Clinical trial results:
A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer

Summary

EudraCT number	2014-002206-20
Trial protocol	ES DK IT IE GB HU NL
Global end of trial date	18 February 2022

Results information

Result version number	v1 (current)
This version publication date	24 February 2023
First version publication date	24 February 2023

Trial information

Trial identification

Sponsor protocol code	3475-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02335424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Street LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Street LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Street LLC, ClinicalTrialsDisclosure@merck.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	18 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2018
Global end of trial reached?	Yes
Global end of trial date	18 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study using pembrolizumab (MK-3475, KEYTRUDA®) for first-line treatment of participants with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy. The primary study objective is to determine the objective response rate (ORR) in all participants and by programmed cell death ligand 1 (PD-L1) status.

With Amendment 4, once a participant has achieved the study objective or the study has ended, the participant will be discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments and treatment.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Guatemala: 4
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 162

Worldwide total number of subjects	374
EEA total number of subjects	94

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)	68
From 65 to 84 years	265
85 years and over	41

Subject disposition

Recruitment

Recruitment details:

Participants were eligible to receive second course treatment with pembrolizumab if they met criteria for re-treatment. Per protocol, only data generated during the initial course of treatment contributed to efficacy and safety outcome measures.

Pre-assignment

Screening details:

The study enrolled 374 participants and 370 participants received ≥1 dose of study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Pembrolizumab 200 mg

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab due to complete response (CR) or completed initial course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to an additional year.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg by intravenous infusion on Day 1 of each 21-day cycle

Number of subjects in period 1	Pembrolizumab 200 mg
Started	374
Treated	370
Received Second Course Treatment	13
Completed	0
Not completed	374
Consent withdrawn by subject	19
Physician decision	13
Participation in study terminated by Sponsor	39
Adverse event, non-fatal	25
Death	273
Screen failure	1

Lost to follow-up	3
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab 200 mg
Reporting group description:	
Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab due to complete response (CR) or completed initial course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to an additional year.	

Reporting group values	Pembrolizumab 200 mg	Total	
Number of subjects	374	374	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	68	68	
From 65-84 years	265	265	
85 years and over	41	41	
Age Continuous Units: Years			
arithmetic mean	73.0		
standard deviation	± 9.9	-	
Sex: Female, Male Units: Participants			
Female	86	86	
Male	288	288	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	
Asian	26	26	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	8	8	
White	332	332	
More than one race	2	2	
Unknown or Not Reported	4	4	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	22	22	
Not Hispanic or Latino	326	326	
Unknown or Not Reported	26	26	

End points

End points reporting groups

Reporting group title	Pembrolizumab 200 mg

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab due to complete response (CR) or completed initial course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to an additional year.

Primary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%[1]

End point description:

ORR was determined in participants who had a PD-L1 CPS of ≥10% as measured by immunohistochemistry assay. ORR was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Primary

End point timeframe:

Up to approximately 80.5 months

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: There was no statistical analysis planned for this endpoint.

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	47.3 (37.7 to 57.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in

	Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%[2]

End point description:

ORR was determined in participants who had a PD-L1 CPS of ≥1% as measured by immunohistochemistry assay. ORR was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Primary

End point timeframe:

Up to approximately 80.5 months

Notes:

[2] - 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: There was no statistical analysis planned for this endpoint.

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	32.6 (27.2 to 38.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants[3]

End point description:

ORR was determined in all participants and was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to approximately 80.5 months

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: There was no statistical analysis planned for this endpoint.

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	28.9 (24.3 to 33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by Blinded Independent Central Review (BICR) in All Participants

End point title	Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by Blinded Independent Central Review (BICR) in All Participants

End point description:

PFS was determined in all participants. PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by BICR. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Months				
median (confidence interval 95%)	2.5 (2.1 to 3.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR

	in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

DOR was determined in participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1 by BICR. DOR was the time from first evidence of CR or PR until PD or death and was calculated using the KM method. Participants who had not progressed or died at the time of analysis were censored at the date of last tumor assessment. Per RECIST 1.1, PD was a ≥20% increase in the SOD of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. 9999 indicated that the upper limit of the 95% CI was not reached at time of data cut-off due to an insufficient number of responding participants with relapse. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment, had a PD-L1 positive expression of ≥1% CPS, and had a confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: Months				
median (confidence interval 95%)	35.8 (20.4 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a PD-L1 CPS of ≥10%

End point title	Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a PD-L1 CPS of ≥10%

End point description:

DOR was determined in participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1 by BICR. DOR was the time from first evidence of CR or PR until PD or death and was calculated using the KM method. Participants who had not progressed or died at the time of analysis were censored at the date of last tumor assessment. Per RECIST 1.1, PD was a ≥20% increase in the SOD of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. 9999 indicated that the median and upper limit of the 95% CI was not reached at time of data cut-off due to an insufficient number of responding participants with relapse Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment had a PD-L1 positive expression of ≥10% CPS and had a confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Months				
median (confidence interval 95%)	9999 (18.1 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by Blinded Independent Central Review (BICR) in All Participants

End point title	Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by Blinded Independent Central Review (BICR) in All Participants

End point description:

DOR was determined in participants who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by BICR. DOR was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death and was calculated using the product-limit (Kaplan-Meier [KM]) method for censored data. Participants who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters (SOD) of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Months				
median (confidence interval 95%)	33.4 (18.2 to 48.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Progression Free Survival (PFS) Per Response Evaluation

	Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

PFS was determined in participants who had a PD-L1 CPS of ≥1% as measured by immunohistochemistry assay. PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by BICR. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Months				
median (confidence interval 95%)	3.4 (2.3 to 4.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in All Participants

End point title	Overall Survival (OS) in All Participants

End point description:

OS was determined for all participants and was defined as the time from randomization to death due to any cause. OS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Months				
median (confidence interval 95%)	11.3 (9.7 to 13.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Progression Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

PFS was determined in participants who had a PD-L1 CPS of ≥10% as measured by immunohistochemistry assay. PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by BICR. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Months				
median (confidence interval 95%)	4.9 (3.8 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in All Participants

End point title	Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in All Participants

End point description:

The PFS rate was determined in all participants at Month 6. PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever

occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 6 was calculated using product-limit (Kaplan-Meier [KM]) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	34.0 (29.2 to 38.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Overall Survival (OS) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

OS was determined in participants who had a PD-L1 CPS of ≥10% as measured by immunohistochemistry assay. OS was defined as the time from randomization to death due to any cause. OS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Months				
median (confidence interval 95%)	18.5 (12.2 to 28.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Overall Survival (OS) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

OS was determined in participants who had a PD-L1 CPS of ≥1%, as measured by immunohistochemistry assay. OS was defined as the time from randomization to death due to any cause. OS was calculated using the product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Months				
median (confidence interval 95%)	12.4 (10.8 to 15.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

The PFS rate was determined in participants who had a PD-L1 CPS of ≥1%, as measured by immunohistochemistry assay, at Month 12. PFS was defined as the time from randomization to the first documented PD or death due to any cause, whichever occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 12 was calculated using product-limit KM method for censored data.

Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	25.8 (20.8 to 31.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in All Participants

End point title	Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in All Participants

End point description:

The PFS rate was determined in all participants at Month 12. PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. Per RECIST 1.1, PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum, or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 12 was calculated using product-limit (Kaplan-Meier [KM]) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	22.9 (18.7 to 27.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

The PFS rate was determined in participants who had a PD-L1 CPS of ≥10%, as measured by immunohistochemistry assay, at Month 6. PFS was defined as the time from randomization to the first documented PD or death due to any cause, whichever occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 6 was calculated using product-limit KM method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	49.0 (39.4 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Progression Free Survival Rate (PFS Rate) at Month 6 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

The PFS rate was determined in participants who had a PD-L1 CPS of ≥1%, as measured by immunohistochemistry assay, at Month 6. PFS was defined as the time from randomization to the first documented PD or death due to any cause, whichever occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 6 was calculated using product-limit KM method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that

received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	37.9 (32.2 to 43.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Progression Free Survival Rate (PFS Rate) at Month 12 As Assessed by BICR in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

The PFS rate was determined in participants who had a PD-L1 CPS of ≥10%, as measured by immunohistochemistry assay, at Month 12. PFS was defined as the time from randomization to the first documented PD or death due to any cause, whichever occurred first, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by BICR. PD was a ≥20% increase in the sum of diameters of target lesions plus an absolute increase of ≥5 mm in the sum or the appearance of ≥1 new lesions. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit was used in the analysis. PFS at Month 12 was calculated using product-limit KM method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	38.6 (29.5 to 47.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 6 in All Participants

End point title	Overall Survival Rate (OS Rate) at Month 6 in All Participants

End point description:

The OS rate was determined for all participants at Month 6 and was defined as the time from randomization to death due to any cause. OS at Month 6 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	67.0 (62.0 to 71.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 6 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Overall Survival Rate (OS Rate) at Month 6 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

The OS rate was determined in participants who had a PD-L1 CPS of ≥1%, as measured by immunohistochemistry assay, at Month 6. OS was defined as the time from randomization to death due to any cause. OS at Month 6 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	71.3 (65.6 to 76.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 12 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Overall Survival Rate (OS Rate) at Month 12 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

The OS rate was determined in participants who had a PD-L1 CPS of ≥1%, as measured by immunohistochemistry assay, at Month 12. OS was defined as the time from randomization to death due to any cause. OS at Month 12 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	50.9 (45.0 to 56.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 12 in All Participants

End point title	Overall Survival Rate (OS Rate) at Month 12 in All Participants

End point description:

The OS rate was determined for all participants at Month 12 and was defined as the time from randomization to death due to any cause. OS at Month 12 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	46.9 (41.8 to 51.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 6 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Overall Survival Rate (OS Rate) at Month 6 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

The OS rate was determined in participants who had a PD-L1 CPS of ≥10%, as measured by immunohistochemistry assay, at Month 6. OS was defined as the time from randomization to death due to any cause. OS at Month 6 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	76.3 (67.2 to 83.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate (OS Rate) at Month 12 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Overall Survival Rate (OS Rate) at Month 12 in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

The OS rate was determined in participants who had a PD-L1 CPS of ≥10%, as measured by immunohistochemistry assay, at Month 12. OS was defined as the time from randomization to death due to any cause. OS at Month 12 was calculated using product-limit (Kaplan-Meier) method for censored data. Participants were censored at the date of their last assessment. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	60.7 (50.9 to 69.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Programmed Cell Death Ligand 1 (PD-L1) Expression Status

End point title	Programmed Cell Death Ligand 1 (PD-L1) Expression Status

End point description:

PD-L1 expression status was determined as the percent of disease tumor cells, from newly obtained tumor biopsies, demonstrating plasma membrane PD-L1 staining of any intensity using an immunohistochemistry (IHC) assay. The assay uses a Combined Positive Score (CPS) as a measure of PD-L1 positivity. The CPS is calculated as the number of PD-L1-positive cells divided by the number of viable tumor cells analyzed multiplied by 100. A CPS of <1%=negative; ≥1%=positive; and ≥10%=strongly positive. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study

End point type	Secondary

End point timeframe:

Day 1

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Participants				
PD-L1 CPS <1%	79			
PD-L1 CPS ≥1% to <10%	172			
PD-L1 CPS ≥10%	110			
Unknown	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE)

End point title	Number of Participants Who Experienced At Least One Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Participants	361			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

End point title	Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 26 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Participants	62			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in All Participants

End point title	Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in All Participants

End point description:

ORR was determined in all participants and was defined as the percentage of participants who had a confirmed Complete Response (CR: complete disappearance of all lesions and no new lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per modified RECIST as assessed by Blinded Independent Central Review (BICR). Modified RECIST differs from RECIST 1.1 in that progressive disease requires confirmation by a repeat radiological assessment no less than 4 weeks from the date of first documented progressive disease. Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment.

End point type	Other pre-specified

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of participants				
number (confidence interval 95%)	30.5 (25.9 to 35.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point title	Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥1%

End point description:

ORR was determined in participants who had a PD-L1 CPS of ≥1% as measured by immunohistochemistry assay. ORR was defined as the percentage of participants who had a confirmed Complete Response (CR: complete disappearance of all lesions and no new lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per modified RECIST as assessed by Blinded Independent Central Review (BICR). Modified RECIST differs from RECIST 1.1 in that progressive disease requires confirmation by a repeat radiological assessment no less than 4 weeks from the date of first documented progressive disease. Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥1% CPS.

End point type	Other pre-specified

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (confidence interval 95%)	34.4 (28.9 to 40.3)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point title	Objective Response Rate (ORR) Per Modified Response Evaluation Criteria in Solid Tumors (modified RECIST) in Participants with a Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) of ≥10%

End point description:

ORR was determined in participants who had a PD-L1 CPS of ≥10% as measured by immunohistochemistry assay. ORR was defined as the percentage of participants who had a confirmed Complete Response (CR: complete disappearance of all lesions and no new lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per modified RECIST as assessed by Blinded Independent Central Review (BICR). Modified RECIST differs from RECIST 1.1 in that progressive disease requires confirmation by a repeat radiological assessment no less than 4 weeks from the date of first documented progressive disease. Participants with missing data were considered non-responders. Per protocol, only data generated during the initial course of treatment contributed to the analysis. The analysis included all participants that received ≥1 dose of study treatment and had a PD-L1 positive expression of ≥10% CPS.

End point type	Other pre-specified

End point timeframe:

Up to approximately 80.5 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of participants				
number (confidence interval 95%)	49.1 (39.4 to 58.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 80.5 months

Adverse event reporting additional description:

AEs=all participants who received ≥1 dose of study treatment; all-cause mortality=all allocated participants. Per protocol, progression of cancer under study was not considered an AE unless related to study drug. MedDRA preferred terms "Neoplasm progression (NP)", "Malignant NP" & "Disease progression" not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Second Course Pembrolizumab

Reporting group description:

Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 21-day cycle for up to 1 year of treatment.

Reporting group title	Pembrolizumab

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 21-day cycle (Q3W) for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab due to complete response (CR) or completed initial course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to an additional year.

Serious adverse events	Second Course Pembrolizumab	Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	190 / 370 (51.35%)	
number of deaths (all causes)	8	305	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
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			
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac complication associated with device			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
General physical health deterioration			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Emphysema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)	6 / 370 (1.62%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract stoma complication			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma obstruction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 13 (15.38%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Central nervous system haemorrhage			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
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	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	6 / 370 (1.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
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	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 13 (7.69%)	13 / 370 (3.51%)	
occurrences causally related to treatment / all	1 / 1	2 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	0 / 13 (0.00%)	12 / 370 (3.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydronephrosis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 13 (0.00%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary incontinence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 13 (0.00%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			

subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 13 (0.00%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Addison's disease			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Crystal arthropathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune arthritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 13 (7.69%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
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 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)	15 / 370 (4.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pyelonephritis			
subjects affected / exposed	0 / 13 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)	9 / 370 (2.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
Septic shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	26 / 370 (7.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 13 (0.00%)	14 / 370 (3.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 4	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Second Course Pembrolizumab	Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	342 / 370 (92.43%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	20 / 370 (5.41%)	
occurrences (all)	0	21	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	20 / 370 (5.41%)	
occurrences (all)	0	22	
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	44 / 370 (11.89%)	
occurrences (all)	0	49	
Chills			
subjects affected / exposed	0 / 13 (0.00%)	27 / 370 (7.30%)	
occurrences (all)	0	31	
Oedema			
subjects affected / exposed	1 / 13 (7.69%)	6 / 370 (1.62%)	
occurrences (all)	1	6	
Influenza like illness			
subjects affected / exposed	0 / 13 (0.00%)	19 / 370 (5.14%)	
occurrences (all)	0	21	
Fatigue			

subjects affected / exposed	0 / 13 (0.00%)	129 / 370 (34.86%)	
occurrences (all)	0	156	
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	63 / 370 (17.03%)	
occurrences (all)	1	74	
Peripheral swelling			
subjects affected / exposed	1 / 13 (7.69%)	7 / 370 (1.89%)	
occurrences (all)	1	7	
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	51 / 370 (13.78%)	
occurrences (all)	0	64	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)	48 / 370 (12.97%)	
occurrences (all)	1	57	
Cough			
subjects affected / exposed	1 / 13 (7.69%)	76 / 370 (20.54%)	
occurrences (all)	1	92	
Atelectasis			
subjects affected / exposed	1 / 13 (7.69%)	3 / 370 (0.81%)	
occurrences (all)	1	3	
Emphysema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 13 (7.69%)	17 / 370 (4.59%)	
occurrences (all)	2	19	
Pleural effusion			
subjects affected / exposed	1 / 13 (7.69%)	12 / 370 (3.24%)	
occurrences (all)	1	15	
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	12 / 370 (3.24%)	
occurrences (all)	1	14	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	29 / 370 (7.84%)	
occurrences (all)	0	29	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	27 / 370 (7.30%)	
occurrences (all)	0	31	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	27 / 370 (7.30%)	
occurrences (all)	0	31	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 13 (0.00%)	27 / 370 (7.30%)	
occurrences (all)	0	30	
Blood creatinine increased			
subjects affected / exposed	0 / 13 (0.00%)	53 / 370 (14.32%)	
occurrences (all)	0	67	
Inspiratory capacity decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	2 / 13 (15.38%)	44 / 370 (11.89%)	
occurrences (all)	2	47	
White blood cell count decreased			
subjects affected / exposed	1 / 13 (7.69%)	2 / 370 (0.54%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Stoma site haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 13 (0.00%)	22 / 370 (5.95%)	
occurrences (all)	0	26	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	20 / 370 (5.41%)	
occurrences (all)	1	23	

Dizziness			
subjects affected / exposed	2 / 13 (15.38%)	35 / 370 (9.46%)	
occurrences (all)	2	41	
Cognitive disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 13 (23.08%)	73 / 370 (19.73%)	
occurrences (all)	3	84	
Ear and labyrinth disorders			
Ear swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 13 (7.69%)	6 / 370 (1.62%)	
occurrences (all)	1	6	
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	47 / 370 (12.70%)	
occurrences (all)	1	57	
Ascites			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	3 / 13 (23.08%)	87 / 370 (23.51%)	
occurrences (all)	3	100	
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	56 / 370 (15.14%)	
occurrences (all)	0	79	
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	77 / 370 (20.81%)	
occurrences (all)	1	89	

Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	23 / 370 (6.22%)	
occurrences (all)	0	23	
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	82 / 370 (22.16%)	
occurrences (all)	0	121	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 13 (0.00%)	59 / 370 (15.95%)	
occurrences (all)	0	83	
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	87 / 370 (23.51%)	
occurrences (all)	1	114	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 13 (7.69%)	21 / 370 (5.68%)	
occurrences (all)	1	23	
Pollakiuria			
subjects affected / exposed	1 / 13 (7.69%)	16 / 370 (4.32%)	
occurrences (all)	1	16	
Haematuria			
subjects affected / exposed	0 / 13 (0.00%)	53 / 370 (14.32%)	
occurrences (all)	0	63	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 13 (7.69%)	42 / 370 (11.35%)	
occurrences (all)	1	42	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	54 / 370 (14.59%)	
occurrences (all)	0	74	
Pain in extremity			
subjects affected / exposed	0 / 13 (0.00%)	30 / 370 (8.11%)	
occurrences (all)	0	31	
Joint stiffness			
subjects affected / exposed	1 / 13 (7.69%)	3 / 370 (0.81%)	
occurrences (all)	1	3	
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	26 / 370 (7.03%)	
occurrences (all)	0	29	
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	20 / 370 (5.41%)	
occurrences (all)	0	22	
Neck pain			
subjects affected / exposed	1 / 13 (7.69%)	5 / 370 (1.35%)	
occurrences (all)	1	5	
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	47 / 370 (12.70%)	
occurrences (all)	1	55	
Vertebral lesion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	16 / 370 (4.32%)	
occurrences (all)	1	17	
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	19 / 370 (5.14%)	
occurrences (all)	0	23	
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	76 / 370 (20.54%)	
occurrences (all)	1	98	
Tooth infection			

subjects affected / exposed	1 / 13 (7.69%)	2 / 370 (0.54%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 13 (7.69%)	102 / 370 (27.57%)	
occurrences (all)	1	116	
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	19 / 370 (5.14%)	
occurrences (all)	0	19	
Hyperglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	37 / 370 (10.00%)	
occurrences (all)	1	51	
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	24 / 370 (6.49%)	
occurrences (all)	1	29	
Hypoalbuminaemia			
subjects affected / exposed	0 / 13 (0.00%)	19 / 370 (5.14%)	
occurrences (all)	0	26	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	41 / 370 (11.08%)	
occurrences (all)	0	53	
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	14 / 370 (3.78%)	
occurrences (all)	1	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2014	Amendment 1 revised text in the inclusion criteria section to clearly state that participants must be refractory to available or standard therapy for treatment of their bladder cancer to participate in the biomarker cut-point determination part of the study if they do not meet cisplatin-ineligible criteria. The amendment also revised the safety and tolerability objective to state that safety and tolerability will be evaluated in all subjects regardless of programmed cell death ligand 1(PD-L1) status.
16 March 2016	Amendment 2 added objectives for programmed cell death ligand 1 (PD-L1) positive and PD-L1 strongly positive populations and removed hypotheses testing. Revisions were made to the statistical methods to adjust for the removal of the hypotheses testing.
19 December 2017	Amendment 3 added guidelines for dose modification in the event of myocarditis and updated guidelines for several other conditions.
20 September 2019	Amendment 4 added language regarding the potential for participants to be enrolled in an extension study if one becomes available.
21 May 2021	Amendment 5 updated the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported