



Clinical trial results:

An open-label, multicenter, Phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in participants with stage IV non-small cell lung cancer

Summary

EudraCT number	2018-003704-39
Trial protocol	ES BE NL DE GB
Global end of trial date	30 January 2023

Results information

Result version number	v1 (current)
This version publication date	26 January 2024
First version publication date	26 January 2024

Trial information

Trial identification

Sponsor protocol code	19781
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03996473
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	10 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1: To assess the safety of the combination of radium-223 dichloride and pembrolizumab and to determine the recommended Phase 2 dose (RP2D). Phase 2: To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone)

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	06 March 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	10
EEA total number of subjects	9

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)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 4 countries between 06 March 2020 (first subject first visit) and 30 January 2023 (last subject last visit).

Pre-assignment

Screening details:

Overall, 10 subjects were screened. Of them, 2 subjects were screen failures. 8 subjects were assigned to study treatment, of which 7 received the study treatment and 1 subject never received the treatment in the Phase 1.

Period 1

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

Arms

Arm title	Radium-223 Dichloride + Pembrolizumab
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Arm description:

Participants received radium-223 dichloride at 55 kBq/kg every 6 weeks in combination with pembrolizumab every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg, IV infusion, every 3 weeks for a maximum of up to 35 administrations

Investigational medicinal product name	Radium-223 Dichloride
Investigational medicinal product code	BAY88-8223
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

55 kBq/kg, intravenous (IV) injection, every 6 weeks for up to 6 administrations

Number of subjects in period 1 ^[1]	Radium-223 Dichloride + Pembrolizumab
Started	7
Completed	0
Not completed	7
Consent withdrawn by subject	1
Progressive disease	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The study was terminated early during the Phase 1 part of the study. No subjects started in Phase 2 part of the study prior to study termination.

Baseline characteristics

Reporting groups

Reporting group title	Radium-223 Dichloride + Pembrolizumab
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Reporting group description:

Participants received radium-223 dichloride at 55 kBq/kg every 6 weeks in combination with pembrolizumab every 3 weeks.

Reporting group values	Radium-223 Dichloride + Pembrolizumab	Total	
Number of subjects	7	7	
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	63.6 ± 10.7	-	
Gender Categorical Units: Subjects			
Female	5	5	
Male	2	2	
Race Units: Subjects			
White	7	7	
Black or African American	0	0	
Asian	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Multiple	0	0	
Not reported	0	0	

End points

End points reporting groups

Reporting group title	Radium-223 Dichloride + Pembrolizumab
Reporting group description: Participants received radium-223 dichloride at 55 kBq/kg every 6 weeks in combination with pembrolizumab every 3 weeks.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF consisted of all subjects who received at least 1 administration of study treatment.	
Subject analysis set title	Dose limiting toxicities (DLT) analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: DLT analysis set included all the following participants: a. participants who experienced a DLT during the DLT observation window; b. participants who did not experience a DLT, and who were not dropouts. Dropouts were eligible participants who withdrew during the DLT observation window (within 6 weeks after the first administration of pembrolizumab) for reasons other than experiencing a DLT, and who did not complete both 1 dose of radium-223 dichloride and 2 cycles of pembrolizumab.	
Subject analysis set title	Efficacy analysis set (EFF)
Subject analysis set type	Sub-group analysis
Subject analysis set description: EFF included all subjects who received at least 1 administration of planned dose of any study treatment In Phase 1.	

Primary: Number of subjects with treatment-emergent adverse events in Phase 1

End point title	Number of subjects with treatment-emergent adverse events in Phase 1 ^[1]
End point description: A treatment-emergent adverse event (TEAE) was any untoward medical occurrence in a subject, whether or not related to the treatment, arising or worsening after start of study treatment administration until the end of treatment visit (EoT visit, i.e. 30 [+7] days after last dose of study treatment). Severities of the TEAEs are summarized overall and by the maximum grade experienced by the subjects for any TEAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.5.0.	
End point type	Primary
End point timeframe: Up to 218 days	

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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[2]			
Units: Subjects				
Any TEAE	7			
Any TEAE - Maximum Grade 1	0			
Any TEAE - Maximum Grade 2	3			
Any TEAE - Maximum Grade 3	2			

Any TEAE - Maximum Grade 4	0			
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Notes:

[2] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent serious adverse events in Phase 1

End point title	Number of subjects with treatment-emergent serious adverse events in Phase 1 ^[3]
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End point description:

A treatment-emergent serious adverse event (TESAE) was any untoward medical occurrence that resulting in death, initial or prolonged inpatient hospitalization, life-threatening, persistent disability/incapacity, congenital anomaly/birth defect, another medical important serious event as judged by the investigator arising or worsening after start of study treatment administration until 90 days after the cessation of study treatment for serious AE (regardless of causality) or until the end of treatment visit (EoT visit, i.e. 30 [+7] days after last dose of study treatment) visit if the subject initiated new anti-cancer therapy, whichever was earlier.

End point type	Primary
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End point timeframe:

Up to 278 days

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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[4]			
Units: Subjects				
Any TESAE	2			

Notes:

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with dose limiting toxicities (DLTs) in Phase 1

End point title	Number of subjects with dose limiting toxicities (DLTs) in Phase 1 ^[5]
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End point description:

Any of following toxicities (exceptions as in protocol) during the DLT window was considered a DLT if assessed by investigator to be possibly, probably or definitely related to study treatment: 1. Grade 4 non-hematologic toxicity. 2. Grade 4 hematologic toxicity ≥ 7 days. 3. Any non-hematologic AE (excl. lab) \geq Grade 3. 4. Any Grade 3 non-hematologic lab value if clinically significant medical intervention required, or the abnormality led to hospitalization, or the abnormality persisted for >1 week. 5. Grade 3 abnormality in AST, ALT, or bilirubin without liver metastases at screening; The abnormality results in a

Drug-induced Liver Injury. 6.Febrile neutropenia Grade 3 or 4. 7.Prolonged delay (>2 weeks) in initiating Cycle 2 of pembrolizumab due to treatment-related toxicity 8.Any treatment-related toxicity that caused the subject to discontinue treatment during Cycle 1 or 2. 9.Missing >25% of pembrolizumab doses as a result of drug-related AE(s) during the first cycle. 10.Grade 5 toxicity

End point type	Primary
End point timeframe:	
Within 6 weeks after the first administration of pembrolizumab	

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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	6 ^[6]			
Units: Subjects				
Any TESAE	0			

Notes:

[6] - DLT analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Objective response rate (ORR) per RECIST v1.1 in Phase 2

End point title	Objective response rate (ORR) per RECIST v1.1 in Phase 2 ^[7]
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End point description:

ORR was defined as the percentage of subjects with best overall response of complete response (CR) or partial response (PR) during the course of the study. RECIST: Response Evaluation Criteria in Solid Tumors

End point type	Primary
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End point timeframe:

0 day as Phase 2 never started due to the early termination of the study

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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[8]			
Units: Percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[8] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants categorized by best tumor responses per RECIST v1.1 in Phase 1

End point title	Number of participants categorized by best tumor responses per RECIST v1.1 in Phase 1
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End point description:

The RECIST v1.1 criteria were used for efficacy evaluation of response and disease control. RECIST: Response Evaluation Criteria in Solid Tumors

End point type	Secondary
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End point timeframe:

Up to 188 days

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[9]			
Units: Subjects				
Stable disease (SD)	1			
Progressive disease (PD)	5			
Missing	1			

Notes:

[9] - EFF

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) per RECIST v1.1 in Phase 1

End point title	Objective response rate (ORR) per RECIST v1.1 in Phase 1
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End point description:

ORR was defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR) during the course of the study. RECIST: Response Evaluation Criteria in Solid Tumors

End point type	Secondary
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End point timeframe:

Up to 188 days

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[10]			
Units: Percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[10] - ORR wasn't analyzed due to no responder reported before study termination among low number subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per RECIST v1.1 in Phase 1

End point title	Duration of response (DoR) per RECIST v1.1 in Phase 1
End point description:	
DoR was defined as the time interval from the date of first response (CR or PR) to the date of disease progression or death, whichever comes first. RECIST: Response Evaluation Criteria in Solid Tumors	
End point type	Secondary
End point timeframe:	
Up to 188 days	

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[11]			
Units: Days				
median (confidence interval 95%)	(to)			

Notes:

[11] - DoR wasn't analyzed due to no responder reported before study termination among low number subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) per RECIST v1.1 in Phase 1

End point title	Disease control rate (DCR) per RECIST v1.1 in Phase 1
End point description:	
DCR was defined as the percentage of subjects with CR or PR, or SD for at least 6 weeks during the course of the study. RECIST: Response Evaluation Criteria in Solid Tumors	
End point type	Secondary
End point timeframe:	
Up to 188 days	

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[12]			
Units: Percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[12] - DCR wasn't analyzed due to study termination and the low number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per RECIST v1.1 in Phase 2

End point title	Duration of response (DoR) per RECIST v1.1 in Phase 2
End point description:	
DoR was defined as the time interval from the date of first response (CR or PR) to the date of disease progression or death, whichever comes first. RECIST: Response Evaluation Criteria in Solid Tumors	
End point type	Secondary
End point timeframe:	
0 day as Phase 2 never started due to the early termination of the study	

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[13]			
Units: Days				
median (confidence interval 95%)	(to)			

Notes:

[13] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) per RECIST v1.1 in Phase 2

End point title	Disease control rate (DCR) per RECIST v1.1 in Phase 2
End point description:	
DCR was defined as the percentage of subjects with CR or PR, or SD for at least 6 weeks during the course of the study. RECIST: Response Evaluation Criteria in Solid Tumors	
End point type	Secondary
End point timeframe:	
0 day as Phase 2 never started due to the early termination of the study	

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[14]			
Units: Percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[14] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) per RECIST v1.1 in Phase 2

End point title	Progression free survival (PFS) per RECIST v1.1 in Phase 2
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End point description:

Progression free survival (PFS) was defined as the time from start of any study treatment to the date of earliest radiological progression per RECIST 1.1 or death due to any cause, whichever occurs first. Subjects who were alive and without progression at the time of database cut-off would be censored at the date of the last evaluable tumor assessment. RECIST: Response Evaluation Criteria in Solid Tumors

End point type	Secondary
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End point timeframe:

0 day as Phase 2 never started due to the early termination of the study

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[15]			
Units: Days				
median (confidence interval 95%)	(to)			

Notes:

[15] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in Phase 2

End point title	Overall survival (OS) in Phase 2
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End point description:

Overall survival (OS) was defined as the time from start of any study treatment to the date of death due to any cause. Subjects who were alive at the time of database cut-off would be censored at the last date known to be alive or the database cut-off date, whichever occurs first.

End point type	Secondary
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End point timeframe:

0 day as Phase 2 never started due to the early termination of the study

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[16]			
Units: Days				
median (confidence interval 95%)	(to)			

Notes:

[16] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events in Phase 2

End point title	Number of subjects with treatment-emergent adverse events in Phase 2
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End point description:

A treatment-emergent adverse event (TEAE) was any untoward medical occurrence in a subject, whether or not related to the treatment, arising or worsening after start of study treatment administration until the end of treatment visit (EoT visit, i.e. 30 [+7] days after last dose of study treatment). Severities of the TEAEs are summarized overall and by the maximum grade experienced by the subjects for any TEAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.5.0.

End point type	Secondary
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End point timeframe:

0 day as Phase 2 never started due to the early termination of the study

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[17]			
Units: Subjects				

Notes:

[17] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment-emergent serious adverse events in Phase 2

End point title	Number of participants with treatment-emergent serious adverse events in Phase 2
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End point description:

A treatment-emergent serious adverse event (TESAE) was any untoward medical occurrence that resulting in death, initial or prolonged inpatient hospitalization, life-threatening, persistent

disability/incapacity, congenital anomaly/birth defect, another medical important serious event as judged by the investigator arising or worsening after start of study treatment administration until 90 days after the cessation of study treatment for serious AE (regardless of causality) or until the end of treatment visit (EoT visit, i.e. 30 [+7] days after last dose of study treatment) visit if the subject initiated new anti-cancer therapy, whichever was earlier.

End point type	Secondary
End point timeframe:	
0 day as Phase 2 never started due to the early termination of the study	

End point values	Radium-223 Dichloride + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[18]			
Units: Subject				

Notes:

[18] - No subject started in Phase 2 part of the study prior to study termination

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment to 90 days after cessation of study treatment or 30 days after last dose of study treatment (EoT visit) if subject started new anti-cancer therapy (whichever was earlier) for serious TEAEs; or until EoT visit for other TEAEs

Adverse event reporting additional description:

Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the entire study before the last contact (i.e. from signing ICF until the end of follow-up)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Radium-223 + Pembrolizumab
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Reporting group description:

Subjects received radium-223 dichloride every 6 weeks for up to 6 administrations in combination with pembrolizumab every 3 weeks for up to 35 cycles.

Serious adverse events	Radium-223 + Pembrolizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	2		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Radium-223 + Pembrolizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Investigations			
Weight decreased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Nausea subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Constipation subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Gastritis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Sputum discoloured subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Productive cough			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p> <p>2 / 7 (28.57%)</p> <p>2</p> <p>1 / 7 (14.29%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p> <p>2 / 7 (28.57%)</p> <p>2</p> <p>2 / 7 (28.57%)</p> <p>2</p>		
<p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p>		
<p>Metabolism and nutrition disorders</p> <p>Hyponatraemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p> <p>2 / 7 (28.57%)</p> <p>2</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2019	Protocol amendment 1 was prepared to clarify and strengthen guidance on tumor assessment, eligibility criteria, toxicity management and DLT criteria.
18 September 2020	Protocol amendment 2 was mainly prepared to address the following points: clarification on eligibility criteria, concomitant therapy and dose modification rules, tumor assessment per iRECIST 1.1 moved from secondary to exploratory endpoints, clarification on statistical assumptions and planned analyses, provision of additional guidance to the participating sites, and additional background information on study rationale.

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.

The study was terminated early during the Phase 1 part of the study. Due to the early termination, tumor responses were only listed, none of the efficacy outcome measures were actually analyzed.

Notes: