Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	PARABO - **P**ain evaluation in **Ra**dium-223 (Xofigo®) treated mCRPC patients with **bo**ne metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 JUN 2021
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS9020
Active substance	Radiopharmaceuticals (V10XX03), Radium-223 dichloride
Medicinal product	Xofigo®
Product reference	EU/1/13/873/001
Procedure number	Not applicable
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumed all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures have changed.
Research question and objectives	This observational prospective single arm cohort study was designed to assess pain and bone pain related quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 in a real life nuclear medicine practice setting. In addition, overall survival, time to next tumor treatment (TTNT), time to first symptomatic skeletal event (SSE), course of blood counts, and safety were assessed.
Country of study	Germany
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Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumed all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures have changed.
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1. Abstract

Acronym/Title	PARABO - **P**ain evaluation in **Ra**dium-223 (Xofigo®) treated mCRPC patients with **bo**ne metastases – a non-interventional study in nuclear medicine centers
Report version and date Author	v1.0; 01 JUN 2021 PPD Bayer Vital GmbH Building K 56 51368 Leverkusen, Germany PPD Alcedis GmbH, CRO Winchesterstrasse 3 35394 Giessen, Germany
Keywords	Prostate Cancer, Oncology, Xofigo®, Bone Metastases, Pain Control
Rationale and background	Phase III ALSYMPCA trial in metastatic castration-resistant prostate cancer (mCRPC) demonstrated that Radium-223 improves overall survival (OS), quality of life (QoL) and indicated a reduction of bone pain compared to placebo+best standard of care. However, the real-world data on effect of Radium-223 on pain reduction and bone pain-related QoL is scarce.
Research question and objectives	This study aimed to assess bone pain in mCRPC patients receiving Radium-223 in the real-world setting. The primary objective was evaluation of pain response (two points improvement from baseline in worst pain score on BPI-SF questionnaire) Secondary objectives included evaluation of change from baseline in pain related assessments, symptomatic skeletal event (SSE) including fractures, time to: next tumor treatment (TTNT) and first SSE (TSSE), overall survival, blood values and treatment-emergent adverse events (TEAE).
Study design	Prospective, non-interventional, multi-center, single arm

	cohort study.
Setting	Twenty-seven nuclear medicine clinics and practices throughout Germany. Patients were observed from start of Radium-223 therapy until death, withdrawal of consent, loss to follow-up or regular end of the study.
Subjects and study size, including dropouts	Included were men aged ≥18 years with mCRPC and with symptomatic bone metastases and no known visceral metastases and initiating Radium-223 therapy.
Variables and data sources	Historic demographic and clinical data were obtained from medical records or through patient interview. Clinical, pain assessment and QoL data were collected during treatment and follow-up visits.
Results	Out of 358 patients were enrolled, 356 initiated Radium-223 therapy. 354 patients were included in the efficacy analysis. 73.4% had Eastern Cooperative Oncology Group performance status 0-1. 214 patients (60.1%) completed 6 Ra-223 cycles and 242 (68.4%) of the patients had at least one prior systemic anticancer therapy. 52.5% received concomitant bone-health agents. Primary objective analysis revealed that 59.3% of patients had at least one clinically meaningful pain response during the study. Patients with 5-6 Radium-223 injections more often achieved pain response than those with 1-4 injections (67.12% vs 42.86%). Mean BPI-SF component scores were maintained from baseline during the treatment with Radium-223. Pain control rate was 67.13% (95%CI 60.43-73.35 Mean FACT-BP score was 35.93 (SD=14.79) at baseline and 41.85 (SD=14.50) at visit 6. Median OS (time from the start of Radium-223 therapy to death due to any cause) was 17.15 months (95%CI 15.33-18.97) Median TSSE was not reached (95%CI 37.45-NR). Prior or concomitant therapy with abiraterone/prednisone or enzalutamide did not appear to increase fracture incidence. 56.2% of patients experienced at least one TEAE, most often Anaemia, Fatigue and Diarrhoea. Serious TEAE occurred in 26.97% of patients, most frequently Anaemia and Pancytopenia. 25.84% of patients experienced a drug-related TEAE, most often anaemia (9.3%), diarrhoea (4.8%), and

	fatigue (2.8%). 11.2% of patients experienced grade ≥3 drug-related TEAEs. 21.4% and 8.2% of patients discontinued Radium-223 due to TEAE or drug-related TEAE, respectively. The most common reasons for early termination were adverse events (12.1%) and disease progression (10.1%).
Discussion	In this real-world study 59.3 % of the patients had a clinically meaningful pain response. A higher number of patients with 5-6 Radium-223 injections achieved a pain response. The overall clinical outcomes with Radium-223, including pain response, safety and OS, were consistent with previous observations.
Marketing Authorization Holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumed all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures have changed.
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request).

2. List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AG	Aktiengesellschaft
ALP	Alkaline Phosphatase Level Test
BHA	Bone Health Agents
BL	Baseline
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory Short Form
BSI	Bone Scan Index
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
DOT	Duration of Therapy
EC	Exclusion criterion
ECOG	The Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
EU	European Union
FACT-BP	Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with Bone Pain
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FU	Follow-up
HRPC	Hormone-Refractory Prostate Cancer
IC	Inclusion Criterion
ICF	Informed Consent Form
ID	Identifier
iEAP	international Early Access Program
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MAH	Marketing Authorization Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
NR	Not Reached
OS	Overall Survival
PAS	Post-Authorization Study

PASS	Post-Authorization Safety Study
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible For Pharmacovigilance
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SSE	Symptomatic Skeletal Events
TEAE	Treatment-Emergent Adverse Events
TESAE	Treatment-Emergent Serious Adverse Events
TSSE	Time to First Symptomatic Skeletal Event
TTNT	Time to Next Tumor Treatment
WHO	World Health Organization

3. Investigators

Contact details of the principal investigator, co-investigators and other site personnel for site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request.

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5. Milestones

Study milestones are shown in Table 1.

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	31 MAR 2015	19 MAR 2015	
End of data collection (LPLV)	30 JUN 2023	20 MAY 2020	The study has been prematurely terminated.
Registration in the EU PAS register	Q1 2015	20 MAR 2015	
IEC or IRB approval		First approval: 15 JAN 2015 Last approval: 19 Nov 2018	
Interim analysis	1. when approximately 200 patients ended the treatment course of Radium-223 2. 6 months after LPFV: (30 JUN 2018)	1. Data cut off: 18 MAY 2017 2. Data cut off: 29 JUN 2018	
Database Clean	31 SEP 2023	15 JUL 2020	
Final report of study results	31 MAR 2024	01 JUN 2021	

*A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request.

6. Rationale and background

Prostate cancer is the most common non-cutaneous malignancy in men in Germany. In 2016, there were 58 780 new cases, and 14 417 died from the disease (1). The estimated age-standardized rate for prostate cancer incidence in Germany is 91.6 per 100 000 (1). It is expected that by the year 2030, the burden of prostate cancer will increase to approximately 79 300 new cases and 18 700 new deaths in Germany (EU: 391 000 and 88 300, respectively (2)).

Prostate cancer is unique amongst solid tumors in that the greatest threat to a patient's survival and quality of life is posed by bone metastases rather than visceral involvement. Indeed, large number of treatments of the advanced stage are directed toward eradicating or limiting osseous metastases or palliating their side effects (3). In addition, several therapies target both visceral and osseous

metastases, including androgen pathway inhibitors: abiraterone acetate and enzalutamide and chemotherapy drugs: docetaxel and cabazitaxel (4). Cellular invasion and migration, cell matrix adhesion or cell-to-cell adhesions, interaction with endothelial cells, regulation of growth factors, and stimulation of osteoclasts and osteoblasts are thought to contribute to development of skeletal metastases (5-7). Once prostate cancer becomes metastatic, survival of patients depends on the extent of the disease and the site of metastases. The most common site of metastases for advanced prostate cancer is the skeletal system which is involved in more than 90% of the castration-resistant prostate cancer (CRPC) patients (8-12).

Prostate cancer cells are stimulated by androgens, in particular by testosterone. Conventional androgen deprivation therapy (ADT) in patients with bone metastases aims to reach castration levels of testosterone (i.e. ≤50 ng/mL or 1.7 nmol/L) which can be initially effective controlling the metastases in the bone. However, the majority of patients soon become castration resistant, i.e. progression occurs even at castration levels of testosterone (13). The commonly accepted term "CRPC" is used throughout this document. Already early stages of CRPC with bone metastases are associated with substantial pain and with rising levels of prostate-specific antigen (PSA) as seen in 35% and 90% of patients, respectively. The extent of PSA control after initial ADT affects prognosis: after 7 months of ADT, patients with PSA <0.2 ng/ml (undetectable) have a better prognosis than patients with PSA ≥4 ng/ml (14).

In normal bone tissue, homeostasis is carried out by the balanced interplay between osteoclasts and osteoblasts which are cell types specialized in bone decomposition and bone formation, respectively. In the presence of malignant neoplasms and following hematological dissemination of tumor cells into the bone, bone metastases develop as a result of a pathologic interaction between tumor cells on the one hand and osteoblasts as well as osteoclasts on the other hand (15).

The development of bone metastases is a serious threat to the patients' quality of life and survival, with survival being impacted by the number of metastases. Median survival time after diagnosis of bone metastasis amounts to 210 days (16). One- and 5-year survival in patients with prostate cancer without bone metastasis is 87% and 56%, and 47% and 3% in those with bone metastasis, and 40% and less than 1% in those with bone metastasis and skeletal related events, respectively (17, 18). The associated complications present a substantial disease and economic burden (19). Untreated patients face severe morbidity, including bone pain, bone fractures, compression of the spinal cord and hematological consequences of bone marrow involvement such as anemia. As presence of bone metastases represents a major clinical problem for patients with metastatic castration-resistant prostate cancer (mCRPC), specific treatment options for this condition are needed. Control of bone metastases leads to improved quality of life and symptoms, including bone pain, as well as prolongs overall survival (OS, (20)).

Regardless of the nature and location of bone metastases, the use of bone targeted treatments, including bone health agents (BHA, e.g. zoledronic acid (21) or denosumab (22)) can decrease the risk of skeletal related events including fractures. Accordingly, European Association of Urology guidelines and The German S3 Guideline Prostate Cancer recommend the use of BHA in mCRPC (23, 24).

Radium-223 selectively targets bone metastases with high-energy, short-range alpha-particles. In phase III, double-blind, randomized trial ALSYMPCA (**Alp**haradin in **Sym**ptomatic **P**rostate **Ca**ncer, started in 2008, (25)), a total of 921 patients with CRPC and symptomatic bone metastases who were receiving best standard of care and were post-docetaxel or unfit for or declined docetaxel were randomized (2:1) to receive 6 injections of Radium-223 dichloride (50 kBq/kg intravenous) or

matching placebo every 4 weeks. Of note, 50kBq/kg dose is an equivalent to 55 kBq/kg BW after implementation of the National Institute of Standards and Technology (NIST) update 2015 (26). The primary endpoint was OS. Main secondary efficacy endpoints were time to first skeletal-related event and various biochemical endpoints. Based on data of an interim analysis (n=809), the study was unblinded in July 2011, since Radium-223 significantly improved OS, compared to placebo (the median OS was 14.0 vs. 11.2 months, respectively; HR=0.70; p=0.002). The updated analysis (performed in June 2012; n=921) also showed that Radium-223 significantly improved OS compared to placebo + best standard of care (median OS 14.9 vs. 11.3 months, respectively; HR=0.70; p<0.001). Symptomatic skeletal events (SSE) were lower in the Radium-223 arm, and time to first SSE was significantly delayed (the median time to SSE was 15.6 months, versus 9.8 months, respectively; HR=0.66; p<0.001). A low incidence of myelosuppression was observed in Radium-233 group and in placebo + best standard of care arm, with grade 3/4 events of neutropenia (3% and 1%) and thrombocytopenia (6% and 2%). Adverse events of any grade were described in 93% of the subjects who received radium-223 dichloride; versus 96% in the placebo arm (grade 3/4 adverse events were described for 56% and 62%, respectively). Radium-223 dichloride was authorized in the European Union as Xofigo® in November 2013 (27) and is the first targeted alpha therapeutic proving a survival benefit to mCRPC patients. As a calcium mimetic, it is incorporated in areas with high bone turnover and can induce there intense local cytotoxic effects in cancer cells and surrounding tumor microenvironment. Radium-223 is the only targeted alpha therapeutic with the highest ranking of approved mCRPC treatments in the ESMO Magnitude of Clinical Benefit Scale (28).

In addition to improvement in OS, sub-analysis from ALSYMPCA revealed a pronounced potential for pain reduction, prolonged time to use of external beam radiation therapy (EBRT) for pain palliation and time to opioid use (29). The distinct reduction of local symptoms from bone metastases delayed substantially the distortion of quality of life (QoL) compared with placebo (29). This pronounced reduction in tumor related symptoms is an important benefit for patients in the castration resistant stage of prostate cancer where cure is not an option anymore but good symptom palliation is the main focus of any treatment.

The effect of Radium-223 on pain and QoL preservation in mCRPC patients was, as described, to some extent demonstrated in the pivotal phase 3 ALSYMPCA trial. A significantly higher percentage of patients in Radium-223 than in placebo+ best standard of care arm had a meaningful improvement in the quality of life according to the FACT-P total score (i.e. an increase in the score of ≥10 points on a scale of 0 to 156) during the period of study-drug administration (24.6% vs. 16.1%, p=0.02, (29)). Furthermore, fewer patients who received radium-223, as compared with those who received placebo, had serious adverse event bone pain (10% and 16%, (25)). However, the ALSYMPCA trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. Therefore, the aim of this non-interventional prospective study was to further examine the effect of Radium-223 on pain palliation and bone pain related QoL in mCRPC patients in more detail and in a more heterogeneous patient population under routine daily practice conditions in Germany.

To assess pain, the “Brief pain inventory short form” (BPI-SF) questionnaire was used. BPI-SF is a short, self-administered questionnaire with 11 items, which was designed to evaluate the intensity of, and the impairment caused by pain (30). All BPI-SF items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (“no pain”) to 10 (“pain as bad you can imagine”) by numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work,

relations with other people, sleep and enjoyment of life) using 0 (no interference) to 10 (complete interference) by rating scales.

For QoL assessment, the questionnaire "Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain" (FACT-BP) was used. The FACT-BP consists of 16 items including general functioning and physical and bone pain and uses a 0-4 Likert-scale; recall period of the questionnaire is 7 days (31).

The phase 3b open-label, multicenter, single arm international early access program (iEAP) provided access to Radium-223 prior to regulatory approval and evaluated its safety and efficacy in patients with progressive bone-predominant mCRPC (32). Radium-223 was generally well tolerated with no new safety concerns compared with those treated in ALSYMPCA. In contrast to ALSYMPCA, patients with prior or concomitant abiraterone or enzalutamide were eligible. In iEAP and ALSYMPCA, OS was longer in patients receiving 5-6 versus 1-4 injections. Radium-223 administered with either abiraterone and/or enzalutamide was generally well tolerated in patients with bone metastases, with no new safety signals reported. Further Phase III studies on Radium-223 in combination with docetaxel and enzalutamide and darolutamide are ongoing: DORA (NCT03574571), PEACE III (NCT02194842) and ESCALATE (NCT04237584). In the real-world setting, the interim analysis of prospective observational single arm cohort study REASSURE, demonstrated OS of 15.6 months after a median number of 6 Radium-223 injections 6. 34% of patients had a clinically meaningful pain response in the BPI-SF worst pain item at treatment 6 (33).

Identification of patients likely to receive the full treatment of 6 Radium-223 injections may be important to achieve an OS benefit as demonstrated by the ALSYMPCA trial. The exploratory analyses of iEAP and the ALSYMPCA trail suggest that patients with less advanced disease were more likely to receive 5-6 versus 1-4 Radium-223 injections. Furthermore, patients with worse Eastern Cooperative Oncology Group (ECOG) performance status (PS) in the interim analysis of PARABO study data and those with prior chemotherapy in the non-interventional study REASSURE had a lower number of Radium-223 injections (34, 35).

Use of Radium-223 earlier in the treatment paradigm may allow patients to receive the full course of Radium-223 treatment. In the present study, patients suffering from mCRPC treated with Radium-223 in a real life nuclear medicine practice setting in Germany were analyzed for factors predicting the potential to receive the full treatment course of Radium-223 (5-6 injections) by estimating the duration of therapy (DOT) and covariates predictive of receiving 5-6 injections.

The phase 3 ERA-223 trial evaluated the safety and efficacy of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic CRPC (study number 15396, NCT02043678, (36)). Ad hoc independent analysis revealed an increased fracture risk in the active treatment arm compared with the placebo arm. Following the recommendation of Pharmacovigilance Risk Assessment Committee, the contraindication to use of Radium-223 dichloride in combination with abiraterone plus prednisone/prednisolone was implemented in the product information in March 2018 and in the Amendment 5 (dated 30 April 2018) to the study protocol. The observation was terminated for patients with Radium-223 and abiraterone therapy after 18 March 2018. In order to collect comprehensive safety information across all clinical trials with Radium-223 dichloride, pathological fractures (as part of symptomatic skeletal events), non-pathological fractures and bone associated events were documented in the PARABO study and were assessed in all patients available for safety analysis. Therefore, all patients enrolled into the PARABO study that were treated with the combination of Radium-223 and abiraterone plus

prednisone/prednisolone are presented thoroughly and separately in this report in order to further substantiate any increased risk in bone fractures in those patients.

Since the release of updated product information of Radium-223 in EU in March 2018 (27), Radium-223 should not be given concurrently with abiraterone plus prednisone/prednisolone. Based on the available data on Radium-223, the option of starting BHA should be considered taking into consideration applicable guidelines.

7. Research question and objectives

This observational prospective single arm cohort study was designed to assess pain and bone pain related quality of life of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223 in a real life nuclear medicine practice setting in Germany. In addition, overall survival, time to next tumor treatment (TTNT), time to first symptomatic skeletal event (SSE), course of blood counts, and safety were assessed.

7.1 Primary objective

The primary objective of this study was to evaluate pain response during Radium-223 treatment of mCRPC patients in a real life nuclear medicine practice setting.

7.2 Secondary objective(s)

The secondary objectives in this study were:

- To describe the change from baseline in pain related assessments
    - The change of pain and bone pain related quality of life over time during treatment phase
    - Pain control rate
    - Pain progression rate
    - Time to first pain progression
    - Time to first opioid use
    - Covariates on pain response of mCRPC patients during treatment phase
    - Pain response related to the extent of bone metastases at baseline
    - The relation between bone uptake in known lesions and pain palliation (only in patients with bone scan prior to start of treatment and a second scan during or within 6 weeks after end of Radium-223 treatment)
- To describe further clinical assessments:
    - Radium-223 treatment patterns

- Treatments and time to subsequent mCRPC treatment (TTNT)
- The time to first symptomatic skeletal event (SSE)
- Effect of concomitant drug treatment on pain, QoL, and overall survival
- Time from castration resistance to treatment with Radium-223
- Duration of therapy
- Factors positively influencing mCRPC patients to get ≥ 5 injections versus ≤ 4 injections (e.g. concomitant use of antihormonal therapy, no pre-treatment of chemotherapy)
- Overall survival (OS)
- Bone Scan Index (BSI) as Imaging Biomarker in mCRPC

- Treatment-emergent adverse events (TEAE, up to 30 days after last administration of Radium-223)
- To describe the course of blood counts in patients with different extent of disease and in the whole patient population
- To calculate the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and up to 5 year follow-up period

8. Amendments and updates

Study protocol amendments are shown in Table 2.

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
1	18 Nov 2014	9.2.1 Eligibility	Amendment	Clarification of in- and exclusion criteria to include only adults in the study. To prevent evaluation of the same patient in different studies as well as double reporting of AEs, participation in other observational study with Radium-223 (e.g. URANIS) were added as exclusion criteria.
2	06 Nov 2015	8.2 Secondary objective(s)	Amendment	Evaluation of BSI as Imaging Biomarker was added to the secondary objectives because it is a promising approach in evaluating the response of bone metastases treatment which currently lacks reliable parameters.

3	16 Feb 2017	6 Milestones, 8.2 Secondary objective(s), 9.2.4 Withdrawal	Amendment	- Extension of recruitment until December 31, 2017 and milestones; - Addition of new interim analysis on safety when approximately 200 patients ended the treatment course of Radium-223. The additional interim analyses focused primarily on AE, but trends in changes in pain and Qol assessment were also be described. Based on the interim analysis appropriate measures to improve data quality were to be implemented if needed; - Addition of 4 new secondary objectives (endpoints, outcomes and analysis are adapted accordingly) to describe new aspects on clinical efficiency from Radium-223 under real life conditions; • Effect of concomitant drug treatment on pain, QoL, and overall survival • Time from castration resistance to treatment with Radium-223 • Duration of therapy • Factors positively influencing mCRPC patients to get ≥ 5 injections versus ≤ 4 injections (e.g. concomitant use of antihormonal therapy, no pre-treatment of chemotherapy) - The secondary objectives were grouped and structured in order to give a more intuitive overview of the assessments; - Section 9.2.4 (withdrawal) was changed according to applicable Bayer SOP; - The wording in most of the protocol was changed from "evaluate" to "describe" to reflect and emphasize more clearly the descriptive character of the data analysis, although the statistical assessment has not changed.
4	14 Jul 2017	9.5 Study Size, 11.1 Definitions	Amendment	• Extension of patient number from 300 to 350 patients. • Addition of (S)AE exception "disease progression" The reason for the extension of patient number to 350 patients is that only 64 % of the patients from the first interim analysis are valid for the primary endpoint based on formal criteria.

				A (S)AE-exception was added (section 11.1) to clarify that a tumor progression itself should be collected as an outcome parameter and not as an (S)AE.
5	30 Apr 2018	11.2 Collection, 8.2 Secondary objective(s), 7 Introduction: Background and Rationale, 9.2.4 Withdrawal, 9.2.7 Visits	Amendment	• Prolongation of follow-up period for up to 5 years after last Radium-223 treatment. • Addition of secondary objective to calculate incidence of pathological fractures, non-pathological fractures and bone associated events during the treatment and up to 5 year follow-up period. • Initiation of BHAs including bisphosphonates or denosumab, should be considered by investigator. • The wording regarding the withdrawal has been updated. The reason for this amendment was a request by the PRAC to amend all study protocols in ongoing Xofigo studies based on the findings of the interim analysis of the ERA-223 study. Following the release of the new version of the product information for Radium-223 (dated March 2018), Radium-223 should not be given concurrently with abiraterone plus prednisone/prednisolone. The collection of pathological fractures, non-pathological fractures and bone associated events (e.g. osteoporosis) during the treatment and up to 5 year follow-up period was added to provide more safety insights from routine practice.

9. Research methods

9.1 Study design

This study was a prospective, non-interventional, multi-center, single arm cohort study conducted in nuclear medicine clinics and practices throughout Germany. Sites were selected based on the experience of the attending physician with the indication and the treatment with Radium-223. It was planned to enroll 350 patients with CRPC with bone metastases for whom the attending physician decided according to his/her medical practice to treat the patient with Radium-223. Treatment with Radium-223 should follow the approved product information.

For each patient, the investigator documented data in standardized case report forms at initial, follow-up and final visits during treatment phase. Data were collected using electronic case report forms (eCRF). 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 this study (maximum of 5 years after last administration of Radium-223), whichever came first in time.

The medication was used within the routine clinical practice setting. Commercially available product was used to treat the patients.

9.1.1 Primary endpoint(s)

The primary endpoints were:

- **Pain response** as determined by the worst pain item on the BPI-SF patient questionnaire. A clinically meaningful pain response was defined as an improvement of two points from the baseline BPI-SF worst pain score (37) at any post-baseline assessment.

9.1.2 Secondary endpoint(s)

The secondary endpoints were:

- To describe the change from baseline in pain related assessments:
  - **Changes of pain over time** by evaluating the worst pain item as well as the subscale scores for pain severity and pain interference as determined by patient responses on the BPI-SF questionnaire. The worst pain item and subscales were presented separately for each post-baseline assessment.
  - **Changes in bone pain related quality of life** as determined by patient responses on the bone pain specific FACT-BP questionnaire. The FACT-BP score were presented separately for each post-baseline assessment.
  - **Pain control rate** as determined by the worst pain item on the BPI-SF patient questionnaire. Pain control was defined as no increase by two points from the baseline BPI-SF worst pain score.
  - **Pain progression rate** as determined by the worst pain item on the BPI-SF patient questionnaire. Pain progression was defined as an increase by two points from the baseline BPI-SF worst pain score at any post baseline assessment.
  - **Time to first pain progression** was defined as the time between the first injection of Radium-223 until an increase in the BPI-SF worst pain item by at least two points.
  - **Time to first opioid use** in patients who did not take opioids at study entry is defined as the time from first injection of Radium-223 until first intake of opioid analgesics.
  - **Description of covariates on pain response** of mCRPC patients during treatment with Radium-223. The following covariates were analyzed:
    - opioid use
    - assessment of extent of bone metastases (<6, 6-20, > 20, superscan)
    - location of bone metastases

- level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)
- PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
- WHO pain score at baseline (WHO-Score 0+1 and WHO-Score 2+3)
- pretreatment with chemotherapy (yes/no)
- pretreatment with deep androgen ablation by treatment with abiraterone or enzalutamide (yes/no)
- extent of bone uptake in known lesions (like surrounding bone, only faint, higher uptake, and strong uptake compared to surrounding bone)
- BSI

- **Relation between bone uptake in known lesions and pain palliation** (only in patients with bone scan prior to start of treatment and a second scan during or within 6 weeks after end of Radium-223 treatment)

- To describe further clinical assessments:
  - For **Radium-223 treatment patterns** dosage and number of injections of Radium-223 was analyzed.
  - **Time to next tumor treatment(s) (TTNT)** was defined as the time from the first application of Radium-223 until start of next mCRPC treatment including e.g. chemotherapy and/or hormonal treatment.
  - **Time to first symptomatic skeletal event (SSE)** was defined as the time between the first injection of Radium-223 until the occurrence of first SSE defined as the first use of external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathological vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention
  - **Effect of concomitant drug treatment on pain, QoL, and overall survival;** Exploration of the influence of abiraterone, enzalutamide, opioids and denosumab on OS by number of injections (5-6 vs. 1-4)
  - **Time from castration resistance to treatment with Radium-223**; time from verified castration resistance to first injection of Radium-223
  - **Description of covariates on DOT** (to get ≥ 5 injections versus ≤ 4 injections) of mCRPC patients during treatment with Radium-223. The following covariates were described:
    - Opioid use
    - Assessment of extent of bone metastases (<6, 6-20, > 20, superscan)
    - Level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)

- PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
- Pretreatment with chemotherapy (yes/no)
- Pretreatment with deep androgen ablation (by treatment with abiraterone or enzalutamide) and denosumab (yes/no)
- Concomitant treatment with deep androgen ablation (by treatment with abiraterone or enzalutamide) and denosumab (yes/no)

- **Overall survival** was defined as the time interval from the start of Radium-223 therapy to death, due to any cause. Patients alive at the end of the study were censored at the last date known to be alive. Date and cause of death was collected.
- **To evaluate BSI as Imaging Biomarker in mCRPC** by comparing BSI values before and after Radium-223 treatment as well as investigating the association of BSI with other outcome parameters like OS.

- **Course of blood counts** in patients with different extent of disease and in the whole patient population was presented as percentage of patients below limit for further injections according to the local product information
- **Treatment-emergent Adverse Events (TEAE)** - Patients were monitored for TEAE using the NCI-CTCAE Version 4.03. Detailed information collected for each TEAE included: a description of the event, duration, whether the TEAE was serious, intensity, relationship to Radium-223, action taken, clinical outcome
- Estimation of the incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and long-term follow-up period

9.1.3 Strengths of study design

This was a prospective, non-interventional, multi-center, single arm cohort study of CRPC patient with bone metastases who received Radium-223 from routine clinical practice settings. This study included patients in a real life scenario and thus from a more diversified and less selected patient population than in a clinical trial setting, using fewer eligibility criteria to be as much representative to the general CRPC patients with bone metastases as possible.

9.2 Setting

The study was conducted in 27 nuclear medicine clinics and practices throughout Germany. Data were collected from 358 patients (excluded are two patients who withdrew informed consent and refused further use of data). The observation period for each patient enrolled in this study was the time from start of therapy with Radium-223 until death, withdrawal of consent, loss to follow-up or regular end of the study which was defined as up to five years (prolonged from the initial two years with amendment 5) after the last administration of Radium-223, whatever came first in time.

Patients who were participating in the study when amendment 5 became active were informed about prolongation and adaption of the follow-up period from two to five years. These patients were asked to provide written informed consent to prolonged study participation.

First patient first visit (FPFV) was on 19 March 2015, last patient first visit (LPFV) was on 20 December 2017 and last patient last visit (LPLV) was on 20 May 2020.

The sponsor decided to discontinue the study prematurely after 2 year follow-up due to insufficient number of patients to gain any meaningful knowledge on long term safety of those patients who were treated with Radium-223. The protocol amendment 5 became effective after LPFV. Twelve out of 356 treated patients signed the additional informed consent for the prolonged follow-up period of up to five years from the last administration of Radium-223. However, only 5 out of these patients (1.4% of all treated patients) were still in follow-up after two years of last Radium-223 dose. The low participation in the long term follow-up may be partly due to these patients being in the late-stage of the disease and Radium-223 treatment had already ended.

9.3 Subjects

Male patients with a diagnosis of CRPC with symptomatic bone metastases without known visceral metastases were enrolled after the decision for treatment with Radium-223 had been made by the attending physician according to his/her medical practice.

9.3.1 Inclusion criterion/criteria

- Adult male patients diagnosed with CRPC with symptomatic bone metastases without known visceral metastases
- Decision to initiate treatment with Radium-223 was made as per investigator's routine treatment practice.
- Signed informed consent

9.3.2 Exclusion criterion/criteria

- Patients participating in an investigational program with interventions outside of routine clinical practice or participating in another observational study with Xofigo®

9.3.3 Withdrawal

In this observational study, withdrawal from the study was independent of the underlying therapy and did not affect the patient's medical care. Each patient could withdraw from the study at any time and without giving a reason. If a patient wanted to terminate the study participation, no further data were collected. However, the patient was asked whether he agrees that the data collected so far can be used. In case the patient did not agree, his data were deleted from the study database and were not be used for any study-related analysis. In case a patient withdrew the consent given earlier, he

should inform his doctor and the site should document the withdrawal and the extent of withdrawal in the Case Report Form as well as in the patient medical records.

9.3.4 Replacement

Patients were not replaced after drop out.

9.3.5 Representativeness

No further selection than outlined by inclusion and exclusion criteria was made and consecutive patients were enrolled at each site in order to avoid any selection bias. With respect to site selection this study used a convenience sample of sites with Radium-223 availability (nuclear medicine licensed facility) and experience with prostate cancer management and treatment. As of August 2014, there were 105 nuclear medicine licensed facilities in Germany. For sites participating in the study it was planned to include 8 to 10 patients per site.

9.4 Visits

Information on the patients, outcomes and other variables was recorded using Electronic Data Capture (EDC) by the treating physician (nuclear medicine physician or any other physician licensed in the administration of radioisotopes) or designated medical person at different time points. After the patient and treating physician agreed on a treatment decision, the patient was informed about the study and had to sign an informed consent in order to participate. Baseline information was recorded with the status before the first Radium-223 administration during patient visit. For each treatment cycle, information from patient medical records was documented and entered to EDC system by the physician or designated medical person. These visits occurred during routine practice, the study protocol did not define exact referral dates. An overview of the assumed visits is given in Figure 1.

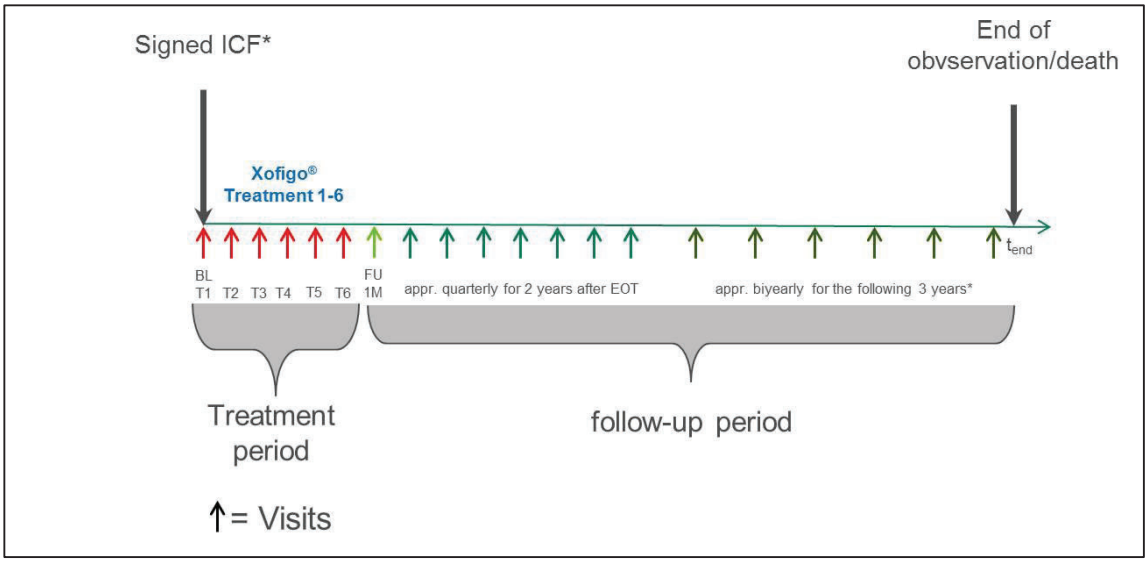

Figure 1: Overview of the assumed visits. BL, Baseline; EOT, End of treatment; FU, follow-up; ICF, Informed consent form. *Additional signed informed consent for prolonged FU period was necessary. Twelve patients signed the additional informed consent for follow-up for up to 5 years after the end of treatment.

Baseline/First treatment visit

Once a patient was found eligible for inclusion, the investigator informed the patient about the study. This included discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

Typical information collected at the baseline/first treatment visit included:

- Date of first treatment visit
- Demography
- Vital signs
- Medical history including date of castration resistance
- Prostate cancer history
- Concomitant diseases
- Opioid use and other concomitant medication (including any BHA treatment)
- Concomitant anti-cancer therapy
- WHO pain score
- ECOG status
- Bone scan

- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP), filled out by the patient prior to the first injection of Radium-223
- Laboratory parameters including ALP, PSA, and blood counts
- Dose of Radium-223 administered
- Adverse Events (including non-pathological fractures and bone associated events)

Further treatment visits

Further treatment visits occurred during routine praxis, typically every four weeks according to the approved label of Radium-223. Information collected at further treatment visits included:

- Date of treatment visit
- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP), filled out by the patient prior to each injection of Radium-223
- Dose of Radium-223 administered
- WHO pain score
- ECOG status
- Changes in pain medication or other concomitant medication (including any BHA treatment)
- Changes in concomitant anti-cancer therapy
- Bone Scan, if available
- Laboratory parameters including ALP, PSA, and blood counts
- Adverse events (including non-pathological fractures and bone associated events)
- Symptomatic skeletal events (e.g. pathological fractures)

Follow-up visit after end of treatment

If within routine clinical practice, data were collected from a follow-up visit approximately one month after end of treatment. Typical information collected at this follow-up visit after treatment included:

- Date of visit
- Patient questionnaires on pain (BPI-SF) and QoL (FACT-BP) filled out by the patient
- WHO pain score
- ECOG status
- Changes in pain medication
- Changes in anti-cancer therapy

- Bone Scan, if available
- Laboratory parameters including ALP, PSA, and blood counts
- Adverse events up to 30 days after last treatment
- Symptomatic skeletal events (e.g. pathological fractures)
- All other (non-pathological) fractures and bone associated events (e. g. osteoporosis)

Long-term follow-up

For long term follow-up either the patient or treating physician contacted by phone, mail or email after end of treatment until death, patient's withdrawal, loss to follow-up, or end of study (whatever came first in time) for of two years approximately quarterly and the following three years biyearly. The maximum follow-up period for a patient was up to 5 years.

After implementation of amendment 5, not only symptomatic skeletal events but also non-pathological fractures and bone associated events were collected for all enrolled patients in the follow-up visits after end of treatment.

Typical information collected at long-term follow-up included:

- Date of follow-up
- Survival status
- Opioid use after last administration of Radium-223 yes/no, if yes, date of first use (only in patients without prior opioid use)
- Symptomatic skeletal events (e.g. pathological fractures)
- All other (non-pathological) fractures and bone associated events (e. g. osteoporosis)
- Further anti-cancer therapy

End of Observation

The reason for end of observation was documented, if the patient died, withdrew his consent or was lost to follow up. In case of death, date of death and primary cause of death were documented. The treating physician was encouraged to document the reason for the end of observation for all patients immediately after recognition but latest 60 months after end of treatment. A follow-up period of 60 months applied only to patients who consented to prolonged follow-up. For patients who did consent to a prolonged follow-up period of 60 months, the reason for end of observation was documented at the latest 24 months after end of treatment.

9.5 Variables

The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient (Table 3). Likewise, the investigator collected treatment related data during treatment visits and follow-up visits. The investigator documented the study-relevant data for each patient in the case report form (CRF).

Table 3: Tabulated overview on variables collected during the study

Variables	Baseline and first treatment	Further Treatment visits	Follow-up after end of treatment	Long-term follow-up	End of observation
Date of visit	X	X	X	X	X
Patient informed consent	X				
Demography	X				
Vital Signs	X				
Co-morbidities (medical history, concomitant diseases)	X				
Prostate cancer history (initial diagnosis, date of castration resistance, diagnostic and therapeutic procedures)	X				
WHO pain score	X	X	X		
Performance Status (ECOG)	X	X	X		
Questionnaires BPI-SF and FACT-BP	X	X	X		
Location of bone pain	X	X	X		
Number and location of skeletal lesions (bone scan) and BSI*	X	X	X		
Exposure/treatment (dose of Radium-223)	X	X			
Concurrent diagnostic and therapeutic procedures for mCRPC	X	X			
Laboratory parameters including ALP, PSA, blood counts	X	X	X		
Opioid use	X	X	X	X***	
Concomitant medication	X	X	X****	X****	

Variables	Baseline and first treatment	Further Treatment visits	Follow-up after end of treatment	Long-term follow-up	End of observation
(including any BHA treatment)					
Adverse Events	X	X	X**		
Symptomatic skeletal events (e.g. pathological fractures)		X	X#	X#	
All other (non-pathological) fractures and bone associated events (e.g. osteoporosis) during follow up period			X#	X#	
Further treatment for mCRPC		X	X	X	
Survival assessment				X	
Reason for end of observation					X

*if available, an additional bone scan can be documented independently from visits.

**up to 30 days after last treatment with Radium-223.

***only opioid use yes/no and date of first use

****only BHA treatment

#to be documented on AE form up to 5 years follow-up period

9.5.1 Variables to determine the primary endpoint(s)

The variables for primary objectives were:

- Pain severity was measured using the worst pain score of the BPI-SF questionnaire. The BPI-SF was administered prior to each injection of Radium-223 and, if within routine clinical practice, at a follow-up visit approximately one month after the last injection of Radium-223.

9.5.2 Variables to determine the secondary endpoint(s)

The outcome variables for secondary objectives were:

- Change of pain over time: In addition to pain severity, the subscales of the BPI-SF questionnaire were evaluated: **The total pain severity subscale** of the BPI-SF is based on the sum of the four items least, worst, average, and current pain. **The pain interference subscale** of the BPI-SF is based on the seven pain interference items.
- Quality of Life: Bone pain related QoL was measured by evaluation of the total score of the FACT-BP questionnaire. The questionnaire was filled out together with the BPI-SF prior to each injection of Radium-223 and, if within routine clinical practice, at a follow-up visit approximately one month after the last injection of Radium-223.

- Pain control rate, pain progression rate, and time to first pain progression were measured using the worst pain score of the BPI-SF questionnaire.
- Description of covariates on pain response:
    - opioid use
    - number of known bone metastases (<6, 6-20, > 20, superscan) at baseline based on the latest bone scintigraphy before the first injection of Radium-223 (not older than 8 weeks)
    - location of bone metastases based on bone scintigraphy
    - level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)
    - PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
    - WHO pain score at baseline (WHO-Score 0+1 and WHO-Score 2+3)
    - pretreatment with chemotherapy (yes/no)
    - pretreatment with deep androgen ablation by treatment with abiraterone or enzalutamide (yes/no)
    - bone uptake in known lesions (like surrounding bone, only faint, higher uptake, and strong uptake compared to surrounding bone)
    - BSI evaluated by EXINI®bone^{BSI} software
- location of bone pain
- Radium-223 treatment patterns were analyzed using dosage, number of treatments and time between treatments
- Course of blood counts
- BSI evaluated by EXINI®boneBSI software
- Treatment-emergent Adverse Events (TEAE) including a description of the event, duration, whether the TEAE was serious, intensity, relationship to Radium-223, action taken, clinical outcome. Patients were monitored for TEAEs using the NCI-CTCAE Version 4.03.
- Tumor treatment(s) starting after the first application of Radium-223
- Symptomatic skeletal event (SSE) (external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathological vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention)
- Date and cause of death
- Time from castration resistance to treatment with Radium-223
- Duration of therapy determined as number of Radium-223 injections

- Incidence of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment and long-term follow-up period.

9.5.3 Demography

For demographic / socio-demographic assessment, the following data were recorded:

- Year of birth
- Race
- Basic patient characteristics (height, weight)

9.5.4 Co-morbidities (medical history, concomitant diseases)

Any relevant medical finding that was present before start of therapy with Radium-223, independent on whether or not they were still present, had to be documented in the Medical History/Concomitant Diseases section.

9.5.5 Prior and concomitant medication

All medication taken in addition to the product for any indication (either initiated before study start or during the study) was termed concomitant medication.

Information to be collected for medication except for opioid use included: trade name or INN, start date, stop date/ongoing, total daily dose, unit, and indication.

Opioid use was documented on a separate form. Information to be collected included trade name or INN, start date, stop date/ongoing, dose, unit, frequency, application route. In addition, the use of pain medication within 24 h of completing the BPI-SF was collected.

9.5.6 Exposure / treatment

Information to be documented at each Radium-223 administration included:

- Date
- Number of injection cycle
- Dose
- Unit (kBq/kg)
- Reasons for any significant delay/interruption/discontinuation of treatment

9.5.7 Assessment of therapy

Not applicable

9.5.8 Visits

- Date of visit

9.5.9 Medical History of prostate cancer

Findings meeting the criteria listed below were considered to be relevant to the study indication and were documented:

- Prostate cancer classification
    - date of initial diagnosis
    - Gleason score
    - status of primary tumor at study entry
    - progression/relapse
    - date of castration resistance
    - date of initial diagnosis of bone metastases
- prior diagnostic or therapeutic procedures associated with mCRPC
    - surgery/biopsy
    - systemic anti-cancer therapy
    - radiotherapy
    - blood transfusions
- Number of metastases and extent of disease
- Baseline ECOG performance status

9.6 Data sources and measurement

The investigator collected historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collected treatment related data, results of tumor assessments and other disease status information, also documented in the medical record, during visits that took place in routine practice. For patient reported outcomes, questionnaires filled out by the patient during routine visits were used. For any adverse events that occurred, information was directly obtained from the patient. In case a patient was seen by more than one physician for his/her disease (e.g. the patient was monitored by a physician other than the initial investigator), the initial investigator collected information on any visits (including results) that took place outside the investigator's site due to the patient's disease, for example by interviewing the respective physician or patient or by obtaining an accompanying letter with detailed information and results.

Alcedis GmbH (a contract research organization, CRO) was assigned for EDC system development. The CRF was a part of the EDC system which allowed documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request.

Patient questionnaires were collected via paper forms which were then entered into the study database by the CRO.

Each patient was assigned an unique central patient identification code. This code was only used for study purposes. The patient code consisted of a combination of a country code, site number and patient number. For the duration of the study and afterwards, only the study team is able to identify the patient based on the patient identification code.

The Study Database contains all (pseudonymous) study data. The development of this application and the development and setup was performed by applying Good Automated Manufacturing Practice standards, fulfilling the FDA 21 CFR Part 11 and EU EudraLex V4 Annex 11 regulations. A set of SOPs and guidelines were used during the study lifecycle project to supporting all study phases from specification, development, study start, deployment and change management and up to study termination.

Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Annex 1: List of stand-alone documents).

For information on quality control, refer to section 9.11.

9.7 Bias

This prospective observational cohort study provided an opportunity to collect data of real-life patient benefit and safety information that can be analyzed and disseminated in a timely manner. However this study was a single arm cohort study without an active comparison group. Thus, in addition to subgroup analyses within this study, the results can only be compared with historical data from clinical trials and other observational studies, which is prone to bias and confounding as these data are generally not collected using the same way and the same or similar information may not be available. This caution applies in particular to the collection of pathological and non-pathological fractures and bone associated events with special attention to those occurring under concomitant treatment with abiraterone plus prednisone/prednisolone (until amendment 5 came into force).

Additionally, there are potential limitations for assessing BSI in a non-interventional setting. Not all sites were expected to have access to the software necessary to determine the BSI of bone scans (selection bias) or there might be specific reasons for obtaining bone scans such as disease progression or specific symptoms (selection bias). Also, interpretation of BSI might be impaired by the collection at different times post treatment. To address this last point, only the BSI of bone scans obtained within 8 weeks post Radium-223 treatment were included in the analysis.

9.8 Study size

Aim of the sample size consideration is to assess the precision of the estimate for the pain response rate (the primary outcome) which is defined by the width of the 95% confidence interval with a given sample size. Assuming that at least 60% of patients will be evaluable for the primary analysis of pain response at a post-baseline assessment and 30% to 70% of patients will show a pain response, at least 350 patients had to be included to reach a precision of <20%. Table 4 shows the different scenarios for actual pain response ranging from 30% to 70%.

Table 4: Width of the 95% CI for the pain response rate, assuming 210 evaluable patients

Actual pain response	Lower Limit of 95% CI	Upper Limit of 95% CI	Width of 95% CI
0.7	0.638	0.762	0.124
0.65	0.585	0.715	0.13
0.6	0.534	0.666	0.132
0.55	0.483	0.617	0.134
0.5	0.432	0.568	0.136
0.45	0.383	0.517	0.134
0.4	0.334	0.466	0.132
0.35	0.285	0.415	0.13
0.3	0.238	0.362	0.124

350 patients were considered realistic to enroll in the enrollment period, based on current patient numbers and available sites for the treatment. With this sample size and a pain response rate of 65% a precision of <20 % could be reached assuming subgroups to be at least of 50% of this size (i.e. 105 patients). From a clinical point of view, this precision is regarded as meaningful, taking the variance of pain measurements into account. Calculations were performed with nQuery 7. It was planned to increase sample size if the number of patients not evaluable for pain response proves to be higher than the expected 30%.

9.9 Data transformation

9.9.1 Analysis of demography, disease details, prior and concomitant medication and other baseline data

Demography and baseline characteristics are described with summary statistics. Concomitant medication is coded using WHO's drug dictionary.

Use of the anti-hormonal agents abiraterone plus prednisone/prednisolone or enzalutamide and other anti-androgens is tabulated according to timing of use relative to Radium-223 dichloride, to include sequential use, concurrent use and layered use.

9.9.2 Analysis of treatment data

Summary statistics is provided for the treatment duration, the number of injections, starting dose and average dose, the number of patients with dose modification (interruption, delay and discontinuation), number of dose modifications, and reasons for dose modifications. Duration of therapy is summarized in the population of patients by number of injections (≥5 versus ≤4 injections). The duration of therapy is defined as number of treatment cycle injections.

9.9.3 Analysis of primary outcome(s)

The primary analysis of pain response is summarized in the population of patients with a score >1 (0="no pain") for the baseline measurement of the 'Worst Pain'-item of the BPI-SF. For each post-baseline assessment, the incidence proportion is provided, along with the exact 95% confidence interval. Pain response is defined as an improvement of two points from the baseline BPI-SF worst pain score at any post-baseline assessment, which is considered clinically meaningful (38).

In addition, the incidence proportion is provided by number of injections (≥ 5 versus ≤ 4 injections).

Further details are given in the SAP.

9.9.4 Analysis of secondary outcome(s)

- Change of pain over time: The responses to each of the BPI-SF items and the following two dimensions which are aggregated from BPI-SF items is summarized descriptively:
    - Pain severity index:

      It uses the sum of the four items on the pain intensity. All four severity items must be completed for aggregating the pain severity index.
    - Pain interference index:

      It uses the sum of the seven pain interference items. The pain interference index is scored as the mean of the item scores multiplied by seven, given that at least four of the seven items have been completed.

  Summary statistics, including mean and change from baseline, is provided for each assessment time point. For the summary of each post-baseline assessment, patients were excluded if there was no corresponding post-baseline measurement.
- For bone pain related quality of life assessment summary statistics including mean and change from baseline are provided for each assessment time point of the FACT-BP questionnaire. For the summary of each post-baseline assessment, patients were excluded if there was no corresponding post-baseline measurement.
- Pain control rate is summarized. Pain control is defined as no increase by two or more points from the baseline measurement of the 'Worst Pain'-item of the BPI-SF (Question 3) at any post-baseline assessment.
- Pain progression rate is summarized. Pain progression is defined as two or more points increase from the baseline measurement of the 'Worst Pain'-item of the BPI-SF (Question 3) at any post-baseline assessment.
- Time to first pain progression is summarized by Kaplan-Meier (KM) estimates.
- Pain response is additionally summarized descriptively for the subgroups defined in 'evaluation of covariates on pain response' in Section 9.1.2.

An analysis of covariance model was used to assess changes in pain severity, as measured by the worst pain score on the BPI-SF, at each post-baseline assessment time point. The baseline worst pain score was used as a covariate in each analysis of covariance model.

- The relation between bone uptake in known lesions and pain palliation is analyzed (only in patients with bone scan prior to start of treatment and at least one further documented bone scan during or after end of Radium-223 treatment).
- The course of blood counts is analyzed. Incidence of blood counts below limit for further injections according to the local product information in patients with different extent of disease and in the whole patient population is calculated. The incidence proportion is provided, along with the exact 95% confidence interval.
- Time to event variables (TTNT, SSE, OS) is summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals are presented. Censoring rules are defined in the SAP.
- BSI as Imaging Biomarker in mCRPC is analyzed by comparing BSI evaluated by EXINI®boneBSI software before and after Radium-223 treatment. In addition, association of BSI with time dependent outcomes like OS is analyzed using the Cox regression model.
- Incidence of treatment emergent and drug-related AEs is presented using the NCI-CTCAE Version 4.03. Additional subcategories are based on event intensity and relationship to study drug.
- Time from castration resistance to treatment with Radium-223 is calculated.
- Data on concomitant medication is described to identify signals for an influence on efficacy variables (e.g. pain, OS, SSE) and safety.
- Pain related outcomes and OS are provided by number of injections (≥5 versus ≤4 injections), in addition to overall.
- Pain related outcomes, OS, SSE and adverse events are additionally provided for patients who received and did not receive concomitant BHA with Radium-223.
- Incidence proportions and incidence rates of pathological fractures (as part of symptomatic skeletal events (SSE)), non-pathological fractures and bone associated events during the treatment (reported as adverse events) and long-term follow-up period are presented. Fractures reported as adverse events were identified by the MedDRA High Level Group Term of 'Fractures'. In addition, all fractures and bone associated events are listed, along with information regarding use of the anti-hormonal agents abiraterone plus prednisone/prednisolone, enzalutamide, or use of other anti-androgens, and timing with respect to radium-223 use.

Further details are given in the SAP.

9.10 Statistical methods

9.10.1 Main summary measures

Continuous variables are described by sample statistics (i.e. mean, standard deviation, minimum, median and maximum) and as change from baseline per analysis time point, if applicable. Categorical variables are described with frequency tables displaying the actual number of patients in a category as well as percentages. The number of patients with missing data is presented as a separate category. Percentages are calculated based on missing and non-missing values.

9.10.2 Main statistical methods

The statistical evaluation was performed using software package SAS release 9.4 (SAS Institute Inc., Cary, NC, USA), except when noted otherwise.

The statistical analysis was explorative.

The analyses of pain related endpoints were done according to opioid use (yes vs. no). If the change of pain (worst pain, least pain, average pain and current pain, respectively) differed between patients with and without opioid use, the difference was investigated using Wilcoxon-Mann-Whitney test.

Two univariate logistic regression analyses were performed. First univariate logistic regression was performed for the dependent variable pain response with the categories “pain response” and “no pain response”. The independent covariates used for the analysis included:

- Opioid used at baseline (Yes, No)
- Number of known bone metastases at baseline (<6, 6-20, >20, superscan)
- Location of bone metastases at baseline (Corresponding to the number of various locations, groupings might be done)
- Level of alkaline phosphatase at baseline (<150mU/l, 150-300 mU/l, and >300 mU/l)
- PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
- WHO pain score at baseline (WHO-Score 0+1 and WHO-Score 2+3)
- Pretreatment with chemotherapy (yes/no)
- Pretreatment with deep androgen ablation (2nd generation AR pathway inhibitors) by treatment with abiraterone or enzalutamide (yes/no)
- Highest extent of bone uptake in known lesions at baseline (only faint, higher uptake, and strong uptake compared to surrounding bone)

Afterwards, all independent covariates, mentioned above, were entered into a stepwise multivariate logistic regression for the dependent variable. The entry level was p=0.5 and the stay level p=0.1. All covariates being still significant were considered as associated to pain response.

Second univariate logistic regression was performed for the dependent variable number of injections with the categories “1-4 injections” and “5-6 injections”. The independent covariates used for the analysis included:

- Opioid use at baseline (Yes, No)

- Assessment of extent of bone metastases at baseline (<6, 6-20, > 20, superscan)
- Level of alkaline phosphatase at baseline (<150 mU/l, 150-300 mU/l, and >300 mU/l)
- PSA level at baseline (<50 µg/l, 50-200 µg/l, and >200 µg/l)
- Pretreatment with chemotherapy (yes/no)
- Pretreatment with deep androgen ablation (by treatment with abiraterone or enzalutamide) and BHAs (yes/no)
- Concomitant treatment with deep androgen ablation BHAs (yes/no)

Afterwards, all independent covariates, mentioned above, were entered into a stepwise multivariate logistic regression for the above mentioned dependent variable. The entry level was p=0.5 and the stay level p=0.1. All covariates being still significant were considered as associated to higher number of injections

9.10.3 Missing values

Missing values were not imputed or carried forward unless otherwise specified in the relevant section. Missing data regarding questionnaires were handled according to the corresponding manuals for the specific questionnaires. Partially missing dates were handled as described below. The imputation was done for date of initial diagnosis, date of first/most recent progression, opioids, adverse events and date of castration resistance.

Partially missing start date

Partially missing start dates were set to the earliest logically possible date:

- In case that only the day was missing, the date was imputed as the first day of the month.
- In case that the day and the month were missing, i.e. only the year was available, the day and month were imputed by January 1st or date of initial visit, whichever came later.
- In the cases where the start date was missing completely, the start date was replaced with the minimum of date of initial visit and the stop date.

Partially missing stop date

Partially missing stop dates were set to the latest logically possible date:

- In case that only the day was missing, the date was imputed as minimum of date of death, date of last contact and day of incomplete date replaced by last day of the month;
- In case that the day and the month were missing, i.e. only the year was available, the date was imputed as the minimum of date of death, date of last contact and day and month of incomplete date replaced by December 31st.
- In case that the stop date was missing completely the date was imputed as the minimum of date of death and date of last contact.

In addition, all stop dates imputed after date of death were set to date of death. For partial documented death dates (i.e. day was missing), the missing day was imputed by day 15. If date of last contact was after imputed death date, the date of last contact was used.

9.10.4 Sensitivity analyses

Sensitivity analysis was done for evaluation of BPI-SF and FACT-BP questionnaires. In this context, all questionnaires between two visits were pooled and the mean value per patient was used for calculations of changes from baseline for continuous outcomes.

9.10.5 Amendments to the statistical analysis plan

SAP (version 3.0, dated 06 JUL 2020) was finalized before data base lock. There were no amendments to the SAP after database lock.

9.11 Quality control

9.11.1 Data quality

Before study start at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations and understood the study protocol and the CRF.

Alcedis GmbH (CRO) was assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates were recorded in a standardized CRF. After data entry, missing or implausible data were queried and the data was validated. A check for multiple documented patients was performed.

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

Medical Review of the data was performed according to the Medical Review Plan (MRP). 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. Detailed information on the Medical review are described in the MRP, which is available upon request (see Annex 1: List of stand-alone documents).

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (eCRF) was validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA)(39). The documentation is available upon request.

9.11.2 Quality review

During on-site data reviews, data of a total of 150 patients were reviewed at 23 study sites. The purpose was to review a selection of the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors accessed medical records on site for data verification. Detailed measures for quality reviews are described in the Quality Review Plan available upon request.

9.11.3 Storage of records and archiving

The sponsor ensures that all relevant documents of this study including CRFs and other patient records will be stored after end or discontinuation of the study for at least 15 years. Other instructions for storage of medical records remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to also store documents for a retention period of at least 15 years.

Statistical programming performed to generate results will be stored at the sponsor's site for at least 15 years.

10. Results

10.1 Participants

10.1.1 Patient disposition

Three hundred fifty eight patients were enrolled into the study (excluded are two patients who withdrew informed consent and refused further use of data) at 27 study sites (Table 5). The maximal number of enrolled patients was 60 in one study site. Two patients withdrew informed consent and refused further use of their data (see Annex 1: List of stand-alone documents). The data of these patients were deleted from study database and were not included in any analysis set according to patients wish. Further, two patients did not receive Radium-223, therefore, 356 patients were available for safety analysis (SAF set). One patient in SAF violated IC 01 and another patient violated EC 01 (Table 5). Therefore, 354 patients were included in the full analysis set (FAS). Two hundred sixteen patients had data required for Pain response analysis, 274 for BPI-SF analysis and 271 patients had data for FACT-BP analysis. Time to first opioid use could be assessed in 238 patients. Most of the patients (n=214, 60.1% of 358 patients included in the study database) received all six recommended injections of Radium-223. Among the remaining patients, the most frequent reasons for premature termination of treatment were AE (n=43, 12.1%), progression of underlying disease (n=36, 10.1%), patient's decision (n=27, 7.6%) and death (n=22, 6.2%, Table 5). Twelve patients signed additional informed consent for follow-up period up to 5 years after end of treatment.

Table 5: Patient disposition

Disposition	N	%
Number of enrolled patients*	358	100.00
Number of patients valid for SAF	356	99.44
Patients without dose of Radium-223	2	0.56
Number of patients valid for FAS	354	98.88
Violation of IC 01	1	0.28
Violation of EC 01	1	0.28
Number of patients valid for QoL-Set- Pain-response	216	60.34
Number of patients valid for QoL-Set- BPI-SF	274	76.54
Number of patients valid for QoL-Set- FACT-BP	271	75.70
Number of patients valid for Time to first opioid use	238	66.48
Patients with documentation of end of treatment**	355	99.72
Patient completed the regular treatment with Radium-223	214	60.11
End of treatment due to death	22	6.18
End of treatment due to lost to follow-up	1	0.28
End of treatment due to patient's decision	27	7.58
End of treatment due to progression of underlying disease	36	10.11
End of treatment due to non AE-related medical reasons (physician decision)	6	1.69
End of treatment due to Adverse Event	43	12.08
End of treatment due to other reason	6	1.69
Patients with additional signed informed consent for follow-up period up to 5 years after end of treatment	12	3.37

*excluded are two patients who withdrew informed consent and refused further use of data

**One patient in SAF with missing documentation of the end of treatment violated the exclusion criterion.

Source: Table 1 (modified), TLF v6.0

10.1.2 Population Characteristics, treatment data and end of observation

Median age at registration was PPD (range PPD Table 6). Mean height was 176 cm (SD=6.5), mean weight was 85.4 kg (SD=16) and mean BMI was 27.3 kg/m² (SD=4.3). Almost all patients were PPD ECOG performance status (PS) was 1 in the majority of patients at each study visit, followed by patients with PS 2 and PS 0. Median ALP level at baseline was 133 U/l (range: 29.8-1129) and median PSA level was 58 µg/l (range: 0-2130). Docetaxel was most often received prior anticancer therapy (n=119, 33.6%), followed by Bicalutamide (n=103, 29.1%), Abiraterone (n=83, 23.5%), Enzalutamide (n=51, 14.4%), and Cabazitaxel (n=29, 8.2%). At baseline, most patients had >20 metastatic lesions (but not a superscan, 37.6%), followed by those with 6-20 metastatic lesions (36.1%), and superscan (15.5%).

Table 6: Age, ECOG PS, serum marker levels, prior anti-cancer therapy and extent of disease at registration (FAS)

Characteristic	Total (n=354)
Median Age, years (range)	PPD
ECOG PS, n (%)	
0	56 (15.8)
1	204 (57.6)
2	61 (17.2)
3-4	27 (7.6)
Missing	6 (1.7)
Median serum marker levels (range)	
ALP [U/l]	133 (29.8-1129)
PSA [µg/l]	58 (0-2130)
Prior anticancer therapy, n (%)[#]	
Abiraterone	83 (23.5)
Cabazitaxel	29 (8.2)
Docetaxel	119 (33.6)
Enzalutamide	51 (14.4)
Anti-Androgens	1 (0.3)
Bicalutamide	103 (29.1)
Flutamide	12 (3.4)
Extent of disease	n=335
Normal or abnormal because of benign bone disease*	5 (1.5)
<6 metastatic sites	45 (13.4)
6-20 metastatic sites	121 (36.1)
>20 metastatic lesions but not a superscan	126 (37.6)
Superscan	52 (15.5)

[#]Prior therapy defined as therapy that started and ended before the start of Radium-223

*In addition to EOD 0 the existence of bone metastases are documented for these patients

Source: Table 4, 19, 153, 24, 35(modified), TLF v6.0

Median time from diagnosis to baseline visit was 54.9 months (range: 1.9-321.1). Median time from diagnosis of bone metastases to baseline visit was 27.7 months (range: 0-243.2). On median, time from diagnosis of castration resistance to baseline visit was 10.1 months (range 0-155.3). Gleason score at initial diagnosis was most often 9 (n=105, 29.7%), 7 (n=78, 22%) or 8 (n=56, 15.8%); Gleason score was unknown for 23.7% of patients (n=84). Patients were most frequently diagnosed

with stage IV (n=130, 36.7%) or stage III prostate cancer (n=56, 15.8%); cancer stage was unknown for 37% of patients (n=131). At study entry, tumor was not resected in most patients (n=199, 56.2%). In the remaining patients, tumor was most often completely resected with all margins histologically negative (n=63, 17.8%) or it was resected, however, the status of residual tumor was unknown (n=44, 12.4%). Most of the patients had disease progression or relapse (n=341, 96.3%). Median time from first progression to initiation visit was 24.7 months (range: 0.3-243.2) and median time from the most recent progression to initiation visit was 2.3 months (range: 0.0-155.3). On median, the cancer became castration resistant 10.1 months (range: 0.0-155.3) before the initiation visit.

Apart from mCRPC, 232 patients (65.5%) had prior medical findings, most often Hypertension (22.3%) or Essential hypertension (17.2%), Coronary artery disease (8.8%), Atrial fibrillation (6.8%), Diabetes mellitus and Type 2 diabetes mellitus (5.9%, both) and Myocardial ischemia (5.7%, see Table 17, TLF v6.0).

At each study visit, most of the patients had no pain or WHO pain score 1 (mild pain, Table 7). From baseline to visit 6, the percentage of patients with pain score 1 increased from 68.6% to 75.6%, whereas percentage of patients with higher pain scores decreased (from 20.9% to 16.4% for Score 2, moderate, and from 10.5% to 8% for Step 3, severe pain). At follow-up visit, percentage of patients with pain score 1 was 68.1%, with Score 2 was 19.4%, and with Score 3 was 12.5%.

Table 7: Step of the WHO pain score (FAS)

WHO pain score		N	%
Baseline visit	No pain/Step 1	243	68.64
	Step 2	74	20.90
	Step 3	37	10.45
	Number of patients	354	100.00
Treatment visit 2	No pain/Step 1	250	74.18
	Step 2	56	16.62
	Step 3	31	9.20
	Number of patients	337	100.00
Treatment visit 3	No pain/Step 1	227	73.94
	Step 2	58	18.89
	Step 3	22	7.17
	Number of patients	307	100.00
Treatment visit 4	No pain/Step 1	203	73.82
	Step 2	50	18.18
	Step 3	22	8.00
	Number of patients	275	100.00
Treatment visit 5	No pain/Step 1	180	76.27
	Step 2	41	17.37
	Step 3	15	6.36
	Number of patients	236	100.00
Treatment visit 6	No pain/Step 1	161	75.59
	Step 2	35	16.43
	Step 3	17	7.98
	Number of patients	213	100.00
Follow-up visit	No pain/Step 1	158	68.10
	Step 2	45	19.40
	Step 3	29	12.50
	Number of patients	232	100.00

Source: Table 18, TLF v6.0

The median follow-up, covering the Radium-223 treatment, follow-up after end of treatment and long-term follow-up, amounted to 319.5 days. During that entire follow-up period, 31 patients (8.8%) had any new EBRT to relieve skeletal symptoms (bone pain), 26 patients (7.3%) experienced any new symptomatic pathological bone fractures (vertebral or non-vertebral), 8 patients (2.3%) had any tumor-related orthopedic surgical intervention and 10 patients (2.8%) experienced any spinal cord compression (Table 8). Patients with prior abiraterone therapy (i.e. the therapy that started and ended before first Radium-223 dose) more often than those without pretreatment received any new EBRT (13.3% vs 7.4%) and experienced any spinal cord compression (4.8% vs 2.2%), however, there were no relevant differences in the percentage of patients with any new symptomatic

pathological bone fractures or tumor-related orthopedic surgical interventions (see Table 20C, TLF v6.0). Pretreatment with enzalutamide, and concomitant therapy (i.e. the therapy that overlapped with Radium-223 treatment) with abiraterone or enzalutamide had no impact on frequency of any type of SSE (see Table 20D, Table 20E and Table 20F, TLF v6.0).

During Radium-223 treatment, 15 patients (4.2%) had new symptomatic pathological fractures, 18 patients (5.1%) had a new EBRT to relieve skeletal symptoms due to bone pain, 3 patients (0.9%) had a tumor-related orthopedic surgical intervention and 6 patients had spinal cord compression (1.7%, Table 9). During the follow-up after end of treatment, new symptomatic pathological bone fractures occurred in 8 patients (3.5%), new EBRT to relieve skeletal symptoms was received by 3 (1.3%), tumor-related orthopedic surgical intervention was performed in one patient (0.4%) and spinal cord compression occurred in 2 patients (0.9%). During the long-term follow-up, 6 patients (2.9%) experienced any new symptomatic pathological bone fractures, 11 (5.3%) received any new EBRT to relieve skeletal symptoms, 4 patients (1.9%) underwent any tumor-related orthopedic surgical intervention and 2 patients (1%) experienced any spinal cord compression.

Table 8: Symptomatic skeletal events cumulative (during Radium-223 treatment, follow-up after end of treatment and long-term follow-up, multiple answers possible) (FAS)

Symptomatic skeletal events	N	%
Patient received any new external beam radiation therapy to relieve skeletal symptoms (bone pain)	31	8.76
Patient experienced any new symptomatic pathological bone fractures (vertebral or non-vertebral)	26	7.34
Patient undergone any tumor-related orthopedic surgical intervention	8	2.26
Patient experienced any spinal cord compression	10	2.82
Number of patients	354	100.00

Source: Table 20B, TLF v6.0

Table 9: Symptomatic skeletal events (multiple answers possible) (FAS)

	Symptomatic skeletal events	N	%
During Radium-223 treatment	Patient received any new external beam radiation therapy to relieve skeletal symptoms (bone pain)	18	5.08
	Patient experienced any new symptomatic pathological bone fractures (vertebral or non-vertebral)	15	4.24
	Patient undergone any tumor-related orthopedic surgical intervention	3	0.85
	Patient experienced any spinal cord compression	6	1.69
	Number of patients	354	100.0
Follow-up after end of treatment	Patient received any new external beam radiation therapy to relieve skeletal symptoms (bone pain)	3	1.29
	Patient experienced any new symptomatic pathological bone fractures (vertebral or non-vertebral)	8	3.45
	Patient undergone any tumor-related orthopedic surgical intervention	1	0.43
	Patient experienced any spinal cord compression	2	0.86
	Number of patients	232	100.0
During long-term follow-up	Patient received any new external beam radiation therapy to relieve skeletal symptoms (bone pain)	11	5.29
	Patient experienced any new symptomatic pathological bone fractures (vertebral or non-vertebral)	6	2.88
	Patient undergone any tumor-related orthopedic surgical intervention	4	1.92
	Patient experienced any spinal cord compression	2	0.96
	Number of patients	208	100.0

Note 1: SSEs during treatment include the SSEs that started up to 30 days since last Ra-223 injection; SSEs during follow-up after end of treatment include those that started more than 30 days but within 90 days after last Ra-223 injection; SSEs during long-term follow-up include those that started more than 90 days after last Ra-223 injection.

Note 2: Only the first spinal cord compression was counted for each patient. Other SSEs were assigned in each time frame.

Note 3: Table is patient based.

Source: Table 20, TLF v6.0

After baseline, symptomatic skeletal event (SSE) occurred in 52 patients (14.7%, see Table 129, TLF v6.0). EBRT for relief of skeletal symptoms was used in 31 patients (8.8%), 26 patients had a new symptomatic pathological bone fracture (7.3%), 8 patients (2.3%) had a tumor-related orthopedic surgical intervention and 10 patients (2.8%) had a spinal cord compression (Table 10). Frequency of SSE was also analyzed in 83 patients with and in 271 patients without prior abiraterone treatment (Table 10) and in 51 patients with and 303 patients without prior enzalutamide treatment (Table 11). Compared to patients without pretreatment, those pretreated with abiraterone

more often had EBRT for relief of skeletal symptoms (13.3% vs 7.4%) and Spinal cord compression 4.8% vs 2.2%). Rate of new symptomatic pathological bone fractures (7.2% and 7.4%) and of tumor-related orthopedic surgical intervention (2.4% and 2.2%) was similar in those with and without abiraterone pretreatment. Patients with and without enzalutamide pretreatment had a similar rates of EBRT for relief of skeletal symptoms (9.8% and 8.6%), new symptomatic bone fractures (5.9% and 7.6%), tumor-related orthopedic surgical intervention (2% and 2.3%) and spinal cord compression (3.9% and 2.6%).

Table 10: First post-baseline symptomatic skeletal event (SSE) (FAS) – by pretreatment with Abiraterone

Pre-, concomitant and post-treatments	Patients with pretreatment with Abiraterone		Patients without pretreatment with Abiraterone		Total	
	N	%	N	%	N	%
External radiotherapy for relief of skeletal symptoms	11	13.25	20	7.38	31	8.76
New symptomatic pathological bone fracture	6	7.23	20	7.38	26	7.34
Tumor-related orthopedic surgical intervention	2	2.41	6	2.21	8	2.26
Spinal cord compression	4	4.82	6	2.21	10	2.82
Number of patients	83	100.00	271	100.00	354	100.00

Source: Table 20C, TLF v6.0

Table 11: First post-baseline symptomatic skeletal event (SSE) (FAS) – by pretreatment with Enzalutamide

Pre-, concomitant and post-treatments	Patients with pretreatment with Enzalutamide		Patients without pretreatment with Enzalutamide		Total	
	N	%	N	%	N	%
External radiotherapy for relief of skeletal symptoms	5	9.80	26	8.58	31	8.76
New symptomatic pathological bone fracture	3	5.88	23	7.59	26	7.34
Tumor-related orthopedic surgical intervention	1	1.96	7	2.31	8	2.26
Spinal cord compression	2	3.92	8	2.64	10	2.82
Number of patients	51	100.00	303	100.00	354	100.00

Source: Table 20D, TLF v6.0

10.1.3 Concomitant medication

Forty-four patients (12.4%) received at least one medication due to AE, most often Metamizole or Ibuprofen (n=7, 2%, both), Dexamethasone (n=6, 1.7%) and Iron or Diclofenac (n=5, 1.4%, both, see Table 21, TLF v6.0).

Two hundred ninety-two patients (82.5%) received at least one medication due to concomitant disease, most often Denosumab or Zoledronic Acid (n=118, 33.3%, both), Acetylsalicylic Acid (n=49, 13.8%), Ramipril (n=44, 12.4%), Metoprolol (n=39, 11%) and Bisoprolol (n=38, 10.7%, see Table 22, TLF v6.0). Twenty five patients (7.1%) used medications containing calcium (Calcium, Calcium Carbonate, Colecalciferol).

Two hundred fifty patients (70.6%) received at least one other medication or a medication with missing indication and not including opioids or anti-cancer-therapy, most often Metamizole (n=124, 35%), Ibuprofen (n=104, 29.4%), Pantoprazole (n=43, 12.2%) and Diclofenac (n=39, 11%, see Table 23, TLF v6.0). Sixty-five patients (18.4%) used calcium-containing medication (Calcium, Calcium Carbonate, colecalciferol, Calcium Gluconate, Calcium Saccharate).

10.1.4 Pre-, concomitant and post-treatments

Figure 2 demonstrates the definitions of (A) prior treatment, (B) prior and concomitant treatment, (C) prior, concomitant and posttreatment, (D) concomitant treatment, (E) concomitant and posttreatment, and (F) posttreatment.

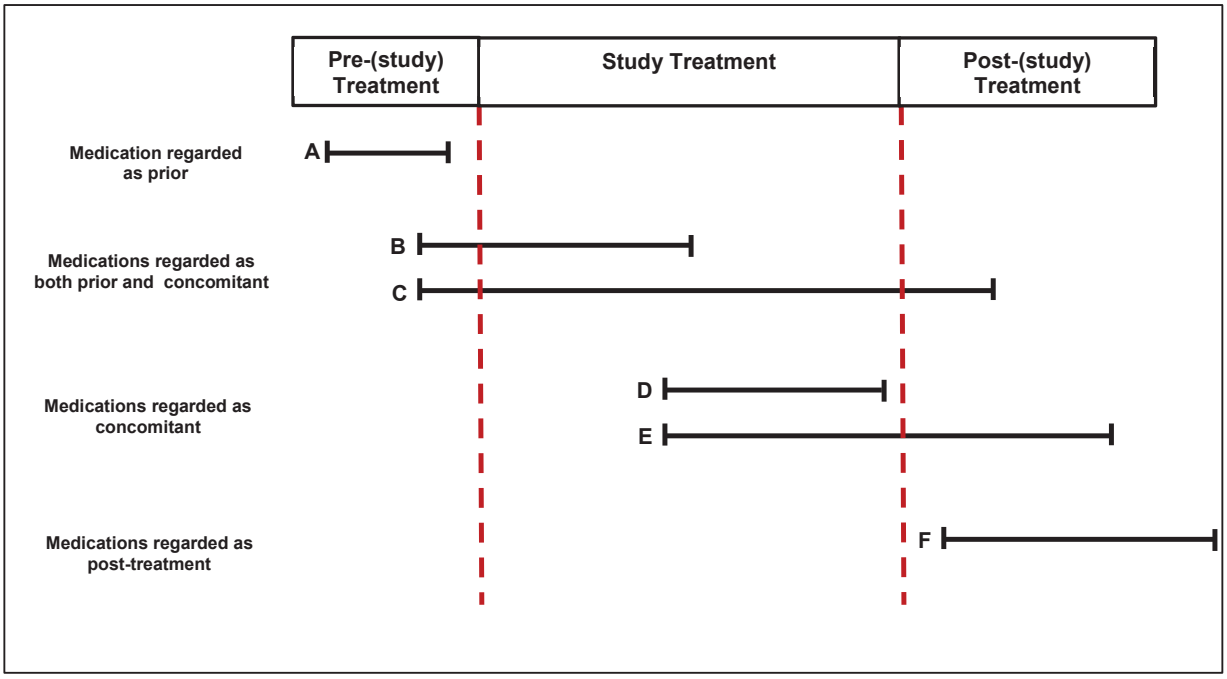

Figure 2: Definition of treatment periods

Source: Figure 0, TLF v6.0

At least one prior systemic anti-cancer treatment (group A) was received by 219 patients (61.9%), most often Docetaxel (n=119, 33.6%), followed by Bicalutamide (n=103, 29.1%), Abiraterone

(n=83, 23.5%), Enzalutamide (n=51, 14.4%), Cabazitaxel (n=29, n=8.2), Flutamide (n=12, 3.4%) and Anti-Androgens (n=1, 0.3%, see Table 24, TLF v6.0). 45 patients (12.7%) receive at least one prior treatments with BHA, including Bisphosphonates (n=29, 8.2%) and Denosumab (n=19, 5.4%, see Table 24B, TLF v6.0).

At least one prior and concomitant systemic anti-cancer treatment (group B) was received by 27 patients (7.6%), including Abiraterone (n=14, 4%), Enzalutamide (n=9, 2.5%), Bicalutamide (n=5, 1.4%), Docetaxel (n=2, 0.6%, see table 25, TLF v6.0). 14 patients (4%) received at least one prior and concomitant BHA treatment, including Bisphosphonates (n=9, 2.5%) and Denosumab (n=5, 1.4%, see table 25B, TLF v6.0).

Two patients received concomitant (group D) Abiraterone and Enzalutamide (n=1, 0.3%, each. see Table 26, TLF v6.0). Two patients (0.6%) received Denosumab during Radium-223 therapy (see Table 26B, TLF v6.0).

155 patients (43.8%) received at least one systemic anti-cancer therapy prior, concomitant and post-Radium-233 treatment (group C), most often Abiraterone (n=64, 18.1%), Enzalutamide (n=55, 15.5%), Bicalutamide (n=50, 14.1%), Flutamide (n=3, 0.9%), Docetaxel (n=1, 0.3%, see Table 27, TLF v6.0). 163 patients (46.1%) received at least one BHA therapy prior, concomitant and post-Radium-223 treatment, including Denosumab (n=86, 24.3%) and Bisphosphonates (n=81, 22.9%, see Table 27B, TLF v6.0).

At least one systemic anti-cancer therapy during and after Radium-233 treatment (group E) was received by 16 patients (4.5%), most often Enzalutamide (n=10, 2.8%), Abiraterone (n=3, 0.9%), Docetaxel (n=2, 0.6%), Bicalutamide (n=1, 0.3%, see Table 28, TLF v6.0). 10 patients (2.8%) received at least one BHA therapy during and post-Radium-223 treatment, including Bisphosphonates (n=6, 1.7%) and Denosumab (n=4, 1.1%, see Table 28B, TLF v6.0).

Systemic anti-cancer therapy after Radium-223 (group F) was administered to 82 patients (23.2%), most often Enzalutamide (n=36, 10.2%), Abiraterone (n=32, 9%), Docetaxel (n=25, 7.1%), Cabazitaxel (n=18, 5.1%), Bicalutamide (n=2, 0.6%, see Table 29, TLF v6.0). Ten patients (2.8%) received at least one BHA therapy after Radium-223 treatment, including Bisphosphonates (n=7, 2%) and Denosumab (n=3, 0.9%, see Table 29B, TLF v6.0).

10.1.5 Opioids use

Prior or at baseline, at least one opioid use was documented in 116 (32.8%) of patients, most frequently, Hydromorphone (n=44, 12.4%), Naloxone;tilidine (n=28, 7.9%) and Fentanyl (n=18, 5.1%, Table 30, TLF v6.0). After baseline, 95 patients (26.9%) used at least one type of opioid, most often Hydromorphone (n=51, 14.4%) and Fentanyl (n=30, 8.5%, Table 31, TLF v6.0).

At baseline, opioid use according to WHO ladder was No opioids/Step I in 71.2% of patients, followed by Step III in 19.8% and Step II in 9% (Table 12). Use of opioids remained stable throughout the Radium-223 therapy. At follow-up after end of treatment, the proportion of patients with Step III opioid use was increased relatively to baseline (22.9%) and then decreased towards long-term follow up visit 2 (19%). From end of treatment to long-term follow-up visit 2, the proportion of patients with Step II slightly decreased (from 9% to 7.6%), whereas the proportion of patients with No opioid / Step I slightly increased (from 71.2% to 73.4%). The percentage of patients with no opioid / Step I, Step II and Step III was 65.9%, 9.1% and 25%, respectively, at the time of death and 71.2%, 9% and 19.8%, respectively, at the end of study.

Table 12: Change from baseline in opioid use according to WHO ladder (FAS)

	Before/at Baseline					
	No opioid / Step I		Step II		Step III	
	N	%	N	%	N	%
Baseline visit	252	71.19	32	9.04	70	19.77
Treatment visit 2	238	70.62	32	9.50	67	19.88
Treatment visit 3	217	70.68	28	9.12	62	20.20
Treatment visit 4	197	71.64	24	8.73	54	19.64
Treatment visit 5	169	71.61	20	8.47	47	19.92
Treatment visit 6	155	72.77	16	7.51	42	19.72
End of treatment	252	71.19	32	9.04	70	19.77
Follow-up visit after end of treatment	49	70	5	7.14	16	22.86
Long-term follow-up visit 1	150	72.12	14	6.73	44	21.15
Long-term follow-up visit 2	116	73.42	12	7.59	30	18.99
Date of death	116	65.91	16	9.09	44	25
End of study	252	71.19	32	9.04	70	19.77

Source: Table 32, TLF v6.0

10.1.6 General assessments- Bone scan during observation

335 patients (94.6%) had a bone scan prior to Radium-223 treatment, whereas 141 patients (39.8%) had a bone scan during the observation period (time between the first Radium-223 treatment and day 42 after the last dose of Radium-223). Technetium-99m scintigraphy was most commonly used method for bone scan (used in over 99% of patients prior treatment and during the observation period).

Prior to Radium-223 treatment, extent of disease (EOD) in most of the patients was 3 (>20 metastatic lesions but not a superscan, 37.6%), followed by EOD 2 (6-20 metastatic lesions, 36.1%), superscan (15.5%), EOD 1 (<6 metastatic lesions, 13.4%). Five patients (1.5%) prior to Radium-233 treatment had EOD 0, however, metastatic bone lesions were documented for these patients. During or within 6 weeks after end of Radium-223 treatment, most of the patients had EOD 3 (45.4%), followed by EOD 2 (35.5%), superscan (14.9%), EOD 1 (11.4%) and EOD 0 (1.4%). The maximum EOD during therapy for most of the patients was 3 (45.4%), followed by EOD 2 (30.5%), superscan (14.9%), EOD 1 (8.5%) and EOD 0 (0.7%). In the majority of patients (75%), maximum EOD did not change from baseline, in 21.1% it was higher than at baseline, and in 3.9% of patients it was lower than at baseline. Prior to the Radium-223 treatment and during observation period, bone scan-detected at least one lesion most often in Thoracic vertebra (70.8% and 73.8%); Lumbar vertebra (64.2% and 70.9%); Ribs, left (56.1% and 62.4%); Pelvis, left (57% and 61.7%); Pelvis, right (55.8% and 60.3%); Ribs, right (56.1% and 58.9%); Sacrum and coccyx (43.3% and 48.9%); Sternum (35.2% and 41.8%); Thigh, right (35.8% and 40.4%); Shoulder, right (29.9% and 34.8%); Thigh, left (37.3% and 31.9%); Skull (29.6% and 31.9%, respectively, Table 13).

Table 13: Bone scan- Bone uptake- Body region where at least one lesion was documented (multiple answers possible) (FAS)

Bone scan- Bone uptake- Body region where at least one lesion was documented	Prior to Ra-223 treatment bone scan		Bone scan during observation	
	N	%	N	%
Skull	99	29.55	45	31.91
Sternum	118	35.22	59	41.84
Clavicle, right	22	6.57	16	11.35
Clavicle, left	26	7.76	17	12.06
Shoulder, right	100	29.85	49	34.75
Shoulder, left	80	23.88	38	26.95
Upper arm, right	86	25.67	41	29.08
Upper arm, left	63	18.81	36	25.53
Forearm, right	4	1.19	1	0.71
Forearm, left	1	0.30	1	0.71
Ribs, right	188	56.12	83	58.87
Ribs, left	188	56.12	88	62.41
Pelvis, right	187	55.82	85	60.28
Pelvis, left	191	57.01	87	61.70
Cervical vertebra	94	28.06	42	29.79
Thoracic vertebra	237	70.75	104	73.76
Lumbar vertebra	215	64.18	100	70.92
Sacrum and coccyx	145	43.28	69	48.94
Thigh, right	120	35.82	57	40.43
Thigh, left	125	37.31	45	31.91
Lower leg, right	8	2.39	2	1.42
Lower leg, left	9	2.69	2	1.42
Hand, right	4	1.19	1	0.71
Hand, left	4	1.19	1	0.71
Foot, right	5	1.49		
Foot, left	4	1.19		
Patients with bone scan	335	100.00	141	100.00

Note: Prior to Ra-223 treatment bone scans started prior to first treatment with Ra-223. Bone scan during observation started after first treatment up to 42 days after last treatment with Ra-223.

Source: Table 38, TLF v6.0

Prior to Radium-223 treatment and during observation, metastatic bone lesions were detected most often in Thoracic vertebra (in 237 and 104 patients); Lumbar vertebra (in 215 and 100 patients); Pelvis, left (in 191 and 87 patients); Ribs, left (in188 and 88 patients); Ribs, right (in 188 and 83 patients); Pelvis, right (in 187 and 85 patients); Sacrum and coccyx (in 145 and 69 patients); Thigh,

left (in 125 and 45 patients); Thigh, right (in 120 and 57 patients); Sternum (in 118 and 59 patients); Shoulder, right (in 100 and 49 patients); Skull (in 99 and 45 patients); Cervical vertebra (in 94 and 42 patients); Upper arm, right (in 86 and 41 patients); Shoulder, left (in 80 and 38 patients); and Upper arm, left (in 63 and 36 patients, respectively, see Table 39, TLF v6.0). More than three metastatic lesions were detected prior to Radium-233 treatment and during observation period in the following body areas which were positive for metastatic lesions in at least 35% of patients: Sternum (24.6% and 25.4%), Ribs, right (51.1% and 55.4%), Ribs, left (53.7% and 52.3%), Pelvis, right (49.7% and 47.1%), Pelvis, left (46.1% and 40.2%), Thoracic vertebra (62% and 65.4%), Lumbar vertebra (46.5% and 41%), Sacrum and coccyx (31.7% and 30.4%), Thigh, right (15% and 17.5%), Thigh, left 12.8% and 11.1%, respectively, see Table 39, TLF v6.0).

The highest uptake of a lesion prior to Radium-223 treatment was higher than surrounding bone in Skull (41.4% of patients); Sternum (40.7%); Shoulder, right (44%); Upper arm, right (51.2%); Upper arm, left (42.9%); Ribs, right (55.9%); Ribs, left (55.3%); Cervical vertebra (42.6%); Thoracic vertebra (46%); Lumbar vertebra (42.3%; Thigh, right (40.8%); Thigh, left (40%); and strong in Shoulder, left (40%); Pelvis, right (48.1%), Pelvis, left (48.2%); Sacrum and coccyx (45.5%, see Table 40, TLF v6.0).

During observation, the highest uptake of a lesion was higher than surrounding bone in Skull (46.7%); Sternum (57.6%); Shoulder, right (44.9%); Shoulder, left (52.6%); Upper arm, right (48.8%); Upper arm, left (41.7%); Ribs, left (51.1%); Pelvis, right (47.1%); Pelvis, left (43.7%); Thoracic vertebra (44.2%); Lumbar vertebra (43%); Sacrum and coccyx (43.5%); and strong in Ribs, right (20.5%); Cervical vertebra (16.7%); Thigh, right (22.8%); Thigh, left (15.6%).

10.1.7 General assessments- Radiotherapy during observation

Radiotherapy for prostate cancer was documented for 194 patients (54.8%) prior to Radium-223 therapy and in 11 patients (3.1%) during the Radium-223 treatment (time between the first Radium-223 treatment and day 42 after the last dose of Radium-223). Median number of radiotherapies was 1 prior to Radium-223 treatment (range: 1-5) and 1 during Radium-223 treatment (range: 1-2). Two patients (0.6%) underwent a radiotherapy (once, both) with indication other than prostate cancer during Radium-223 treatment.

Prior to Radium-223 treatment, regions most often irradiated with indication prostate cancer included Prostate (n=96, 49.5%), Vertebral column (n=72, 37.1%), Other (n=61, 31.4%) and Pelvis (n=59, 30.4%). Vertebral column was the most often irradiated region due to prostate cancer during Radium-223 treatment (n=7, 63.6%). Two patients with radiotherapy with indication other than prostate cancer received irradiation targeting Pelvic bone and Skull.

The intent of the radiotherapy prior to Radium-223 treatment was most frequently Palliative (n=117, 60.3%), followed by Curative (n=61, 31.4%) and Adjuvant (n=41, 21.1%). Radiotherapy concomitant to Radium-223 treatment was Palliative in all 11 patients with radiotherapy indication prostate cancer and in two patients with other indication. Type of radiotherapy due to prostate cancer that was received prior or during to Radium-223 therapy was most frequently EBRT (n=153, 78.9% and n=6, 54.6%, respectively), Intensity modulated radiation therapy (IMRT, n=18, 9.3% and n=4, 36.4%, respectively) and Stereotactic radiotherapy (n=16, 8.3% and n=1, 9.1%, respectively). Patients that received radiotherapy due to the reason other than prostate cancer received EBRT and Stereotactic radiotherapy. Median total cumulative dose of radiotherapy due to prostate cancer was 66.6 Gy (range: 8-291.6) prior to and 30 Gy (range: 30-72) during radium-223 treatment. One

patient with concomitant radiotherapy due to reason other than prostate cancer received 30 Gy (data were not available for the other patient). Median total dose of concomitant palliative radiotherapy was 30 Gy (range: 30-36) in five patients with Vertebral column irradiation, 35 Gy (range: 30-40) in two patients with Pelvic bone irradiation, and 33 Gy (range: 30-36) in two patients with irradiation of other region; two patients with skull irradiation received 30 Gy, both. Furthermore, in three patients with irradiation of Ribs, Sternum and Pelvis, total dose of concomitant palliative radiotherapy was 36 Gy (Ribs and Sternum, both) and 30 Gy (Pelvis).

10.1.8 General assessments- Systemic anti-cancer therapy for prostate cancer during observation

At least one systemic anti-cancer treatment (including specifically Abiraterone, Cabazitaxel, Docetaxel and Enzalutamide) was administered to 242 patients (68.4%) prior to Radium-223 therapy; these treatments were finished before the start or were continued during Radium-223 therapy (see Table 49, TLF v6.0). In these patients, the median number of prior systemic therapy regimens was 2 (range: 1-6). One hundred nineteen patients (33.6%) received one line of prior anticancer therapy, 65 patients (18.4) had two lines and 58 patients (16.4%) received more than two lines of prior anticancer therapy. Among all 354 patients in FAS, the median number of prior systemic therapy regimens was 1 (range: 0-6).

10.1.9 Diagnostic and therapeutic procedures for prostate cancer during observation

Two hundred twenty eight patients (64.4%) received at least one diagnostic or therapeutic procedure prior to Radium-223 treatment, most often Other (n=136 patients, 59.7%) or Prostatectomy (n=110 patients, 48.3%, see Table 51 and Table 52, TLF v6.0). Eighteen patients (5.1%) received at least one diagnostic or therapeutic procedure during Radium-223 treatment, most often Other (n=17 patients, 94.4%).

Median number of diagnostic or therapeutic procedures was 1 prior to (range: 1-13) and during Radium-223 therapy (range: 1-5, see Table 53, TLF v6.0). Diagnostic or therapeutic procedures were most often performed to the Prostate (n=208, 91.2%), Other (n=21, 9.2%) and Vertebral Column (n=13, 5.7%) prior to Radium-223 treatment, and to Other during the Radium-223 therapy (n=10, 55.6%, see Table 54, TLF v6.0). 100 patients (43.9%) and 11 patients (61.1%) had a diagnostic procedure for prostate cancer prior to and during Radium-223 therapy, respectively (see Table 55, TLF v6.0). Therapeutic procedures were performed in 91 patients (39.9%) prior to and in 6 patients (n=33.3%) during Radium-223 therapy. 56 patients (24.6%) had a diagnostic and therapeutic procedures prior to Radium-223 therapy. Diagnostic and therapeutic procedures were most often performed with Curative (n=121, 53.1%) or Unknown intent (n=72, 31.6%) prior to Radium-223 treatment and with Palliative (n=10, 55.6%) or Unknown intent during Radium-223 therapy (n=8, 44.4%, see Table 56, TLF v6.0).

10.1.10 Blood transfusions during observation

Twenty-five patients (7.1%) and 29 patients (8.2%) received a blood transfusion prior to or during Radium-223 therapy, respectively (see Table 57, TLF v6.0). Overall, median number of blood

transfusions prior to Radium-223 treatment was 1 (range: 1-6) prior to and 2 (range:1-5) during Radium-223 therapy (see Table 59, TLF v6.0). Packed red blood cells were most often used; anemia was the most frequent reason for the blood transfusion (see Table 58 and Table 60, TLF v6.0).

10.1.11 Long-term follow-up and end of observation

Phone contact, followed by on site visit and information from other treating physician were the most frequent types of contact during the long-term follow-up. The percentage of patients using opioids progressively decreased from 6.7% at long-term follow-up visit 1 to none at visit 15 (see Table 63, TLF v6.0). End of observation was initially defined as up to two years after the last administration of Radium-223 which was changed to five years with amendment 5. Among the patients participating in the study when amendment 5 became active, 12 patients provided written informed consent to prolonged study participation. Five out of these 12 patients were in the long-term follow-up at the time of premature termination of the study; the observation was terminated in these patients.

Reasons for the end of observation were patient died (n=176, 49.7%), patient lost to follow-up (n=64, 18.1%), other (n=53, 15%), regular end of study (n=44, 12.4%) and patient withdrew consent and allowed data-use (n=17, 4.8%) (Table 64, TLF v6.0).

10.2 Outcome data

216/354 patients in FAS (61%) had a baseline worst pain score >1 and were therefore included in the analysis of pain response, pain control rate, pain progression rate, time to first pain progression, description of covariates on pain response and evaluation of relationship between bone uptake in known lesions and pain reduction (QoL-Set- Pain-response set).

274/354 patients in FAS (77.4%) filled out BPI-SF questionnaire and were therefore included in the analysis of change in pain over time (QoL-Set- BPI-SF set).

271/354 patients in FAS (76.6%) filled out FACT-BP questionnaire and were therefore included in the analysis of bone pain related quality of life (QoL-Set- FACT-BP set).

Radium-223 treatment patterns, time to next tumor treatment(s), time to first symptomatic skeletal event, time from castration resistance to treatment with Radium-223, description of covariates on duration of treatment, overall survival, evaluation of BSI as Imaging Biomarker in mCRPC, Incidence rates and incidence proportions for (non-) pathological fractures and bone associated events and Course of blood count was analyzed in FAS (n=354 patients).

Time to first opioid use was analyzed in 238 patients who did not have prior or baseline use of opioid.

TEAE, serious TEAE and drug-related TEAE were analyzed in SAF (n=356 patients).

Pain response Change in pain over time pain control rate, pain progression rate time to first pain progression Time to next tumor treatment(s) Time to first symptomatic skeletal event Duration of Radium-223 therapy, overall survival Evaluation of Bone scan index as imaging biomarker in mCRPC were analyzed according to the number of Radium-223 injections (1-4 vs 5-6) and according to the concomitant BHA use (yes vs no).

Additionally analysis of bone fractures and bone associated events was analyzed according to the concomitant BHA use (yes vs no).

10.3 Main results

10.3.1 Primary endpoint

The primary objective of this study was to evaluate pain response during Radium-223 treatment. A clinically meaningful pain response is defined as an improvement of two points from the baseline in BPI-SF worst pain score at any post-baseline assessment. The primary endpoint was also analyzed by subgroups: number of Radium-223 injections (1-4 vs 5-6) and concomitant BHA use (yes vs no).

For all patients, rate of pain response monotonously increased from 31.73 (95%CI 25.47- 38.52, n=66/208) at visit 2 to 45.45 (95%CI 37.12-53.99, n=65/143) at visit 5 with no further improvement at visit 6; rate of pain response at follow-up after end of treatment was 42.03 (95%CI 30.24- 54.52, n=29/69, Table 14). Rate of pain response was comparable at visit 2 to 4 between patients with 1-4 and 5-6 Radium-223 injections (see Table 2, TLF v6.0 by injection number) and between patients with and without concomitant BHA use (see Table 2, TLF v6.0 by BHA use). Overall, the percentage of patients with at least one pain response during observation was 59.3% (95%CI 52.39- 65.88) and it was higher in patients with 5-6 injections (67.12%, 95%CI 58.87- 74.67) compared to those with 1-4 injections (42.86%, 95%CI 31.09- 55.25) and similar between those with concomitant BHA treatment (57.14%, 95%CI 47.75- 66.17) and patients without BHA treatment (61.86%, 95%CI 51.43- 71.53, Figure 3).

Table 14: Number of patients with pain response for each visit (QoL-Set-Pain Response)

Treatment Visit	*N*	*Number of patients with pain response*	*Rate*	*CI 95%*
Treatment, No. 02	208	66	31.73	25.47 - 38.52
Treatment, No. 03	189	75	39.68	32.66 - 47.04
Treatment, No. 04	167	67	40.12	32.62 - 47.97
Treatment, No. 05	143	65	45.45	37.12 - 53.99
Treatment, No. 06	126	57	45.24	36.36 - 54.35
Follow-up after end of treatment	69	29	42.03	30.24 - 54.52

Only patients with assessed questionnaires at respective timepoints were evaluated; missing pain responses were considered as no pain response

Source: Table 66, TLF v6.0

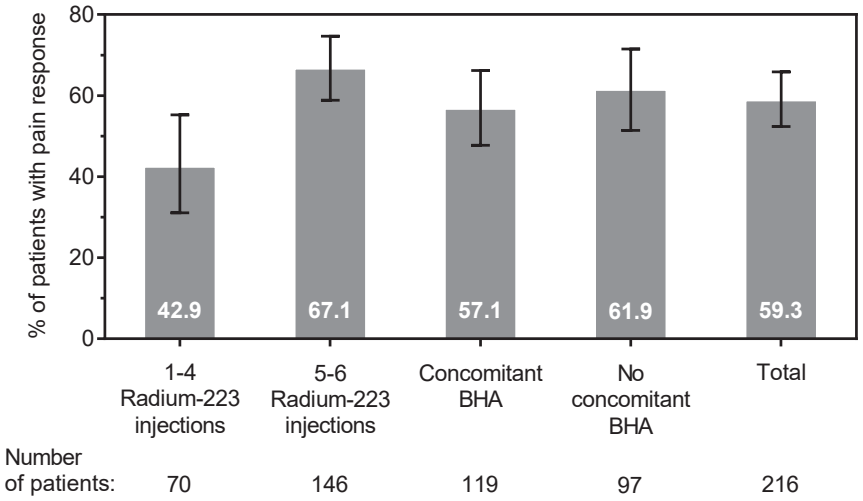

Figure 3: Number of patients with pain response by number of Radium-223 injections and by concomitant BHA use

Source: Table 3, TLF v6.0 by number of injections and TLF v6.0 by BHA use

For all patients, mean worst pain score decreased from 4 (SD 2.6) at baseline to 2.9 (SD 2.6) at visit 6; mean worst pain score at follow-up visit after treatment was 3.3 (SD 3.1, see Table 68, TLF v6.0,). Mean worst pain change from baseline for the total population was -0.5 (SD 2.1) at visit 2, -0.4 (SD 2.4) at visit 3, -0.4 (SD 2.7) at visit 4, -0.8 (SD 2.7) at visit 5, -0.6 (SD 3.1) at visit 6 and -0.1 (SD 3.3) at follow-up after treatment end (Table 15).

Table 15: BPI-SF- Worst pain- Changes from baseline (QoL-Set BPI-SF)

BPI-SF- Worst pain- Changes from baseline	N	Mean	SD	Median	Min	Max	NMiss
Treatment, No. 02	254	-0.46	2.10	0.00	-7.00	6.00	10
Treatment, No. 03	238	-0.42	2.36	0.00	-7.00	6.00	7
Treatment, No. 04	209	-0.36	2.70	0.00	-8.00	10.00	9
Treatment, No. 05	181	-0.81	2.70	0.00	-7.00	8.00	5
Treatment, No. 06	162	-0.64	3.05	0.00	-8.00	10.00	5
Follow-up after end of treatment	92	-0.08	3.28	0.00	-7.00	10.00	3

Source: Table 69, TLF v6.0

10.3.2 Secondary endpoints

10.3.2.1 Changes of pain over time

Overall, median change in BPI-SF questionnaire scores from baseline to follow-up after end of treatment amounted to 0 (range: -7, 10) for sub-component worst pain, 0 (range: -10, 10) for least pain, 0 (range: -7, 10) for Pain on average, 0 (range: -9, 10) for current pain, and -0.14 (range: -7.57, 7.14) for pain interference (see Table 69, Table 80, Table 83, Table 86, Table 90, TLF v6.0). The median changes was 0 also at the earlier time-points, with the exception of visit 5 for average pain (median -1, range: -7, 5) and visit 2 (median -0.14, range: -4.86, 6.29), visit 5 (median -0.14, range: -7, 6.29) and visit 6 (median -0.14, range: -7.86, 8.71) for pain interference. Analysis of change of pain over time between the patients with 1-4 and 5-6 injections and between patients with and without concomitant BHA use is shown in Table 5, Table 16, Table 19, Table 22, Table 26 in TLF v6.0 by number of injections and TLF v6.0 by BHA use.

Overall, the proportion of patients with more than everyday kind of pain decreased from 49.6% (n=136) a baseline to 37.9% (n=100) at visit 2, 39.2% (n=96) at visit 3, 37.6% (n=82) at visit 4, 40.9% (n=76) at visit 5, 34.7% (n=58) at visit 6 and 35.8% (n=34) at follow-up after end of treatment (see Table 76, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 12 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Among all patients, body areas that were indicated as hurting the most by ≥10% of patients at baseline included Thoracic vertebra in 11.7% of patients (n=32), Lumbar vertebra in 18.3% (n=50), Pelvis, left in 16.1% (n=44), Pelvis, right in 17.5% (n=48), Thigh, left in 11.3% (n=31) and Thigh, right in 14.6% (n=40, Figure 4, see Table 77, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 13 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). At follow-up visit after end of treatment, fewer patients indicated these areas as hurting most: Thoracic vertebra (4.2%, n=4), Lumbar vertebra (8.4%, n=8), Pelvis, left (8.4%, n=8), Pelvis, right (13.7%, n=13), Thigh, left (5.3%, n=5), and Thigh, right (6.3%, n=6).

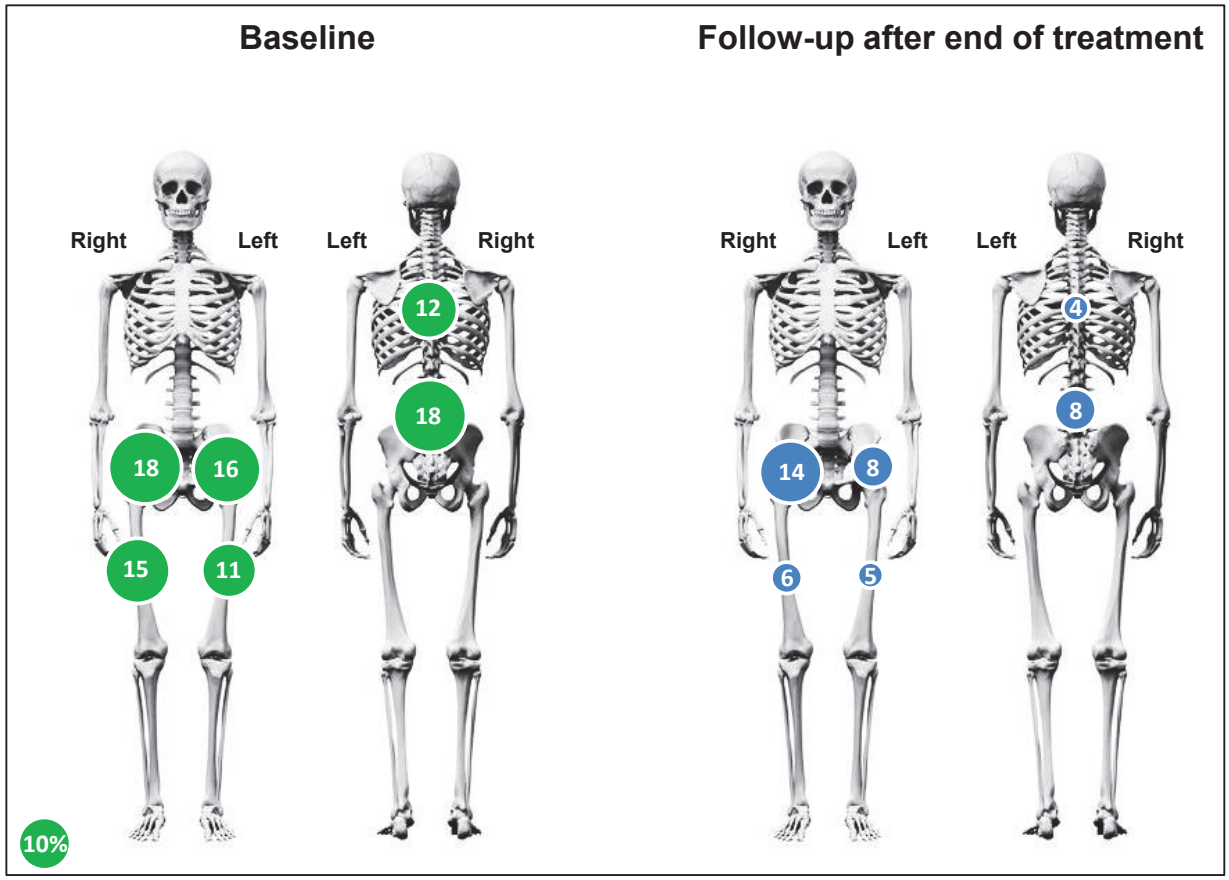

Figure 4: Area that hurts most at baseline and at follow-up after end of treatment among all patients (QoL-Set BPI-SF). Cut-off of ≥10% total at baseline. Patients may have reported pain in more than one area. Circles indicate the pelvis (left and right), thigh (left and right), thoracic vertebrae, and lumbar vertebrae. The size of each circle represents the percentage area that hurts the most at baseline and during observation. A 10% reference scale is shown.

Source: Table 77, TLF v6.0

The majority of patients had a least pain score 0-3 at each study visit: 83.6% at baseline, 81.8% at visit 2, 81.6% at visit 3, 82.6% at visit 4, 87.6% at visit 5, 89.2% at visit 6, and 81.1% at follow-up after end of treatment (see Table 78, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 14 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Overall, mean scores for Least pain decreased from 1.88 (SD=1.79) at baseline to 1.56 (SD=1.92) at visit 6; mean score at follow-up after end of treatments was 1.84 (SD=2.31). Mean score change from baseline amounted to -0.06 (SD=1.64) at visit 2, -0.01 (SD=1.69) at visit 3, -0.09 (SD=2.04) at visit 4, -0.26 (SD=1.94) at visit 5, -0.19 (SD=2.37) at visit 6, and 0.09 (SD=2.70) at follow-up after end of treatment (see Table 80, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 16 in TLF: TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Overall, mean scores for item Average pain decreased from 3.25 (SD=2.06 at baseline to 2.43 (SD=2.25) at visit 6; mean score at follow-up after end of treatments was 2.69 (SD=2.64). Mean score change from baseline amounted to -0.39 (SD=1.67) at visit 2, -0.32 (SD=1.73) at visit 3, -0.34 (SD=2.23) at visit 4, -0.66 (SD=2.20) at visit 5, -0.49 (SD=2.49) at visit 6, and -0.15 (SD=3.00) at follow-up after end of treatment (see Table 83, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 19 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Among all patients, mean scores for item Current pain decreased from 2.83 (SD=2.48) at baseline to 2.24 (SD=2.45) at visit 6; mean score at follow-up after end of treatments was 2.55 (SD=2.88). Mean score change from baseline amounted to -0.25 (SD=2.09) at visit 2, -0.27 (SD=2.24) at visit 3, -0.01 (SD=2.84) at visit 4, -0.41 (SD=2.78) at visit 5, -0.32 (SD=2.99) at visit 6, and 0.11 (SD=3.14) at follow-up after end of treatment (see Table 86, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 22 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Overall, mean scores for subscale Pain total decreased from 3.22 (SD=2.10) at baseline to 2.42 (SD=2.21) at visit 6; mean score at follow-up after end of treatments was 2.69 (SD=2.53, Table 16, for analysis according to injection number and according to concomitant BHA see Table 27 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). Mean score change from baseline amounted to -0.22 (SD=1.49) at visit 2, -0.19 (SD=1.57) at visit 3, -0.19 (SD=1.94) at visit 4, -0.38 (SD=2.08) at visit 5, -0.40 (SD=2.26) at visit 6, and -0.05 (SD=2.61) at follow-up after end of treatment (Table 17; for analysis according to injection number and according to concomitant BHA see Table 28 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Table 16: BPI-SF subscale – Pain total (QoL-Set- BPI-SF)

BPI-SF- Pain total	N	Mean	SD	Median	Min	Max	NMiss
Baseline and first treatment	255	3.22	2.10	3.09	0.00	8.18	19
Treatment, No. 02	243	3.03	2.15	2.91	0.00	9.09	21
Treatment, No. 03	228	2.99	2.09	2.82	0.00	8.36	17
Treatment, No. 04	202	2.82	2.19	2.45	0.00	9.18	16
Treatment, No. 05	177	2.62	2.16	2.18	0.00	8.73	9
Treatment, No. 06	159	2.42	2.21	1.91	0.00	9.82	8
Follow-up after end of treatment	92	2.69	2.53	1.95	0.00	10.00	3

Source: Table 91, TLF v6.0

Table 17: BPI-SF- Total score- Changes from baseline (QoL-Set- BPI-SF)

BPI-SF- Pain total- Change from baseline	N	Mean	SD	Median	Min	Max	NMiss
Treatment, No. 02	230	-0.22	1.49	-0.18	-3.94	5.73	34
Treatment, No. 03	215	-0.19	1.57	-0.09	-4.82	4.82	30
Treatment, No. 04	192	-0.19	1.94	-0.09	-6.18	5.86	26
Treatment, No. 05	166	-0.38	2.08	-0.23	-6.09	6.36	20
Treatment, No. 06	149	-0.40	2.26	-0.27	-6.55	9.18	18
Follow-up after end of treatment	87	-0.05	2.61	-0.18	-6.27	8.18	8

Source: Table 92, TLF v6.0

Among all patients, almost complete to complete pain relief due to medication (defined as 80–100% relief) was reported by n=49/274 (17.9%) at first visit, n=49/264 (18.6%) at visit 2, n=47/245 (19.2%) at visit 3, n=39/218 (17.9%) at visit 4, n=43/186 (23.1%) at visit 5, n=40/167 (24%) at visit 6, and n=15/95 (15.8%) at follow-up after end of treatment (see Table 93, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 29 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). Overall, mean scores for item Pain relief slightly increased from 46.97 (SD=32.45) at baseline to 48.19 (SD=34.95) at visit 6; mean score at follow-up after end of treatments was 41.34 (SD=37.05, see Table 94, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 30 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). Mean score change for item Pain relief from baseline amounted to 3.29 (SD=35.41) at visit 2, 0.68 (SD=35.13) at visit 3, 1.39 (SD=34.46) at visit 4, 9.01 (SD=37.98) at visit 5, 5.32 (SD=38.46) at visit 6, and 3.95 (SD=43.72) at follow-up after end of treatment (Table 18; for analysis according to injection number and according to concomitant BHA see Table 31 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Table 18: BPI-SF– Pain relief- Changes from baseline (QoL-Set-BPI-SF)

BPI-SF– Pain relief- Changes from baseline	N	Mean	SD	Median	Min	Max	NMiss
Treatment, No. 02	146	3.29	35.41	0.00	-90.00	90.00	118
Treatment, No. 03	132	0.68	35.13	0.00	-80.00	90.00	113
Treatment, No. 04	108	1.39	34.46	0.00	-80.00	90.00	110
Treatment, No. 05	91	9.01	37.98	0.00	-90.00	90.00	95
Treatment, No. 06	79	5.32	38.46	0.00	-90.00	90.00	88
Follow-up after end of treatment	38	3.95	43.72	5.00	-70.00	90.00	57

Source: Table 95, TLF v6.0

Overall, mean scores on subscale Pain severity decreased from 2.98 (SD=1.98) at baseline to 2.27 (SD=2.17) at visit 6; mean score at follow-up after end of treatments was 2.60 (SD=2.62, see Table 87, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 23 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). Mean score change

was -0.27 (SD=1.51) at visit 2, -0.28 (SD=1.60) at visit 3, -0.19 (SD=2.12) at visit 4, -0.48 (SD=2.11) at visit 5, -0.39 (SD=2.41) at visit 6, and 0.01 (SD=2.72) at follow-up after end of treatment (see Table 88, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 24 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Mean scores for Pain interference at each study visit were: 3.36 (SD=2.38) at baseline, 3.17 (SD=2.38) at visit 2, 3.17 (SD=2.40) at visit 3, 2.94 (SD=2.38) at visit 4, 2.76 (SD=2.41) at visit 5, 2.50 (SD=2.36) at visit 6, and 2.79 (SD=2.57) at follow-up after end of treatment (see Table 89, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 25 in TLF v6.0 by number of injections and TLF v6.0 by BHA use). Mean score change from baseline amounted to -0.18 (SD=1.77) at visit 2, -0.08 (SD=1.89) at visit 3, -0.16 (SD=2.17) at visit 4, -0.34 (SD=2.33) at visit 5, -0.44 (SD=2.35) at visit 6, and -0.11 (SD=2.70) at follow-up (see Table 90, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 26 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

10.3.2.2 Pain control rate

Pain control rate was 67.13 (95%CI 26.65- 39.57, see Table 96, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 32 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

10.3.2.3 Pain progression rate

Pain progression rate was 32.87 (95%CI 60.43- 73.35, see Table 97, TLF v6.0; for analysis according to injection number and according to concomitant BHA see Table 33 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

10.3.2.4 Time to first pain progression

Overall, median time to first pain progression was 6.70 months (95%CI 6.44 - NR, Table 19, Figure 5). Median time to first pain progression was not reached (95%CI 5.57 - NR) in patients without concomitant BHA use (see Table 34, TLF v6.0 by BHA use; for analysis according to injection number see Table 34 in TLF v6.0 by number of injections).

Table 19: Time to first pain progression [months] (QoL-Set- Pain-Response)

	N	Pain Progression	Censored	Q1	95%-CI of Q1	Median	95% CI for median	Q3	95% CI for Q3
Total	216	71	145	2.89	1.86 - 4.28	6.70	6.44 - NR	NR	NR - NR

Source: Table 98, TLF v6.0

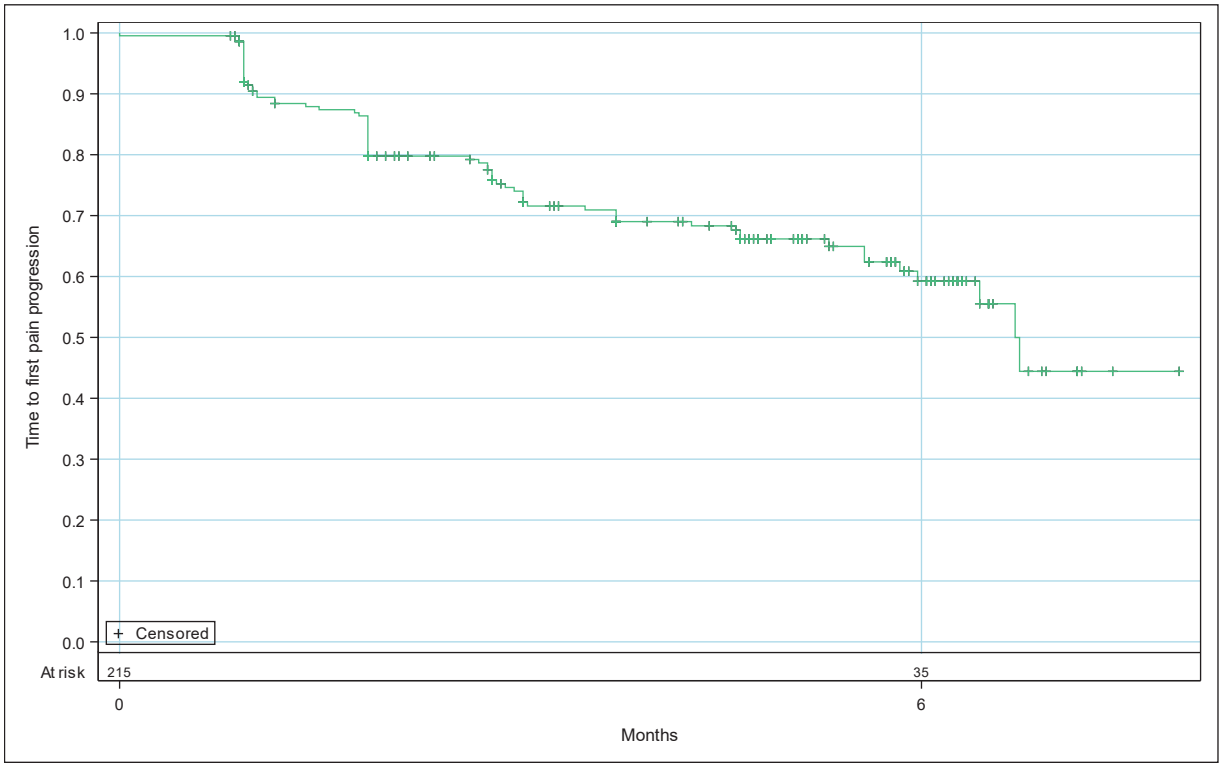

Figure 5: Time to first pain progression

Source: Figure 1, TLF v6.0

10.3.2.5 Changes in bone pain-related quality of life

Mean FACT-BP score for all patients analyzed increased from 35.93 (SD=14.79) at baseline to 41.85 (SD=14.50) at visit 6; mean FACT-BP score at follow-up after end of treatment was 40.89 (SD=15.60, Figure 6). Mean change of FACT-BP score from baseline was 3.01 (SD=9.34) at visit 2, 2.35 (SD=11.22) at visit 3, 2.50 (SD=13.45) at visit 4, 3.17 (SD=13.25) at visit 5, 3.75 (SD=13.96) at visit 6, and 1.99 (SD=16.57) at follow-up (see Table 100 in TLF v6.0).

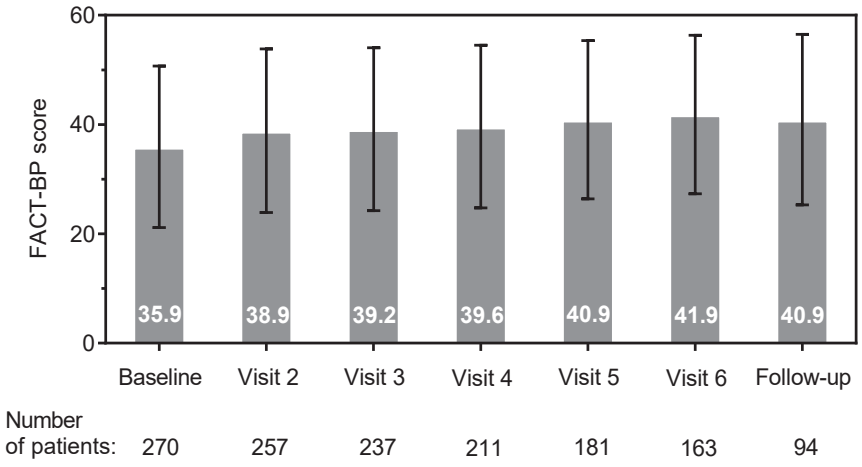

Figure 6: FACT-BP score at each study visit

Source: Table 99, TLF v6.0

10.3.2.6 Time to first opioid use

238 patients did not use opioid prior or at baseline. 53 out of 238 patients started using opioids during the Radium-223 therapy. Median time to first opioid use was not reached (95%CI NR- NR, Figure 7).

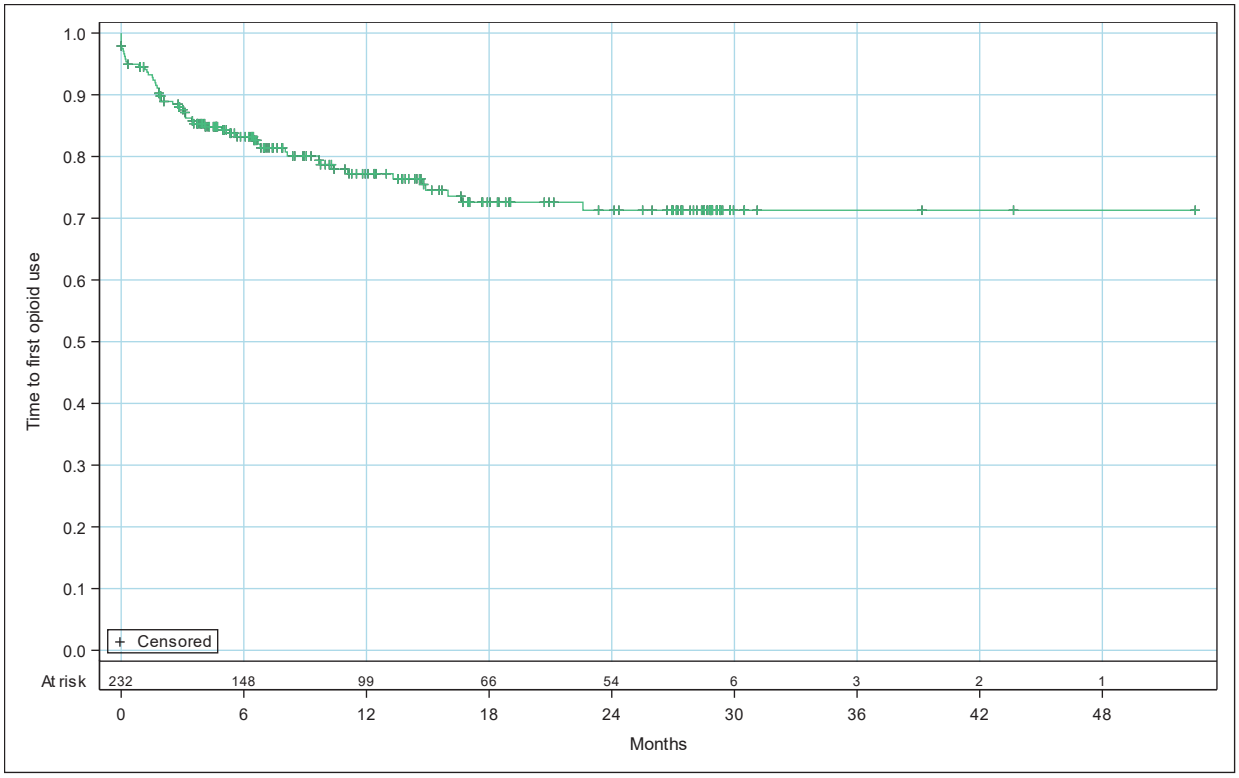

Figure 7: Time to first opioid use

Source: Figure 2, TLF v6.0

10.3.2.7 Description of covariates on pain response

Evaluation of covariates considered for logistic regression analysis of pain response is shown in TLF v6.0: opioid use at baseline (Table 102), number of known bone metastases at baseline (Table 103), location of bone pain at baseline (Table 104), level of alkaline phosphatase at baseline (Table 105), PSA level at baseline (Table 106), WHO pain score at baseline (Table 107), pretreatment with chemotherapy (Table 108), abiraterone (Table 108B), enzalutamide (Table 108C) or BHAs (Table 109), and extent of bone uptake in known lesions at baseline (Table 110).

Type III analysis of variance did not identify statistically significant interaction between Pain response and of the covariates analyzed (all p-values were >0.05, see Table 111, TLF v6.0). Univariate logistic regression analysis identified PSA level at baseline (>200 µg/l vs. <50 µg/l) was statistically significantly associated with pain response (OR 0.4286, 95%CI 0.1822-1.0081, p-value = 0.0235, Table 20).

Table 20: Logistic regression for pain response- Univariate logistic regression (QoL-Set-Pain-Response)

Covariate	Parameter vs. Reference value	Estimate (Parameter)	Standard error	p-value	Odds ratio	CI 95%
Opioid use (N=216)	yes vs. no	-0.1020	0.1430	0.4757	0.8155	0.4656-1.4283
Number of known bone metastases (N=207)	6-20 vs. <6	-0.1079	0.2361	0.6475	0.5702	0.2103-1.5457
	>20 vs. <6	-0.1275	0.2317	0.5822	0.5591	0.2079-1.5039
	Superscan vs. <6	-0.2185	0.3261	0.5029	0.5105	0.1575-1.6550
Location of bone metastases (N=216)	Extremities vs. None	0.8606	0.5010	0.0858	2.5972	0.6732-10.019
	Trunk vs. None	-0.2328	0.2545	0.3603	0.8702	0.4653-1.6277
	Both vs. None	-0.5340	0.2943	0.0696	0.6439	0.3047-1.3607
Level of ALP at baseline (N=131)	150-300U/l vs. <150U/l	-0.1968	0.2773	0.4779	0.7619	0.3476-1.6700
	>300U/l vs. <150U/l	0.1217	0.3373	0.7183	1.0476	0.3777-2.9060
PSA level at baseline (N=147)	50-200µg/l vs. <50µg/l	0.4069	0.2557	0.1116	1.2053	0.5549-2.6184
	>200µg/l vs. <50µg/l	-0.6271	0.2769	0.0235	0.4286	0.1822-1.0081
WHO pain score at baseline (N=216)	Step vs. No pain/Step 1	0.2051	0.2468	0.4059	1.0167	0.5245-1.9706
	Step vs. No pain/Step 1	-0.3937	0.3022	0.1926	0.5586	0.2299-1.3574
Pretreatment with chemotherapy (N=216)	Yes vs. No	-0.1205	0.1434	0.4008	0.7859	0.4480-1.3786
Pretreatment with abiraterone (N=216)	Yes vs. No	0.1892	0.1395	0.1750	1.4601	0.8449-2.5231
Pretreatment with enzalutamide (N=216)	Yes vs. No	0.2035	0.1503	0.1759	1.5023	0.8333-2.7082
Pretreatment with BHA (N=216)	Yes vs. No	-0.0847	0.1416	0.5498	0.8442	0.4846-1.4706
Bone uptake in known lesions (N=176)	Strong vs. Less than Strong uptake	-0.0404	0.1645	0.8059	0.9223	0.4839-1.7580

Source: Table 112, TLF v6.0

Following the stepwise selection, only PSA level at baseline was included in the multivariate logistic regression analysis (see Table 113, TLF v6.0). However, PSA level at baseline was not significantly associated with pain response in multivariate logistic regression analysis (Table 21).

Table 21: Logistic regression for pain response- Multivariate logistic regression- Final model (QoL-Set-Pain-Response)

Covariate	Parameter vs. Reference value	Parameter estimate	Standard error	Odds ratio	95% CI for OR	p-value
Intercept		-0.0464	0.2300			0.8401
PSA level at baseline	<50µg/l	0.4180	0.2847	3.8667	1.29-11.59	0.1421
PSA level at baseline	50-200µg/l	0.5164	0.3272	4.2667	1.25-14.55	0.1145

Source: Table 114, TLF v6.0

Results of type III analysis of variance are demonstrated in Table 115, TLF v6.0. The analysis identified that worst pain score at baseline was statistically significantly associated with pain response at visit 5 (p-value = 0.0045) and pretreatment with enzalutamide was statistically significantly associated with pain response at visit 6 (p-value = 0.0446).

10.3.2.8 Relation between bone uptake in known lesions and pain palliation

Changes from baseline in scores for BPI-SF item worst pain at each study visit in patients with less than strong and strong bone uptake at baseline is shown in Table 22. At each study visit, decrease in worst pain scores was larger in patients with strong bone uptake than in those with less than strong bone uptake at baseline.

Table 22: Relation between bone uptake and pain response*

Changes in worst pain measured by BPI-SF		N	Mean	SD	Median	Min	Max	NMiss
Treatment, No. 02	Less than Strong uptake	53	-0.57	1.95	-1.00	-7.00	3.00	0
	Strong uptake	113	-0.77	2.20	-1.00	-7.00	5.00	3
	Total	166	-0.70	2.12	-1.00	-7.00	5.00	3
Treatment, No. 03	Less than Strong uptake	50	-0.62	2.10	-1.00	-5.00	6.00	0
	Strong uptake	107	-0.86	2.45	-1.00	-7.00	5.00	1
	Total	157	-0.78	2.34	-1.00	-7.00	6.00	1
Treatment, No. 04	Less than Strong uptake	47	-0.83	2.56	0.00	-7.00	4.00	1
	Strong uptake	93	-1.00	2.63	-1.00	-8.00	5.00	2
	Total	140	-0.94	2.60	-1.00	-8.00	5.00	3
Treatment, No. 05	Less than Strong uptake	41	-0.95	2.66	0.00	-7.00	6.00	0
	Strong uptake	83	-1.48	2.61	-1.00	-7.00	4.00	1
	Total	124	-1.31	2.63	-1.00	-7.00	6.00	1
Treatment, No. 06	Less than Strong uptake	39	-1.28	3.10	-1.00	-7.00	7.00	0
	Strong uptake	72	-1.32	2.94	-1.00	-8.00	5.00	1
	Total	111	-1.31	2.99	-1.00	-8.00	7.00	1
Follow-up after end of treatment	Less than Strong uptake	22	-0.36	3.75	-0.50	-7.00	8.00	0
	Strong uptake	38	-0.97	2.75	-1.00	-6.00	4.00	0
	Total	60	-0.75	3.13	-1.00	-7.00	8.00	0

*Patients from QoL-Set-Pain-Response with one bone scan at baseline and another bone scan during or within 6 weeks after end of Radium-223 treatment were considered for this analysis.

Source: Table 116, TLF v6.0

10.3.2.9 Radium-223 treatment patterns

Patients received a median number of 6 Radium-223 treatments (range: 1-6, mean 4.86 treatments, SD=1.61, see Table 117, TLF v6.0). The majority of patients received 6 Radium-223 injections (n=213, 60.2%, Table 23). Two hundred thirty-six patients (66.7%) received >4 Radium-223 injections and 118 (33.3%) received ≤4 injections (see Table 119, TLF v6.0). Mean Radium-223 dose was 53.49 kBq/kg (SD=4.65) at baseline visit, 52.72 kBq/kg (SD=3.39) at visit 2, 52.49 kBq/kg (SD=3.77) at visit 3, 52.57 kBq/kg (SD=4.03) at visit 4, 52.81 kBq/kg (SD=4.17) at visit 5, and 52.76 kBq/kg (SD=3.99) at visit 6 (see Table 120, TLF v6.0). Mean dose per patient over all post-baseline injections was 52.53 kBq/kg (SD=3.32).

Table 23: Radium-223- Number of injections (FAS)

Radium-223- Number of injections	N	%
1 injection	17	4.80
2 injection	30	8.47
3 injection	32	9.04
4 injection	39	11.02
5 injection	23	6.50
6 injection	213	60.17
Number of patients	354	100.00

Source: Table 118, TLF v6.0

Radium-223 treatment delays/interruptions were documented in 23 patients (6.5%). Median number of Radium-223 treatment delays/interruptions per patient was 0 (range:0-2). Overall, there were 27 treatment delays/interruptions; the most frequent reason for treatment delay/interruption was AE (n=11, 40.7%), Other (n=6, 22.2%), non-AE-related medical reason (physician decision, n=5, 18.5%), patient's decision (n=4, 14.8%) and radiotherapy (n=1, 3.7%).

10.3.2.10 Time to next tumor treatment(s)

10.3.2.10.1 Time to next tumor treatment(s) according to the number of Radium-223 injections

Overall, median time to next tumor treatment(s) (TTNT) was 20.04 months (95%CI 12.64 - NR, Table 24, Figure 8). Median TTNT in patients with 1-4 Radium-223 injections was 12.11 months (95%CI 7.20 - NR) and 21.83 months (95%CI 14.83 - NR) in patients with 5-6 injections (Table 24, Figure 8). Median TTNT was not different between patients with and without concomitant BHA (see Table 35 and Figure 2, TLF v6.0 by BHA use).

Table 24: Time to next tumor treatment(s) (TTNT) (FAS)- by number of injections

TTNT (months)	N	TTNT	Censored	Q1	95%-CI of Q1	Median	95% CI for median
Patients with 1-4 injections	118	25	93	5.67	4.35 - 8.36	12.11	7.20 - NR
Patients with 5-6 injections	236	90	146	8.59	7.53 - 9.92	21.83	14.83 - NR
Total	354	115	239	7.83	6.70 - 9.06	20.04	12.64 - NR

Source: Table 35, TLF v6.0 by injection number

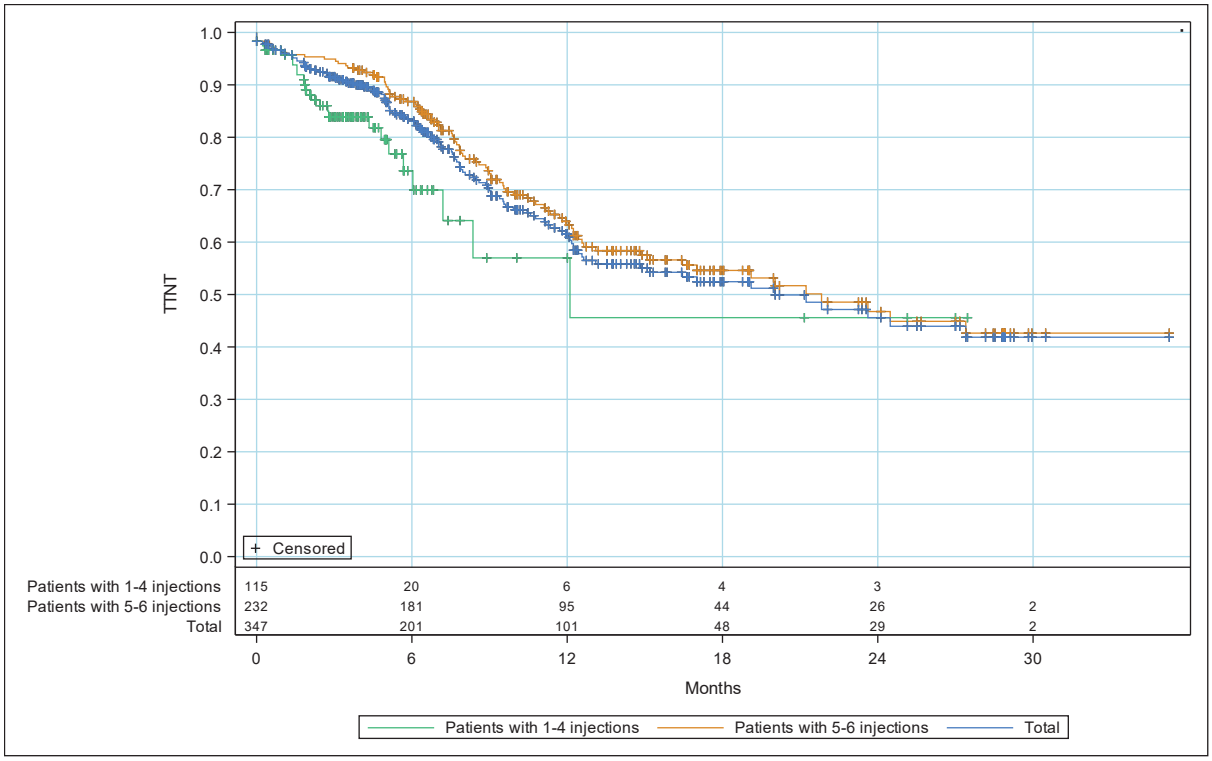

Figure 8: TTNT- by number of injections

Source: Figure 2, TLF v6.0 injection number

10.3.2.11 Time to first symptomatic skeletal event

10.3.2.11.1 Radium-223 injections

Overall, median time to first symptomatic skeletal event (TSSE) was not reached (95%CI 37.45 - NR, Table 25, Figure 9). Median TSSE in patients with 1-4 injections was not reached (95%CI 24.05 - NR) and not reached in patients with 5-6 injections (95%CI 37.45 - NR, Table 25, Figure 9).

Table 25: Time to first symptomatic skeletal event (TSSE) [months] (FAS)- by number of injections

SSE	N	SSE	Censored	Q1	95%-CI of Q1	Median	95% CI for median	Q3	95% CI for Q3
Patients with 1-4 injections	118	18	100	24.05	4.35-NR	NR	24.05-NR	NR	NR-NR
Patients with 5-6 injections	236	34	202	37.45	21.89-NR	NR	37.45-NR	NR	37.45-NR
Total	354	52	302	37.45	21.23-NR	NR	37.45-NR	NR	37.45-NR

Source: Table 36, TLF v6.0 by injection number

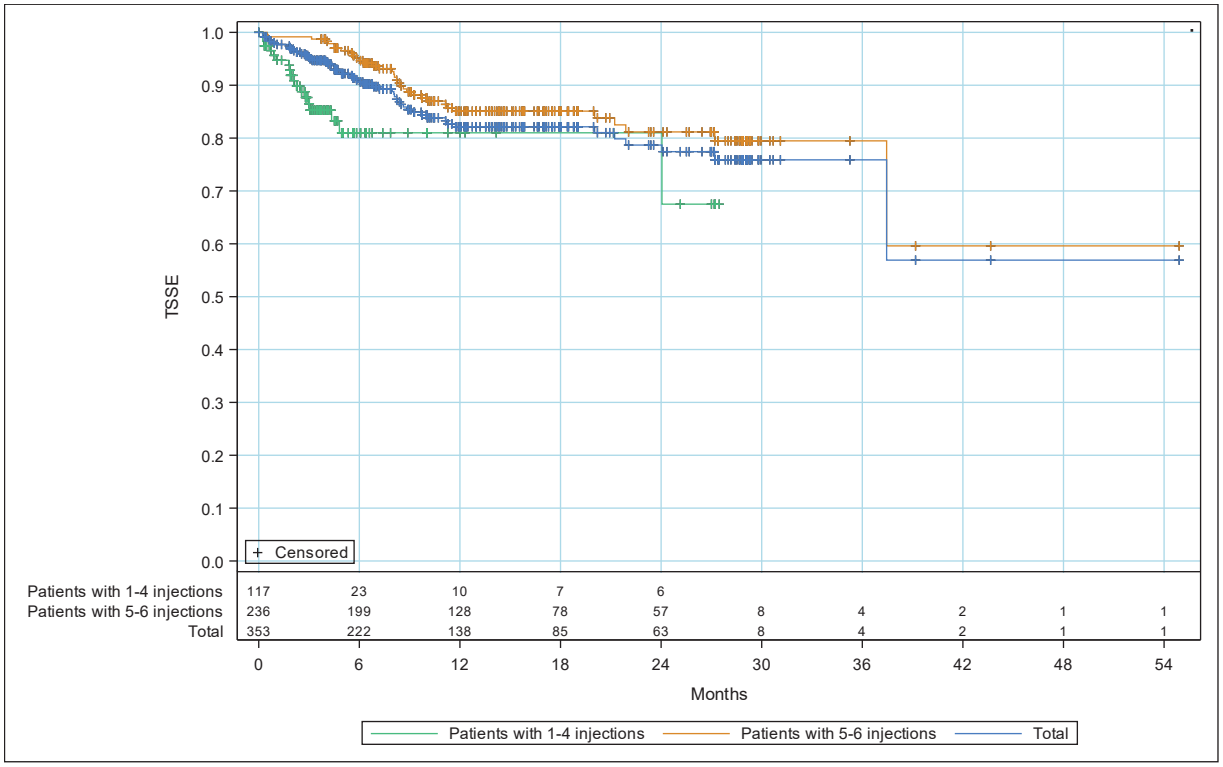

Figure 9: TSSE- by number of injections

Source: Figure 3, TLF v6.0 by injection number

10.3.2.11.2 Time to first symptomatic skeletal event according to the concomitant BHA treatment

Median TSSE was not reached in patients with concomitant BHA (95%CI 37.45 - NR) and in patients without concomitant BHA use (95%CI NR - NR, Table 26, Figure 10).

Table 26: Time to first symptomatic skeletal event (TSSE) [months] (FAS)- by use of BHA

SSE	N	TSSE	Censored	Q1	95%-CI of Q1	Median	95% CI for median	Q3	95% CI for Q3
Concomitant BHA	186	29	157	37.45	21.23-NR	NR	37.45-NR	NR	37.45-NR
No concomitant BHA	168	23	145	NR	8.26-NR	NR	NR-NR	NR	NR-NR
Total	354	52	302	37.45	21.23-NR	NR	37.45-NR	NR	37.45-NR

Source: Table 36, TLF v6.0 by BHA use

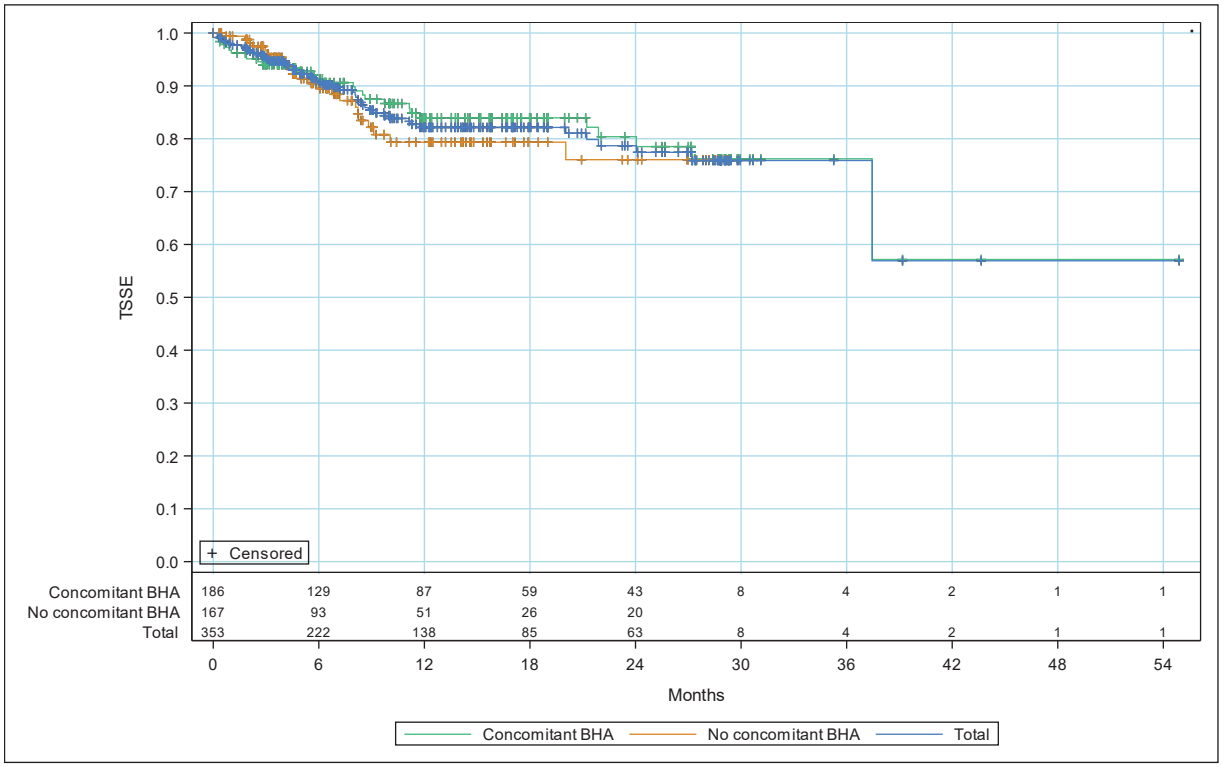

Figure 10: TSSE- by use of BHA

Source: Figure 3, TLF v6.0 by BHA use

10.3.2.11.3 Time to first symptomatic skeletal event according to the pretreatment or concomitant treatment with abiraterone or enzalutamide

Median TSSE was 37.45 months (95%CI NR - NR) in patients pretreated with abiraterone and it was not reached in patients without abiraterone pretreatment (95%CI NR – NR, see Table 129B, TLF v6.0). Median TSSE was 37.45 months (95%CI 21.89 - 37.45) in patients pretreated with

enzalutamide and it was not reached in patients without enzalutamide pretreatment (95%CI NR – NR, see Table 129C, TLF v6.0).

Median TSSE was not reached in patients with (95%CI NR - NR) or without concomitant abiraterone (95%CI 37.45 - NR, see Table 129D TLF v6.0). Median TSSE was 37.45 months (95%CI NR - NR) in patients with concomitant enzalutamide and it was not reached in those without concomitant enzalutamide treatment (95%CI NR – NR, see Table 129E, TLF v6.0).

10.3.2.12 Time from castration resistance to treatment with Radium-223

Median time from castration resistance to treatment with Radium-223 was 10.05 months (range: 0.00-155.28; mean time: 19.69 months (SD=26.12), see Table 130, TLF v6.0).

10.3.2.13 Duration of Radium-223 therapy according to the number of Radium-223 injections and concomitant BHA treatment

Median duration of Radium-223 therapy was 4.64 months overall (range: 0.00-7.17; mean duration: 3.78 months (SD=1.62)), 1.86 months in patients with 1-4 injections (range: 0.00-5.31; mean duration: 1.77 months (SD=1.13)), 4.64 months in patients with 5-6 injections (range: 3.68-7.17; mean duration: 4.79 months (SD=0.52), see Table 37, TLF v6.0 by injection number), 4.64 months in patients with concomitant BHA (range: 0.00-7.17; mean duration: 3.88 months (SD=1.61)) and 4.64 months in patients without concomitant BHA (range: 0.00-6.50; mean duration: 3.68 months (SD=1.63), see Table 37, TLF v6.0 by BHA use).

10.3.2.14 Description of covariates on duration of treatment with Radium-223

Type III analysis of variance identified an interaction between higher number of injections Radium-223 and Opioid use (p-value=0.0007), Number of known bone metastases (p-value=0.0003), Level of ALP at baseline (p-value=0.0001), PSA level at baseline (p-value=0.0002), Pretreatment with chemotherapy (Cabazitaxel or Docetaxel, p-value=0.0121) and Concomitant treatment with enzalutamide (p-value=0.0144, see Table 124, TLF v6.0). In univariate logistic regression analysis, higher number of Radium-233 injections was associated with Opioid use (yes vs. no, OR 0.4466, 95%CI 0.2810-0.7099, p-value=0.0007), Number of known bone metastases (Superscan vs. <6, OR 0.1513, 95%CI 0.0543-0.4216, p-value<0.0001), Level of ALP at baseline (150-300U/l vs. <150U/l, OR 0.2762, 95%CI 0.1397-0.5460, p-value=0.0384), PSA level at baseline (>200µg/l vs. <50µg/l, OR 0.2707, 95%CI 0.1408-0.5204, p-value<0.0001), Pretreatment with chemotherapy (Yes vs. No, OR 0.5572, 95%CI 0.3528-0.8800, p-value=0.0121) and Concomitant treatment with enzalutamide (Yes vs. No, OR 2.1250, 95%CI 1.1618-3.8867, p-value=0.0144, Table 27).

Table 27: Logistic regression for higher number of injections- Univariate logistic regression (FAS)

Covariate	Parameter vs. Reference value	Estimate (Parameter)	Standard error	p-value	Odds ratio	CI 95%
Opioid use (N=354)	yes vs. no	-0.4030	0.1182	0.0007	0.4466	0.2810-0.7099
Number of known bone metastases (N=335)	6-20 vs. <6	0.2798	0.2106	0.1840	0.5236	0.2002-1.3694
	>20 vs. <6	-0.2449	0.1987	0.2179	0.3098	0.1208-0.7947
	Superscan vs. <6	-0.9618	0.2465	<0.0001	0.1513	0.0543-0.4216
Level of ALP at baseline (N=230)	150-300U/l vs. <150U/l	-0.4592	0.2218	0.0384	0.2762	0.1397-0.5460
	>300U/l vs. <150U/l	-0.3682	0.2322	0.1128	0.3025	0.1472-0.6217
PSA level at baseline (N=249)	50-200µg/l vs. <50µg/l	0.3764	0.2108	0.0742	0.9151	0.4681-1.7887
	>200µg/l vs. <50µg/l	-0.8415	0.2062	<0.0001	0.2707	0.1408-0.5204
Pretreatment with chemotherapy (N=354)	Yes vs. No	-0.2924	0.1166	0.0121	0.5572	0.3528-0.8800
Pretreatment with BHA (N=354)	Yes vs. No	-0.0262	0.1146	0.8193	0.9490	0.6056-1.4871
Pretreatment with abiraterone (N=354)	Yes vs. No	-0.1368	0.1132	0.2269	0.7606	0.4881-1.1855
Pretreatment with enzalutamide (N=354)	Yes vs. No	0	0.1206	1.0000	1.0000	0.6232-1.6047
Concomitant treatment with BHA (N=354)	Yes vs. No	0.0509	0.1128	0.6516	1.1073	0.7115-1.7233
Concomitant treatment with abiraterone (N=354)	Yes vs. No	0.1985	0.1398	0.1557	1.4875	0.8598-2.5735
Concomitant treatment with enzalutamide (N=354)	Yes vs. No	0.3769	0.1540	0.0144	2.1250	1.1618-3.8867

Note 1: Pretreatment is defined as treatment that started before Ra-223 therapy.

Note 2: Concomitant treatment is defined as treatment overlapping with Ra-223 therapy.

Note 3: Chemotherapy is defined as Cabazitaxel and Docetaxel.

Source: Table 125, TLF v6.0

Following the stepwise selection, PSA level at baseline and Level of ALP at baseline were included in the multivariate logistic regression analysis. PSA level >200µg/l at baseline was significantly associated with higher number of Radium-223 injections in multivariate logistic regression analysis (OR 0.2979, 95%CI 0.14-0.65, p-value=0.0005, Table 28).

Table 28: Logistic regression for higher number of injections- Multivariate logistic regression- Final model (FAS)

Covariate	Parameter vs. Reference value	Parameter estimate	Standard error	Odds ratio	95% CI for OR	p-value
Intercept		0.4918	0.1778			0.0057
Level of ALP at baseline	150-300U/l	-0.4207	0.2531	0.3290	0.15-0.71	0.0965
Level of ALP at baseline	>300U/l	-0.2703	0.2699	0.3824	0.17-0.88	0.3165
PSA level at baseline	50-200µg/l	0.4637	0.2548	1.0943	0.48-2.49	0.0687
PSA level at baseline	>200µg/l	-0.8373	0.2416	0.2979	0.14-0.65	0.0005

Source: Table 127, TLF v6.0

10.3.2.15 Overall survival

Overall, median overall survival (OS, time from the start of Radium-223 therapy to death due to any cause) was 17.15 months (95%CI 15.33 - 18.97, Table 29, Figure 11). Median OS was 13.9 months (95%CI 10.02 - 17.28) in patients with prior abiraterone therapy and 17.91 months (95%CI 15.86 - 24.35) in patients without prior abiraterone therapy (see Table 132B, TLF v6.0). Median OS was 13.53 months (95%CI 7.89 - 17.91) in patients with prior enzalutamide therapy and 17.51 months (95%CI 15.79 - 20.04) in patients without prior enzalutamide therapy (see Table 132C, TLF v6.0). Median OS in patients with concomitant abiraterone therapy was 17.51 months (95%CI 13.53 - 22.06) and 17.05 months (95%CI 14.20 - 19.67) in those without concomitant abiraterone treatment (see Table 132D, TLF v6.0). Median OS in patients with concomitant enzalutamide therapy was 14.46 months (95%CI 11.74 - 18.97) and 17.51 months (95%CI 15.69 - 21.16) in those without concomitant treatment (see Table 132E, TLF v6.0).

Median OS amounted to 5.71 months (95%CI 4.71 - 6.40) in patient with 1-4 Radium-223 injections and 20.70 months (95%CI 17.98 - 28.53) in those with 5-6 injections (Table 29, Figure 11). Median OS in patients with concomitant BHA was 17.48 months (95%CI 14.46 - 20.70) and in those without concomitant BHA median OS was 15.79 months (95%CI 13.73 - 20.04, see Table 38, TLF v6.0 by BHA use).

Table 29: Overall survival [months] (FAS)- by number of injections

	N	Death	Censored	Q1	95%-CI of Q1	Median	95% CI for median	Q3	95% CI for Q3
Patients with 1-4 injections	118	72	46	3.75	3.18- 4.28	5.71	4.71 - 6.40	10.05	6.83 - 25.01
Patients with 5-6 injections	236	104	132	13.77	12.24 - 15.72	20.70	17.98 - 28.53	NR	35.26 - NR
Total	354	176	178	8.89	6.60- 10.08	17.15	15.33 - 18.97	39.18	35.26 - NR

Source: Table 38, TLF v6.0 by injection number

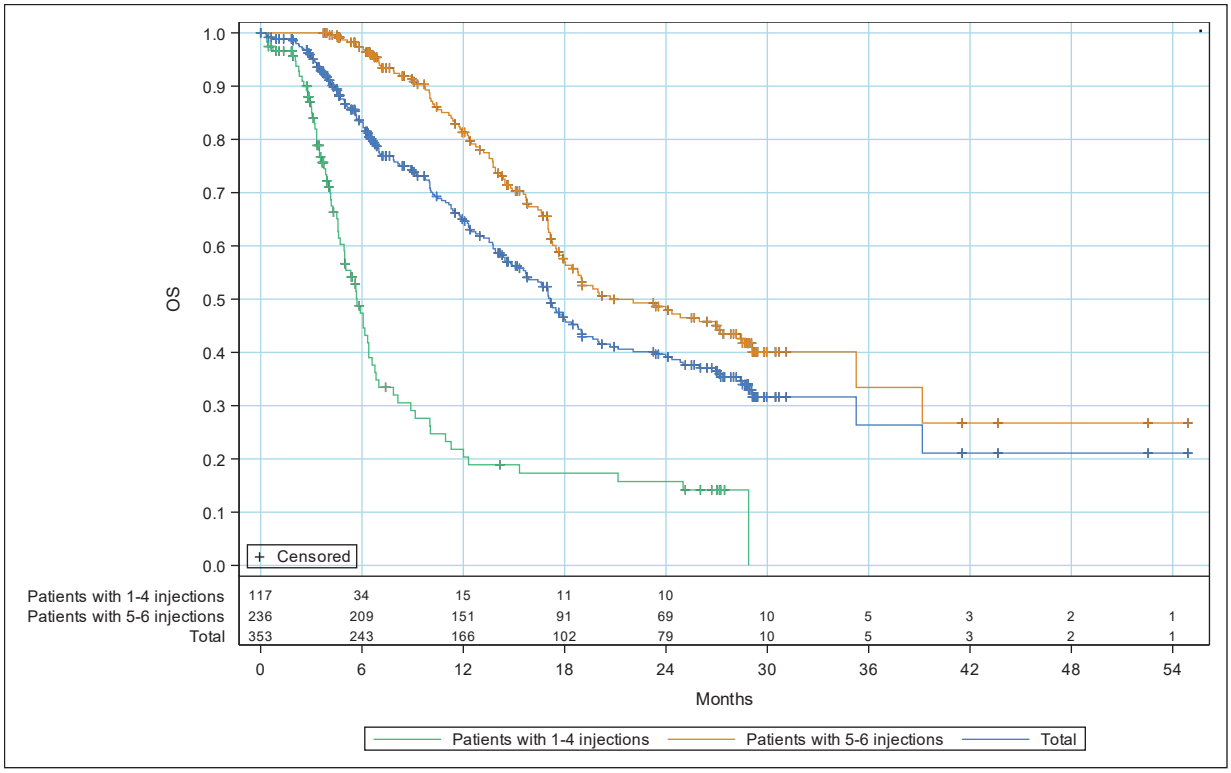

Figure 11: OS- by number of injections

Source: Figure 4, TLF v6.0 by injection number

10.3.2.16 Evaluation of Bone scan index as imaging biomarker in mCRPC

10.3.2.16.1 Evaluation of Bone scan index as imaging biomarker in mCRPC according to the number of Radium-223 injections

Percentage of patients with bone scan index (BSI) data among all patients and according to the number of Radium-223 injections is shown in Table 133, TLF v6.0. Up to approximately 7% of patients had BSI data at any study visit; no patients had BSI at treatment visit 3, 5 and 6, and at long-term follow-up visit 3 to 7. Overall, mean BSI decreased from 5.29% (SD=4.30%) at baseline to 2.85% (SD=2.25%) at visit 4, 2.92% (SD=2.43%) at follow-up and 0.60% (SD=0.56%) at long-term follow-up visit 2 (see Table 134, TLF v6.0). Mean BSI change from baseline for all patients was -0.99% (SD=1.62%) at visit 4, -1.10% (SD=2.53%) at follow-up visit, and -3.27% (SD=3.04%) at long-term follow-up visit 1 (Table 30).

Table 30: Bone Scan Index (BSI) [%]- Change from baseline (FAS)

BSI- Change from baseline	N	Mean	SD	Median	Min	Max	NMiss
Treatment visit 2	0						1
Treatment visit 4	10	-0.99	1.62	-0.90	-3.81	1.78	3
Follow-up visit	12	-1.10	2.53	-0.65	-6.10	3.28	5
Long-term follow-up visit 1	3	-3.27	3.04	-3.52	-6.17	-0.11	4
Long-term follow-up visit 2	0						5

Source: Table 135, TLF v6.0

10.3.2.17 Course of blood count

Percentage of patients with platelet count below limit for further injections decreased from 6.51% (n=22) at baseline to 3.73% (n=5) at follow-up visit (none of the patients had a platelet count below the limit at long-term follow-up visit 1, see Table 152, TLF v6.0). The proportion of patients with platelets count below limit for further injections was similar between those with EOD 0-2 and EOD 3-4.

Percentage of patients with hemoglobin value below limit for further injections increased from 11.61% (n=39) at baseline to 28.15% (n=38) at follow-up visit; hemoglobin value was below limit in 50% of patients (n=5) at long-term follow-up visit 1. More patients with EOD 3-4 than those with EOD 0-2 had hemoglobin value below limit for further injections baseline visit (16.47% vs 5.77%), visit 2 (16.05% vs 3.14%), visit 3 (18.18% vs 6.12%), visit 4 (23.02% vs 5.38%), visit 5 (20.59% vs 6.61%), visit 6 (25.84% vs 6.14%), follow-up visit (45.16% vs 11.59%), and long-term follow-up visit 1 (80% vs 20%).

Neutrophil count was below limit for further injections was documented for only a single patient at baseline visit (0.48%, with EOD 3) and at visit 6 (0.71%, with EOD 4).

10.3.2.18 Laboratory parameters

Laboratory parameters at baseline are shown in Table 31. For post baseline (median of all post-baseline visits) and change from baseline, see Table 154 and Table 155, TLF v6.0). Median platelet count decreased from 226.00 10^9/l (range: 0-4400) at baseline to 199 10^9/l (range: 0-564) during the study; median change amounted to -27.5 10^9/l (range: -3921.00-356.10). Median neutrophil percentage decreased from 67.12% (range: 3.9-92.86%) at baseline to 59% (range: 1.41-87.4%) during the study; median change amounted to -5.1% (range: -87.76-17.08). Median ALP levels decreased from 133 U/l (range: 29.8-1129) at baseline to 95.3 U/l (range: 27-790) during the study; median change amounted to -17 U/l (range: -710-412.5). Median PSA levels increased from 58.04 µg/l (range: 0-2130) at baseline to 90.72 µg/l (range: 0-6419.5) during the study; median change was 14.9 µg/l (range: -1138.55-1681). Other laboratory parameters did not change throughout the study.

Table 31: Laboratory values at baseline (SAF)

Laboratory values at baseline	N	Mean	SD	Median	Min	Max	NMiss
Platelets [10⁹/l]	338	239.84	246.29	226.00	0.00	4400.00	0
Haemoglobin [g/dl]	336	12.14	1.56	12.20	8.30	16.20	0
Erythrocytes [/pl]	255	4.06	0.50	4.10	2.50	5.30	0
Hematocrit [%]	256	36.40	4.50	36.90	25.00	50.00	0
Leucocytes [10⁹/l]	302	6.71	2.62	6.40	0.01	18.50	0
Neutrophiles [%]	188	66.38	11.97	67.12	3.90	92.86	21
Lymphocytes [%]	159	21.03	9.08	20.10	0.32	54.55	2
Monocytes [%]	153	8.71	2.91	9.00	0.49	15.19	0
Eosinophils [10⁹/l]	146	2.17	1.69	1.90	0.00	7.10	0
Basophils [10⁹/l]	146	0.45	0.32	0.40	0.00	1.40	0
ALP [U/l]	231	225.69	242.93	133.00	29.80	1129.00	0
PSA [µg/l]	251	195.36	354.65	58.04	0.00	2130.00	0

Source: Table 153, TLF v6.0

10.3.2.19 Incidence rates and incidence proportions for (non-) pathological fractures and bone associated events

The overall incidence proportion for pathological fractures, non-pathological fractures and bone associated events other than fractures during treatment or long-term follow-up period was 0.0960 (95%CI 0.0654 - 0.1267) for fractures, 0.0876 (95%CI 0.0581 - 0.1170) for pathological fractures, 0.0085 (95%CI 0.0011 - 0.0180) for non-pathological fractures (all in patients with 5-6 Radium-223 injections and no concomitant BHA) and 0.1949 (95%CI 0.1536 - 0.2362) for bone associated events other than fractures. Incidence proportion of fractures appeared to be similar in patients with and those without concomitant BHA use (0.0645, 95%CI 0.0292 - 0.0998 and 0.1310, 95%CI 0.0799 - 0.1819, respectively). Incidence proportion of pathological fractures (0.0645, 95%CI 0.0292 - 0.0998 and 0.1131, 95%CI 0.0652 - 0.1609) and bone associated events other than fractures (0.2258 95%CI 0.1657 - 0.2858 and 0.1607, 95%CI 0.105 - 0.2162) was similar between patients with and without concomitant BHA use (Table 32). The incidence proportion for pathological fractures, non-pathological fractures and bone associated events other than fractures during treatment or long-term follow-up period according to injection number is shown in Table 8, TLF v6.0 by injection number).

Table 32: Incidence proportion for pathological fractures, non-pathological fractures and bone associated events during treatment or long-term follow-up period (FAS)- by use of BHA

		N	Events	Incidence proportion	CI 95%
Concomitant BHA	Fractures	186	12	.0645	0.0292 - 0.0998
	Pathological fractures	186	12	.0645	0.0292 - 0.0998
	Non-Pathological fractures	186	0	.0000	
	Bone associated events other than fracture	186	42	.2258	0.1657 - 0.2858
No concomitant BHA	Fractures	168	22	.1310	0.0799 - 0.1819
	Pathological fractures	168	19	.1131	0.0652 - 0.1609
	Non-Pathological fractures	168	3	.0179	-0.002 - 0.0378
	Bone associated events other than fracture	168	27	.1607	0.105 - 0.2162
Total	Fractures	354	34	.0960	0.0654 - 0.1267
	Pathological fractures	354	31	.0876	0.0581 - 0.1170
	Non-Pathological fractures	354	3	.0085	-.0011 - 0.0180
	Bone associated events other than fracture	354	69	.1949	0.1536 - 0.2362

Note: Bone associated events include SSEs and events identified by AEs excluding fractures - Fractures are the sum of pathological and non-pathological fractures. Events that started up to 30 days since last Ra-223 injection are assigned to during treatment. Otherwise they are assigned to follow-up.

Source: Table 72, TLF v6.0; Table 8, TLF v6.0 by BHA use

The incidence proportion of pathological fractures, non-pathological fractures and bone-associated events other than fractures were additionally calculated for treatment period (see Table 70 in TLF v6.0 and Table 6 in TLF v6.0 by number of injections and TLF v6.0 by BHA use) and for long-term follow-up period (see Table 71 TLF v6.0 and Table 7 in TLF v6.0 by number of injections and TLF v6.0 by BHA use).

Incidence rates of pathological fractures, non-pathological fractures and bone-associated events other than fractures are shown in Table 73 (TLF v6.0) and Table 9 (TLF v6.0 by number of injections and TLF v6.0 by BHA use) for treatment period, Table 74 (TLF v6.0) and Table 10 (TLF v6.0 by number of injections and TLF v6.0 by BHA use) for follow-up period and Table 75 (TLF v6.0) and Table 11 (TLF v6.0 by number of injections and TLF v6.0 by BHA use) for treatment and follow-up period.

10.4 Other analyses

Sensitivity analysis was performed for primary and secondary objectives by deriving mean scores for BPI-SF and for FACT-BP questionnaires from all patients included in SAF at each study visit which were then used for calculation of changes from baseline. Sensitivity analysis of BPI-SF item worst pain demonstrated that the changes in worst pain scores from baseline were similar between SAF and QoL-Set (see Table 69 and Table 157, TLF v6.0). FACT-BP scores were similar between

QoL-Set and in the SAF (see Table 99 and Table 170, TLF v6.0) although the change in FACT-BP scores was numerically slightly higher in SAF than in QoL-Set (see Table 100 and Table 171, TLF v6.0).

10.5 Adverse events/adverse reactions

Two hundred patients (56.2%) experienced at least one TEAE (Table 33). Grade ≥3 TEAE occurred in 99 patients (27.81%); 27 patients died (7.58%). Serious TEAE occurred in 96 patients (26.97%); in one patient (0.28%), serious TEAE led to modification of Radium-233 dose, whereas 76 patients (21.35%) permanently discontinued the study drug. Ninety-two patients (25.84%) experienced a drug-related TEAE. Grade ≥3 drug-related TEAE occurred in 40 patients (11.24%); five patients died (1.4%). Drug-related TEAE led to permanently discontinued the study drug in 29 patients (8.15%).

Table 33: Adverse events- Overview (SAF)

Overview of TEAE	N (%)
Number of patients	356 (100.0)
Number of patients with any TEAE	200 (56.18)
Grade 3	65 (18.26)
Grade 4	7 (1.97)
Grade 5 (death)	27 (7.58)
Serious	96 (26.97)
Leading to dose modification (i.e. reduced or increased)	1 (0.28)
Leading to permanent discontinuation of study drug	76 (21.35)
Number of patients with any drug-related TEAE	92 (25.84)
Grade 3	33 (9.27)
Grade 4	2 (0.56)
Grade 5 (death)	5 (1.40)
Serious	28 (7.87)
Leading to dose modification (i.e. reduced or increased)	0 (0.00)
Leading to permanent discontinuation of study drug	29 (8.15)
Number of patients with any TESAE	96 (26.97)
Grade 3	46 (12.92)
Grade 4	7 (1.97)
Grade 5 (death)	27 (7.58)
Leading to dose modification (i.e. reduced or increased)	0 (0.00)
Leading to permanent discontinuation of study drug	58 (16.29)

Source: Table 136, TLF v6.0

10.5.1 TEAE

Most frequently occurring TEAE by System Organ Class (SOC) included Blood and lymphatic system disorders (17.7%), General disorders and administration site conditions (14.04%), Gastrointestinal disorders (11.8%), Neoplasms benign, malignant and unspecified (incl cysts and polyps, 10.39%), and Musculoskeletal and connective tissue disorders (9.55%, Table 34, see Table 137, TLF v6.0). TEAEs (by Preferred Term, PT) occurring in more than 2% of patients included Anaemia (13.2%), Fatigue (7.87%), Diarrhoea (5.06%), Nausea (4.49%), Pain (3.09%), Metastases to liver (3.09%), and Pancytopenia, Thrombocytopenia, Vomiting, Back pain, and Bone pain (2.3%). TEAEs related to the bone fractures included Pathological fracture (n=3, 0.8%), Lumbar vertebral fracture, Rib fracture and Spinal compression fracture (n=2, 0.6%, each), and Femoral neck fracture, Spinal fracture and Stress fracture (n=1, 0.3%, each, see table 137, TLF v6.0). TEAEs related to bone pain included Bone pain (n=8, 2.3%), and Musculoskeletal pain and Spinal pain (n=2, 0.6%, both). Most frequently occurring grade ≥3 TEAEs were Anaemia (6.18%), General physical health deterioration (2.25%), Pancytopenia (2.24%), Metastases to liver (1.96%), Neoplasm progression (1.68%), Pain (1.4%).

Table 34: TEAE according to MedDRA-SOC and PT- Worst grade (SAF)

TEAE		Grade 3		Grade 4		Grade 5		Total	
		N	%	N	%	N	%	N	%
Any SOC		65	18.26	7	1.97	27	7.58	200	56.18
Blood and lymphatic system disorders	Any PT	27	7.58	3	0.84	4	1.12	63	17.70
	Anaemia	21	5.90	1	0.28			47	13.20
	Pancytopenia	2	0.56	2	0.56	4	1.12	8	2.25
	Thrombocytopenia	3	0.84					8	2.25
Gastrointestinal disorders	Any PT	3	0.84	1	0.28	1	0.28	42	11.80
	Diarrhoea							18	5.06
	Nausea							16	4.49
	Vomiting							8	2.25
General disorders and administration site conditions	Any PT	13	3.65			4	1.12	50	14.04
	Fatigue	3	0.84					28	7.87
	Pain	5	1.40					11	3.09
Infections and infestations	Any PT	4	1.12	1	0.28			10	2.81
Injury, poisoning and procedural complications	Any PT	4	1.12					12	3.37
Investigations	Any PT	5	1.40			1	0.28	17	4.78
Musculoskeletal and connective tissue disorders	Any PT	13	3.65					34	9.55
	Back pain	1	0.28					8	2.25
	Bone pain	2	0.56					8	2.25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any PT	10	2.81	3	0.84	11	3.09	37	10.39
	Metastases to liver	2	0.56	1	0.28	4	1.12	11	3.09
Nervous system disorders	Any PT	5	1.40	1	0.28	2	0.56	22	6.18
Respiratory, thoracic and mediastinal disorders	Any PT	3	0.84	1	0.28			8	2.25
Patients without TEAE								156	43.82
Number of patients								356	100.00

Shown are TEAEs of all grades that occurred in at least 2% of patients.

Source: Table 137, TLF v6.0

TEAEs recovered/resolved in 79 patients out of 200 patients with TEAE (39.50%), were recovering/resolving at the end of observation period in six patients (3.00%), recovered/resolved with sequelae in seven (3.50%), and did not recover/ resolve in 63 patients (31.50%, see Table 138, TLV v3.0). The outcome was fatal in 27 patients (13.50%), and it was unknown in 18 patients (9.00%). Radium-223 dose was most frequently not changed due to TEAE (n=107 patients, 53.50%, see Table 139, TLV v3.0). In 76 patients (38%), Radium-223 was withdrawn due to TEAE,

interrupted/delayed in 29 (14.50%), or reduced in one patient (0.50%). Patients most often did not receive any additional treatment due to TEAE (n=117, 58.50%); 58 patients (29%) received remedial drug therapy and 88 patients (44%) received other type of therapy.

10.5.2 Drug-related TEAE

Among the 92 patients with drug-related TEAE, most often occurring drug-related TEAE (by SOC) were Blood and lymphatic system disorders (13.2%), Gastrointestinal disorders (7.3%), General disorders and administration site conditions (4.49%), Investigations (2.25%), Musculoskeletal and connective tissue disorders (1.69%), and Metabolism and nutrition disorders (1.12%, Table 35, see Table 141, TLF v6.0). Most often occurring drug-related TEAEs by PT included Anaemia (9.27%), Diarrhoea (4.78%), Nausea (2.81%), Fatigue (2.53%), Pancytopenia and Thrombocytopenia (2.25%, both). Drug-related bone fractures included Spinal fracture and Pathological fracture (n=1, 0.3%, both). Two patients (0.6%) experienced bone pain which was related to the study drug. Grade ≥3 drug-related TEAEs that occurred in most often were: Anaemia (5.06%), Pancytopenia (2.24%), Thrombocytopenia (0.84%), Leukopenia (0.56%), General physical health deterioration (0.56%), Bone marrow failure (0.56%) and Osteonecrosis of jaw (0.56%).

Table 35: Drug-related TEAE according to MedDRA-SOC and PT- Worst grade (SAF)

Drug-related TEAE		Grade 3		Grade 4		Grade 5		Total	
		N	%	N	%	N	%	N	%
Any SOC		33	9.27	2	0.56	5	1.40	92	25.84
Blood and lymphatic system disorders	Any PT	22	6.18	2	0.56	4	1.12	47	13.20
	Anaemia	18	5.06					33	9.27
	Pancytopenia	2	0.56	2	0.56	4	1.12	8	2.25
	Thrombocytopenia	3	0.84					8	2.25
Gastrointestinal disorders	Any PT							26	7.30
	Diarrhoea							17	4.78
	Nausea							10	2.81
General disorders and administration site conditions	Any PT	4	1.12					16	4.49
	Fatigue	1	0.28					9	2.53
Investigations	Any PT	2	0.56					8	2.25
Patients without events								264	74.16
Number of patients								356	100.00

Shown are drug-related TEAEs that occurred in at least 2% of patients.

Source: Table 141, TLF v6.0

Drug-related TEAEs recovered/resolved in 47 patients out of 92 patients with drug-related TEAE (51.09%), were recovering/resolving at the end of observation period in one patient (1.09%), recovered/resolved with sequelae in two patients (2.17%), and did not recovered/not resolve in 28

patients (30.43%). The outcome was fatal in five patients (5.43%), and it was unknown in nine patients (9.78%). Radium-223 dose was most frequently not changed due to drug-related TEAE (n=53, 57.61%). In 29 patients (31.52%), Radium-223 dose was withdrawn due to drug-related TEAE, or interrupted/delayed in 11 patients (11.96%).

10.5.3 Serious TEAE

Among the 96 patients with serious TEAE, the most often occurring serious TEAE (by SOC) included Neoplasms benign, malignant and unspecified (incl. cysts and polyps, n=29, 8.15%), Blood and lymphatic system disorders (n=27, 7.58%), General disorders and administration site conditions (n=15, 4.21%), Nervous system disorders (n=11, 3.09%), Musculoskeletal and connective tissue disorders (n=10, 2.81%), Gastrointestinal disorders (n=8, 2.25%), and Injury, poisoning and procedural complications (n=4, 1.12%, see Table 144, TLF v6.0). Serious TEAEs by PT occurring in more than 1% of patients included Anaemia (n=15, 4.21%), Metastases to liver (n=9, 2.53%), Pancytopenia (n=8, 2.25%), General physical health deterioration (n=7, 1.97%), Neoplasm progression (n=6, 1.69%), Pain and Metastases to central nervous system (n=5, 1.4%, both). Serious TEAE related to bone fractures included: Femoral neck fracture (n=1, 0.28%), Spinal compression fracture (n=2, 0.56%) and Pathological fracture (n=3, 0.84%); one patient (0.28%) had Bone pain.

In 96 patients with serious TEAE, Necessary or prolonged hospitalization was the most frequent reason for seriousness of TEAE (n=63, 65.63%), followed by death (n=27, 28.13%), Life threatening (n=25, 26.04%), Other medically important serious event (n=17, 17.71%) and Persistent or significant disability/incapacity (n=10, 10.42%, see table 145, TLF v6.0).

Among the 96 patients with serious TEAE, 28 (29.17%) had serious drug-related TEAE (see Table 146, TLF v6.0). Serious drug-related TEAE by SOC included Blood and lymphatic system disorders (n=21, 5.93% of SAF), General disorders and administration site conditions (n=3, 0.85%), Musculoskeletal and connective tissue disorders (n=2, 0.56%), and Gastrointestinal disorders, Infections and infestations, Metabolism and nutrition disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps) in 0.28%, each (n=1, see Table 147, TLF v6.0). Serious drug-related TEAEs by PT included Anaemia (n=10, 2.82%), Pancytopenia (n=8, 2.26%), Bone marrow failure, Thrombocytopenia, General physical health deterioration (n=2, 0.56%, each), and Leukopenia, Colitis, Fatigue, Infection, Hypercalcaemia, Osteonecrosis of jaw, Pathological fracture and Metastases to soft tissue (n=1, 0.28%, each). Necessary or prolonged hospitalization was the reason of seriousness of serious drug-related TEAE in 18 patients (64.29%), Life threatening in six patients (21.43%), death in five patients (17.86%), Other medically important serious event in four patients (14.29%), and Persistent or significant disability/incapacity in one patient (3.57%). Radium-223 was most frequently withdrawn due to serious TEAE (n=58 patients, 60.42%). In 15 patients (15.63%), Radium-223 dose was interrupted/delayed due to serious TEAE; dose was not changed in further 15 patients. Serious TEAEs recovered/resolved in 18 patients (18.75%), were recovering/resolving at the end of observation period in one patient (1.04%), recovered/resolved with sequelae in nine (9.38%), and did not recovered/not resolve in 33 (34.38%). The outcome was fatal in 27 patients (28.13%), and it was unknown in eight patients (8.33%).

11. Discussion

11.1 Key results

Analysis of the primary objective of the study revealed that 59.3% of patients had at least one clinically meaningful pain response on BPI-SF questionnaire (two points improvement from baseline in the worst pain score) at any study visit. A clinically meaningful pain response was achieved by approximately third of patients already at treatment visit 2. However, there was no difference in rate of clinically meaningful pain response in patients with and without concomitant BHA use. Furthermore, the scores for Worst pain item were maintained throughout the study.

In patients treated with Radium-223 in the REASSURE study, 34% of patients had a clinically meaningful pain response at third Radium-223 injection (33). Rates of clinically meaningful pain response were higher in an observational study from Canada reaching 52% (40). Also in the ALSYMPCA, incidence of bone pain-related AE and serious AE was lower in patients receiving Radium-223 than in the placebo + best standard of care group (25, 41)). Furthermore, PSA level at baseline (>200 µg/l vs. <50 µg/l) was statistically significantly associated with pain response in the univariate, but not multivariate, logistic regression analysis. Previously, patients with a higher baseline PSA levels were shown to be less likely to receive 5-6 Radium-223 injections (42). Interestingly, more patients with 5-6 Radium-223 injections in our study achieved at least one clinically meaningful pain response than those with lower number of injections. Furthermore, our logistic regression analyses found a statistically significant association between higher number of Radium-223 injections and lower baseline PSA. Taken into account these information, it can be assumed that patients with less advanced disease, given the lower PSA levels, are more likely to receive a higher number of Radium-223 injections and achieve pain response and that patients should receive Radium-223 as early as possible within the current label.

Secondary objectives included the analysis of the remaining items of BPI-SF questionnaire. The percentage of patients with more than everyday kind of pain decreased after the first injection of Radium-223 and remained stable afterwards. Moreover, the percentage of patients with almost complete to complete pain relief monotonously increased, with 24.0% of patients reporting 80%-100% pain relief by cycle 6. Overall, Worst pain, Least pain, average pain, Current pain, Total pain, Pain severity and Pain interference scores were maintained throughout the study. Similarly, Worst Pain, Pain interference and Pain severity scores were maintained in the REASSURE study (33). Furthermore, the proportion of patients that indicated the following body areas as hurting most decreased from baseline to follow-up visit after end of treatment: Thoracic vertebra (from 11.7% to 4.2%), Lumbar vertebra (from 18.3% to 8.4%), Pelvis, left (from 16.1% to 8.4%), Pelvis, right (from 17.5% to 13.7%), Thigh, left (from 11.3% to 5.3%), and Thigh, right (from 14.6% to 6.3%). Above results on the beneficial effect of Radium-223 on bone pain were confirmed by the analysis of the QoL. FACT-BP score at baseline was 35.9 and 41.9 at visit 6 (where a higher score indicates improved QoL). Therefore, these findings indicate QoL is maintained in patients treated with Radium-223. In the ALSYMPCA study, Radium-223 plus standard of care improved QoL as assessed by FACT-P and EQ-5D questionnaires over the standard of care alone (43). Furthermore, also scores for pain-related subscales were improved in the Radium-223 group. Collectively, these data indicate that that Radium-233 is effective in preventing bone pain deterioration.

22.2% of patients started using opioids during the Radium-223 therapy. This percentage was lower than in the ALSYMPCA trial, in which 36% of patients required opioids during the therapy with Radium-223 (44).

In our study, median OS was 17.15 months. In the ALSYMPCA trial, median OS amounted to 14.9 months (45), while several observational studies investigating Radium-223 with abiraterone/prednisone or enzalutamide reported median OS of 14.3-15.6 months (46-48). Median OS was longer in patients with 5-6 injections (20.7 vs 5.7 months in 1-4 injections group) and tended to be longer in patients without prior abiraterone therapy (17.91 vs 13.9 months in prior abiraterone group), and in those without prior (17.51 vs 13.53 months in pretreated group) or concomitant enzalutamide treatment (17.51 vs 14.46 months in concomitant enzalutamide group). There was no difference in OS with respect to concomitant abiraterone or BHA therapy. Other studies found no difference in OS between patients with or without concurrent BHA (45). Real-world evidence indicate that Radium-223 therapy layered with abiraterone/prednisone or enzalutamide induces a longer OS than when these types of drugs were used sequentially (46).

Patients in our analysis received a median number of one prior anti-cancer therapy (including abiraterone, enzalutamide, docetaxel and cabazitaxel that were finished before or during the Radium-223 therapy) thus confirming that in daily clinical practice in mCRPC in Germany, Radium-223 is used in patients pretreated with systemic anticancer treatment. Therefore, survival data obtained in our study reflect the Radium-223 efficacy when used in real-world practice according to the approved label in Europe. Caffo et al. showed that among patients that were treated with at least three lines of anti-cancer therapy, those that received all six planned doses of Radium-223 had a longer OS than those who received fewer injections (49). Furthermore, real-world REACTIVATE study from Canada presented at ASCO Genitourinary Cancers Symposium 2021 demonstrated that patients who received Radium-223 in second-line had a longer survival than those treated with Radium-223 in third- or later-lines (50). Moreover, those that received Radium-223 early received less chemotherapy but still had a better survival than patients with Radium-223 in later line.

Median ALP levels decreased from 133 U/l (range: 29.8-1129) at baseline to 95.3 U/l (range: 27-790) during the study. Median PSA levels increased from 58.04 µg/l (range: 0-2130) at baseline to 90.72 µg/l (range: 0-6419.5) during the study. Furthermore, among the Radium-223-treated patients in the ALSYMPCA trial, those with ALP decrease had a longer OS than patients with no reduction in ALP levels (17.8 vs 10.4 months, HR=0.45; 95%CI: 0.34–0.61; P<0.0001, (51)). Therefore, although the dynamics in PSA levels seem not to be associated with response to therapy, there is a compelling evidence for predictive value of ALP decrease on the improved survival in Radium-223-treated patients (51). This association could be explained by the calcium-mimetic properties of Radium-223 and thus directly decreasing ALP levels (52).

Over the time covering the Radium-223 treatment, follow-up after end of treatment and long-term follow-up, the EBRT for relief of skeletal symptoms was used in 8.8% of patients, 7.3% had a new symptomatic pathological bone fracture, 2.8% had a spinal cord compression and 2.3% of patients had a tumor-related orthopedic surgical intervention. The ERA 223 trial demonstrated that addition of Radium-223 to abiraterone and prednisone or prednisolone in asymptomatic or mildly symptomatic patients without systemic pretreatments for mCRPC increases the risk of fractures (36). However, data obtained in the present study indicate that fracture risk is similar between patients with previous or layered treatment with abiraterone or enzalutamide. This discrepancy could be at least in part attributed to the differences in patient characteristics, with patients in this study suffering from more advances disease, with more pronounced symptoms and undergoing a later-line of therapy as compared to the ERA 223 trial. Interestingly, a recent observational study reports a much lower rate of fractures among the abiraterone-pretreated patients receiving Radium-223 (2.1%

vs 7.2% reported here) further indicating that abiraterone followed by Radium-223 is associated with a low fracture risk (47).

The present study also indicates that patients with prior abiraterone therapy appear to have a higher rate of EBRT and spinal cord compression (13.3% and 4.8%, respectively) than those not pre-treated with abiraterone (7.4% and 2.2%, respectively). Nevertheless, considering that a higher EBRT rates were documented in ALSYMPCA trial (30%) than in our study (8.8%), the EBRT may be underreported in real-world setting. Alternatively, measures other than EBRT may be used nowadays for pain palliation, including palliative (active) tumor treatment with the new anti-hormonal drugs and chemotherapy, which were not available at the time when the ALSYMPCA trials was conducted. Previously, median time to first SSE of 15.6 months was reported for Radium-223-treated patients (53, 54). However, our data were immature for TSSE analysis since SSE occurred only in 14.4% of patients.

Incidence proportion of fractures appeared to be similar in patients with and those without concomitant BHA use (0.0645, 95%CI 0.0292 - 0.0998 and 0.1310, 95%CI 0.0799 - 0.1819, respectively). Furthermore, incidence proportion of pathological fractures (0.0645, 95%CI 0.0292 - 0.0998 and 0.1131, 95%CI 0.0652 - 0.1609) and bone associated events other than fractures (0.2258 95%CI 0.1657 - 0.2858 and 0.1607, 95%CI 0.105 - 0.2162) was similar between patients with and without concomitant BHA. In other observational study, concurrent BHA therapy reduced the incidence rate of SSE and pathological fractures in patients receiving Radium-223 plus abiraterone/prednisone and in those treated with sequential Radium-223 and enzalutamide (46). Furthermore, the impact of BHA on reduced risk of fractures has been recently underscored by the EORTC 1333/PEACE III trial that evaluated enzalutamide plus radium-223 versus enzalutamide alone in patients with asymptomatic/minimally symptomatic mCRPC. In that study, prior BHA therapy reduced the fracture risk in patients treated with Radium-223 (55).

56.2% of patients experienced at least one TEAE, most often Anaemia, Fatigue, Diarrhoea, Nausea, Pain, and Metastases to liver. Grade ≥3 TEAE occurred in 27.81% of patients; 7.58% died. Serious TEAE occurred in 26.97% of patients, most frequently Anaemia, Metastases to liver, Pancytopenia, General physical health deterioration, Neoplasm progression, Pain and Metastases to central nervous system. In one patient (0.28%), serious TEAE led to modification of Radium-233 dose, whereas 21.35% permanently discontinued the study drug. 25.84% of patients experienced a drug-related TEAE, most often Anaemia, Diarrhoea, Nausea, Fatigue, Pancytopenia and Thrombocytopenia. Grade ≥3 drug-related TEAE occurred in 11.24% of patients; 1.4% of patients died. Serious drug-related TEAE led to permanently discontinued the study drug in 8.15% of patients. Compared to our study, the frequency of TEAE, Grade 3 or 4 TEAE and serious TEAE was higher in the ALSYMPCA trial (93%, 56% and 47%, respectively, (44)). Slightly fewer patients discontinued Radium-223 in the ALSYMPCA trial than in the present study (16% vs 21.35%, (25). Furthermore, hematologic TEAE occurred less frequently in the present study than in the ALSYMPCA trial (Anaemia: 13.2 vs 31%; Thrombocytopenia: 2.3% vs 12%, (25). Rates of TEAE, drug-related TEAE and serious TEAE in the REASSURE study was 53%, 38% and 25%, respectively (56). In line with our results, the most frequent TEAE in the REASSURE study included Anemia, Diarrhoea, Nausea and Fatigue while most often documented drug-related TEAE were Anaemia, thrombocytopenia and nausea.

11.2 Limitations

This NIS has several limitations. First, due to a single-arm design, the comparison between patients treated with Radium-223 and those treated with other anti-cancer drugs was not possible. Second, the results can only be compared with historical data from clinical studies and observational studies, which is prone to bias and confounding as these data may not be collected in the same manner. Third, since the study was performed in Germany, the results may not be generalizable to other national healthcare systems. Fourth, data were available for only a few patients at long-term follow-up visits thus limiting an insight into late effects of Radium-223. Finally, prior to participation in this study, patients were cared by urologists and then referred to nuclear physicians who were investigators in this study. Therefore, there is a considerable risk for bias and loss of data during the data collection.

11.3 Interpretation

Results of this observational study confirm the available data on reduction of bone-associated pain in mCRPC patients treated with Radium-223. 59.3% of patients (95%CI 52.39- 65.88) had at least one clinically meaningful pain response during observation and pain control rate was 67.13 (95%CI 60.43- 73.35). Furthermore, clinically meaningful response was less frequently achieved in patients with 1-4 Radium-223 injections (42.9% vs 67.1% in patients with 5-6 injections) suggesting that completion of the entire therapy course may be needed for effective bone pain reduction. Our data also indicated that fewer patients required opioids than in the ALSYMPCA trial. These findings indicate that opioids are relatively infrequently prescribed in the daily clinical practice to ameliorate pain in Radium-223-treated patients. Therefore, a stabilization of tumor symptoms in end-stage mCRPC should be interpreted as a favorable outcome of Radium-223 therapy given that a great majority of patients did not require an increase in pain medication.

Our data furthermore confirmed the previously reported OS duration in clinical trials and observational studies. Patients with a 5-6 Radium-223 injections had a longer median OS than those with 1-4 injections (20.7 vs 5.7 months). Moreover, there was a tendency towards a longer OS in patients without prior abiraterone therapy, and in those without prior or concomitant enzalutamide treatment and no difference in OS with respect to concomitant abiraterone or BHA therapy. These differences in OS may result from the fact that (i) patients with a higher number of injections could have a better performance status and thus were more fit to complete the entire cycle of Radium-223 treatment, and (ii) patients without abiraterone or enzalutamide pretreatment could suffer from a less advanced disease and thus they received a fewer number of prior lines of therapy.

We also found that Radium-223 was used after a median number of one prior systemic anticancer treatment (including abiraterone, enzalutamide, docetaxel and cabazitaxel that were started before the Radium-223 therapy) in the majority of patients thus confirming the Radium-223 efficacy in pretreated patients. Moreover, we observed a higher frequency of EBRT and spinal cord compression in patients pretreated with abiraterone which accounted for a higher SSE rate in that patient group. However, fracture rates in our study were similar between patients with previous or layered treatment with abiraterone or enzalutamide compared to the entire study population. Therefore, prior or concomitant therapy with abiraterone/prednisone or enzalutamide did not appear to increase fracture incidence in this study. Current guidelines for mCRPC and the information in SmPC for Radium-223 regarding the protection against SSE support the use of BHA. The data obtained in the present study could not show a significant effect of BHA on fractures risk. Finally,

obtained results confirmed the previously established efficacy and safety profile of Radium-223 in mCRPC patients. In line with previous clinical trial and real-world data, patients experienced most often Anemia, Diarrhoea, Nausea and Fatigue. Additionally, obtained data confirmed that the occurrence of hematologic toxicities is lower in patients treated with Radium-223 than in those receiving with chemotherapy.

11.4 Generalizability

The obtained results reflect the real-life clinical practice in mCRPC in Germany. This study was performed under routine conditions, with inclusion and exclusion criteria not restricting patient enrollment beyond the contraindications stated in the SmPC for Radium-223. There were no restrictions regarding comorbidities or concomitant medications with the exception of analysis of patients that started concomitant abiraterone plus Radium-223 therapy after March 2018. Patients who were to start Radium-223 therapy as per treating physician decision in accordance with the terms of the marketing authorization were consecutively enrolled into the study. These settings allowed data capture from a broad and heterogeneous patient population. Furthermore, characteristics of patients enrolled into this study were comparable with patient characteristics from other observational studies, including analysis of health records from Flatiron database in US and global study REASSURE (56), in terms of age, ECOG PS, levels of PSA and ALP and prior anti-cancer therapy.

12. Other information

None

13. Conclusion

In this real-world study, 59.3 % of patients treated with Radium-223 had a clinically meaningful pain response. A higher number of patients with 5-6 Radium-223 injections achieved a pain response and prolonged OS compared to those with 1-4 injections. Prior or concomitant therapy with abiraterone/prednisone or enzalutamide did not appear to increase fracture incidence in this study. QoL was maintained in patients suffering from mCRPC. The overall clinical outcomes with Radium-223, including pain response, safety and OS, were consistent with previous observations and confirmed the previously established safety and efficacy profile of Radium-223.

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Appendices

Annex 1: List of stand-alone documents

Table 36: List of stand-alone documents

Document Name	Final version and date (if available)*
Investigator list	V1.0; 19 MAY 2021
List of IEC and IRB	V1.0; 19 MAY 2021
DMP	V2.0; 15 JUL 2019
CRF	V11.0; 15 APR 2019
QRP	V2.0; 17 OCT 2018
MRP	V6.0; 12 DEC 2019
List of informed consent withdrawals	V1.0; 19 MAY 2021
TLF (including TLF by BHA and TLF by injection number)	V6.0; 27 APR 2021
SAP	V3.0; 06 JUL 2020

Annex 2 Additional information

Table 37: List of OS/PASS protocol versions

Document Name	Effective Date
OS/PASS protocol version 1.0	12 SEP 2014
OS/PASS protocol version 2.0	18 NOV 2014
OS/PASS protocol version 3.0	06 NOV 2015
OS/PASS protocol version 4.0	16 FEB 2017
OS/PASS protocol version 5.0	14 JUL 2017
OS/PASS protocol version 6.0	30 APR 2018

Annex 3 Signature Pages

Signature Page - Study Medical Expert

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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

Print Name: PPD

Date, Signature: 2.6.2021, PPD

Signature Page - Study Statistician

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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

Print Name: PPD

Date, Signature: 23-Jun-2021 _____, _____ PPD

Signature Page - Study Epidemiologist

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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

Print Name: PPD

Date, Signature: 22-Jun-2021, PPD

Signature Page - Study Safety Lead

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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Print Name: PPD

Date, Signature: 4.6.21 , PPD

Signature Page - Study Conduct Responsible

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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Print Name: PPD

Date, Signature: 02-Jun-2021, PPD

Signature Page - Study HEOR responsible

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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

Print Name: PPD

Date, Signature: 17.06.21, PPD

Signature Page - Study data manager

Title	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers
Report version and date	v 1.0; 01 Jun 2021
IMPACT study number	17550
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS9020
Medicinal product	Xofigo® (Radium-223 dichloride)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

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

Print Name: PPD

Date, Signature: 02 June 2021, PPD