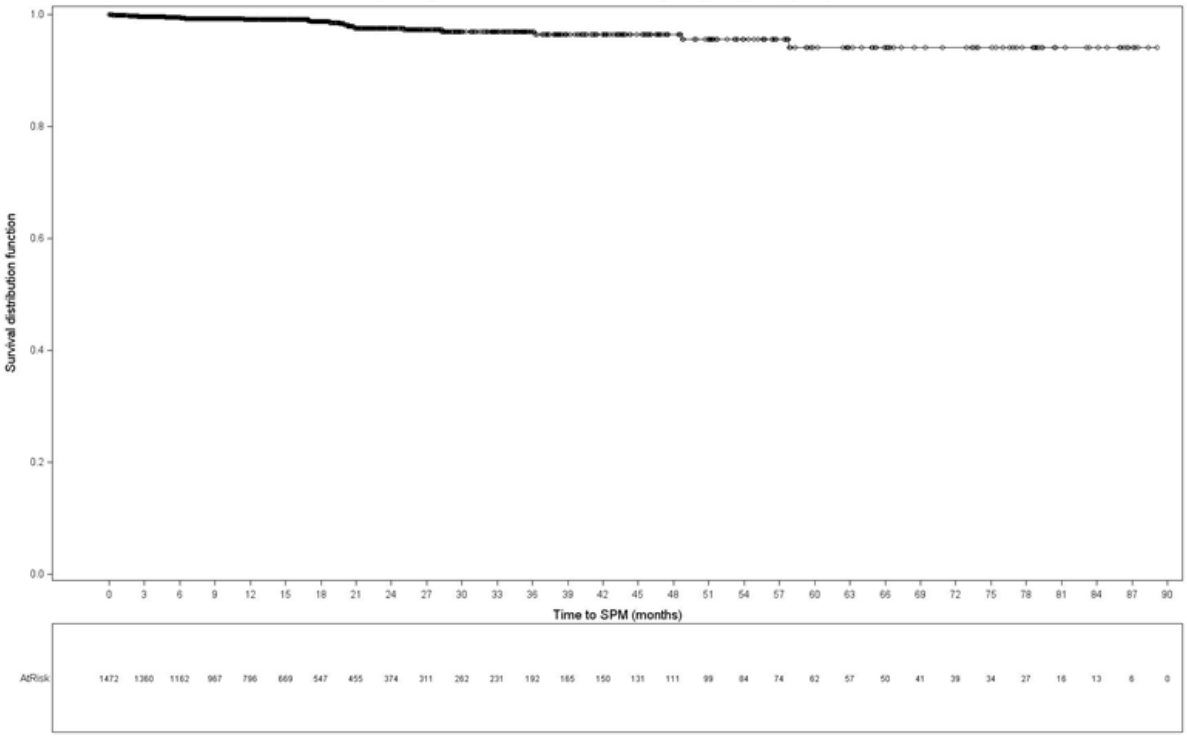

Figure 1: Kaplan-Meier curve of time to SPM (SAF)

SAF: safety analysis set, SPM: second primary malignancy
Source: Figure 14.2.1/1

Of the 1472 patients in the SAF, 24 patients (1.6%) had an SPM and 1448 patients (98.4%) were censored. Patients without an SPM until data cut off were censored at LKAD. Patients who started other radiopharmaceuticals or enrolled into other trials were censored at initiation of the respective radiopharmaceuticals (see Section 9.9.2.3). Due to the low incidence of SPMs, median, first quartile, and third quartile were not applicable (Table 14.2.1/13).

A listing of patients with SPM is given in Table 18. Patient narratives can be found in Annex 2.

Table 18: Listing of patients with SPM (SAF)

Subject identifier	Age	SPM (MedDRA PT)	Histopathological results of SPM	SPM onset day [a]	Treatment duration[b] (weeks)	Number of injections	Total radioactivity injected (kBq)	Relation to treatment	Outcome
PPD	PPD	Squamous cell carcinoma of skin	Grade: GII Tumor thickness: 5.0 mm	196	20.1	6	24163.0	Unrelated	Recovered/ Resolved
PPD	PPD	Squamous cell carcinoma of lung	PT2A,PN1,LO,V1,G3,R0, CMO, IIB	596	20.1	6	34390.0	Unrelated	Recovered/ Resolved
PPD	PPD	Basal cell carcinoma	Low-grade basal cell carcinoma	56	20.1	6	27220.0	Unrelated	Recovered/ Resolved
PPD	PPD	Acute myeloid leukaemia	--	630	8.1	3	12050.0	Related	Fatal
PPD	PPD	Small cell lung cancer	Small cell carcinoma	520	20.6	6	34617.2	Unrelated	Not recovered/ Not resolved
PPD	PPD	Bladder cancer	Papillary tumor of the right lateral wall. Transitional cell carcinoma	1758	20.1	6	22059.0	Unrelated	Not recovered/ Not resolved
PPD	PPD	Pancreatic carcinoma	--	860	22.1	6	19313.6	Unrelated	Fatal
PPD	PPD	Lung adenocarcinoma	Stage IIA (T1BN1M0)	617	21.3	6	27646.4	Unrelated	Not recovered/ Not resolved
PPD	PPD	Transitional cell carcinoma[c]	Papillary urothelial carcinoma	74	8.1	3	10669.7	Unrelated	Recovered/ Resolved with sequelae
PPD	PPD	Squamous cell carcinoma	Left central temple: squamous cell carcinoma extending to the deep tissue edge. Left forearm: atypical endophytic squamous proliferation most consistent with the surface of a well differentiated SCC	144	24.7	6	23516.1	Unrelated	Not recovered/ Not resolved

Subject identifier	Age	SPM (MedDRA PT)	Histopathological results of SPM	SPM onset day [a]	Treatment duration[b] (weeks)	Number of injections	Total radioactivity injected (kBq)	Relation to treatment	Outcome
PPD	PPD	Neuroendocrine carcinoma metastatic	Small cell neuroendocrine carcinoma	184	23.0	6	26026.5	Unrelated	Not recovered/ Not resolved
PPD	PPD	Pancreatic carcinoma	Invasive ductal adenocarcinoma	348	20.4	6	29944.1	Unrelated	Fatal
PPD	PPD	Squamous cell carcinoma of skin	Squamous cell carcinoma moderately differentiated, keratinizing, size: 0.3 cm, histologic grade: 2/4, perineural invasion: none, negative margins	608	21.7	6	25063.8	Unrelated	Recovered/ Resolved
PPD	PPD	Gastrointestinal carcinoma	--	49	4.1	2	8547.0	Unrelated	Fatal
PPD	PPD	Squamous cell carcinoma	Infiltrating squamous cell carcinoma	1481	22.1	6	22670.0	Unrelated	Recovering/ Resolving
PPD	PPD	Pulmonary mass	Not available	8	0.1	1	2750.0	Unrelated	Not recovered/ Not resolved
PPD	PPD	Neuroendocrine carcinoma	Positive for TTF1; small cell carcinoma without known primary origin	514	21.3	6	30750.0	Unrelated	Fatal
PPD	PPD	Transitional cell carcinoma	PT1 worsening to PT2NXMX	634	20.1	6	26220.0	Unrelated	Recovered/ Resolved
		Transitional cell carcinoma	PT2NXMX	856				Unrelated	Recovered/ Resolved
PPD	PPD	Non-Hodgkin's lymphoma	73% lymphocytes with villeus aspect	289	21.1	6	23429.0	Unrelated	Not recovered/ Not resolved
PPD	PPD	Plasma cell myeloma recurrent	Plasma cell myeloma	16	0.1	1	3350.0	Unrelated	Unknown

Subject identifier	Age	SPM (MedDRA PT)	Histopathological results of SPM	SPM onset day [a]	Treatment duration[b] (weeks)	Number of injections	Total radioactivity injected (kBq)	Relation to treatment	Outcome
PPD	PPD	Leukaemia monocytic	No histopathological diagnosis. No bone marrow biopsy performed due to subjects rapidly worsened condition	126	14.1	4	15431.0	Related	Fatal
PPD	PPD	Lung neoplasm malignant	Pleomorphic lung cancer	1099	20.1	6	31527.0	Unrelated	Fatal
PPD	PPD	Neoplasm of appendix	Low-grade apendical mucinosis neoplasia (LAMN)	761	20.1	6	31275.0	Unrelated	Recovered/ Resolved
PPD	PPD	Tumour of ampulla of Vater	Papillary adenocarcinoma	571	21.1	6	23800.0	Unrelated	Recovered/ Resolved

a: SPM onset day relative to start of radium-223.
b: Treatment duration included dose delays and was defined as (weeks): [(Day of last dose) – (day of first dose) +1]/7.
c: In interim report 2, another SPM (Bladder neoplasm) was reported for this patient. This AE was later deleted from the EDC.
Interim report 2 reported an SPM for an additional patient (lung carcinoma cell type unspecified recurrent). This event was later downgraded to a non-SPM AE.
MedDRA 27.0 was used.
AE: adverse event, MedDRA: Medical Dictionary for Regulatory Activities, EDC: electronic data capture system, PT: preferred term, SAF: safety analysis set, SCC: squamous cell carcinoma (skin cancer), SPM: second primary malignancy, TTF1: thyroid transcription factor 1
Source: Table 14.2.1/2 and Table 14.2.1/3

The reported SPMs included:

- Skin cancer in 5 patients, the PTs being squamous cell carcinoma of skin or squamous cell carcinoma in 2 patients each, and basal cell carcinoma in 1 patient
- Lung-related SPMs in 5 patients, the PTs being small cell lung cancer, lung adenocarcinoma, lung neoplasm malignant, pulmonary mass, and squamous cell carcinoma of lung in 1 patient each
- Gastrointestinal SPMs in 5 patients, the PTs being pancreatic carcinoma in 2 patients and gastrointestinal carcinoma, neoplasm of appendix, and tumour of Vater in 1 patient each
- Urinary related SPMs in 3 patients, the PTs being transitional cell carcinoma in 2 patients, one of whom had 2 such SPMs, and bladder cancer in 1 patient
- Neuroendocrine SPMs in 2 patients, the PTs being neuroendocrine carcinoma metastatic and neuroendocrine carcinoma in 1 patient each
- Hematologic SPMs in 2 patients, the PTs being acute myeloid leukaemia, leukaemia monocytic, non-Hodgkins's lymphoma, and plasma cell myeloma recurrent in 1 patient each)

Most patients (18 of 24 patients with SPMs) received 6 injections, and the remaining patients received between 1 and 4 injections. The total injected radioactivity ranged from 2,750 to 34,617.0 kBq. While the treatment duration was between 0.1 to 24.7 weeks (5.7 months), most of the patients (18 patients) were treated for more than 20 weeks.

The outcome was "recovered/resolved" for 8 SPMs (2 of them occurring in the same patient), "fatal" and "not recovered/not resolved" for 7 SPMs each, and "recovering/resolving" and "recovered/resolved with sequelae" for 1 SPM each. For 1 patient the outcome was unknown. Two (2) SPMs, acute myeloid leukaemia and leukaemia monocytic, were assessed by the investigator as being related to radium-223. The patient with fatal acute myeloid leukaemia had received 3 doses of radium-223. He was diagnosed following a 5.56-month regimen of olaparib. The patient with fatal leukaemia monocytic received 4 doses of radium-223, with a prior history of multiple lines of chemotherapy (taxane and alkylating) combined, in addition to several fractions of radiotherapy to the bone (see Annex 2).

All patients with SPMs had received prior systemic anti-cancer therapy, partially still ongoing at study enrollment. All but 1 patient received concomitant systemic anti-cancer therapy. Listings of systemic anti-cancer therapy for patients with SPMs are provided in Table 14.2.1/4 (any prior systemic anti-cancer therapy), Table 14.2.1/5 (prior completed systemic anti-cancer therapy), and Table 14.2.1/6 (concomitant systemic anti-cancer therapy).

More than half of the patients (16 patients) with SPM had received prior radiotherapy, all of which were completed before study enrollment. One (1) patient received concomitant radiotherapy (with an unknown duration). Listings of radiotherapy for patients with SPMs are provided in Table 14.2.1/7 (any prior radiotherapy), Table 14.2.1/8 (prior completed radiotherapy), and Table 14.2.1/9 (concomitant radiotherapy).

10.4.1.1.2 Analysis of SPMs in REASSURE and external secondary data sources

Table 19 shows the demographic and baseline characteristics from the German, Swedish, and US cohort studies to those from the REASSURE study.

Table 19: Demographic and baseline characteristics (German, Swedish, US cohorts; REASSURE)

Characteristics	German cohort (GePaRD) N=2360	Swedish cohort (PCBaSe) N=2849	US cohort (SEER-Medicare) N=2234	REASSURE (SAF) N=1472
Age[a], mean (SD) in years	72.9 (7.8)	75.6 (8.1)	76.6 (6.2)	72.9 (8.4)
Age category, n (%)				
<65 years	315 (13.3%)	291 (10.2%)	N/A[b]	236 (16.0%)
≥65 to <70 years	478 (20.3%)	359 (12.6%)	297 (13.3%)	257 (17.5%)
≥70 to <75 years	563 (23.9%)	515 (18.1%)	625 (28.0%)	328 (22.3%)
≥75 to <80 years	514 (21.8%)	679 (23.8%)	595 (26.6%)	319 (21.7%)
≥80 to <85 years	336 (14.2%)	644 (22.6%)	451 (20.2%)	215 (14.6%)
≥85 years	154 (6.5%)	361 (12.7%)	266 (11.9%)	117 (7.9%)
Time since 1st PC diagnosis, mean (SD) in years	3.4 (2.0) [40.8 months][c]	5.8 (3.0) [69.6 months][c]	3.5 (2.7) [42 months][c]	not calculated
Time since initial diagnosis of prostate cancer to castration-resistant cancer, mean (SD) in months	NA	NA	NA	50.53 (52.76)
Time since castration-resistant cancer to study entry, mean (SD) in months	NA	NA	NA	19.15 (22.30)

a: Three cohort studies: age at cohort entry; REASSURE: age at date of informed consent.
b: Data from SEER-Medicare only included men ≥65 years at cohort entry.
c: Months calculated manually.
GePaRD: German Pharmacoepidemiological Research Database, N: number of patients in cohort/analysis set, n: number of patients, NA: not available, PC: prostate cancer, PCBaSe: Prostate Cancer Data Base Sweden, SAF: safety analysis set, SD: standard deviation, SEER: US Surveillance, Epidemiology and End Results
Source for the three cohort studies: [Vassilev 2020]; source for REASSURE data: Table 14.1.2/3, Table 14.1.2/7

The mean age of the patients was slightly lower in the German cohort and in REASSURE (72.9 years in both studies) than in the Swedish (75.6 years) and US cohorts (76.6 years). This is reflected in the distribution of age categories, which show a trend to higher patient counts in the older age groups for the Swedish and US cohorts.

Mean time from first prostate cancer diagnosis to cohort entry was shorter in the German (3.4 years or 40.8 months) and US cohort (3.5 years or 42 months) than in the Swedish cohort (5.8 years or 69.6 months). This variable was not calculated for REASSURE. When using the sum of time from initial prostate cancer diagnosis to CRPC and time from CRPC to study entry as proxy, the resulting period is comparable to that of the Swedish cohort and longer than the periods in the German and US cohorts.

The overall incidence rates [95% CI] of SPMs were 79.0 [70.4, 88.4] events per 1000 person-years for the German cohort, 101.7 [90.3, 114.5] for the Swedish cohort, and 59 [50, 68] for the US cohort. Small differences in incidence rate between age groups were observed, but no clear trend emerged, either within or across the cohorts.

To put the frequency of SPMs in REASSURE in relation to the cohort studies, the observed number of cases for SPMs in REASSURE was compared to the corresponding expected numbers based on data from the external reference data sources (see Section 9.9.2.5). Age (by 5-year intervals) was accounted for in the analysis. The ratio of the observed and expected number of cases by means of SMR was used as the measure of the increased or decreased incidence rates (Table 20). For this analysis, skin-based SPMs from REASSURE were excluded to align them with the cohort studies, resulting in an incidence of 19 patients with SPMs instead of 24 (see Table 17).

Table 20: Comparison of REASSURE SPM incidence with external data (GePaRD, Germany; SEER-Medicare, USA; PCBaSe, Sweden)

Age groups	External N	External incidence	REASSURE N	REASSURE incidence[a]	Age-specific rate[b]	Expected incidence	SMR	95% CI
German cohort (GePaRD)								
<65 years	315	42	236	0	0.133	31.467	0.099	[0.000, 0.000]
≥65 to <70 years	478	56	257	4	0.117	30.109	0.000	[0.003, 0.263]
≥70 to <75 years	563	79	328	4	0.140	46.025	0.133	[0.002, 0.172]
≥75 to <80 years	514	73	319	4	0.142	45.305	0.087	[0.002, 0.175]
≥80 to <85 years	336	40	215	6	0.119	25.595	0.088	[0.047, 0.422]
≥85 years	154	18	117	1	0.117	13.675	0.234	[-0.070, 0.216]
Standardized total	2360	308	1472	19	N/A	192.176	0.099	[0.054, 0.143]
US cohort (SEER-Medicare)								
<65 years	0[c]	0	236	0	N/A	N/A	N/A	N/A
≥65 to <70 years	297	30	257	4	0.101	25.960	0.154	[0.003, 0.305]
≥70 to <75 years	625	63	328	4	0.101	33.062	0.121	[0.002, 0.240]
≥75 to <80 years	595	37	319	4	0.062	19.837	0.202	[0.004, 0.399]
≥80 to <85 years	451	42	215	6	0.093	20.022	0.300	[0.060, 0.539]
≥85 years	266	0	117	1	0.000	0.000	N/A	N/A
Standardized total	2234	172	1472	19	N/A	98.881	0.192	[0.106, 0.279]
Swedish cohort (PCBaSe)								
<65 years	291	33	236	0	0.113	26.763	0.000	[0.000, 0.000]
≥65 to <70 years	359	34	257	4	0.095	24.340	0.164	[0.003, 0.325]
≥70 to <75 years	515	66	328	4	0.128	42.035	0.095	[0.002, 0.188]
≥75 to <80 years	679	62	319	4	0.091	29.128	0.137	[0.003, 0.272]
≥80 to <85 years	644	51	215	6	0.079	17.026	0.352	[0.070, 0.634]
≥85 years	361	27	117	1	0.075	8.751	0.114	[-0.110, 0.338]
Standardized total	2849	273	1472	19	N/A	148.043	0.128	[0.071, 0.186]

a: For this analysis, skin-based SPMs from REASSURE were excluded.
b: By patient; calculated.
c: Data from SEER-Medicare only included men ≥65 years at cohort entry.
CI: confidence interval, GePaRD: German Pharmacoepidemiological Research Database, N: number of patients in the analysis set or cohort, N/A: not applicable, PCBaSe: PCBaSe: Prostate Cancer Data Base Sweden, SEER: SEER: US Surveillance, Epidemiology and End Results, SMR: standardized morbidity ratio, SPM: second primary malignancy
Source for the three cohort studies: [Vassilev 2020]; source for REASSURE data: Table 14.2.3/1, Table 14.2.3/2, Table 14.2.3/3

The expected incidence of SPMs in REASSURE as derived from the reference data was 192.176 for the German cohort, 98.881 for the US cohort, and 148.043 for the Swedish cohort. The corresponding SMRs were 0.099, 0.192, and 0.128, respectively, showing that the incidence rate of SPMs was smaller in REASSURE than in the three reference studies.

10.4.1.2 Adverse events

The incidence of treatment-emergent SAEs (collected up to 30 days after last administration; see Section 10.4.1.2.3.2), drug-related treatment-emergent AEs (collected up to 30 days after last administration; see Section 10.4.1.2.2), and drug-related SAEs (see Section 10.4.1.2.3.2) was collected as part of the primary outcome variables. Treatment-emergent was defined as any event arising or worsening on the day of or after start of radium-223 until 30 days after last injection.

Additional safety data was collected and is also presented in this section. A by-subject listing of AEs is provided in Table 14.2.4/19.

AEs relating to bone marrow suppression are presented in Section 10.4.1.3.

10.4.1.2.1 Brief summary of adverse events

A summary of AEs is presented in Table 21.

Table 21: Overall summary of patients with adverse events, SAF (N=1472)

AE summary	n	(%)
Number of patients with any type of adverse event as presented below	739	(50.2)
Number of patients with treatment-emergent SAE	325	(22.1)
Number of patients with treatment-emergent SAE resulting in permanent discontinuation of radium-223	108	(7.3)
Number of patients with treatment-emergent SAE resulting in interruption or dose modification of radium-223	39	(2.6)
Number of patients with treatment-emergent SAE resulting in inpatient hospitalization or prolongation of existing hospitalization	248	(16.8)
Number of patients with treatment-emergent SAE resulting in death	94	(6.4)
Number of patients with treatment-emergent drug-related AE	537	(36.5)
Number of patients with treatment-emergent drug-related AE with worst grade ≥ 3	167	(11.3)
Number of patients with treatment-emergent drug-related AE resulting in permanent discontinuation of radium-223	78	(5.3)
Number of patients with treatment-emergent drug-related AE resulting in interruption or dose modification of radium-223	38	(2.6)
Number of patients with treatment-emergent drug-related AE resulting in inpatient hospitalization or prolongation of existing hospitalization	42	(2.9)
Number of patients with treatment-emergent drug-related AE resulting in death	6	(0.4)
Number of patients with drug-related SAE	88	(6.0)
Number of patients with drug-related SAE resulting in permanent discontinuation of radium-223	17	(1.2)
Number of patients with drug-related SAE resulting in interruption or dose modification of radium-223	8	(0.5)
Number of patients with drug-related SAE resulting in inpatient hospitalization or prolongation of existing hospitalization	63	(4.3)
Number of patients with drug-related SAE resulting in death	10	(0.7)

AE summary	n	(%)

Treatment-emergent was defined as any event arising or worsening on the day of or after start of radium-223 until 30 days after last injection.
All SAEs of SPM and all drug-related SAEs were collected up to 7 years after the last administration of radium-223.
Table includes only death information documented as AE.
AE: adverse event, N: number of patients in analysis set, n: number of patients, SAE: serious adverse event, SAF: safety analysis set, SPM: second primary malignancy
Source: Table 14.2.4/1

A total of 739 patients (50.2%) had any type of AE. Treatment-emergent SAEs were observed in 325 patients (22.1%), treatment-emergent drug-related AEs in 537 patients (36.5%) and drug-related SAEs in 88 patients (6.0%).

Interruption or dose modification of radium-223 was reported as a result of treatment-emergent SAEs for 39 patients (2.6%), as a result of treatment-emergent drug-related AEs for 38 patients (2.6%), and as a result of drug-related SAEs for 8 patients (0.5%).

10.4.1.2.2 Treatment-emergent drug-related adverse events

A summary of common **treatment-emergent drug-related AEs** is given in Table 22.

Table 22: Common treatment-emergent drug-related adverse events (≥1.0% of patients), SAF (N=1472)

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR
Patients with at least one treatment-emergent drug-related AE	150 (10.2)	11 (0.7)	6 (0.4)	537 (36.5)	[34.0, 39.0]	1.23	[1.12, 1.33]
Blood and lymphatic system disorders	102 (6.9)	5 (0.3)	4 (0.3)	177 (12.0)	[10.4, 13.8]	0.31	[0.27, 0.36]
Anaemia	91 (6.2)	1 (<0.1)	1 (<0.1)	129 (8.8)	[7.4, 10.3]	0.23	[0.19, 0.27]
Leukopenia	4 (0.3)	0 (0.0)	0 (0.0)	16 (1.1)	[0.6, 1.8]	0.03	[0.02, 0.04]
Neutropenia	8 (0.5)	0 (0.0)	0 (0.0)	19 (1.3)	[0.8, 2.0]	0.03	[0.02, 0.05]
Thrombocytopenia	9 (0.6)	3 (0.2)	2 (0.1)	37 (2.5)	[1.8, 3.4]	0.06	[0.04, 0.09]
Gastrointestinal disorders	8 (0.5)	0 (0.0)	0 (0.0)	285 (19.4)	[17.4, 21.5]	0.57	[0.51, 0.64]
Diarrhoea	4 (0.3)	0 (0.0)	0 (0.0)	161 (10.9)	[9.4, 12.6]	0.30	[0.25, 0.35]
Nausea	2 (0.1)	0 (0.0)	0 (0.0)	135 (9.2)	[7.7, 10.8]	0.24	[0.21, 0.29]
Vomiting	2 (0.1)	0 (0.0)	0 (0.0)	47 (3.2)	[2.4, 4.2]	0.08	[0.06, 0.11]
General disorders and administration site conditions	15 (1.0)	0 (0.0)	0 (0.0)	158 (10.7)	[9.2, 12.4]	0.29	[0.24, 0.34]
Asthenia	3 (0.2)	0 (0.0)	0 (0.0)	28 (1.9)	[1.3, 2.7]	0.05	[0.03, 0.07]
Fatigue	8 (0.5)	0 (0.0)	0 (0.0)	111 (7.5)	[6.2, 9.0]	0.20	[0.16, 0.24]
Pain	4 (0.3)	0 (0.0)	0 (0.0)	18 (1.2)	[0.7, 1.9]	0.03	[0.02, 0.05]
Investigations	27 (1.8)	6 (0.4)	0 (0.0)	57 (3.9)	[2.9, 5.0]	0.10	[0.07, 0.13]
Haemoglobin decreased	12 (0.8)	0 (0.0)	0 (0.0)	14 (1.0)	[0.5, 1.6]	0.02	[0.01, 0.04]
Platelet count decreased	6 (0.4)	5 (0.3)	0 (0.0)	20 (1.4)	[0.8, 2.1]	0.03	[0.02, 0.05]
White blood cell count decreased	2 (0.1)	0 (0.0)	0 (0.0)	21 (1.4)	[0.9, 2.2]	0.04	[0.02, 0.05]
Metabolism and nutrition disorders	4 (0.3)	0 (0.0)	0 (0.0)	47 (3.2)	[2.4, 4.2]	0.08	[0.06, 0.11]
Decreased appetite	1 (<0.1)	0 (0.0)	0 (0.0)	40 (2.7)	[1.9, 3.7]	0.07	[0.05, 0.09]
Musculoskeletal and connective tissue disorders	11 (0.7)	1 (<0.1)	0 (0.0)	69 (4.7)	[3.7, 5.9]	0.12	[0.09, 0.15]
Arthralgia	2 (0.1)	0 (0.0)	0 (0.0)	16 (1.1)	[0.6, 1.8]	0.03	[0.02, 0.04]
Back pain	8 (0.5)	0 (0.0)	0 (0.0)	17 (1.2)	[0.7, 1.8]	0.03	[0.02, 0.05]
Bone pain	2 (0.1)	0 (0.0)	0 (0.0)	20 (1.4)	[0.8, 2.1]	0.03	[0.02, 0.05]
Nervous system disorders	1 (<0.1)	1 (<0.1)	0 (0.0)	34 (2.3)	[1.6, 3.2]	0.06	[0.04, 0.08]

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR

Treatment-emergent was defined as any event arising or worsening on the day of or after start of radium-223 until 30 days after last injection.
This table presents counts of patients. Patients with more than one AE were counted with worst respective grade.
In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
All grades includes patients with grade missing.
CI for incidence was calculated by exact Clopper-Pearson, CI for EAIR was calculated as described in the SAP.
AE: adverse event, CI: confidence interval, EAIR: exposure adjusted incidence rate, MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients, PT: preferred term, SAF: safety analysis set, SAP: statistical analysis plan, SOC: system organ class
Source: Table 14.2.4/7

Treatment-emergent drug-related AEs were reported for 537 patients (36.5%, EAIR per year: 1.23). The most commonly reported worst severity was grade 1 (202 patients, 13.7%), followed by grade 2 (159 patients, 10.8%), and grade 3 (150 patients, 10.2%). Severity grade 4 and grade 5 were reported for 11 patients (0.7%) and 6 patients (0.4%), respectively. For 9 patients (1.0%) severity grades were missing (Table 14.2.4/7).

The most frequently reported SOC was Gastrointestinal disorders in 285 patients (19.4%, EAIR per year: 0.57), with the most common PT of diarrhoea in 161 patients (10.9%, EAIR per year: 0.30), followed by nausea in 135 patients (9.2%, EAIR per year: 0.24). A total of 177 patients (12.0%, EAIR per year: 0.31) reported Blood and lymphatic system disorders with the most common PT of anaemia in 129 patients (8.8%, EAIR per year: 0.23). A total of 158 patients (10.7%, EAIR per year: 0.29) reported General disorders and administration site conditions, with the most common PT of fatigue in 111 patients (7.5%, EAIR per year: 0.20). The remaining treatment-emergent drug-related AEs were reported in <5% of patients each (Table 13.2.4/7).

10.4.1.2.3 Deaths, other serious adverse events, and other significant adverse events

10.4.1.2.3.1 Deaths

Treatment-emergent SAEs resulting in death were reported for 94 patients (6.4% of patients in the SAF, EAIR per year: 0.16). The most frequently reported SOC was Neoplasms benign, malignant and unspecified (incl cysts and polyps) in 30 patients (2.0%, EAIR per year: 0.05), most commonly the worsening of prostate cancer (PTs: prostate cancer in 14 patients [1.0%, EAIR per year: 0.02] and prostate cancer metastatic in 6 patients [0.4%, EAIR per year: 0.01]). General disorders and administration site conditions were reported in 21 patients (1.4%, EAIR per year: 0.04), with the most common PTs of general physical health deterioration in 5 patients (0.3%, EAIR per year: 0.01), multiple organ dysfunction syndrome in 4 patients (0.3%, EAIR per year: 0.01), and death, disease progression, and performance status decreased in 3 patients each (0.2%, EAIR per year: 0.01 each). In addition, Cardiac disorders (8 patients, 0.5%), Blood and lymphatic system disorders (7 patients, 0.5%), Infections and infestations (6 patients, 0.4%), and Hepatobiliary disorders and Nervous system disorders (5 patients each, 0.3%) were among the most commonly reported SOCs. The remaining most common treatment-emergent SAEs at PT level resulting in death were anaemia, cardiac failure, hepatic failure, pneumonia, and renal failure in 3 patients each [0.2%, EAIR per year: 0.01 each]. All other treatment-emergent SAEs resulting in death were reported in 1 or 2 patients each (Table 14.2.4/6).

A total of 6 patients (0.4%, EAIR per year: 0.01) experienced at least one **treatment-emergent drug-related SAE resulting in death**. The most frequently reported SOC was Blood and lymphatic system disorders in 4 patients (0.3%, EAIR per year: 0.01), (PTs: thrombocytopenia in 2 patients [0.1%, EAIR per year: 0.00], anaemia and pancytopenia in 1 patient each [<0.1%, EAIR per year: 0.00, each]). **Drug-related SAEs resulting in death** were reported for 10 patients (0.7%, EAIR per year: 0.02). The most frequently reported SOC was Blood and lymphatic system disorders in 6 patients (0.4%, EAIR per year: 0.01). PTs attributable to bone marrow suppression were anaemia, pancytopenia, and thrombocytopenia in 2 patients each (0.1%, EAIR per year: 0.00), in addition to platelet count decreased and white blood cell count decreased in 1 patient each (<0.1%, EAIR per year: 0.00 each). The remaining drug-related SAEs resulting in death were AML, cardiac failure, general physical

health deterioration, and leukaemia monocytic in 1 patient each (<0.1%, EAIR per year: 0.00 each) (Table 14.2.4/14).

10.4.1.2.3.2 Other serious adverse events

A summary of **common treatment-emergent SAEs** is given in Table 23.

Table 23: Common treatment-emergent SAEs (≥0.5% of patients), SAF (N=1472)

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR
Patients with at least one treatment-emergent SAE	150 (10.2)	38 (2.6)	94 (6.4)	325 (22.1)	[20.0, 24.3]	0.59	[0.53, 0.66]
Blood and lymphatic system disorders	27 (1.8)	7 (0.5)	7 (0.5)	43 (2.9)	[2.1, 3.9]	0.07	[0.05, 0.10]
Anaemia	21 (1.4)	2 (0.1)	3 (0.2)	27 (1.8)	[1.2, 2.7]	0.05	[0.03, 0.07]
Thrombocytopenia	3 (0.2)	3 (0.2)	2 (0.1)	8 (0.5)	[0.2, 1.1]	0.01	[0.01, 0.03]
Cardiac disorders	11 (0.7)	5 (0.3)	8 (0.5)	26 (1.8)	[1.2, 2.6]	0.04	[0.03, 0.06]
Gastrointestinal disorders	16 (1.1)	1 (<0.1)	3 (0.2)	24 (1.6)	[1.0, 2.4]	0.04	[0.03, 0.06]
General disorders and administration site conditions	23 (1.6)	4 (0.3)	21 (1.4)	59 (4.0)	[3.1, 5.1]	0.10	[0.08, 0.13]
Asthenia	7 (0.5)	0 (0.0)	0 (0.0)	8 (0.5)	[0.2, 1.1]	0.01	[0.01, 0.03]
General physical health deterioration	4 (0.3)	2 (0.1)	5 (0.3)	15 (1.0)	[0.6, 1.7]	0.03	[0.01, 0.04]
Pain	5 (0.3)	1 (<0.1)	2 (0.1)	10 (0.7)	[0.3, 1.2]	0.02	[0.01, 0.03]
Hepatobiliary disorders	2 (0.1)	1 (<0.1)	5 (0.3)	8 (0.5)	[0.2, 1.1]	0.01	[0.01, 0.03]
Infections and infestations	26 (1.8)	5 (0.3)	6 (0.4)	44 (3.0)	[2.2, 4.0]	0.07	[0.05, 0.10]
Pneumonia	7 (0.5)	1 (<0.1)	3 (0.2)	14 (1.0)	[0.5, 1.6]	0.02	[0.01, 0.04]
Injury, poisoning and procedural complications	17 (1.2)	2 (0.1)	4 (0.3)	34 (2.3)	[1.6, 3.2]	0.06	[0.04, 0.08]
Investigations	10 (0.7)	6 (0.4)	3 (0.2)	19 (1.3)	[0.8, 2.0]	0.03	[0.02, 0.05]
Metabolism and nutrition disorders	12 (0.8)	0 (0.0)	2 (0.1)	18 (1.2)	[0.7, 1.9]	0.03	[0.02, 0.05]
Musculoskeletal and connective tissue disorders	29 (2.0)	2 (0.1)	0 (0.0)	36 (2.4)	[1.7, 3.4]	0.06	[0.04, 0.08]
Back pain	10 (0.7)	0 (0.0)	0 (0.0)	11 (0.7)	[0.4, 1.3]	0.02	[0.01, 0.03]
Bone pain	8 (0.5)	0 (0.0)	0 (0.0)	8 (0.5)	[0.2, 1.1]	0.01	[0.01, 0.03]
Pain in extremity	6 (0.4)	1 (<0.1)	0 (0.0)	7 (0.5)	[0.2, 1.0]	0.01	[0.00, 0.02]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.4)	4 (0.3)	30 (2.0)	48 (3.3)	[2.4, 4.3]	0.08	[0.06, 0.11]
Prostate cancer	1 (<0.1)	1 (<0.1)	14 (1.0)	16 (1.1)	[0.6, 1.8]	0.03	[0.02, 0.04]
Nervous system disorders	16 (1.1)	6 (0.4)	5 (0.3)	41 (2.8)	[2.0, 3.8]	0.07	[0.05, 0.09]
Spinal cord compression	8 (0.5)	1 (<0.1)	1 (<0.1)	13 (0.9)	[0.5, 1.5]	0.02	[0.01, 0.04]
Renal and urinary disorders	20 (1.4)	0 (0.0)	4 (0.3)	26 (1.8)	[1.2, 2.6]	0.04	[0.03, 0.06]
Respiratory, thoracic and mediastinal disorders	11 (0.7)	1 (<0.1)	4 (0.3)	20 (1.4)	[0.8, 2.1]	0.03	[0.02, 0.05]
Vascular disorders	3 (0.2)	3 (0.2)	2 (0.1)	10 (0.7)	[0.3, 1.2]	0.02	[0.01, 0.03]

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR

Treatment-emergent was defined as any event arising or worsening on the day of or after start of radium-223 until 30 days after last injection.
This table presents counts of patients. Patients with more than one AE were counted with worst respective grade.
In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
All grades includes patients with grade missing.
CI for incidence was calculated by exact Clopper-Pearson, CI for EAIR was calculated as described in the SAP.
AE: adverse event, CI: confidence interval, EAIR: exposure adjusted incidence rate, MedDRA: Medical Dictionary for Regulatory Activities, n: number of patients, N: number of patients in analysis set, PT: preferred term, SAE: serious adverse event, SAF: safety analysis set, SAP: statistical analysis plan, SOC: system organ class
Source: Table 14.2.4/3

Treatment-emergent SAEs were reported for 325 patients (22.1%, EAIR per year: 0.59). The distribution by severity grade was as follows: 0 patients (0.0%) with grade 1, 17 patients (1.2%) with grade 2, 150 patients (10.2%) with grade 3, 38 patients (2.6%) with grade 4, and 94 patients (6.4%) with grade 5. For 26 patients (1.8%) severity grades were missing (Table 14.2.4/3).

The most frequently reported SOC was General disorders and administration site conditions in 59 patients (4.0%, EAIR per year: 0.10), with the most common PTs of general physical health deterioration (15 patients, 1.0%) and pain (10 patients, 0.7%). Neoplasms benign, malignant and unspecified (incl cysts and polyps) were reported in 48 patients (3.3%, EAIR per year: 0.08), most commonly being worsening of prostate cancer (PT: prostate cancer in 16 patients, 1.1%). Infections and infestations were reported in 44 patients (3.0%, EAIR per year: 0.07), with pneumonia being the most frequent PT (14 patients, 1.0%). Blood and lymphatic system disorders were reported in 43 patients (2.9%, EAIR per year: 0.07), the most frequent PTs being anaemia (27 patients, 1.8%) and thrombocytopenia (8 patients, 0.5%). Nervous system disorders were reported in 41 patients (2.8%, EAIR per year: 0.07), with spinal cord compression as the most common PT (13 patients, 0.9%). Musculoskeletal and connective tissue disorders were reported in 36 patients (2.4%, EAIR per year: 0.06) and Injury, poisoning and procedural complications in 34 patients (2.3%, EAIR per year: 0.06). The remaining SOCs were reported in <2% of patients.

Common drug-related SAEs are summarized in Table 24.

Table 24: Common drug-related SAEs (>1 patient), SAF (N=1472)

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR
Patients with at least one drug-related SAE	51 (3.5)	15 (1.0)	10 (0.7)	88 (6.0)	[4.8, 7.3]	0.15	[0.12, 0.18]
Blood and lymphatic system disorders	25 (1.7)	7 (0.5)	6 (0.4)	41 (2.8)	[2.0, 3.8]	0.07	[0.05, 0.09]
Anaemia	18 (1.2)	1 (<0.1)	2 (0.1)	23 (1.6)	[1.0, 2.3]	0.04	[0.02, 0.06]
Pancytopenia	3 (0.2)	0 (0.0)	2 (0.1)	5 (0.3)	[0.1, 0.8]	0.01	[0.00, 0.02]
Thrombocytopenia	4 (0.3)	6 (0.4)	2 (0.1)	12 (0.8)	[0.4, 1.4]	0.02	[0.01, 0.04]
Cardiac disorders	1 (<0.1)	0 (0.0)	1 (<0.1)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Gastrointestinal disorders	4 (0.3)	0 (0.0)	0 (0.0)	5 (0.3)	[0.1, 0.8]	0.01	[0.00, 0.02]
Abdominal pain	1 (<0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Nausea	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
General disorders and administration site conditions	2 (0.1)	0 (0.0)	1 (<0.1)	3 (0.2)	[0.0, 0.6]	0.01	[0.00, 0.01]
Infections and infestations	3 (0.2)	0 (0.0)	0 (0.0)	4 (0.3)	[0.1, 0.7]	0.01	[0.00, 0.02]
Pneumonia	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	[0.0, 0.6]	0.01	[0.00, 0.01]
Injury, poisoning and procedural complications	9 (0.6)	0 (0.0)	0 (0.0)	12 (0.8)	[0.4, 1.4]	0.02	[0.01, 0.03]
Femur fracture	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Humerus fracture	1 (<0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Lumbar vertebral fracture	1 (<0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Stress fracture	1 (<0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Thoracic vertebral fracture	3 (0.2)	0 (0.0)	0 (0.0)	4 (0.3)	[0.1, 0.7]	0.01	[0.00, 0.02]
Investigations	7 (0.5)	8 (0.5)	1 (<0.1)	16 (1.1)	[0.6, 1.8]	0.03	[0.02, 0.04]
Haemoglobin decreased	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	[0.0, 0.6]	0.01	[0.00, 0.01]
Platelet count decreased	2 (0.1)	7 (0.5)	1 (<0.1)	10 (0.7)	[0.3, 1.2]	0.02	[0.01, 0.03]
Red blood cell count decreased	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
White blood cell count decreased	1 (<0.1)	0 (0.0)	1 (<0.1)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Musculoskeletal and connective tissue disorders	4 (0.3)	1 (<0.1)	0 (0.0)	9 (0.6)	[0.3, 1.2]	0.02	[0.01, 0.03]
Osteonecrosis of jaw	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Pathological fracture	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0 (0.0)	2 (0.1)	3 (0.2)	[0.0, 0.6]	0.01	[0.00, 0.01]

MedDRA v27.0 SOC/PT	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR
Nervous system disorders	2 (0.1)	1 (<0.1)	0 (0.0)	4 (0.3)	[0.1, 0.7]	0.01	[0.00, 0.02]
Spinal cord compression	1 (<0.1)	1 (<0.1)	0 (0.0)	2 (0.1)	[0.0, 0.5]	0.00	[0.00, 0.01]

This table presents counts of patients. Patients with more than one AE were counted with worst respective grade.
In addition to the total (including all grades), only grade 3, 4, and 5 are shown in this table, for grade 1, grade 2, and grade missing please refer to the source table.
All grades includes patients with grade missing.
CI for incidence was calculated by exact Clopper-Pearson, CI for EAIR was calculated as described in the SAP.
AE: adverse event, CI: confidence interval, EAIR: exposure adjusted incidence rate, MedDRA: Medical Dictionary for Regulatory Activities, n: number of patients, N: number of patients in analysis set, PT: preferred term, SAE: serious adverse event, SAF: safety analysis set, SAP: statistical analysis plan, SOC: system organ class
Source: Table 14.2.4/11

Drug-related SAEs were reported for 88 patients (6.0%, EAIR per year: 0.15). The distribution by severity grade was as follows: no patients with grade 1, 9 patients (0.6%) with grade 2, 51 patients (3.5%) with grade 3, 15 patients (1.0%) with grade 4, and 10 patients (0.7%) with grade 5. For 3 patients (0.2%), severity grades were missing (Table 14.2.4/11).

The most frequently reported SOC was Blood and lymphatic system disorders in 41 patients (2.8%, EAIR per year: 0.07), with the most common PTs of anaemia (23 patients, 1.6%), and thrombocytopenia (12 patients, 0.8%). Investigations were reported for 16 patients (1.1%, EAIR per year: 0.03), with the most common PT of platelet count decreased (10 patients, 0.7%). The remaining drug-related SAEs occurred in fewer than 10 patients each (Table 14.2.4/11).

10.4.1.2.3.3 Other significant adverse events

Events resulting in permanent discontinuation of radium-223

Treatment-emergent drug-related AEs resulting in permanent discontinuation of radium-223 were reported for 78 patients (5.3%, EAIR per year: 0.13). The distribution by severity grade was as follows: 5 patients (0.3%) with grade 1, 17 patients (1.2%) with grade 2, 44 patients (3.0%) with grade 3, 6 patients (0.4%) with grade 4, and 3 patients (0.2%) with grade 5. For 3 patients (0.2%) severity grades were missing.

The most frequently reported SOC was Blood and lymphatic system disorders in 53 patients (3.6%, EAIR per year: 0.09), followed by the SOC Investigations with 12 patients (0.8%, EAIR per year: 0.02) and Gastrointestinal disorders with 8 patients (0.5%, EAIR per year: 0.01). PTs related to bone marrow suppression were anaemia in 30 patients (2.0%, EAIR per year: 0.05), thrombocytopenia in 18 patients (1.2%, EAIR per year: 0.03), pancytopenia and platelet count decreased in 6 patients each (0.4%, EAIR per year: 0.01 each), haemoglobin decreased in 5 patients (0.3%, EAIR per year: 0.01), in addition to leukopenia, neutropenia, haematocrit decreased, and red blood cell count decreased in fewer than 5 patients each (Table 14.2.4/8).

Treatment-emergent SAEs resulting in permanent discontinuation of radium-223 were reported for 108 patients (7.3%, EAIR per year: 0.18). The distribution by severity grade was as follows: 1 patient (<0.1%) with grade 1, 2 patients (0.1%) with grade 2, 42 patients (2.9%) with grade 3, 17 patients (1.2%) with grade 4, and 34 patients (2.3%) with grade 5. For 12 patients (0.8%) severity grades were missing.

The most frequently reported SOC was Neoplasms benign, malignant and unspecified (incl cysts and polyps) in 21 patients (1.4%, EAIR per year: 0.04), most commonly the worsening of prostate cancer (PTs: prostate cancer in 5 patients [0.3%, EAIR per year: 0.01] and prostate cancer metastatic in 2 patients [0.1%, EAIR per year: 0.00]). General disorders and administration site conditions were reported in 19 patients (1.3%, EAIR per year: 0.03), with the most common PTs of general physical health deterioration and pain in 5 patients each (0.3%, EAIR per year: 0.01 each). Blood and lymphatic system disorders were reported in 15 patients (1.0%, EAIR per year: 0.03), most commonly the PTs anaemia in 6 patients (0.4%, EAIR per year: 0.01), followed by pancytopenia and thrombocytopenia in 4 patients each (0.3%, EAIR per year: 0.01 each). Infections and infestations were reported in 12 patients (0.8%, EAIR per year: 0.02), with the most common PTs of sepsis and urosepsis in 3 patients each (0.2% each, EAIR per year: 0.01 each) (Table 14.2.4 /4).

Drug-related SAEs resulting in permanent discontinuation of radium-223 were reported for 17 patients (1.2%, EAIR per year: 0.03). The distribution by severity grade was as follows: no patients with grade 1 or grade 2, 10 patients (0.7%) with grade 3, 4 patients (0.3%) with grade 4, and 3 patients (0.2%) with grade 5.

The most frequently reported SOC was Blood and lymphatic system disorders in 13 patients (0.9%, EAIR per year: 0.02). The SOCs General disorders and administration site conditions, Investigations, and Musculoskeletal and connective tissue disorders were reported in 2 patients each (0.1%, EAIR per year 0.00 each). PTs attributable to bone marrow suppression were anaemia, pancytopenia, and thrombocytopenia in 4 patients each (0.3%, EAIR per year: 0.01 each), in addition to haemoglobin decreased and platelet count decreased in 1 patient each (<0.1%, EAIR per year: 0.00 each). All remaining PTs occurred in 1 patient each (<0.1% each, EAIR per year: 0.00) (Table 14.2.4/12).

Events resulting in inpatient hospitalization or prolongation of existing hospitalization

Treatment-emergent drug-related AEs resulting in inpatient hospitalization or prolongation of existing hospitalization were reported for 42 patients (2.9%, EAIR per year: 0.07). The distribution of severity grades was as follows: no patients with grade 1, 2 patients (0.1%) with grade 2, 32 patients (2.2%) with grade 3, 5 patients (0.3%) with grade 4, and 2 patients (0.1%) with grade 5. For 1 patient (<0.1%) the severity grade was missing.

The most frequently reported SOC was Blood and lymphatic system disorders in 19 patients (1.3%, EAIR per year: 0.03) followed by Investigations in 6 patients (0.4%, EAIR per year: 0.01). PTs attributable to bone marrow suppression included anaemia in 12 patients (0.8%, EAIR per year: 0.02), thrombocytopenia in 4 patients (0.3%, EAIR per year: 0.01), haemoglobin decreased in 2 patients (0.1%, EAIR per year: 0.00), neutropenia, pancytopenia, platelet count decreased, and red blood cell count decreased in 1 patient each (<0.1%, EAIR per year: 0.00 each). At the PT level, the other most common treatment-emergent drug-related AEs resulting in inpatient hospitalization or prolongation of existing hospitalization were pneumonia in 3 patients (0.2%, EAIR per year 0.01), followed by abdominal pain and nausea in 2 patients each (0.1%, EAIR per year: 0.00 each). The remaining PTs occurred in 1 patient each (Table 14.2.4/9).

Treatment-emergent SAEs resulting in inpatient hospitalization or prolongation of existing hospitalization were reported for 248 patients (16.8%, EAIR per year: 0.45). The distribution by severity grade was as follows: no patients with grade 1, 13 patients (0.9%) with grade 2, 156 patients (10.6%) with grade 3, 32 patients (2.2%) with grade 4, and 21 patients (1.4%) with grade 5. For 26 patients (1.8%) severity grades were missing.

The most frequently reported SOC was General disorders and administration site conditions in 46 patients (3.1%, EAIR per year: 0.08), with the most common PTs of general physical health deterioration in 12 patients (0.8%, EAIR per year: 0.02) and pain in 9 patients (0.6%, EAIR per year: 0.02). Infections and infestations were reported in 40 patients (2.7%, EAIR per year: 0.07), including most commonly the PT pneumonia in 12 patients (0.8%, EAIR per year: 0.02). Nervous system disorders were reported in 36 patients (2.4%, EAIR per year: 0.06), with the most common PT of spinal cord compression in 12 patients (0.8%, EAIR per year: 0.02). Musculoskeletal and connective tissue disorders were reported in 32 patients (2.2%, EAIR per year: 0.05), with the most common PT of back pain in 11 patients (0.7%, EAIR per year: 0.02). Blood and lymphatic system disorders were reported in 31 patients (2.1%, EAIR per year: 0.05), most commonly the PTs: anaemia in 22 patients (1.5%, EAIR

per year: 0.04), thrombocytopenia in 5 patients (0.3%, EAIR per year: 0.01), and pancytopenia in 2 patients (0.1%, EAIR per year: 0.00) (Table 14.2.4/5).

Drug-related SAEs resulting in inpatient hospitalization or prolongation of inpatient hospitalization were reported for 63 patients (4.3%, EAIR per year: 0.11). The distribution by severity grade was as follows: no patients with grade 1, 3 patients (0.2%) with grade 2, 47 patients (3.2%) with grade 3, 7 patients (0.5%) with grade 4, and 3 patients (0.2%) with grade 5. For 3 patients (0.2%) severity grades were missing.

The most frequently reported SOC was Blood and lymphatic system disorders in 26 patients (1.8%, EAIR per year: 0.04). Injury, poisoning and procedural complications and Investigations were reported in 9 patients each (0.6%, EAIR per year: 0.02 each), with all other SOCs reported in <0.5% of patients. PTs attributable to bone marrow suppression were anaemia in 18 patients (1.2%, EAIR per year: 0.03), thrombocytopenia in 5 patients (0.3%, EAIR per year: 0.01), platelet count decreased in 4 patients (0.3%, EAIR per year: 0.01), haemoglobin decreased in 2 patients (0.1%, EAIR per year: 0.00), in addition to neutropenia, pancytopenia, red blood cell count decreased, and white blood cell count decreased in 1 patient each (<0.1%, EAIR per year: 0.00 each). At the PT level, the other most common drug-related SAEs resulting in inpatient hospitalization or prolongation of inpatient hospitalization were pneumonia and thoracic vertebral fracture in 3 patients each (0.2%, EAIR per year 0.01 each), followed by abdominal pain, femur fracture, nausea, pathological fracture, and spinal cord compression in 2 patients each (0.1%, EAIR per year: 0.00 each). The remaining PTs occurred in 1 patient each (Table 14.2.4/13).

Post-radium-223 treatment-emergent drug-related serious adverse events

A summary of patients with post-radium-223 treatment-emergent drug-related SAEs is presented in Table 25.

Table 25: Overall summary of patients with post-radium-223 treatment-emergent drug-related SAEs, SAF (N=1472)

Post-radium-223 treatment-emergent drug-related SAE summary	n	(%)
Number of patients with post-radium-223 treatment-emergent drug-related SAE	38	(2.6)
Number of patients with post-radium-223 treatment-emergent drug-related SAE resulting in inpatient hospitalization or prolongation of existing hospitalization	25	(1.7)
Number of patients with post-radium-223 treatment-emergent drug-related SAE resulting in death	4	(0.3)

Treatment-emergent was defined as any event arising or worsening on the day of or after start of radium-223 until 30 days after last injection. Post-radium-223 treatment-emergent drug-related SAEs were collected up to 7 years after last injection.
Table includes only death information documented as an AE.
AE: adverse event, N: number of patients in analysis set, n: number of patients, SAE: serious adverse event, SAF: safety analysis set
Source: Table 14.2.4/2

A total of 38 patients (2.6%) reported any post-radium-223 treatment-emergent drug-related SAE. The most common events (PT and worst severity grade) were (Table 14.2.4/15):

- Anaemia in 9 patients (7 patients with grade 3, 1 patient with grade 5, and 1 patient with grade missing)
- Thrombocytopenia in 5 patients (4 patients with grade 4 and 1 patient with grade 3)
- Platelet count decreased in 4 patients (3 patients with grade 4 and 1 patient with grade 5)

- Thoracic vertebral fracture in 4 patients (3 patients with grade 3 and 1 patient with grade 2)
- Humerus fracture in 2 patients (1 patient with grade 3 and 1 patient with grade 2)
- Stress fracture in 2 patients (1 patient with grade 3 and 1 patient with grade 2)
- Pathological fracture in 2 patients (1 patient with grade 2 and 1 patient with grade missing)
- White blood cell count decreased in 2 patients (1 patient with grade 3 and 1 patient with grade 5)

All other PTs were reported in 1 patient each.

Post-radium-223 treatment-emergent drug-related SAEs resulting in inpatient hospitalization or prolongation of inpatient hospitalization were reported for 25 patients (1.7%). The most common events (PT and worst severity grade) were (Table 14.2.4/17):

- Anaemia in 8 patients (6 patients with grade 3, 1 patient with grade 5, and 1 patient with grade missing)
- Platelet count decreased in 3 patients (2 patients with grade 4 and 1 patient with grade 5)
- Thoracic vertebral fracture in 3 patients (grade 3)
- Pathological fracture in 2 patients (1 patient with grade 2 and 1 patient with grade missing)

All other PTs were reported in 1 patient each.

Post-radium-223 treatment-emergent drug-related SAEs resulting in death were reported in 4 patients (0.3%). These included 1 patient each with acute myeloid leukaemia, anaemia, general physical health deterioration, pancytopenia, platelet count decreased, and white blood cell count decreased, all classified by worst severity as grade 5 (Table 14.2.4/18).

10.4.1.3 Bone marrow suppression

Therapeutic or preventive treatments for bone marrow suppression up to 6 months after last administration of radium-223 by prior chemotherapy is shown in Table 26.

Table 26: Patients with therapeutic or preventive treatments for bone marrow suppression from start of radium-223 up to 6 months (183 days) after last injection by prior chemotherapy, SAF

	No prior chemotherapy n (%)	With prior chemotherapy n (%)	Total n (%)
Total	875 (100.0)	597 (100.0)	1472 (100.0)
Patients with at least one of the bone marrow suppression relevant treatments			
No	720 (82.3)	413 (69.2)	1133 (77.0)
Yes	155 (17.7)	184 (30.8)	339 (23.0)
Patients with any blood transfusions			
No	730 (83.4)	425 (71.2)	1155 (78.5)
Yes	145 (16.6)	172 (28.8)	317 (21.5)

	No prior chemotherapy n (%)	With prior chemotherapy n (%)	Total n (%)
Total	875 (100.0)	597 (100.0)	1472 (100.0)
Patients receiving erythropoiesis stimulating drugs			
No erythropoiesis stimulating drugs	860 (98.3)	588 (98.5)	1448 (98.4)
Erythropoietin and erythropoietin mimetics	15 (1.7)	9 (1.5)	24 (1.6)
Patients with colony stimulating factors			
No	867 (99.1)	581 (97.3)	1448 (98.4)

Prior chemotherapy refers to therapy occurring before first radium-223 injection, regardless of chemotherapy stop date.
Erythropoietin and colony stimulating factors are defined in the SAP and are listed in Listing 14.5/2.
n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan
Source: Table 14.2.2/1

Bone marrow suppression relevant treatments were reported for 339 patients (23.0%), i.e., blood transfusions for 317 patients (21.5%), erythropoiesis stimulating drugs for 24 patients (1.6%), and colony stimulating factors for 24 patients (1.6%).

Patients with prior chemotherapy more often had bone marrow suppression relevant treatments than patients without prior chemotherapy (30.8% versus 17.7%, respectively), and they also more often had blood transfusions (28.8% versus 16.6%). The proportions of patients who received erythropoiesis stimulating drugs or colony stimulating factors were similar in patients with or without prior chemotherapy.

Therapeutic or preventive treatments related to bone marrow suppression from start of radium-223 up to 6 months (183 days) after last injection by subsequent chemotherapy is shown in Table 27.

Table 27: Patients with therapeutic or preventive treatments for bone marrow suppression from start of radium-223 up to 6 months (183 days) after last injection by subsequent chemotherapy, SAF

	No subsequent chemotherapy n (%)	With subsequent chemotherapy n (%)	Total n (%)
Total	1081 (100.0)	391 (100.0)	1472 (100.0)
Patients with at least one of the bone marrow suppression relevant treatments			
No	838 (77.5)	295 (75.4)	1133 (77.0)
Yes	243 (22.5)	96 (24.6)	339 (23.0)
Patients with any blood transfusions			
No	849 (78.5)	306 (78.3)	1155 (78.5)
Yes	232 (21.5)	85 (21.7)	317 (21.5)
Patients receiving erythropoiesis stimulating drugs			
No erythropoiesis stimulating drugs	1065 (98.5)	383 (98.0)	1448 (98.4)
Erythropoietin and erythropoietin mimetics	16 (1.5)	8 (2.0)	24 (1.6)
Patients with colony stimulating factors			
No	1074 (99.4)	374 (95.7)	1448 (98.4)
Yes	7 (0.6)	17 (4.3)	24 (1.6)

	No subsequent chemotherapy n (%)	With subsequent chemotherapy n (%)	Total n (%)
Total	1081 (100.0)	391 (100.0)	1472 (100.0)

Subsequent chemotherapy refers to therapy starting after the last dose of radium-223.
Erythropoietin and colony stimulating factors are defined in the SAP and are listed in Listing 14.5/2.
n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan
Source: Table 14.2.2/2

Of the 391 patients with subsequent chemotherapy, bone marrow suppression relevant treatments were reported for 96 patients (24.6%), blood transfusions for 85 patients (21.7%), erythropoiesis stimulating drugs for 8 patients (2.0%), and colony stimulating factors for 17 patients (4.3%). Results for patients with and patients without subsequent chemotherapy were comparable.

Therapeutic or preventive treatments related to bone marrow suppression from start of radium-223 but not limited to 6 months after last injection are shown in Table 14.2.2/3 (by prior chemotherapy) and in Table 14.2.2/4 (by subsequent chemotherapy).

The incidence of post-radium-223 treatment (and up to 6 months [183 days] from last radium-223 administration) grade 3/4 hematological AEs based on bone marrow suppression is presented in Table 28.

Table 28: Incidences of post-radium-223 treatment and up to 6 months (183 days) from last radium-223 grade 3/4 hematological AEs based on bone marrow suppression, SAF (MedDRA v27.0) (N=1472)

Bone marrow suppression category[a]	Grade 3		Grade 4		Total	
	n (%)	95%CI	n (%)	95% CI	n (%)	95% CI
Any bone marrow suppression relevant event	217 (14.74)	[12.97, 16.66]	26 (1.77)	[1.16, 2.58]	227 (15.42)	[13.61, 17.37]
MLG: Leukopenia not further specified	5 (0.34)	[0.11, 0.79]	3 (0.20)	[0.04, 0.59]	8 (0.54)	[0.23,1.07]
MLG: Neutropenia	11 (0.75)	[0.37, 1.33]	4 (0.27)	[0.07, 0.69]	15 (1.02)	[0.57, 1.68]
MLG: Pancytopenia	7 (0.48)	[0.19, 0.98]	1 (0.07)	[0.00, 0.38]	8 (0.54)	[0.23, 1.07]
MLG: Thrombocytopenia	37 (2.51)	[1.78, 3.45]	20 (1.36)	[0.83, 2.09]	57 (3.87)	[2.95, 4.99]
SMQ: Haematopoietic erythropenia (SMQ)	184 (12.50)	[10.85, 14.30]	2 (0.14)	[0.02, 0.49]	186 (12.64)	[10.98, 14.44]

a: Bone marrow suppression categories are defined in the SAP.
Table includes only post-radium-223 treatment AEs that occurred within 183 days from last radium-223 injection and CTCAE grade 3 or 4.
This table contains incidences of patients, multiple AEs per category are assigned by worst grade.
AE: adverse event, CI: confidence interval according to exact Clopper-Pearson, CTCAE: Common Terminology Criteria for Adverse Events, MedDRA: Medical Dictionary for Regulatory Activities, MLG: MedDRA labeling group, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan, SMQ: standardized MedDRA queries
Source: Table 14.2.2/5

Post-radium-223 treatment grade 3 or 4 bone marrow suppression relevant events (up to 6 months [183 days] from last radium-223 administration) were reported for 227 patients (15.42%). The most common reported post-radium-223 treatment graded 3 or 4 bone marrow suppression category was anaemia, defined as SMQ: 'haematopoietic erythropenia (SMQ)' (186 patients, 12.64%), followed by MLG: 'thrombocytopenia' (57 patients, 3.87%). Other bone marrow suppression categories such as MLG: 'neutropenia' (15 patients, 1.02%), MLG: 'pancytopenia', and MLG: 'leukopenia not further specified' (8 patients each, 0.54%) were rare.

Of the 227 patients, 217 experienced grade 3 events and 26 patients experienced grade 4 events (20 patients with thrombocytopenia, 4 patients with neutropenia, 3 patients with leukopenia not further specified, 2 patients with haematopoietic erythropenia, and 1 patient with pancytopenia).

The incidence of post-radium-223 treatment grade 3/4 hematological AEs based on bone marrow suppression from start of radium-223 but not limited to 6 months after last injection is shown in Table 14.2.2/6.

The incidences of lab values relevant for bone marrow suppression from radium-223 initiation to 30 days after last dose and from 30 days after last dose to 6 months after last dose by prior chemotherapy and by subsequent chemotherapy are presented in Table 29.

Table 29: Incidences of laboratory values relevant for bone marrow suppression from radium-223 initiation to 30 days after last dose and from 30 days after last dose to 6 months after last dose by prior chemotherapy, SAF

	No prior chemotherapy n (%)	With prior chemotherapy n (%)	No subsequent chemotherapy n (%)	With subsequent chemotherapy n (%)	Total n (%)
Total	875 (100)	597 (100)	1081 (100.0)	391 (100.0)	1472 (100.0)
From radium-223 initiation to 30 days after last dose					
Abnormal platelet count (<50x10^9/L)					
No	809 (92.5)	538 (90.1)	978 (90.5)	369 (94.4)	1347 (91.5)
Yes	19 (2.2)	19 (3.2)	35 (3.2)	3 (0.8)	38 (2.6)
Missing	47 (5.4)	40 (6.7)	68 (6.3)	19 (4.9)	87 (5.9)
Abnormal neutrophil count (<1x10^9/L)					
No	512 (58.5)	368 (61.6)	626 (57.9)	254 (65.0)	880 (59.8)
Yes	24 (2.7)	19 (3.2)	36 (3.3)	7 (1.8)	43 (2.9)
Missing	339 (38.7)	210 (35.2)	419 (38.8)	130 (33.2)	549 (37.3)
From 30 days after last dose of radium-223 to 6 months after last dose					
Abnormal platelet count (<50x10^9/L)					
No	252 (28.8)	146 (24.5)	248 (22.9)	150 (38.4)	398 (27.0)
Yes	22 (2.5)	27 (4.5)	33 (3.1)	16 (4.1)	49 (3.3)
Missing	601 (68.7)	424 (71.0)	800 (74.0)	225 (57.5)	1025 (69.6)
Abnormal neutrophil count (<1x10^9/L)					
No	159 (18.2)	88 (14.7)	153 (14.2)	94 (24.0)	247 (16.8)
Yes	1 (0.1)	5 (0.8)	1 (<0.1)	5 (1.3)	6 (0.4)
Missing	715 (81.7)	504 (84.4)	927 (85.8)	292 (74.7)	1219 (82.8)

The percentages are based on the number of patients with at least one reported lab value within the relevant time period.
Prior chemotherapy refers to therapy occurring before first radium-223 injection, regardless of chemotherapy stop date.
n: number of patients, SAF: safety analysis set
Source: Table 14.2.2/7, Table 14.2.2/8, Table 14.2.2/9, and Table 14.2.2/10

In the period from radium-223 initiation to 30 days after the last injection, 38 patients (2.6%) showed abnormal platelet count, i.e., a count <50x10^9/L, and 43 patients (2.9%) showed abnormal neutrophil count, i.e., a count <1x10^9/L.

In the period from 30 days after the last injection of radium-223 to 6 months later, 49 patients (3.3%) showed abnormal platelet count and 6 patients (0.4%) showed abnormal neutrophil count, though the majority of values were missing for both variables.

In the analysis by prior chemotherapy, no marked differences were seen between the groups without and the group with prior chemotherapy.

The analysis by subsequent chemotherapy showed that the vast majority of men with an abnormal platelet count between radium-223 initiation and 30 days after last dose did not receive subsequent chemotherapy (35 of 38 patients, 92%[6]). The proportion of patients without subsequent chemotherapy was markedly higher than in the overall SAF, where roughly three quarters of patients (1081 of 1472 patients) did not receive subsequent chemotherapy. A similar, albeit less pronounced trend was observed for patients with an abnormal neutrophil count (36 of 43 patients, >80%[6]); this result, however, might be impacted by the high number of missing values.

Regarding febrile neutropenia or haemorrhage events in the 391 patients who underwent subsequent chemotherapy, a total of 23 patients (5.9%) experienced at least one such AE from first dose of subsequent chemotherapy up to 6 months (183 days) after the last administration of subsequent chemotherapy. At the PT level, the most common of these AEs was febrile neutropenia (8 patients, 2.0%), followed by epistaxis and haematuria (4 patients each, 1.0%), rectal haemorrhage in 3 patients (0.8%), and haematochezia in 2 patients (0.5%). Disseminated intravascular coagulation, duodenal ulcer haemorrhage, gastrointestinal haemorrhage, small intestinal haemorrhage, and upper gastrointestinal haemorrhage were reported in 1 patient each (0.3%). A breakdown of these AEs by prior chemotherapy can be found in Table 14.2.2/11. Please note that due to the low numbers of patients with such events (with/without subsequent chemotherapy: 10/13 patients), no meaningful comparison can be done. A summary of febrile neutropenia or haemorrhage events from first dose up to 30 days after the last administration of subsequent chemotherapy by prior chemotherapy is provided in Table 14.2.2/12. The definition list of bone marrow suppression, febrile neutropenia, and haemorrhage events coded by MedDRA version 27.0 is given in Listing 14.5/1.

10.4.2 Analysis of secondary outcome variables

The secondary objectives of this study were:

- To determine the OS in mCRPC patients treated with radium-223 in the routine clinical setting
- To evaluate pain over time using the BPI-SF questionnaire
- To assess the incidence of bone fractures and bone-associated events (e.g., osteoporosis)

[6] Percentage manually calculated

10.4.2.1 Overall survival

The KM curve for the OS is presented in Figure 2.

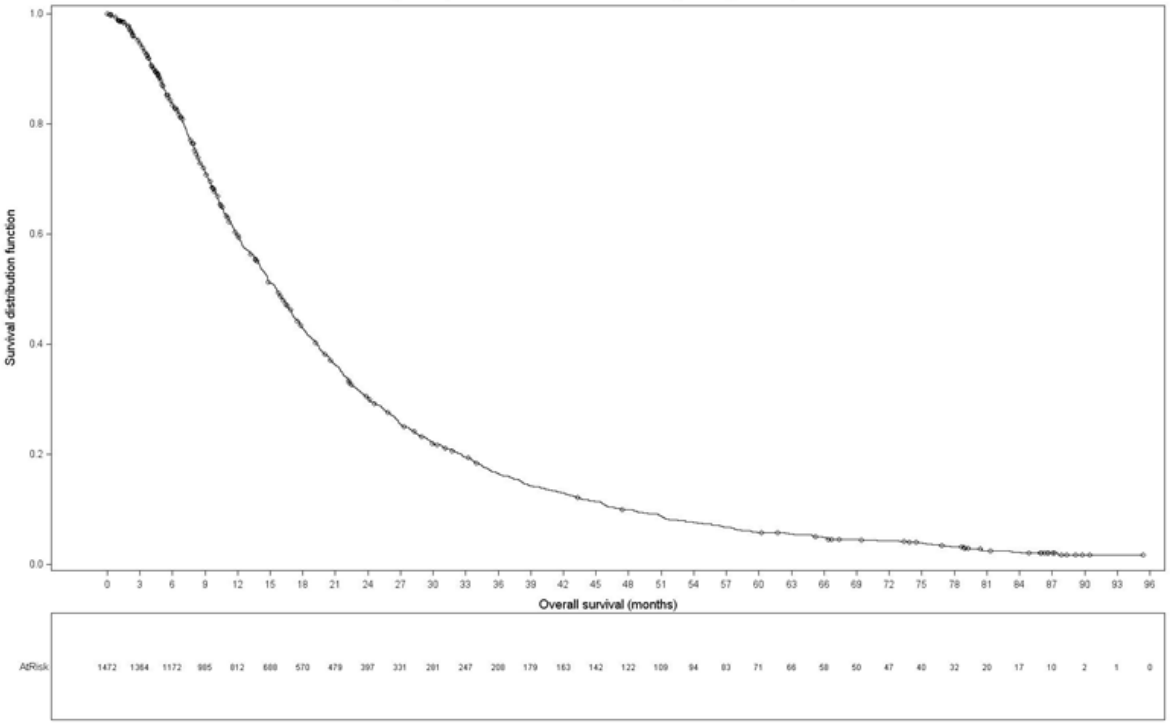

Figure 2: Kaplan-Meier curve for overall survival (SAF)

SAF: safety analysis set
Source: Figure 14.3.1/1

Of the 1472 patients in the SAF, 1308 patients (88.9%) died and 164 patients (11.1%) were censored (patients who were alive or patients whose death was not confirmed at the time of data cut). These patients were censored at the LKAD. Of the patients who died, 67 patients (4.6%) died within 30 days of the last dose of radium-223 and 1241 patients (84.3%) died after 30 days of the last dose (Table 14.3.1/1 and Table 14.3.1/4). The median OS was 15.6 months (95% CI: [14.6, 16.4]) with a first quartile of 8.09 months and a third quartile of 27.5 months (Table 14.3.1/4). For comparison: the median follow-up time (i.e., time from start of radium-223 to LKAD) overall was 13.97 months (see Section 10.1).

Cause of death was documented at end of observation and categorized by the medical expert. A summary is presented in Table 14.3.1/2. Progressive disease was reported as the main cause of death in 948 patients (72.5%). Other (specified as non-cancer-related medical condition) was reported as the cause of death in 128 patients (9.8%), AE in 35 patients (2.7%), and Other (without further specification) in 3 patients (0.2%). Cause of death was unknown in 168 patients (12.8%) and missing for 26 patients (2.0%).

A by-subject listing of cause of death is provided in Table 14.3.1/3. The details of death for each patient can be found in Table 14.3.1/5.

10.4.2.2 Brief pain inventory short form

The means and changes from baseline of the BPI-SF pain severity score and pain interference score are presented in Table 30 for the overall SAF. Higher scores represent greater pain (pain severity score) or greater interference (pain interference score), and a clinically meaningful change is defined as a change ≥2 points. A bespoke analysis of clinically meaningful

improvement is presented further below (see Table 31). Please note that the analysis of the overall SAF also includes patients with a baseline pain severity or interference score <2 points.

Table 30: BPI-SF pain severity score and pain interference score means and change from baseline (SAF)

Score	Value at visit		Change from baseline	
Time point	n	Mean (SD)	n	Mean (SD)
Pain severity score				
Baseline/Treatment 1	1356	3.003 (2.189)	N/A	N/A
Treatment 2	1182	2.760 (2.251)	1142	-0.211 (1.892)
Treatment 3	1090	2.464 (2.222)	1045	-0.421 (2.057)
Treatment 4	943	2.436 (2.309)	910	-0.367 (2.204)
Treatment 5	828	2.261 (2.223)	797	-0.474 (2.258)
Treatment 6	736	2.262 (2.210)	705	-0.361 (2.349)
First available follow-up measurement	502	2.458 (2.307)	480	-0.258 (2.447)
Last available follow-up measurement	502	2.629 (2.424)	480	-0.070 (2.629)
Pain interference score				
Baseline/Treatment 1	1364	3.283 (2.664)	N/A	N/A
Treatment 2	1185	2.965 (2.588)	1150	-0.282 (2.230)
Treatment 3	1091	2.656 (2.469)	1051	-0.433 (2.356)
Treatment 4	937	2.587 (2.525)	909	-0.406 (2.428)
Treatment 5	826	2.358 (2.408)	799	-0.558 (2.478)
Treatment 6	736	2.495 (2.425)	708	-0.293 (2.602)
First available follow-up measurement	503	2.809 (2.570)	483	-0.069 (2.756)
Last available follow-up measurement	504	3.107 (2.774)	484	0.205 (3.088)

The methods for calculation of the pain severity and interference scores are described in Section 9.9.2.4.
When there was only one follow-up (i.e., post-radium-223 treatment) pain measurement available, the patient was counted in the first as well as in the last available follow-up measurement.
Pain assessment was done prior radium-223 injection; baseline value was derived as last pain assessment prior first radium-223 injection.
BPI-SF: brief pain inventory short form, n: number of patients, N/A: not applicable, SAF: safety analysis set, SD: standard deviation
Source: Table 14.3.2/1 and Table 14.3.2/2

The mean pain severity score was consistently lower while on treatment and during follow-up than at baseline, implying that pain tended to improve (higher scores represent greater pain), but the improvements were not clinically meaningful (defined as change ≥2 points).
At baseline, the mean pain severity score was 3.003; at the post-baseline treatments, it ranged from 2.760 at treatment 2 to 2.261 at treatment 5. At the follow-up visits, i.e., after the radium-223 injections, the pain severity score increased slightly but remained below the baseline value. The mean change from baseline to post-baseline treatments ranged from -0.211 at treatment 2 to -0.474 at treatment 5, implying small improvements in pain that were, however, not clinically meaningful. During follow-up, the mean change from baseline became smaller, being -0.070 at the last available follow-up. Please note the large spread of the change from baseline, the SD being >1.8 at all post-baseline treatments. The means and changes from baseline values for the individual items of the pain severity score can be found in Table 14.3.2/1.

The mean pain interference score showed similar trends to the pain severity score.
At baseline, the mean pain interference score was 3.283; at the post-baseline treatments, it ranged from 2.965 at treatment 2 to 2.358 at treatment 5. At the follow-up visits, the pain

interference score increased but remained below the baseline value. The mean change from baseline to post-baseline treatments ranged from -0.293 at treatment 6 to -0.558 at treatment 5, implying small improvements in pain that were, however, not clinically meaningful. At the last available follow-up measurement, the mean change to baseline was +0.205. Please again note the large spread of the change from baseline, with an SD >2.2 at all post-baseline measurements. The means and changes from baseline values for the individual items of the pain interference score can be found in Table 14.3.2/2.

Table 31 presents the number of patients with a clinically meaningful pain response (i.e., decrease from baseline by ≥2 points) in worst pain item overall (prespecified analysis) and restricted to evaluable patients (post-hoc analysis). Evaluable patients were patients with a baseline worst pain score ≥2.

Table 31: Number of patients with a clinically meaningful pain response in worst pain item (SAF)

Time point	N	With pain response n (%)	Without pain response n (%)
All patients			
Treatment 2	1157	324 (28.0)	833 (72.0)
Treatment 3	1058	330 (31.2)	728 (68.8)
Treatment 4	919	314 (34.2)	605 (65.8)
Treatment 5	804	279 (34.7)	525 (65.3)
Treatment 6	710	241 (33.9)	469 (66.1)
First available follow-up measurement	485	152 (31.3)	333 (68.7)
Last available follow-up measurement	485	148 (30.5)	337 (69.5)
Evaluable patients[a]			
Treatment 2	897	324 (36.1)	573 (63.9)
Treatment 3	814	330 (40.5)	484 (59.5)
Treatment 4	697	314 (45.1)	383 (54.9)
Treatment 5	601	279 (46.4)	322 (53.6)
Treatment 6	526	241 (45.8)	285 (54.2)
First available follow-up measurement	369	152 (41.2)	217 (58.8)
Last available follow-up measurement	369	148 (40.1)	221 (59.9)

a: This was a post-hoc analysis. Patients evaluable for pain response are patients with a baseline worst pain score ≥2.
The method for the calculation of clinically meaningful pain response is described in Section 9.9.2.4.
When there was only one follow-up (i.e., post-radium-223 treatment) pain measurement available, the patient was counted in the first as well as in the last available follow-up measurement.
Pain assessment was done prior radium-223 injection; baseline value was derived as last pain assessment prior first radium-223 injection.
N: number of patients with available questionnaires at baseline and corresponding visit, n: number of patients, SAF: safety analysis set
Source: Table 14.3.2/3, Table 14.3.2/4

In the overall SAF, the proportion of patients with a clinically meaningful pain response in worst pain item increased slightly over the treatment time points, ranging from 28.0% at treatment 2 to 34.7% at treatment 5, and decreased again afterwards, to 30.5% at the last available follow-up measurement.

In the subset of evaluable patients, the proportion of patients with a clinically meaningful pain response in worst pain item was constantly higher than in the overall SAF. It increased from 36.1% at treatment 2 to 46.4% at treatment 5, afterwards decreasing again to 40.1% at the last available follow-up visit.

10.4.2.3 Bone fractures and bone-associated events

Bone fractures and bone-associated events were reported as AEs for up to 7 years after last administration of radium-223. They were identified by MedDRA HLGTs (see Section 9.9.2.4). The definition list of bone fractures and bone-associated events is presented in Listing 14.5/3.

The incidence of patients with bone fractures and bone-associated events is presented in Table 32.

Table 32: Incidences of patients with bone fractures and bone-associated events, SAF (N=1472)

MedDRA HLGT	Total n (%)	95% CI for incidence	EAIR per year	95% CI for EAIR
Patients with at least one such AE	247 (16.8)	[14.9, 18.8]	0.36	[0.32, 0.41]
Bone disorders (excl congenital and fractures)	125 (8.5)	[7.1, 10.0]	0.20	[0.17, 0.24]
Fractures	143 (9.7)	[8.2, 11.3]	0.21	[0.18, 0.25]

This table presents counts of patients.
The median follow-up time was 5.622 months.
Follow-up time for EAIR is defined according to the SAP.
Bone fractures and bone-associated events are defined in the SAP (also see Section 9.9.2.4). They were collected as AEs for up to 7 years after last administration of radium-223.
Definition of high-level group terms "Bone disorders (excl congenital and fractures)" and "Fractures" are listed according to MedDRA 27.0 in Listing 14.5/3.
CI and EAIR as defined in the SAP (also see Section 9.9.2.4).
AE: adverse event, CI: confidence interval, EAIR: exposure adjusted incidence rate, excl: excluding, HLGT: high-level group term, MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan
Source: Table 14.3.3/2

Overall, 16.8% of patients in the SAF had at least one bone fracture or bone-associated event during the observation period (treatment period and follow-up period), with an EAIR per year of 0.36. Bone disorders (excl congenital and fractures) occurred in 8.5% (EAIR per year: 0.20) and Fractures in 9.7% of patients (0.21). At PT level, bone pain was the most common event (74 patients, 5.0%), followed by osteonecrosis of jaw and pathological fracture (22 patients, 1.5% each) (Table 14.3.3/8).

A listing of all AEs considered as bone fractures or bone-associated events is presented in Table 14.3.3/1.

Incidence of bone fractures or bone-associated events was also analyzed by BHA treatment (yes/no) before first radium-223 injection, in addition to radium-223, or after last radium-223 injection. The number of patients who received BHA treatment in the respective periods is presented in Table 33.

Table 33: Number of patients with bone health agents (WHO-DD version 03/2024), SAF (N=1472)

Preferred base name(s)	Any prior BHA[a] n (%)	Prior completed BHA[b] n (%)	Concomitant BHA[c] n (%)	Post-radium-223 BHA[d] n (%)	Subsequent BHA[e] n (%)
Patients with at least one such BHA	724 (49.2)	221 (15.0)	605 (41.1)	629 (42.7)	96 (6.5)
Alendronic acid	15 (1.0)	2 (0.1)	13 (0.9)	13 (0.9)	0 (0.0)
Bisphosphonates	4 (0.3)	0 (0.0)	4 (0.3)	6 (0.4)	2 (0.1)
Clodronic acid	4 (0.3)	1 (<0.1)	3 (0.2)	3 (0.2)	0 (0.0)
Denosumab	457 (31.0)	90 (6.1)	411 (27.9)	426 (28.9)	60 (4.1)
Ibandronic acid	5 (0.3)	3 (0.2)	3 (0.2)	2 (0.1)	0 (0.0)
Pamidronic acid	6 (0.4)	3 (0.2)	3 (0.2)	3 (0.2)	1 (<0.1)
Risedronic acid	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Zoledronic acid	298 (20.2)	137 (9.3)	186 (12.6)	203 (13.8)	39 (2.6)

a: Any prior medication was defined as medication before first radium-223 injection.
b: Prior completed medication was defined as medication with stop date prior to first radium-223 injection.
c: Concomitant medication was defined as medication in addition to radium-223.
d: Post medication was defined as medication after the last radium-223 injection, i.e., continued or started after last radium-223 injection.
e: Subsequent medication was defined as medication starting after last dose of radium-223.
Subjects may have more than one entry.
BHAs are defined in the SAP.
Preferred base name was defined based on WHO-DD drug number, sequence #1='01' and sequence #2='001'
BHA: bone health agent, N: number of patients in analysis set, n: number of patients, SAF: safety analysis set, SAP: statistical analysis plan, WHO-DD: World Health Organization drug dictionary
Source: Table 14.3.3/3, Table 14.3.3/4, Table 14.3.3/5, Table 14.3.3/6, and Table 14.3.3/7

About half of the patients in the SAF (49.2%) had received BHA treatment before the first radium-223 injection ("prior") and 15.0% completed BHA therapy before start of radium-223 treatment. BHA therapy was given concomitantly to radium-223 ("concomitant") in 41.1% of patients. Slightly more patients (42.7%) received BHA therapy after the last radium-injection ("post-radium-223"), with 6.5% of patients initiating this treatment only after the last injection ("subsequent").

In patients with **prior BHA therapy**, the incidence of bone fractures or bone-associated events during the observation period was lower than in patients without prior BHA therapy. Of the 724 patients with prior BHA therapy, 94 patients (13.0%) had at least one bone fracture or bone-associated event (Fractures: 5.9%; Bone disorders [excl congenital and fractures]: 8.4%). Of the 748 patients without prior BHA therapy, 153 patients (20.5%) had at least one bone fracture or bone-associated event (Fractures: 13.4%; Bone disorders [excl congenital and fractures]: 8.6%). This trend was reflected at PT level. Notable differences in incidence were observed for pathological fractures (with – without such therapy 0.6% versus 2.4%) and bone pain (4.1% versus 5.9%). Smaller differences were seen for thoracic vertebral fracture (0.3% versus 1.7%), spinal fracture (0.0% versus 1.1%), spinal pain (0.6% versus 1.5%), humerus fracture (0.3% versus 1.2%), and spinal compression fracture (0.8% versus 1.7%) (Table 14.3.3/8).

Regarding **prior completed BHA therapy**, the incidence of bone fractures or bone-associated events during the observation period was comparable in patients with (16.3%) and without such therapy (16.9%). At PT level, notable differences in incidence were observed for bone pain (with – without such therapy: 3.2% versus 5.4%) and osteonecrosis of jaw (3.6% versus 1.1%). A smaller difference was seen for spinal compression fracture (0.5% versus 1.4%) (Table 14.3.3/9).

In patients with **concomitant BHA therapy**, the incidence of bone fractures or bone-associated events during the observation period was lower than in patients without such therapy, mainly driven by the difference in incidence of fractures. Of the 605 patients with concomitant BHA therapy, 84 patients (13.9%) had at least one bone fracture or bone-associated event (Fractures: 6.8%; Bone disorders [excl congenital and fractures]: 8.6%). Of the 867 patients without concomitant BHA therapy, 163 patients (18.8%) had at least one bone fracture or bone-associated event (Fractures: 11.8%; Bone disorders [excl congenital and fractures]: 8.4%). At PT level, a notable difference in incidence was seen for pathological fracture (with – without such therapy: 0.7% versus 2.1%). Smaller differences were seen for thoracic vertebral fracture (0.5% versus 1.4%), humerus fracture (0.2% versus 1.2%), and spinal pain (0.5% versus 1.4%). The incidence of osteonecrosis of jaw was similar in both groups (with – without such therapy: 1.8% versus 1.3%) (Table 14.3.3/10).

In patients with BHA therapy continuing or starting after the last dose of radium-223 (**post-radium-223 BHA therapy**), the incidence of bone fractures or bone-associated events during the observation period was slightly lower than in patients without such therapy. Of the 629 patients with post-radium-223 BHA therapy, 95 patients (15.1%) had at least one bone fracture or bone-associated event (Fractures: 8.3%; Bone disorders [excl congenital and fractures]: 8.4%). Of the 843 patients without post-radium-223 BHA therapy, 152 patients (18.0%) had at least one bone fracture or bone-associated event (Fractures: 10.8%; Bone disorders [excl congenital and fractures]: 8.5%). At PT level, small differences in incidence were observed for bone pain (with – without such therapy: 4.5% versus 5.5%), osteonecrosis of jaw (2.1% versus 1.1%), spinal pain (0.5% versus 1.4%), pathological fracture (1.0% versus 1.9%), and femur fracture (1.7% versus 0.8%) (Table 14.3.3/11).

In patients with BHA therapy starting after the last dose of radium-223 (**subsequent BHA therapy**), the incidence of bone fractures or bone-associated events during the observation period was slightly lower than in patients without such therapy. Of the 96 patients with such therapy, 30 patients (31.3%) had at least one bone fracture or bone-associated event (Fractures: 19.8%; Bone disorders [excl congenital and fractures]: 14.6%). Of the 1376 patients without such therapy, 271 patients (15.8%) had at least one bone fracture or bone-associated event (Fractures: 9.0%; Bone disorders [excl congenital and fractures]: 8.1%). At PT level, differences in incidence were observed for a range of PTs, the most pronounced being osteonecrosis of jaw (with – without such therapy: 8.3% versus 1.0%) and thoracic vertebral fracture (4.2% versus 0.8%) (Table 14.3.3/12).

10.5 Other analyses

10.5.1 Time to progression

Progressive disease was a composite of SSE, PSA, radiological imaging, and unequivocal clinical progression (see Section 9.9.2.7).

Of the 1472 patients in the SAF, 1155 patients (78.5%) had progressive disease, 302 patients (20.5%) did not have a progression, and for 15 patients (1.0%), progression status was missing (Table 14.4.1/1).

The KM curve for the TTP is presented in Figure 3.

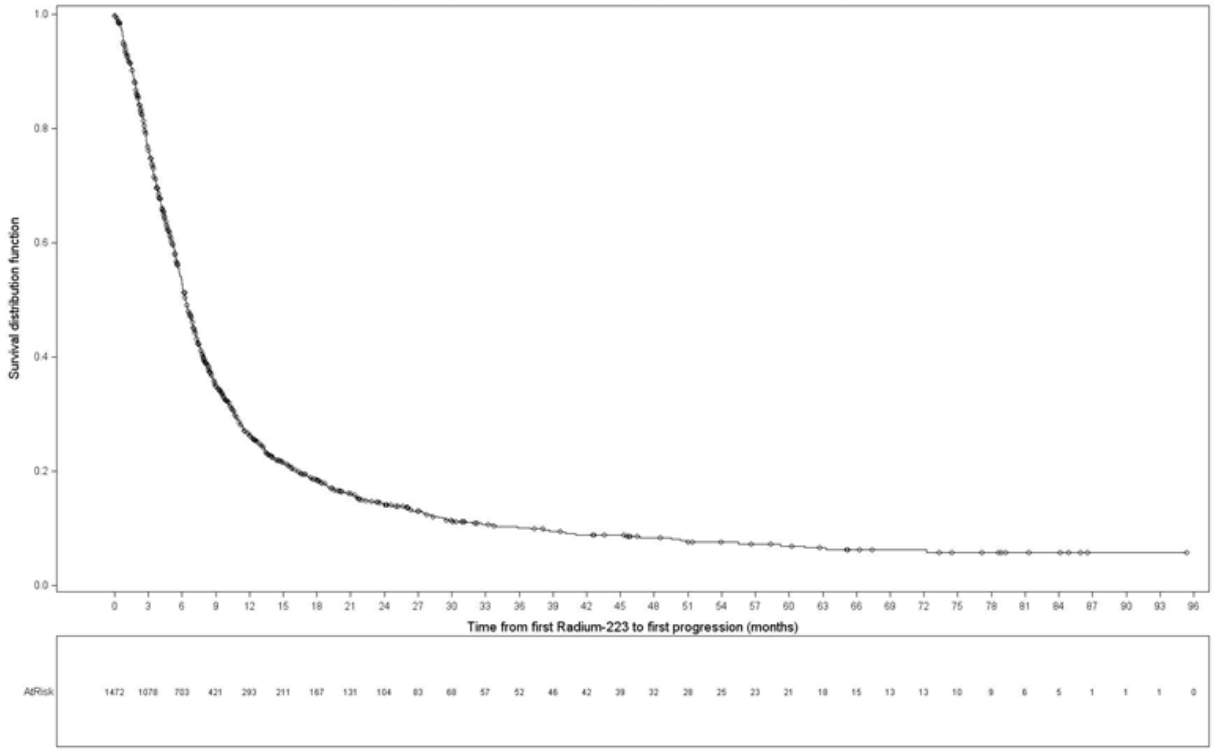

Figure 3: Kaplan-Meier curve for TTP (SAF)

TTP: time to progression, SAF: safety analysis set
Source: Figure 14.4.1/1

For the Kaplan-Meier analysis, 1149 patients had progressive disease and 323 patients were censored at LKAD. Patients without progression date were censored, even if progressive

disease was documented for them. The median TTP was 6.31 months (95% CI: [6.02, 6.71]) with a first quartile of 3.16 months and a third quartile of 12.8 months (Table 14.4.1/2).

10.5.2 Laboratory

The following laboratory parameters were recorded, if available:

Platelets	Alkaline Phosphatase (AP)	Aspartate aminotransferase
Hemoglobin	PSA	Alanine aminotransferase
Erythrocytes	Lactate dehydrogenase (LDH)	Gamma glutamyl transferase
Hematocrit	Sodium	Creatinine
Leukocytes	Potassium	Urea
Neutrophils	Chloride	Bilirubin, total
Lymphocytes	Calcium	Albumin
Monocytes	Phosphate	Protein, total
Eosinophils	Magnesium	
Basophils		

Table 34 presents a summary of laboratory values (AP, LDH, PSA, neutrophils, platelets, hemoglobin) over the course of the study. Since the number of patients with laboratory values decreased considerably over time, only values up to follow-up visit 3 plus the end of observation visit are included in the table. A summary of all laboratory parameters and all visits is available in the TLF (Table 14.1.7/1; see Annex 1).

Please note that the basis for the percentage is the number of patients for whom at least one laboratory assessment was performed at the respective visit. This is different from what was done in Table 10, where the basis for the percentage of the laboratory data at baseline was the overall number of patients in the SAF (N=1472).

Table 34: Laboratory values over time (SAF)

	Baseline N=1373 n (%)	Treatment 1 N=257 n (%)	Treatment 2 N=1251 n (%)	Treatment 3 N=1161 n (%)	Treatment 4 N=1031 n (%)	Treatment 5 N=902 n (%)	Treatment 6 N=775 n (%)	Follow-up 1 N=465 n (%)	Follow-up 2 N=307 n (%)	Follow-up 3 N=173 n (%)	EOO N=44 n (%)
Platelets											
missing	33 (2.4)	23 (8.9)	37 (3.0)	28 (2.4)	31 (3.0)	10 (1.1)	12 (1.5)	57 (12.3)	48 (15.6)	38 (22.0)	4 (9.1)
<100 10^9/L	14 (1.0)	7 (2.7)	25 (2.0)	26 (2.2)	28 (2.7)	28 (3.1)	24 (3.1)	81 (17.4)	39 (12.7)	23 (13.3)	19 (43.2)
≥100 10^9/L	1326 (96.6)	227 (88.3)	1189 (95.0)	1107 (95.3)	972 (94.3)	864 (95.8)	739 (95.4)	327 (70.3)	220 (71.7)	112 (64.7)	21 (47.7)
Hemoglobin											
missing	22 (1.6)	17 (6.6)	29 (2.3)	19 (1.6)	24 (2.3)	10 (1.1)	9 (1.2)	56 (12.0)	47 (15.3)	36 (20.8)	6 (13.6)
<10 g/dL	113 (8.2)	48 (18.7)	130 (10.4)	127 (10.9)	110 (10.7)	96 (10.6)	101 (13.0)	169 (36.3)	97 (31.6)	62 (35.8)	27 (61.4)
≥10 g/dL	1238 (90.2)	192 (74.7)	1092 (87.3)	1015 (87.4)	897 (87.0)	796 (88.2)	665 (85.8)	240 (51.6)	163 (53.1)	75 (43.4)	11 (25.0)
Neutrophils											
missing	579 (42.2)	137 (53.3)	564 (45.1)	504 (43.4)	470 (45.6)	404 (44.8)	324 (41.8)	228 (49.0)	166 (54.1)	102 (59.0)	22 (50.0)
<1.5 10^9/L	49 (3.6)	11 (4.3)	33 (2.6)	31 (2.7)	22 (2.1)	31 (3.4)	27 (3.5)	18 (3.9)	11 (3.6)	4 (2.3)	1 (2.3)
≥1.5 10^9/L	745 (54.3)	109 (42.4)	654 (52.3)	626 (53.9)	539 (52.3)	467 (51.8)	424 (54.7)	219 (47.1)	130 (42.3)	67 (38.7)	21 (47.7)
AP											
missing	304 (22.1)	89 (34.6)	279 (22.3)	257 (22.1)	233 (22.6)	208 (23.1)	167 (21.5)	133 (28.6)	99 (32.2)	63 (36.4)	21 (47.7)
<140 U/L	557 (40.6)	77 (30.0)	604 (48.3)	627 (54.0)	599 (58.1)	561 (62.2)	495 (63.9)	210 (45.2)	119 (38.8)	62 (35.8)	5 (11.4)
≥140 U/L	512 (37.3)	91 (35.4)	368 (29.4)	277 (23.9)	199 (19.3)	133 (14.7)	113 (14.6)	122 (26.2)	89 (29.0)	48 (27.7)	18 (40.9)
<220 U/L	749 (54.6)	108 (42.0)	746 (59.6)	773 (66.6)	710 (68.9)	632 (70.1)	559 (72.1)	260 (55.9)	154 (50.2)	82 (47.4)	9 (20.5)
≥220 U/L	320 (23.3)	60 (23.3)	226 (18.1)	131 (11.3)	88 (8.5)	62 (6.9)	49 (6.3)	72 (15.5)	54 (17.6)	28 (16.2)	14 (31.8)
PSA											
missing	268 (19.5)	111 (43.2)	376 (30.1)	327 (28.2)	282 (27.4)	247 (27.4)	189 (24.4)	108 (23.2)	86 (28.0)	49 (28.3)	30 (68.2)
0-4 ng/mL	112 (8.2)	15 (5.8)	106 (8.5)	116 (10.0)	99 (9.6)	108 (12.0)	94 (12.1)	54 (11.6)	38 (12.4)	20 (11.6)	0 (0.0)
>4-100 ng/mL	550 (40.1)	57 (22.2)	415 (33.2)	376 (32.4)	359 (34.8)	308 (34.1)	251 (32.4)	119 (25.6)	85 (27.7)	51 (29.5)	4 (9.1)
>100 ng/mL	443 (32.3)	74 (28.8)	354 (28.3)	342 (29.5)	291 (28.2)	239 (26.5)	241 (31.1)	184 (39.6)	98 (31.9)	53 (30.6)	10 (22.7)
LDH											
missing	799 (58.2)	170 (66.1)	796 (63.6)	726 (62.5)	654 (63.4)	567 (62.9)	488 (63.0)	301 (64.7)	219 (71.3)	127 (73.4)	29 (65.9)
<250 U/L	259 (18.9)	39 (15.2)	210 (16.8)	195 (16.8)	176 (17.1)	165 (18.3)	138 (17.8)	62 (13.3)	42 (13.7)	18 (10.4)	2 (4.5)
≥250 U/L	315 (22.9)	48 (18.7)	245 (19.6)	240 (20.7)	201 (19.5)	170 (18.8)	149 (19.2)	102 (21.9)	46 (15.0)	28 (16.2)	13 (29.5)

Baseline was defined as last assessment before initiation of Radium-223. Post-baseline measurements were summarized as the closest measurement date to the treatment or follow-up date. In case of ties, the earlier measurement was summarized.

The % base is the number of patients for whom at least one assessment was performed at the respective visit.

AP: alkaline phosphatase, EOO: end of observation, LDH: lactate dehydrogenase, N: number of patients for whom at least one assessment was performed at the respective visit, n: number of patients, PSA: prostate specific antigen level, SAF: safety analysis set

Source: Table 14.1.7/1

The proportion of patients with a platelet level ≥100 10^9/L was 96.6% at baseline, remaining relatively stable throughout the treatment phase and dropping in follow-up. A similar course was observed for hemoglobin and, to a lesser extent, neutrophils.

At baseline, 40.6% of patients had a normal alkaline phosphatase level of <140 U/L. A similar proportion of patients (37.3%) had an elevated alkaline phosphatase level ≥140 U/L. When further examining the patients with elevated alkaline phosphatase levels, 23.3% had values ≥220 U/L. The proportion of patients with an alkaline phosphatase level of <140 U/L increased during the treatment phase, while decreasing again during follow-up.

Concerning PSA, most patients had values >4-100 ng/mL (40.1%) or >100 ng/mL (32.3%) at baseline. The remaining 8.2% of patients had prostate specific antigen values of 0 – 4 ng/mL. The proportion of patients with values >100 ng/mL remained relatively stable during treatment and follow-up, with the exception of an increase (39.6%) at follow-up visit 1. The proportion of patients with values >4-100 ng/mL decreased in treatment and follow-up, reflected by an increase of patients with values 0-4 ng/mL.

In general, the meaningfulness of comparisons over time is limited , since the number of patients with assessments differs considerably between the visits.

10.6 Adverse events/adverse reactions

One of the primary objectives of this study was to assess the incidence of treatment-emergent SAEs (collected up to 30 days after last administration of radium-223), drug-related AEs (collected up to 30 days after last administration of radium-223), and incidence of drug-related SAEs. These results, together with other safety information, are presented in Section 10.4.1.2. Information on treatment-emergent AEs is presented in Section 10.4.1.2.2, on deaths in Section 10.4.1.2.3.1, on SAEs in Section 10.4.1.2.3.2, and on other significant AEs in Section 10.4.1.2.3.3.

11. Discussion

11.1 Key results

The REASSURE study was an observational, prospective, single-arm cohort study in patients with mCRPC. Conducted across 191 sites globally, it captured real-world utilization of radium-223 in routine clinical practice. This report represents the final analysis.

Of the 1550 patients who were screened, 1473 patients (95.0%) were included in this study. One patient withdrew consent before initiation of study treatment and was therefore excluded from the SAF (N=1472).

More than half of the patients in the SAF (59.6%) completed all 6 radium-223 injections. The most common primary reason for end of treatment was treatment completion (59.7%), followed by progressive disease (19.4%) and AE (10.2%). When analyzed by region, the proportion of patients who ended the treatment because of progressive disease was slightly higher in Europe (22.3%) than in North America (14.7%) and ROW (15.4%).

The median time from start of radium-223 to either death or LKAD was 13.97 months. The most common primary reason for end of observation was death (88.9%), followed by lost to follow-up (5.7%) and withdrawal of consent (3.5%). Only few patients (1.5%) completed the full observation period.

The majority of patients in the SAF originated from Europe (61.3%) or North America (36.0%). Representative of these geographies, most were White (88.0%), 4.3% were Black or African American, 1.1% were Asian, 0.1% were Multiple and <0.1% were American Indian or Alaska Native. The median age at informed consent was 73.0 years (range: 44-94 years).

At initial diagnosis, the most frequently reported AJCC tumor stage was Stage IV (37.4%) and almost half of the patients (48.2%) had a Gleason score of 8-10. The status of the primary tumor at study entry was most commonly reported as unresected (64.3%). As expected in this androgen deprivation–resistant patient group, almost all patients (98.7%) had received at least one prior systemic anti-cancer therapy and 63.1% of patients had received prior radiotherapy. Concomitant systemic anti-cancer therapy during treatment with radium-223 was reported in 86.3% of patients and concomitant radiotherapy in 10.5% of patients.

The **first primary objective** of this study was to assess the **incidence of SPMs** in mCRPC patients treated with radium-223 in routine clinical practice setting. Of the 1472 patients in the SAF, 24 patients (1.6%) experienced 25 SPMs. The reported SPMs included skin cancer, lung-related SPMs, and gastrointestinal SPMs in 5 patients each, urinary related SPMs in 3 patients, and neuroendocrine and hematologic SPMs in 2 patients each. The median time to SPM onset relative to start of radium-223 was 17.03 months (range: 0.3-57.8 months). Most patients within this group (18 of 24 patients with SPMs) received 6 injections, with a total injected radioactivity ranging from 2,750 to 34,617 kBq, reflective of patients receiving 1 to 6 doses of radium-223. Nearly a third of the SPMs were resolved prior to the end of observation. One SPM remained resolving and one SPM resolved with sequelae. For 1 patient the outcome was unknown. An additional 7 SPMs remained unresolved and 7 SPMs were fatal. Two (2) of the 25 events were assessed as related to radium-223 by the investigator. The patient with fatal acute myeloid leukaemia had received 3 doses of radium-223. He was diagnosed following a 5.56-month regimen of olaparib. The patient with fatal leukaemia monocytic received 4 doses of radium-223, with a prior history of multiple lines of chemotherapy (taxane and alkylating) combined, in addition to several fractions of radiotherapy to the bone.

To contextualize these findings among the general prostate cancer patient population SPM incidence data from three population-based, retrospective cohort studies from Germany, Sweden, and the USA were used as reference. The mean age at cohort/study entry was similar in the German cohort and in REASSURE (72.9 years in both studies) and slightly lower than in the Swedish (75.6 years) and US cohorts (76.6 years). Mean time from first prostate cancer diagnosis to cohort entry was shorter in the German (3.4 years or 40.8 months) and US cohort (3.5 years or 42 months) than in the Swedish cohort (5.8 years or 69.6 months). This variable was not calculated for REASSURE. When using the sum of time from initial prostate cancer diagnosis to CRPC and time from CRPC to study entry as proxy, the resulting period is comparable to that of the Swedish cohort and longer than the periods in the German and US cohorts.

The expected incidence of SPMs in REASSURE as derived from the reference data was 192.176 for the German cohort, 98.881 for the US cohort, and 148.043 for the Swedish cohort. The corresponding SMRs were 0.099, 0.192, and 0.128, respectively, showing that the incidence of SPMs observed over the course of the study was below the incidences in the external references.

The **second primary objective** of this study was to assess the incidence of treatment-emergent SAEs (collected up to 30 days after last administration), treatment-emergent drug-related AEs (collected up to 30 days after last administration), and

drug-related SAEs. The PT anaemia was among the most common events, appearing consistently across these three types of AEs/SAEs. Anaemia was also among the most commonly reported prior diseases (100 patients, 6.8%) and concomitant diseases (96 patients, 6.5%).

Specifically, **treatment-emergent SAEs** were reported for 325 patients (22.1%, EAIR per year: 0.59). The most common treatment-emergent SAE was anaemia (27 patients, 1.8%), followed by worsening of prostate cancer (PT: prostate cancer; 16 patients, 1.1%), general physical health deterioration (15 patients, 1.0%), pneumonia (14 patients, 1.0%), and spinal cord compression (13 patients, 0.9%). **Treatment-emergent drug-related AEs** were reported for 537 patients (36.5%, EAIR per year: 1.23). The most common treatment-emergent drug-related AE was diarrhoea (161 patients, 10.9%), followed by nausea (135 patients, 9.2%), anaemia (129 patients, 8.8%), and fatigue (111 patients, 7.5%). **Drug-related SAEs** were reported for 88 patients (6.0%, EAIR per year: 0.15). The most commonly reported drug-related SAEs were hematological, including anaemia (23 patients, 1.6%), thrombocytopenia (12 patients, 0.8%), and platelet count decreased (10 patients, 0.7%).

Safety data beyond the scope of the primary objective was also collected. **Treatment-emergent SAEs resulting in death** were reported for 94 patients (6.4%, EAIR per year: 0.16) and were mostly attributed to disease progression with the PTs prostate cancer (14 patients, 1.0%) and prostate cancer metastatic (6 patients, 0.4%). **Treatment-emergent drug-related SAEs resulting in death** were reported in 6 patients (0.4%, EAIR per year: 0.01), mainly attributable to bone marrow suppression, with the PTs thrombocytopenia (2 patients, 0.1%), anaemia and pancytopenia (1 patients each, <0.1%). **Drug-related SAEs resulting in death** were reported for 10 patients (0.7%, EAIR per year: 0.02), also mainly attributable to bone marrow suppression, the PTs including anaemia, pancytopenia, and thrombocytopenia (2 patients each, 0.1%), and platelet count decreased and white blood cell count decreased (1 patient each, <0.1%).

Permanent discontinuation of radium-223 was reported as a result of treatment-emergent drug-related AEs for 78 patients (5.3%), as a result of treatment-emergent SAEs for 108 patients (7.3%), and as result of drug-related SAEs for 17 patients (1.2%). **Inpatient hospitalization or prolongation of existing hospitalization** was reported as a result of treatment-emergent drug-related AEs for 42 patients (2.9%), as a result of treatment-emergent SAEs for 248 patients (16.8%), and as a result of drug-related SAEs for 63 patients (4.3%).

A total of 38 patients (2.6%) reported any **post-radium-223 treatment-emergent drug-related SAE**. Post-treatment-emergent drug-related SAEs resulting in inpatient hospitalization or prolongation of inpatient hospitalization were reported for 25 patients (1.7%). Post-treatment-emergent drug-related SAEs resulting in death were reported in 4 patients (0.3%).

The **third primary objective** was to assess **bone marrow suppression**. Bone marrow suppression relevant treatments up to 6 months after last administration of radium-223 were reported for 339 patients (23.0%). Specifically, these were blood transfusions for 317 patients (21.5%), erythropoiesis stimulating drugs for 24 patients (1.6%), and colony stimulating factors for 24 patients (1.6%). Patients with prior chemotherapy more often had bone marrow suppression relevant treatments than patients without prior chemotherapy (30.8% versus 17.7%, respectively), and they also more often had blood transfusions (28.8% versus 16.6%). There were no differences between those patients with and without subsequent chemotherapy, consistent with the previous reports [Sartor 2016].

Post-radium-223 treatment grade 3 or 4 bone marrow suppression relevant events (up to 6 months from last radium-223 administration) were reported for 227 patients (15.42%). The most common reported post-radium-223 treatment grade 3 or 4 bone marrow suppression category was anaemia, defined as SMQ 'haematopoietic erythropenia (SMQ)' (186 patients, 12.64%), followed by MLG: 'thrombocytopenia' (57 patients, 3.87%). Other bone marrow suppression categories such as MLG: 'neutropenia' (15 patients, 1.02%), MLG: 'pancytopenia', and MLG: 'leukopenia not further specified' (8 patients each, 0.54%) were rare.

In the period from radium-223 initiation to 30 days after the last injection, 38 patients (2.6%) showed abnormal platelet count, i.e., a count $<50x10^9$/L, and 43 patients (2.9%) showed abnormal neutrophil count, i.e., a count $<1x10^9$/L. In the period from 30 days after the last injection of radium-223 to 6 months later, 49 patients (3.3%) showed abnormal platelet count and 6 patients (0.4%) showed abnormal neutrophil count, though the majority of values were missing for both variables. No marked differences were seen between the groups without and without prior chemotherapy. The vast majority of men with an abnormal platelet count between radium-223 initiation and 30 days after last dose did not receive subsequent chemotherapy (35 of 38 patients, >90%). A similar, albeit less pronounced trend was observed for patients with an abnormal neutrophil count but might be impacted by the high number of missing values.

Regarding febrile neutropenia or haemorrhage events in the 391 patients who underwent subsequent chemotherapy, a total of 23 patients (5.9%) experienced at least one such AE from first dose of subsequent chemotherapy up to 6 months (183 days) after the last administration of subsequent chemotherapy. At the PT level, the most common of these AEs was febrile neutropenia (8 patients, 2.0%), followed by epistaxis and haematuria (4 patients each, 1.0%), rectal haemorrhage in 3 patients (0.8%), and haematochezia in 2 patients (0.5%).

The **first secondary objective** of this study was to assess **OS** in mCRPC patients treated with radium-223 in routine clinical practice setting. Of the 1472 patients in the SAF, 1308 patients (88.9%) died and 164 patients (11.1%) were censored. Of the patients who died, 67 patients (4.6%) died within 30 days of the last dose of radium-223 and 1241 patients (84.3%) died after 30 days of the last dose. OS was calculated from start of radium-223 to death due to any cause. The median OS was 15.6 months, the median follow-up time (i.e., time from start of radium-223 to LKAD) overall being 13.97 months. Based on a review of cause of death, progressive disease was identified as the main cause of death in 948 patients (72.5%).

The **second secondary objective** was to evaluate **pain over time** using the BPI-SF questionnaire. The pain severity score was consistently lower while on treatment and during follow-up than at baseline, implying that pain tended to improve (higher scores represent greater pain). At baseline, the mean pain severity score was 3.003; at the post-baseline treatments, it ranged from 2.760 at treatment 2 to 2.261 at treatment 5. The pain interference score showed similar trends, the mean pain interference score being 3.283 at baseline and ranging from 2.965 at treatment 2 to 2.358 at treatment 5. The pain severity score and pain interference scores increased slightly at the follow-up visits (after radium-223 injections) in comparison to post-baseline treatment measurements but remained below the baseline values.

The proportion of patients with a clinically meaningful pain response in worst pain item in the overall SAF increased slightly over the treatment time points, ranging from 28.0% at treatment 2 to 34.7% at treatment 5, and decreased again afterwards. In the post-hoc analysis restricted to evaluable patients, i.e., patients with a baseline worst pain score ≥2, the proportion of patients with a clinically meaningful pain response in worst pain item was

constantly higher than in the overall SAF. It increased from 36.1% at treatment 2 to 46.4% at treatment 5 and decreased again afterwards.

The **third secondary objective** was to assess the **incidence of bone fractures and bone-associated events**. A total of 247 patients (16.8%; EAIR per year: 0.36) had at least one bone fracture or bone-associated event during the observation period (treatment period and follow-up period). Bone disorders (excl congenital and fractures) occurred in 8.5% and Fractures in 9.7% of patients.

The incidence of fractures was relatively low considering that only half of the patients in the SAF (n=724, 49.2%) were treated with BHA before the first radium-223 injection, with 221 of them (15.0% of patients in the SAF) completing BHA therapy before radium-223 treatment. BHA was given concomitantly to radium-223 in 605 patients (41.1%). Slightly more patients (n=629, 42.7%) received BHA therapy after the last radium-injection, with 96 patients (6.5%) initiating this treatment only after the last injection.

Indeed, among patients with **prior BHA therapy** (n=724), the incidence of bone fractures or bone-associated events during the observation period was lower than in patients without prior BHA therapy (13.0% versus 20.5%). At PT level, notable differences in incidence were observed for pathological fractures (with – without such therapy 0.6% versus 2.4%) and bone pain (4.1% versus 5.9%). Of note, the incidence of bone fractures or bone-associated events among patients with prior completed BHA therapy was higher than in patients with prior BHA therapy (16.3% versus 13.0%).

In patients with **concomitant BHA therapy** (n=605), the incidence of bone fractures or bone-associated events during the observation period was slightly lower than in patients without such therapy (13.9% versus 18.8%). At PT level, a notable difference in incidence was seen for pathological fracture (with – without such therapy: 0.7% versus 2.1%).

In patients with BHA therapy continuing or starting after the last dose of radium-223 (**post-radium-223 BHA therapy**; n=629), the incidence of bone fractures or bone-associated events during the observation period was slightly lower than in patients without such therapy (15.1% versus 18.0%). At PT level, small differences in incidence were observed for several PTs.

In patients with BHA therapy starting after the last dose of radium-223 (**subsequent-radium-223 BHA therapy**; n=96), the incidence of bone fractures or bone-associated events during the observation period was slightly lower than in patients without such therapy (31.3% versus 15.8%). At PT level, the most pronounced differences in incidence were observed for osteonecrosis of jaw and thoracic vertebral fracture.

Of note, a number of patients had prior diseases that increased the risk of bone fracture or bone-associated events, including osteoporosis (20 patients, 1.4%), osteopenia (19 patients, 1.3%), and osteonecrosis of jaw (14 patients, 1.0%), though the lack of routine diagnosis means that these rates could likely be underreported.

11.2 Limitations

This prospective observational study provided an opportunity to collect data of real-life safety and effectiveness information. Its limitations are associated with all observational studies, including the lack of blinding and randomization, the heterogeneity of the patient population in terms of disease stage and pre-treatment status, and a high amount of missing or inconsistent data. Furthermore, this study is a single-arm cohort study without an active comparison group. To contextualize SPM incidence data from REASSURE, three population-based, retrospective

cohort studies from Germany, Sweden, and the USA were used as reference. While attempts were made to harmonize the SPM definitions across the external databases, these external databases could have issues with coding, limiting the precision of the definitions identified through prospective assessment. Though the primary objectives of the study were achieved, the extended follow-up demanded in this study makes it difficult to reconcile observations and events observed > 5 years after the completion of study treatment.

As all data collection in this study was part of routine clinical practice, the treating physician decided on the prescription of the respective medication and inclusion of the patient in the study. This may have influenced the patients' decisions and course of treatment, thereby introducing bias. Patients who discontinued the documentation during the observation period might have created an outcome bias. Also, as most examinations were not mandatory due to the observational nature of the study, this might have led to underreporting of certain events. Especially data not directly linked to the primary and secondary endpoints, such as other supporting laboratory parameters, are likely to be underreported.

In spite of the relatively long protocol-mandated follow-up time, the advanced stage of disease greatly reduced the observed time on study. Additionally due to challenges associated with the evaluation and documentation of events, the observation was stopped for the reasons "lost to follow-up", "withdrawal by patient", or "physician decision" (i.e., reasons other than "death" or "completed") for less than 10% of patients. Nevertheless, careful attention should be applied to the interpretation of the summary measures since there could be potential underestimation of events.

11.3 Interpretation

The analysis was based on the 1472 patients in the SAF, i.e., those who signed informed consent and had at least one documented radium-223 injection. More than half of the patients in the SAF (59.6%) completed all 6 radium-223 injections, which was slightly higher than the proportions reported in other real-world analyses (42% to 57%) [Buscombe 2020, Dadhania 2018, George 2022, Taich 2022]. The median time from start of radium-223 to either death or LKAD was 13.97 months.

The Phase III ALSYMPCA trial [Parker 2013] enrolled patients with progressive CRPC with two or more bone metastases who had received, were unfit for or declined docetaxel. The patients in the REASSURE SAF had a similar median age (REASSURE: 73.0 years versus ALSYMPCA: 71 years), but a lower percentage of them had an ECOG performance score of 0-1 (79.5% versus 87%). Additionally, the percentage of patients with higher EOD (i.e., EOD 3 and EOD 4 at baseline) was smaller in REASSURE than in the ALSYMPCA study population (25.7% versus 41%). More patients had received prior systemic therapies (such as abiraterone, enzalutamide, docetaxel, cabazitaxel, and sipuleucel-T) in REASSURE since most of those treatments were not available when ALSYMPCA was conducted.

The more recent Phase III trial ERA 223 [Smith 2019] enrolled patients with histologically confirmed, progressive, chemotherapy-naive, asymptomatic or mildly symptomatic CRPC and bone metastases, with an ECOG status of 0-1. The patients in the REASSURE SAF had a similar median age as the patients in the radium-223 treatment group of ERA 223 (REASSURE: 73.0 years versus ERA 223: 71 years). The observed median age is also consistent with several published real-world patient cohorts [Lunan 2025]. A smaller proportion of patients in REASSURE had a Gleason score ≥8 (48.2% versus 61%) and an ECOG score of 0-1 (79.5% versus 99%). A similar proportion of patients in both studies had an EOD 3 or 4 at baseline (25.7% versus 23%).

The first primary objective of the REASSURE study was to assess the **incidence of SPMs**. To contextualize these findings among the general prostate cancer patient population, SPM incidence data from three population-based, retrospective cohort studies from Germany, Sweden, and the USA were used as reference [Vassilev 2020].

With 24 patients (1.6%) reporting at least one SPM in REASSURE, the incidence proportion was at the lower end of the expected range (1.1 to 6.9%). The SMR analysis showed that the incidence of SPMs observed over the course of the study was below the incidences in the external references.

Since most of the reported SPMs are common SPMs observed in mCRPC, attribution to an event other than radium-223 cannot be ruled out. Furthermore, the many concomitant treatments, the late treatment history and patients already having malignancies when they enrolled makes it challenging to attribute the incidence of SPMs to radium-223 alone.

The second primary objective of this study was to assess the incidence of treatment-emergent SAEs, treatment-emergent drug-related AEs, and treatment-emergent drug-related SAEs.

Treatment-emergent drug-related AEs were reported for 537 patients (36.5%), most commonly diarrhoea (10.9%), nausea (9.2%), anaemia (8.8%), and fatigue (7.5%). The occurrence of anaemia is consistent with the disease itself, and nausea and diarrhoea are in line with the known safety profile of radium-223. Diarrhoea and nausea are listed as very common adverse reaction in the product label [Bayer AG 2018].

Treatment-emergent SAEs were reported for 325 patients (22.1%). This rate is lower than the one seen in the radium-223 groups in the ALSYMPCA (47%) and ERA 223 trials (radium-223: 41%). This lower incidence rate of treatment-emergent SAEs in the REASSURE study compared to the radium-223 groups in the ALSYMPCA and ERA 223 trials may be attributed to potential underreporting commonly associated with observational studies, where data collection relies on routine clinical practice and may not capture all relevant adverse events. The most common treatment-emergent SAE in REASSURE was anaemia (1.8%), followed by worsening of prostate cancer (PT: prostate cancer [1.1%]), general physical health deterioration and pneumonia (1.0% each), and spinal cord compression (0.9%). A total of 88 patients (6.0%) reported **drug-related SAEs**, most commonly anaemia (1.6%).

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with radium-223. Thus, the third primary objective of this study was to assess bone marrow suppression. While for the majority of patients no treatments relevant to bone marrow suppression up to 6 months after last administration of radium-223 and no abnormal platelet count or neutrophil count up to 30 days after last administration were reported, a certain percentage of patients had relevant events (15.42%; specifically haematopoietic erythropenia [12.64%], thrombocytopenia [3.87%], neutropenia [1.02%], and pancytopenia and leukopenia not further specified [0.54% each]). The incidences of thrombocytopenia and neutropenia in the present study are lower than in the radium-223 group in the ALSYMPCA trial (thrombocytopenia: 12%, neutropenia: 5%). Furthermore, these events are consistent with the disease itself, as bone marrow involvement by prostate cancer is often manifested by anaemia, pancytopenia, thrombocytopenia, and neutropenia.

The first secondary objective of this study was to assess **OS** in mCRPC patients treated with radium-223 in routine clinical practice setting. Of the 1472 patients in the SAF, 1308 patients (88.9%) died and 164 patients (11.1%) were censored. The main cause of death was

progressive disease (72.5%). The median OS was 15.6 months. The median OS in the present study was shorter than in the radium-223 group of the Phase III ERA 223 trial (30.7 months) but similar to that of ALSYMPCA (14.9 months) and similar to or longer than in the cohort studies used as external references (German cohort: 15.6 months[7], Swedish: 7.2 months, US: 14.4 months). A systematic literature review of real-world studies in men with mCRPC treated with radium-223 showed that, while most of the real-world analyses (81%) reported median OS of ≥12 months, less than half reported median OS ≥14 months [Lunan 2025]. As such, the observed OS in REASSURE is consistent with and among the longer survival outcomes in patients treated with radium-223.

The second secondary objective was to evaluate **pain over time** using the BPI-SF questionnaire. Both the pain severity score (mean change from baseline to post-baseline treatments range: -0.211 to -0.474) and pain interference score (mean change from baseline to post-baseline treatments range: -0.282 to -0.558) were consistently lower at post-baseline treatments than at baseline. This is in line with, though less pronounced than, the results of a Phase II study which found that radium-223 significantly reduced pain severity at 8 weeks, ranging from -1.6 to -2.1 depending on the dose [Nilsson 2012]. However, when comparing the studies, it must be taken into consideration that this Phase II study only included patient with a score ≥2 on the BPI, meaning pain scores at baseline were higher and it was therefore possible to obtain a meaningful decrease in pain scores more easily.

The third secondary objective was to assess the **incidence of bone fractures and bone associated events**. This objective was added in the protocol amendment from 20 AUG 2018 to better asses the fracture risk in the routine practice in the approved indication in alignment with several health authorities. All events that were reported prior to the amendment were included retrospectively. A total of 247 patients (16.8%) had at least one bone fracture or bone-associated event (Bone disorders (excl congenital and fractures) in 8.5% of patients and Fractures in 9.7%) during the observation period (treatment period and follow-up period). About half of the patients (49.2%) had been treated with at least one BHA before the first radium-223 injection, which was a relatively low proportion considering bone support recommendations in current guidance [Lowrance 2023] and other studies [George 2022]. BHA was given concomitantly to 41.14% of patients, and 42.7% received BHA therapy after the last radium-injection, with 6.5% of patients initiating this treatment only after the last injection.

Patients with any exposure to BHAs had higher incidence of osteonecrosis of the jaw. It has been observed that a rare, but well documented side effect of antiresorptive therapies (including bisphosphonates and denosumab) is osteonecrosis of the jaw. In a large comprehensive study of BHA use in patients with breast cancer, the incidence [95% CI] in those treated with denosumab only was 11.6% [8.0, 15.3] and with bisphosphonates only was 2.8% [0.7, 4.8]. Onset was as early as 4.6 years after treatment start among those treated with denosumab [Brunner 2025]. Appropriate considerations should be made when providing bone support to men being treated with chronic androgen-deprivation therapies.

A number of patients had prior diseases that increased the risk of bone fracture or bone associated events, including osteoporosis (20 patients, 1.4%), osteopenia (19 patients, 1.3%), and osteonecrosis of jaw (14 patients, 1.0%), though the lack of routine diagnosis means that these rates could likely be underreported. As per protocol, the option of starting a bone health agent was to take applicable local guidelines into consideration. Interpretation should be done

[7] To facilitate interpretation, the periods given in years in the referenced publication was converted into months.

with caution considering that the lack of routine imaging meant that 433 bone scans were conducted at the post-treatment follow-up visit. However, all bone fracture or bone associated events were collected regardless of causality assessment and are in line with the prescribing information [Bayer AG 2018]. According to the prescribing information, the incidence of fractures was reported to be 28.6% in patients treated with radium-223 in combination with abiraterone acetate plus prednisone/prednisolone. In the ALSYMPCA trial, symptomatic skeletal events occurred in 33% of patients in the radium-223 group [Sartor 2014]. In the ERA 223 trial, 49% of patients treated with radium-223 plus abiraterone and prednisone/prednisolone had at least one symptomatic skeletal event or died, and 29% had at least one fracture. The above-mentioned systematic literature review reported an incidence of fractures <10% in most of the analyzed studies [Lunan 2025], which is in line with the incidence of fractures in REASSURE (9.7%). The incidence of bone fractures and bone-associated events reported in REASSURE reflects the observational nature of this study with a diverse study population and reporting performed in a routine clinical setting.

11.4 Generalizability

The study allowed the enrollment of a heterogeneous patient population with regard to demographic and disease characteristics and, thus, the patient population in this study is assumed to reflect the real-life situation in patients with mCRPC who are treated with radium-223. Patients were treated according to daily practice conditions. The observational design of the study allowed to collect real-life data, without influencing the physicians' treatment decisions. The outcomes are valuable, but as the last patient completed therapy in 2017, caution should be taken when extrapolating the results to the current treatment landscape.

12. Other information

Not applicable.

13. Conclusion

The findings from this study indicate that the safety profile of radium-223 in patients with mCRPC remains consistent with previously established data. The incidence of SPMs was observed to be 1.6% among the study population. The SMR analysis showed that the incidence of SPMs observed over the course of the study was below the incidences in the external references.

The magnitude of safety risks, particularly concerning hematological toxicities such as anemia and thrombocytopenia, was noted, with treatment-emergent SAEs reported in 22.1% of patients. However, it is essential to recognize that most treatment-emergent SAEs were not hematological in nature but rather reflective of the deterioration of patients' conditions due to progressive disease. Additionally, the study reported that 16.8% of patients experienced at least one bone fracture (9.7%) or bone-associated event (8.5%) during the observation period (treatment and follow-up period), further contributing to the safety profile of this treatment. However, the clinical relevance of these findings is tempered by the overall management of AEs in clinical practice, where monitoring and supportive care can mitigate these risks effectively.

The safety and tolerability profile of Xofigo seen in REASSURE study is acceptable in the target population and the most common treatment-emergent AEs are manageable with standard of care treatment.

The low incidence of related treatment-emergent AEs leading to the permanent discontinuation of radium-223 treatment indicates further that AEs did not trigger a substantial dosing disruption due to intolerance. Additionally, the low incidence of SPMs and the manageable occurrence of bone fractures further supports the clinical significance of radium-223, particularly in a population that is often considered vulnerable due to the advanced stage of mCRPC. Therefore, the benefit-risk profile for radium-223 in the context of this study considered favorable.

The study provides a robust dataset demonstrating a low incidence of SPMs and manageable treatment-emergent AEs. The generalizability of these results is supported by the diverse patient population across multiple countries, reflecting real-world clinical settings. Therefore, the study confirms that radium-223 maintains a favorable benefit-risk profile in the treatment of mCRPC, reinforcing its role as a therapeutic option for patients with bone metastases. Considering these findings, no immediate further evidence is deemed necessary to confirm the safety profile of radium-223 in patients with mCRPC. However, it is important to note that ongoing research and surveillance efforts are in place to continuously monitor long-term outcomes and safety in this patient population.

The results of the present study do not raise new safety concerns or warrant changes to the known benefit-risk profile of radium-223 in the authorized indication.

14. References

Bayer. Investigator's Brochure: BAY 88-8223 Version 5.0 ed. 2015.

Bayer AG. Xofigo - Summary of Product Characteristics.2018. Available from: https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf.

Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer. 2000;88(2):398-406.

Broder MS, Gutierrez B, Cherepanov D, Linhares Y. Burden of skeletal-related events in prostate cancer: unmet need in pain improvement. Support Care Cancer. 2015;23(1):237-247.

Brunner C, Arvandi M, Marth C, et al. Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Breast Cancer During a 20-Year Follow-Up: A Population-Based Multicenter Retrospective Study. J Clin Oncol. 2025;43(2):180-188.

Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol. 2000;31(5):578-583.

Buscombe J, Gillett D, Bird N, Powell A, Heard S, Aloj L. Quantifying the survival benefit of completing all the six cycles of radium-223 therapy in patients with castrate-resistant prostate cancer with predominant bone metastases. World J Nucl Med. 2020;20(2):139-144.

Buyse M, Burzykowski T, Carroll K, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol. 2007;25(33):5218-5224.

Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018;16(5S):620-623.

Clopper CJ, Pearson ES. The use of confidende or fiducial limits ilustrated in the case of the binomial. Biometrika. 1934;26(4):404-413.

Dadhania S, Alonzi R, Douglas S, et al. Single-centre Experience of Use of Radium 223 with Clinical Outcomes Based on Number of Cycles and Bone Marrow Toxicity. Anticancer Res. 2018;38(9):5423-5427.

Food and Drug Administration. Code of Federal Regulations. Title 21. Volume 1. 21CFR11: Electronic records; electronic signatures. 62 FR 13464, Mar. 20, 1997. Revised 01.04.2012. 2012.

George DJ, Agarwal N, Sartor O, et al. Real-world patient characteristics associated with survival of 2 years or more after radium-223 treatment for metastatic castration-resistant prostate cancer (EPIX study). Prostate Cancer Prostatic Dis. 2022;25(2):306-313.

Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011;65(11):1180-1192.

Korn RL, Crowley JJ. Overview: progression-free survival as an endpoint in clinical trials with solid tumors. Clin Cancer Res. 2013;19(10):2607-2612.

Lowrance W, Dreicer R, Jarrard DF, et al. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). J Urol. 2023;209(6):1082-1090.

Lunan M, Raval A, Phan N, Korn M, Quintero V, McKay R. Effectiveness and safety of radium-223 in men with metastatic castration-resistant prostate cancer (mCRPC): A systematic literature review of 48 real-world studies. Journal of Clinical Oncology. 2025;43:81-81.

Nekolla EA, Walsh L, Spiess H. Incidence of malignant diseases in humans injected with radium-224. Radiat Res. 2010;174(3):377-386.

Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer. 2012;48(5):678-686.

Parker C, Coleman RE, Nilsson S, et al. Quality of life (QOL), updated survival, and safety of radium-223 dichloride in patients with castration-resiistant prosate cancer (CPRC) with bone metastases frm the phase 3 double-blind randomized, multinatinal study (ALSYMPCA)(Poster 898PD). Vienna, Austria: ESMO; 2012.

Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-223.

Saltus CW, Vassilev ZP, Zong J, et al. Incidence of Second Primary Malignancies in Patients with Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the United States. Prostate Cancer. 2019;2019:4387415.

Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol. 2014;15(7):738-746.

Sartor O, Hoskin P, Coleman RE, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. Prostate. 2016;76(10):905-916.

Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025;75(1):10-45.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.

Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(3):408-419.

Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer. 1988;61(1):195-202.

Tablazon IL, Howard LE, De Hoedt AM, et al. Predictors of skeletal-related events and mortality in men with metastatic, castration-resistant prostate cancer: Results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cancer. 2019;125(22):4003-4010.

Taich L, Zhao H, Stock SR, et al. Radium-223 Utilization Patterns and Outcomes in Clinical Practice. Urol Pract. 2022;9(5):405-413.

Vassilev ZP, Gabarro MS, Kaye JA, et al. Incidence of second primary malignancies in metastatic castration-resistant prostate cancer: results from observational studies in three countries. Future Oncol. 2020;16(25):1889-1901.

Appendices

Annex 1: List of stand-alone documents

Table 35: List of stand-alone documents

Document name	Final version and date (if available)
Investigator list	24 MAR 2025
Country & Site list	24 MAR 2025
List of Health Authority/IEC/IRB submissions and approvals	02 APR 2025
Protocol	Version 5.0, 20 AUG 2018
CRF	Version 12.0, 03 MAR 2020
BPI-SF	Version 1.0, 23 JUN 2014
SAP	Version 3.0, 23 OCT 2024
Tables, Listings, Figures	27 FEB 2025
Data Management Plan	Version 5.0, 22 OCT 2024
Quality Review Plan	Version 3.0, 31 JUL 2017
Final Quality Review Report	Version 1.0, 23 OCT 2024
Validity Review and Data Decision Report	Version 3.0, 31 MAR 2025

Annex 2: Subject narratives

Annex 3: Additional information

Not applicable