Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	URANIS – Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS24796
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 sought to evaluate overall survival (OS) of metastatic Castration Resistant Prostate Cancer (mCRPC) patients receiving Radium-223-dichloride in a real life urooncology practice setting in Germany. In addition, symptomatic skeletal event free survival (SSE-FS), time to next tumor treatment (TTNT), safety, QoL, mobility and self-care, activities of daily living and body function were explored.
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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	URANIS – Data collection in **u**rological centers during treatment with **Ra**-223 dichloride (Xofigo) within the framework of a **n**on-**i**nterventional **s**tudy assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date **Author**	V 1.0, 01 SEP 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®, overall survival, quality of life
Rationale and background	Phase III ALSYMPCA trial in metastatic castration-resistant prostate cancer (mCRPC) demonstrated that Radium-223 improves overall survival (OS) compared to placebo plus best standard of care. However, the real-world data on effect of Radium-223 on OS is scarce.
Research question and objectives	This observational study sought to evaluate (OS) in mCRPC patients receiving Radium-223 in daily clinical practice. The primary objective was evaluation of OS. Secondary objectives included evaluation of symptomatic skeletal events (SSEs) and SSE-free survival (SSE-FS), estimation of pathological and non-pathological fractures and bone associated events, treatment-emergent adverse events (TEAE), type and time to next tumor treatment (TTNT), safety, quality of life (QoL, using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire), activities of daily living (using the Katz-Index) and body function (using MOSES questionnaire).
Study design	Prospective, non-interventional, multi-center, single arm cohort study.
Setting	Thirty-six departments of urooncology 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 symptomatic bone metastases and no known visceral metastases and initiating Radium-223 therapy. 82 patients were available for safety analysis (SAF set); and 73 patients were included in the full analysis set (FAS).
Variables and data sources	Historic demographic and clinical data were obtained from medical records. Clinical and patient-reported data were collected during treatment and follow-up visits.
Results	Median age at registration was PPD 82.2% had Eastern Cooperative Oncology Group performance status 0-1. Patients had a median number of 1 prior systemic anti-cancer therapy. Median number of Radium-223 injections was 6; 64.4% of patients received BHA prior to or overlapping with Radium-223. Overall, median OS was 16.72 months (95%CI 12.65-23.72) and it was longest in patients without prior/concomitant chemotherapy (20.47 months, 95%CI 13.67-26.09) and in patients with prior/concomitant abiraterone (23.52 months, 95%CI 9.76-not reached (NR)). Median SSE-FS was 14.98 months (95%CI 11.40-20.90). Seven patients (8.5%) had SSEs, including external radiotherapy for relief of skeletal symptoms (n=5, 6.1%) and new symptomatic pathological bone fracture (n=4, 4.5%). Median TTNT was 14.42 months (95%CI 10.12-NR); 28 patients (38.4%) received a mCRPC therapy after the first Radium-223 injection. Mean FACT-P total score remained stable form baseline (109.66, SD 19.94) until follow-up after 6 months (108.08, SD 25.83). Mean Katz index total score remained stable at a high level from baseline (5.6, SD 0.9) until follow-up after 1 month (5.3, SD 1.4). Scores for most of the domains in MOSES remained at the same level from baseline until follow up after 1 month. 61% and 25.6% of patients experienced at least one TEAE or drug-related TEAE, respectively, most often anemia, fatigue and diarrhea. Serious TEAE occurred in 29.3% of patients, most frequently anemia (in 3.7%).
Discussion	This real-world study confirmed an efficacy of Radium-223 to prolong OS, TTNT and SSE-FS in mCRPC patients. Occurrence of SSEs was similar as previously reported. QoL, functional status and ability to independently perform activities of daily living remained

	stable throughout the study. Finally, this study confirmed the favorable safety profile of Radium-223.
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
BHA	Bone Health Agents
CFR	Code of Federal Regulations
CI	Confidence Interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
EBRT	External Beam Radiation Therapy
EC	European Commission
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
EOD	Extent of Disease
EU	European Union
EWB	Emotional Well-Being
FACT-P	Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with prostate cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FWB	Functional Well-Being
HEOR	Health Economics and Outcomes Research
HR	Hazard Ratio
ID	Identifier
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
MOSES	Mobility, Self-Care, and Domestic Life questionnaire
MRP	Medical Review Plan
N/A	Not Applicable
NCI- CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCS	Prostate Cancer Subscale
PMCF	Post Market Clinical Follow-up
PWB	Physical Well-Being
PSA	Prostate-Specific Antigen
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible for Pharmacovigilance
QRP	Quality Review Plan
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SSE	Symptomatic Skeletal Event
SSE-FS	Symptomatic Skeletal Event Free Survival
SWB	Social/Family Well-Being
TEAE	Treatment-Emergent Adverse Events
TLF	Tables, listings and figures
TTNT	Time to Next Tumor Treatment

3. Investigators

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

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5. Milestones

The study milestones are shown in Table 1.

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 MAY 2015	28 MAY 2015	
End of data collection (LPLV)	31 DEC 2023	30 JUN 2020	The study has been prematurely terminated.
Registration in the EU PAS register	Q2 2018	01 AUG 2018	Study was changed to a post authorization safety study (PASS) with protocol V.4.0.
IEC approval*		First approval: 04 MAY 2015 Last approval: 04 SEP 2018	
Database Clean	31 MAR 2024	17 SEP 2020	
Final report of study results	30 SEP 2024	01 SEP 2021	

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

6. Rationale and background

Prostate cancer is the most common non-cutaneous malignancy in men in Germany. In 2017, there were 62 230 new cases, and 14 318 died from the disease (1). The estimated age-standardized rate for prostate cancer incidence in Germany is 95.9 per 100 000 (1). Incidence rates increase sharply beyond the age of 50 years. For men aged 50-54 years, the incidence rate is 58 per 100 000 men; ten years later, at age 60-64 years, the rate is more than five times higher at 328 per 100 000, and at 70-74 years the rate is almost eleven times higher at 634 per 100 000 (2). 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, nearly all treatments of the advanced stage are directed toward eradicating or limiting osseous metastases or palliating their side effects (3). 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 (4-6). 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 metastatic castration-resistant prostate cancer (mCRPC) patients (7-11).

Prostate cancer cells are stimulated by androgens, in particular testosterone. Conventional androgen deprivation therapy (ADT) in patients with bone metastases aims to reach castration levels of testosterone (i.e. ≤50 ng/dL 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 (12). Already early stages of mCRPC 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 (13).

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 (14).

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. 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 (15, 16). The associated complications present a substantial disease and economic burden (17). 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 mCRPC, specific treatment options for this condition are needed. Control of bone metastases is expected to lead to improved symptoms and quality of life as well as prolonged overall survival (OS, (18)). Regardless of the nature and location of bone metastases, the use of bone targeted treatments, including bone health agents (BHA, e.g. zoledronic acid (19) or denosumab (20)) 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 (21, 22).

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, (23)), 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 update 2015 (24). 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 plus best standard of care (median OS 14.9 vs. 11.3 months, respectively; HR=0.70; p<0.001). Symptomatic skeletal events (SSEs) 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-223 group and in placebo plus 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 (25) 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 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 (26).

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 (27). The distinct reduction of local symptoms from bone metastases delayed substantially the distortion of quality of life (QoL) compared with placebo (27). 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. It is very likely that the extended OS and time to SSE did not only preserve the QoL but also the independence in activities of daily living and body function which may itself build the basis for the perceived long-term preservation in QoL observed in patient treated with Radium-223 dichloride in ALSYMPCA. If this would be the case it is likely that the treatment with Radium-223 dichloride would save substantial costs for patient care in mCRPC patients.

The effect of Radium-223 on the independence in activities of daily living and body function in mCRPC patients was not investigated in the pivotal Phase 3 ALSYMPCA trial but data on QoL were collected in this closely defined patient population according to strict inclusion and exclusion criteria. This non-interventional prospective study was designed to further examine the effect of Radium-223 on QoL and activities of daily living and body function in mCRPC patients in more detail and in a more heterogeneous patient population under routine daily practice conditions in Germany. In contrast to the NIS PARABO, which focused on the assessment of pain, and the NIS REASSURE, which focused on the long-term safety for Radium-223 treated patients, this study collected data on overall survival, time to first SSE, QoL and activity of daily living in mCRPC patients. The inclusion of patients for the above mentioned NIS was organized by urooncologists at study sites in different areas.

For QoL examination, the questionnaire “Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with prostate cancer” (FACT-P, (28)) was used. The FACT-P questionnaire version 4 is a 39-item questionnaire consisting of five domains; ‘Physical well-being’, ‘Social/Family well-being’, ‘Emotional well-being’, ‘Functional well-being’ and ‘Additional concerns’ (consisting of items relating specifically to prostate cancer and/or its treatment) and uses a 0-4 Likert-scale; recall period of the questionnaire is 7 days (28). The activities of daily living were examined using the KATZ index (29, 30) and body function by the MOSES questionnaire (31). Comorbidities was captured in all patients using the cumulative illness rating scale for Geriatrics (CIRS-G, (32)).

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 mCRPC (study number 15396, NCT02043678, (33)). 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 (25) and in the Amendment 3 (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 URANIS study and were assessed in all patients available for safety analysis.

Since the release of updated product information of Radium-223 in EU in March 2018 (25), 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 sought to evaluate overall survival OS of mCRPC patients receiving Radium-223-dichloride in a real life setting at urooncological centers in Germany. In addition, symptomatic skeletal event free survival (SSE-FS), estimates of fractures and bone associated events, time to next tumor treatment (TTNT), safety, QoL, mobility and self-care, activities of daily living and body function were explored.

7.1. Primary objective

The primary objective of this study was to evaluate the overall survival during Radium-223 dichloride treatment of mCRPC patients in a real life setting.

7.2. Secondary objective(s)

The secondary objectives in this study were:

- To explore SSE-FS.
- To examine the incidence of treatment-emergent adverse events (TEAE) (up to 30 days after last administration of Radium-223).
- To calculate the incidence of pathological fractures (as part of SSEs), non-pathological fractures and bone associated events during the treatment and up to 5 year follow-up period.
- To explore treatments and time to subsequent mCRPC treatment (TTNT).
- To examine the QoL as patient reported outcome using FACT-P.

- To explore the independence in activities of daily living by using the Katz-Index.
- To explore body function in dimensions of "mobility", "self-care", and "domestic life" (MOSES questionnaire)

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	23 FEB 2017	Section 6: Milestones Section 9.1 Study design Section 9.2. Setting Section 9.5: Study size	Amendment	• Reduction of sample size from 500 patients to 250 planned patients due to previously unexpected delays in enrolment. • Extension of enrollment period from 24 months to 40 months. • Number of patients for interim analyses reduced from 100 to 75 and from 400 to 180, respectively. The reduction of patient number and elongation of recruitment period were calculated by taking into account the patient availability under real life conditions which differs from the initial site feasibility statements significantly: Initial feasibility statements were 8 patients per site per year. A follow-up assessment 1 year after FPFV showed that the number of eligible patients was only between 0-6 per site and year in reality. More sites are planned to be opened after recruitment of the two other Xofigo® NIS PARABO and REASSURE ended recruitment in Germany (Q1/2017) to reach a site number of 100-125. The intended increase of study sites in 2017 has been taken into account for the calculation of the time needed to enroll 250 patients. With 100 sites becoming active during 2017, the aim to enroll 250 patients until Q3 2018 is from today`s point of view a realistic estimate.
2	14 AUG 2017	Section 6: Milestones Section 9.2.3 Exclusion criterion/criteria Section 9.5: Study size Section 9.7.1 Statistical consideration Section 11 Management and reporting of	Amendment	• Deletion of 2nd exclusion criterion to allow for enrollment of chemotherapy pretreated patients • Addition of (S)AE exception "disease progression" • Provision that all analyses will be provided for the complete study population, as well as separately for the chemotherapy naïve vs non naïve study population. The reason for this amendment is to allow the enrollment of chemotherapy pretreated patients based on the observation that the mCPRC therapy landscape in Germany has changed significantly since study start. Chemotherapy with Docetaxel in combination with conventional androgen ablation therapy will now be offered to all suitable patients with hormone sensitive metastasizing prostate cancer (about 20% of all patients). In addition

		adverse events/adverse reactions		chemotherapy with Docetaxel is now increasingly used in earlier lines of therapy in suitable mCRPC patients (younger and without important comorbidities) to delay the development of a disease which is refractory to androgen receptor targeted therapies. The inclusion of chemotherapy pretreated patients more likely allows to draw conclusions about the safety and efficacy under real world conditions and not only in a subgroup of Xofigo® patients.
3	30 APR 2018	Observational study information 6 Milestones 8.2 Secondary objective(s) 9.1 Study design 9.1.2 Secondary endpoint(s) 9.2.4 Withdrawal 9.2.7 Visits 9.3.2 Variables to explore the secondary endpoint(s), 9.5 Study size 10.5 Patient information and informed consent	Amendment	• Study was changed to a post authorization safety study (PASS) as a consequence of the fact that fractures have been classified as an "important potential risk" as one result of the interim analysis of the ERA-223 study. • Initiation of BHAs including bisphosphonates or denosumab, should be considered by investigator. • Early stop of recruitment period in Q2 2018 due to low patient enrolment. Sample size considerations were therefore adapted to a sample size of 75 patients and initially planned interim analyses were cancelled due to reduced sample size. • Prolongation of follow-up period for up to 5 years after last Radium-223 treatment. • Removal of subgroup analyses (with exception of presenting patients previously treated versus not previously treated with chemotherapy). • Addition of secondary objective to calculate incidence of pathological fractures, non-pathological fractures and bone associated events during the treatment and 5 year follow-up period. • The wording regarding the withdrawal has been updated. The reason for this amendment is 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. The collection of pathological fractures, non-pathological fractures and bone associated events (e.g. osteoporosis) during the treatment and 5 year follow-up period will 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 departments of urooncology throughout Germany. Study 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 at least 75 patients with mCRPC with symptomatic bone metastases without known visceral metastases for whom the attending physician decided according to his/her medical practice to treat the patient with Radium-223 dichloride. Treatment with Radium-223 dichloride followed 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 (CRF). The observation period for each patient enrolled in this study was the time from start of therapy with Radium-223 dichloride 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.

This study used 2 types of data sources: primary data collection from clinical visits and secondary data based on medical charts. Medical history of mCRPC patients was collected retrospectively from defined time-points to capture the clinical course of disease before inclusion into the study.

9.1.1. Primary endpoint(s)

The primary endpoint was OS defined as the time interval from the start of Radium-223 dichloride 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 were collected.

9.1.2. Secondary endpoint(s)

The secondary endpoints were:

- **Exploration of SSE-FS** of mCRPC patients was defined as the time from start of treatment to the occurrence of one of the following:

  (1) An on-study SSE, which was defined as:

  - the use of EBRT to relieve skeletal symptoms
  - the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
  - the occurrence of spinal cord compression
  - a tumor related orthopedic surgical intervention.

  (2) Death from any cause

- **Estimation of the incidence of pathological fractures** (as part of SSEs)**, non-pathological fractures** and **bone associated events** during the treatment and up to 5 year follow-up period.
- **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.
- **Incidence of TEAE** up to 30 days after last administration of Radium-223. 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 event was serious, intensity, relationship to Radium-223 dichloride, action taken and clinical outcome.

- **Quality of life as patient reported outcome** estimated using FACT-P questionnaire. Changes in QoL as determined by patient response on the FACT-P questionnaire. Analyses of QoL were performed for patients with evaluable patient questionnaires (FACT-P) at each visit.
- **Activities of daily living** explored according to the Katz-Index.
- **Body function** explored in dimensions of "mobility", "self-care" and "domestic life" using the MOSES questionnaire.

9.2. Setting

Initially, it was planned to collect the data from 500 patients enrolled at 125 departments of urooncology throughout Germany. However, the sample size was stepwise reduced to 250 patients (Amendment 1) and to 75 patients as a result of the decision to terminate enrollment early (Amendment 3). This decision was taken due to the very slow enrollment rate. Ultimately, 88 patients were enrolled into the study at 36 study sites. 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 then as up to five years (prolonged from the initial two years with amendment 3) after the last administration of Radium-223, whatever came first in time.

Patients who were participating in the study when amendment 3 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 28 MAY 2015, last patient first visit (LPFV) was on 18 MAY 2018 and last patient last visit (LPLV) was on 30 JUN 2020.

The sponsor decided to discontinue the study prematurely due to insufficient number of patients to gain any meaningful knowledge on long term safety (obtained during more than 2-year follow-up period) of those patients who were treated with Radium-223. The protocol amendment 3 became effective only three weeks before LPFV. Three out of 82 treated patients (3.7%) 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 two out of these patients (2.4% of all treated patients) were still in follow-up two years after the last Radium-223 dose. The low participation in the prolonged 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 mCRPC with symptomatic bone metastases without known visceral metastases were enrolled after the decision for treatment with Radium-223-dichloride has been made by the attending physician according to his/her medical practice.

Inclusion criterion/criteria

- Male patients diagnosed with castration resistant adenocarcinoma of the prostate 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

Exclusion criterion/criteria

- Patients participating in an investigational program with interventions outside of routine clinical practice and also in all non-interventional studies focusing on Radium-223-dichloride.

9.3.1. Withdrawal

In this observational study, withdrawal from the study was independent of the underlying therapy and it 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 could 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 data. In case a patient wanted to withdraw the consent given earlier, he informed his doctor and the site documented the withdrawal and the extend of withdrawal in the Case Report Form as well as in the patient´s medical record.

9.3.2. Replacement

Patients were replaced after dropout.

9.3.3. Representativeness

No further selection than outlined above was made and patients were enrolled consecutively in order to avoid any selection bias. With respect to site selection, this study could have a potential limited representativeness (at convenience sample) as only the sites with experience with prostate cancer management and treatment were considered for the participation in the study.

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.

Information on predefined retrospective visits captured the clinical course of disease before inclusion in the study. These retrospective visits were defined as time spans of ±4 weeks at 6 months, 12 months, 18 months and 24 months prior the date of informed consent. If the documented data were outside the predefined ± 4 weeks for the retrospective visit, the treating physicians were encouraged to document these data under the next closest predefined visit.

Data of first and second visit during treatment were documented after second and fourth application of Radium-223, respectively. The further course of disease was captured in follow-up visits after end of active treatment with Radium-223 approximately after 3, 6, 9, 12, 18, 24 and 30 months after end of treatment.

For each treatment cycle, information from patient medical records was documented and entered in the EDC system by the physician or designated medical person. These visits occurred during routine clinical practice, the study protocol did not define exact referral dates. The planned schedule of visits for this non-interventional trial is given as an overview in Figure 1.

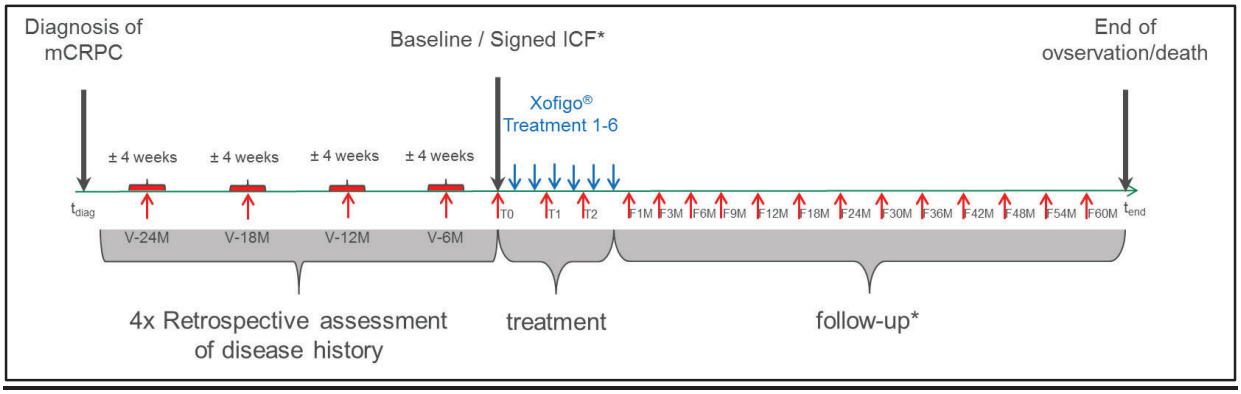

Figure 1: Overview of the planned visit schedule. ICF: Informed consent form; *Additional signed informed consent for prolonged follow-up (longer than 24 months after end of treatment with Radium-223 was necessary) period was necessary. Three patients signed the additional informed consent for follow-up for up to 5 years after the end of treatment.

Retrospective visit

The retrospective visits were defined as time spans of ±4 weeks at 6 months, 12 months, 18 months and 24 months prior the date of informed consent. It was assumed that retrospective visits were completed within 2 months after inclusion based on available clinical documentation.

Typical information to be collected at the retrospective visits for the respective time spans included:

- Date of visit
- Laboratory parameters including alkaline phosphatase (ALP), PSA and blood counts
- Prior anti-cancer therapy
- Eastern Cooperative Oncology Group performance status (ECOG PS)

Baseline 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 to be collected at the baseline/first treatment visit included:

- Date of visit
- Demography
- Medical history
- Concomitant diseases
- CIRS-G index
- Prostate cancer history
- Concomitant anti-cancer therapy
- Chemotherapy status (naïve / non naïve)
- WHO pain score
- ECOG status
- Pain medication or other concomitant medication
- Patient questionnaire on QoL (FACT-P), filled out by the patient prior to the first injection of Radium-223
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire)
- Laboratory parameters including ALP, PSA, blood counts
- Treating nuclear medicine physician

First and Second visit during treatment

Typical information to be collected at second treatment visit included:

- Date of visit
- WHO pain score
- ECOG status
- Patient questionnaires on QoL (FACT-P), filled out by the patient prior to the injection of Radium-223
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire)
- Changes in pain medication or other concomitant medication (including any BHA treatment)
- Changes in concomitant anti-cancer therapy

- Laboratory parameters including blood counts
- Dose of Radium-223 administered for treatment session 1-2 or 3-4
- Adverse events (including non-pathological fractures and bone associated events (e.g. osteoporosis))
- Symptomatic skeletal events (e.g. pathological fractures)
- Further treatment for mCRPC
- Survival assessment

Follow-up visit after end of treatment

If within routine clinical practice, data were collected from a follow-up visit approximately 4 weeks after end of treatment. Further follow-up visits were performed approximately after 3, 6, 9, 12, 18, 24 and 30 months after end of treatment.

After implementation of amendment 3, 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 to be collected at this follow-up visit after treatment included:

- Date of visit
- WHO pain score
- ECOG status
- Patient questionnaires on QoL (FACT-P)
- Questionnaires on Activities of daily living (Katz-Index) and Body function (MOSES questionnaire) during first follow-up visit
- Changes in pain medication and any BHA treatment
- Changes in anti-cancer therapy
- Laboratory parameters including blood counts
- Dose of Radium-223 administered (only at first follow up visit for treatment session 5 and 6)
- 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)
- Survival assessment
- Further treatment for mCRPC

End of Observation

The reason for end of observation was documented which could occur two years after the last administration of Radium-223, if the patient died, withdrew his consent or was lost to follow up. In case of death the 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 only applied to patients who consented to prolonged follow-up. For patients who did not 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, see Table 3) from medical records if available, or else by interviewing the patient. 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). The CRF is available upon request (see Table 20: List of stand-alone documents, Annex 1).

Table 3: Tabulated overview on variables collected during the study

Variables	Retrospective visit	Baseline visit	1st and 2nd visit during treatment	Follow-up after end of treatment	End of observation
Date of visit	X	X	X	X	X
Patient informed consent		X			
Demography		X			
Co-morbidities (medical history, concomitant diseases)		X			
Prostate cancer history (initial diagnosis, diagnostic and therapeutic procedures)		X			
WHO pain score		X	X	X	
Performance Status (ECOG)	X	X	X	X	
CIRS-G index		X			
FACT-P questionnaire		X	X	X	
KATZ-Index		X	X	X*	
MOSES questionnaire		X	X	X*	
Exposure/treatment (dose of Radium-223)		X	X		
Concurrent diagnostic and therapeutic procedures for mCRPC		X	X		
Laboratory parameters	X	X	X	X	
Concomitant medication (including any BHA treatment)		X	X	X**	
Any Adverse Events			X	X***	
Symptomatic skeletal events (e.g. pathological fractures)			X	X#	
All other (non-pathological) fractures and bone associated events (e.g. osteoporosis) during follow-up period				X#	
Prior anti-cancer therapy	X				
Further treatment for mCRPC			X	X	
Survival assessment			X	X	
Reason for end of observation					X

*only during first follow-up visit

**only change of pain medication and any BHA treatment

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

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

Variables to determine the primary endpoint(s)

The variables for primary objectives were:

- **Overall survival** was defined as the time interval from the start of Radium-223 dichloride 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 were collected.

Variables to explore the secondary endpoint(s)

The outcome variables for secondary objectives were:

- **SSE-FS** of mCRPC patients (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, or death)
- **TTNT** - Tumor treatment(s) after the last application of Radium-223 were collected.
- **Incidence of TEAE**
- **Incidence of pathological fractures (as part of SSEs), non-pathological fractures** and **bone associated events** during the treatment and 5 year follow-up period.
- **Quality of life as patient reported outcome** estimated using FACT-P.
- **Activities of daily living** assessed according to the Katz-Index.
- **Body function** assessed in dimensions of "mobility", "self-care" and "domestic life" using the MOSES questionnaire.

Demography

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

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

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, were documented in the Medical History/Concomitant Diseases section. The comorbidities were assessed according to CIRS-G index.

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 included: trade name or INN, start date, stop date/ongoing, total daily dose, unit, and indication.

Exposure / treatment

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

- Date
- Dose
- Unit
- Reasons for any significant delay/interruption/discontinuation of treatment

Visits

- Date of visit

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 initial diagnosis of bone metastases
- date of mCRPC diagnosis defined as confirmed rise of PSA despite conventional androgen ablation therapy (e.g. luteinizing hormone-releasing hormone analogs)
- prior diagnostic or therapeutic procedures associated with mCRPC
  - surgery/biopsy
  - systemic anti-cancer therapy including chemotherapy
  - 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 take place in routine practice. For patient reported outcomes, the 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 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 entered into the study database by Alcedis GmbH.

Each patient was identified by a 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 was able to identify the patient based on the patient identification code.

The Study Database contained all (pseudonymous) study data. The development of this application and the development and setup was done 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 for 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 Table 20: List of stand-alone documents, Annex 1).

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 safety and effectiveness information that can be explored and disseminated in a timely manner. However, a limitation of the study is related to the reduced sample size of 75 patients, which results in less precise estimates, as compared to the earlier sample sized of 250 and 500 patients. Therefore, interpretation of results should proceed with caution, taking into consideration the reduced precision of estimates.

Since this study was a single arm cohort study without an active comparison group, caution should be applied when making any comparisons, including comparisons of subgroups within the study, and comparisons with historical results from clinical studies. Due to the non-controlled design with one cohort only, any observed effects in this study may not be attributed to treatment with Radium-223 alone but will also reflect the natural course of disease. Differentiation of treatment effect and natural course of disease is not possible with this design.

9.8. Study size

The expected number of deaths, and the precision of estimates for median OS, for the sample sizes of 500 (original protocol) and sample sizes of 250, 150, 125 and 100, which may be defined by pretreatment with chemotherapy or chemotherapy-naïve patients (Amendment 2), are provided in Table 4. These estimates for the sample size of 100, 125, 150 and 250 patients assumed an exponentially distributed OS with a median of 20 months, an enrolment period of 40 months, a follow-up period of 24 months after the last Radium-223 injection/treatment of the last enrolled patient (and thus a total observation period of 70 months) and a 10% loss-to-follow-up rate per year (Amendment 2). The estimates for the sample size of 500 patients include the same assumptions, with the exception of an enrolment period of 24 months, and total observation period of 54 months, as planned in the original protocol.

Table 4: Expected number of deaths and confidence interval for median OS for different sample sizes

Sample Size	Expected Number of Deaths	Expected 95% confidence Interval for Median OS
500	331	17.5 – 22.8 months
250	173	16.5 – 24.0 months
150	104	15.5 – 25.4 months
125	87	15.1 – 25.9 months
100	69	14.6 – 26.8 months

The sample size was stepwise reduced from originally 500 to 250 patients (Amendment 1) and from 250 to an expected 75 patients as a result of the decision to terminate enrollment early (Amendment 3). This decision was taken due to the very slow enrollment rate which was not expected to be improving.

For a sample size of 75 patients and follow-up time of 5 years after last radium-223 treatment, the expected number of deaths was 52, and the expected 95% confidence interval for median OS was 13.8 – 28.0 months. These estimates assumed an exponentially distributed OS with a median of 20 months, an enrollment period of 36 months, and thus a total observation period of 102 months, and a 10% loss-to-follow-up rate per year.

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 are 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 are provided for the treatment duration, number of injections, the number of patients with dose modification due to TEAE (interruption, delay and discontinuation), number of dose modifications.

9.9.3. Analysis of primary outcome(s)

The primary analysis of Overall survival (OS) is based on recorded dates of death. OS is defined as the time interval from the start of Radium-223 dichloride 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.

OS is summarized using Kaplan-Meier estimates. Median event times together with the 25th and 75th percentiles and associated 95% confidence intervals are presented.

9.9.4. Analysis of secondary outcome(s)

- For quality of life exploration summary statistics including mean and mean change from baseline are provided for each assessment time point of the FACT-P questionnaire. For the summary of each post-baseline assessment, patients were excluded if there was no corresponding post-baseline measurement.
- Time to event variables (SSE-FS, TTNT) are 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 (see Table 20: List of stand-alone documents, Annex 1).
- Incidence of treatment emergent and drug-related AEs are presented. Additional subcategories are based on worst grade as reported using CTCAE and relationship to study drug.
- Incidence proportions and incidence rates of pathological fractures (as part of SSEs), non-pathological fractures and bone associated events during the treatment and follow-up period (reported as adverse events) are presented. 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 (see Table 20: List of stand-alone documents, Annex 1).

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.

Statistical analyses were primarily of explorative and descriptive nature.

All analyses were provided for the defined analysis groups. Additionally, the primary efficacy endpoint was analyzed according to prior chemotherapy, and prior treatment with abiraterone and enzalutamide. Given the lower than expected number of patients to be accrued, no additional subgroup analysis was performed.

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 next mCRPC treatment, date of dosing as well as start and end date of adverse events.

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

No sensitivity analyses were performed.

9.10.5. Amendments to the statistical analysis plan

SAP (version 3.0, dated 21 AUG 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. It was ensured that investigators had a chance to discuss and develop a common understanding of 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 (see Table 20: List of stand-alone documents, Annex 1).

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 Table 20: List of stand-alone documents, Annex 1).

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (eCRF) were validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA)(34). The documentation is available upon request.

9.11.2. Quality review

During on-site data reviews, data of a total of 83 patients were reviewed at 35 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 is described in the Quality Review Plan (QRP). The QRP is available upon request, see Table 20: List of stand-alone documents, Annex 1).

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

Eighty-eight patients were enrolled into the study at 36 study sites (Table 5). Six patients did not receive Radium-223, therefore, 82 patients (93.2%) were available for safety analysis (SAF set). Five patients (5.7%) in SAF violated IC 1 (Male patients diagnosed with castration resistant adenocarcinoma of the prostate with symptomatic bone metastases without known visceral metastases) and another three patients (3.4%) violated IC 2 (Decision to initiate treatment with Radium-223 was made as per investigator's routine treatment practice). Furthermore, informed consent was back dated in another patient. Therefore, 73 patients (83%) were included in the full analysis set (FAS). End of treatment was documented in 82 patients (93.2%), including 36 patients (40.9%) with irregular end of treatment, most frequently due to progression of mCRPC (n=18, 20.5%), AE (n=9, 10.2%) and patient's decision to end the treatment (n=4, 4.6%). End of observation was documented in 84 patients (95.5%). The most frequent reasons for end of observation was patient's death (n=45, 51.1%), regular end of study or patient lost to follow-up (n=11, 12.5%, both). Three patients (3.4%) signed additional informed consent for follow-up period up to 5 years after end of treatment. Among the 73 patients in FAS, 65 patients (89%) attended visit 1, and 47 patients (64.4%) attended visit 2. Follow-up was documented for 49 (67.1%) patients after month 1, 41 (56.2%) patients after month 3, 34 (46.6%) patients after month 6, 27 (37%) patients after month 9, 22 (30.1%) patients after month 12, 17 (23.3%) patients after month 18, 8 (11%) patients after month 24, and in 2 patients (2.7%) after month 30 (see Table 69 in TLF v1.0).

Table 5: Patient disposition

Patient disposition	N (%)
Number of patients enrolled	88 (100.00)
Patients without dose of Radium-223	6 (6.82)
Number of patients valid for SAF*	82 (93.18)
Violated inclusion criteria	8 (9.09)
Adult male patients diagnosed with CRPC with symptomatic bone metastases without known visceral metastases	5 (5.68)
Decision to initiate treatment with Radium-223 was made as per investigator's routine treatment practice	3 (3.41)
Backdated informed consent	1 (1.14)
Number of patients valid for FAS**	73 (82.95)
Number of patients with documented end of treatment	82 (93.18)
Number of patients with irregular end of treatment	36 (40.91)
Patient died	2 (2.27)
Patient withdrew consent (treatment with Radium-223 ongoing)	1 (1.14)
Patient's decision to end treatment	4 (4.55)
Progression of underlying disease	18 (20.45)
Non AE-related medical reasons (physician decision)	1 (1.14)
Adverse event	9 (10.23)
Other***	1 (1.14)
Number of patients with documented end of observation	84 (95.45)
End of observation- Type of contact	
On-site visit	18 (20.45)
Phone contact	26 (29.55)
Email	2 (2.27)
Postal mail	7 (7.95)
Information from other treating physician	14 (15.91)
Other source	17 (19.32)
Main reason for end of observation	
Regular end of study	11 (12.50)
Patient died	45 (51.14)
Patient lost to follow-up	11 (12.50)
Patient withdrew consent*****	7 (7.95)
Other****	10 (11.36)
Number of patients with an additional signed informed consent for follow-up period up to 5 years after end of treatment	3 (3.41)

* Patients receiving at least one dose of Radium-223 will be considered valid for safety analysis set.
** Patients from SAF not violating any inclusion or exclusion criterion and not receiving their first dose of Radium-223 before baseline visit will be considered valid for full analysis set.
***For other reason for irregular end of treatment see appendix 4, TLF v1.0.
**** For other main reason for end of observation see appendix 5, TLF v1.0.
***** Withdrew consent but agreed to further use of collected data
Source: Table 1, TLF v1.0

10.2. Descriptive data

10.2.1. Patient characteristics at baseline

Median age at registration was PPD (range PPD Table 6). Mean height was 174.3 cm (SD=8.5 cm), mean weight was 86.2 kg (SD=15.9 kg) and mean BMI was 28.1 kg/m² (SD=4.6 kg/m²). All patients were white. Baseline ECOG performance status (PS) was 1 in the majority of patients (63%), followed by patients with PS 0 (19.2%) and PS 2 (13.7%, Table 6). Eight patients (11%) received abiraterone, 5 (6.9%) received enzalutamide and 7 (9.6%) received chemotherapy prior to Radium-223. As a prior anti-cancer therapy which overlapped with Radium-223 (see Figure 2 for definition of treatment periods), Abiraterone was used in 23 patients (31.5%), Enzalutamide in 20 patients (27.4%) and chemotherapy in 10 patients (13.7%). Abiraterone and Enzalutamide were used in 17 (23.3%) and 19 patients (26%), respectively, as a concomitant therapy with Radium-223. At baseline, most patients had 6-20 metastatic lesions (37%), followed by those with <6 metastatic lesions (30.1%) and patients with >20 metastatic lesions (but not a superscan, 17.8%).

Table 6: Baseline characteristics

Baseline characteristics	Total (n=73)
Median age, years (range)	PPD
ECOG PS, n (%)	
Grade 0	14 (19.18)
Grade 1	46 (63.01)
Grade 2	10 (13.70)
Grade 3	3 (4.11)
Grade 4	0 (0.00)
Prior anti-cancer therapy, n (%)*	
Abiraterone	8 (10.96)
Enzalutamide	5 (6.85)
Chemotherapy	7 (9.59)
Prior anti-cancer therapy including overlap to Ra-223 therapy, n (%)**	
Abiraterone	23 (31.51)
Enzalutamide	20 (27.40)
Chemotherapy	10 (13.70)
Concomitant anti-cancer therapy, n (%)***	
Abiraterone	17 (23.29)
Enzalutamide	19 (26.03)
Bone scan - Extent of disease (EOD)	
EOD 0: Normal or abnormal caused by benign bone disease****	2 (2.74)
EOD 1: <6 metastases location	22 (30.14)
EOD 2: 6-20 Metastases location	27 (36.99)
EOD 3: >20 lesions, but no super scan	13 (17.81)
EOD 4: Super scan	1 (1.37)
Missing	8 (10.96)

*'Prior treatment' refers to medications that are in group A in Figure 2.
**'Prior treatment including overlapping to Radium-223' refers to medications that are in group A, B or C in Figure 2.
***'Concomitant treatment' refers to medications that are in group B, C, D or E in Figure 2.
****In addition to EOD 0 the existence of bone metastases is documented for these patients.
Source: Table 2, TLF v1.0

Mean number of affected systems according to CIRS-G was 2.7 (SD 2.1, see Table 4 in TLF v1.0). Mean total score was 4.6 (SD 4.2) and the mean severity index was 1.4 (SD 0.9). Mean number of systems with level 3 and level 4 severity was 0.3 (SD 0.8) and 0.1 (SD 0.5), respectively (see Table 4 in TLF v1.0).

Most patients had CIRS-G 0 for each organ system (Table 7). Three patients (4.1%) had CIRS-G 3 for heart, one patient (1.4%) had CIRS-G 4 for vascular system, two patients (2.7%) had CIRS-G 3 for Respiratory system, two patients had CIRS-G 3 and 4 for upper gastrointestinal tract (GI, 1.4%,

both), two patients had CIRS-G 3 and 4 for renal system (1.4%, both), five patients (6.9%) had CIRS-G 3 and another five patients had CIRS-G 4 for genitourinary system, 11 patients (15.1%) had CIRS-G 3 and further 2 patients (2.7%) had CIRS-G 4 for musculoskeletal/integument system, one patient (1.4%) had CIRS-G 3 for neurological system, and one patient had CIRS-G 3 for endocrine/metabolic and breast. The comorbidity assessed according to CIRS-G was ongoing at study entry for musculoskeletal/integument in 46 patients (63%), heart in 34 patients (46.6%), genitourinary in 26 patients (35.6%), vascular in 25 patients (34.3%), renal in 14 patients (19.2%), endocrine/metabolic and breast in 12 patients (16.4%), hematopoietic and respiratory systems in 7 patients each (9.6%), eyes, ears, nose, and throat and larynx in 3 patients (4.1%), upper GI, lower GI, neurological and psychiatric illness in 3 patients each (4.1%) and for liver in 1 patient (1.4%, Table 7).

Table 7: Cumulative illness rating scale for geriatrics (CIRS-G) at baseline (FAS)

CIRS-G	N (%)
Number of patients	73 (100.00)
Number of patients with available CIRS-G	73 (100.00)
Heart	
0	36 (49.32)
1	22 (30.14)
2	12 (16.44)
3	3 (4.11)
Vascular	
0	45 (61.64)
1	16 (21.92)
2	11 (15.07)
4	1 (1.37)
Hematopoietic	
0	65 (89.04)
1	6 (8.22)
2	2 (2.74)
Respiratory	
0	63 (86.30)
1	7 (9.59)
2	1 (1.37)
3	2 (2.74)
Eyes, ears, nose and throat and larynx	
0	69 (94.52)
1	3 (4.11)
2	1 (1.37)
Upper GI	
0	69 (94.52)

CIRS-G	N (%)
1	1 (1.37)
2	1 (1.37)
3	1 (1.37)
4	1 (1.37)
Lower GI	
0	66 (90.41)
1	5 (6.85)
2	2 (2.74)
Liver	
0	72 (98.63)
1	1 (1.37)
Renal	
0	58 (79.45)
1	12 (16.44)
2	1 (1.37)
3	1 (1.37)
4	1 (1.37)
Genitourinary	
0	50 (68.49)
1	8 (10.96)
2	5 (6.85)
3	5 (6.85)
4	5 (6.85)
Musculoskeletal/Integument	
0	30 (41.10)
1	15 (20.55)
2	15 (20.55)
3	11 (15.07)
4	2 (2.74)
Neurological	
0	69 (94.52)
1	1 (1.37)
2	2 (2.74)
3	1 (1.37)
Endocrine/metabolic and breast	
0	61 (83.56)
1	9 (12.33)
2	2 (2.74)
3	1 (1.37)
Psychiatric illness	
0	70 (95.89)

CIRS-G	N (%)
1	3 (4.11)
Ongoing at study entry [multiple answers possible]	
Heart	34 (46.58)
Vascular	25 (34.25)
Hematopoietic	7 (9.59)
Respiratory	7 (9.59)
Eyes, ears, nose, and throat and larynx	3 (4.11)
Upper GI	3 (4.11)
Lower GI	3 (4.11)
Liver	1 (1.37)
Renal	14 (19.18)
Genitourinary	26 (35.62)
Musculoskeletal/integument	46 (63.01)
Neurological	3 (4.11)
Endocrine/metabolic and breast	12 (16.44)
Psychiatric illness	3 (4.11)

Source: Table 3, TLF v1.0

10.2.2. 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.

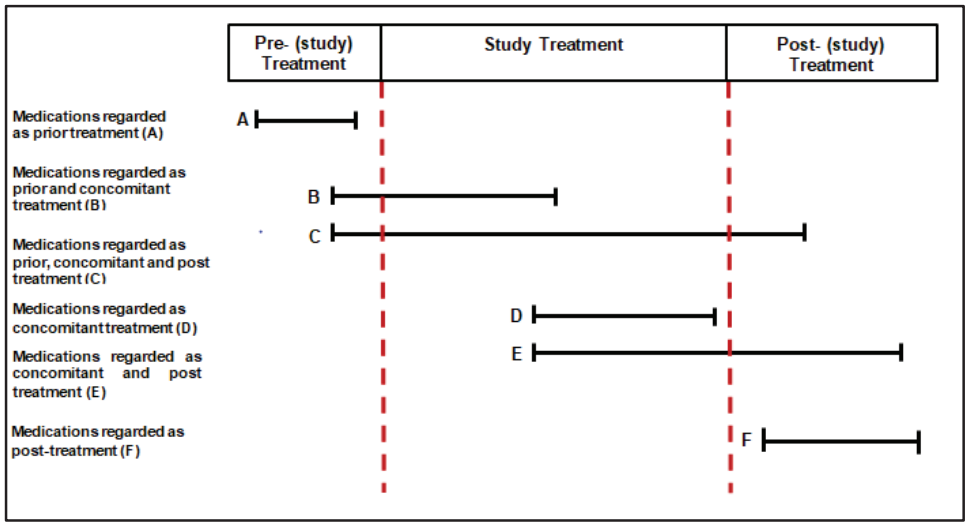

Figure 2: Definition of treatment periods

Source: Figure 15, TLF v1.0

Prior systemic anti-cancer therapy (including therapy overlapping with Radium-223) was received by 39 patients from FAS (53.4%), with the mean number of 1.3 therapies (SD 0.6) and median number of 1 therapy (range 1-3, see Table 68, only EU-approved medications for mCRPC were considered, see Table 68 in TLF v1.0).

At least one systemic anti-cancer treatment prior to Radium-223 (group A) was received by 32 patients (43.8%), most often Bicalutamide (n=17, 23.3%), Abiraterone (n=8, 11%), Docetaxel (n=6, 8.2%), Enzalutamide (n=5, 6.9%), Leuprorelin (n=5, 6.9%) and Degarelix (n=4, 5.5%, Table 8). Five patients (6.9%) receive at least one prior treatment with BHA, Pamidronic acid (n=2, 2.7%) and Zoledronic acid (n=3, 4.1%, Table 9).

At least one systemic anti-cancer treatment administered prior to and concomitantly with Radium-223 (group B) was received by 4 patients (5.5%), including Abiraterone, Enzalutamide, Bicalutamide and Leuprorelin (n=1, 1.4%, each, Table 8). One patient (1.4%) received Zoledronic acid prior to and concomitantly with Radium-223 (Table 9).

Fifty-six patients (76.7%) received at least one systemic anti-cancer therapy prior, concomitant and post-Radium-223 treatment (group C), most often Leuprorelin (n=27, 37%), Abiraterone (n=14, 19.2%), Enzalutamide (n=14, 19.2%), Bicalutamide (n=8, 11%) and Buserelin (n=6, 8.2%, Table 8). Forty patients (54.8%) received at least one BHA therapy prior, concomitant and post-Radium-223 treatment, most often Denosumab (n=24, 32.9%) and Zoledronic acid (n=13, 17.8%, Table 9).

None of the patients received a concomitant systemic anti-cancer treatment or BHA that was started and finished during the Radium-223 therapy (group D, Table 8 and Table 9).

At least one systemic anti-cancer therapy during and after Radium-223 treatment (group E) was received by 8 patients (11%), including Enzalutamide (n=4, 5.5%), Abiraterone (n=2, 2.7%), Leuprorelin (n=2, 2.7%) and Cyproterone (n=1, 1.4%, Table 8). One patient (1.4%) received Denosumab during and after Radium-223 treatment (Table 9).

Systemic anti-cancer therapy after Radium-223 (group F) was administered to 27 patients (37%), most often Docetaxel (n=13, 17.8%), Abiraterone (n=10, 13.7%), and Enzalutamide (n=9, 12.3%, Table 8). Seven patients (9.6%) received at least one BHA therapy after Radium-223 treatment, including Denosumab (n=5, 6.9%), and Pamidronic acid and Zoledronic acid (n=1, 1.4%, both, Table 9).

Table 8: Number of systemic prior, concomitant and post anti-cancer treatments (FAS)

Number of systemic anti-cancer treatments N (%)	Prior treatment (Group A)	Prior and concomitant treatment (Group B)	Prior, concomitant and post treatment (Group C)	Only Concomitant treatment (Group D)	Concomitant and post treatment (Group E)	Post treatment (Group F)
At least one medication	32 (43.84)	4 (5.48)	56 (76.71)	0	8 (10.96)	27 (36.99)
Docetaxel	6 (8.22)	-	2 (2.74)	-	-	13 (17.81)
Cabazitaxel	1 (1.37)	-	-	-	-	2 (2.74)
Abiraterone	8 (10.96)	1 (1.37)	14 (19.18)	-	2 (2.74)	10 (13.70)
Enzalutamide	5 (6.85)	1 (1.37)	14 (19.18)	-	4 (5.48)	9 (12.33)
Bicalutamide	17 (23.29)	1 (1.37)	8 (10.96)	-	-	
Buserelin	2 (2.74)	-	6 (8.22)	-	-	
Degarelix	4 (5.48)	-	3 (4.11)	-	-	
Leuprorelin	5 (6.85)	1 (1.37)	27 (36.99)	-	2 (2.74)	
Triptorelin	1 (1.37)	-	2 (2.74)	-	-	
Cyproterone	-	-	2 (2.74)	-	1 (1.37)	
Gonadorelin	-	-	2 (2.74)	-	-	
Imatinib						1 (1.37)
Mitoxantrone						1 (1.37)
Radium-223						2 (2.74)

Prior treatment is defined as medication started and ended before the start of Radium-223 treatment (A in Figure 2).

Prior and concomitant treatment is defined as medication started before the start of Radium-223, and ended during the Radium-223 treatment (B in Figure 2).

Prior, concomitant and post treatment is defined as medications started before the start of Radium-223 and ended after the end of Radium-223 (C in Figure 2).

Concomitant treatment is defined as medication started and ended during the Radium-223 treatment (D in Figure 2).

Concomitant and post treatment is defined as medication started during the Radium-223 treatment and ended after the end of Radium-223 (E in Figure 2).

Post treatment is defined as medication started and ended after Radium-223 (F in Figure 2).

Source: Tables 56, 57, 58, 59, 60, 61, TLF v1.0

Table 9: Number of prior, concomitant and post BHA treatments (FAS)

Number of systemic anti-cancer treatments N (%)	Prior treatment (Group A)	Prior and concomitant treatment (Group B)	Prior, concomitant and post treatment (Group C)	Only Concomitant treatment (Group D)	Concomitant and post treatment (Group E)	Post treatment (Group F)
At least one medication	5 (6.85)	1 (1.37)	40 (54.79)	0	1 (1.37)	7 (9.59)
Pamidronic acid	2 (2.74)	-	1 (1.37)	-	-	1 (1.37)
Zoledronic acid	3 (4.11)	1 (1.37)	13 (17.81)	-	-	1 (1.37)
Denosumab	-	-	24 (32.88)	-	1 (1.37)	5 (6.85)
Clodronic acid	-	-	1 (1.37)	-	-	-
Ibandronic acid	-	-	1 (1.37)	-	-	-

Prior treatment is defined as medication started and ended before the start of Radium-223 treatment (A in Figure 2).

Prior and concomitant treatment is defined as medication started before the start of Radium-223, and ended during the Radium-223 treatment (B in Figure 2).

Prior, concomitant and post treatment is defined as medications started before the start of Radium-223 and ended after the end of Radium-223 (C in Figure 2).

Concomitant treatment is defined as medication started and ended during the Radium-223 treatment (D in Figure 2).

Concomitant and post treatment is defined as medication started during the Radium-223 treatment and ended after the end of Radium-223 (E in Figure 2).

Post treatment is defined as medication started and ended after Radium-223 (F in Figure 2).

Source: Tables 62, 63, 64, 65, 66, 67, TLF v1.0

Twenty-three patients (28.1%) received at least one medication for the treatment of AEs (excluding anti-cancer therapies and BHA), most often Ibuprofen and Metamizole (n=5, 6.1%, both), Red Blood Cells (n=4, 4.9%), Ciprofloxacin, Fentanyl and Hydromorphone (n=3, 3.7%, each) and "Calcium Chloride; glucose; magnesium Chloride; potassium; sodium Chloride", Levofloxacin, "Naloxone; tilidine", Prednisolone, Pregabalin and Tramadol (n=2, 2.4%, each); "Calcium; calcium Carbonate" was used in one patient (1.2%, see Table 53 in TLF v1.0).

At least one medication for the treatment of concomitant disease (excluding anti-cancer therapies and BHA) were used in 42 patients (57.5%), most often Acetylsalicylic Acid (n=13, 17.8%), Metamizole and Ramipril (n=11, 15.1%, both), Amlodipine (n=10, 13.7%), Bisoprolol (n=9, 12.3%), Valsartan (n=6, 8.2%), Metoprolol and Simvastatin (n=5, 6.9%, both), and Allopurinol, Levothyroxine and Torasemide (n=4, 5.5%, each); three patients (4.1%) received "Calcium Carbonate; colecalciferol", and one patient each (1.4%) received Calcium and "Calcium; colecalciferol" (see Table 54 in TLF v1.0).

Fifty-four patients (74%) received at least one medication with missing indication (excluding anti-cancer therapies and BHA), most often Metamizole (n=22, 30.1%), Ibuprofen (n=14, 19.2%), Hydromorphone and Pantoprazole (n=9, 12.3%, both), "Naloxone; tilidine" (n=7, 9.6%), "Calcium Carbonate; colecalciferol", Fentanyl, Prednisolone and Tramadol (n=6, 8.2%, each), Pregabalin (n=5, 6.9%) and Metoclopramide (n=4, 5.5%, see Table 55 in TLF v1.0).

10.2.3. Treatment with Radium-223

Patients received a median number of 6 Radium-223 treatments (range: 1-6, mean 4.74 treatments, SD=1.62, see Table 47 in TLF v1.0). The majority of patients (61.6%) received 5-6 Radium-223 injections (see Table 49 in TLF v1.0). Median duration of Radium-223 therapy was 4.6 months (range: 0.03-6.31, see Table 48 in TLF v1.0). The Radium-223 treatment was delayed in 4 patients (5.5%, in each patient the treatment was delayed once) due to AE in two patients, a physician decision given the non-AE-related medical reasons in one patient, and delivery failure in another patient (see Tables 50, 51 and 52 in TLF v1.0).

10.3. Outcome data

The primary endpoint (OS) and the secondary endpoints (SSE-FS, TTNT, QoL according to FACT-P questionnaire, activities of daily living according to Katz-Index, and body function according to MOSES questionnaire) were analyzed in all 73 patients in FAS. The analysis of the secondary endpoint: incidence of pathological fractures, non-pathological fractures and bone associated events and safety analysis were performed in 82 patients from SAF.

OS was analyzed according the use of chemotherapy, abiraterone and enzalutamide prior to or prior to and overlapping treatment with Radium-223.

Of note, data on OS, SSE-FS, incidence of (non-)pathological fractures and bone associated events during the treatment and follow-up period and TTNT could have been affected by early study termination.

10.4. Main results

10.4.1. Primary objective analysis

The primary objective of this study was to evaluate the duration of OS defined as the time interval from the start of Radium-223 dichloride therapy to death, due to any cause. Median follow-up duration was 5.5 months (range 0-34.7). Forty patients in FAS (54.8%) died during the study. Overall, the median OS was 16.72 months (95%CI 12.65-23.72, Table 10, Figure 3).

Median OS was 15.01 months (95%CI 0.56-16.72) in patients with prior chemotherapy and 20.47 months (95%CI 12.65-26.09) in those without chemotherapy (Table 10, Figure 4). Median OS was 15.01 months (95%CI 0.56-16.72) in patients with chemotherapy that ended prior to or during Radium-223 treatment and 20.47 months (95%CI 13.67-26.09) in those without chemotherapy (Table 10, Figure 5).

Median OS was 17.86 months (95%CI 3.65-not reached, NR) in patients with prior abiraterone and 16.72 months (95%CI 13.67-23.95) in those without abiraterone treatment (Table 10, Figure 6). Median OS was 23.52 months (95%CI 9.76-NR) in patients with abiraterone therapy that ended prior to or during Radium-223 treatment and 15.34 months (95%CI 12.65-21.91) in those without abiraterone treatment (Table 10, Figure 7).

Median OS was 11.99 months (95%CI 2.04- NR) in patients with prior enzalutamide and 16.72 months (95%CI 13.67-23.95) in those without enzalutamide treatment (Table 10, Figure 8). Median OS was 12.65 months (95%CI 8.02-23.95) in patients with enzalutamide therapy that ended prior to

or during Radium-223 treatment and 16.72 months (95%CI 14.65-26.09) in those without enzalutamide treatment (Table 10, Figure 9).

Table 10: Overall survival [months] (FAS).

	N	Death	Censored	Q1	95%-CI of Q1	Median	95% CI for median	Q3	95% CI for Q3
Total	73	40	33	8.74	6.70-12.65	16.72	12.65-23.72	40.34	23.52-NR
OS by prior chemotherapy[A]									
Prior chemotherapy	7	7	0	4.11	0.56-15.01	15.01	0.56-16.72	16.72	11.40- NR
No prior chemotherapy	66	33	33	8.74	6.74-13.67	20.47	12.65-26.09	40.34	23.95- NR
OS by prior chemotherapy including overlapping with Radium-223 therapy[ABC]									
Prior chemotherapy	10	8	2	6.74	0.56-15.01	15.01	0.56-16.72	16.72	11.40- NR
No prior chemotherapy	63	32	31	8.90	7.10-13.67	20.47	13.67-26.09	40.34	23.95- NR
OS by prior treatment with abiraterone[A]									
Prior abiraterone treatment	8	5	3	10.58	3.65-23.72	17.86	3.65- NR	NR	11.40- NR
No prior abiraterone treatment	65	35	30	8.28	6.70-13.67	16.72	13.67-23.95	40.34	21.91- NR
OS by prior treatment with abiraterone including overlapping with Radium-223 therapy[ABC]									
Prior abiraterone treatment	23	13	10	9.76	3.42-14.98	23.52	9.76- NR	NR	23.52- NR
No prior abiraterone treatment	50	27	23	8.28	5.09-13.67	15.34	12.65-21.91	40.34	20.47- NR
OS by prior treatment with enzalutamide[A]									
Prior enzalutamide treatment	5	3	2	11.40	2.04- NR	11.99	2.04- NR	NR	2.04- NR
No prior enzalutamide treatment	68	37	31	8.74	6.70-13.67	16.72	13.67-23.95	40.34	23.72- NR
OS by prior treatment with enzalutamide including overlapping with Radium-223 therapy[ABC]									
Prior enzalutamide treatment	20	11	9	8.02	2.04-11.99	12.65	8.02-23.95	23.95	11.99-NR
No prior enzalutamide treatment	53	29	24	9.59	6.70-14.98	16.72	14.65-26.09	40.34	23.52-NR

[A]Therapy started and ended before the start of Radium-223 (A in Figure 2)
[ABC]Therapy started before the start of Radium-223 (A, B or C in Figure 2)
NR, not reached
Source: Table 7, 9, 11, 13, 15, 17, 19 (modified), TLF v1.0

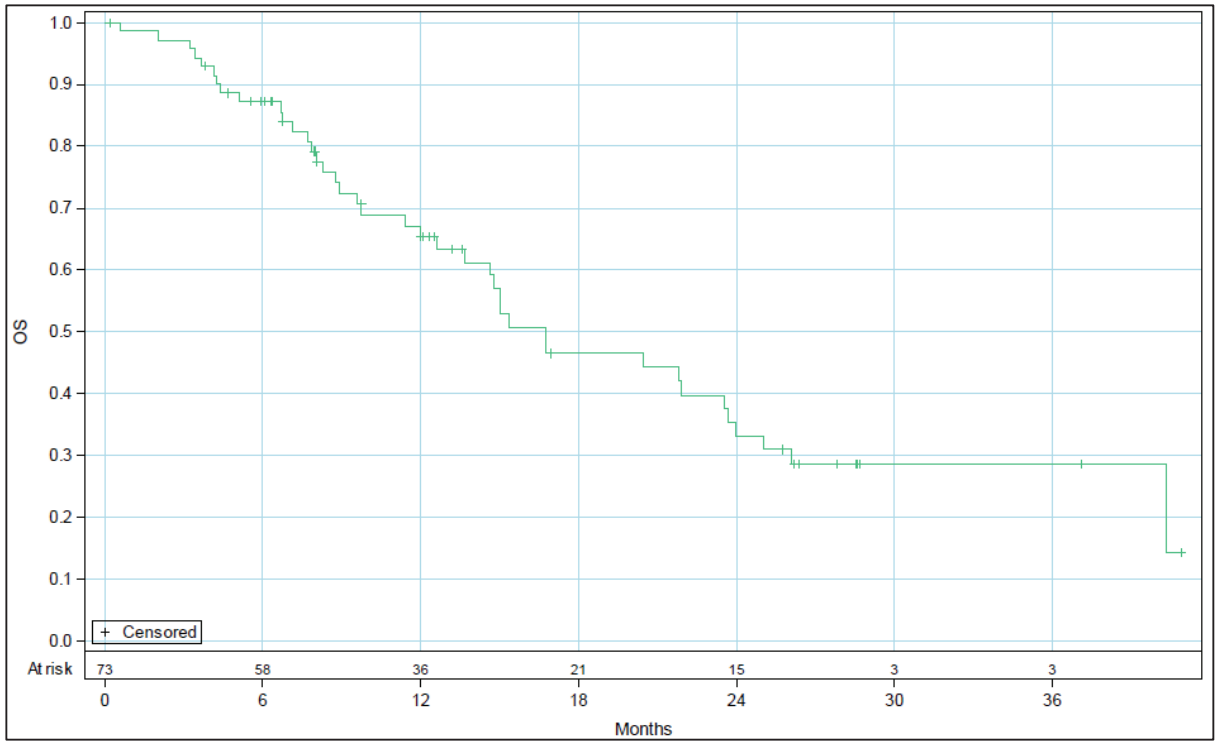

Figure 3: Overall survival in the total population (FAS).

Source: Figure 1, TLF v1.0

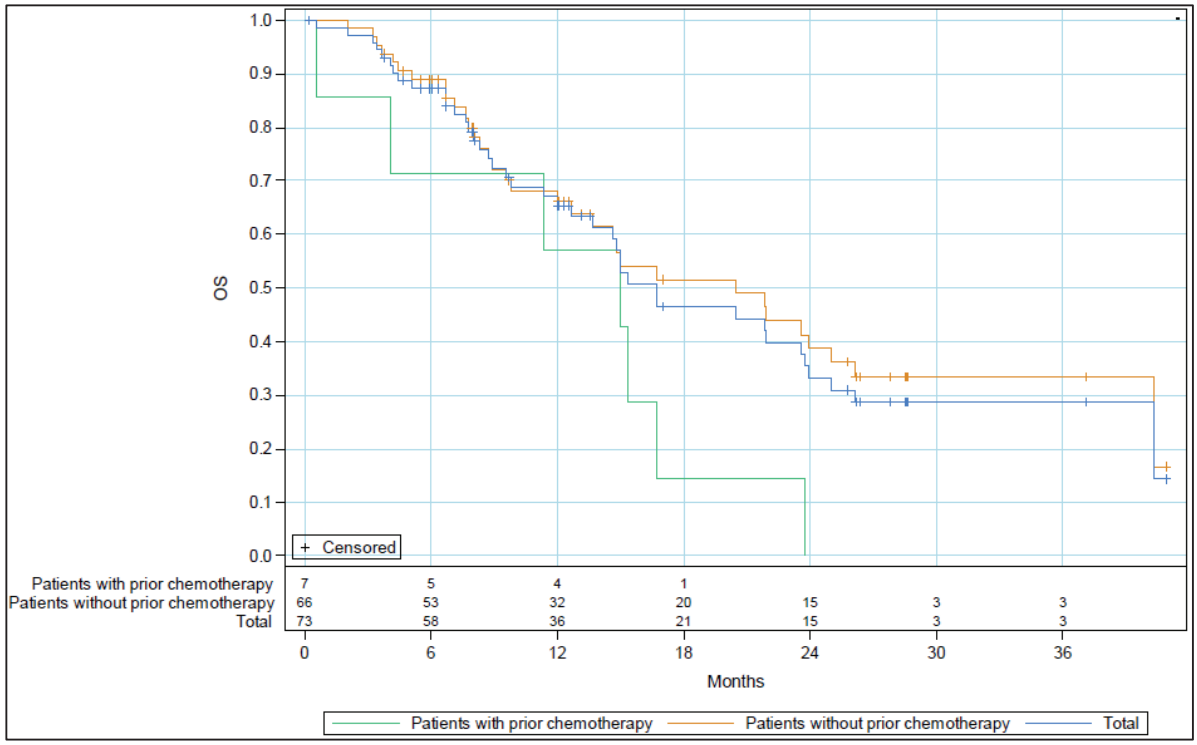

Figure 4: Overall survival by prior chemotherapy (FAS). Prior chemotherapy in this figure is defined as chemotherapy started and ended before the start of Radium-223 (A in Figure 2).

Source: Figure 2, TLF v1.0

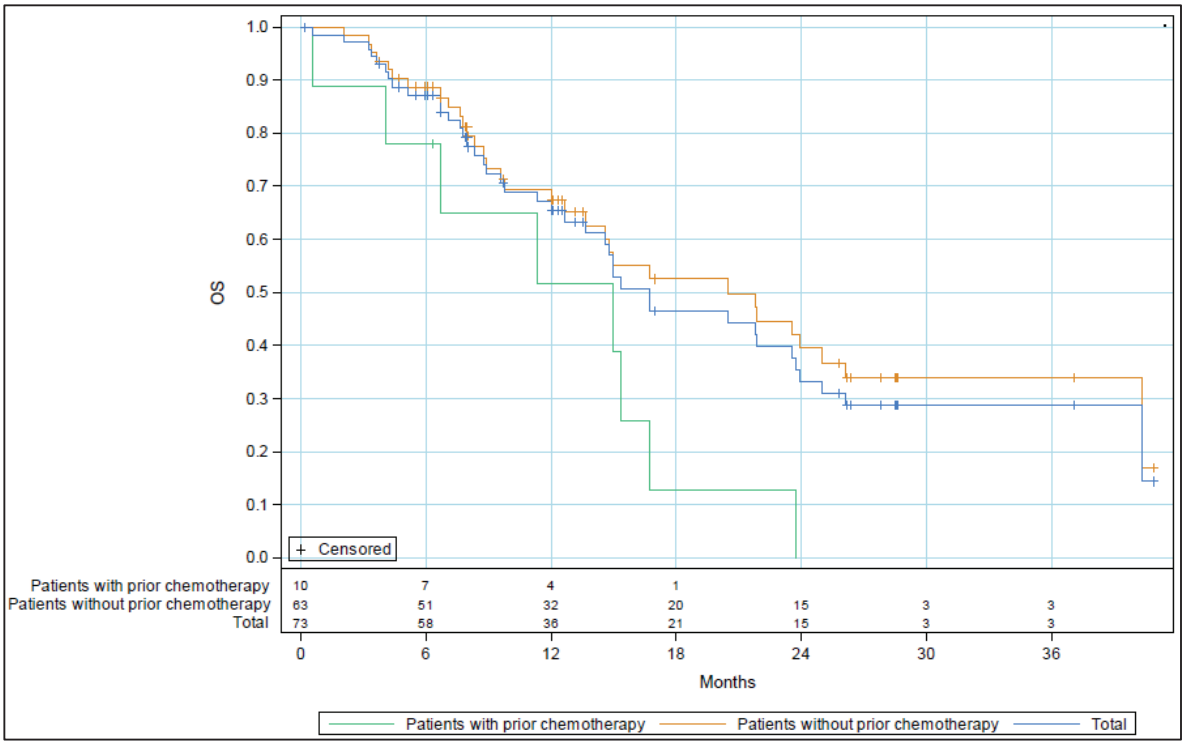

Figure 5: Overall survival by prior chemotherapy including overlapping to Radium-223 therapy (FAS). Prior chemotherapy in this figure is defined as chemotherapy started before the start of Radium-223 (A, B or C in Figure 2).

Source: Figure 3, TLF v1.0

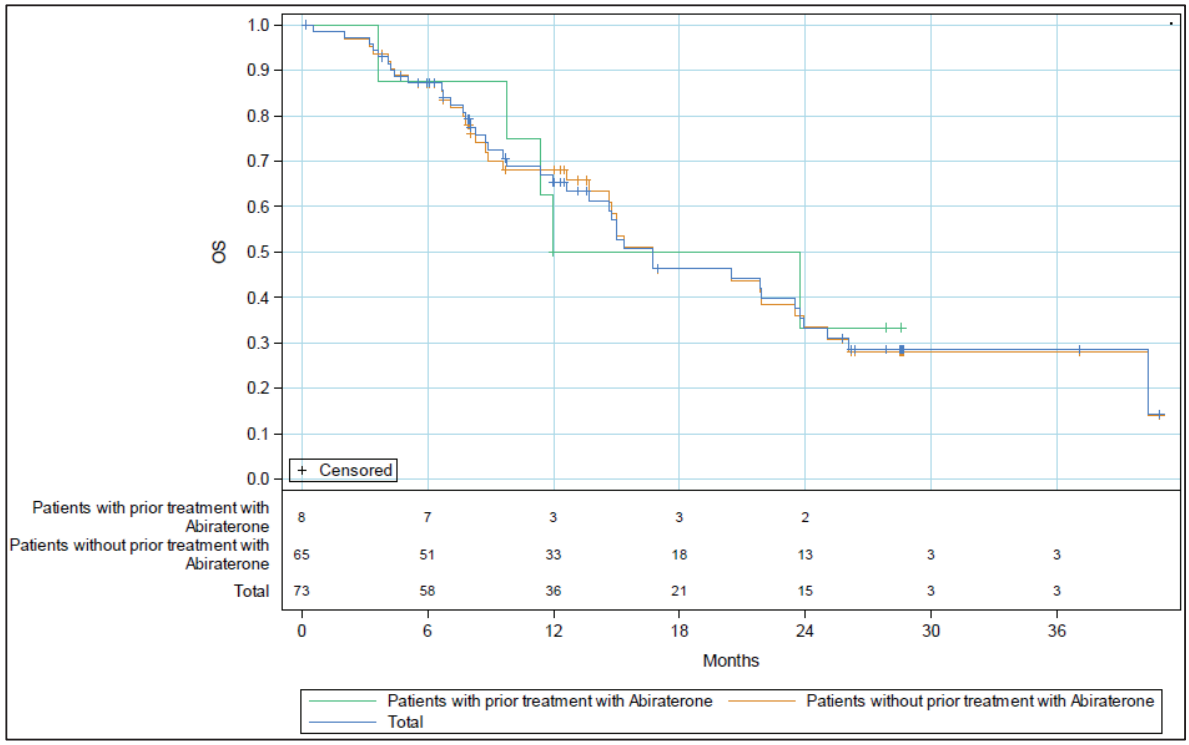

Figure 6: Overall survival by prior treatment with abiraterone (FAS). Prior treatment with abiraterone in this figure is defined as abiraterone started and ended before the start of Radium-223 (A in Figure 2).

Source: Figure 4, TLF v1.0

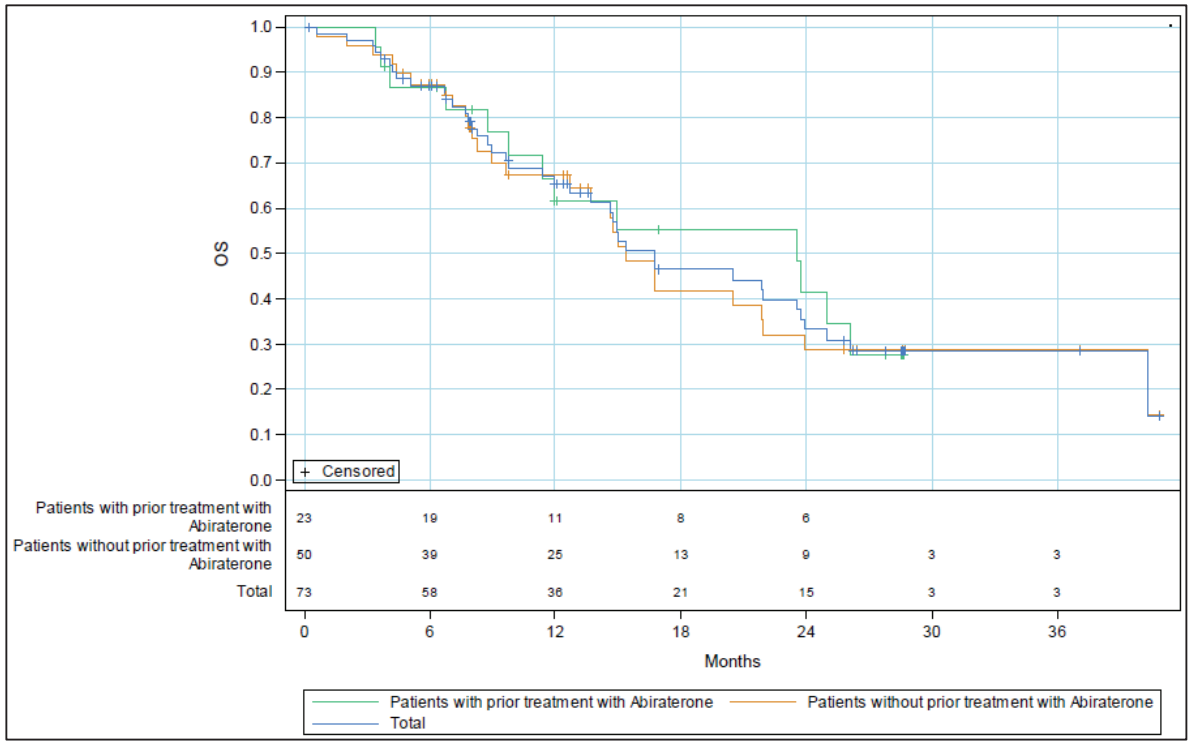

Figure 7: Overall survival by prior treatment with abiraterone including overlapping to Radium-223 therapy (FAS). Prior treatment with abiraterone in this table is defined as abiraterone started before the start of Radium-223 (A, B or C in Figure 2).

Source: Figure 5, TLF v1.0

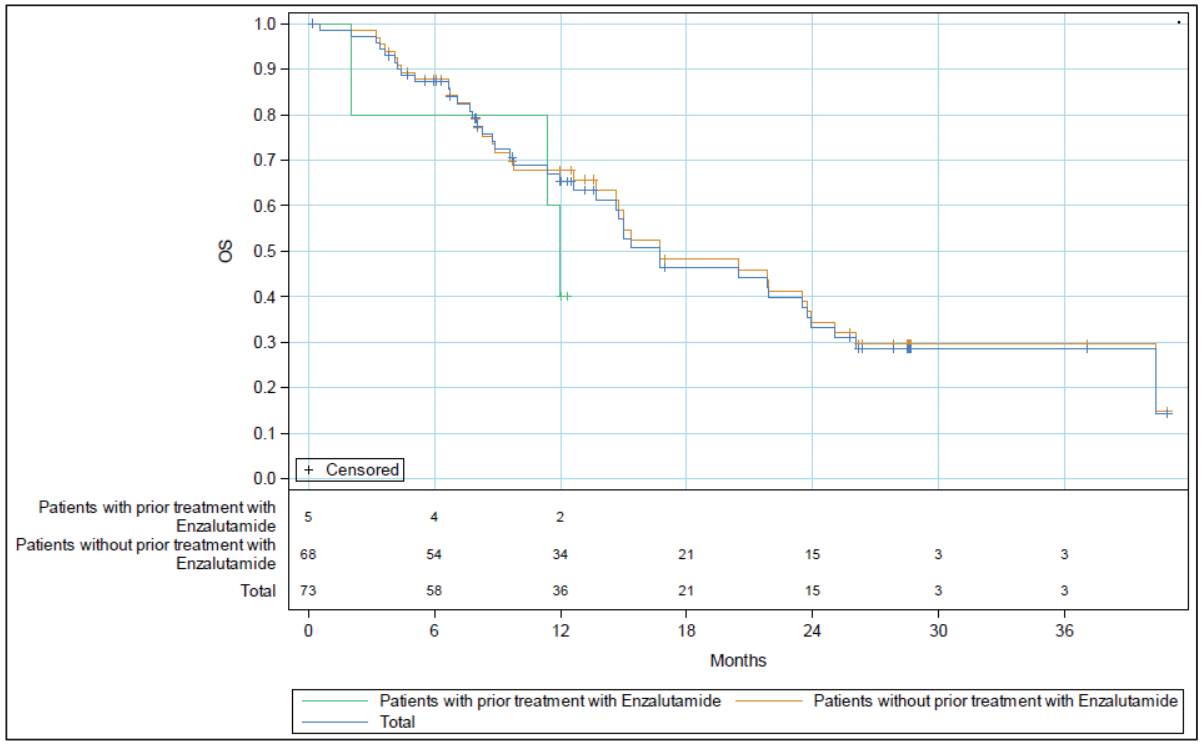

Figure 8: Overall survival by prior treatment with enzalutamide (FAS). Prior treatment with enzalutamide in this figure is defined as enzalutamide started and ended before the start of Radium-223 (A in Figure 2).

Source: Figure 6, TLF v1.0

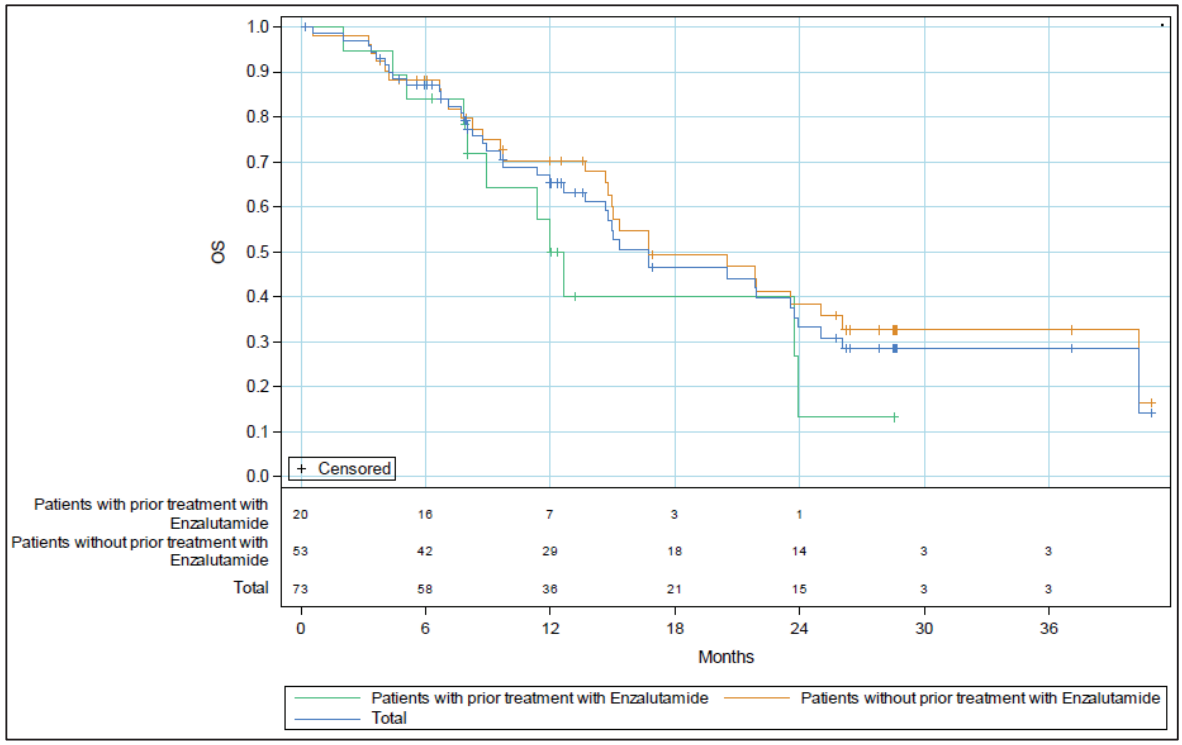

Figure 9: Overall survival by prior treatment with enzalutamide including overlapping to Radium-223 therapy (FAS). Prior treatment with enzalutamide in this figure is defined as enzalutamide started before the start of Radium-223 (A, B or C in Figure 2).

Source: Figure 7, TLF v1.0

12-month and 24-month OS rates are shown in Table 11. Overall, 12-month and 24-month OS rates were 65.32% (95%CI 52.07-75.74) and 33.18% (95%CI 20.62-46.26), respectively.

In patients with prior chemotherapy and in those without, 12-month OS rates were 57.14% (95%CI 17.19-83.71) and 66.22% (95%CI 52.07-77.08), respectively. All 7 patients with prior chemotherapy died during the second year of the study. 24-month OS rate in patients without prior chemotherapy was 38.73% (95%CI 24.49-52.76).

In patients with prior chemotherapy that ended prior to or during Radium-223 treatment and in those without chemotherapy, 12-month OS rates were 51.85% (95%CI 16.41-78.77) and 67.30% (95%CI 53.03-78.10), respectively. Out of 10 patients with chemotherapy that ended prior to or during Radium-223 treatment, 8 patients died during the second year of the study (the remaining two patients were censored). 24-month OS rate in patients without chemotherapy that ended prior to or during Radium-223 treatment was 39.36% (95%CI 24.90- 53.51).

In patients with prior abiraterone and in those without abiraterone therapy, 12-month OS rates were 50% (95%CI 15.20-77.49) and 68.01% (95%CI 53.92-78.62), respectively, and 24-month OS rates were 33.33% (95%CI 5.62-65.76) and 33.41% (95%CI 19.92-47.48), respectively. In patients with abiraterone therapy that ended prior to or during Radium-223 treatment and in those without abiraterone therapy, 12-month OS rates were 61.44% (95%CI 37.24-78.65) and 67.42% (95%CI

51.03-79.38), respectively, and 24-month OS rates were 41.47% (95%CI 18.71-62.99) and 29.02% (95%CI 14.85-44.82), respectively.

In patients with prior enzalutamide and in those without enzalutamide therapy, 12-month OS rates were 40% (95%CI 5.20-75.28) and 67.74% (95%CI 53.99-78.17), respectively, and 24-month OS rates were 40% (95%CI 5.20-75.28) and 34.41% (95%CI 21.36-47.83), respectively. In patients with enzalutamide therapy that ended prior to or during Radium-223 treatment and in those without enzalutamide therapy, 12-month OS rates were 50.18% (95%CI 23.94-71.70) and 70.47% (95%CI 55.12-81.41), respectively, and 24-month OS rates were 13.38% (95%CI 0.85-42.76) and 38.57% (95%CI 23.66-53.27), respectively.

Table 11: Overall survival rates derived by Kaplan-Meier methods (FAS).

	12-month OS rate				24-month OS rate			
	N	Death	OS rate	CI 95%	N	Death	OS rate	CI 95%
Total	73	22	65.32	52.07- 75.74	73	37	33.18	20.62- 46.26
OS by prior chemotherapy[A]								
Prior chemotherapy	7	3	57.14	17.19- 83.71	7	7	0.00	N/A
No prior chemotherapy	66	19	66.22	52.07- 77.08	66	30	38.73	24.49- 52.76
OS by prior chemotherapy including overlapping with Radium-223 therapy[ABC]								
Prior chemotherapy	10	4	51.85	16.41- 78.77	10	8	0.00	N/A
No prior chemotherapy	63	18	67.30	53.03- 78.10	63	29	39.36	24.90- 53.51
OS by prior treatment with abiraterone[A]								
Prior abiraterone treatment	8	4	50.00	15.20- 77.49	8	5	33.33	5.62- 65.76
No prior abiraterone treatment	65	18	68.01	53.92- 78.62	65	32	33.41	19.92- 47.48
OS by prior treatment with abiraterone including overlapping with Radium-223 therapy[ABC]								
Prior abiraterone treatment	23	8	61.44	37.24- 78.65	23	11	41.47	18.71- 62.99
No prior abiraterone treatment	50	14	67.42	51.03- 79.38	50	26	29.02	14.85- 44.82
OS by prior treatment with enzalutamide[A]								
Prior enzalutamide treatment	5	3	40.00	5.20- 75.28	5	3	40.00	5.20- 75.28
No prior enzalutamide treatment	68	19	67.74	53.99- 78.17	68	34	34.41	21.36- 47.83
OS by prior treatment with enzalutamide including overlapping with Radium-223 therapy[ABC]								
Prior enzalutamide treatment	20	8	50.18	23.94- 71.70	20	11	13.38	0.85- 42.76
No prior enzalutamide treatment	53	14	70.47	55.12- 81.41	53	26	38.57	23.66- 53.27

[A]Therapy started and ended before the start of Radium-223 (A in Figure 2)
[ABC]Therapy started before the start of Radium-223 (A, B or C in Figure 2)
Source: Table 8, 10, 12, 14, 16, 18, 20 (modified), TLF v1.0

10.4.2. Secondary objective analysis

10.4.2.1. Symptomatic skeletal event free survival (SSE-FS)

SSEs occurred in five patients (6.9%), including external radiotherapy for relief of skeletal symptoms in four patients (5.5%) and new symptomatic pathological bone fracture in one patient (1.4%, Table 12) as their first SSE. There were no spinal cord compressions and tumor-related orthopedic surgical interventions documented.

One (12.5%) out of eight patients with prior Abiraterone therapy had external radiotherapy for relief of skeletal symptoms, while four (6.2%) out of 65 patients without prior abiraterone had SSEs, including external radiotherapy for relief of skeletal symptoms (n=3, 4.6%) and new symptomatic pathological bone fracture (n=1, 1.5%, Table 12) as their first SSE. In 23 patients with prior abiraterone therapy that ended before or during Radium-223 treatment, two (8.7%) had external radiotherapy for relief of skeletal symptoms; three (6%) out of 50 patients without prior abiraterone had SSEs, including external radiotherapy for relief of skeletal symptoms (n=2, 4%) and new symptomatic pathological bone fracture (n=1, 2%, Table 12) as their first SSEs.

None out of five patients with prior Enzalutamide therapy had SSEs, all SSEs occurred in five (7.4%) out of 68 patients without prior Enzalutamide, including external radiotherapy for relief of skeletal symptoms in four patients (5.9%) and new symptomatic pathological bone fracture in one patient (1.5%, Table 13). In 20 patients with prior Enzalutamide therapy that ended before or during Radium-223 treatment, one (5%) had external radiotherapy for relief of skeletal symptoms as their first SSE; four (7.6%) out of 53 patients without prior Enzalutamide had SSEs, including external radiotherapy for relief of skeletal symptoms in three patients (5.7%) and new symptomatic pathological bone fracture in one patient (1.9%, Table 13) as their first SSE.

Table 12: First symptomatic skeletal events according to prior Abiraterone therapy (FAS)

Any first symptomatic skeletal event occurred N (%)	Prior therapy that ended before Radium-223 treatment[A]		Prior therapy that ended before or during Radium-223 treatment[ABC]		Total
	Abiraterone (n=8)	No abiraterone (n=65)	Abiraterone (n=23)	No abiraterone (n=50)	(n=73)
Number of patients with SSE	1 (12.50)	4 (6.15)	2 (8.70)	3 (6.00)	5 (6.85)
External radiotherapy for relief of skeletal symptoms	1 (12.50)	3 (4.62)	2 (8.70)	2 (4.00)	4 (5.48)
New symptomatic pathological bone fracture	0 (0.00)	1 (1.54)	0 (0.00)	1 (2.00)	1 (1.37)
Spinal cord compression	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tumor-related orthopedic surgical intervention	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

[A]'Prior therapy that ended before Radium-223 treatment ' refers to treatment within group A in Figure 2.
[ABC]'Prior therapy that ended before, during or after Radium-223 treatment ' refers to treatment within group A, B and C in Figure 2.
SSE is defined as external radiotherapy for relief of skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention.
In addition to the SSEs reported on the SSE page, potential SSEs were identified from a manual review of Adverse Events, Radiotherapy, Diagnostic and therapeutic procedures pages
Note: A patient can have more than one SSE.
Source: Table 24 and 25, TLF v1.0

Table 13: First symptomatic skeletal events according to prior Enzalutamide therapy (FAS)

Any first symptomatic skeletal event occurred N (%)	Prior therapy that ended before Radium-223 treatment[A]		Prior therapy that ended before or during Radium-223 treatment[ABC]		Total
	Enzalutamide (n=5)	No Enzalutamide (n=68)	Enzalutamide (n=20)	No Enzalutamide (n=53)	(n=73)
Number of patients with SSE	0 (0.00)	5 (7.35)	1 (5.00)	4 (7.55)	5 (6.85)
External radiotherapy for relief of skeletal symptoms	0 (0.00)	4 (5.88)	1 (5.00)	3 (5.66)	4 (5.48)
New symptomatic pathological bone fracture	0 (0.00)	1 (1.47)	0 (0.00)	1 (1.89)	1 (1.37)
Spinal cord compression	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tumor-related orthopedic surgical intervention	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

[A]'Prior therapy that ended before Radium-223 treatment ' refers to treatment within group A in Figure 2.
[ABC]'Prior therapy that ended before, during or after Radium-223 treatment ' refers to treatment within group A, B and C in Figure 2.
SSE is defined as external radiotherapy for relief of skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention.
In addition to the SSEs reported on the SSE page, potential SSEs were identified from a manual review of Adverse Events, Radiotherapy, Diagnostic and therapeutic procedures pages
Note: A patient can have more than one SSE.
Source: Table 26 and 27, TLF v1.0

Median SSE-FS was 14.98 months (95%CI 11.40-20.90, see Table 21 in TLF v1.0 and Figure 10); three out of five SSEs occurred in patients that later died. Two SSEs occurred during the first 6 months of the study and one SSE was documented between month 7 and 12; 6-month and 12-month SSE-FS rates were 84.35% (95%CI 73.52-91.02) and 60.54% (95%CI 47.20-71.50), respectively (see Table 22 in TLF v1.0).

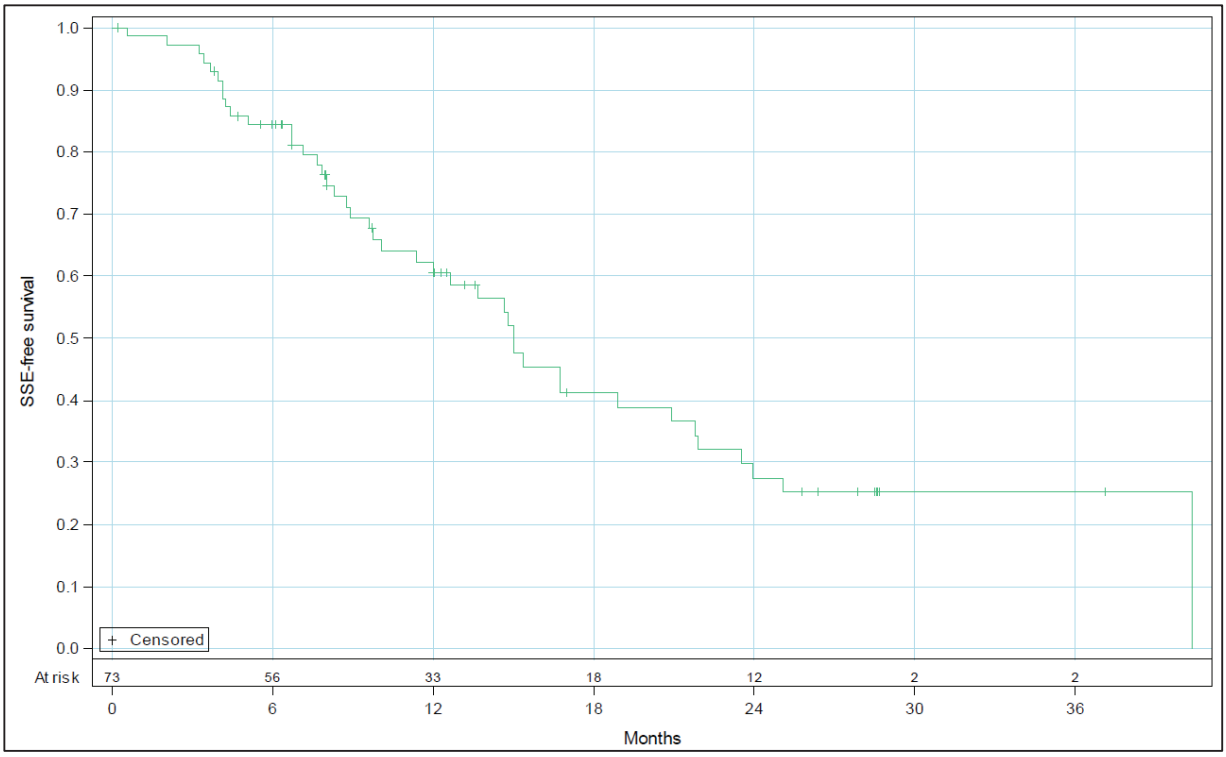

Figure 10: Symptomatic skeletal event free survival [months] - Kaplan-Meier (FAS)

Source: Figure 8, TLF v1.0

10.4.2.2. Incidence of pathological fractures (as part of SSEs), non-pathological fractures and bone associated events during the treatment and follow-up period.

Incidence of pathological fractures (as part of SSEs), non-pathological fractures and bone associated events during the treatment and follow-up period was analyzed in SAF. Seven (8.5%) among the 82 patients in SAF had at least one SSE, including external radiotherapy for relief of skeletal symptoms in five patients (6.1%) and new symptomatic pathological bone fracture in four patients (4.9%, Table 14). There were no spinal cord compressions and tumor-related orthopedic surgical intervention documented in SAF.

One (12.5%) out of eight patients with prior Abiraterone therapy had external radiotherapy for relief of skeletal symptoms, while six (8.1%) out of 74 patients without prior abiraterone had SSEs, including external radiotherapy for relief of skeletal symptoms (n=4, 5.4%) and new symptomatic pathological bone fracture (n=4, 5.4%, Table 14). In 27 patients with prior abiraterone therapy that ended before or during Radium-223 treatment, three (11.1%) had SSEs, including external radiotherapy for relief of skeletal symptoms (n=2, 7.4%) and new symptomatic pathological bone fracture (n=2, 7.4%). Four (7.3%) out of 55 patients without prior abiraterone had SSEs, including external radiotherapy for relief of skeletal symptoms (n=3, 5.5%) and new symptomatic pathological bone fracture (n=2, 3.6%, Table 14).

None out of five patients with prior Enzalutamide therapy had SSEs, all SSEs occurred in seven (9.1%) out of 77 patients without prior Enzalutamide, including external radiotherapy for relief of skeletal symptoms in five patients (6.5%) and new symptomatic pathological bone fracture in four patients (5.2%, Table 15). In 21 patients with prior Enzalutamide therapy that ended before or during Radium-223 treatment, one (4.8%) had external radiotherapy for relief of skeletal symptoms; six (9.8%) out of 61 patients without prior Enzalutamide had SSEs, including external radiotherapy for relief of skeletal symptoms in four patients (6.6%) and new symptomatic pathological bone fracture in four patients (6.6%, Table 15).

Table 14: Symptomatic skeletal events according to prior Abiraterone therapy (SAF)

Any symptomatic skeletal event occurred N (%)	Prior therapy that ended before Radium-223 treatment[A]		Prior therapy that ended before or during Radium-223 treatment[ABC]		Total
	Abiraterone (n=8)	No abiraterone (n=74)	Abiraterone (n=27)	No abiraterone (n=55)	(n=82)
Number of patients with SSE	1 (12.50)	6 (8.11)	3 (11.11)	4 (7.27)	7 (8.54)
External radiotherapy for relief of skeletal symptoms	1 (12.50)	4 (5.41)	2 (7.41)	3 (5.45)	5 (6.10)
New symptomatic pathological bone fracture	0 (0.00)	4 (5.41)	2 (7.41)	2 (3.64)	4 (4.88)
Spinal cord compression	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tumor-related orthopedic surgical intervention	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

[A]'Prior therapy that ended before Radium-223 treatment ' refers to treatment within group A in Figure 2.
[ABC]'Prior therapy that ended before, during or after Radium-223 treatment ' refers to treatment within group A, B and C in Figure 2.
SSE is defined as external radiotherapy for relief of skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention.
In addition to the SSEs reported on the SSE page, potential SSEs were identified from a manual review of Adverse Events, Radiotherapy, Diagnostic and therapeutic procedures pages
Note: A patient can have more than one SSE.
Source: Table 30 and 31, TLF v1.0

Table 15: Symptomatic skeletal events according to prior Enzalutamide therapy (SAF)

Any symptomatic skeletal event occurred N (%)	Prior therapy that ended before Radium-223 treatment[A]		Prior therapy that ended before or during Radium-223 treatment[ABC]		Total
	Enzalutamide (n=5)	No Enzalutamide (n=77)	Enzalutamide (n=21)	No Enzalutamide (n=61)	(n=82)
Number of patients with SSE	0 (0.00)	7 (9.09)	1 (4.76)	6 (9.84)	7 (8.54)
External radiotherapy for relief of skeletal symptoms	0 (0.00)	5 (6.49)	1 (4.76)	4 (6.56)	5 (6.10)
New symptomatic pathological bone fracture	0 (0.00)	4 (5.19)	0 (0.00)	4 (6.56)	4 (4.88)
Spinal cord compression	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tumor-related orthopedic surgical intervention	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

[A]'Prior therapy that ended before Radium-223 treatment ' refers to treatment within group A in Figure 2.
[ABC]'Prior therapy that ended before, during or after Radium-223 treatment ' refers to treatment within group A, B and C in Figure 2.
SSE is defined as external radiotherapy for relief of skeletal symptoms, new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention.
In addition to the SSEs reported on the SSE page, potential SSEs were identified from a manual review of Adverse Events, Radiotherapy, Diagnostic and therapeutic procedures pages
Note: A patient can have more than one SSE.
Source: Table 32 and 33, TLF v1.0

Given that no pathological fractures, non-pathological fractures or bone associated events occurred up to 30 days since last Radium-223 injection, the overall incidence proportion and person-time incidence rate of these SSEs was 0 during that time period (each, see Table 34 and 36 in TLF v1.0). Four pathological fractures and four bone associated events occurred after 30 days since the last Radium-223 injection. The overall incidence proportion of pathological fractures and bone associated events that occurred during that time period was 0.048 (95%CI 0.002-0.093, both, see Table 35 in TLF v1.0); person-time incidence rate was 0.039 (95%CI 0.010-0.099, both, see Table 37 in TLF v1.0). No non-pathological fractures occurred after 30 days since the last Radium-223 injection.

10.4.2.3. Time to next tumor treatment(s)

Twenty-eight patients in FAS (38.4%) received a mCRPC therapy (including Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Mitoxantrone or a retreatment with Radium-223) after the first injection of Radium-223 within this study (see Table 38 in TLF v1.0). Overall, median TTNT (defined as the time from the first application of Radium-223 until start of next mCRPC treatment) was 14.42 months (95%CI 10.12-NR, see Table 38 in TLF v1.0, Figure 11).

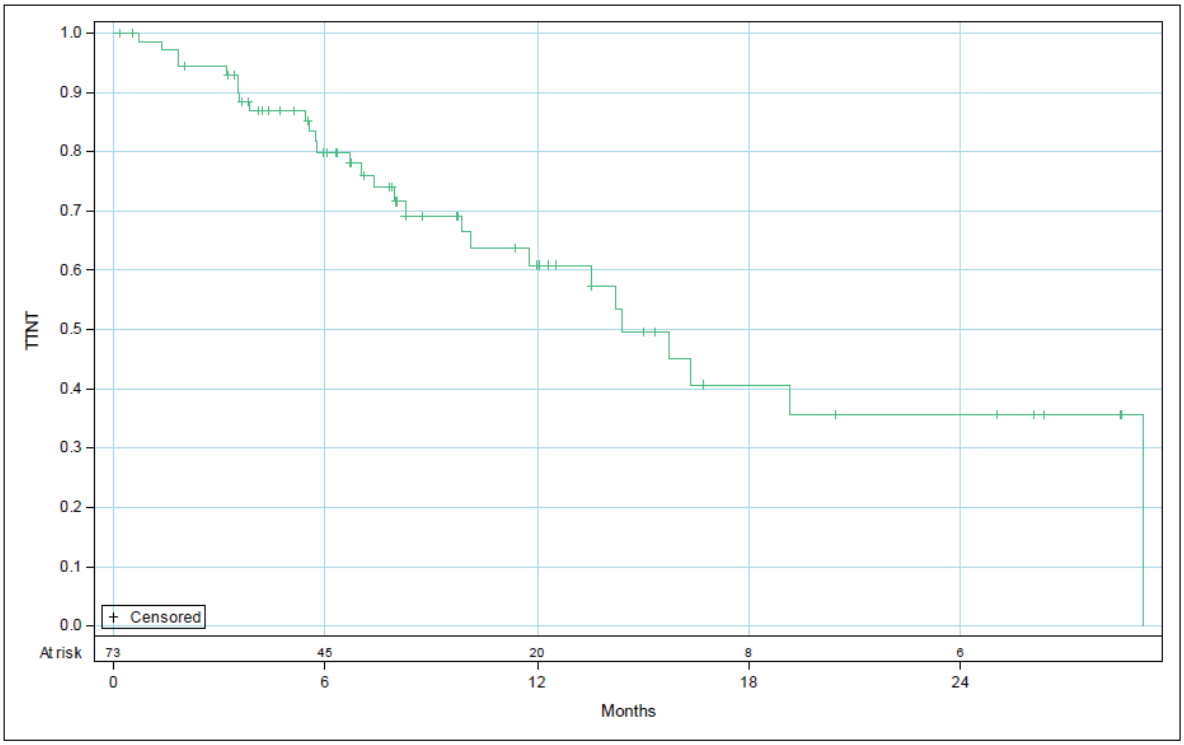

Figure 11: Time to next tumor treatment(s) (TTNT) [months] - Kaplan-Meier (FAS)

Note: Includes next tumor treatments with Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Mitoxantrone or a retreatment with Ra-223

Source: Figure 10, TLF v1.0

10.4.2.4. Quality of life estimated using FACT-P questionnaire.

Mean FACT-P total score was 109.66 (SD 19.94) at baseline, 112.02 (SD 22.54) at visit 2, 109.91 (SD 21.07) at follow-up after month 1, 108.08 (SD 25.83) at follow-up after month 6, 103.05 (SD 30.43) at follow-up after month 12, and 92.9 (SD 8.63) at follow-up after month 24 (Figure 12, Table 16). Mean change from baseline in FACT-P total score was -0.69 (SD 17.55) at visit 2, -2.51 (SD 19.14) at follow-up after month 1, -7.59 (SD 9.92) at follow-up after month 6, -10.11 (SD 30.6) at follow-up after month 12, and -25.43 (in a single patient analyzed) at follow-up after month 24 (Figure 13, see Table 40 in TLF v1.0).

Mean FACT-G total score was 77.99 (SD 14.84) at baseline, 78.69 (SD 17.78) at visit 2, 77.04 (SD 14.72) at follow-up after month 1, 76.02 (SD 13.89) at follow-up after month 6, 72 (SD 23.66) at follow-up after month 12, and 60.63 (SD 7.12) at follow-up after month 24 (Table 16). Mean change from baseline in FACT-G total score was -1.96 (SD 13.68) at visit 2, -3.71 (SD 14.58) at follow-up after month 1, -7.57 (SD 9.82) at follow-up after month 6, -7.28 (SD 20.64) at follow-up after month 12, and -18.23 (in a single patient analyzed) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean FACT-P trial outcome index score was 70.06 (SD 14.31) at baseline, 71.65 (SD 15.33) at visit 2, 70.03 (SD 16.37) at follow-up after month 1, 69.73 (SD 21.7) at follow-up after month 6, 68.33 (SD 18.89) at follow-up after month 12, and 59.77 (SD 6.46) at follow-up after month 24 (Table 16). Mean change from baseline in FACT-P trial outcome index score was -0.79 (SD 13.57) at visit 2, -2.33 (SD 14.46) at follow-up after month 1, -0.02 (SD 18.01) at follow-up after month 6, -5.56 (SD 21.39) at follow-up after month 12, and -8.83 (SD 14.66) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean Emotional well-being score was 17.3 (SD 4.52) at baseline, 17.41 (SD 4.52) at visit 2, 16.7 (SD 4.19) at follow-up after month 1, 17.2 (SD 3.55) at follow-up after month 6, 15.67 (SD 6.03) at follow-up after month 12, and 14 (SD 2.83) at follow-up after month 24 (Table 16). Mean change from baseline in Emotional well-being score was -0.16 (SD 4.82) at visit 2, -0.56 (SD 4.68) at follow-up after month 1, -1.62 (SD 3.61) at follow-up after month 6, -1.33 (SD 2.89) at follow-up after month 12, and -5.8 (SD 0.28) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean Functional well-being score was 17.68 (SD 5.87) at baseline, 18.81 (SD 5.8) at visit 2, 16.69 (SD 5.37) at follow-up after month 1, 16.92 (SD 5.86) at follow-up after month 6, 18.67 (SD 6.51) at follow-up after month 12, and 12 (SD 2.83) at follow-up after month 24 (Table 16). Mean change from baseline in Functional well-being score was 0.34 (SD 4.86) at visit 2, -2.05 (SD 5.74) at follow-up after month 1, -0.87 (SD 5.96) at follow-up after month 6, 1.67 (SD 3.51) at follow-up after month 12, and -2 (SD 2.83) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean Physical well-being score was 20.82 (SD 4.37) at baseline, 19.5 (SD 5.78) at visit 2, 20.59 (SD 5.27) at follow-up after month 1, 19.5 (SD 5.52) at follow-up after month 6, 18.61 (SD 6.09) at follow-up after month 12, and 15.5 (SD 2.12) at follow-up after month 24 (Table 16). Mean change from baseline in Physical well-being score was -2.4 (SD 5.76) at visit 2, -1.63 (SD 5.02) at follow-up after month 1, -3.02 (SD 3.74) at follow-up after month 6, -4.39 (SD 8.18) at follow-up after month 12, and -8.5 (SD 0.71) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean Prostate cancer subscale score was 31.42 (SD 7.5) at baseline, 33.34 (SD 6.45) at visit 2, 32.74 (SD 7.89) at follow-up after month 1, 33.31 (SD 12.62) at follow-up after month 6, 31.05 (SD 8.41) at follow-up after month 12, and 32.27 (SD 1.51) at follow-up after month 24 (Table 16). Mean change from baseline in Prostate cancer subscale score was 1.27 (SD 5.13) at visit 2, 1.35 (SD 7.42) at follow-up after month 1, 3.87 (SD 11.37) at follow-up after month 6, -2.84 (SD 10.06) at follow-up after month 12, and 1.67 (SD 12.54) at follow-up after month 24 (see Table 40 in TLF v1.0).

Mean Social/Family well-being score was 22.45 (SD 5.35) at baseline, 22.97 (SD 5.42) at visit 2, 23.01 (SD 4.16) at follow-up after month 1, 21.67 (SD 2.79) at follow-up after month 6, 19.06 (SD 7.77) at follow-up after month 12, and 19.13 (SD 0.66) at follow-up after month 24 (Table 16). Mean change from baseline in Social/Family well-being score was 0.27 (SD 3.85) at visit 2, 0 (SD 5.82) at follow-up after month 1, -0.69 (SD 7.06) at follow-up after month 6, -3.22 (SD 6.53) at follow-up after month 12, and -0.23 (in a single patient analyzed) at follow-up after month 24 (see Table 40 in TLF v1.0).

Given that less than 10 patients were analyzed at follow up after month 9 and subsequent time-points (for scores as observed) and at follow up after month 6 and subsequent time-points (for score changes), these results should be interpreted with caution.

Table 16: FACT-P questionnaire (FAS)

FACT-P		N	Mean	SD	CI95%	Q1	Median	Q3	Min.	Max.	N miss
Baseline	PWB	49	20.82	4.37	19,56 -22.08	18.00	21.00	24.00	11.67	28.00	0
	SWB	47	22.45	5.35	20.87 -24.02	20.00	23.00	25.67	5.25	28.00	2
	EWB	47	17.30	4.52	15.97 -18.63	14.00	18.00	21.00	3.00	24.00	2
	FWB	48	17.68	5.87	15.98 -19.39	14.00	17.50	22.00	4.00	28.00	1
	PCS	48	31.42	7.50	29.24 -33.6	26.18	32.73	37.09	13.09	48.00	1
	FACT-P TOI	48	70.06	14.31	65.91 -74.22	61.61	71.44	79.27	37.48	96.17	1
	FACT-G total score	46	77.99	14.84	73.58 -82.39	67.50	79.50	86.17	37.67	105.00	3
	FACT-P total score	46	109.66	19.94	103.74 -115.58	97.68	110.58	121.50	59.48	146.45	3
Visit 1	PWB	34	20.19	6.90	17.78 -22.6	16.00	22.50	25.00	1.00	28.00	0
	SWB	34	23.07	5.72	21.07 -25.06	22.00	24.00	26.83	0.00	28.00	0
	EWB	32	18.38	4.04	16.93 -19.84	16.00	19.00	21.00	7.20	24.00	2
	FWB	34	18.73	5.94	16.66 -20.8	14.00	21.00	24.00	8.00	28.00	0
	PCS	33	32.88	7.78	30.12 -35.64	28.36	33.82	37.20	12.00	52.80	1
	FACT-P TOI	33	71.92	17.74	65.63 -78.21	57.82	74.50	84.73	21.00	108.80	1
	FACT-G total score	32	81.11	15.97	75.35 -86.87	68.42	80.50	93.83	44.20	106.00	2
	FACT-P total score	32	114.06	21.52	106.30 -121.81	98.28	113.47	130.89	56.20	158.80	2
Visit 2	PWB	26	19.50	5.78	17.17 -21.83	17.00	21.00	23.00	8.00	28.00	0
	SWB	26	22.97	5.42	20.78 -25.16	22.00	23.67	26.60	3.00	28.00	0
	EWB	26	17.41	4.52	15.58 -19.23	15.00	18.00	20.00	7.00	24.00	0
	FWB	26	18.81	5.80	16.46 -21.15	15.00	19.50	24.00	6.00	28.00	0
	PCS	26	33.34	6.45	30.73 -35.94	29.45	33.27	38.18	21.82	45.60	0
	FACT-P TOI	26	71.65	15.33	65.45 -77.84	57.80	72.59	84.27	44.00	93.18	0
	FACT-G total score	26	78.69	17.78	71.50 -85.87	65.00	82.80	93.67	40.00	106.00	0
	FACT-P total score	26	112.02	22.54	102.92 -121.13	89.80	115.94	132.93	69.45	144.18	0
Follow-up after 1 month	PWB	27	20.59	5.27	18.51 -22.68	17.00	22.00	24.00	8.00	28.00	0
	SWB	26	23.01	4.16	21.33 -24.69	19.83	23.67	26.60	13.00	28.00	1
	EWB	27	16.70	4.19	15.05 -18.36	13.00	17.00	20.00	7.00	23.00	0

	FACT-P	N	Mean	SD	CI95%	Q1	Median	Q3	Min.	Max.	N miss
	FWB	27	16.69	5.37	14.57 -18.81	13.00	17.00	21.00	7.00	28.00	0
	PCS	27	32.74	7.89	29.62 -35.86	28.36	32.73	37.09	13.09	46.91	0
	FACT-P TOI	27	70.03	16.37	63.55 -76.5	60.36	69.73	84.27	39.09	93.91	0
	FACT-G total score	26	77.04	14.72	71.09 -82.98	68.00	76.58	90.00	45.67	99.00	1
	FACT-P total score	26	109.91	21.07	101.39 -118.42	97.36	106.95	129.91	67.48	141.55	1
Follow-up after 3 months	PWB	15	20.08	5.25	17.17 -22.98	14.00	21.00	24.00	12.00	28.00	0
	SWB	14	21.05	3.95	18.77 -23.33	18.67	21.50	22.17	14.00	28.00	1
	EWB	15	16.60	4.93	13.87 -19.33	14.00	18.00	20.00	4.00	24.00	0
	FWB	15	15.53	7.38	11.45 -19.62	9.00	14.00	22.00	3.00	26.00	0
	PCS	15	33.50	7.64	29.27 -37.73	27.27	34.00	39.27	21.60	48.00	0
	FACT-P TOI	15	69.11	17.80	59.25 -78.97	53.00	68.27	84.27	39.60	96.00	0
	FACT-G total score	14	73.56	16.68	63.93 -83.19	63.83	77.08	85.00	40.83	102.00	1
	FACT-P total score	14	106.21	22.63	93.15 -119.28	92.77	106.87	126.00	64.83	141.60	1
Follow-up after 6 months	PWB	10	19.50	5.52	15.55 -23.45	14.00	19.50	23.00	13.00	28.00	0
	SWB	9	21.67	2.79	19.52 -23.81	21.00	22.17	22.17	16.33	26.83	1
	EWB	10	17.20	3.55	14.66 -19.74	16.00	18.50	19.00	10.00	21.00	0
	FWB	10	16.92	5.86	12.73 -21.11	12.00	19.00	22.00	6.00	24.00	0
	PCS	10	33.31	12.62	24.29 -42.34	26.18	32.73	44.57	9.82	51.60	0
	FACT-P TOI	10	69.73	21.70	54.20 -85.25	53.60	73.51	83.00	35.82	100.77	0
	FACT-G total score	9	76.02	13.89	65.34 -86.7	67.17	78.17	88.00	55.33	90.50	1
	FACT-P total score	9	108.08	25.83	88.23 -127.93	94.77	107.62	125.83	65.82	142.10	1
Follow-up after 9 months	PWB	4	16.25	6.55	5.83 -26.67	12.50	13.50	20.00	12.00	26.00	0
	SWB	4	18.50	5.96	9.02 -27.98	14.25	19.50	22.75	10.50	24.50	0
	EWB	4	16.90	1.64	14.30 -19.5	15.90	16.80	17.90	15.00	19.00	0
	FWB	4	11.00	7.96	-1.66 -23.66	6.00	9.50	16.00	3.00	22.00	0
	PCS	4	29.86	5.37	21.32 -38.41	26.45	30.27	33.27	22.91	36.00	0
	FACT-P TOI	4	57.11	16.04	31.58 -82.64	46.45	55.00	67.77	39.91	78.55	0

	FACT-P	N	Mean	SD	CI95%	Q1	Median	Q3	Min.	Max.	N miss
	FACT-G total score	4	62.65	17.89	34.18 -91.12	50.15	57.05	75.15	48.50	88.00	0
	FACT-P total score	4	92.51	20.20	60.37 -124.66	76.60	88.40	108.42	74.71	118.55	0
Follow-up after 12 month	PWB	3	18.61	6.09	3.48 -33.75	12.00	19.83	24.00	12.00	24.00	0
	SWB	3	19.06	7.77	-0.24 -38.35	10.50	21.00	25.67	10.50	25.67	0
	EWB	3	15.67	6.03	0.69 -30.64	10.00	15.00	22.00	10.00	22.00	0
	FWB	3	18.67	6.51	2.50 -34.83	12.00	19.00	25.00	12.00	25.00	0
	PCS	3	31.05	8.41	10.16 -51.95	24.00	28.80	40.36	24.00	40.36	0
	FACT-P TOI	3	68.33	18.89	21.40 -115.26	52.80	62.83	89.36	52.80	89.36	0
	FACT-G total score	3	72.00	23.66	13.23 -130.77	49.50	69.83	96.67	49.50	96.67	0
	FACT-P total score	3	103.05	30.43	27.46 -178.65	78.30	93.83	137.03	78.30	137.03	0
Follow-up after 18 months	PWB	2	21.50	6.36	-35.68 -78.68	17.00	21.50	26.00	17.00	26.00	0
	SWB	2	20.92	1.53	7.15 -34.68	19.83	20.92	22.00	19.83	22.00	0
	EWB	2	18.00	7.07	-45.53 -81.53	13.00	18.00	23.00	13.00	23.00	0
	FWB	2	16.00	8.49	-60.24 -92.24	10.00	16.00	22.00	10.00	22.00	0
	PCS	2	34.69	4.94	-9.67 -79.05	31.20	34.69	38.18	31.20	38.18	0
	FACT-P TOI	2	72.19	19.79	-105.58 -249.96	58.20	72.19	86.18	58.20	86.18	0
	FACT-G total score	2	76.42	23.45	-134.29 -287.13	59.83	76.42	93.00	59.83	93.00	0
	FACT-P total score	2	111.11	28.39	-143.96 -366.18	91.03	111.11	131.18	91.03	131.18	0
Follow-up after 24 months	PWB	2	15.50	2.12	-3.56 -34.56	14.00	15.50	17.00	14.00	17.00	0
	SWB	2	19.13	0.66	13.20 -25.06	18.67	19.13	19.60	18.67	19.60	0
	EWB	2	14.00	2.83	-11.41 -39.41	12.00	14.00	16.00	12.00	16.00	0
	FWB	2	12.00	2.83	-13.41 -37.41	10.00	12.00	14.00	10.00	14.00	0
	PCS	2	32.27	1.51	18.71 -45.82	31.20	32.27	33.33	31.20	33.33	0
	FACT-P TOI	2	59.77	6.46	1.74 -117.79	55.20	59.77	64.33	55.20	64.33	0
	FACT-G total score	2	60.63	7.12	-3.32 -124.59	55.60	60.63	65.67	55.60	65.67	0
	FACT-P total score	2	92.90	8.63	15.39 -170.41	86.80	92.90	99.00	86.80	99.00	0

PWB, Physical well-being; SWB, Social/Family well-being; EWB, Emotional well-being; FWB, Functional well-being; PCS, Prostate cancer subscale.

Source: Table 39, TLF v1.0

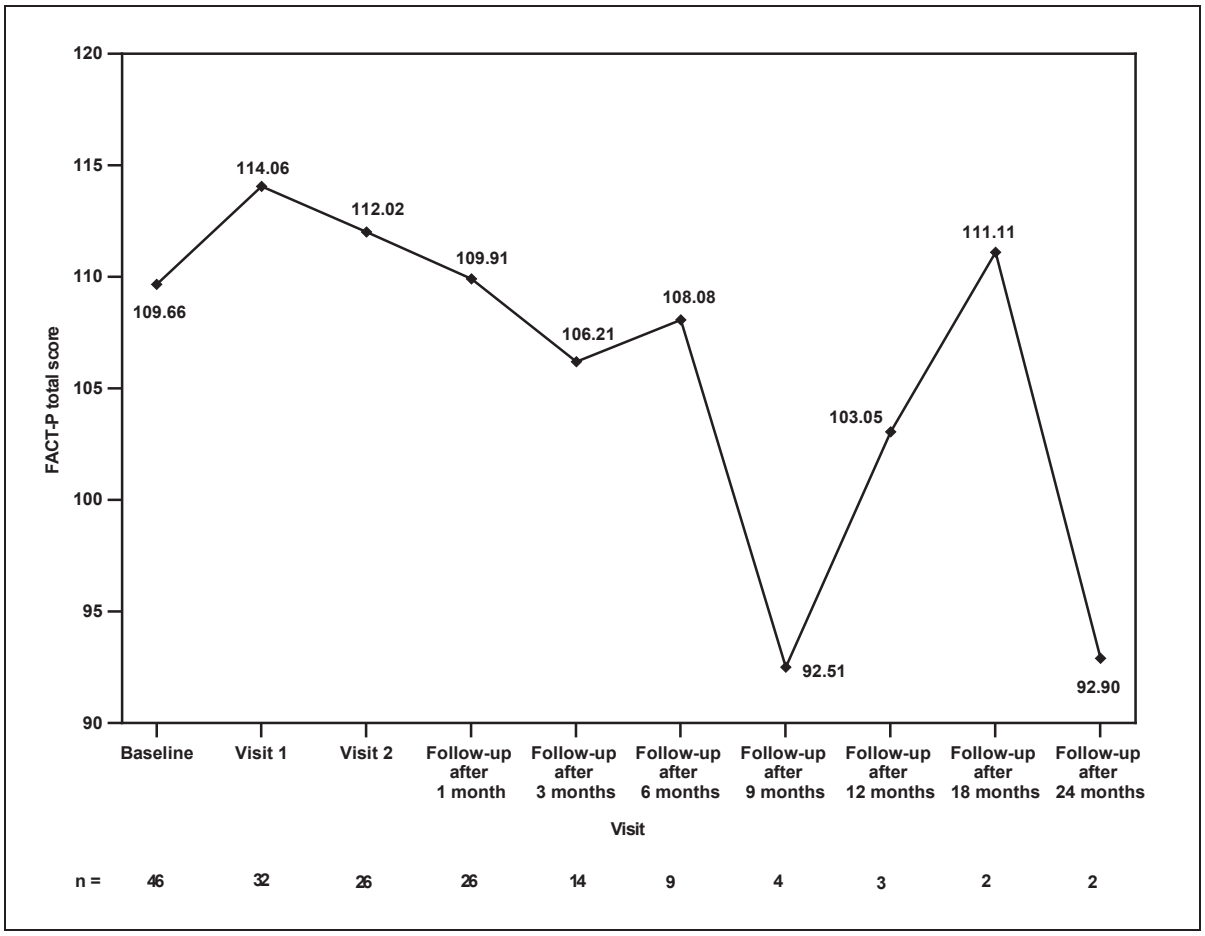

Figure 12: FACT-P questionnaire- Total score- Line plot (FAS)

Source: Figure 11, TLF v1.0

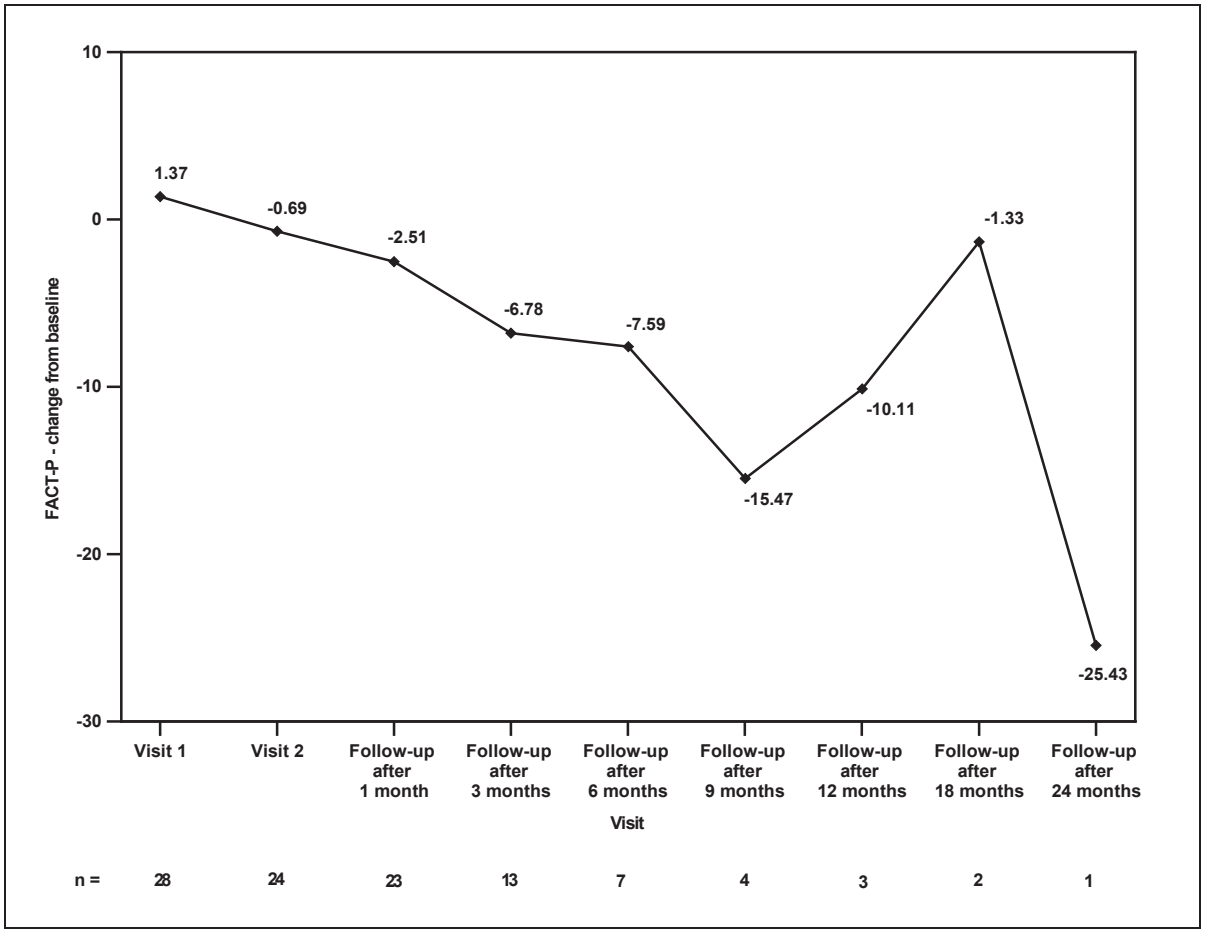

Figure 13: FACT-P questionnaire- Total score- Change from baseline- Line plot (FAS)

Source: Figure 12, TLF v1.0

10.4.2.5. Activities of daily living explored according to the Katz-Index.

Mean Katz index total score was 5.6 (SD 0.9, n=54) at baseline, 5.4 (SD 1.2, n=51) at visit 1, 5.6 (SD 0.7, n=34) at visit 2 and 5.3 (SD 1.4, n=28) at follow-up after 1 month (Figure 14, see Table 42 in TLF v1.0). Mean change in total score from baseline amounted to -0.26 (SD 0.62, n=43) at visit 1, -0.19 (SD 0.75, n=31) at visit 2 and -0.27 (SD 0.67, n=26) at follow-up after 1 month (Figure 15, see Table 43 in TLF v1.0).

At visit 1, total score decreased from 4 at baseline to 2 in 3 patients (7%) and from 6 at baseline to 5 in 6 patients (14%, see Table 44 in TLF v.10). At visit 2, total score increased from 5 at baseline to 6 in 2 patients (6.5%) and decreased from 6 at baseline to 5 in 6 (19.4%) or to 3 in one patient (3.2%). At Follow-up after 1 month, total score decreased from 4 at baseline to 2 in 2 (7.7%) patients and from 6 at baseline to 5 or 4 in 2 (7.7%) patients).

The percentage of patients able to bath independently decreased from 94.4% (n=51) at baseline to 90.2% (n=46) at visit 1, 88.2% (n=30) at visit 2 and 85.7% (n=24) at follow-up after 1 month (see Table 41 in TLF v1.0). The percentage of patients able to independently maintain continence decreased from 77.8% (n=42) at baseline to 68.6% (n=35) at visit 1, 73.5% (n=25) at visit 2 and 71.4% (n=20) at follow-up after 1 month. The percentage of patients able to dress independently was 94.4% (n=51) at baseline, 90.2% (n=46) at visit 1, 100% (n=34) at visit 2 and 89.3% (n=25) at follow-up after 1 month. The percentage of patients able to do toileting independently decreased from 96.3% (n=52) at baseline to 92.2% (n=47) at visit 1, 97.1% (n=33) at visit 2 and 89.3% (n=25) at follow-up after 1 month. The percentage of patients able to transfer independently was 96.3% (n=52) at baseline, 94.1% (n=48) at visit 1, 97.1% (n=33) at visit 2 and 92.9% (n=26) at follow-up after 1 month. All patients were able to feed independently at each study visit and at follow-up after 1 month (see Table 41 in TLF v1.0).

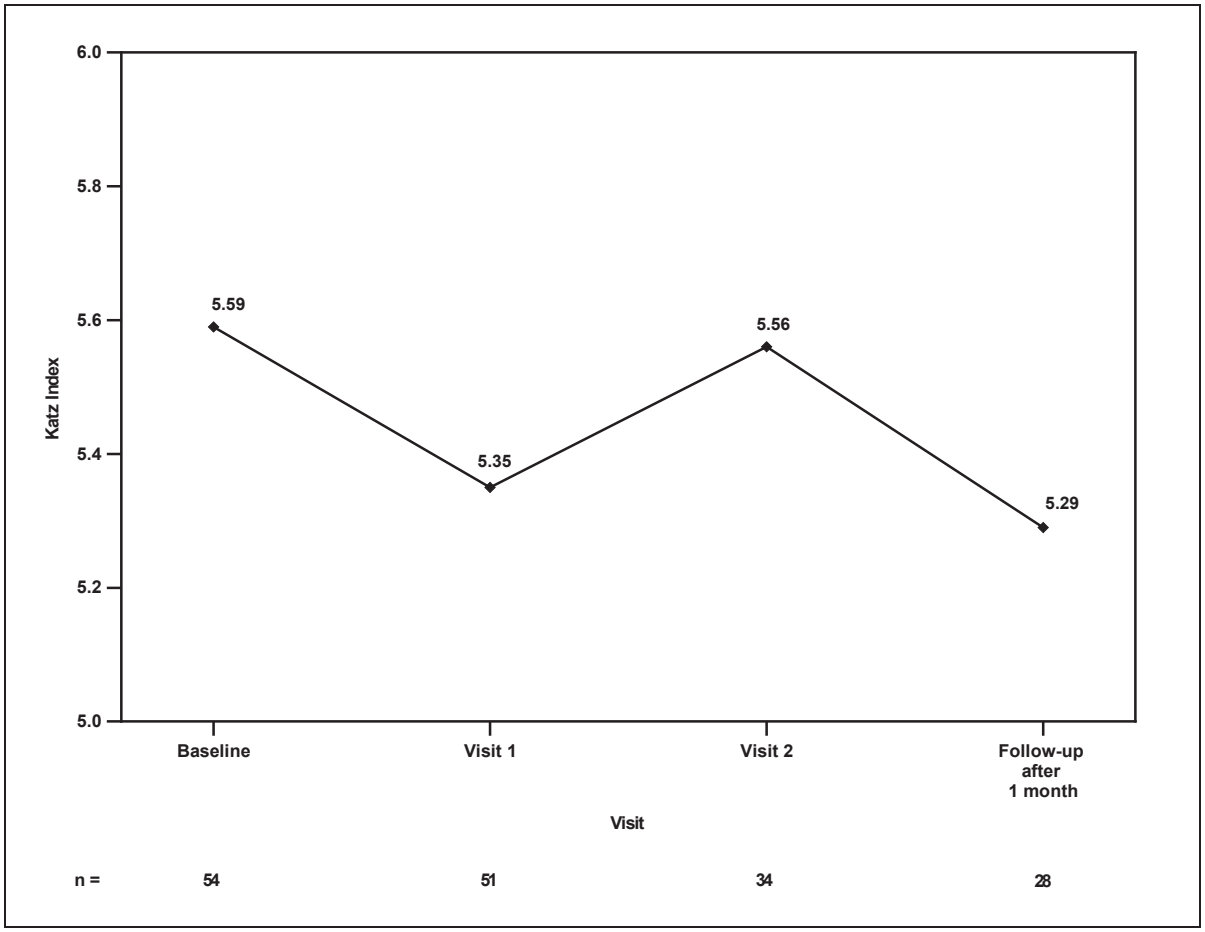

Figure 14: Katz-Index-Total points- Line plot (FAS)

Source: Figure 13, TLF v1.0

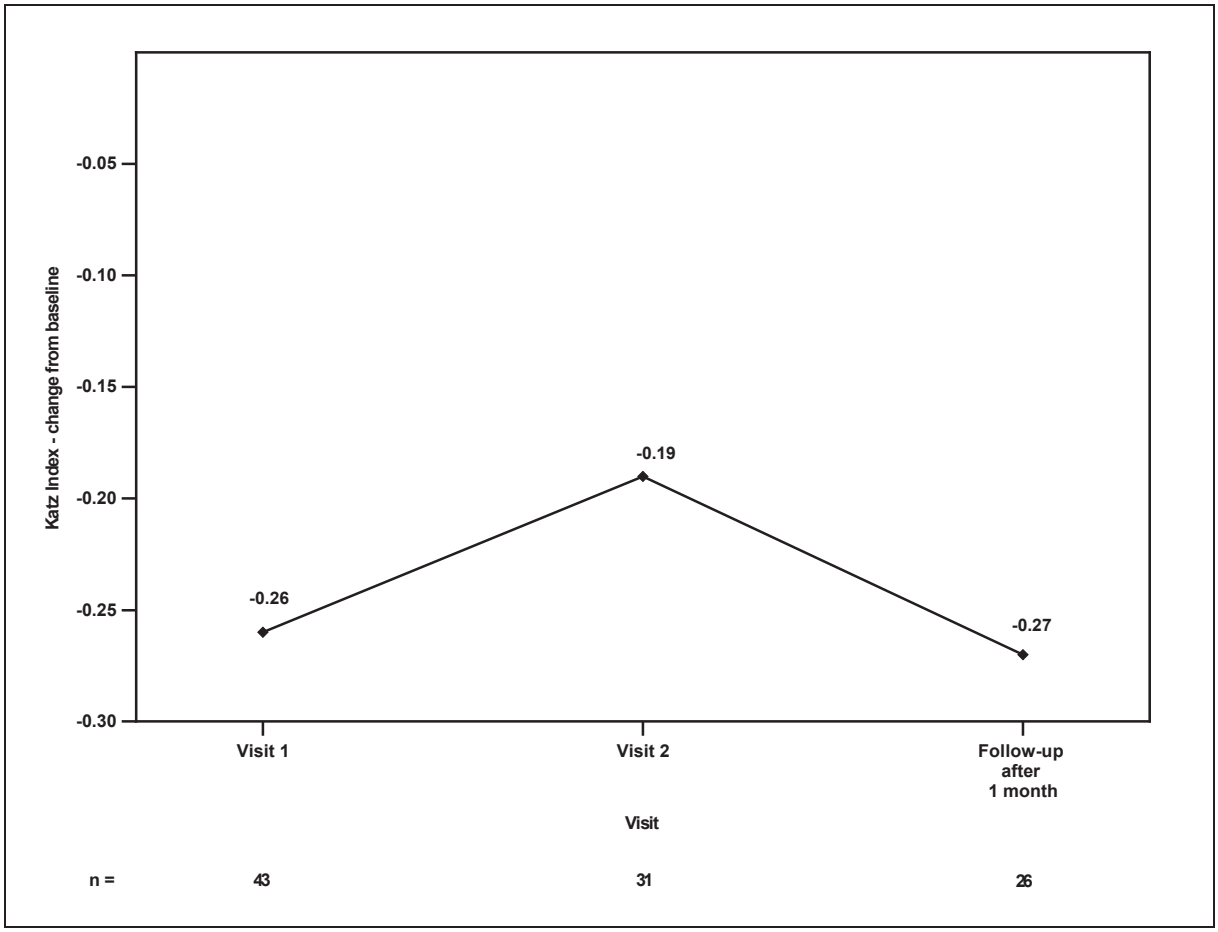

Figure 15: Katz-Index- Total points- Change from baseline- Line plot (FAS)

Source: Figure 14, TLF v1.0

10.4.2.6. Body function explored in dimensions of "mobility", "self-care" and "domestic life" using the MOSES questionnaire.

Mean score for domain acquiring the necessities of life was 0.83 (SD 1.05) at baseline, 1.03 (SD 1.3) at visit 1, 0.94 (SD 1.01) at visit 2 and 1.08 (SD 1.33) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0 (SD 0.65) at visit 1, 0.29 (SD 0.75) at visit 2, and 0.17 (SD 0.72) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain carrying objects was 1.14 (SD 1.43) at baseline, 1.14 (SD 1.56) at visit 1, 1.15 (SD 1.34) at visit 2 and 1.28 (SD 1.72) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.01 (SD 0.87) at visit 1, 0.34 (SD 0.96) at visit 2, and -0.22 (SD 1.01) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain changing a body position was 0.73 (SD 0.94) at baseline, 0.85 (SD 1.01) at visit 1, 0.81 (SD 0.73) at visit 2 and 1.03 (SD 1.09) at follow-up after 1 month (see Table 45 in TLF

v1.0). Mean score change from baseline was 0.08 (SD 0.57) at visit 1, 0.22 (SD 0.7) at visit 2, and 0.21 (SD 0.9) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain dressing was 0.22 (SD 0.57) at baseline, 0.25 (SD 0.66) at visit 1, 0.13 (SD 0.3) at visit 2 and 0.38 (SD 0.89) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.01 (SD 0.43) at visit 1, -0.03 (SD 0.27) at visit 2, and 0.07 (SD 0.24) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain eating and drinking was 0.04 (SD 0.27) at baseline, 0 (SD 0) at visit 1 and visit 2, and 0.02 (SD 0.1) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0 (SD 0) at visit 1, -0.06 (SD 0.36) at visit 2, and 0.02 (SD 0.1) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain housework was 0.7 (SD 0.93) at baseline, 0.81 (SD 1.05) at visit 1, 0.68 (SD 0.68) at visit 2 and 0.98 (SD 1.05) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.07 (SD 0.43) at visit 1, 0.2 (SD 0.58) at visit 2, and 0.27 (SD 0.5) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain lower extremities was 0.33 (SD 0.88) at baseline, 0.26 (SD 0.64) at visit 1, 0.24 (SD 0.6) at visit 2 and 0.39 (SD 0.88) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was -0.11 (SD 0.7) at visit 1, 0.05 (SD 0.45) at visit 2, and -0.03 (SD 0.33) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain maintaining position was 0.79 (SD 0.98) at baseline, 1.1 (SD 1.06) at visit 1, 1.14 (SD 1.05) at visit 2 and 1.43 (SD 1.18) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.24 (SD 0.61) at visit 1, 0.37 (SD 0.61) at visit 2, and 0.4 (SD 0.82) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain moving about (using equipment) was 0.32 (SD 0.69) at baseline, 0.26 (SD 0.63) at visit 1, 0.25 (SD 0.59) at visit 2 and 0.58 (SD 0.92) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was -0.1 (SD 0.49) at visit 1, -0.02 (SD 0.42) at visit 2, and 0.17 (SD 0.79) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain self-care was 0.02 (SD 0.1) at baseline, 0.05 (SD 0.29) at visit 1, 0 (SD 0) at visit 2 and 0.15 (SD 0.46) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.04 (SD 0.22) at visit 1, -0.01 (SD 0.06) at visit 2, and 0.13 (SD 0.37) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain use of hands and arms was 0.08 (SD 0.3) at baseline, 0.1 (SD 0.31) at visit 1, 0.17 (SD 0.47) at visit 2 and 0.14 (SD 0.44) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was -0.01 (SD 0.25) at visit 1, 0.08 (SD 0.4) at visit 2, and 0.08 (SD 0.39) at follow-up after 1 month (see Table 46 in TLF v1.0).

Mean score for domain walking (without equipment) was 1.26 (SD 1.14) at baseline, 1.34 (SD 1.26) at visit 1, 1.29 (SD 1.14) at visit 2 and 1.61 (SD 1.29) at follow-up after 1 month (see Table 45 in TLF v1.0). Mean score change from baseline was 0.14 (SD 0.7) at visit 1, 0.16 (SD 0.99) at visit 2, and 0.22 (SD 0.77) at follow-up after 1 month (see Table 46 in TLF v1.0).

10.5. Other analyses

Not applicable

10.6. Adverse events/adverse reactions

Fifty patients (60.98%) experienced at least one TEAE (Table 17). Grade ≥3 TEAE occurred in 25 patients (30.49%); seven patients died (8.53%). In 19 patients (23.17%), Radium-223 was withdrawn due to TEAE. Twenty-one patients (25.61%) had a drug-related TEAE. Grade ≥3 drug-related TEAE occurred in four patients (4.86%); two patients died (2.43%). Drug-related TEAE led to permanent discontinuation of Radium-223 in five patients (6.10%). Serious TEAE occurred in 24 patients (29.27%). In 13 patients (15.85%), serious TEAE led to permanent discontinuation of the study drug. Three patients (3.66%) had serious drug-related TEAE, two patients died (2.43%).

Table 17: Treatment-emergent adverse events - Overview (SAF)

Overview of TEAE	N (%)
Number of patients	82 (100.0)
Number of patients with any TEAE	50 (60.98)
Grade 3	16 (19.51)
Grade 4	2 (2.43)
Grade 5 (death)	7 (8.53)
Leading to permanent discontinuation of study drug	19 (23.17)
Number of patients with any drug-related TEAE	21 (25.61)
Grade 3	2 (2.43)
Grade 4	0 (0.00)
Grade 5 (death)	2 (2.43)
Leading to permanent discontinuation of study drug	5 (6.10)
Number of patients with any serious TEAE	24 (29.27)
Grade 5 (death)	7 (8.53)
Leading to permanent discontinuation of study drug	13 (15.85)
Number of patients with any serious drug-related TEAE	3 (3.66)
Grade 5 (death)	2 (2.43)

Source: Table 70, Table 71, Table 78, Table 82 and Table 71, TLF v1.0

10.6.1. TEAE

Most frequently occurring TEAE by System Organ Class (SOC) included general disorders and administration site conditions (19.51%, n=16), gastrointestinal disorders (18.29%, n=15), blood and lymphatic system disorders (13.41%, n=11), musculoskeletal and connective tissue disorders (12.19%, n=10), neoplasms benign, malignant and unspecified (incl cysts and polyps) (10.97%, n=9,

Table 18). TEAEs (by Preferred Term, PT) occurring in more than 2% of patients included anemia and fatigue (13.41%, n=11, both), diarrhea (10.97%, n=9), bone pain (8.53%, n=7), dyspnea (4.87%, n=4), nausea, general physical health deterioration, pain and weight decreased (3.65%, each, n=3), influenza, pneumonia, platelet count decreased, decreased appetite, dehydration, back pain, acute kidney injury, (2.43%, n=2, each, Table 18). Most frequently occurring grade ≥3 TEAEs were anemia (6.09%, n=5), and fatigue, bone pain, dyspnea, and acute kidney injury (2.43%, n=2, each, Table 18).

Table 18: TEAE according to MedDRA-SOC, PT and worst CTCAE grade (patient based) (SAF)

TEAE (patient based) (MedDRA v23.0)		Grade 3	Grade 4	Grade 5	Total (including all grades)
		N (%)	N (%)	N (%)	N (%)
Number of patients					82 (100.00)
Any SOC		16 (19.51)	2 (2.43)	7 (8.53)	50 (60.97)
Blood and lymphatic system disorders	Any PT	4 (4.87)	1 (1.21)	1 (1.21)	11 (13.41)
	Anemia	4 (4.87)		1 (1.21)	11 (13.41)
Cardiac disorders	Any PT				2 (2.43)
Gastrointestinal disorders	Any PT	1 (1.21)			15 (18.29)
	Diarrhea				9 (10.97)
	Nausea				3 (3.65)
General disorders and administration site conditions	Any PT	2 (2.43)	1 (1.21)		16 (19.51)
	Fatigue	2 (2.43)			11 (13.41)
	General physical health deterioration		1 (1.21)		3 (3.65)
	Pain	1 (1.21)			3 (3.65)
Infections and infestations	Any PT	3 (3.65)			7 (8.53)
	Influenza				2 (2.43)
	Pneumonia	1 (1.21)			2 (2.43)
Injury, poisoning and procedural complications	Any PT	1 (1.21)			3 (3.65)
Investigations	Any PT	1 (1.21)			6 (7.31)
	Platelet count decreased	1 (1.21)			2 (2.43)
	Weight decreased				3 (3.65)
Metabolism and nutrition disorders	Any PT	1 (1.21)		1 (1.21)	5 (6.09)
	Decreased appetite				2 (2.43)
	Dehydration	1 (1.21)			2 (2.43)
Musculoskeletal and connective tissue disorders	Any PT	3 (3.65)			10 (12.19)
	Back pain	1 (1.21)			2 (2.43)
	Bone pain	2 (2.43)			7 (8.53)

TEAE (patient based) (MedDRA v23.0)		Grade 3	Grade 4	Grade 5	Total (including all grades)
		N (%)	N (%)	N (%)	N (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any PT		1 (1.21)	4 (4.87)	9 (10.97)
Nervous system disorders	Any PT	1 (1.21)			5 (6.09)
Renal and urinary disorders	Any PT	4 (4.87)		1 (1.21)	6 (7.31)
	Acute kidney injury	1 (1.21)		1 (1.21)	2 (2.43)
Respiratory, thoracic and mediastinal disorders	Any PT	1 (1.21)	1 (1.21)		4 (4.87)
	Dyspnea	1 (1.21)	1 (1.21)		4 (4.87)
Vascular disorders	Any PT	2 (2.43)			3 (3.65)

Shown are TEAEs of all grades that occurred in at least 2% of patients.
Source: Table 71, TLF v1.0

TEAEs recovered/resolved in 26 patients out of 50 patients with TEAE (52%), were recovering/resolving at the end of observation period in one patient (2%) and did not recover/ resolve in 13 patients (26%, see Table 76 in TLF v1.0). The outcome was fatal in 7 patients (14%), and it was unknown in three (6%). Radium-223 dose was most frequently not changed due to TEAE (n=24 patients, 48%, see Table 74 in TLF v1.0). In 19 patients (38%), Radium-223 was withdrawn due to TEAE and interrupted/delayed in six (12%). TEAE that most frequently led to withdrawal of Radium-223 were anemia (4.87%, n=4) and fatigue, general physical health deterioration and bone pain (2.43%, n=2, each, see Table 75 in TLF v1.0). Twenty-one patients (42%) received remedial drug therapy due to TEAE, 17 patients (34%) received other treatment and 38 patients (76%) received no treatment (see Table 77 in TLF v1.0).

10.6.2. Drug-related TEAE

Among the 82 patients with TEAE, 21 patients (25.6%) had drug-related TEAE. Most often occurring drug-related TEAE (by SOC) were gastrointestinal disorders (12.19%, n=10), general disorders and administration site conditions (8.53%, n=7), blood and lymphatic system disorders (6.09%, n=5), and investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, and nervous system disorders (2.43%, n=2, each, Table 19). Most often occurring drug-related TEAEs by PT included diarrhea (9.75%, n=8), fatigue (8.53%), anemia (6.09%, n=5), and platelet count decreased, decreased appetite and bone pain (2.43%, n=2, each, Table 19). Grade ≥3 drug-related TEAEs were fatigue and anemia (2.43%, n=2, both), and platelet count decreased, pancytopenia and acute kidney injury (1.21%, n=1, each, Table 19).

Table 19: Drug-related TEAE according to MedDRA-SOC, PT and worst CTCAE grade (patient based) (SAF)

Drug-related TEAE (patient based) (MedDRA v23.0)		Grade 3	Grade 4	Grade 5	Total (including all grades)
		N (%)	N (%)	N (%)	N (%)
Number of patients					82 (100.00)
Any SOC		2 (2.43)		2 (2.43)	21 (25.60)
Blood and lymphatic system disorders	Any PT	1 (1.21)	1 (1.21)	1 (1.21)	5 (6.09)
	Anemia	1 (1.21)		1 (1.21)	5 (6.09)
	Leukopenia				1 (1.21)
	Pancytopenia		1 (1.21)		1 (1.21)
Cardiac disorders	Any PT				1 (1.21)
	Cardiovascular symptom				1 (1.21)
Gastrointestinal disorders	Any PT				10 (12.19)
	Diarrhea				8 (9.75)
	Dry mouth				1 (1.21)
	Nausea				1 (1.21)
	Vomiting				1 (1.21)
General disorders and administration site conditions	Any PT	2 (2.43)			7 (8.53)
	Fatigue	2 (2.43)			7 (8.53)
Investigations	Any PT	1 (1.21)			2 (2.43)
	Platelet count decreased	1 (1.21)			2 (2.43)
	White blood cell count decreased				1 (1.21)
Metabolism and nutrition disorders	Any PT				2 (2.43)
	Decreased appetite				2 (2.43)
Musculoskeletal and connective tissue disorders	Any PT				2 (2.43)
	Bone pain				2 (2.43)
Nervous system disorders	Any PT				2 (2.43)
	Burning sensation				1 (1.21)
	Hypoesthesia				1 (1.21)
Renal and urinary disorders	Any PT			1 (1.21)	1 (1.21)
	Acute kidney injury			1 (1.21)	1 (1.21)
Respiratory, thoracic and mediastinal disorders	Any PT				1 (1.21)
	Dyspnea				1 (1.21)

Source: Table 78, TLF v1.0

Drug-related TEAEs recovered/resolved in 14 patients out of 21 patients with drug-related TEAE (66.67%) and did not recovered/resolve in four patients (19.04%, see Table 81 in TLF v1.0). The

outcome was fatal in two patients (9.52%), and it was unknown in one patient (4.76%). Radium-223 dose was most frequently not changed due to drug-related TEAE (n=14, 66.67%, see Table 80 in TLF v1.0). In five patients (23.81%), Radium-223 dose was withdrawn due to drug-related TEAE, or interrupted 2 patients (9.52%).

10.6.3. Serious TEAE

Among the 24 patients with serious TEAE, the most often occurring serious TEAE (by SOC) included neoplasms benign, malignant and unspecified (incl cysts and polyps, 8.53%, n=7), general disorders and administration site conditions and renal and urinary disorders (6.09%, n=5, each), blood and lymphatic system disorders and infections and infestations (4.87%, n=4, each), musculoskeletal and connective tissue disorders and 'respiratory, thoracic and mediastinal disorders' (2.43%, n=2, each, see Table 82 in TLF v1.0). Serious TEAEs by PT occurring in more than 2% of patients included anemia (3.65%, n=3), fatigue, general physical health deterioration, pain, pneumonia, acute kidney injury and dyspnea (2.43%, n=2, each, see Table 82 in TLF v1.0).

Necessary or prolonged hospitalization was the most frequent reason for seriousness of TEAE (n=18, 75%), followed by death (n=7, 29.17%), life threatening (n=5, 20.83%), other medically important serious event (n=4, 16.67%) and persistent or significant disability/incapacity (n=2, 8.33%, see Table 83, TLF v1.0). Fatal serious TEAE were anemia, cachexia, hormone-refractory prostate cancer, metastases to liver, metastases to lymph nodes, prostate cancer metastatic and acute kidney injury (n=1, 1.21%, each, see Table 88 in TLF v1.0).

Among the patients with serious TEAEs, Radium-223 was withdrawn in 13 patients (54.17%). In four patients (16.67%), Radium-223 dose was interrupted; dose was not changed in five patients (20.83%, see Table 86 in TLF v1.0). Serious TEAEs recovered/resolved in 13 patients (54.17%), did not recovered/ resolve in three (12.50%). The outcome was fatal in seven patients (29.16%), and it was unknown in one patient (4.16%, see Table 87 in TLF v1.0).

Three patients (3.65%) had serious drug-related TEAE (see Table 84 in TLF v1.0), including blood and lymphatic system disorders (3.65%, n=3), general disorders and administration site conditions and renal and urinary disorders (1.21%, n=1, both). Serious drug-related TEAEs by PT included anemia (2.43%, n=2) and pancytopenia, fatigue and acute kidney injury (1.21%, n=1, each). Necessary or prolonged hospitalization was the reason of seriousness of serious drug-related TEAE in three patients, death in two patients and other medically important serious event in one patient (see Table 85 in TLF v1.0).

11. Discussion

11.1. Key results

Analysis of the primary objective of the study demonstrated that median OS was 16.72 months (95%CI 12.65-23.72), which is comparable with the median OS reported in the ALSYMPCA trial (14.9 months (35)). Furthermore, median OS tended to be longer in patients without prior chemotherapy. A similar tendency in OS between patients with and without prior docetaxel was observed in Radium-223-treated group in the ASLYMPCA trial (14.4 vs 16.1 months, (36)). Several observational studies investigating Radium-223 reported median OS of 14.3-15.6 months (37-39).

In the present study, the median number of prior systemic anti-cancer therapy regimens per patient (including therapy overlapping with Radium-223) was 1 (range 1-3). This indicates that in routine clinical practice in mCRPC in Germany, Radium-223 is used in patients pretreated with systemic anti-cancer treatment, in this study most often with abiraterone or enzalutamide. Our results also reflect other real-world data in patients with one prior systemic anti-cancer treatment. For instance, in the observational study REACTIVATE from Canada presented at ASCO Genitourinary Cancers Symposium 2021, patients who received Radium-223 in earlier lines of therapy had a longer median survival than those treated with Radium-223 in later-lines (40). Moreover, those that received Radium-223 early received less chemotherapy but still had a better survival than patients with Radium-223 in later line.

Secondary objectives included analysis of SSE-FS, incidence of pathological fractures (as part of SSEs), non-pathological fractures and bone associated events, TTNT, estimation of QoL using the FACT-P questionnaire, activities of daily living according to the Katz-Index, and body function using the MOSES questionnaire. Median SSE-FS was 14.98 months (95%CI 11.40-20.90). Previously, a comparable median time to first SSE of 15.6 months was reported for Radium-223-treated patients (41, 42) although a shorter (10-11 months, (43)) or longer SSE-FS (22.3 months, (33)) were also documented. SSEs occurred in 6.9% of patients in FAS (8.5% in SAF) and they most often included external radiotherapy for relief of skeletal symptoms (5.5% in FAS; 6.1% in SAF). These SSE rates are similar to those obtained in the PARABO study. At 30%, rates of external radiotherapy were considerably higher in the ALSYMPCA trial (44). This indicates that external radiotherapy may be underreported in real-world setting. However, it may be that pain management has shifted in the last years from the use of external radiotherapy towards palliative (active) tumor treatment with the new anti-hormonal drugs, which were not available at the time when the ALSYMPCA trials was conducted.

In addition, 4.9% of patients in SAF (4.1% in FAS) had a new symptomatic pathological bone fracture. Interestingly, new symptomatic pathological bone fractures occurred only in patients without prior abiraterone or enzalutamide. Similarly, low rate of fractures among the abiraterone-pretreated patients receiving Radium-223 (2.1%) was recently reported in the real-world setting by Caffo et al (38). In contrast, addition of Radium-223 to abiraterone and prednisone or prednisolone in asymptomatic or mildly symptomatic patients without systemic pretreatments for mCRPC was associated with an increased fracture risk in the ERA 223 trial (33). Overall, results obtained within the present study suggest that abiraterone followed by Radium-223 is associated with a low incidence of fractures. However, these data should be interpreted with caution given the low number of patients. Of note, more than half of the patients (64.4% in FAS) received BHA prior to or overlapping with Radium-223. Current data from the PEACE III trial confirm that concomitant usage of BHA for treatment of mCRPC patients with Radium-223 reduces the risk of fractures (45).

Overall, median TTNT was 14.42 months (95%CI 10.12-NR). Similar TTNT (15.9 months) was recently reported for patients treated with Radium-223 plus enzalutamide (46). 38.4% of patients in the present study received a mCRPC therapy after the first injection of Radium-223 (including cabazitaxel, docetaxel, abiraterone, enzalutamide, mitoxantrone or a retreatment with Radium-223).

FACT-P total score remained stable throughout therapy with Radium-223 and during the first month of follow-up period. This trend was consistent across all FACT-P subscales. Compared to the ALSYMPCA trial (27), patients in the present study had a higher baseline FACT-P total score and scores in each FACT-P components indicating a better QoL. Reduction in FACT-P total score was -7.59 vs -4.83 in the ALSYMPCA trial during a comparable period of 6 months after the last

Radium-223 injection. However, this difference was based on a low number of patients (n=7) and therefore, these results should be interpreted with caution. In the ALSYMPCA trial a higher percentage of Radium-223-treated patients experienced meaningful improvement in QoL (based on FACT-P and EQ-5D utility score) and a lower percentage experienced meaningful worsening in QoL than in the placebo group (27). Overall, Katz index total remained stable from baseline (5.6) until follow-up after 1 month (5.3, -0.27 change). Furthermore, most of the activities covered by the Katz index remained stable at a high level of more than 5 points till follow up after one month (a score of 6 points indicates full function. 4 points indicates moderate impairment). The percentage of patients who were independent in their daily activities slightly decreased in the time period until the end of first month after end of Radium-223 therapy. A notable exception was activities related to feeding as all patients were able to feed independently at each study visit and at follow-up after 1 month. The MOSES questionnaire is used in rehabilitation medicine after orthopedic intervention. It was used in URANIS to gain information about patients and the function of daily activities regarding their skeletal system. The functional status assessed by MOSES questionnaire (expressed as a mean score change from baseline) was unaffected throughout the study. Therefore, these data stress the importance of identification of limitations in daily activities experienced by some mCRPC patients who may be in need for supportive care. Overall, the analyses of FACT-P, Katz Index and MOSES questionnaire data consistently showed a maintenance of QoL, ability to perform activities of daily living and body function status during treatment period. However, data should be interpreted with caution due to low numbers of patients in the follow up after 3 months.

61% of patients in SAF experienced at least one TEAE, most often anemia and fatigue (13.4%, both), and diarrhea (11%). Grade ≥3 TEAE occurred in 30.5% of patients; 8.5% died. 38% of patients with TEAE permanently discontinued Radium-223 while therapy was interrupted or delayed in 12% (corresponding to 23.2% and 7.3%, respectively, of all patients in SAF). The frequency of TEAE, Grade 3 or 4 TEAE was higher in the ALSYMPCA trial (93%, 56%, respectively, (23)) while TEAE rate was similar in the REASSURE study (53%, (47)). A comparable proportion of patients discontinued Radium-223 due to TEAE in the ALSYMPCA trial (16%, compared to 23.2% in the present study, (23)). In line with our results, the most frequent TEAE in the ALSYMPCA trial and in the interim analysis of the REASSURE study included anemia, diarrhea, nausea and fatigue and additionally bone pain in the ALSYMPCA trial (23, 47). Interestingly, in addition to prolonging OS, the ALSYMPCA trial showed a positive effect on bone pain. Bone pain rates were higher in the placebo group compared to the radium-223 group (all grades: 62% vs 50%; and grade 3/4 with 26% vs 21%). Consistent rates on bone pain was also demonstrated in the PARABO study (48). Anemia occurred in 13.4% of patients in the present study which was less frequently than in the ALSYMPCA trial (31%, (23)) but more often than in the REASSURE study (10%, (47)). Serious TEAE occurred in 29.3% of patients, most frequently anemia (3.65%), fatigue, general physical health deterioration, pain, pneumonia, acute kidney injury and dyspnea (2.43%, each). Radium-223 was permanently or temporarily withdrawn by 54.2% and 16.7% of patients with serious TEAEs, respectively (corresponding to 15.9% and 4.9%, respectively, of all patients in SAF). Compared to our study, the frequency of serious TEAE was higher in the ALSYMPCA trial (47%, (23)) and similar in the REASSURE study (25%, (47)). Furthermore, a comparable percentage of patients discontinued Radium-223 due to serious TEAE in the REASSURE and in the present study (12% and 15.9%, respectively, (47)). 25.6% of patients experienced a drug-related TEAE, most often diarrhea, fatigue and anemia. Grade ≥3 drug-related TEAE occurred in 4.9% of patients; 2.4% of patients died. Radium-223 was permanently or temporarily withdrawn by 23.8% and 9.5% due to drug-related TEAE, respectively (corresponding to 6.1% and 2.4%, respectively, of all patients in SAF). At 38% and 9%, rates of drug-related TEAE

of all grades and Grade ≥3, respectively, in the REASSURE study was higher than in the present study (47). Conversely, a comparable percentage of patients (6%) permanently discontinued Radium-223 due to a drug-related TEAE in the REASSURE study. In line with our results, the most frequent drug-related TEAE in the REASSURE were diarrhea, fatigue and anemia (47).

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 is not possible. Furthermore, any observed effects in this study may not be attributed to treatment with Radium-223 alone but will also reflect the natural course of disease and the effect other treatments received before, during or after study treatment. For this reason, differentiation of different treatment effects and natural course of disease is not possible with this design. 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 might not have been 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, relatively small sample size of the study limited its potential to draw strong conclusions. Moreover, data were available for only a few patients at long-term follow-up visits thus limiting an insight into late effects of Radium-223. Fifth, patients may have received prior care in different medical practices that were not necessarily participating in the study. Radium-223 was administered by nuclear physicians and referred to investigators. Therefore, there is a potential risk for bias and loss of data during the data collection. Sixth, data on OS, SSE-FS, incidence of (non-) pathological fractures and bone associated events during the treatment and follow-up period and TTNT could have been affected by early study termination. Finally, with respect to site selection, this study could have a potential limited representativeness (at convenience sample) as only the sites with Radium-223 dichloride availability (nuclear-medicine licensed facilities) and experience with prostate cancer management and treatment were considered for the participation in the study.

11.3. Interpretation

The obtained data confirmed the previously reported OS duration in clinical trials and observational studies. Moreover, there was a tendency towards a longer OS in patients without prior chemotherapy. These data have to be interpreted with caution as they reflect a low number of patients and may result from the fact that patients without chemotherapy could suffer from a less advanced disease and that patients receiving abiraterone had a different number of prior therapy lines. We also found that Radium-223 was used after a median number of one prior systemic anti-cancer treatment in the majority of patients thus confirming the Radium-223 efficacy in pretreated patients. The present study additionally supported the evidence on the efficacy of Radium-223 to delay the need to start next line of therapy for mCRPC. In accordance with prior clinical trial and observational data, the median number of injections was 6. Furthermore, more than half of the patients got BHA prior to or concomitant with Radium-223, which is recommended for treatment of mCRPC patients in current guidelines.

Moreover, SSE-FS and incidence rate of fractures and bone associated events was similar to previously reported data. A lower percentage of patients received external radiotherapy than previously shown, although this effect potentially could be attributed to the bias in reporting.

Gathered data also indicated that Radium-223 therapy is effective in maintaining QoL. Furthermore, patients preserve their functional status and ability to independently perform their daily activities. Therefore, patients under Radium-223 therapy remain functional in terms of mobility, self-care and performing domestic activities and do not have an increased need for a care from family caregivers or nursing assistants.

Finally, obtained results confirmed the previously established efficacy and safety profile of Radium-223 in mCRPC patients. TEAE, Grade ≥3 TEAE and serious TEAE occurred less frequently than in the ALSYMPCA trial. Treatment discontinuation rate was comparable to previously published data. In line with previous clinical trial and real-world data, most often documented TEAEs included anemia, fatigue and diarrhea. Among the serious TEAEs, patients most often experienced anemia (in 3.7% of patients). At 3.7%, rate of serious drug-related TEAE was low.

11.4. Generalizability

The obtained results reflect the real-life urooncologic 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 (37) and global study REASSURE (47), in terms of age and prior anti-cancer therapy.

12. Other information

None

13. Conclusion

This real-world study corroborates previously reported data on the OS and TTNT of Radium-223 in mCRPC patients. This study showed similar SSE rate and time to first occurrence of SSE as reported in Radium-223 arms of previous studies. Most of the patients got BHA prior to or concomitant with Radium-223 treatment. Overall, QoL, functional status and ability to independently perform activities of daily living remained stable throughout the study. Finally, the safety results of this study are consistent with the previously established safety profile of Radium-223.

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Appendices

Annex 1: List of stand-alone documents

Table 20: List of stand-alone documents

Document Name	Final version and date
Investigator list	V1.0, 20 AUG 2021
List of IEC and IRB	V1.0, 20 AUG 2021
DMP	V2.0, 01 OCT 2019
CRF	V11, 15 APR 2019
QRP	V2.0, 27 SEP 2018
MRP	V4.0, 12 DEC 2019
TLF	V1.0, 07 MAY 2021
SAP	V3.0, 21 AUG 2020

Annex 2: Additional information

Table 21: List of OS/PASS protocol versions

Document Name	Effective Date
OS/PASS protocol version 1.0	28 JAN 2015
OS/PASS protocol version 2.0	23 FEB 2017
OS/PASS protocol version 3.0	14 AUG 2017
OS/PASS protocol version 4.0	30 APR 2018

Annex 3: Signature Pages

Signature Page - Study safety lead

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
IMPACT study number	18043
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS24796
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-Sep-2021 _____, _____ PPD

Signature Page - Study medical expert

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
IMPACT study number	18043
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS24796
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-Sep-2021 _____, _____ PPD

Signature Page - Study conduct responsible

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
IMPACT study number	18043
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS24796
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: 01-Sep-2021 _____, _____ PPD

Signature Page - Study statistician

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 01-Sep-2021 _____, _____ PPD

Signature Page - Study Epidemiologist

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
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Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 01-Sep-2021 _____, _____ PPD

Signature Page - Study HEOR responsible

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

Print Name: PPD

Date, Signature: 02-Sep-2021 _____, _____ PPD

Signature Page - Study data manager

Title	URANIS – Data collection in urological centers during treatment with Ra-223 dichloride (Xofigo) within the framework of a non-interventional study assessing overall survival (OS) and effectiveness predictors of Ra-223 dichloride treated mCRPC patients in a real life setting in Germany
Report version and date	V 1.0, 01 SEP 2021
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Print Name: PPD

Date, Signature: 01-Sep-2021 _____, _____ PPD

DocuSign

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Please DocuSign: 18043_URANIS_OSR_final v1.0_2021-09-01_clean.pdf
Source Envelope:
Document Pages: 91 Signatures: 7
Certificate Pages: 5 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC+01:00) Brussels, Copenhagen, Madrid, Paris

Envelope Originator:
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Digital Signature Competence Center Building B151, R508
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Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Bayer PROD CFR Part XI Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2021 6:56:37 PM Viewed: 9/1/2021 8:07:47 PM Signed: 9/1/2021 8:09:16 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Ich genehmige dieses Dokument	Sent: 9/1/2021 6:56:36 PM Viewed: 9/2/2021 7:31:02 AM Signed: 9/2/2021 7:33:11 AM
Electronic Record and Signature Disclosure: Accepted: 3/26/2021 12:44:14 PM ID: PPD		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 9/2/2021 9:52:37 AM ID: PPD	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Ich bin der Verfasser dieses Dokuments	Sent: 9/1/2021 6:56:36 PM Viewed: 9/2/2021 9:52:37 AM Signed: 9/2/2021 9:56:26 AM
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PPD PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	PPD Signature Adoption: Uploaded Signature Image Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2021 6:56:37 PM Viewed: 9/1/2021 6:59:08 PM Signed: 9/1/2021 7:01:46 PM
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	9/1/2021 10:08:57 PM
Signing Complete	Security Checked	9/1/2021 10:10:17 PM
Completed	Security Checked	9/2/2021 11:57:54 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Signatures – Consent and Privacy statement

Herewith, signers agree that the electronic signatures are intended to be the legally binding equivalent of traditional handwritten signatures according to CFR – Code of Federal Regulations Title 21, Part 11 Electronic Records; Electronic Signatures, Subpart C – Electronic Signatures.

Bayer AG (hereinafter "us" or "we") wishes to inform you about **processing of your personal data in the context of Electronic Signatures**. Your personal data will be processed when you use the technical platform DocuSign Digital Transaction Management Platform ("DocuSign Website") and as part of electronically signing or approving a document. DocuSign Inc., United States of America, provides the technical platform. For respective data processing, please refer to the privacy statement from DocuSign Inc. available on the DocuSign Website. The Privacy Statement at hand informs about the personal data processed by Bayer AG as part of electronically signing or approving a document.

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The personal data, which we process, are **identifying information** like your name, e-mail address and contact details, and **document management and signature related information** like date of signature, history of document-related actions (e.g. review, sign and IP address). Furthermore, the electronically signed documents may contain **personal data of any type** that is not directly related to the electronic signature process.

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Your personal data may be transferred to and processed in a country outside the European Economic Area for which the European Commission has not decided that it ensures an adequate level of data protection. In such cases, we will set up appropriate protection measures as required by GDPR. For example, we generally will apply the so-called "standard

data protection clauses" adopted by the European Commission. You can obtain a copy from us on request. Alternative protection measures may be implemented as well.

Your personal data will be **retained and archived** according to legally required retention and archiving periods applicable to business related files. Your personal data will then be deleted if there are no other legal reasons to further processing.

You have the right to request information from us about your personal data, access to and rectification or erasure of personal data or restriction of processing concerning your personal data or to object to processing as well as the right to data portability. You also have the right to lodge a complaint with the data protection supervisory authority.

For any questions, you may have with respect to data privacy, please contact PPD

Last updated: November 12, 2020.