Clinical trial results:
Radium-223 Dichloride (Alpharadin) in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients with Bone Metastasis

Summary

EudraCT number	2012-000075-16
Trial protocol	SE DE NO FI BE ES CZ IE GB IT DK NL AT
Global end of trial date	28 February 2016

Results information

Result version number	v1 (current)
This version publication date	01 March 2017
First version publication date	01 March 2017

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/16216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01618370
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
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	28 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were to:
•assess the acute and long-term safety of radium-223 dichloride
•assess the overall survival of this subject population.

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. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could 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 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Spain: 90
Country: Number of subjects enrolled	Sweden: 95
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Finland: 38
Country: Number of subjects enrolled	Germany: 124
Country: Number of subjects enrolled	Ireland: 26
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Switzerland: 48
Country: Number of subjects enrolled	Israel: 84
Country: Number of subjects enrolled	Norway: 54

Worldwide total number of subjects	708
EEA total number of subjects	543

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)	138
From 65 to 84 years	522
85 years and over	48

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 115 study centers in 15 countries, between 22 July 2012 (first subject first visit) and 28 February 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 852 subjects were screened. Of these, 143 subjects failed screening and one subject did not receive any study drug, remaining 708 subjects were allocated to treatment.

Period 1

Period 1 title	Overall Trial (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) 50 kBg/kg

Arm description:

Subjects received a slow bolus intravenous (iv) injection of Radium-223 dichloride (Xofigo; BAY88-8223), at a dose of 50 kilobecquerel per kilogram (kBq/kg) body weight, based on National Institute of Standards and Technology (NIST) 2010 standardization, at intervals of every 4 weeks for up to 6 cycles. Follow-up assessments for safety were conducted every 6 months until the subject died or until the program was terminated by the sponsor.

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

Dosage and administration details:

Subjects received a slow bolus iv injection of Radium-223 dichloride (Xofigo; BAY88-8223), at a dose of 50 kBq/kg body weight, based on NIST 2010 standardization, at intervals of every 4 weeks for up to 6 cycles.

Number of subjects in period 1	Radium-223 dichloride (Xofigo; BAY88-8223) 50 kBg/kg
Started	708
Completed	411
Not completed	297
AE associated with clinical disease progression	110
Physician decision	4
Disease progression	5
Non-compliant with study procedures	1
Clinical deterioration	5

AE un-associated with clinical disease progression	66
PD radiological progression	3
Consent withdrawn by subject	25
Patient decision	2
Progressive disease (PD)	64
Death	7
PD clinical progression	2
Unspecified	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 dichloride (Xofigo; BAY88-8223) 50 kBg/kg
Reporting group description:	
Subjects received a slow bolus intravenous (iv) injection of Radium-223 dichloride (Xofigo; BAY88-8223), at a dose of 50 kilobecquerel per kilogram (kBq/kg) body weight, based on National Institute of Standards and Technology (NIST) 2010 standardization, at intervals of every 4 weeks for up to 6 cycles. Follow-up assessments for safety were conducted every 6 months until the subject died or until the program was terminated by the sponsor.	

Reporting group values	Radium-223 dichloride (Xofigo; BAY88-8223) 50 kBg/kg	Total	
Number of subjects	708	708	
Age categorical			
Units: Subjects			
Age continuous			
Units: Years			
arithmetic mean	71.7		
standard deviation	± 8.56	-	
Gender categorical			
Units: Subjects			
Male	708	708	
Eastern Co-operative Oncology Group (ECOG)			
ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair.			
Units: Subjects			
ECOG 0	265	265	
ECOG 1	353	353	
ECOG 2	89	89	
ECOG 3	0	0	
ECOG 4	1	1	
Alkaline phosphatase (ALP) (n=703)			
Baseline value of total-ALP from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Units per liter (U/L)			
median	150		
full range (min-max)	19 to 4236	-	
Alanine aminotransferase (ALT) (n=704)			
Baseline value of total-ALT from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Units per liter (U/L)			
median	17		
full range (min-max)	4 to 286	-	
Aspartate aminotransferase (AST)			

(n=703)			
Baseline value of total-AST from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Units per liter (U/L)			
median	25		
full range (min-max)	7 to 379	-	
Basophils (n=575)			
Baseline value of total-basophils count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Giga per liter (G/L)			
median	0.02		
full range (min-max)	0 to 0.28	-	
Bilirubin (n=707)			
Baseline value of total-bilirubin count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Milligram per deciliter (mg/dL)			
median	0.43		
full range (min-max)	0.06 to 1.93	-	
Eosinophils (n=576)			
Baseline value of total-eosinophils count from the last value was collected prior to the first injection of study drug in cycle 1.			
Units: Giga per liter (G/L)			
median	0.1		
full range (min-max)	0 to 1.29	-	
Serum Creatinine (n=705)			
Baseline value of total-serum creatinine count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Milligram per deciliter (mg/dL)			
median	0.9		
full range (min-max)	0.49 to 2.2	-	
Hematocrit (n=706)			
Baseline value of total-hematocrit count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Percentage (%)			
median	36.95		
full range (min-max)	25.1 to 51	-	
Hemoglobin (n=708)			
Baseline value of total-hemoglobin count from the last value was collected prior to the first injection of study drug in cycle 1.			
Units: Gram per deciliter (g/dL)			
median	12.2		
full range (min-max)	8.4 to 18	-	
Lymphocytes (n=703)			
Baseline value of total-lymphocytes count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Giga per liter (G/L)			
median	1.3		
full range (min-max)	0.16 to 6	-	
Monocytes (n=576)			
Baseline value of total-monocytes count from the last value collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Giga per liter (G/L)			
median	0.5		
full range (min-max)	0.12 to 1.7	-	
Neutrophils (n=707)			

Baseline value of total-neutrophils count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Giga per liter (G/L)			
median	4.43		
full range (min-max)	1.03 to 11.6	-	
Platelets (n=708)			
Baseline value of total-platelets count from the last value was collected prior to the first injection of study drug in cycle 1.			
Units: Giga per liter (G/L)			
median	234		
full range (min-max)	47 to 664	-	
Prostate specific antigen (PSA) (n=702)			
Baseline value of total-PSA from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Microgram per liter (mcg/L)			
median	143.3		
full range (min-max)	0 to 12150	-	
Erythrocytes (n=705)			
Baseline value of total-erythrocytes count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Tera per liter (T/L)			
median	4.1		
full range (min-max)	2.56 to 5.93	-	
Sodium (n=705)			
Baseline value of total-sodium level from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Millimole per liter (mmol/L)			
median	139		
full range (min-max)	129 to 151	-	
Leukocytes (n=705)			
Baseline value of total-leukocytes count from the last value was collected prior to the first injection of study drug in cycle 1. 'n' signifies evaluable number of subjects.			
Units: Giga per liter (G/L)			
median	6.6		
full range (min-max)	2.8 to 15.8	-	
Brief Pain Inventory (Short Form) (BPI-SF): Worst Pain in Past 24 hours (n=681)			
BPI-SF was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess severity of pain related to cancer. The worst pain in last 24 hours was scored by averaging the scores. Scores ranges from 0-10, higher score indicates a higher level of pain/interference. 'n'=evaluable subjects whose last value were collected prior to the first injection of radium-223			
Units: Score on the scale			
arithmetic mean	3.8		
standard deviation	± 2.97	-	
BPI-SF: Pain Severity (n=679)			
BPI-SF was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess severity of pain related to cancer. The pain severity score was established by the developers of the instrument and it is the average of the four pain questions (worst pain in last 24 hours, least pain in last 24 hours, average pain, and pain experienced right now). Scores ranges from 0-10, higher score indicates a higher level of pain/interference. 'n'=evaluable subjects whose last value were collected prior to the first injection of radium-223 dichloride.			
Units: Score on the scale			
arithmetic mean	2.65		
standard deviation	± 2.13	-	
BPI-SF: Pain Interference (n=677)			
BPI-SF was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to			

assess severity of pain related to cancer. The pain interference questionnaire were based on the average of seven question designed to assess the degree of pain which interferes common feeling and function (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Scores ranges from 0-10, higher score indicates a higher level of pain/interference. 'n'=evaluable subjects whose last value were collected prior to the first injection of radium-223 dichloride.			
Units: Score on the scale			
arithmetic mean	2.91		
standard deviation	± 2.58	-	

End points

End points reporting groups

Reporting group title	Radium-223 dichloride (Xofigo; BAY88-8223) 50 kBg/kg

Reporting group description:

Subjects received a slow bolus intravenous (iv) injection of Radium-223 dichloride (Xofigo; BAY88-8223), at a dose of 50 kilobecquerel per kilogram (kBq/kg) body weight, based on National Institute of Standards and Technology (NIST) 2010 standardization, at intervals of every 4 weeks for up to 6 cycles. Follow-up assessments for safety were conducted every 6 months until the subject died or until the program was terminated by the sponsor.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N=708) included all subjects who received at least one dose of the study drug.

Primary: Overall Survival

End point title	Overall Survival[1]

End point description:

Overall survival was defined as time from the start of therapy to death due to any cause. Subjects alive at the time of analysis were censored at the last date known to be alive. Median, percentiles and 95% confidence interval were computed using Kaplan-Meier estimates. '99999' indicates that data were not calculated.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[2]			
Units: Months				
median (confidence interval 95%)	15.869 (13.372 to 99999)			

Notes:

[2] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Eastern Cooperative Oncology Group (ECOG): Shift Change From Baseline Performance Status During Treatment Period

End point title	Eastern Cooperative Oncology Group (ECOG): Shift Change From Baseline Performance Status During Treatment Period[3]

End point description:

ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but

ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% waking hours, 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair. In the below table only those category has been reported for which shift from baseline were occurred. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[4]			
Units: Score on a scale				
number (not applicable)				
Cycle 2, 0/+2 (n=666)	3			
Cycle 2, 0/+1 (n=666)	36			
Cycle 2, 0/0 (n=666)	214			
Cycle 2, 1/+2 (n=666)	4			
Cycle 2, 1/+1 (n=666)	23			
Cycle 2, 1/0 (n=666)	272			
Cycle 2, 1/-1 (n=666)	36			
Cycle 2, 2/+2 (n=666)	1			
Cycle 2, 2/+1 (n=666)	8			
Cycle 2, 2/0 (n=666)	54			
Cycle 2, 2/-1 (n=666)	14			
Cycle 2, 4/0 (n=666)	1			
Cycle 3, 0/+2 (n=624)	1			
Cycle 3, 0/+1 (n=624)	52			
Cycle 3, 0/0 (n=624)	193			
Cycle 3, 1/+2 (n=624)	4			
Cycle 3, 1/+1 (n=624)	34			
Cycle 3, 1/0 (n=624)	235			
Cycle 3, 1/-1 (n=624)	35			
Cycle 3, 2/+1 (n=624)	3			
Cycle 3, 2/0 (n=624)	53			
Cycle 3, 2/-1 (n=624)	13			
Cycle 3, 2/-2 (n=624)	1			
Cycle 4, 0/+2 (n=561)	3			
Cycle 4, 0/+1 (n=561)	57			
Cycle 4, 0/0 (n=561)	170			
Cycle 4, 1/+2 (n=561)	6			
Cycle 4, 1/+1 (n=561)	33			
Cycle 4, 1/0 (n=561)	197			
Cycle 4, 1/-1 (n=561)	35			
Cycle 4, 2/+1 (n=561)	1			
Cycle 4, 2/0 (n=561)	46			

Cycle 4, 2/-1 (n=561)	13			
Cycle 5, 0/+3 (n=487)	1			
Cycle 5, 0/+2 (n=487)	4			
Cycle 5, 0/+1 (n=487)	56			
Cycle 5, 0/0 (n=487)	148			
Cycle 5, 1/+2 (n=487)	3			
Cycle 5, 1/+1 (n=487)	31			
Cycle 5, 1/0 (n=487)	165			
Cycle 5, 1/-1 (n=487)	33			
Cycle 5, 2/+1 (n=487)	3			
Cycle 5, 2/0 (n=487)	34			
Cycle 5, 2/-1 (n=487)	9			
Cycle 6, 0/+2 (n=420)	8			
Cycle 6, 0/+1 (n=420)	58			
Cycle 6, 0/0 (n=420)	124			
Cycle 6, 1/+2 (n=420)	2			
Cycle 6, 1/+1 (n=420)	34			
Cycle 6, 1/0 (n=420)	133			
Cycle 6, 1/-1 (n=420)	27			
Cycle 6, 2/0 (n=420)	27			
Cycle 6, 2/-1 (n=420)	6			
Cycle 6, 2/-2 (n=420)	1			

Notes:

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Time to Skeletal-Related Events (SRE) - Overall Study

End point title	Time to Skeletal-Related Events (SRE) - Overall Study[5]

End point description:

SRE were defined as the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); or the occurrence of spinal cord compression; or a tumor-related orthopedic surgical intervention. The median time to SRE could not be fully computed because of the small number of events recorded due to the short follow-up. “99999” signifies value cannot be estimated due to censored data or data were not available.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[6]			
Units: Month				

median (confidence interval 95%)	99999 (18.103 to 99999)			

Notes:

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Emergent Adverse Events of Grade 3-5 (TEAEs) During Treatment Period

End point title	Number of Subjects With Treatment-Emergent Adverse Events of Grade 3-5 (TEAEs) During Treatment Period[7]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment emergent AEs were classified in to five grades based upon their severity. On the basis of that grade 3 AEs are severe or medically significant but not immediately life-threatening; which may leads hospitalization or prolongation of hospitalization; disabling; limiting self-care activities of daily living. Grade 4 AEs are life-threatening consequences; urgent intervention. Grade 5 AE is related to Death.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[8]			
Units: Subjects				
During Treatment Period: Grade 3	233			
During Treatment Period: Grade 4	32			
During Treatment Period: Grade 5	35			
During Follow-up Period: Grade 3	53			
During Follow-up Period: Grade 4	10			
During Follow-up Period: Grade 5	24			

Notes:

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alkaline Phosphatase (ALP) at Specified Time Point

End point title	Change from Baseline in Alkaline Phosphatase (ALP) at Specified Time Point[9]

End point description:

Changes in total-ALP from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[10]			
Units: Units per liter (U/L)				
median (full range (min-max))				
Change at Cycle 2 (n=654)	-24 (-2803 to 705)			
Change at Cycle 3 (n=607)	-36.6 (-3082 to 501)			
Change at Cycle 4 (n=547)	-42 (-3198 to 630)			
Change at Cycle 5 (n=482)	-42 (-3148 to 570)			
Change at Cycle 6 (n=417)	-41 (-3615 to 1071)			

Notes:

[10] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) of Any Grade Leading to Drug Discontinuation During Treatment and Follow up Period

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) of Any Grade Leading to Drug Discontinuation During Treatment and Follow up Period[11]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent adverse events were defined as adverse events that started or worsened after the start of study drug administration up to 30 days after last drug administration during the follow-up period. Drug discontinuation occurred due to any AE were reported in this endpoint.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[12]			
Units: Subjects				
Treatment Period	147			
Follow-up Period	24			

Notes:

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alanine Aminotransferase (ALT) at Specified Time Point

End point title	Change from Baseline in Alanine Aminotransferase (ALT) at Specified Time Point[13]

End point description:

Changes in total-ALT from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[14]			
Units: Units per liter (U/L)				
median (full range (min-max))				
Change at Cycle 2 (n=657)	0 (-170 to 143.5)			
Change at Cycle 3 (n=612)	0.6 (-135 to 1353)			
Change at Cycle 4 (n=551)	0.6 (-114 to 261)			
Change at Cycle 5 (n=484)	0 (-114 to 157)			
Change at Cycle 6 (n=414)	0 (-111 to 210)			

Notes:

[14] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Aspartate Aminotransferase (AST) at Specified Time Point

End point title	Change from Baseline in Aspartate Aminotransferase (AST) at Specified Time Point[15]

End point description:

Changes in total-AST from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[15] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[16]			
Units: Units per liter (U/L)				
median (full range (min-max))				
Change at Cycle 2 (n=649)	0 (-352 to 338)			
Change at Cycle 3 (n=606)	0 (-343 to 391)			
Change at Cycle 4 (n=544)	0 (-326 to 224)			
Change at Cycle 5 (n=486)	0 (-255 to 92)			
Change at Cycle 6 (n=413)	0 (-267 to 134)			

Notes:

[16] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Basophils at Specified Time Point

End point title	Change from Baseline in Basophils at Specified Time Point[17]

End point description:

Changes in total-basophils count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[17] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[18]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=525)	0 (-0.28 to 0.6)			
Change at Cycle 3 (n=491)	0 (-0.23 to 0.1)			
Change at Cycle 4 (n=445)	0 (-0.12 to 0.5)			
Change at Cycle 5 (n=387)	0 (-0.1 to 0.1)			
Change at Cycle 6 (n=332)	0 (-0.14 to 0.1)			

Notes:

[18] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bilirubin at Specified Time Point

End point title	Change from Baseline in Bilirubin at Specified Time Point[19]

End point description:

Changes in total-bilirubin count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[19] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[20]			
Units: Milligram per deciliter (mg/dL)				
median (full range (min-max))				
Change at Cycle 2 (n=652)	0 (-0.8 to 1.2)			
Change at Cycle 3 (n=607)	0 (-0.8 to 1.58)			
Change at Cycle 4 (n=547)	0 (-0.64 to 2.1)			
Change at Cycle 5 (n=485)	0 (-0.82 to 1)			
Change at Cycle 6 (n=407)	0 (-0.7 to 0.58)			

Notes:
[20] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Serum Creatinine at Specified Time Point

End point title	Change from Baseline in Serum Creatinine at Specified Time Point[21]

End point description:

Changes in total-serum creatinine count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[21] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[22]			
Units: Milligram per deciliter (mg/dL)				
median (full range (min-max))				
Change at Cycle 2 (n=662)	-0.005 (-0.6 to 2.88)			
Change at Cycle 3 (n=617)	-0.011 (-0.8 to 0.96)			
Change at Cycle 4 (n=557)	-0.011 (-0.89 to 0.85)			
Change at Cycle 5 (n=491)	-0.02 (-0.69 to 3.07)			
Change at Cycle 6 (n=420)	-0.005 (-0.67 to 1.58)			

Notes:
[22] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Eosinophils at Specified Time Point

End point title	Change from Baseline in Eosinophils at Specified Time Point[23]

End point description:

Changes in total-eosinophils count from the last value collected prior to the first injection of study drug

in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[23] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[24]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=527)	-0.01 (-1.16 to 0.7)			
Change at Cycle 3 (n=492)	-0.02 (-0.87 to 2.3)			
Change at Cycle 4 (n=446)	-0.013 (-1.12 to 0.3)			
Change at Cycle 5 (n=388)	-0.03 (-1.15 to 0.5)			
Change at Cycle 6 (n=333)	-0.02 (-0.72 to 0.36)			

Notes:

[24] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematocrit at Specified Time Point

End point title	Change from Baseline in Hematocrit at Specified Time Point[25]

End point description:

Changes in total-hematocrit count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[25] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[26]			
Units: Percentage (%)				
median (full range (min-max))				
Change at Cycle 2 (n=661)	-0.3 (-13 to 7)			
Change at Cycle 3 (n=621)	-1 (-18 to 8.5)			
Change at Cycle 4 (n=558)	-1.9 (-15 to 11.1)			
Change at Cycle 5 (n=489)	-2 (-20 to 13.7)			
Change at Cycle 6 (n=416)	-3 (-18.5 to 8.3)			

Notes:

[26] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hemoglobin at Specified Time Point

End point title	Change from Baseline in Hemoglobin at Specified Time Point[27]

End point description:

Changes in total-hemoglobin count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[27] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[28]			
Units: Gram per deciliter (g/dL)				
median (full range (min-max))				
Change at Cycle 2 (n=667)	-0.1 (-3.9 to 2.6)			
Change at Cycle 3 (n=625)	-0.3 (-5.7 to 3.1)			
Change at Cycle 4 (n=562)	-0.5 (-4.3 to 3.5)			
Change at Cycle 5 (n=492)	-0.7 (-6 to 4.5)			
Change at Cycle 6 (n=421)	-1 (-6.2 to 2.9)			

Notes:
[28] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Lymphocytes at Specified Time Point

End point title	Change from Baseline in Lymphocytes at Specified Time

End point description:

Changes in total-lymphocytes count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported. 'n'= evaluable subjects for the respective category.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[29] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[30]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=651)	-0.13 (-5.4 to 1.4)			
Change at Cycle 3 (n=613)	-0.2 (-4.6 to 1.13)			
Change at Cycle 4 (n=554)	-0.3 (-4.7 to 0.81)			
Change at Cycle 5 (n=484)	-0.36 (-2.9 to 1)			
Change at Cycle 6 (n=416)	-0.4 (-2.48 to 1.03)			

Notes:
[30] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Monocytes at Specified Time Point

End point title	Change from Baseline in Monocytes at Specified Time Point[31]

End point description:

Changes in total-monocytes count from the last value collected prior to the first injection of study drug

in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[31] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[32]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=527)	-0.02 (-1.4 to 0.7)			
Change at Cycle 3 (n=493)	-0.04 (-0.81 to 0.69)			
Change at Cycle 4 (n=447)	-0.04 (-0.6 to 0.7)			
Change at Cycle 5 (n=389)	-0.06 (-0.8 to 0.66)			
Change at Cycle 6 (n=333)	-0.07 (-0.7 to 1.13)			

Notes:

[32] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Neutrophils at Specified Time Point

End point title	Change from Baseline in Neutrophils at Specified Time Point[33]

End point description:

Changes in total-neutrophils count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[33] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[34]			
Units: Giga per liter (G/L)				

median (full range (min-max))				
Change at Cycle 2 (n=660)	-0.86 (-8.4 to 28.7)			
Change at Cycle 3 (n=618)	-0.9 (-8.1 to 26.31)			
Change at Cycle 4 (n=557)	-0.9 (-7 to 19.15)			
Change at Cycle 5 (n=488)	-1 (-9.2 to 6.66)			
Change at Cycle 6 (n=418)	-1.025 (-7.12 to 7.85)			

Notes:

[34] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Platelets at Specified Time Point

End point title	Change from Baseline in Platelets at Specified Time Point[35]

End point description:

Changes in total-platelets count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[35] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[36]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=666)	-16 (-291 to 241)			
Change at Cycle 3 (n=625)	-20 (-424 to 241)			
Change at Cycle 4 (n=561)	-23 (-323 to 128)			
Change at Cycle 5 (n=493)	-24 (-412 to 150)			
Change at Cycle 6 (n=419)	-27 (-318 to 208)			

Notes:

[36] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Prostate Specific Antigen (PSA) at Specified Time Point

End point title	Change from Baseline in Prostate Specific Antigen (PSA) at Specified Time Point[37]

End point description:

Changes in PSA level from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[37] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[38]			
Units: Microgram per liter (mcg/L)				
median (full range (min-max))				
Change at Cycle 2 (n=630)	11 (-4075.2 to 3435.29)			
Change at Cycle 3 (n=592)	16.05 (-4115.74 to 7549)			
Change at Cycle 4 (n=532)	24 (-3124.95 to 8740)			
Change at Cycle 5 (n=479)	22.3 (-3280.03 to 6024)			
Change at Cycle 6 (n=409)	19.5 (-4184.84 to 9255)			

Notes:

[38] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Erythrocytes at Specified Time Point

End point title	Change from Baseline in Erythrocytes at Specified Time

End point description:

Changes in total-erythrocytes count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[39] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[40]			
Units: Tera per liter (T/L)				
median (full range (min-max))				
Change at Cycle 2 (n=659)	-0.02 (-1.46 to 0.82)			
Change at Cycle 3 (n=619)	-0.14 (-2.24 to 1.19)			
Change at Cycle 4 (n=557)	-0.2 (-1.78 to 1.77)			
Change at Cycle 5 (n=489)	-0.3 (-2.4 to 1.1)			
Change at Cycle 6 (n=417)	-0.4 (-2.07 to 0.87)			

Notes:

[40] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Sodium at Specified Time Point

End point title	Change from Baseline in Sodium at Specified Time Point[41]

End point description:

Changes in sodium level from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[41] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[42]			
Units: Millimole per liter (mmol/L)				
median (full range (min-max))				
Change at Cycle 2 (n=656)	0 (-12 to 10)			
Change at Cycle 3 (n=608)	0 (-15 to 8)			
Change at Cycle 4 (n=550)	0 (-10 to 11)			

Change at Cycle 5 (n=486)	0 (-14 to 12)			
Change at Cycle 6 (n=416)	0 (-10 to 10)			

Notes:

[42] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Leukocytes at Specified Time Point

End point title	Change from Baseline in Leukocytes at Specified Time Point[43]

End point description:

Changes in total-leukocytes count from the last value collected prior to the first injection of study drug in each cycle was determined. Median and range (minimum-maximum) were reported.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[43] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[44]			
Units: Giga per liter (G/L)				
median (full range (min-max))				
Change at Cycle 2 (n=664)	-1.12 (-10.7 to 30.5)			
Change at Cycle 3 (n=622)	-1.2 (-10.1 to 26.8)			
Change at Cycle 4 (n=560)	-1.4 (-8.3 to 19.92)			
Change at Cycle 5 (n=490)	-1.5 (-10.6 to 6.48)			
Change at Cycle 6 (n=419)	-1.6 (-7.83 to 7.57)			

Notes:

[44] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) Treatment Emergent Serious Adverse Events (TESAEs) – During Follow up Period

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) Treatment Emergent Serious Adverse Events (TESAEs) – During Follow up Period[45]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent adverse events were defined as adverse events that started or worsened after the start of study drug administration up to 30 days after last drug administration during the follow-up period. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another med important serious event as judged by the investigator. In the below table data was provided for the follow-up period.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[45] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[46]			
Units: Subjects				
TEAE during Follow-up Period	143			
TESAE during Follow-up Period	59			

Notes:

[46] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAE) Treatment Emergent Serious Adverse Events (TESAE) – During Treatment Period

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAE) Treatment Emergent Serious Adverse Events (TESAE) – During Treatment Period[47]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another med important serious event as judged by the investigator. Treatment-emergent adverse events were defined as adverse events that started or worsened after the start of study drug administration up to 30 days after last drug administration during the treatment period.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[47] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[48]			
Units: Subjects				
TEAE during Treatment Period	533			
TESAE during Treatment Period	246			

Notes:

[48] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Secondary Malignancies

End point title	Number of Subjects With Secondary Malignancies[49]

End point description:

Number of subjects with secondary or additional malignancies including acute myeloid leukemia, and hematological conditions such as myelodysplastic syndrome, aplastic anemia, myelofibrosis et cetera (etc), as well as information on additional anticancer treatments received were analyzed.

End point type	Primary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

Notes:

[49] - 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) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[50]			
Units: Subjects	9			

Notes:

[50] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BPI-SF Questionnaire (Brief Pain Inventory-Short Form) Score

End point title	Change From Baseline in BPI-SF Questionnaire (Brief Pain Inventory-Short Form) Score

End point description:

BPI-SF was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess severity of pain related to cancer. The worst pain in last 24 hours was scored by averaging the scores. The pain severity score was established by the developers of the instrument and it is the average of the four pain questions (worst pain in last 24 hours, least pain in last 24 hours, average pain,

and pain experienced right now). The pain interference questionnaire were based on the average of seven question designed to assess the degree of pain which interferes common feeling and function (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Scores ranges from 0-10, higher score indicates a higher level of pain/interference. In the below table 'n'=evaluable subjects whose last value were collected prior to the first injection of radium-223 dichloride; EOT=End of treatment; FU=Follow-up.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 30 days of last study drug administration

End point values	Radium-223 dichloride (Xofigo; BAY88-8223) 50 kBg/kg			
Subject group type	Reporting group			
Number of subjects analysed	708[51]			
Units: Score on the scale				
arithmetic mean (standard deviation)				
Worst pain, Change at Cycle 2 (n=623)	-0.5 (± 2.44)			
Worst pain, Change at Cycle 3 (n=580)	-0.5 (± 2.56)			
Worst pain, Change at Cycle 4 (n=520)	-0.3 (± 2.83)			
Worst pain, Change at Cycle 5 (n=455)	-0.3 (± 2.78)			
Worst pain, Change at Cycle 6 (n=394)	-0.2 (± 2.9)			
Worst pain, Change at EOT (n=426)	0 (± 3.19)			
Worst pain, Change at active-FU 1 (n=103)	-0.4 (± 2.78)			
Pain Severity, Change at Cycle 2 (n=618)	-0.31 (± 1.71)			
Pain Severity, Change at Cycle 3 (n=576)	-0.33 (± 1.78)			
Pain Severity, Change at Cycle 4 (n=516)	-0.17 (± 2.03)			
Pain Severity, Change at Cycle 5 (n=451)	-0.22 (± 1.97)			
Pain Severity, Change at Cycle 6 (n=392)	-0.23 (± 2.06)			
Pain Severity, Change at EOT (n=423)	-0.03 (± 2.2)			
Pain Severity, Change at active-FU 1 (n=101)	-0.26 (± 2.06)			
Pain Interference, Change at Cycle 2 (n= 616)	-0.25 (± 1.91)			
Pain Interference, Change at Cycle 3 (n= 575)	-0.28 (± 2.2)			
Pain Interference, Change at Cycle 4 (n=514)	-0.1 (± 2.25)			
Pain Interference, Change at Cycle 5 (n=445)	-0.14 (± 2.11)			
Pain Interference, Change at Cycle 6 (n=391)	-0.11 (± 2.35)			
Pain Interference, Change at EOT (n=425)	0.21 (± 2.46)			
Pain Interference, Change at active-FU 2 (n=103)	0.12 (± 2.5)			

Notes:
[51] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected From start of study drug administration up to 30 days of last study drug administration

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Radium-223 DiChloride 50 kBq/kg

Reporting group description:

Subjects received Radium-223 dichloride, at a dose of 50 kBq/kg body weight, based on NIST 2010 standardization, at every 4 weeks up to 6 cycles.

Serious adverse events	Radium-223 DiChloride 50 kBq/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	246 / 708 (34.75%)		
number of deaths (all causes)	224		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kaposi's sarcoma classical type			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic neoplasm				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Malignant melanoma				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic pain				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Venous thrombosis limb				

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic venous thrombosis				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral venous disease				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	3 / 708 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Device occlusion				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial pain				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	27 / 708 (3.81%)			
occurrences causally related to treatment / all	2 / 35			
deaths causally related to treatment / all	0 / 18			
Malaise				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	4 / 708 (0.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	5 / 708 (0.71%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Genital pain				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic pain				

subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pneumothorax			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Pulmonary hypertension			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	4 / 708 (0.56%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
Pulmonary thrombosis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Investigations				
Aspiration bronchial				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				

subjects affected / exposed	5 / 708 (0.71%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fractured sacrum			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				

subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	5 / 708 (0.71%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 3		
Atrial flutter			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Aphasia				
subjects affected / exposed	4 / 708 (0.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cauda equina syndrome				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intracranial venous sinus thrombosis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metabolic encephalopathy				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Paraplegia				

subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Paraparesis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Post-traumatic headache				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	19 / 708 (2.68%)			
occurrences causally related to treatment / all	1 / 19			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VIth nerve disorder				

subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Trigeminal neuralgia			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 708 (3.25%)		
occurrences causally related to treatment / all	7 / 28		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Bone marrow failure			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	4 / 708 (0.56%)		
occurrences causally related to treatment / all	19 / 20		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Ear pain				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoacusis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vertigo				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular disorder				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Diplopia				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eyelid oedema				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	3 / 708 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Constipation			
subjects affected / exposed	5 / 708 (0.71%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	7 / 708 (0.99%)			
occurrences causally related to treatment / all	7 / 10			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stenosis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Renal and urinary disorders				

Acute kidney injury			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 1		
Bladder tamponade			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	7 / 708 (0.99%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	9 / 708 (1.27%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract obstruction			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	4 / 708 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Back pain			
subjects affected / exposed	16 / 708 (2.26%)		
occurrences causally related to treatment / all	2 / 16		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	12 / 708 (1.69%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	0 / 0		
Fracture pain			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal pain			

subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Appendicitis			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	2 / 708 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infection			
subjects affected / exposed	4 / 708 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Meningitis			

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic infection				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	9 / 708 (1.27%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 1			
Post procedural infection				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Respiratory tract infection				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	6 / 708 (0.85%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 4			
Upper respiratory tract infection				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	5 / 708 (0.71%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	6 / 708 (0.85%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 708 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	1 / 708 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 708 (0.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	3 / 708 (0.42%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Radium-223 DiChloride 50 kBq/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	356 / 708 (50.28%)		
Investigations			
Weight decreased			
subjects affected / exposed	50 / 708 (7.06%)		
occurrences (all)	61		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	64 / 708 (9.04%)		
occurrences (all)	71		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	132 / 708 (18.64%)		
occurrences (all)	269		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	77 / 708 (10.88%)		
occurrences (all)	102		
Nausea			
subjects affected / exposed	90 / 708 (12.71%)		
occurrences (all)	123		
Vomiting			
subjects affected / exposed	36 / 708 (5.08%)		
occurrences (all)	48		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	39 / 708 (5.51%)		
occurrences (all)	48		
Bone pain			
subjects affected / exposed	104 / 708 (14.69%)		
occurrences (all)	121		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 708 (6.78%)		
occurrences (all)	53		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2012	-Changed Radium-223 Chloride and Ra223 Cl to Radium-223 Dichloride and radium-223 dichloride respectively, following receipt of the official United States Adopted Name for the product -Clarification on the inclusion/exclusion criteria particularly the definition of progressive disease and acceptable diagnostic procedures -Inclusion of subjects with history of spinal cord compression who have completely recovered -Clarification regarding inclusion of subjects who received prior radiotherapy -Inclusion of allowed concomitant treatments, abiraterone and denosumab -Provided additional guidance on the collection of safety data -Provided additional guidance on safety protection during dose preparation -Extension of the screening period from 21 days to 28 days and extension of the timeframe for laboratory assessments from 24 hours to within 72 hours -Substituted follow-up visits with phone call follow-ups for deteriorating subjects -Addition of long-term follow-up section -Clarification regarding AEs that lead to discontinuation -Clarification on AEs/SAEs documentation and reporting -In addition, administrative changes were made, corrected Bone Pain Index terminology to Brief Pain Inventory, and minor editorial changes and clarifications
02 April 2013	-Exclusion from the active follow up of subjects who receive further anticancer treatment including radium 223 dichloride administered either within a clinical study or as commercially available drug, and to follow them up for survival status only. -Addition of a time window of 3 months for bone scan due to differences in the standard of care in the involved sites -Provide clarifications and guidance on: a. Washout period of 4 weeks applicable for all prior anticancer therapies b. Anticancer therapies allowed during the study treatment period c. Guidance on when rescreening is allowed d. Definition of end of screening period -Reconfirmation of eligibility -Active follow-up Sections were updated to allow collection by means of phone follow-up of long-term safety data in all study subjects, including those who are no longer fit to travel to the investigational site due to deteriorating conditions. -In addition, administrative changes were made, including the change of the Sponsor’s medical expert as well as minor editorial changes and abbreviations were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±” in relation with geometric CV is auto-generated. Decimal places were automatically truncated if last decimal equals zero. ‘99999’ indicates that data were not calculated.

Notes: