Clinical trial results:
A re-treatment safety study of radium-223 dichloride in subjects with castration-resistant prostate cancer with bone metastases who received an initial course of six doses of radium-223 dichloride 50 kBq/kg every four weeks

Summary

EudraCT number	2013-003046-17
Trial protocol	SE NO FI IT ES GB DE
Global end of trial date	12 April 2017

Results information

Result version number	v1 (current)
This version publication date	12 March 2018
First version publication date	12 March 2018

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/16506

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01934790
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of re-treatment with up to 6 doses of radium-223 dichloride 50 kBq/kg given every 4 weeks in subjects with castration-resistant prostate cancer (CRPC) with bone metastases who received an initial course of 6 doses of radium-223 dichloride 50 kBq/kg.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	44
EEA total number of subjects	16

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	26
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Overall, 59 subjects were enrolled into the study centers in 7 countries worldwide, from 22-Dec-2013 (first patient first visit) to 12-Apr-2017 (last patient last visit).

Pre-assignment

Screening details:

The study was conducted at 16 study centers that screened 59 subjects. Of them, 14 were screening failures and the remaining 45 subjects were assigned to treatment.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Radium-223 dichloride (Xofigo, BAY88-8223)

Arm description:

Subjects received intravenous (IV) injection of radium-223 dichloride 50 kBq/kg body weight every 4 weeks up to 6 injections.

Arm type	Experimental
Investigational medicinal product name	Radium-223 dichloride
Investigational medicinal product code	BAY88-8223
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intravenous (IV) injection of radium-223 dichloride 50 kBq/kg body weight every 4 weeks up to 6 injections.

Number of subjects in period 1	Radium-223 dichloride (Xofigo, BAY88-8223)
Started	44
Entered active Follow up	34
Entered long term Follow up	12 [1]
Completed	29
Not completed	15
Clinical progression	6
Consent withdrawn by subject	2
Radiological progression	4
Adverse event, non-fatal	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to database constraint, number of subjects entering each study phase was reported as milestones.

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 dichloride (Xofigo, BAY88-8223)
Reporting group description:	
Subjects received intravenous (IV) injection of radium-223 dichloride 50 kBq/kg body weight every 4 weeks up to 6 injections.	

Reporting group values	Radium-223 dichloride (Xofigo, BAY88-8223)	Total	
Number of subjects	44	44	
Age categorical			
Units: Subjects			
< 65 years	13	13	
>=65 years	31	31	
Age continuous			
Units: years			
median	71		
full range (min-max)	52 to 91	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	44	44	
Baseline Eastern Cooperative Oncology Group (ECOG) Performance status (PS) score			
Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is a scale that measures how cancer affects a patient. The scale ranges from 0 (fully active) to 5 (dead).			
Units: Subjects			
ECOG PS score=0	14	14	
ECOG PS score=1	27	27	
ECOG PS score=2	3	3	
Number of bone lesions			
Units: Subjects			
1-5	18	18	
6-20	15	15	
> 20, not a superscan	6	6	
Superscan	5	5	
Prostate specific antigen (PSA) - mean value			
Units: microgram per liter			
arithmetic mean	211.59		
standard deviation	± 452.84	-	
Total alkaline phosphatase (ALP) -mean value			
Units: Unit per liter			
arithmetic mean	122.60		
standard deviation	± 118.49	-	
Time from initial diagnosis of bone metastasis			
Units: Months			

median	43.12		
full range (min-max)	7.6 to 172.4	-	
Time from initial diagnosis Units: Months			
median	80.34		
full range (min-max)	11.8 to 287.9	-	
Time since initial treatment with radium-223 dichloride Units: Months			
median	6.05		
full range (min-max)	1.2 to 17.1	-	
Prostate specific antigen (PSA) - median value Units: microgram per liter			
median	67.66		
full range (min-max)	0.05 to 2349.04	-	
Total alkaline phosphatase (ALP) - median value Units: Unit per liter			
median	85		
full range (min-max)	29 to 705	-	

End points

End points reporting groups

Reporting group title	Radium-223 dichloride (Xofigo, BAY88-8223)
Reporting group description:	
Subjects received intravenous (IV) injection of radium-223 dichloride 50 kBq/kg body weight every 4 weeks up to 6 injections.	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of study drug	
Subject analysis set title	Active Follow-up Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who were reported in the End of Treatment (EOT) electronic case report form (eCRF) as planning to participate in the active follow-up.	

Primary: Number of subjects with treatment-emergent adverse events (AEs)

End point title	Number of subjects with treatment-emergent adverse events (AEs)[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. A treatment-emergent adverse events (TEAE) is defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of radium-223 dichloride.	
End point type	Primary
End point timeframe:	
Up to 2.5 years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[2]			
Units: Subjects				
number (not applicable)	41			

Notes:

[2] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent serious adverse events (SAEs)

End point title	Number of subjects with treatment-emergent serious adverse events (SAEs)[3]

End point description:

TESAE occurred after the start of radium-223 dichloride treatment until 30 days after the last dose and results in death; is life-threatening; requires inpatient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly / birth defect; is another medically important serious event as judged by the investigator; or is an occurrence of leukemia, myelodysplastic syndrome, aplastic anemia, myelofibrosis, and primary bone cancer or any other new primary malignancy, such as acute myeloid leukemia.

End point type	Primary

End point timeframe:

Up to 2.5 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[4]			
Units: Subjects				
number (not applicable)	13			

Notes:

[4] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with Radium-223 dichloride-related AEs in the active follow-up period

End point title	Number of subjects with Radium-223 dichloride-related AEs in the active follow-up period[5]

End point description:

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study.

End point type	Primary

End point timeframe:

Up to 2 years after last treatment

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[6]			
Units: Subjects				
number (not applicable)	1			

Notes:

[6] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with Radium-223 dichloride-related SAEs in the active follow-up period

End point title	Number of subjects with Radium-223 dichloride-related SAEs in the active follow-up period[7]

End point description:

Treatment-related SAE is any SAE that, according to the investigator's causality assessment, is possibly or probably related to treatment with radium-223 dichloride.

End point type	Primary

End point timeframe:

Up to 2 years after last treatment

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[8]			
Units: Subjects				
number (not applicable)	0			

Notes:

[8] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with high/low abnormalities in hematology variables at any visit after treatment start

End point title	Number of subjects with high/low abnormalities in hematology variables at any visit after treatment start[9]

End point description:

End point type	Primary

End point timeframe:

Up to 2.5 years

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[10]			
Units: Subjects				
number (not applicable)				
Eosinophils (GIGA/L) - High	1			
Ery. Mean Corpuscular HGB Conc. (g/dL) - High	1			
Ery. Mean Corpuscular Hemoglobin (pg) - High	16			
Ery. Mean Corpuscular Volume (fL) - High	22			
Leukocytes (GIGA/L) - High	5			
Monocytes (GIGA/L) - High	7			
Neutrophils (GIGA/L) - High	9			
Platelets (GIGA/L) - High	1			
Basophils (GIGA/L) - Low	2			
Eosinophils (GIGA/L) - Low	7			
Ery. Mean Corpuscular HGB Conc. (g/dL) - Low	17			
Ery. Mean Corpuscular Hemoglobin (pg) - Low	4			
Ery. Mean Corpuscular Volume (fL)	3			
Erythrocytes (T/L) - Low	43			
Hematocrit (%) - Low	43			
Hemoglobin (g/dL) - Low	43			
Leukocytes (GIGA/L) - Low	21			
Lymphocytes (GIGA/L) - Low	36			
Monocytes (GIGA/L) - Low	2			
Neutrophils (GIGA/L) - Low	10			
Platelets (GIGA/L) - Low	11			

Notes:

[10] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with high/low abnormalities in biochemistry variables at any visit after treatment start

End point title	Number of subjects with high/low abnormalities in biochemistry variables at any visit after treatment start[11]

End point description:

End point type	Primary

End point timeframe:

Up to 2.5 years

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[12]			
Units: Subjects				
number (not applicable)				
Alanine Aminotransferase (U/L) - High	2			
Alkaline Phosphatase (U/L) - High	14			
Aspartate Aminotransferase (U/L) - High	6			
Bilirubin (mg/dL) - High	1			
Creatinine (mg/dL) - High	7			
Sodium (mmol/L) - High	6			
Alanine Aminotransferase (U/L) - Low	4			
Albumin (g/dL) - Low	10			
Aspartate Aminotransferase (U/L) - Low	1			
Bilirubin (mg/dL) - Low	4			
Creatinine (mg/dL) - Low	7			
Sodium (mmol/L) - Low	14			

Notes:

[12] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who discontinued Radium-223 dichloride treatment due to treatment emergent AEs or death

End point title	Number of subjects who discontinued Radium-223 dichloride treatment due to treatment emergent AEs or death[13]

End point description:

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. A treatment-emergent adverse events (TEAE) is defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of radium-223 dichloride.

End point type	Primary

End point timeframe:

Up to 2.5 years

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[14]			
Units: Subjects				
number (not applicable)	2			

Notes:

[14] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Radiological progression free survival (rPFS)

End point title	Radiological progression free survival (rPFS)

End point description:

Radiological progression-free survival (rPFS) was defined as the time from the treatment start date to the date of radiological disease progression or death from any cause (if death occurred before such progression), as documented by the investigator. Subjects not experiencing death or radiological disease progression at the database cutoff for primary completion were censored at the last radiological disease progression assessment.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[15]			
Units: Months				
median (confidence interval 95%)	9.9 (6.9 to 12.9)			

Notes:

[15] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to radiological bone progression

End point title	Time to radiological bone progression

End point description:

Time to radiological bone progression was defined as the time (days) from the treatment start date to the date of radiological bone progression (according to the adapted PCWG2 [Prostate Cancer Clinical Trials Working Group 2] criteria), as documented by the investigator. Subjects not experiencing radiological bone progression at the database cutoff for primary completion were censored at the last radiological bone progression assessment. An entry of '99999' indicates that the value could not be estimated due to censored values.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[16]			
Units: Months				
median (confidence interval 95%)	99999 (9.9 to 99999)			

Notes:

[16] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects with total alkaline phosphatase (ALP) response

End point title	Percentage of subjects with total alkaline phosphatase (ALP) response

End point description:

Total alkaline phosphatase (ALP) response was defined as ≥ 30% reduction of the blood total ALP level compared with the baseline values. Total ALP response rate was defined as the number of subjects with total ALP response divided by the total number of subjects evaluable for total ALP response.

End point type	Other pre-specified

End point timeframe:

Up to 2.5 years

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[17]			
Units: Percentage of subjects				
number (confidence interval 95%)				
12 Week, n=33	39.4 (22.9 to 57.9)			
24 Week, n=36	30.6 (16.3 to 48.1)			
Anytime, n=44	43.2 (28.3 to 59.0)			

Notes:

[17] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to total ALP progression

End point title	Time to total ALP progression

End point description:

Total ALP progression was defined as a ≥ 25% increase above the nadir (lowest baseline or post-baseline) value to at least 1.5 x ULN (upper limit of normal). The time to total ALP progression was defined as the time (days) from the treatment start date to the date of first total ALP progression. Subjects not experiencing ALP progression at the database cutoff date, whether or not surviving, were censored at the last ALP laboratory assessment. An entry of '99999' indicates that the value could not be estimated due to censored values.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[18]			
Units: Months				
median (confidence interval 95%)	99999 (11.9 to 99999)			

Notes:

[18] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent change in total ALP

End point title	Percent change in total ALP

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline and Week 12, Week 24

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[19]			
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12, n=33	-17.1 (± 32.74)			

Week 24, n=36	-15.0 (± 35.10)			

Notes:

[19] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects with prostate specific antigen (PSA) response

End point title	Percentage of subjects with prostate specific antigen (PSA) response

End point description:

Prostate specific antigen (PSA) response was defined as a ≥ 30% reduction of blood PSA level compared with the baseline value, confirmed by a second subsequent PSA value with a ≥ 30% reduction from baseline approximately 4 or more weeks later. Prostate specific antigen response rate was defined as the number of subjects with PSA response divided by the total number of subjects evaluable for PSA response.

End point type	Other pre-specified

End point timeframe:

Up to 2.5 years

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[20]			
Units: Percentage of subjects				
number (confidence interval 95%)				
12 Week, n=32	6.3 (0.8 to 20.8)			
24 Week, n=36	0 (0 to 9.7)			
Anytime, n=44	9.1 (2.5 to 21.7)			

Notes:

[20] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to PSA progression

End point title	Time to PSA progression

End point description:

Prostate specific antigen progression was defined as a ≥ 25% increase above the nadir (lowest baseline or post-baseline) value, and an increase in absolute value of ≥ 2 ng/mL above nadir. The time to PSA progression was defined as the time (days) from the treatment start date to the date of first PSA progression. Subjects without PSA progression as of the database cutoff for primary completion, whether or not surviving, were censored at the last PSA laboratory assessment.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[21]			
Units: Months				
median (confidence interval 95%)	2.2 (1.8 to 3.1)			

Notes:

[21] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was defined as the time (days) from the treatment start date to the date of death due to any cause. For subjects who were still alive or who were lost to follow-up as of the database cutoff date for the primary completion, OS was censored at the last known alive date on or prior to the database cutoff date.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[22]			
Units: Months				
median (confidence interval 95%)	24.4 (14.9 to 28.6)			

Notes:

[22] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects with pain improvement

End point title	Percentage of subjects with pain improvement

End point description:

Pain improvement was defined in evaluable subjects (subjects with worst pain score [WPS] of 4 at baseline) as a 30% and 2-point decrease in WPS over 2 consecutive measurements conducted at least 4 weeks apart, without an increase in pain management. Pain improvement rate was the number of subjects with pain improvement, divided by the total number of evaluable subjects WPS was the mean of the WPS in the last 24 hours from the preceding 7 days.

End point type	Other pre-specified

End point timeframe:

Up to 2.5 years

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[23]			
Units: Percentage of subjects				
number (confidence interval 95%)				
12 Week, n=6	0 (0 to 45.9)			
24 Week, n=8	0 (0 to 36.9)			
Anytime, n=12	8.3 (0.2 to 38.5)			

Notes:

[23] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to pain progression

End point title	Time to pain progression

End point description:

Pain progression was defined in subjects evaluable for pain progression at baseline, i.e., subjects with a WPS of ≤ 7 at the baseline assessment. Pain assessment occurred daily for 1 week, beginning 1 week prior to each visit and including the day of the visit. An evaluable pain assessment interval required completion of a minimum of 4 out of 7 daily questions. Pain progression was defined as the occurrence of either a pain increase or an increase in pain management with respect to baseline, whichever occurred first. An entry of '99999' indicates that the value could not be estimated due to censored values.

End point type	Other pre-specified

End point timeframe:

Up to 2.5 years

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[24]			
Units: Months				

median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[24] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to first symptomatic skeletal event (SSE)

End point title	Time to first symptomatic skeletal event (SSE)

End point description:

Time to first symptomatic skeletal event (SSE) is the time (days) from the treatment start date to the first SSE on or following the start date. Subjects not experiencing an SSE at the database cutoff date for primary completion, whether or not surviving, were censored at the last assessment for SSEs. An entry of '99999' indicates that the value could not be estimated due to censored values.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[25]			
Units: Months				
median (confidence interval 95%)	16.7 (9.7 to 99999)			

Notes:

[25] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: SSE-free survival

End point title	SSE-free survival

End point description:

The SSE-FS is the time (days) from the treatment start date to the first SSE on or following the start date or death, whichever occurred first. Subjects not experiencing death or an SSE at the database cutoff date for primary completion were censored at the last assessment for SSEs.

End point type	Other pre-specified

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[26]			
Units: Months				
median (confidence interval 95%)	12.8 (9.5 to 24.4)			

Notes:

[26] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with new SSE related AEs during the follow-up period

End point title	Number of subjects with new SSE related AEs during the follow-up period

End point description:

End point type	Post-hoc

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[27]			
Units: Subjects				
number (not applicable)	0			

Notes:

[27] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with new primary malignancies during study treatment or follow-up period

End point title	Number of subjects with new primary malignancies during study treatment or follow-up period

End point description:

End point type	Post-hoc

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[28]			
Units: Subjects				
number (not applicable)	1			

Notes:

[28] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of deaths during study treatment or follow-up period

End point title	Number of deaths during study treatment or follow-up period

End point description:

End point type	Post-hoc

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	44[29]			
Units: Subjects				
number (not applicable)				
During Treatment Period	1			
During Active follow-up Period	23			
During Long-term follow-up Period	4			

Notes:

[29] - Safety Analysis Set (SAF)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with significant meaningful changes for clinical laboratory NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) toxicity grades during the follow-up period

End point title	Number of subjects with significant meaningful changes for clinical laboratory NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) toxicity

	grades during the follow-up period

End point description:

End point type	Post-hoc

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[30]			
Units: Subjects				
number (not applicable)	0			

Notes:

[30] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with body weight changes during the follow-up period

End point title	Number of subjects with body weight changes during the follow-up period

End point description:

Subjects were counted once during active follow-up for both increases (using the maximum body weight) and decreases (using the minimum body weight).

End point type	Post-hoc

End point timeframe:

Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[31]			
Units: Subjects				
number (not applicable)				
Increases < 5%	23			
Increases 5-10%	4			
Increases > 10%	0			
Decreases < 5%	13			
Decreases 5-10%	9			
Decreases > 10%	5			

Notes:
[31] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score worsened to >=3 during the follow-up period

End point title	Number of subjects with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score worsened to >=3 during the follow-up period

End point description:

End point type	Post-hoc

End point timeframe:
Up to 2 years after last treatment

End point values	Radium-223 dichloride (Xofigo, BAY88-8223)			
Subject group type	Reporting group			
Number of subjects analysed	34[32]			
Units: Subjects				
number (not applicable)	4			

Notes:
[32] - Active Follow-up Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment until 30 days after last dose of study medication up to 2.5 years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Radium-223 dichloride (Xofigo, BAY88-8223)
Reporting group description:	
Subjects received intravenous (IV) injection of radium-223 dichloride 50 kBq/kg body weight every 4 weeks up to 6 injections	

Serious adverse events	Radium-223 dichloride (Xofigo, BAY88-8223)		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 44 (29.55%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Stomatitis radiation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Radium-223 dichloride (Xofigo, BAY88-8223)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 44 (79.55%)		
Investigations			
White blood cell count decreased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 8		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	 4 / 44 (9.09%) 4 12 / 44 (27.27%) 12 4 / 44 (9.09%) 5		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea	 3 / 44 (6.82%) 3 3 / 44 (6.82%) 3 9 / 44 (20.45%) 11		

subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Spinal pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2013	The following changes were made: - Terminology changes, including the following which impacted endpoints: the pain endpoint was changed from pain response to pain improvement; skeletal-related event was changed to SSE. - Clarification of selection criteria of subjects for whom re-treatment was indicated, including baseline rising PSA level and substantial worsening of pain. - Specified that a separate, extended safety follow-up study protocol is being implemented and will capture the long-term follow-up of subjects on this study. - The definition of bone progression was revised based on the adapted PCWG2 criteria for consistency across the radium-223 dichloride program. - Assessment schedules for multiple variables were clarified or updated based on current regulatory requirements and recommendations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported