Clinical trial results:
A Phase II Trial to Investigate Genetic Markers of Response to Pembrolizumab (MK-3475, SCH 900475) Combined with Chemotherapy as a First-line Treatment for Non-Small Cell Lung Cancer (KEYNOTE-782)

Summary

EudraCT number	2018-002598-22
Trial protocol	HU ES
Global end of trial date	05 November 2021

Results information

Result version number	v1 (current)
This version publication date	09 November 2022
First version publication date	09 November 2022

Trial information

Trial identification

Sponsor protocol code	3475-782

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03664024
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: KEYNOTE-782

Notes:

Sponsors

Sponsor organisation name	Merck Sharp and 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 and Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp and 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	05 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2021
Global end of trial reached?	Yes
Global end of trial date	05 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Participants with Stage IV nonsquamous non-small cell lung cancer (NSCLC) without prior systemic treatment will be treated with standard of care pembrolizumab combined with platinum-doublet chemotherapy for 4 cycles, then pembrolizumab plus pemetrexed maintenance for up to 31 additional cycles. The platinum doublet would be pemetrexed plus the investigator's choice of either cisplatin or carboplatin. The primary objective is to evaluate if total baseline tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA) is predictive of objective response per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by the investigator by estimating the level of association.

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	30 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	118
EEA total number of subjects	93

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)	60
From 65 to 84 years	57
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened in 5 countries for this study.

Period 1

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

Arms

Arm title	Pembrolizumab plus platinum-doublet chemotherapy

Arm description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg, Day 1 of each 21-day cycle (Q3W)

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m^2 every 3 weeks

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AUC 5 mg/mL/min, Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4). Investigator's choice of either cisplatin or carboplatin.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m^2, Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4). Investigator's choice of either cisplatin or carboplatin.

Number of subjects in period 1	Pembrolizumab plus platinum-doublet chemotherapy
Started	118
Treated	117
Completed	0
Not completed	118
Consent withdrawn by subject	2
Death	80
Follow-up discontinued by sponsor	34
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab plus platinum-doublet chemotherapy
Reporting group description:	
Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years.	

Reporting group values	Pembrolizumab plus platinum-doublet chemotherapy	Total	
Number of subjects	118	118	
Age categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	60	60	
From 65-84 years	57	57	
85 years and over	1	1	
Age Continuous Units: Years			
arithmetic mean	64.5		
standard deviation	± 9.1	-	
Sex: Female, Male Units: Participants			
Female	46	46	
Male	72	72	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	114	114	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	116	116	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Pembrolizumab plus platinum-doublet chemotherapy

Reporting group description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years.

Subject analysis set title	Pembrolizumab plus platinum-doublet chemotherapy overall
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years. This analysis set includes all responders and non-responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

Subject analysis set title	Pembrolizumab plus platinum-doublet chemotherapy responder
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years. Participants in this analysis set were considered responders if they had a complete or partial response. This analysis set is a subset of the overall arm and includes only responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

Subject analysis set title	Pembrolizumab plus platinum-doublet chemotherapy non-responder
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m^2 IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 IV infusion for up to 31 additional cycles up to ~2 years. Participants were considered non-responders if they did not have complete or partial response. This analysis set is a subset of the overall arm and includes only non-responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

Primary: Objective Response Rate

End point title	Objective Response Rate[1]

End point description:

Objective response rate is the proportion of participants who have a confirmed complete response (CR) or partial response (PR). Objective response rate is assessed by investigator review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants with an ORR is presented.

End point type	Primary

End point timeframe:

Up to ~25 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Pembrolizumab plus platinum-doublet chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Percentage of Participants				
number (confidence interval 95%)	40.2 (31.2 to 49.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA)

End point title	Tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA)[2]

End point description:

Cell-free ctDNA allows the exploration of tumor features from blood samples. TMB is a measure of mutational load in tumor cells and expressed as the number of somatic mutations per megabase (Mut/MB) of DNA. Participants with missing data are considered non-responders. The analysis population consisted of all participants who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis. The mean TMB in cell-free ctDNA of participants is presented.

End point type	Primary

End point timeframe:

Baseline (Day 1)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Pembrolizumab plus platinum-doublet chemotherapy overall	Pembrolizumab plus platinum-doublet chemotherapy responder	Pembrolizumab plus platinum-doublet chemotherapy non-responder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	101	42	59	
Units: Mut/MB				
arithmetic mean (standard deviation)	9 (± 11.6)	8 (± 8.3)	10 (± 13.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS is defined as the time from the start of treatment to death due to any cause. The analysis population consisted of all participants who received at least one dose of study intervention. The Kaplan-Meier estimate of median PFS using the product-limit (Kaplan-Meier) method for censored data is presented.

End point type	Secondary

End point timeframe:

Up to ~36 months

End point values	Pembrolizumab plus platinum-doublet chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Months				
median (confidence interval 95%)	18.1 (13.5 to 25.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from enrollment to the first documented disease progression or death due to any cause, whichever occurs first as assessed by investigator review according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The analysis population consisted of all participants who received at least one dose of study intervention. The Kaplan-Meier estimate of median PFS using the product-limit (Kaplan-Meier) method for censored data is presented.

End point type	Secondary

End point timeframe:

Up to ~36 months

End point values	Pembrolizumab plus platinum-doublet chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Months				
median (confidence interval 95%)	7.2 (5.6 to 9.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who experienced one or more adverse events (AEs)

End point title	Percentage of Participants who experienced one or more adverse events (AEs)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants who experienced an AE is presented.

End point type	Secondary

End point timeframe:

Up to ~31 months

End point values	Pembrolizumab plus platinum-doublet chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Percentage of Participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants discontinuing study intervention due to an AE.

End point title	Percentage of participants discontinuing study intervention due to an AE.

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants who discontinued the study intervention due to an AE is presented.

End point type	Secondary

End point timeframe:

Up to ~28 months

End point values	Pembrolizumab plus platinum-doublet chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: Percentage of Participants				
number (not applicable)	38.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For All-Cause Mortality: from allocation up to ~36 months. For AEs from start of treatment up to ~31 months.

Adverse event reporting additional description:

All-cause mortality: All allocated participants. AEs: All allocated participants who received at least 1 dose of study intervention. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Pembrolizumab + Pemetrexed + Platinum Agent

Reporting group description: -

Serious adverse events	Pembrolizumab + Pemetrexed + Platinum Agent		
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 117 (51.28%)		
number of deaths (all causes)	80		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			

subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	3 / 117 (2.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	2 / 2			
Pleural effusion				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				

Confusional state			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Troponin increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract stoma complication			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiotoxicity			

subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral ischaemia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar insufficiency				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	3 / 117 (2.56%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	3 / 117 (2.56%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Anaemia				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	5 / 117 (4.27%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	2 / 2		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	4 / 117 (3.42%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture malunion			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			

subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related bacteraemia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung abscess				

subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	11 / 117 (9.40%)			
occurrences causally related to treatment / all	3 / 13			
deaths causally related to treatment / all	0 / 2			
Pulmonary sepsis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory tract infection				
subjects affected / exposed	4 / 117 (3.42%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pembrolizumab + Pemetrexed + Platinum Agent		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 117 (97.44%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 117 (25.64%)		
occurrences (all)	46		
Chest pain			
subjects affected / exposed	7 / 117 (5.98%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	25 / 117 (21.37%)		
occurrences (all)	39		
Mucosal inflammation			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	16 / 117 (13.68%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	16 / 117 (13.68%)		
occurrences (all)	25		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 117 (10.26%)		
occurrences (all)	13		
Pneumonitis			

subjects affected / exposed	7 / 117 (5.98%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	17 / 117 (14.53%)		
occurrences (all)	20		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 117 (15.38%)		
occurrences (all)	33		
Amylase increased			
subjects affected / exposed	9 / 117 (7.69%)		
occurrences (all)	14		
Alanine aminotransferase increased			
subjects affected / exposed	20 / 117 (17.09%)		
occurrences (all)	32		
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	14 / 117 (11.97%)		
occurrences (all)	14		
Neutrophil count decreased			
subjects affected / exposed	7 / 117 (5.98%)		
occurrences (all)	8		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 117 (6.84%)		
occurrences (all)	10		
Blood creatinine increased			
subjects affected / exposed	17 / 117 (14.53%)		
occurrences (all)	30		
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	10		
Dysgeusia			

subjects affected / exposed	7 / 117 (5.98%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	9 / 117 (7.69%)		
occurrences (all)	10		
Neuropathy peripheral			
subjects affected / exposed	7 / 117 (5.98%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	72 / 117 (61.54%)		
occurrences (all)	109		
Leukopenia			
subjects affected / exposed	13 / 117 (11.11%)		
occurrences (all)	16		
Neutropenia			
subjects affected / exposed	29 / 117 (24.79%)		
occurrences (all)	50		
Thrombocytopenia			
subjects affected / exposed	17 / 117 (14.53%)		
occurrences (all)	23		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	14 / 117 (11.97%)		
occurrences (all)	14		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	21 / 117 (17.95%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	27 / 117 (23.08%)		
occurrences (all)	44		
Nausea			
subjects affected / exposed	36 / 117 (30.77%)		
occurrences (all)	44		
Vomiting			

subjects affected / exposed occurrences (all)	22 / 117 (18.80%) 27		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 6 / 117 (5.13%) 8 7 / 117 (5.98%) 13		
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	 9 / 117 (7.69%) 10		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all)	 14 / 117 (11.97%) 17 7 / 117 (5.98%) 8		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 6 / 117 (5.13%) 8 16 / 117 (13.68%) 22 12 / 117 (10.26%) 13		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Urinary tract infection	 7 / 117 (5.98%) 7 		

subjects affected / exposed occurrences (all)	13 / 117 (11.11%) 19		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 25 / 117 (21.37%) 26		
Hyperglycaemia subjects affected / exposed occurrences (all)	 21 / 117 (17.95%) 25		
Hypokalaemia subjects affected / exposed occurrences (all)	 8 / 117 (6.84%) 9		
Hypomagnesaemia subjects affected / exposed occurrences (all)	 6 / 117 (5.13%) 7		
Hypophosphataemia subjects affected / exposed occurrences (all)	 6 / 117 (5.13%) 9		
Hyponatraemia subjects affected / exposed occurrences (all)	 9 / 117 (7.69%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2019	Amendment one includes direction for re-consenting participants upon disease progression, moving the collection time point of one of the primary endpoint samples, and correcting errors in the Schedule of Activities.
30 September 2021	Amendment two includes instruction that allows participants to be enrolled in a pembrolizumab extension study upon study completion, add final analysis in the statistical analysis plan, and update the Sponsor's branding information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported