Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-controlled Trial of Pembrolizumab (MK-3475/SCH900475) in Combination with Etoposide/Platinum (Cisplatin or Carboplatin) for the First-line Treatment of Subjects with Extensive Stage Small Cell Lung Cancer (KEYNOTE-604)

Summary

EudraCT number	2016-004309-15
Trial protocol	DE GB ES PL FR HU
Global end of trial date	21 September 2021

Results information

Result version number	v1 (current)
This version publication date	22 September 2022
First version publication date	22 September 2022

Trial information

Trial identification

Sponsor protocol code	3475-604

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03066778
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: KEYNOTE-604, JAPIC-CTI: 173744

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@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2019
Global end of trial reached?	Yes
Global end of trial date	21 September 2021
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 plus standard of care (SOC) chemotherapy (etoposide/platinum [EP]) in participants with newly diagnosed extensive stage small cell lung cancer who have not previously received systemic therapy. The primary study hypotheses are that pembrolizumab+EP prolongs Progression-free Survival per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by blinded independent central review and Overall Survival compared with placebo+EP. In this study, RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. With protocol Amendment 07 (03-Oct-2018), the outcome measure of "Change from Baseline at Weeks 12 and 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale" was replaced with a single time point analysis at Week 18.

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	02 May 2017
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: 14
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 29
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Switzerland: 14

Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Turkey: 33
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	453
EEA total number of subjects	142

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)	216
From 65 to 84 years	237
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants in the pembrolizumab+EP arm were eligible to receive second course treatment with pembrolizumab if they met criteria for retreatment. Per protocol, response, progression, patient reported outcomes, or adverse events during second course did not count towards efficacy or safety outcome measures.

Pre-assignment

Screening details:

One participant who was randomized to pembrolizumab+EP was inadvertently treated with placebo+EP. For efficacy analyses this participant will be included in the arm they were initially randomized into and for safety analyses the participant will be included by treatment received.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab+EP

Arm description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Arm type	Experimental
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 pembrolizumab administered by intravenous (IV) infusion on Day 1 of each 21-day cycle prior to chemotherapy

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

Dosage and administration details:

100 mg/m^2 etoposide administered by IV infusion on Days 1, 2, and 3 of each 21-day cycle

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

Dosage and administration details:

area under the plasma drug concentration-time curve (AUC) 5 carboplatin administered by IV infusion on Day 1 of each 21-day cycle

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

Dosage and administration details:

75 mg/m^2 cisplatin administered by IV infusion on Day 1 of each 21-day cycle

Arm title	Placebo+EP

Arm description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1).

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

Dosage and administration details:

saline placebo administered by IV infusion on Day 1 of each 21-day cycle prior to chemotherapy

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

Dosage and administration details:

100 mg/m^2 etoposide administered by IV infusion on Days 1, 2, and 3 of each 21-day cycle

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

Dosage and administration details:

area under the plasma drug concentration-time curve (AUC) 5 carboplatin administered by IV infusion on Day 1 of each 21-day cycle

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

Dosage and administration details:

75 mg/m^2 cisplatin administered by IV infusion on Day 1 of each 21-day cycle

Number of subjects in period 1	Pembrolizumab+EP	Placebo+EP
Started	228	225
Treated	223	223
Received Second Course of Pembrolizumab	1 [1]	0 [2]
Completed	28	13
Not completed	200	212
Consent withdrawn by subject	5	7
Death	195	205

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is for added to account for the participant that received a second course of pembrolizumab after the the initial study course was completed.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is for added to account for the participant that received a second course of pembrolizumab after the the initial study course was completed.

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab+EP

Reporting group description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Reporting group title	Placebo+EP

Reporting group description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1).

Reporting group values	Pembrolizumab+EP	Placebo+EP	Total
Number of subjects	228	225	453
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	115	101	216
From 65-84 years	113	124	237
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	64.2	65.2	
standard deviation	± 8.4	± 8.2	-
Sex: Female, Male Units: Participants			
Female	76	83	159
Male	152	142	294
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	52	34	86
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	162	177	339
More than one race	0	1	1
Unknown or Not Reported	13	13	26

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	13	19
Not Hispanic or Latino	204	192	396
Unknown or Not Reported	18	20	38
Eastern Cooperative Oncology Group (ECOG) Performance Status			
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) was required for inclusion in the study and randomization was stratified by ECOG score.			
Units: Subjects			
ECOG = 0	60	56	116
ECOG = 1	168	169	337
Lactate Dehydrogenase (LDH) Status at Baseline			
Randomization of participants in the study was stratified by LDH measurement at baseline (≤ or > upper limit of normal).			
Units: Subjects			
LDH = ≤ Upper Limit of Normal	100	95	195
LDH = > Upper Limit of Normal	127	129	256
LDH Result Missing	1	1	2
Platinum Therapy Administered			
Randomization of participants was stratified by type of platinum therapy administered during the study.			
Units: Subjects			
Cisplatin	63	66	129
Carboplatin	161	156	317
Not Treated with Platinum Therapy	4	3	7

End points

End points reporting groups

Reporting group title	Pembrolizumab+EP

Reporting group description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Reporting group title	Placebo+EP

Reporting group description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1).

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

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

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD, as determined by RECIST 1.1, was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. 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. For this study, RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The PFS was calculated using the non-parametric Kaplan-Meier method (KM) for censored data and presented for the first course of study treatment per protocol.

End point type	Primary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	225		
Units: Months				
median (confidence interval 95%)	4.8 (4.3 to 5.4)	4.3 (4.2 to 4.5)		

Statistical analyses

Statistical analysis title	Hazard Ratio: Pembrolizumab+EP/Placebo+EP

Statistical analysis description:

Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by platinum chemotherapy, ECOG, and LDH

Comparison groups	Pembrolizumab+EP v Placebo+EP
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00069 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.88

Notes:

[1] - One-sided p-value based on log-rank test stratified by platinum chemotherapy, ECOG, and LDH

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the analysis were censored at the date of the last follow up. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The OS was calculated using the non-parametric Kaplan-Meier method for censored data and presented for the first course of study treatment per protocol.

End point type	Primary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	225		
Units: Months				
median (confidence interval 95%)	10.8 (9.2 to 12.9)	9.7 (8.6 to 10.7)		

Statistical analyses

Statistical analysis title	Hazard Ratio: Pembrolizumab+EP/Placebo+EP

Statistical analysis description:

Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by platinum chemotherapy, ECOG, and LDH

Comparison groups	Pembrolizumab+EP v Placebo+EP

Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01643 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.98

Notes:

[2] - One-sided p-value based on log-rank test stratified by platinum chemotherapy, ECOG, and LDH

Secondary: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point description:

ORR was defined as the percentage of participants who achieve a best objective response of complete response (CR) or partial response (PR) per RECIST 1.1. CR was defined as the disappearance of all target lesions. PR was defined as ≥30% decrease in the sum of diameters of target lesions taking as a reference the baseline sum diameters. In this study, RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The ORR was calculated using the Miettinen & Nurminen method stratified by type of platinum therapy (carboplatin or cisplatin), baseline ECOG performance status (0 or 1), and baseline LDH (≤ or > upper limit of normal) and presented for the first course of study treatment per protocol.

End point type	Secondary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	225		
Units: Percentage of Participants				
number (confidence interval 95%)	70.6 (64.2 to 76.4)	61.8 (55.1 to 68.2)		

Statistical analyses

Statistical analysis title	Percent Difference

Statistical analysis description:

Based on Miettinen & Nurminen method stratified by platinum chemotherapy, ECOG, and LDH. Cisplatin, ECOG 0, LDH ≤ULN and Cisplatin, ECOG 0, LDH >ULN were combined into one stratum because of small sample size

Comparison groups	Pembrolizumab+EP v Placebo+EP
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0227 [3]
Method	Miettinen & Nurminen
Parameter estimate	Percent Difference
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	17.4

Notes:

[3] - One-sided p-value for testing. H0: difference in percent = 0 versus H1: difference in percent >0

Secondary: Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

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

End point description:

DOR was defined as the time from first documented evidence of a CR or PR per RECIST 1.1 until first instance of PD per RECIST 1.1 or death of any cause. CR=disappearance of all target lesions. PR=≥30% decrease in the sum of diameters (SOD) of target lesions taking the baseline SOD as reference. PD=≥20% increase in SOD. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of ≥1 new lesions was also considered PD. RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population=all randomized participants who were included in the treatment group to which they were randomized and experienced a CR or PR. The DOR was calculated using the KM method for censored data and is presented for the first course of study treatment per protocol. 9999=median DOR and upper and lower limits not reached due to no progressive disease by time of last disease assessment.

End point type	Secondary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	139		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

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 defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have had a causal relationship with this treatment. An adverse event could be any unfavourable and unintended sign (i.e. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The analysis population consisted of all participants who received ≥1 dose of study treatment. The number of participants who experienced an AE was reported for each arm according to the treatment received and is presented for the first course of study treatment per protocol.

End point type	Secondary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Participants	223	222		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have had a causal relationship with this treatment. An adverse event could be any unfavourable and unintended sign (i.e. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The analysis population consisted of all participants who received ≥1 dose of study treatment. The number of participants who discontinued due to an AE was reported for each arm according to treatment received and is presented for the first course of study treatment per protocol.

End point type	Secondary

End point timeframe:

Up to approximately 26 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Participants	33	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Any Grade 3 to 5 Adverse Events (AE) as Assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03)

End point title	Number of Participants Experiencing Any Grade 3 to 5 Adverse Events (AE) as Assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03)

End point description:

The CTCAE uses Grades 1 through 5 correlating to AE severity criteria. Grade 1=mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2=moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Grade 3=severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4=life-threatening consequences; urgent intervention indicated. Grade 5=death related to AE. The analysis population consisted of all participants who received ≥1 dose of study treatment. The number of participants who experienced any Grade 3 to 5 AE was reported for each arm according to the treatment received and is presented for the first course of study treatment per protocol.

End point type	Secondary

End point timeframe:

Up to approximately 30.5 months

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Participants	175	172		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 18 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

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

End point description:

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Change from baseline scores were calculated using a constrained longitudinal data analysis model. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population=all participants who received ≥1 dose of study medication and had non-missing assessments at baseline and Week 18. Data are presented for the first course of study treatment per protocol.

End point type	Secondary

End point timeframe:

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 18

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	218		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	8.66 (5.26 to 12.06)	4.23 (0.93 to 7.52)		

Statistical analyses

Statistical analysis title	Difference in Least Square Means
Comparison groups	Pembrolizumab+EP v Placebo+EP
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Logrank
Parameter estimate	Difference in Least Square Means
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	8.66

Secondary: Change from Baseline at Week 12 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

End point title	Change from Baseline at Week 12 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

End point description:

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population included all participants who received ≥1 dose of treatment and had non-missing assessments at baseline and Week 12. Per protocol data were to be presented for the first course of study treatment.

End point type	Secondary

End point timeframe:

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 12

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	(to)		

Notes:

[4] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

[5] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

End point title	Change from Baseline at Week 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

End point description:

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population included all participants who received ≥1 dose of treatment and had non-missing assessments at baseline and Week 24. Per protocol, data were to be presented for the first course of study treatment.

End point type	Secondary

End point timeframe:

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 24

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	(to)		

Notes:

[6] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

[7] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to True Deterioration (TTD) in the Composite Endpoint of Cough, Chest Pain, and Dyspnea Using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Lung Cancer Module 13 (QLQ-LC13)

End point title	Time to True Deterioration (TTD) in the Composite Endpoint of Cough, Chest Pain, and Dyspnea Using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Lung Cancer Module 13 (QLQ-LC13)

End point description:

TTD in patient-reported lung cancer symptoms of cough (QLQ-LC-13 Item 1), chest pain (QLQ-LC-13 Item 10), and dyspnea (QLQ-C30 Item 8) was a composite endpoint defined as: time to first onset of ≥10 point deterioration from baseline in an item confirmed by a second adjacent ≥10 point deterioration. The QLQ-LC13 consists of 13 measures of lung cancer symptoms and side effects from chemotherapy/radiation scored on a 4-point scale (1=none, 2=a little, 3=quite a bit, 4=very much). Scores were transformed to a range of 0-100 using a standard algorithm. Higher scores represented increasing symptom severity. The analysis population=all participants who received ≥1 dose of study medication and had non-missing assessments. TTD was calculated using the product-limit KM method for censored data and is presented for the first course of study treatment per protocol. 9999=Median TTD, lower or upper limit not reached (no protocol-specified deterioration criteria reached by time of last assessment).

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1-9, Day 1 of every other cycle for Cycles 10-17 and 30 days after last dose of study treatment (Up to approximately 27 months)]

End point values	Pembrolizumab +EP	Placebo+EP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	218		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	8.7 (5.9 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio: Pembrolizumab+EP/Placebo+EP

Statistical analysis description:

Based on Cox regression model with treatment as a covariate stratified by platinum chemotherapy ECOG, and LDH. Cisplatin, ECOG 0, LDH ≤ULN and Cisplatin, ECOG 0, LDH >ULN were combined into one stratum because of small sample size

Comparison groups	Pembrolizumab+EP v Placebo+EP
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.208 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.14

Notes:

[8] - Two-sided p-value based on stratified log-rank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First Course: Up to 49.5 months; Second Course: Up to 37.9 months. First and second course dosing occurred concurrently

Adverse event reporting additional description:

All-cause mortality (ACM)=all randomized participants; AE=participants treated ≥1 dose. Per protocol, MedDRA terms neoplasm progression (NP), malignant NP, disease progression unrelated to treatment are excluded. ACM was adjusted for participant randomized to pembrolizumab+EP and treated with placebo+EP. AEs presented by actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Pembrolizumab+EP

Reporting group description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Reporting group title	Pembrolizumab Second Course

Reporting group description:

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

Reporting group title	Placebo+EP

Reporting group description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m^2 IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m^2 IV on Day 1).

Serious adverse events	Pembrolizumab+EP	Pembrolizumab Second Course	Placebo+EP
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 223 (49.78%)	1 / 1 (100.00%)	89 / 223 (39.91%)
number of deaths (all causes)	196	1	212
number of deaths resulting from adverse events	6	0	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	2 / 223 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraneoplastic syndrome			

subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	4 / 223 (1.79%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	0 / 4	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 4	0 / 0	3 / 3
Fatigue			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 223 (1.79%)	0 / 1 (0.00%)	2 / 223 (0.90%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	2 / 223 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoxia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	5 / 223 (2.24%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	5 / 5	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumothorax			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	5 / 223 (2.24%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	2 / 223 (0.90%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 2
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			

subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	4 / 223 (1.79%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			

subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cardiopulmonary failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limbic encephalitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 223 (0.00%)	1 / 1 (100.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 223 (3.14%)	0 / 1 (0.00%)	10 / 223 (4.48%)
occurrences causally related to treatment / all	6 / 7	0 / 0	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	15 / 223 (6.73%)	0 / 1 (0.00%)	14 / 223 (6.28%)
occurrences causally related to treatment / all	15 / 15	0 / 0	13 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	11 / 223 (4.93%)	0 / 1 (0.00%)	6 / 223 (2.69%)
occurrences causally related to treatment / all	10 / 11	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	5 / 223 (2.24%)
occurrences causally related to treatment / all	3 / 3	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Autoimmune uveitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Food poisoning			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subacute cutaneous lupus erythematosus			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 223 (2.24%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	4 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic bladder			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypopituitarism			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	3 / 3	0 / 0	1 / 1
Paracancerous pneumonia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	17 / 223 (7.62%)	0 / 1 (0.00%)	12 / 223 (5.38%)
occurrences causally related to treatment / all	3 / 20	0 / 0	3 / 13
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia haemophilus			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Serratia sepsis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			

subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	3 / 223 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 223 (1.35%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	2 / 223 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 223 (0.00%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	1 / 223 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	2 / 223 (0.90%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	4 / 223 (1.79%)	0 / 1 (0.00%)	5 / 223 (2.24%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 223 (0.45%)	0 / 1 (0.00%)	0 / 223 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pembrolizumab+EP	Pembrolizumab Second Course	Placebo+EP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	221 / 223 (99.10%)	1 / 1 (100.00%)	216 / 223 (96.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	10 / 223 (4.48%)
occurrences (all)	15	0	14
Hypotension			
subjects affected / exposed	9 / 223 (4.04%)	0 / 1 (0.00%)	16 / 223 (7.17%)
occurrences (all)	11	0	21
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	38 / 223 (17.04%)	0 / 1 (0.00%)	43 / 223 (19.28%)
occurrences (all)	46	0	48
Fatigue			
subjects affected / exposed	61 / 223 (27.35%)	0 / 1 (0.00%)	60 / 223 (26.91%)
occurrences (all)	76	0	78
Chest pain			
subjects affected / exposed	11 / 223 (4.93%)	0 / 1 (0.00%)	21 / 223 (9.42%)
occurrences (all)	11	0	24
Oedema peripheral			

subjects affected / exposed	17 / 223 (7.62%)	0 / 1 (0.00%)	26 / 223 (11.66%)
occurrences (all)	20	0	32
Pyrexia			
subjects affected / exposed	32 / 223 (14.35%)	0 / 1 (0.00%)	14 / 223 (6.28%)
occurrences (all)	37	0	17
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 223 (20.18%)	0 / 1 (0.00%)	45 / 223 (20.18%)
occurrences (all)	62	0	51
Dyspnoea			
subjects affected / exposed	37 / 223 (16.59%)	0 / 1 (0.00%)	37 / 223 (16.59%)
occurrences (all)	41	0	41
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 223 (11.21%)	0 / 1 (0.00%)	28 / 223 (12.56%)
occurrences (all)	26	0	34
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 223 (7.62%)	0 / 1 (0.00%)	21 / 223 (9.42%)
occurrences (all)	20	0	24
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 223 (8.52%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	22	0	15
Blood creatinine increased			
subjects affected / exposed	15 / 223 (6.73%)	0 / 1 (0.00%)	8 / 223 (3.59%)
occurrences (all)	23	0	8
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	6 / 223 (2.69%)
occurrences (all)	15	0	8
Weight decreased			
subjects affected / exposed	22 / 223 (9.87%)	0 / 1 (0.00%)	20 / 223 (8.97%)
occurrences (all)	24	0	23
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 223 (13.90%)	0 / 1 (0.00%)	15 / 223 (6.73%)
occurrences (all)	36	0	17

Headache			
subjects affected / exposed	29 / 223 (13.00%)	0 / 1 (0.00%)	34 / 223 (15.25%)
occurrences (all)	34	0	41
Dysgeusia			
subjects affected / exposed	14 / 223 (6.28%)	0 / 1 (0.00%)	12 / 223 (5.38%)
occurrences (all)	14	0	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	101 / 223 (45.29%)	0 / 1 (0.00%)	96 / 223 (43.05%)
occurrences (all)	122	0	115
Leukopenia			
subjects affected / exposed	49 / 223 (21.97%)	0 / 1 (0.00%)	45 / 223 (20.18%)
occurrences (all)	84	0	70
Neutropenia			
subjects affected / exposed	120 / 223 (53.81%)	0 / 1 (0.00%)	114 / 223 (51.12%)
occurrences (all)	217	0	207
Thrombocytopenia			
subjects affected / exposed	57 / 223 (25.56%)	0 / 1 (0.00%)	46 / 223 (20.63%)
occurrences (all)	85	0	80
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 223 (6.73%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	18	0	13
Constipation			
subjects affected / exposed	65 / 223 (29.15%)	0 / 1 (0.00%)	59 / 223 (26.46%)
occurrences (all)	78	0	69
Abdominal pain upper			
subjects affected / exposed	13 / 223 (5.83%)	0 / 1 (0.00%)	5 / 223 (2.24%)
occurrences (all)	14	0	5
Dyspepsia			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	7 / 223 (3.14%)
occurrences (all)	13	0	7
Dysphagia			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	6 / 223 (2.69%)
occurrences (all)	12	0	6
Diarrhoea			

subjects affected / exposed	46 / 223 (20.63%)	0 / 1 (0.00%)	41 / 223 (18.39%)
occurrences (all)	67	0	48
Nausea			
subjects affected / exposed	85 / 223 (38.12%)	0 / 1 (0.00%)	96 / 223 (43.05%)
occurrences (all)	135	0	144
Stomatitis			
subjects affected / exposed	14 / 223 (6.28%)	0 / 1 (0.00%)	15 / 223 (6.73%)
occurrences (all)	17	0	17
Vomiting			
subjects affected / exposed	36 / 223 (16.14%)	0 / 1 (0.00%)	39 / 223 (17.49%)
occurrences (all)	48	0	49
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	75 / 223 (33.63%)	0 / 1 (0.00%)	84 / 223 (37.67%)
occurrences (all)	77	0	87
Dry skin			
subjects affected / exposed	13 / 223 (5.83%)	0 / 1 (0.00%)	10 / 223 (4.48%)
occurrences (all)	13	0	10
Erythema			
subjects affected / exposed	13 / 223 (5.83%)	0 / 1 (0.00%)	4 / 223 (1.79%)
occurrences (all)	14	0	4
Pruritus			
subjects affected / exposed	25 / 223 (11.21%)	0 / 1 (0.00%)	18 / 223 (8.07%)
occurrences (all)	33	0	23
Rash			
subjects affected / exposed	30 / 223 (13.45%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	39	0	17
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	6 / 223 (2.69%)
occurrences (all)	12	0	7
Hypothyroidism			
subjects affected / exposed	26 / 223 (11.66%)	0 / 1 (0.00%)	5 / 223 (2.24%)
occurrences (all)	27	0	5
Inappropriate antidiuretic hormone secretion			

subjects affected / exposed	1 / 223 (0.45%)	1 / 1 (100.00%)	1 / 223 (0.45%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 223 (13.00%)	0 / 1 (0.00%)	19 / 223 (8.52%)
occurrences (all)	37	0	22
Back pain			
subjects affected / exposed	25 / 223 (11.21%)	0 / 1 (0.00%)	26 / 223 (11.66%)
occurrences (all)	27	0	27
Pain in extremity			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	15	0	16
Musculoskeletal chest pain			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	6 / 223 (2.69%)
occurrences (all)	14	0	6
Infections and infestations			
Pneumonia			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	13	0	14
Upper respiratory tract infection			
subjects affected / exposed	17 / 223 (7.62%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	22	0	16
Nasopharyngitis			
subjects affected / exposed	12 / 223 (5.38%)	0 / 1 (0.00%)	9 / 223 (4.04%)
occurrences (all)	15	0	9
Urinary tract infection			
subjects affected / exposed	10 / 223 (4.48%)	1 / 1 (100.00%)	8 / 223 (3.59%)
occurrences (all)	12	1	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	69 / 223 (30.94%)	0 / 1 (0.00%)	54 / 223 (24.22%)
occurrences (all)	85	0	68
Hypokalaemia			
subjects affected / exposed	15 / 223 (6.73%)	0 / 1 (0.00%)	13 / 223 (5.83%)
occurrences (all)	20	0	19
Hyponatraemia			

subjects affected / exposed occurrences (all)	21 / 223 (9.42%) 26	0 / 1 (0.00%) 0	16 / 223 (7.17%) 23

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2017	Amendment 1 corrected a typographical error in the numbering of the inclusion criteria.
14 March 2017	Amendment 2 corrected the timeframe associated with the exclusion criterion for major surgery.
17 April 2017	Amendment 3 removed the option to crossover from the placebo+ etoposide+platinum arm to pembrolizumab treatment after documentation of progressive disease.
06 July 2017	Amendment 4 removed the requirement for unblinding treatment assignment after documentation of progressive disease because the option to cross over to pembrolizumab was removed and, with it, the need to unblind.
11 September 2017	Amendment 5 clarified the exclusion criterion regarding study participation for participants with brain metastases.
21 December 2017	Amendment 6 updated the dose modification guidelines for pembrolizumab to include information regarding the treatment of myocarditis, revised the requirements for survival follow-up to allow for more frequent data collection, and added a Day 8 visit during Cycles 1 through 4 to allow for more frequent safety monitoring.
06 November 2018	Amendment 7 updated criteria for the first and second interim analyses to calendar time from the time the first patient was randomized to ensure sufficient follow-up time for PFS analyses and manage the gap between the first two interim analysis, changed the alpha spending strategy for PFS to calendar time to align with the interim analyses, and changed the alpha allocation between the primary (OS and PFS) and key secondary (ORR) hypothesis on the basis of accumulating external data on PFS and OS in immunotherapy-chemotherapy combinations in small cell lung cancer to allow more alpha to be allocated to the primary endpoints.
15 January 2019	Amendment 8 changed the alpha spending function for PFS analysis from Hwang Shih DeCani to Lan-DeMets O'Brien Fleming, the alpha spending approach was changed from time-based to information fraction-based spending, the assumption for median PFS in the control arm was changed to 4.3 months based on external data published from other clinical trials, and the power and efficacy bound calculations were updated to reflect the change in PFS median assumption and an alpha spending approach.
24 May 2019	Amendment 9 updated criteria for the final OS analysis to be a minimum of 294 events, or 31 months from study start, whichever occurs later to ensure sufficient follow-up time for the final OS analysis, added clarification to describe the alpha-spending strategy for PFS and OS in detail, and corrected a publishing error in Amendment 08.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported