Clinical trial results:
A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with exemestane and everolimus versus placebo in combination with exemestane and everolimus when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases.

Summary

EudraCT number	2014-002114-23
Trial protocol	IT GB ES AT CZ NL DE BE FR
Global end of trial date	28 October 2022

Results information

Result version number	v1
This version publication date	08 November 2023
First version publication date	08 November 2023

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/17096

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02258451
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, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, 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 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess efficacy and safety of radium 223 dichloride in combination with exemestane and everolimus in subjects with human epidermal growth factor receptor 2 (HER2) negative, hormone receptor positive breast cancer with bone metastases.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the 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	04 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Singapore: 17
Country: Number of subjects enrolled	Israel: 29
Country: Number of subjects enrolled	Korea, Republic of: 14

Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	283
EEA total number of subjects	152

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)	185
From 65 to 84 years	95
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted with first subject first visit on 04-JUN-2015 and last subject last visit on 28-OCT-2022.

Pre-assignment

Screening details:

Overall, 389 subjects were screened and 283 were assigned to treatment. Of these, 142 subjects in the radium 223 dichloride arm and 141 subjects in the placebo arm.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Radium-223 + EXE/EVE

Arm description:

Subjects randomized to treatment with radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology (NIST) update) also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.

Arm type	Experimental
Investigational medicinal product name	Radium-223 dichloride (Xofigo, BAY88-8223)
Investigational medicinal product code	BAY88-8223
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

Up to 6 cycles of radium-223 dichloride 50kBq/kg body (55kBq/kg after implementation of NIST update).

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 25 mg tablet once daily after a meal.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The recommended dose of everolimus administered in the study was 10 mg once daily with or without food.
Starting dose, dose modifications, and administration of exemestane and everolimus were in compliance with the local labels in each of the participating countries and/or in line with local standard of practice.

Arm title	Placebo + EXE/EVE

Arm description:	
Subjects randomized to treatment with placebo, also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection
Dosage and administration details:	
Up to 6 cycles of saline injection.	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
One 25 mg tablet once daily after a meal.	
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
The recommended dose of everolimus administered in the study was 10 mg once daily with or without food. Starting dose, dose modifications, and administration of exemestane and everolimus were in compliance with the local labels in each of the participating countries and/or in line with local standard of practice.	

Number of subjects in period 1	Radium-223 + EXE/EVE	Placebo + EXE/EVE
Started	142	141
Completed	0	0
Not completed	142	141
Stop all drugs due to AE not associated with CP	8	1
Stop all drugs due to AE associated with CP	8	6
Stop all drugs due to physician decision	-	2
Stop all drugs due to other reason	1	1
Stop all drugs due to end point reached	1	1
Stop all drugs due to clinical progression (CP)	7	7
Stop all drugs due to withdrawal by subjects	21	13
Never treated	2	3
Stop all drugs due to study terminated by sponsor	-	3
Stop all drugs due to death	4	3

Stop all drugs due to radiological progression	90	101

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 + EXE/EVE
Reporting group description:	
Subjects randomized to treatment with radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology (NIST) update) also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.	
Reporting group title	Placebo + EXE/EVE
Reporting group description:	
Subjects randomized to treatment with placebo, also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.	

Reporting group values	Radium-223 + EXE/EVE	Placebo + EXE/EVE	Total
Number of subjects	142	141	283
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.95	59.08	
standard deviation	± 10.40	± 11.64	-
Gender categorical			
Units: Subjects			
Female	142	141	283

End points

End points reporting groups

Reporting group title	Radium-223 + EXE/EVE

Reporting group description:

Subjects randomized to treatment with radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology (NIST) update) also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.

Reporting group title	Placebo + EXE/EVE

Reporting group description:

Subjects randomized to treatment with placebo, also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.

Subject analysis set title	Intent-to-treat analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

included all randomized subjects.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

included all randomized subjects who received at least one dose of any study medication (radium 223 dichloride or placebo, exemestane, and everolimus). Subjects were assigned to the Radium-223 dichloride arm if they received any dose of Radium-223 dichloride, otherwise to the placebo arm.

Subject analysis set title	Radium-223 + EXE/EVE
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received treatment with radium-223 dichloride, 50 kBq/kg body weight (55 kBq/kg after implementation of NIST update) also received exemestane (EXE), 25 mg tablet once daily (after a meal), and everolimus (EVE), 10 mg once daily (with or without food), and supportive care as per the local or institutional standard of practice.

Subject analysis set title	Placebo + EXE/EVE
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects did not receive any radium-223 dichloride, but received treatment with any study treatment (placebo, exemestane [25 mg tablet once daily (after a meal)], and everolimus [10 mg once daily (with or without food)]), and supportive care as per the local or institutional standard of practice.

Primary: Symptomatic skeletal event-free survival (SSE-FS)

End point title	Symptomatic skeletal event-free survival (SSE-FS)

End point description:

Time from date of randomization to occurrence of one of the following, whichever happened earlier: 1) an on study SSE, which was defined as the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms, the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral), the occurrence of spinal cord compression, a tumor related orthopedic surgical intervention; or 2) death from any cause.

Per Protocol Amendment 10, following primary analysis completion, further assessments were focused on safety, and only limited efficacy data including SSE and survival were collected and not designed to support reconsideration of the primary analysis efficacy conclusions. Accordingly, no formal statistical analyses were performed for primary and secondary efficacy outcomes in the final analysis. All primary and secondary efficacy outcome measures presented in this document came from the primary completion analysis.

End point type	Primary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[1]	141[2]		
Units: Months				
median (confidence interval 95%)	21.1 (17.1 to 23.6)	19.9 (16.2 to 24.2)		

Notes:

[1] - Intent-to-treat analysis set

[2] - Intent-to-treat analysis set

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)

Statistical analysis description:

The 1-sided null hypothesis that treatment with radium-223 dichloride does not result in superior SSE-FS to treatment with placebo in subject population was tested against the 1-sided alternative hypothesis that the treatment with radium-223 dichloride results in superior SSE-FS time to treatment the placebo.
H0: SSE-FS Radium-223+Exemestane/Everolimus <= SSE-FS Placebo+Exemestane/Everolimus, versus
HA: SSE-FS Radium-223+Exemestane/Everolimus > SSE-FS Placebo+Exemestane/Everolimus

Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4843 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.891
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.72
upper limit	1.102

Notes:

[3] - 1-sided SSE-FS hypotheses were tested using a log-rank test with a 2-sided alpha of 0.2, stratified by the randomization stratification factors

Secondary: Overall survival

End point title	Overall survival

End point description:

The time from the date of randomization to the date of death due to any cause.

Per Protocol Amendment 10, following primary analysis completion, further assessments were focused on safety, and only limited efficacy data including SSE and survival were collected and not designed to support reconsideration of the primary analysis efficacy conclusions. Accordingly, no formal statistical analyses were performed for primary and secondary efficacy outcomes in the final analysis. All primary and secondary efficacy outcome measures presented in this document came from the primary completion analysis.

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[4]	141[5]		
Units: Months				
median (confidence interval 95%)	25.0 (23.0 to 31.4)	26.4 (21.7 to 28.9)		

Notes:

[4] - Intent-to-treat analysis set

[5] - Intent-to-treat analysis set

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)
Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8438 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.343

Notes:

[6] - P-value was calculated using a 2-sided log-rank test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Time to opiate use for cancer pain

End point title	Time to opiate use for cancer pain

End point description:

Interval from the date of randomization to the date of opiate use.

95% Confidence Interval = 99999, value cannot be estimated due to censored data. Insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[7]	139[8]		
Units: Months				
median (confidence interval 95%)	21.4 (13.2 to 99999)	18.4 (8.3 to 99999)		

Notes:

[7] - Safety analysis set
99999 = Insufficient number of subjects with events.
[8] - Safety analysis set
99999 = Insufficient number of subjects with events.

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)
Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8811 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.962
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.577
upper limit	1.604

Notes:

[9] - P-value was calculated using a 2-sided log-rank test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Time to pain progression

End point title	Time to pain progression

End point description:

Time from randomization to the first date a subject experienced pain progression based on worst pain score (WPS). Pain progression was defined as an increase of 2 or more points in the Brief Pain Inventory-Short Form (BPI-SF) "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart or an increase in pain management (IPM) with respect to baseline, whichever occurred first. An IPM is defined as the initiation of any opioid in subjects not taking opioids at baseline, the initiation of a strong opioid in subjects taking a weak opioid at baseline, or the initiation of an additional strong opioid in subjects taking a strong opioid at baseline.

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[10]	139[11]		
Units: Months				
median (confidence interval 95%)	7.6 (6.2 to 13.2)	5.7 (4.9 to 8.5)		

Notes:

[10] - Safety analysis set

[11] - Safety analysis set

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)

Statistical analysis description:

Subjects with baseline WPS > 8 were included in the analysis population but censored at Day 1.

Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6537 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.928
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.667
upper limit	1.289

Notes:

[12] - P-value was calculated using a 2-sided log-rank test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Time to cytotoxic chemotherapy

End point title	Time to cytotoxic chemotherapy

End point description:

Time from the date of randomization to the date of the first cytotoxic chemotherapy

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[13]	141[14]		
Units: Months				
median (confidence interval 95%)	13.7 (9.9 to 15.8)	11.6 (9.0 to 16.4)		

Notes:

[13] - Intent-to-treat analysis set

[14] - Intent-to-treat analysis set

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)
Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4496 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.884
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.641
upper limit	1.219

Notes:

[15] - P-value was calculated using a 2-sided log-rank test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Radiological progression-free survival (rPFS)

End point title	Radiological progression-free survival (rPFS)

End point description:

Time from the date of randomization to the date of confirmed radiological progression in either soft tissue, viscera or bone, or death (if death occurs before progression). Progression is defined using the modified RECIST 1.1 criteria (the modification refers to bone lesions assessment). Progression is defined as a 20% increase in the sum of the longest diameter of target lesions, or an unequivocal increase in non-target lesions, or the appearance of new lesions. All bone lesions are considered non-measurable and new bone lesions identified by bone scan should be confirmed by further imaging (CT/MRI). If a new bone lesion or unequivocal increase in size of bone lesions is only visible on a CT/MRI and not visible on a technetium-99m bone scan, progression should be declared without further confirmation.

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[16]	141[17]		
Units: Months				
median (confidence interval 95%)	7.9 (6.2 to 9.7)	6.7 (5.4 to 8.1)		

Notes:

[16] - Intent-to-treat analysis set

[17] - Intent-to-treat analysis set

Statistical analyses

Statistical analysis title	Hazard ratio (Radium-223 / Placebo)
Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3467 [18]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.874
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.157

Notes:

[18] - P-value was calculated using a 2-sided log-rank test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Percentage of subjects with pain improvement

End point title	Percentage of subjects with pain improvement

End point description:

In the percentage of subjects with confirmed pain improvement. Confirmed pain improvement is defined a 2-point decrease or more in BPI-SF WPS from baseline over 2 consecutive measurements conducted at least 4 weeks apart, without an increase in pain management (IPM). An IPM is defined as the initiation of any opioid in subjects not taking opioids at baseline, the initiation of a strong opioid in subjects taking a weak opioid at baseline, or the initiation of an additional strong opioid in subjects taking a strong opioid at baseline.

Safety analysis set with baseline WPS >= 2: all randomized subjects who received at least one dose of any study medication (radium 223 dichloride or placebo exemestane, or everolimus), and who in addition had baseline BPI-SF WPS >= 2. Subjects were assigned to the Radium-223 dichloride arm if they received any dose of Radium-223 dichloride, otherwise to the placebo arm.

End point type	Secondary

End point timeframe:

Up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[19]	96[20]		
Units: percentage of subjects				
number (confidence interval 95%)	38.5 (28.4 to 49.2)	34.4 (25.0 to 44.8)		

Notes:

[19] - Safety analysis set

[20] - Safety analysis set

Statistical analyses

Statistical analysis title	Difference (Radium-223 - Placebo)
Comparison groups	Radium-223 + EXE/EVE v Placebo + EXE/EVE

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	18.4

Notes:

[21] - P-value was calculated using a 2-sided Cochran-Mantel-Haenszel test stratified by the same stratification factors as randomization. No alpha adjustment for multiplicity was applied.

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)

End point description:

An AE was any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. AEs were considered to be treatment-emergent if they started or worsened after first application of study intervention up to 30 days after end of treatment with study intervention. A 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 inpatient hospitalization; life-threatening; persistent or significant disability/incapacity; congenital anomaly; another medical important serious event as judged by the investigator and an occurrence of any additional malignancies, including acute myelocytic leukemia or hematological conditions.

End point type	Secondary

End point timeframe:

From first dosing up to 30 days after the last administration of study treatments, up to 89 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[22]	139[23]		
Units: Subjects				
Any TEAE	139	136		
Serious TEAE	57	55		
Radium-223/Placebo-related TEAEs	73	50		
Exemestane-related TEAEs	75	64		
Everolimus-related TEAEs	130	125		

Notes:

[22] - Safety analysis set

[23] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with post-treatment chemotherapy related adverse

events

End point title	Number of subjects with post-treatment chemotherapy related adverse events

End point description:

According to protocol amendment 10, all subjects who completed the EOT visit will be transferred to a separate extended safety follow-up study for their remaining follow-up. Thus, no further post-treatment data were collected after protocol amendment 10.

End point type	Secondary

End point timeframe:

From post-treatment till end of study, up to 89 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[24]	139[25]		
Units: Subjects				
All system organ classes_Any_Grade 3	1	0		
All system organ classes_Any_Grade 4	1	0		
Blood and lymphatic system disorders_Any_Grade 3	1	0		
Febrile neutropenia_Grade 3	1	0		
Investigations_Any_Grade 4	1	0		
Investigations_Neutrophil count decreased_Grade 4	1	0		

Notes:

[24] - Safety analysis set

[25] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with hematological toxicities: Worst Grade under Treatment

End point title	Number of subjects with hematological toxicities: Worst Grade under Treatment

End point description:

Safety analysis set with at least one hematology lab assessment: all randomized subjects who received at least one dose of any study medication (radium 223 dichloride or placebo, exemestane, and everolimus), and who in addition had at least one hematology lab assessment. Subjects were assigned to the Radium-223 dichloride arm if they received any dose of Radium-223 dichloride, otherwise to the placebo arm.

End point type	Secondary

End point timeframe:

From first dosing up to 30 days after the last administration of study treatments, up to 89 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[26]	137[27]		
Units: Subjects				
Anemia Grade 1	61	57		
Anemia Grade 2	43	55		
Anemia Grade 3	21	11		
Anemia Grade 4	0	0		
Anemia Normal	14	14		
Leukocytosis Grade 1	0	0		
Leukocytosis Grade 2	0	0		
Leukocytosis Grade 3	0	0		
Leukocytosis Grade 4	0	0		
Leukocytosis Normal	139	137		
Hemoglobin increased Grade 1	0	0		
Hemoglobin increased Grade 2	1	0		
Hemoglobin increased Grade 3	0	0		
Hemoglobin increased Grade 4	0	0		
Hemoglobin increased Normal	138	137		
Lymphocyte count decreased Grade 1	20	33		
Lymphocyte count decreased Grade 2	63	45		
Lymphocyte count decreased Grade 3	43	24		
Lymphocyte count decreased Grade 4	2	0		
Lymphocyte count decreased Normal	11	35		
Lymphocyte count increased Grade 1	0	0		
Lymphocyte count increased Grade 2	2	2		
Lymphocyte count increased Grade 3	0	0		
Lymphocyte count increased Grade 4	0	0		
Lymphocyte count increased Normal	137	135		
Neutrophil count decreased Grade 1	23	30		
Neutrophil count decreased Grade 2	48	28		
Neutrophil count decreased Grade 3	19	0		
Neutrophil count decreased Grade 4	0	2		
Neutrophil count decreased Normal	49	77		
Platelet count decreased Grade 1	60	60		
Platelet count decreased Grade 2	7	3		
Platelet count decreased Grade 3	7	0		
Platelet count decreased Grade 4	1	0		
Platelet count decreased Normal	64	74		
White blood cell decreased Grade 1	37	48		
White blood cell decreased Grade 2	59	37		
White blood cell decreased Grade 3	17	3		
White blood cell decreased Grade 4	1	1		
White blood cell decreased Normal	25	48		

Notes:

[26] - Safety analysis set

[27] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new primary malignancies

End point title	Number of subjects with new primary malignancies

End point description:

End point type	Secondary

End point timeframe:

From first dosing till end of study, up to 89 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[28]	139[29]		
Units: Subjects	1	0		

Notes:

[28] - Safety analysis set

[29] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with treatment-emergent adverse events (TEAEs) (From first dosing till primary analysis)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) (From first dosing till primary analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

From first dosing till primary analysis cutoff date, up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[30]	139[31]		
Units: Subjects				
Any TEAE	139	136		
Serious TEAE	57	53		
Radium-223/Placebo-related TEAEs	73	50		
Exemestane-related TEAEs	75	64		
Everolimus-related TEAEs	130	125		

Notes:

[30] - Safety analysis set

[31] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with post-treatment chemotherapy related adverse events (From first dosing till primary analysis)

End point title	Number of subjects with post-treatment chemotherapy related adverse events (From first dosing till primary analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

From post-treatment till primary analysis cutoff date, up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[32]	139[33]		
Units: Subjects				
All system organ classes_Any_Grade 3	1	0		
All system organ classes_Any_Grade 4	1	0		
Blood and lymphatic system disorders_Any_Grade 3	1	0		
Febrile neutropenia_Grade 3	1	0		
Investigations_Any_Grade 4	1	0		
Investigations_Neutrophil count decreased_Grade 4	1	0		

Notes:

[32] - Safety analysis set

[33] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with hematological toxicities: Worst Grade under Treatment (From first dosing till primary analysis)

End point title	Number of subjects with hematological toxicities: Worst Grade under Treatment (From first dosing till primary analysis)

End point description:

Safety analysis set with at least one hematology lab assessment: all randomized subjects who received at least one dose of any study medication (radium 223 dichloride or placebo, exemestane, and everolimus), and who in addition had at least one hematology lab assessment. subjects were assigned to the Radium-223 dichloride arm if they received any dose of Radium-223 dichloride, otherwise to the placebo arm.

End point type	Other pre-specified

End point timeframe:

From first dosing till primary analysis cutoff date, up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[34]	137[35]		
Units: Subjects				
Anemia Grade 1	61	57		
Anemia Grade 2	43	55		
Anemia Grade 3	21	11		
Anemia Grade 4	0	0		
Anemia Normal	14	14		
Leukocytosis Grade 1	0	0		
Leukocytosis Grade 2	0	0		
Leukocytosis Grade 3	0	0		
Leukocytosis Grade 4	0	0		
Leukocytosis Normal	139	137		
Hemoglobin increased Grade 1	0	0		
Hemoglobin increased Grade 2	1	0		
Hemoglobin increased Grade 3	0	0		
Hemoglobin increased Grade 4	0	0		
Hemoglobin increased Normal	138	137		
Lymphocyte count decreased Grade 1	20	33		
Lymphocyte count decreased Grade 2	63	45		
Lymphocyte count decreased Grade 3	43	24		
Lymphocyte count decreased Grade 4	2	0		
Lymphocyte count decreased Normal	11	35		
Lymphocyte count increased Grade 1	0	0		
Lymphocyte count increased Grade 2	2	2		
Lymphocyte count increased Grade 3	0	0		
Lymphocyte count increased Grade 4	0	0		
Lymphocyte count increased Normal	137	135		
Neutrophil count decreased Grade 1	24	29		
Neutrophil count decreased Grade 2	47	28		
Neutrophil count decreased Grade 3	19	0		
Neutrophil count decreased Grade 4	0	2		
Neutrophil count decreased Normal	49	78		
Platelet count decreased Grade 1	60	61		
Platelet count decreased Grade 2	7	2		
Platelet count decreased Grade 3	7	0		
Platelet count decreased Grade 4	1	0		
Platelet count decreased Normal	64	74		
White blood cell decreased Grade 1	37	47		
White blood cell decreased Grade 2	59	36		
White blood cell decreased Grade 3	17	3		
White blood cell decreased Grade 4	1	1		
White blood cell decreased Normal	25	50		

Notes:

[34] - Safety analysis set

[35] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with new primary malignancies during study treatment till primary analysis

End point title	Number of subjects with new primary malignancies during study treatment till primary analysis

End point description:

End point type	Other pre-specified

End point timeframe:

From first dosing till primary analysis cutoff date, up to 55 months

End point values	Radium-223 + EXE/EVE	Placebo + EXE/EVE		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[36]	139[37]		
Units: Subjects	1	0		

Notes:

[36] - Safety analysis set

[37] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For AE: After providing written informed consent for participation in the study till end of study, up to 90 months.

Adverse event reporting additional description:

Time Frame for death: Considers all deaths that occurred at any time during the study of 17096 before the last contact, up to 90 months.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo + EXE/EVE

Reporting group description:

Subjects were randomized to treatment with placebo, also with exemestane and everolimus and supportive care as per the local or institutional standard of practice

Reporting group title	Radium-223 + EXE/EVE

Reporting group description:

Subjects were randomized to treatment with radium-223 dichloride, also with exemestane and everolimus and supportive care as per the local or institutional standard of practice

Serious adverse events	Placebo + EXE/EVE	Radium-223 + EXE/EVE	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 139 (40.29%)	61 / 139 (43.88%)	
number of deaths (all causes)	67	66	
number of deaths resulting from adverse events	8	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Appendix cancer metastatic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			

subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Metastases to ovary			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 139 (2.16%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Performance status decreased			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	3 / 139 (2.16%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injection site extravasation			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 139 (1.44%)	7 / 139 (5.04%)	
occurrences causally related to treatment / all	0 / 2	4 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 139 (3.60%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Biopsy lung			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bell's palsy			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Medullary compression syndrome			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmetria			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 139 (3.60%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	8 / 12	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 139 (0.00%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	2 / 139 (1.44%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haematoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 139 (2.16%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	4 / 139 (2.88%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Back pain			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 139 (2.88%)	5 / 139 (3.60%)	
occurrences causally related to treatment / all	0 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomembranous colitis			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 139 (1.44%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + EXE/EVE	Radium-223 + EXE/EVE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 139 (97.12%)	139 / 139 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 139 (5.04%)	13 / 139 (9.35%)	
occurrences (all)	11	22	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 139 (18.71%)	29 / 139 (20.86%)	
occurrences (all)	52	48	
Fatigue			
subjects affected / exposed	41 / 139 (29.50%)	38 / 139 (27.34%)	
occurrences (all)	60	66	
Oedema peripheral			
subjects affected / exposed	25 / 139 (17.99%)	26 / 139 (18.71%)	
occurrences (all)	34	37	
Pyrexia			
subjects affected / exposed	13 / 139 (9.35%)	20 / 139 (14.39%)	
occurrences (all)	16	27	

Peripheral swelling			
subjects affected / exposed	10 / 139 (7.19%)	8 / 139 (5.76%)	
occurrences (all)	17	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 139 (18.71%)	25 / 139 (17.99%)	
occurrences (all)	40	37	
Dyspnoea			
subjects affected / exposed	17 / 139 (12.23%)	16 / 139 (11.51%)	
occurrences (all)	25	20	
Epistaxis			
subjects affected / exposed	14 / 139 (10.07%)	9 / 139 (6.47%)	
occurrences (all)	15	12	
Pneumonitis			
subjects affected / exposed	16 / 139 (11.51%)	16 / 139 (11.51%)	
occurrences (all)	19	20	
Oropharyngeal pain			
subjects affected / exposed	8 / 139 (5.76%)	7 / 139 (5.04%)	
occurrences (all)	10	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 139 (10.07%)	15 / 139 (10.79%)	
occurrences (all)	16	15	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 139 (16.55%)	21 / 139 (15.11%)	
occurrences (all)	52	51	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 139 (15.11%)	19 / 139 (13.67%)	
occurrences (all)	40	44	
Blood cholesterol increased			
subjects affected / exposed	10 / 139 (7.19%)	15 / 139 (10.79%)	
occurrences (all)	22	22	
Blood creatinine increased			
subjects affected / exposed	10 / 139 (7.19%)	11 / 139 (7.91%)	
occurrences (all)	23	26	

Lymphocyte count decreased			
subjects affected / exposed	7 / 139 (5.04%)	8 / 139 (5.76%)	
occurrences (all)	14	36	
Neutrophil count decreased			
subjects affected / exposed	6 / 139 (4.32%)	14 / 139 (10.07%)	
occurrences (all)	11	43	
Platelet count decreased			
subjects affected / exposed	12 / 139 (8.63%)	12 / 139 (8.63%)	
occurrences (all)	28	42	
Weight decreased			
subjects affected / exposed	22 / 139 (15.83%)	28 / 139 (20.14%)	
occurrences (all)	31	37	
White blood cell count decreased			
subjects affected / exposed	13 / 139 (9.35%)	13 / 139 (9.35%)	
occurrences (all)	31	43	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 139 (6.47%)	9 / 139 (6.47%)	
occurrences (all)	12	11	
Dysgeusia			
subjects affected / exposed	13 / 139 (9.35%)	17 / 139 (12.23%)	
occurrences (all)	14	26	
Headache			
subjects affected / exposed	30 / 139 (21.58%)	25 / 139 (17.99%)	
occurrences (all)	42	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 139 (28.78%)	55 / 139 (39.57%)	
occurrences (all)	146	191	
Neutropenia			
subjects affected / exposed	11 / 139 (7.91%)	29 / 139 (20.86%)	
occurrences (all)	11	73	
Thrombocytopenia			
subjects affected / exposed	9 / 139 (6.47%)	21 / 139 (15.11%)	
occurrences (all)	19	58	
Leukopenia			

subjects affected / exposed	2 / 139 (1.44%)	12 / 139 (8.63%)	
occurrences (all)	3	49	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 139 (0.72%)	8 / 139 (5.76%)	
occurrences (all)	1	10	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 139 (7.91%)	7 / 139 (5.04%)	
occurrences (all)	13	7	
Abdominal pain upper			
subjects affected / exposed	7 / 139 (5.04%)	15 / 139 (10.79%)	
occurrences (all)	8	18	
Constipation			
subjects affected / exposed	20 / 139 (14.39%)	6 / 139 (4.32%)	
occurrences (all)	23	7	
Diarrhoea			
subjects affected / exposed	31 / 139 (22.30%)	42 / 139 (30.22%)	
occurrences (all)	54	66	
Dry mouth			
subjects affected / exposed	9 / 139 (6.47%)	10 / 139 (7.19%)	
occurrences (all)	9	13	
Dyspepsia			
subjects affected / exposed	7 / 139 (5.04%)	7 / 139 (5.04%)	
occurrences (all)	8	8	
Mouth ulceration			
subjects affected / exposed	10 / 139 (7.19%)	3 / 139 (2.16%)	
occurrences (all)	19	3	
Nausea			
subjects affected / exposed	30 / 139 (21.58%)	41 / 139 (29.50%)	
occurrences (all)	42	55	
Stomatitis			
subjects affected / exposed	69 / 139 (49.64%)	66 / 139 (47.48%)	
occurrences (all)	172	144	
Vomiting			

subjects affected / exposed	22 / 139 (15.83%)	25 / 139 (17.99%)	
occurrences (all)	31	32	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	9 / 139 (6.47%)	7 / 139 (5.04%)	
occurrences (all)	31	11	
Dry skin			
subjects affected / exposed	14 / 139 (10.07%)	8 / 139 (5.76%)	
occurrences (all)	15	8	
Pruritus			
subjects affected / exposed	14 / 139 (10.07%)	17 / 139 (12.23%)	
occurrences (all)	20	18	
Rash			
subjects affected / exposed	30 / 139 (21.58%)	20 / 139 (14.39%)	
occurrences (all)	44	29	
Rash maculo-papular			
subjects affected / exposed	7 / 139 (5.04%)	9 / 139 (6.47%)	
occurrences (all)	14	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 139 (30.22%)	30 / 139 (21.58%)	
occurrences (all)	81	51	
Back pain			
subjects affected / exposed	26 / 139 (18.71%)	16 / 139 (11.51%)	
occurrences (all)	36	17	
Bone pain			
subjects affected / exposed	24 / 139 (17.27%)	16 / 139 (11.51%)	
occurrences (all)	34	31	
Musculoskeletal pain			
subjects affected / exposed	8 / 139 (5.76%)	4 / 139 (2.88%)	
occurrences (all)	10	4	
Myalgia			
subjects affected / exposed	7 / 139 (5.04%)	9 / 139 (6.47%)	
occurrences (all)	8	10	
Pain in extremity			

subjects affected / exposed	25 / 139 (17.99%)	21 / 139 (15.11%)	
occurrences (all)	37	28	
Pathological fracture			
subjects affected / exposed	15 / 139 (10.79%)	16 / 139 (11.51%)	
occurrences (all)	23	22	
Musculoskeletal chest pain			
subjects affected / exposed	12 / 139 (8.63%)	6 / 139 (4.32%)	
occurrences (all)	15	7	
Osteonecrosis of jaw			
subjects affected / exposed	2 / 139 (1.44%)	9 / 139 (6.47%)	
occurrences (all)	4	12	
Spinal pain			
subjects affected / exposed	9 / 139 (6.47%)	7 / 139 (5.04%)	
occurrences (all)	13	10	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	12 / 139 (8.63%)	12 / 139 (8.63%)	
occurrences (all)	14	16	
Conjunctivitis			
subjects affected / exposed	3 / 139 (2.16%)	8 / 139 (5.76%)	
occurrences (all)	3	8	
Cystitis			
subjects affected / exposed	7 / 139 (5.04%)	4 / 139 (2.88%)	
occurrences (all)	8	4	
Nasopharyngitis			
subjects affected / exposed	5 / 139 (3.60%)	7 / 139 (5.04%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	20 / 139 (14.39%)	15 / 139 (10.79%)	
occurrences (all)	38	22	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	6 / 139 (4.32%)	12 / 139 (8.63%)	
occurrences (all)	9	28	
Hyperglycaemia			

subjects affected / exposed	18 / 139 (12.95%)	17 / 139 (12.23%)	
occurrences (all)	41	36	
Hypertriglyceridaemia			
subjects affected / exposed	11 / 139 (7.91%)	12 / 139 (8.63%)	
occurrences (all)	38	29	
Hypocalcaemia			
subjects affected / exposed	8 / 139 (5.76%)	4 / 139 (2.88%)	
occurrences (all)	14	4	
Hypokalaemia			
subjects affected / exposed	14 / 139 (10.07%)	19 / 139 (13.67%)	
occurrences (all)	27	29	
Hypophosphataemia			
subjects affected / exposed	8 / 139 (5.76%)	11 / 139 (7.91%)	
occurrences (all)	37	16	
Decreased appetite			
subjects affected / exposed	35 / 139 (25.18%)	48 / 139 (34.53%)	
occurrences (all)	43	68	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2015	Amendment 1 (global amendment) forming integrated protocol Version 2.0, dated 16 MAR 2015, was an amendment to the original protocol.
29 July 2015	Amendment 3 (global amendment) forming integrated protocol Version 3.0, dated 29 JUL 2015, is an amendment to the Version 2.0 of the protocol.
09 March 2016	Amendment 5 (global amendment) forming integrated protocol Version 4.0, dated 09 MAR 2016, is an amendment to the Version 3.0 of the protocol.
23 May 2017	Amendment 8 (global amendment) forming integrated protocol Version 5.0, dated 23 MAY 2017, is an amendment to the Version 4.0 of the protocol.
03 April 2018	Amendment 9 (global amendment) forming integrated protocol Version 6.0, dated 03 APR 2018, is an amendment to the Version 5.0 of the protocol, dated 23 MAY 2017. This was the protocol in effect leading up to the primary analysis discussed in this report.
04 December 2019	Amendment 10 (global amendment) forming integrated protocol Version 7.0, dated 04 DEC 2019, is an amendment to the Version 6.0 of the protocol, dated 03 APR 2018. This amendment was planned to go into effect once the primary analysis was completed. The data analyzed in clinical study report were collected using the study conduct described in Protocol Amendment 9; however, Protocol Amendment 10 is being included in this summary for completeness as it was approved prior to the database clean date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported