Clinical trial results:
A Phase 3, randomized, double-blind trial of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) in participants with treatment-naïve, metastatic nonsmall cell lung cancer (NSCLC) whose tumors have a tumor proportion score (TPS) greater than or equal to 1% (LEAP-007)

Summary

EudraCT number	2018-003794-98
Trial protocol	EE HU PL IT
Global end of trial date	24 April 2024

Results information

Result version number	v1 (current)
This version publication date	11 April 2025
First version publication date	11 April 2025

Trial information

Trial identification

Sponsor protocol code	7902-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03829332
WHO universal trial number (UTN)	-
Other trial identifiers	Eisai Protocol Number: E7080-G000-314, MSD: LEAP-007, APIC-CTI: 194670

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.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	24 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2021
Global end of trial reached?	Yes
Global end of trial date	24 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety and efficacy of pembrolizumab (MK-3475) combined with lenvatinib (MK-7902/E7080) compared to pembrolizumab alone (with placebo for lenvatinib) in treatment-naïve adults with no prior systemic therapy for their metastatic non-small cell lung cancer (NSCLC) whose tumors have a programmed cell death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) greater than or equal to 1%.
The primary study hypotheses are that: 1) the combination of pembrolizumab and lenvatinib is superior to pembrolizumab alone as assessed by Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); and 2) the combination of pembrolizumab and lenvatinib is superior to pembrolizumab alone as assessed by Overall Survival (OS).

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	13 March 2019
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: 5
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	China: 80
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 31
Country: Number of subjects enrolled	Malaysia: 36
Country: Number of subjects enrolled	Mexico: 41
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Russian Federation: 38

Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Türkiye: 43
Country: Number of subjects enrolled	Ukraine: 65
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	623
EEA total number of subjects	159

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)	279
From 65 to 84 years	341
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 623 total participants randomized in the MK-7902-007 global study, 80 were also randomized in the China extension study for MK-7902-007 (NCT04676412).

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Lenvatinib

Arm description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	MK-7902 E7080 LENVIMA®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity.

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:

200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years)

Arm title	Pembrolizumab + Placebo

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

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

Dosage and administration details:

oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity

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:

200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years)

Number of subjects in period 1	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo
Started	309	314
Treated	309	312
Completed	0	0
Not completed	309	314
Physician decision	1	-
Consent withdrawn by subject	11	9
Death	225	230
Sponsor Decision	71	72
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Lenvatinib
Reporting group description:	
Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.	
Reporting group title	Pembrolizumab + Placebo
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.	

Reporting group values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo	Total
Number of subjects	309	314	623
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	64.6	65.4	
standard deviation	± 9.6	± 8.8	-
Sex: Female, Male Units: Participants			
Female	79	90	169
Male	230	224	454
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	7	3	10
Asian	103	104	207
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	188	193	381
More than one race	3	3	6
Unknown or Not Reported	8	10	18
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	32	30	62
Not Hispanic or Latino	266	269	535
Unknown or Not Reported	11	15	26
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Randomization of participants in the study was stratified by an ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).			
Units: Subjects			
ECOG = 0	110	108	218
ECOG = 1	199	206	405
Programmed Cell Death Ligand 1 (PD-L1) Status at Baseline			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Randomization of participants in the study was stratified by PD-L1 tumor proportion score (TPS) at baseline (1-49% or ≥ 50%). Higher percentages of PD-L1 TPS staining correspond to higher positivity of PD-L1 on a tumor.			
Units: Subjects			
TPS = 1-49%	172	175	347
TPS = ≥ 50%	137	139	276
Geographic Region			
Randomization of participants in this study was stratified by geographic region of the enrolling site (East Asia or non-East Asia).			
Units: Subjects			
East Asia	103	104	207
Non-East Asia	206	210	416

End points

End points reporting groups

Reporting group title	Pembrolizumab + Lenvatinib

Reporting group description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

Reporting group title	Pembrolizumab + Placebo

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

Primary: Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

PFS was defined as the time from date of randomization to the date of the first documentation of progressive disease (PD) or death from any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Data are from the product-limit (Kaplan-Meier) method for censored data. PFS as assessed by blinded independent central review (BICR) per RECIST 1.1 was presented. The analysis population consisted of all randomized participants.

End point type	Primary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	314		
Units: Months				
median (confidence interval 95%)	6.6 (6.1 to 8.2)	4.2 (4.1 to 6.2)		

Statistical analyses

Statistical analysis title	Hazard Ratio

Statistical analysis description:

Hazard ratio (HR) and 95% confidence interval (CI) were calculated using 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 baseline PD-L1 Status (1% to 49% versus >=50%).

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00624
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.95

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from date of randomization to date of death from any cause. OS was presented. The analysis population consisted of all randomized participants.

End point type	Primary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	314		
Units: Months				
median (confidence interval 95%)	14.1 (11.4 to 19.0)	16.4 (12.6 to 20.6)		

Statistical analyses

Statistical analysis title	Hazard Ratio

Statistical analysis description:

HR and 95% CI were calculated using 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 baseline PD-L1 Status (1% to 49% versus >=50%).

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo

Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.79744
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.39

Secondary: Change from Baseline in European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core30 (QLQ-C30) Combined Global Health Status/Quality of Life (Items 29 & 30) Scale Combined Score

End point title	Change from Baseline in European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core30 (QLQ-C30) Combined Global Health Status/Quality of Life (Items 29 & 30) Scale Combined Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall quality of life (QoL) of cancer patients. Participant responses to questions regarding Global Health Status (GHS; "How would you rate your overall health during the past week?") and QoL ("How would you rate your overall quality of life during the past week?") are scored on a 7-point scale (1= Very poor to 7=Excellent). The combined score of GHS (Item 29) and QoL (Item 30) is computed by averaging the raw scores of the 2 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. Per protocol, the change from baseline in GHS and QoL combined score was presented. All randomized participants who have received at least one dose of the study intervention and had at least one EORTC QLQ-C30 assessment data available for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	308		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.48 (-4.09 to 1.13)	2.42 (-0.24 to 5.08)		

Statistical analyses

Statistical analysis title	Difference in LS Means
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo

Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0262
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.34
upper limit	-0.47

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

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

End point description:

An AE was any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who discontinued study treatment due to an AE were reported. The analysis population consisted of all randomized participants.

End point type	Secondary

End point timeframe:

Through last dose of study treatment (Up to approximately 24 months)

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	312		
Units: Participants	98	41		

Statistical analyses

No statistical analyses for this end point

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 any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who experienced an AE were reported. The analysis population consisted of all randomized participants.

End point type	Secondary

End point timeframe:

Through 90 days post last dose of study treatment (Up to approximately 27 months)

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	312		
Units: Participants	306	294		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

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

End point description:

ORR was defined as the percentage of participants in the analysis population 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. ORR as assessed by BICR per RECIST 1.1 is presented. The analysis population consisted of all randomized participants.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	314		
Units: Percentage of Participants				
number (confidence interval 95%)	40.5 (34.9 to 46.2)	27.7 (22.8 to 33.0)		

Statistical analyses

Statistical analysis title	Percent Difference

Statistical analysis description:

Percent difference and 95% CI were calculated using Miettinen & Nurminen method stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and baseline PD-L1 Status (1% to 49% versus >=50%).

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo

Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00037
Method	Stratified Miettinen & Nurminen
Parameter estimate	Percent Difference
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	20.1

Secondary: Change from Baseline in Dyspnea (EORTC QLQ-C30 Item 8) Score

End point title	Change from Baseline in Dyspnea (EORTC QLQ-C30 Item 8) Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to the question: "Were you short of breath?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-C30 dyspnea (Item 8) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 8 assessment data available.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	308		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.35 (-4.75 to 2.04)	-0.47 (-3.94 to 3.00)		

Statistical analyses

Statistical analysis title	Difference in LS Means
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7088
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.49
upper limit	3.74

Secondary: Change from Baseline in Cough (EORTC Quality of Life Questionnaire-Lung Cancer Module 13 [QLQ-LC13] Item 31) Score

End point title	Change from Baseline in Cough (EORTC Quality of Life Questionnaire-Lung Cancer Module 13 [QLQ-LC13] Item 31) Score

End point description:

The EORTC QLQ-LC13 is a lung cancer-specific supplemental questionnaire used in combination with the EORTC QLQ-C30. Participant responses to the question "How much did you cough?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in cough (EORTC QLQ-LC13 Item 31) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 31 assessment data available.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	307		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-9.53 (-12.94 to -6.13)	-5.04 (-8.51 to -1.57)		

Statistical analyses

Statistical analysis title	Difference in LS Means
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0461 [1]
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.91
upper limit	-0.08

Notes:

[1] - Two-sided p-value based on cLDA model with covariates for treatment by study visit interaction; stratified by ECOG, region & baseline PDL-1.

Secondary: Change from Baseline in Chest Pain (EORTC QLQ-LC13 Item 40) Score

End point title	Change from Baseline in Chest Pain (EORTC QLQ-LC13 Item 40) Score

End point description:

The EORTC QLQ-LC13 is a lung cancer-specific supplemental questionnaire used in combination with the EORTC QLQ-C30. Participant responses to the question "Have you had pain in your chest?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-LC13 chest pain (Item 40) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 40 assessment data available.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	307		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-4.64 (-7.45 to -1.84)	-3.55 (-6.42 to -0.68)		

Statistical analyses

Statistical analysis title	Difference in LS Means
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5596
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.78
upper limit	2.59

Secondary: Change from Baseline in Physical Functioning (EORTC QLQ-C30 Items 1-5) Score

End point title	Change from Baseline in Physical Functioning (EORTC QLQ-C30

	Items 1-5) Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to 5 questions about their physical functioning (Items 1 to 5) are scored on a 4-point scale (1=Not at All to 4=Very Much). The combined score of items 1 to 5 was computed by averaging the raw scores of the 5 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-C30 physical functioning (Items 1-5) combined score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Items 1-5 assessment data available.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	308		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-6.73 (-9.35 to -4.10)	-3.72 (-6.40 to -1.04)		

Statistical analyses

Statistical analysis title	Difference in LS Means
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1116
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.71
upper limit	0.7

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-LC13 Chest Pain (Item 40) Scale Score

End point title	Time to True Deterioration (TTD) in EORTC QLQ-LC13 Chest Pain (Item 40) Scale Score

End point description:

EORTC QLQ-LC13 is a lung cancer specific questionnaire. Participant responses to the question: "Have you had pain in your chest?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0-100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change

(decrease) from baseline in cough (Item 40). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-LC13 Item 40 assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	294		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7457
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.56

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-LC13 Cough (Item 31) Scale Score

End point title	Time to True Deterioration (TTD) in EORTC QLQ-LC13 Cough (Item 31) Scale Score

End point description:

EORTC QLQ-LC13 is a lung cancer specific questionnaire. Participant responses to the question: "How much did you cough?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0-100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change (decrease) from baseline in cough (Item 31). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-LC13 Item assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	294		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0079
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.88

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-C30 Combined Global Health Status /Quality of Life (Items 29 & 30) Scale Combined Score

End point title	Time to True Deterioration (TTD) in EORTC QLQ-C30 Combined Global Health Status /Quality of Life (Items 29 & 30) Scale Combined Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess QoL of cancer patients. Participant responses to questions on GHS ("How would you rate your overall health during the past week?") and QoL ("How would you rate your overall QoL during the past week?") were scored on a 7-point scale (1= Very poor to 7=Excellent). The combined score of GHS (Item 29) and QoL (Item 30) was computed by averaging raw scores of the 2 items and applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change (decrease) from baseline in GHS-QoL combined score. A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 29 and Item 30 assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	297		
Units: Months				
median (confidence interval 95%)	9999 (14.1 to 9999)	9999 (19.3 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9601
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.33

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in the Composite Endpoint of Cough (EORTC QLQ-LC13 Item 31), Chest Pain (EORTC QLQ-LC13 Item 40), or Dyspnea (EORTC QLQ-C30 Item 8)

End point title	Time to True Deterioration (TTD) Based on Change from Baseline in the Composite Endpoint of Cough (EORTC QLQ-LC13 Item 31), Chest Pain (EORTC QLQ-LC13 Item 40), or Dyspnea (EORTC QLQ-C30 Item 8)

End point description:

The EORTC QLQ-C30 is a 30-item questionnaire developed to assess QoL of cancer patients, including a single-item scale score for dyspnea (Item 8; score range:1=Not at All to 4=Very Much). Used in combination with QLQ-C30, the EORTC QLQ-LC13 is a supplemental lung cancer-specific module, including a single-item scale score for cough (Item 31; score range:1=Not at All to 4=Very Much) and chest pain (Item 40, score range: 1=Not at All to 4=Very Much). The combined score was computed by averaging raw scores of all items; then applying a linear transformation to standardize average score. Combined scores range from 0-100. A higher score indicates a better outcome. TTD in the composite endpoint (Items 31, 40, & 8) scale score was presented, defined as time to first onset of a ≥10point. 9999 value indicates that no data were calculated. All randomized participants who received at least 1 dose of study treatment & have at least one EORTC-QLQ-C30 or QLQ-LC13 assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	55		
Units: Months				
median (confidence interval 95%)	5.78 (2.79 to 9999)	9999 (3.45 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4068
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.46

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-C30 Dyspnea (Item 8) Scale Score

End point title	Time to True Deterioration (TTD) in EORTC QLQ-C30 Dyspnea (Item 8) Scale Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to the question: "Were you short of breath?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change (decrease) from baseline in dyspnea (Item 8). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ Item 8 assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	297		
Units: Months				
arithmetic mean (confidence interval 95%)	9999 (9999 to 9999)	9999 (20.8 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8122
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.44

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score

End point title	Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to 5 questions about their physical functioning (Items 1 to 5) are scored on a 4-point scale (1=Not at All to 4=Very Much). The combined score of items 1 to 5 was computed by averaging the raw scores of the 5 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change (decrease) from baseline in physical functioning (Items 1 to 5). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Items 1-5 assessment data available.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	297		
Units: Months				
median (confidence interval 95%)	18.8 (14.1 to 9999)	9999 (20.0 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.148
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 61 months

Adverse event reporting additional description:

All-cause mortality includes all randomized participants (n=623). Adverse events (AEs) include all randomized participants who received ≥1 dose of study drug. Cancer disease progression was not an AE unless study related. MedDRA terms neoplasm progression, malignant neoplasm progression & disease progression unrelated to study drug were excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo + Pembrolizumab
Reporting group description: -	
Reporting group title	Lenvatinib + Pembrolizumab

Reporting group description: -

Serious adverse events	Placebo + Pembrolizumab	Lenvatinib + Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 312 (37.82%)	192 / 309 (62.14%)	
number of deaths (all causes)	232	229	
number of deaths resulting from adverse events	23	60	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenoma			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin angiosarcoma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tumour necrosis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Embolism arterial			

subjects affected / exposed	2 / 312 (0.64%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous thrombosis limb			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 312 (0.64%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	1 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	0 / 312 (0.00%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	1 / 312 (0.32%)	13 / 309 (4.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 13	
deaths causally related to treatment / all	1 / 1	0 / 13	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial fistula			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchospasm			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 312 (1.92%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory disease			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 312 (0.96%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 312 (0.64%)	9 / 309 (2.91%)	
occurrences causally related to treatment / all	0 / 2	7 / 9	
deaths causally related to treatment / all	0 / 0	4 / 6	
Immune-mediated lung disease			
subjects affected / exposed	5 / 312 (1.60%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 312 (1.92%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 312 (0.96%)	7 / 309 (2.27%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	1 / 1	2 / 2	
Pneumothorax			
subjects affected / exposed	1 / 312 (0.32%)	7 / 309 (2.27%)	
occurrences causally related to treatment / all	0 / 1	3 / 7	
deaths causally related to treatment / all	0 / 0	1 / 4	
Pulmonary embolism			
subjects affected / exposed	8 / 312 (2.56%)	7 / 309 (2.27%)	
occurrences causally related to treatment / all	2 / 8	5 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 1	2 / 2	
Pulmonary oedema			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 312 (0.32%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Organising pneumonia			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 312 (0.32%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 312 (0.32%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	2 / 312 (0.64%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation time prolonged			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
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 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal fracture			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
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	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Bradycardia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac tamponade			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac ventricular thrombosis			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 312 (0.96%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	3 / 312 (0.96%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 312 (0.00%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune-mediated myocarditis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 312 (0.32%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelination			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypersomnia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (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 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	4 / 312 (1.28%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 312 (0.00%)	8 / 309 (2.59%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 312 (0.32%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	2 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 312 (0.64%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal pseudo-obstruction			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 312 (0.32%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
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 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 312 (0.00%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatosis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated dermatitis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion inflammation			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vancomycin infusion reaction			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
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	3 / 312 (0.96%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	2 / 312 (0.64%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
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			
Myalgia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Connective tissue disorder			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue mass			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondyloarthropathy			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (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 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Empyema			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	4 / 312 (1.28%)	8 / 309 (2.59%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 4	
COVID-19			
subjects affected / exposed	1 / 312 (0.32%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	2 / 312 (0.64%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	17 / 312 (5.45%)	32 / 309 (10.36%)	
occurrences causally related to treatment / all	3 / 19	4 / 38	
deaths causally related to treatment / all	0 / 4	0 / 7	
Urinary tract infection			
subjects affected / exposed	0 / 312 (0.00%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 312 (0.00%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 312 (0.32%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	2 / 312 (0.64%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 312 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 312 (0.64%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 312 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 312 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	0 / 312 (0.00%)	7 / 309 (2.27%)	
occurrences causally related to treatment / all	0 / 0	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Pembrolizumab	Lenvatinib + Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	275 / 312 (88.14%)	296 / 309 (95.79%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	46 / 312 (14.74%)	122 / 309 (39.48%)	
occurrences (all)	52	150	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 312 (10.26%)	33 / 309 (10.68%)	
occurrences (all)	41	42	
Oedema peripheral			
subjects affected / exposed	18 / 312 (5.77%)	31 / 309 (10.03%)	
occurrences (all)	20	42	
Fatigue			
subjects affected / exposed	37 / 312 (11.86%)	44 / 309 (14.24%)	
occurrences (all)	40	58	
Chest pain			
subjects affected / exposed	15 / 312 (4.81%)	23 / 309 (7.44%)	
occurrences (all)	15	26	
Asthenia			
subjects affected / exposed	35 / 312 (11.22%)	57 / 309 (18.45%)	
occurrences (all)	37	86	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 312 (8.01%)	29 / 309 (9.39%)	
occurrences (all)	27	38	
Dysphonia			

subjects affected / exposed	4 / 312 (1.28%)	26 / 309 (8.41%)	
occurrences (all)	4	29	
Dyspnoea			
subjects affected / exposed	27 / 312 (8.65%)	34 / 309 (11.00%)	
occurrences (all)	29	36	
Haemoptysis			
subjects affected / exposed	27 / 312 (8.65%)	25 / 309 (8.09%)	
occurrences (all)	49	29	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 312 (4.17%)	17 / 309 (5.50%)	
occurrences (all)	13	18	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	32 / 312 (10.26%)	60 / 309 (19.42%)	
occurrences (all)	42	79	
Amylase increased			
subjects affected / exposed	10 / 312 (3.21%)	30 / 309 (9.71%)	
occurrences (all)	11	45	
Aspartate aminotransferase increased			
subjects affected / exposed	32 / 312 (10.26%)	62 / 309 (20.06%)	
occurrences (all)	49	89	
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 312 (5.45%)	35 / 309 (11.33%)	
occurrences (all)	29	47	
Blood creatinine increased			
subjects affected / exposed	19 / 312 (6.09%)	23 / 309 (7.44%)	
occurrences (all)	23	27	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	7 / 312 (2.24%)	24 / 309 (7.77%)	
occurrences (all)	11	29	
Lipase increased			
subjects affected / exposed	15 / 312 (4.81%)	29 / 309 (9.39%)	
occurrences (all)	18	50	
Platelet count decreased			

subjects affected / exposed	7 / 312 (2.24%)	32 / 309 (10.36%)	
occurrences (all)	11	46	
Weight decreased			
subjects affected / exposed	25 / 312 (8.01%)	83 / 309 (26.86%)	
occurrences (all)	27	98	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 312 (3.21%)	19 / 309 (6.15%)	
occurrences (all)	11	25	
Headache			
subjects affected / exposed	13 / 312 (4.17%)	28 / 309 (9.06%)	
occurrences (all)	13	40	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	68 / 312 (21.79%)	57 / 309 (18.45%)	
occurrences (all)	88	84	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 312 (13.46%)	70 / 309 (22.65%)	
occurrences (all)	76	116	
Diarrhoea			
subjects affected / exposed	39 / 312 (12.50%)	109 / 309 (35.28%)	
occurrences (all)	62	208	
Constipation			
subjects affected / exposed	44 / 312 (14.10%)	37 / 309 (11.97%)	
occurrences (all)	50	42	
Abdominal pain upper			
subjects affected / exposed	13 / 312 (4.17%)	24 / 309 (7.77%)	
occurrences (all)	13	27	
Abdominal pain			
subjects affected / exposed	6 / 312 (1.92%)	27 / 309 (8.74%)	
occurrences (all)	6	33	
Vomiting			
subjects affected / exposed	17 / 312 (5.45%)	35 / 309 (11.33%)	
occurrences (all)	26	56	
Stomatitis			

subjects affected / exposed	12 / 312 (3.85%)	52 / 309 (16.83%)	
occurrences (all)	12	71	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 312 (0.96%)	34 / 309 (11.00%)	
occurrences (all)	3	37	
Rash			
subjects affected / exposed	33 / 312 (10.58%)	44 / 309 (14.24%)	
occurrences (all)	37	57	
Pruritus			
subjects affected / exposed	29 / 312 (9.29%)	33 / 309 (10.68%)	
occurrences (all)	33	44	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	17 / 312 (5.45%)	22 / 309 (7.12%)	
occurrences (all)	25	30	
Proteinuria			
subjects affected / exposed	36 / 312 (11.54%)	101 / 309 (32.69%)	
occurrences (all)	55	169	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	35 / 312 (11.22%)	127 / 309 (41.10%)	
occurrences (all)	36	171	
Hyperthyroidism			
subjects affected / exposed	20 / 312 (6.41%)	30 / 309 (9.71%)	
occurrences (all)	25	35	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 312 (10.58%)	39 / 309 (12.62%)	
occurrences (all)	43	50	
Back pain			
subjects affected / exposed	24 / 312 (7.69%)	26 / 309 (8.41%)	
occurrences (all)	26	28	
Myalgia			
subjects affected / exposed	10 / 312 (3.21%)	17 / 309 (5.50%)	
occurrences (all)	10	20	

Pain in extremity			
subjects affected / exposed	14 / 312 (4.49%)	20 / 309 (6.47%)	
occurrences (all)	16	23	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	19 / 312 (6.09%)	25 / 309 (8.09%)	
occurrences (all)	33	39	
Pneumonia			
subjects affected / exposed	14 / 312 (4.49%)	27 / 309 (8.74%)	
occurrences (all)	15	28	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	51 / 312 (16.35%)	77 / 309 (24.92%)	
occurrences (all)	55	92	
Hyperglycaemia			
subjects affected / exposed	23 / 312 (7.37%)	25 / 309 (8.09%)	
occurrences (all)	30	39	
Hypoalbuminaemia			
subjects affected / exposed	20 / 312 (6.41%)	34 / 309 (11.00%)	
occurrences (all)	31	39	
Hypocalcaemia			
subjects affected / exposed	11 / 312 (3.53%)	24 / 309 (7.77%)	
occurrences (all)	12	31	
Hypokalaemia			
subjects affected / exposed	23 / 312 (7.37%)	28 / 309 (9.06%)	
occurrences (all)	28	34	
Hyponatraemia			
subjects affected / exposed	23 / 312 (7.37%)	37 / 309 (11.97%)	
occurrences (all)	29	49	
Hyperkalaemia			
subjects affected / exposed	12 / 312 (3.85%)	17 / 309 (5.50%)	
occurrences (all)	12	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2019	The major changes for amendment 1 (AM 1) were to add clarification for pharmacokinetic blood draws and added that complete urinalysis is required at screening and every 4 cycles.
09 August 2019	The major changes for AM2 included updates to contraception requirements for males and WOCBP. Male participants must agree to protocol-specific contraception during the intervention period and for at least 30 days after the last dose of lenvatinib/placebo. WOCBP must use a contraceptive method that is highly effective with low user dependency or be abstinent from heterosexual intercourse during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib/matching placebo, whichever occurs last.
16 January 2020	The major change for AM3 was to clarify that ECG is only required at EOT and safety follow up visits when lenvatinib/matching placebo is discontinued.
20 April 2021	The major change for AM5 was to remove collection of pembrolizumab and lenvatinib PK and pembrolizumab ADA sampling.
24 November 2021	The major change for AM6 included unblinding of the study and removing lenvatinib and matching placebo from the study, stopping collection of ePRO data and to add that the study will remain open to allow ongoing participants to continue treatment with open-label pembrolizumab monotherapy up to a maximum of 35 administrations.
13 December 2022	The major change for AM7 was to do the entity name change and update the address.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported