Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab (MK-3475) in Combination With Epacadostat or Placebo in Subjects with Unresectable or Metastatic Melanoma (KEYNOTE-252 / ECHO-301)

Summary

EudraCT number	2015-004991-31
Trial protocol	SE NL DK IE ES PL FR BE GB IT
Global end of trial date	16 August 2019

Results information

Result version number	v1 (current)
This version publication date	15 August 2020
First version publication date	15 August 2020

Trial information

Trial identification

Sponsor protocol code	INCB24360-301/MK3475-252/Keynote252

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02752074
WHO universal trial number (UTN)	-
Other trial identifiers	INCB24360-301: Study ID

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cut-Off, Wilmington,, United States, 19803
Public contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.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	16 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression-free survival (PFS) of the combination of pembrolizumab and epacadostat versus pembrolizumab and placebo (i.e. 2 treatment groups) based on RECIST 1.1 by independent central review; and To compare overall survival (OS) of the 2 treatment groups.

Protection of trial subjects:

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below. -Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake. -Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 60
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Chile: 38
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 29
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	South Africa: 42
Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 10

Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Sweden: 31
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	France: 91
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Ireland: 8
Worldwide total number of subjects	706
EEA total number of subjects	326

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)	376
From 65 to 84 years	317
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 135 centers in 23 countries

Pre-assignment

Screening details:

This study was conducted at one hundred and thirty-five (135) centers, screened 928 participants and 706 participants enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Epacadostat

Arm description:

Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Epacadostat will be administered orally daily starting at Day 1 (Week 1).

Arm type	Experimental
Investigational medicinal product name	Epacadostat
Investigational medicinal product code	
Other name	INCB024360
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Epacadostat will be administered orally daily starting at Day 1 (Week 1) for a maximum duration of treatment(35 infusions)

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

Dosage and administration details:

Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1) for a maximum duration treatment (35 infusions)

Arm title	Pembrolizumab + Placebo

Arm description:

Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Placebo will be administered orally daily starting at Day 1 (Week 1).

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo will be administered orally daily starting at Day 1 (Week 1) for a maximum duration of

treatment(35 infusions)

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

Dosage and administration details:

Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1) for a maximum duration of treatment (35 infusions).

Number of subjects in period 1	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo
Started	354	352
Treated	353	352
Completed	198	209
Not completed	156	143
Consent withdrawn by subject	9	10
Deaths	146	129
Lost to follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Epacadostat
Reporting group description:	
Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Epacadostat will be administered orally daily starting at Day 1 (Week 1).	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Placebo will be administered orally daily starting at Day 1 (Week 1).	

Reporting group values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo	Total
Number of subjects	354	352	706
Age Categorical Units:			
< 65 years	183	193	376
≥ 65 years	171	159	330
Age continuous Units: years			
arithmetic mean	61.4	61.6	
standard deviation	± 13.9	± 13.7	-
Sex: Female, Male Units:			
Female	137	146	283
Male	217	206	423
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	36	27	63
Not Hispanic or Latino	302	306	608
Unknown or Not Reported	16	19	35
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	40	36	76
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	311	315	626
More than one race	2	1	3
Unknown or Not Reported	1	0	1
Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
Fully active	261	267	528
Restricted in physically strenuous activity	93	85	178

End points

End points reporting groups

Reporting group title	Pembrolizumab + Epacadostat
Reporting group description:	
Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Epacadostat will be administered orally daily starting at Day 1 (Week 1).	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Placebo will be administered orally daily starting at Day 1 (Week 1).	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
Progression-free survival, defined as the time from date of randomization until the earliest date of disease progression, as determined by independent central review of objective radiographic disease assessments per RECIST 1.1, or death from any cause, whichever comes first.	
End point type	Primary
End point timeframe:	
Assessed every 9 weeks for duration of study participation which is estimated to be 24 months	

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	352		
Units: months				
median (confidence interval 95%)	4.7 (2.9 to 6.8)	4.9 (2.9 to 6.8)		

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Pembrolizumab + Placebo v Pembrolizumab + Epacadostat
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.51711 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.21

Notes:

[1] - One-sided p-value based on log-rank test.

Primary: Overall survival (OS) rate at 6 months

End point title	Overall survival (OS) rate at 6 months

End point description:

Defined as time from date of randomization to date of death due to any cause. OS was calculated using product-limit (Kaplan-Meier) method for censored data.

End point type	Primary

End point timeframe:

Assessed every 9 weeks of study participation which is estimated to be 24 months. The OS rate at Month 6 was calculated.

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	352		
Units: percent probability				
median (confidence interval 95%)	84.1 (79.8 to 87.5)	87.2 (83.2 to 90.3)		

Statistical analyses

Statistical analysis title	Progession Free Survival
Comparison groups	Pembrolizumab + Epacadostat v Pembrolizumab + Placebo
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.80666 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.49

Notes:

[2] - One-sided p-value based on log-rank test.

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Objective response rate (ORR) is defined as the percentage of the participants in the analysis population who have a confirmed complete response (CR) or partial response (PR) based on RECIST 1.1 by independent central review.

End point type	Secondary

End point timeframe:

Assessed every 9 weeks for duration of study participation which is estimated to be 24 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	352		
Units: Number of participants	121	111		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability, as assessed by percentage of participants with adverse events

End point title	Safety and tolerability, as assessed by percentage of participants with adverse events

End point description:

Safety and tolerability, as assessed by percentage of participants with adverse events and changes in laboratory parameters.

End point type	Secondary

End point timeframe:

Through up to 90 days after end of treatment, up to 27 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	352		
Units: Number of participants				
With one or more adverse events	346	345		
Serious adverse events	99	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Defined as the time from the earliest date of qualifying response until earliest date of disease progression, per RECIST v1.1, or death from any cause, whichever comes first. Includes participants with complete response or partial response.

End point type	Secondary

End point timeframe:

Assessed every 9 weeks for duration of study participation which is estimated to be 24 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[3]	352[4]		
Units: months				
median (full range (min-max))	0.0 (0.0 to 14.7)	0.0 (0.0 to 15.0)		

Notes:

[3] - Median not reached

[4] - Median not reached

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent oral clearance (CL/F) of epacadostat

End point title	Apparent oral clearance (CL/F) of epacadostat[5]

End point description:

Defined as oral dose clearance.

End point type	Secondary

End point timeframe:

Through up to 30 days after the end of treatment, up to 25 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There is no hypothesis testing for this endpoint , descriptive analysis is provided.

End point values	Pembrolizumab + Epacadostat			
Subject group type	Reporting group			
Number of subjects analysed	340			
Units: Liter/hour (L/h)				
arithmetic mean (standard deviation)	59.8 (± 17.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution (Vd/F) of epacadostat

End point title	Apparent volume of distribution (Vd/F) of epacadostat[6]

End point description:

Apparent volume of distribution after administration.

End point type	Secondary

End point timeframe:

Through up to 30 days after the end of treatment, up to 25 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There is no hypothesis testing for this endpoint , descriptive analysis is provided.

End point values	Pembrolizumab + Epacadostat			
Subject group type	Reporting group			
Number of subjects analysed	340			
Units: Liter				
arithmetic mean (standard deviation)	139 (± 22.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of pembrolizumab

End point title	Clearance (CL) of pembrolizumab

End point description:

End point type	Secondary

End point timeframe:

Through up to 30 days after the end of treatment, up to 25 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: L/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - No data displayed because Outcome Measure has zero total analyzed

[8] - No data displayed because Outcome Measure has zero total analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution (V) of pembrolizumab

End point title	Volume of distribution (V) of pembrolizumab

End point description:

End point type	Secondary

End point timeframe:

Through up to 30 days after the end of treatment, up to 25 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Liter				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - No data displayed because Outcome Measure has zero total analyzed

[10] - No data displayed because Outcome Measure has zero total analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Formation of anti-pembrolizumab antibodies

End point title	Formation of anti-pembrolizumab antibodies

End point description:

Evaluate the measurement of anti-drug antibodies (ADA).

End point type	Secondary

End point timeframe:

Through up to 30 days after the end of treatment, up to 25 months

End point values	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: ng/ml				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - No data displayed because Outcome Measure has zero total analyzed

[12] - No data displayed because Outcome Measure has zero total analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 27 months.	
Adverse event reporting additional description: All Subjects as Treated (ASaT): All participants who were enrolled and took at least 1 dose of study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Pembrolizumab + Epacadostat
Reporting group description: Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Epacadostat will be administered orally daily starting at Day 1 (Week 1).	
Reporting group title	Pembrolizumab + Placebo
Reporting group description: Pembrolizumab will be administered intravenously every 3 weeks starting at Day 1 (Week 1). Placebo will be administered orally daily starting at Day 1 (Week 1).	

Serious adverse events	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 353 (28.05%)	100 / 352 (28.41%)	
number of deaths (all causes)	147	136	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 353 (0.57%)	4 / 352 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	3 / 353 (0.85%)	3 / 352 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the gastrointestinal			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular thyroid cancer			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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			
Asthenia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 353 (0.57%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			
subjects affected / exposed	1 / 353 (0.28%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	4 / 353 (1.13%)	3 / 352 (0.85%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 353 (0.57%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 353 (0.57%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 353 (1.42%)	3 / 352 (0.85%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 353 (0.57%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary infarction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	2 / 353 (0.57%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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			
Infusion related reaction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 353 (0.00%)	5 / 352 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 353 (0.28%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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			
Anaemia			
subjects affected / exposed	1 / 353 (0.28%)	4 / 352 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 353 (0.57%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			

subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	4 / 353 (1.13%)	5 / 352 (1.42%)	
occurrences causally related to treatment / all	3 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 353 (2.55%)	4 / 352 (1.14%)	
occurrences causally related to treatment / all	3 / 11	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 353 (0.28%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 353 (0.85%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 353 (0.57%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis exfoliative			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 353 (0.28%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen planus			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 353 (0.57%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 353 (0.57%)	3 / 352 (0.85%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	4 / 353 (1.13%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 353 (0.28%)	3 / 352 (0.85%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 353 (0.57%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dupuytren's contracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			

Cellulitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocanaliculitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 353 (1.42%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 353 (0.57%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	0 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 353 (0.00%)	2 / 352 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 352 (0.28%)	
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	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	1 / 353 (0.28%)	0 / 352 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pembrolizumab + Epacadostat	Pembrolizumab + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	327 / 353 (92.63%)	325 / 352 (92.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 353 (7.65%)	21 / 352 (5.97%)	
occurrences (all)	38	29	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	68 / 353 (19.26%)	46 / 352 (13.07%)	
occurrences (all)	99	67	
Fatigue			
subjects affected / exposed	100 / 353 (28.33%)	94 / 352 (26.70%)	
occurrences (all)	124	126	
Oedema peripheral			

subjects affected / exposed	27 / 353 (7.65%)	27 / 352 (7.67%)	
occurrences (all)	36	30	
Pyrexia			
subjects affected / exposed	46 / 353 (13.03%)	38 / 352 (10.80%)	
occurrences (all)	60	53	
Influenza like Illness			
subjects affected / exposed	17 / 353 (4.82%)	22 / 352 (6.25%)	
occurrences (all)	21	33	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	73 / 353 (20.68%)	63 / 352 (17.90%)	
occurrences (all)	93	86	
Dyspnoea			
subjects affected / exposed	22 / 353 (6.23%)	29 / 352 (8.24%)	
occurrences (all)	28	31	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 353 (5.38%)	14 / 352 (3.98%)	
occurrences (all)	21	15	
Insomnia			
subjects affected / exposed	35 / 353 (9.92%)	31 / 352 (8.81%)	
occurrences (all)	39	33	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	39 / 353 (11.05%)	25 / 352 (7.10%)	
occurrences (all)	43	30	
Amylase increased			
subjects affected / exposed	27 / 353 (7.65%)	34 / 352 (9.66%)	
occurrences (all)	38	42	
Aspartate aminotransferase increased			
subjects affected / exposed	36 / 353 (10.20%)	33 / 352 (9.38%)	
occurrences (all)	44	37	
Lipase increased			
subjects affected / exposed	36 / 353 (10.20%)	39 / 352 (11.08%)	
occurrences (all)	62	59	
Weight decreased			

subjects affected / exposed	22 / 353 (6.23%)	17 / 352 (4.83%)	
occurrences (all)	22	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	33 / 353 (9.35%)	32 / 352 (9.09%)	
occurrences (all)	38	45	
Headache			
subjects affected / exposed	66 / 353 (18.70%)	74 / 352 (21.02%)	
occurrences (all)	121	114	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 353 (9.92%)	36 / 352 (10.23%)	
occurrences (all)	43	40	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	37 / 353 (10.48%)	37 / 352 (10.51%)	
occurrences (all)	47	43	
Abdominal pain upper			
subjects affected / exposed	24 / 353 (6.80%)	16 / 352 (4.55%)	
occurrences (all)	24	19	
Constipation			
subjects affected / exposed	58 / 353 (16.43%)	62 / 352 (17.61%)	
occurrences (all)	78	68	
Diarrhoea			
subjects affected / exposed	90 / 353 (25.50%)	100 / 352 (28.41%)	
occurrences (all)	146	158	
Dry mouth			
subjects affected / exposed	19 / 353 (5.38%)	30 / 352 (8.52%)	
occurrences (all)	20	36	
Nausea			
subjects affected / exposed	103 / 353 (29.18%)	86 / 352 (24.43%)	
occurrences (all)	161	119	
Vomiting			
subjects affected / exposed	51 / 353 (14.45%)	44 / 352 (12.50%)	
occurrences (all)	81	65	
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	23 / 353 (6.52%)	23 / 352 (6.53%)	
occurrences (all)	26	23	
Pruritus			
subjects affected / exposed	83 / 353 (23.51%)	101 / 352 (28.69%)	
occurrences (all)	104	134	
Rash			
subjects affected / exposed	77 / 353 (21.81%)	81 / 352 (23.01%)	
occurrences (all)	105	97	
Rash maculo-papular			
subjects affected / exposed	21 / 353 (5.95%)	18 / 352 (5.11%)	
occurrences (all)	25	22	
Vitiligo			
subjects affected / exposed	51 / 353 (14.45%)	48 / 352 (13.64%)	
occurrences (all)	66	50	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	22 / 353 (6.23%)	27 / 352 (7.67%)	
occurrences (all)	23	27	
Hypothyroidism			
subjects affected / exposed	44 / 353 (12.46%)	35 / 352 (9.94%)	
occurrences (all)	50	37	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	63 / 353 (17.85%)	63 / 352 (17.90%)	
occurrences (all)	95	96	
Back pain			
subjects affected / exposed	47 / 353 (13.31%)	52 / 352 (14.77%)	
occurrences (all)	54	67	
Myalgia			
subjects affected / exposed	26 / 353 (7.37%)	32 / 352 (9.09%)	
occurrences (all)	29	38	
Pain in extremity			
subjects affected / exposed	32 / 353 (9.07%)	28 / 352 (7.95%)	
occurrences (all)	46	34	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	50 / 353 (14.16%)	50 / 352 (14.20%)	
occurrences (all)	74	61	
Upper respiratory tract infection			
subjects affected / exposed	19 / 353 (5.38%)	33 / 352 (9.38%)	
occurrences (all)	21	45	
Urinary tract infection			
subjects affected / exposed	20 / 353 (5.67%)	32 / 352 (9.09%)	
occurrences (all)	28	41	
Influenza			
subjects affected / exposed	19 / 353 (5.38%)	17 / 352 (4.83%)	
occurrences (all)	22	20	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	55 / 353 (15.58%)	44 / 352 (12.50%)	
occurrences (all)	57	57	
Hyperglycaemia			
subjects affected / exposed	23 / 353 (6.52%)	17 / 352 (4.83%)	
occurrences (all)	42	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported