Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of Pembrolizumab plus Ipilimumab vs Pembrolizumab plus Placebo in Previously Untreated, Stage IV, Metastatic Non-small Cell Lung Cancer Subjects Whose Tumors are PD-L1 Positive (TPS 50%) (KEYNOTE-598)

Summary

EudraCT number	2016-004364-20
Trial protocol	IE LV DE GB HU ES FR PL IT
Global end of trial date	07 September 2022

Results information

Result version number	v1 (current)
This version publication date	31 August 2023
First version publication date	31 August 2023

Trial information

Trial identification

Sponsor protocol code	3475-598

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03302234
WHO universal trial number (UTN)	-
Other trial identifiers	KEYNOTE-598: Merck

Notes:

Sponsors

Sponsor organisation name	Merck
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme 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	07 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2020
Global end of trial reached?	Yes
Global end of trial date	07 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the efficacy of pembrolizumab given in combination with either ipilimumab or placebo as first-line treatment in participants with metastatic non-small cell lung cancer (NSCLC). The primary hypothesis of this study is that overall survival (OS) and/or progression-free survival (PFS) is prolonged in participants who receive pembrolizumab and ipilimumab compared to those who receive pembrolizumab and placebo.

With Amendment 6 (effective date: 11-Dec-2020), active participants, investigator, and sponsor personnel or delegate(s) involved in the treatment administration or clinical evaluation of the participants will be unblinded. Participants will discontinue ipilimumab and placebo and participants who remain on treatment will receive open-label pembrolizumab only.

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	14 December 2014
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	Argentina: 22
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Chile: 31
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Mexico: 11

Country: Number of subjects enrolled	Peru: 12
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 21
Country: Number of subjects enrolled	Turkey: 99
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	568
EEA total number of subjects	205

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)	281
From 65 to 84 years	284
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 568 participants randomized to the study, 563 received at least one dose of study treatment (All Treated Population) and were evaluable for all safety analysis.

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 + Ipilimumab

Arm description:

Participants received 200 mg of pembrolizumab by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus 1 mg/kg of ipilimumab by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued ipilimumab and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

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

Dosage and administration details:

Administered as an IV infusion every 6 weeks (Q6W)

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:

Administered as an intravenous (IV) infusion every 3 weeks (Q3W)

Arm title	Pembrolizumab + Placebo

Arm description:

Participants received 200 mg of pembrolizumab by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus placebo by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal saline solution administered as an IV infusion Q6W

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:

Administered as an IV infusion Q3W

Number of subjects in period 1	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo
Started	284	284
Completed	0	0
Not completed	284	284
Adverse event, serious fatal	191	192
Consent withdrawn by subject	2	2
Not Reported	1	-
Sponsor Decision	90	89
Laryngeal Carcinoma	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Ipilimumab
Reporting group description:	
Participants received 200 mg of pembrolizumab by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus 1 mg/kg of ipilimumab by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued ipilimumab and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Participants received 200 mg of pembrolizumab by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus placebo by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).	

Reporting group values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo	Total
Number of subjects	284	284	568
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	63.7	64.5	
standard deviation	± 9.3	± 8.8	-
Sex/Gender, Customized Units: Participants			
Male	202	191	393
Female	82	92	174
Undifferentiated	0	1	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	3	7
Asian	33	31	64

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	218	223	441
More than one race	6	5	11
Unknown or Not Reported	22	22	44
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	54	37	91
Not Hispanic or Latino	208	225	433
Unknown or Not Reported	22	22	44
Tumor histology Units: Subjects			
Squamous	77	81	158
Non squamous	207	203	410
Geographic region Units: Subjects			
East Asia	32	31	63
Non-East Asia	252	253	505
Eastern Cooperative Oncology Group (ECOG) performance status Units: Subjects			
0 = Fully active; no performance restrictions	101	104	205
1 = Limited activity, ambulant, can-do light work	183	180	363

End points

End points reporting groups

Reporting group title	Pembrolizumab + Ipilimumab

Reporting group description:

Participants received 200 mg of pembrolizumab by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus 1 mg/kg of ipilimumab by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued ipilimumab and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Reporting group title	Pembrolizumab + Placebo

Reporting group description:

Participants received 200 mg of pembrolizumab by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus placebo by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis were censored at the date of last known contact. The median survival (in months) and the associated 95% confidence intervals (CIs) were reported using Kaplan-Meier method was used. Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and predominant tumor history (squamous versus non-squamous) was used to estimate hazard ratio (HR) and 95% CIs for first course study treatment per protocol. The analysis population included all randomized participants.

End point type	Primary

End point timeframe:

Up to approximately 32 months (through data cut-off date: 01 Sep 2020)

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Months				
median (confidence interval 95%)	21.4 (16.6 to 9999)	21.9 (18.0 to 9999)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Comparison groups	Pembrolizumab + Ipilimumab v Pembrolizumab + Placebo
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.74156 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.37

Notes:

[1] - One-sided p-value based on log-rank test stratified by ECOG, geographic region of the enrolling site, and predominant tumor history.

Primary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR)

End point title	Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR)

End point description:

PFS was defined as time from randomization to first documented disease progression (PD) per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. PD was defined as ≥20% increase in sum of diameters of target lesions. In addition to relative increase of 20%, sum must also demonstrate an absolute increase of ≥5 mm. Appearance of one or more new lesions was also considered PD. RECIST 1.1 was modified to follow maximum of 10 target lesions and maximum of 5 target lesions per organ. The median survival and 95% CIs were reported using Kaplan-Meier method. Cox regression model with Efron's method of tie handling with treatment as covariate stratified by ECOG performance status (0 vs. 1), geographic region of enrolling site (East Asia vs. non-East Asia), and predominant tumor history (squamous vs. non-squamous) was used to estimate HR and 95% CIs for first course study treatment per protocol. The analysis population included all randomized participants.

End point type	Primary

End point timeframe:

Up to approximately 32 months (through data cut-off date 01 Sep 2020)

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Months				
median (confidence interval 95%)	8.2 (6.0 to 10.5)	8.4 (6.3 to 10.5)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Comparison groups	Pembrolizumab + Ipilimumab v Pembrolizumab + Placebo
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7172
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.3

Secondary: Objective Response Rate (ORR) per RECIST 1.1 Based on BICR

End point title	Objective Response Rate (ORR) per RECIST 1.1 Based on BICR

End point description:

ORR was defined as the percentage of participants who have a 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 by BICR. In this study, RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Per protocol the ORR was calculated using the Miettinen & Nurminen method stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and predominant tumor history (squamous versus non-squamous) for the first course of study treatment. The analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Up to approximately 32 months (data cut-off date 01 Sep 2020)

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Percentage of Participants				
number (confidence interval 95%)	45.4 (39.5 to 51.4)	45.4 (39.5 to 51.4)		

Statistical analyses

Statistical analysis title	ORR Difference in percentage
Comparison groups	Pembrolizumab + Ipilimumab v Pembrolizumab + Placebo

Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.50644
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentage
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	8.1

Secondary: Duration of Response (DOR) per RECIST 1.1 Based on BICR

End point title	Duration of Response (DOR) per RECIST 1.1 Based on BICR

End point description:

For participants who demonstrated confirmed CR (Disappearance of all target lesions) or confirmed PR (At least a 30% decrease in sum of diameters of target lesions) per RECIST 1.1, DOR was defined as time from first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as at least 20% increase in sum of diameters of target lesions. In addition to relative increase of 20%, sum must demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions was also considered PD. RECIST 1.1 was modified to follow maximum of 10 target lesions and maximum of 5 target lesions per organ. The DOR was calculated using product-limit (Kaplan-Meier) method for censored data. Per protocol, the DOR for all participants who experienced a CR or PR was presented for the first course of study treatment. The analysis population included all randomized participants with confirmed complete response or partial response.

End point type	Secondary

End point timeframe:

Up to approximately 32 months (data cut-off date 01 Sep 2020)

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: Months				
median (confidence interval 95%)	16.1 (12.7 to 26)	17.3 (14.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to True Deterioration (TTD) in Cough, Pain in Chest, and Shortness of Breath

End point title	Time to True Deterioration (TTD) in Cough, Pain in Chest, and Shortness of Breath

End point description:

TTD was defined as the time to the first onset of a 10-point or greater score deterioration from baseline in any one of the 3 symptoms (cough, pain in chest or shortness of breath), confirmed by a second adjacent 10-point or greater score deterioration from baseline. Cough was based on EORTC QLQ-LC13 question 1, pain in chest was based on EORTC QLQ-LC13 question 10, and shortness of breath was based on EORTC QLQ-C30 question 8. Per protocol, TTD was reported for first course study treatment. The analysis population included all participants randomized who received at least one dose of study treatment and had at least one EORTC QLQ-LC13 and EORTC QLQ-C30 available.

End point type	Secondary

End point timeframe:

Up to approximately 32 months (data cut-off date 01 Sep 2020)

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	270		
Units: Months				
median (confidence interval 95%)	9999 (12.9778 to 9999)	20.0416 (12.7149 to 9999)		

Statistical analyses

Statistical analysis title	TTD Hazard Ratio
Comparison groups	Pembrolizumab + Ipilimumab v Pembrolizumab + Placebo
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9112
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9815
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7386
upper limit	1.3042

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

End point title	Number of Participants Who Experienced an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether or not considered related to the medicinal product or protocol specified procedure. Per protocol, the number of participants who

experienced an AE were reported for the first course of study treatment and follow up. The analysis population included all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 27 months

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	281		
Units: Participants	272	263		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE

End point title	Number of Participants Who Discontinued Study Treatment Due to an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether or not considered related to the medicinal product or protocol specified procedure. Per protocol, the number of participants who discontinued study treatment due to an AE were reported for the first course of study treatment. The analysis population included all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 24 months

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	281		
Units: Participants	105	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)

Global Health Status/Quality of Life (Items 29 and 30) Scale Score to Week 18

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Scale Score to Week 18

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. Participant responses to the questions "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" were scored on a 7-point scale (1= Very poor to 7=Excellent). Using linear transformation, raw scores were standardized, so that scores range from 0 to 100. A higher score indicates a better overall health status. Per protocol, the change from baseline in EORTC QLQ-C30 Items 29 and 30 combined score were presented for first course study treatment. The analysis population included all randomized participants who received at least one dose of study treatment and had at least one EORTC QLQ-C30 assessment available.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + Ipilimumab	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279	280		
Units: Score on a scale				
least squares mean (confidence interval 95%)	3.72 (0.91 to 6.53)	4.14 (1.42 to 6.86)		

Statistical analyses

Statistical analysis title	Difference in LS means
Comparison groups	Pembrolizumab + Ipilimumab v Pembrolizumab + Placebo
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8151
Method	cLDA Model
Parameter estimate	Difference in LS Means
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.96
upper limit	3.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 92 months

Adverse event reporting additional description:

All-cause mortality was reported on all randomized participants. AEs were reported on participants who received atleast 1 dose of treatment. MedDRA preferred terms Neoplasm progression, Malignant neoplasm progression & Disease progression not related to drug were excluded. No participants were eligible for Pembrolizumab+Ipilimumab (2nd course) arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Pembrolizumab+Ipilimumab (First Course)

Reporting group description:

Participants received 200 mg of pembrolizumab by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus 1 mg/kg of ipilimumab by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued ipilimumab and participants who remained on treatment received open-label pembrolizumab only. Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Reporting group title	Pembrolizumab + Placebo (Second Course)

Reporting group description:

Eligible participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) or who attained complete response (CR) but experienced progression of disease (PD), initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Reporting group title	Pembrolizumab+Placebo (First Course)

Reporting group description:

Participants received 200 mg of pembrolizumab by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment plus placebo by IV infusion on Day 1 of each 6-week cycle for up to 18 cycles of treatment. Per Amendment (AM) 6, (effective date: 11-Dec-2020), participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only.

Serious adverse events	Pembrolizumab+Ipilimumab (First Course)	Pembrolizumab + Placebo (Second Course)	Pembrolizumab+Placebo (First Course)
Total subjects affected by serious adverse events			
subjects affected / exposed	146 / 282 (51.77%)	4 / 18 (22.22%)	114 / 281 (40.57%)
number of deaths (all causes)	191	4	188
number of deaths resulting from adverse events	5	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paraneoplastic syndrome			

subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infected neoplasm			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine carcinoma			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angiopathy			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	4 / 281 (1.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 4
Fatigue			
subjects affected / exposed	4 / 282 (1.42%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	2 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 282 (1.77%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related hypersensitivity reaction			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 282 (1.42%)	0 / 18 (0.00%)	6 / 281 (2.14%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	5 / 282 (1.77%)	0 / 18 (0.00%)	5 / 281 (1.78%)
occurrences causally related to treatment / all	4 / 6	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated lung disease			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 282 (1.42%)	0 / 18 (0.00%)	3 / 281 (1.07%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	20 / 282 (7.09%)	0 / 18 (0.00%)	10 / 281 (3.56%)
occurrences causally related to treatment / all	18 / 20	0 / 0	8 / 10
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 282 (1.77%)	0 / 18 (0.00%)	10 / 281 (3.56%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 5
Pulmonary granuloma			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Respiratory failure			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	3 / 281 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Weight decreased			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skull fracture			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ilium fracture			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	3 / 282 (1.06%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 282 (0.00%)	1 / 18 (5.56%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Autoimmune pericarditis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	4 / 282 (1.42%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	4 / 281 (1.42%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			

subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Autoimmune encephalopathy			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysaesthesia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 282 (0.00%)	2 / 18 (11.11%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebral ischaemia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory disturbance			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmoplegia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	3 / 282 (1.06%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	7 / 282 (2.48%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	9 / 10	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	6 / 282 (2.13%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	4 / 6	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal discomfort			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Inguinal hernia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland calculus			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			

subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis migration			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestatic liver injury			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	5 / 282 (1.77%)	0 / 18 (0.00%)	3 / 281 (1.07%)
occurrences causally related to treatment / all	4 / 5	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Myositis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic fasciitis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral lesion			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Adrenalitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 282 (1.06%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 282 (0.00%)	1 / 18 (5.56%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cellulitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			

subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	3 / 282 (1.06%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	3 / 281 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	21 / 282 (7.45%)	0 / 18 (0.00%)	20 / 281 (7.12%)
occurrences causally related to treatment / all	2 / 24	0 / 0	1 / 24
deaths causally related to treatment / all	0 / 6	0 / 0	0 / 3
Pneumonia aspiration			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	3 / 281 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	3 / 282 (1.06%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	4 / 282 (1.42%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombophlebitis septic			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	2 / 281 (0.71%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			

subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 282 (0.00%)	0 / 18 (0.00%)	1 / 281 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	2 / 282 (0.71%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 282 (0.35%)	0 / 18 (0.00%)	0 / 281 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pembrolizumab+Ipilimumab (First Course)	Pembrolizumab + Placebo (Second Course)	Pembrolizumab+Placebo (First Course)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	251 / 282 (89.01%)	10 / 18 (55.56%)	232 / 281 (82.56%)
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 282 (8.51%)	0 / 18 (0.00%)	12 / 281 (4.27%)
occurrences (all)	29	0	13

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	34 / 282 (12.06%)	0 / 18 (0.00%)	27 / 281 (9.61%)
occurrences (all)	40	0	34
Oedema peripheral			
subjects affected / exposed	24 / 282 (8.51%)	0 / 18 (0.00%)	13 / 281 (4.63%)
occurrences (all)	31	0	14
Chest pain			
subjects affected / exposed	15 / 282 (5.32%)	1 / 18 (5.56%)	27 / 281 (9.61%)
occurrences (all)	15	1	31
Asthenia			
subjects affected / exposed	51 / 282 (18.09%)	0 / 18 (0.00%)	44 / 281 (15.66%)
occurrences (all)	66	0	60
Fatigue			
subjects affected / exposed	47 / 282 (16.67%)	1 / 18 (5.56%)	50 / 281 (17.79%)
occurrences (all)	66	1	58
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	2 / 281 (0.71%)
occurrences (all)	1	1	2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 282 (1.06%)	1 / 18 (5.56%)	1 / 281 (0.36%)
occurrences (all)	3	1	1
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	9 / 282 (3.19%)	0 / 18 (0.00%)	18 / 281 (6.41%)
occurrences (all)	9	0	20
Lung infiltration			
subjects affected / exposed	0 / 282 (0.00%)	1 / 18 (5.56%)	0 / 281 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	13 / 282 (4.61%)	1 / 18 (5.56%)	24 / 281 (8.54%)
occurrences (all)	15	1	27
Dyspnoea			

subjects affected / exposed	44 / 282 (15.60%)	0 / 18 (0.00%)	44 / 281 (15.66%)
occurrences (all)	49	0	51
Cough			
subjects affected / exposed	47 / 282 (16.67%)	1 / 18 (5.56%)	58 / 281 (20.64%)
occurrences (all)	53	1	77
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 282 (2.84%)	1 / 18 (5.56%)	16 / 281 (5.69%)
occurrences (all)	10	1	19
Insomnia			
subjects affected / exposed	18 / 282 (6.38%)	0 / 18 (0.00%)	23 / 281 (8.19%)
occurrences (all)	23	0	24
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 282 (13.12%)	1 / 18 (5.56%)	15 / 281 (5.34%)
occurrences (all)	44	1	15
Blood alkaline phosphatase increased			
subjects affected / exposed	20 / 282 (7.09%)	0 / 18 (0.00%)	12 / 281 (4.27%)
occurrences (all)	22	0	13
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	1 / 281 (0.36%)
occurrences (all)	1	1	1
Blood creatinine increased			
subjects affected / exposed	16 / 282 (5.67%)	1 / 18 (5.56%)	16 / 281 (5.69%)
occurrences (all)	22	2	22
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 282 (0.71%)	1 / 18 (5.56%)	3 / 281 (1.07%)
occurrences (all)	8	2	4
Alanine aminotransferase increased			
subjects affected / exposed	31 / 282 (10.99%)	1 / 18 (5.56%)	20 / 281 (7.12%)
occurrences (all)	41	1	26
Blood phosphorus decreased			
subjects affected / exposed	0 / 282 (0.00%)	1 / 18 (5.56%)	4 / 281 (1.42%)
occurrences (all)	0	1	5
C-reactive protein increased			

subjects affected / exposed	4 / 282 (1.42%)	1 / 18 (5.56%)	1 / 281 (0.36%)
occurrences (all)	4	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 282 (3.19%)	1 / 18 (5.56%)	10 / 281 (3.56%)
occurrences (all)	9	1	12
Weight decreased			
subjects affected / exposed	29 / 282 (10.28%)	1 / 18 (5.56%)	26 / 281 (9.25%)
occurrences (all)	33	1	29
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	5 / 281 (1.78%)
occurrences (all)	1	1	5
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 282 (4.96%)	0 / 18 (0.00%)	18 / 281 (6.41%)
occurrences (all)	14	0	20
Amnesia			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	2 / 281 (0.71%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 282 (14.18%)	1 / 18 (5.56%)	40 / 281 (14.23%)
occurrences (all)	50	1	57
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 282 (0.71%)	1 / 18 (5.56%)	0 / 281 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	51 / 282 (18.09%)	0 / 18 (0.00%)	40 / 281 (14.23%)
occurrences (all)	67	0	51
Inguinal hernia			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	0 / 281 (0.00%)
occurrences (all)	1	1	0
Dry mouth			

subjects affected / exposed	15 / 282 (5.32%)	1 / 18 (5.56%)	18 / 281 (6.41%)
occurrences (all)	17	1	19
Diarrhoea			
subjects affected / exposed	70 / 282 (24.82%)	1 / 18 (5.56%)	46 / 281 (16.37%)
occurrences (all)	105	1	74
Constipation			
subjects affected / exposed	39 / 282 (13.83%)	0 / 18 (0.00%)	52 / 281 (18.51%)
occurrences (all)	46	0	57
Vomiting			
subjects affected / exposed	30 / 282 (10.64%)	0 / 18 (0.00%)	27 / 281 (9.61%)
occurrences (all)	44	0	35
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	15 / 282 (5.32%)	0 / 18 (0.00%)	18 / 281 (6.41%)
occurrences (all)	15	0	18
Dermatitis			
subjects affected / exposed	8 / 282 (2.84%)	1 / 18 (5.56%)	7 / 281 (2.49%)
occurrences (all)	12	1	8
Skin lesion			
subjects affected / exposed	3 / 282 (1.06%)	1 / 18 (5.56%)	1 / 281 (0.36%)
occurrences (all)	4	1	2
Rash			
subjects affected / exposed	57 / 282 (20.21%)	0 / 18 (0.00%)	45 / 281 (16.01%)
occurrences (all)	78	0	63
Psoriasis			
subjects affected / exposed	1 / 282 (0.35%)	1 / 18 (5.56%)	3 / 281 (1.07%)
occurrences (all)	1	1	3
Pruritus			
subjects affected / exposed	69 / 282 (24.47%)	0 / 18 (0.00%)	58 / 281 (20.64%)
occurrences (all)	99	0	78
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	43 / 282 (15.25%)	1 / 18 (5.56%)	34 / 281 (12.10%)
occurrences (all)	48	1	37
Hypophysitis			

subjects affected / exposed	8 / 282 (2.84%)	1 / 18 (5.56%)	2 / 281 (0.71%)
occurrences (all)	8	1	3
Hyperthyroidism			
subjects affected / exposed	25 / 282 (8.87%)	1 / 18 (5.56%)	18 / 281 (6.41%)
occurrences (all)	26	1	26
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	18 / 282 (6.38%)	1 / 18 (5.56%)	21 / 281 (7.47%)
occurrences (all)	22	1	25
Back pain			
subjects affected / exposed	31 / 282 (10.99%)	0 / 18 (0.00%)	29 / 281 (10.32%)
occurrences (all)	36	0	34
Arthralgia			
subjects affected / exposed	39 / 282 (13.83%)	1 / 18 (5.56%)	45 / 281 (16.01%)
occurrences (all)	46	1	55
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 282 (3.90%)	0 / 18 (0.00%)	15 / 281 (5.34%)
occurrences (all)	20	0	19
Upper respiratory tract infection			
subjects affected / exposed	13 / 282 (4.61%)	0 / 18 (0.00%)	16 / 281 (5.69%)
occurrences (all)	14	0	17
Nasopharyngitis			
subjects affected / exposed	7 / 282 (2.48%)	0 / 18 (0.00%)	15 / 281 (5.34%)
occurrences (all)	8	0	16
Cystitis			
subjects affected / exposed	5 / 282 (1.77%)	1 / 18 (5.56%)	4 / 281 (1.42%)
occurrences (all)	6	1	5
COVID-19			
subjects affected / exposed	2 / 282 (0.71%)	1 / 18 (5.56%)	4 / 281 (1.42%)
occurrences (all)	2	1	4
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	7 / 282 (2.48%)	1 / 18 (5.56%)	7 / 281 (2.49%)
occurrences (all)	7	1	9
Hyponatraemia			

subjects affected / exposed	18 / 282 (6.38%)	1 / 18 (5.56%)	14 / 281 (4.98%)
occurrences (all)	22	1	19
Hypomagnesaemia			
subjects affected / exposed	8 / 282 (2.84%)	1 / 18 (5.56%)	11 / 281 (3.91%)
occurrences (all)	13	1	14
Hypokalaemia			
subjects affected / exposed	22 / 282 (7.80%)	0 / 18 (0.00%)	16 / 281 (5.69%)
occurrences (all)	30	0	28
Hypoalbuminaemia			
subjects affected / exposed	18 / 282 (6.38%)	0 / 18 (0.00%)	6 / 281 (2.14%)
occurrences (all)	21	0	6
Hyperuricaemia			
subjects affected / exposed	8 / 282 (2.84%)	1 / 18 (5.56%)	7 / 281 (2.49%)
occurrences (all)	17	1	14
Hyperphosphataemia			
subjects affected / exposed	5 / 282 (1.77%)	1 / 18 (5.56%)	3 / 281 (1.07%)
occurrences (all)	9	1	3
Decreased appetite			
subjects affected / exposed	61 / 282 (21.63%)	0 / 18 (0.00%)	39 / 281 (13.88%)
occurrences (all)	73	0	44
Hyperglycaemia			
subjects affected / exposed	17 / 282 (6.03%)	0 / 18 (0.00%)	16 / 281 (5.69%)
occurrences (all)	25	0	25
Hyperkalaemia			
subjects affected / exposed	11 / 282 (3.90%)	0 / 18 (0.00%)	18 / 281 (6.41%)
occurrences (all)	15	0	29

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2017	The major changes of amendment (AM) 1 were to provide details on rationale for the study and use of study treatments and changes to eligibility criteria.
11 January 2018	The major change of AM2 was to add background information on rationale for dose and regimen of ipilimumab.
11 April 2018	The major changes of AM3 were to add an exploratory objective to evaluate the immunogenicity, exposure, anti-drug antibodies (ADA), and pharmacokinetic (PK) samples, addition of thyroid and adrenal (ACTH) function monitoring prior to each dose of ipilimumab/placebo and changes to exclusion criteria.
25 February 2020	The major changes of AM4 were to update the timing of interim and final analyses, add futility rules, add enough time for survival follow up, and update sample size.
24 July 2020	The major changes of AM5 were addition of a secondary objective of evaluation of change in global health status/quality of life score from European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)-C30 (Items 29 and 30) and update the timing of interim and final analyses. Questionnaire (EORTC QLQ)-C30 (items 29 and 30).
29 December 2020	The major change of AM6 was to remove the ipilimumab and matching placebo from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported