Clinical trial results:
A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)

Summary

EudraCT number	2017-004188-11
Trial protocol	SE ES FR DE GB IT
Global end of trial date	02 October 2023

Results information

Result version number	v1 (current)
This version publication date	10 October 2024
First version publication date	10 October 2024

Trial information

Trial identification

Sponsor protocol code	3475-789

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03515837
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp and Dohme LLC, ClinicalTrialsDisclosure@msd.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	02 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2023
Global end of trial reached?	Yes
Global end of trial date	02 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of pemetrexed plus platinum chemotherapy (carboplatin or cisplatin) with or without pembrolizumab (MK-3475; KEYTRUDA®) in the treatment of adults with the following types of tyrosine kinase inhibitor (TKI)-resistant, epidermal growth factor receptor (EGFR)-mutated, metastatic non-squamous non-small cell lung cancer (NSCLC) tumors: 1) TKI-failures (including osimertinib [TAGRISSO®] failure) with T790M-negative mutation tumors, 2) T790M-positive mutation tumors with prior exposure to osimertinib, and 3) first-line osimertinib failure regardless of T790M mutation status.

The primary study hypotheses are that the combination of pembrolizumab plus chemotherapy has superior efficacy compared to saline placebo plus chemotherapy in terms of Progression-free Survival (PFS) and Overall Survival (OS).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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	29 June 2018
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	Brazil: 9
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	China: 112
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hong Kong: 13
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Japan: 79
Country: Number of subjects enrolled	Korea, Republic of: 52

Country: Number of subjects enrolled	Mexico: 23
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Taiwan: 44
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	492
EEA total number of subjects	90

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)	272
From 65 to 84 years	218
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 855 participants screened, 492 randomized; of these, 491 received treatment.

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, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembro + Pemetrexed + Chemo

Arm description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles

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

Dosage and administration details:

75 mg/m^2 via IV infusion Q3W for 4 cycles (Cycles 1-4).

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

Dosage and administration details:

Area Under the Curve (AUC) 5 via IV infusion Q3W for 4 cycles (Cycles 1-4)

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475, SCH-900475, KEYTRUDA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles

Arm title	Placebo + Pemetrexed + Chemo

Arm description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

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

Dosage and administration details:

Saline placebo administered via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475, SCH-900475, KEYTRUDA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

After meeting protocol requirements for ending placebo treatment, pembrolizumab could have been administered 200 mg via IV infusion Q3W for up to 35 cycles

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

Dosage and administration details:

75 mg/m^2 via IV infusion Q3W for 4 cycles (Cycles 1-4).

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

Dosage and administration details:

Area Under the Curve (AUC) 5 via IV infusion Q3W for 4 cycles (Cycles 1-4)

Number of subjects in period 1	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo
Started	245	247
Treated	245	246
Switched over to Pembro monotherapy	0	50
Completed	0	0
Not completed	245	247
Adverse event, serious fatal	219	227
Consent withdrawn by subject	-	4
Participation Was Terminated By Sponsor	26	15
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembro + Pemetrexed + Chemo
Reporting group description:	
Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).	
Reporting group title	Placebo + Pemetrexed + Chemo
Reporting group description:	
Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.	

Reporting group values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo	Total
Number of subjects	245	247	492
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)	146	126	272
From 65-84 years	97	121	218
85 years and over	2	0	2
Age Continuous Units: Years			
arithmetic mean	61.7	63.1	
standard deviation	± 10.9	± 10.0	-
Sex: Female, Male Units: Participants			
Female	152	151	303
Male	93	96	189
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	3	6
Asian	165	163	328
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	5	7
White	67	72	139
More than one race	1	0	1

Unknown or Not Reported	7	4	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	16	19	35
Not Hispanic or Latino	222	221	443
Unknown or Not Reported	7	7	14
Previous use of Tyrosine Kinase Inhibitor (TKI) Treatment History with Osimertinib			
Participants were stratified using previous treatment history with TKI osimertinib: osimertinib or no osimertinib.			
Units: Subjects			
Treated with TKI except for Osimertinib	128	126	254
Treated with first line Osimertinib	28	33	61
Treated with second line Osimertinib	88	88	176
Other	1	0	1
Geographic Region: East Asia			
Participants were stratified by geographic area of the enrolling site: East Asia versus Non-East Asia			
Units: Subjects			
East Asia	150	150	300
Non-East Asia	95	97	192
Geographic Region: US			
Participants were stratified by geographic area of the enrolling site: United States versus Non-United States			
Units: Subjects			
US	3	6	9
Non-EU	242	241	483
Geographic Region: EU			
Participants were stratified by geographic area of the enrolling site: European Union versus Non-European Union			
Units: Subjects			
EU	53	47	100
Non-EU	192	200	392
Programmed Death Ligand 1 (PD-L1) Status			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. PD-L1 status is determined by tumor proportion score (TPS). Participants with a TPS ≥50% were classified as PD-L1 strongly positive and participants with a TPS <50% were classified as not strongly positive.			
Units: Subjects			
TPS ≥ 50%	52	51	103
TPS <50%	181	185	366
Not evaluable	12	11	23
Programmed Death Ligand 1 Status			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. PD-L1 status is determined by tumor proportion score (TPS). Participants with a TPS ≥50% were classified as PD-L1 strongly positive and participants with a TPS <50% were classified as not strongly positive.			
Units: Subjects			
TPS ≥ 50%	52	51	103
TPS ≥1% AND ≤49%	54	72	126
TPS <1%	127	113	240
Not evaluable	12	11	23

End points

End points reporting groups

Reporting group title	Pembro + Pemetrexed + Chemo

Reporting group description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

Reporting group title	Placebo + Pemetrexed + Chemo

Reporting group description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

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

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

End point description:

PFS is defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. PFS was assessed by blinded independent central review (BICR) using RECIST 1.1. Per RECIST 1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions is also considered PD. The PFS presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Up to ~40 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	247		
Units: Months				
median (confidence interval 95%)	5.6 (5.5 to 5.8)	5.5 (5.4 to 5.6)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed +

Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Comparison groups	Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.97

Notes:

[1] - One-sided p-value based on log-rank test stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up. The OS presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Up to ~51 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	247		
Units: Months				
median (confidence interval 95%)	15.9 (13.7 to 18.8)	14.7 (12.7 to 17.1)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed + Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Comparison groups	Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed +

	Chemo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0362 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.02

Notes:

[2] - One-sided p-value based on log-rank test stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Secondary: Objective Response Rate (ORR) Per RECIST 1.1

End point title	Objective Response Rate (ORR) Per RECIST 1.1

End point description:

ORR was assessed by BICR using RECIST 1.1. ORR is defined as the percentage of participants in the analysis population who experience a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The ORR for participants is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to ~51 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	247		
Units: Percentage of Participants				
number (confidence interval 95%)	29.0 (23.4 to 35.1)	27.1 (21.7 to 33.1)		

Statistical analyses

Statistical analysis title	Mean Difference (Final Values)

Statistical analysis description:

Mean difference in final values: "Pembro + Pemetrexed + Chemo" minus "Placebo + Pemetrexed + Chemo". Based on Miettinen & Nurminen method stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Comparison groups	Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo

Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	9.9

Secondary: Duration of Response (DOR) Per RECIST 1.1

End point title	Duration of Response (DOR) Per RECIST 1.1

End point description:

DOR was assessed by BICR using RECIST 1.1. For participants who experience a response of CR or PR, DOR is defined as the time from the earliest date of qualifying response until earliest date of PD or death from any cause, whichever comes first. The DOR presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to ~51 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	246		
Units: Months				
median (confidence interval 95%)	6.3 (5.9 to 8.3)	5.6 (4.4 to 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. Participant responses to the questions regarding Global Health Status (GHS; "How would you rate your overall health during the past week?") and Quality of Life (QoL; "How would you rate your overall quality of life during the past week?") are each scored on a 7-point scale (1=Very poor to 7=Excellent). The two raw scores were averaged into a combined score, then normalized using linear transformation so each

participant's score ranged from 0 to 100 (0=Worst overall health/quality of life and 100=Best overall health/quality of life). The change from baseline in GHS (EORTC QLQ-C30 Item 29) and QoL (EORTC QLQ-C30 Item 30) combined score is presented. The analysis population included all randomized participants who had at least 1 patient reported outcome (PRO) assessment available and had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and Week 18

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	243		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-0.46 (-3.17 to 2.25)	-2.05 (-4.74 to 0.64)		

Statistical analyses

Statistical analysis title	Difference in Least Squares (LS) Means

Statistical analysis description:

Difference in LS Means: "Pembro + Pemetrexed + Chemo" minus "Placebo + Pemetrexed + Chemo". Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factors PD-L1 expression, treatment history, and geographic region of the enrolling site as covariates.

Comparison groups	Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	5.1

Secondary: Time to True Deterioration (TTD) in the EORTC Questionnaire Composite Endpoint of Cough, Chest Pain or Dyspnea

End point title	Time to True Deterioration (TTD) in the EORTC Questionnaire Composite Endpoint of Cough, Chest Pain or Dyspnea

End point description:

TTD is the time from baseline to first onset of 10 points or more deterioration from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline in the composite endpoint of cough [EORTC QLQ-Lung Cancer Module 13 (LC13) Item 1; How much did you cough?], chest pain [EORTC QLQ-LC13 Item 10; Have you had pain in your chest?], or dyspnea [EORTC QLQ-C30 Item 8; Were you short of breath?]. Individual responses are given on a 4-point scale (1=Not at all;

4=Very much), with a lower score indicating a better outcome. TTD was analyzed using the product-limit (Kaplan-Meier) method for censored data. The time to true deterioration in the composite endpoint of cough, chest pain or dyspnea is presented. The analysis population included all randomized participants who had at least 1 patient reported outcome (PRO) assessment available and had received at least 1 dose of study intervention. 9999 = Median and/or upper range time to deterioration were not reached.

End point type	Secondary
End point timeframe:	
Baseline and up to ~51 months	

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	236		
Units: Months				
median (confidence interval 95%)	9999 (10.05 to 9999)	17.97 (6.67 to 9999)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed + Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

Comparison groups	Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.27

Secondary: Percentage of participants who experienced an adverse event (AE)

End point title	Percentage of participants who experienced an adverse event (AE)

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The percentage of participants who experienced an AE is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to ~44 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	246		
Units: Percentage of Participants				
number (not applicable)	97.6	98.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Discontinued Study Treatment Due to AEs

End point title	Percentage of Participants who Discontinued Study Treatment Due to AEs

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The percentage of participants who discontinued study treatment due to an adverse event is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Up to ~41 months

End point values	Pembro + Pemetrexed + Chemo	Placebo + Pemetrexed + Chemo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	246		
Units: Percentage of Participants				
number (not applicable)	19.2	17.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to ~59 months

Adverse event reporting additional description:

AEs include all participants who received ≥1 dose of study drug. Deaths include all randomized participants. Per protocol, progression of cancer under study was not an AE unless related to study treatment. Thus, MedDRA terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" not related to treatment are excluded as AEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Pembro + Pemetrexed + Chemo

Reporting group description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

Reporting group title	Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy

Reporting group description:

Participants who received placebo + pemetrexed + chemo per their randomized treatment assignment and had BICR-verified progressive disease were eligible to receive pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

Reporting group title	Placebo + Pemetrexed + Chemo

Reporting group description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

Serious adverse events	Pembro + Pemetrexed + Chemo	Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy	Placebo + Pemetrexed + Chemo
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 245 (35.10%)	8 / 50 (16.00%)	70 / 246 (28.46%)
number of deaths (all causes)	219	44	186
number of deaths resulting from adverse events	5	0	12
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			

subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Breast cancer			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Acute myeloid leukaemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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			
Hypertension			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	1 / 1	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	1 / 245 (0.41%)	1 / 50 (2.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Sudden death			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	5 / 245 (2.04%)	1 / 50 (2.00%)	4 / 246 (1.63%)
occurrences causally related to treatment / all	2 / 5	0 / 1	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
General physical health deterioration			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	3 / 246 (1.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Fatigue			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	0 / 246 (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
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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			
Interstitial lung disease			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			

subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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 effusion			
subjects affected / exposed	7 / 245 (2.86%)	0 / 50 (0.00%)	4 / 246 (1.63%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated lung disease			
subjects affected / exposed	0 / 245 (0.00%)	1 / 50 (2.00%)	0 / 246 (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
Respiratory failure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			

subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Pneumonitis			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 245 (1.63%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 245 (1.63%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	5 / 245 (2.04%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	5 / 5	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Platelet count decreased			
subjects affected / exposed	8 / 245 (3.27%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	9 / 9	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	5 / 245 (2.04%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	5 / 5	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			
subjects affected / exposed	0 / 245 (0.00%)	1 / 50 (2.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Craniocerebral injury			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Femoral neck fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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

Hip fracture			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Road traffic accident			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Spinal fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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 access complication			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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			
Atrial flutter			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac tamponade			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Pericardial effusion			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	0 / 246 (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
Myocarditis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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			
Cerebrovascular accident			
subjects affected / exposed	5 / 245 (2.04%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	3 / 246 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			

subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Nervous system disorder			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Ischaemic stroke			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Headache			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke in evolution			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Status epilepticus			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paresis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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	6 / 245 (2.45%)	0 / 50 (0.00%)	8 / 246 (3.25%)
occurrences causally related to treatment / all	6 / 6	0 / 0	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Febrile neutropenia			
subjects affected / exposed	4 / 245 (1.63%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniere's disease			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Macular hole			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Colitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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

Constipation			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	3 / 246 (1.22%)
occurrences causally related to treatment / all	2 / 2	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Haematemesis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Diverticulum intestinal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal ulcer haemorrhage			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	5 / 246 (2.03%)
occurrences causally related to treatment / all	1 / 2	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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 acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
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			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Autoimmune hepatitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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			

Lichenoid keratosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	0 / 245 (0.00%)	1 / 50 (2.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated nephritis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 245 (0.41%)	1 / 50 (2.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Flank pain			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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			
Bacteraemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Appendicitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	0 / 246 (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
Escherichia bacteraemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Erysipelas			

subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Sepsis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	4 / 246 (1.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	8 / 245 (3.27%)	1 / 50 (2.00%)	5 / 246 (2.03%)
occurrences causally related to treatment / all	1 / 8	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Endocarditis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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 infection			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			

subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Urinary tract infection			
subjects affected / exposed	2 / 245 (0.82%)	0 / 50 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 245 (0.00%)	1 / 50 (2.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	1 / 245 (0.41%)	0 / 50 (0.00%)	0 / 246 (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
Decreased appetite			
subjects affected / exposed	4 / 245 (1.63%)	0 / 50 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 1
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	Pembro + Pemetrexed + Chemo	Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy	Placebo + Pemetrexed + Chemo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 245 (95.10%)	31 / 50 (62.00%)	225 / 246 (91.46%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 245 (4.49%)	0 / 50 (0.00%)	14 / 246 (5.69%)
occurrences (all)	16	0	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 245 (11.84%)	0 / 50 (0.00%)	28 / 246 (11.38%)
occurrences (all)	41	0	31
Chest pain			
subjects affected / exposed	17 / 245 (6.94%)	3 / 50 (6.00%)	9 / 246 (3.66%)
occurrences (all)	17	3	10
Fatigue			
subjects affected / exposed	60 / 245 (24.49%)	1 / 50 (2.00%)	49 / 246 (19.92%)
occurrences (all)	81	1	81
Malaise			
subjects affected / exposed	18 / 245 (7.35%)	1 / 50 (2.00%)	23 / 246 (9.35%)
occurrences (all)	31	1	30
Oedema peripheral			
subjects affected / exposed	28 / 245 (11.43%)	1 / 50 (2.00%)	24 / 246 (9.76%)
occurrences (all)	42	2	28
Pyrexia			
subjects affected / exposed	33 / 245 (13.47%)	3 / 50 (6.00%)	21 / 246 (8.54%)
occurrences (all)	54	3	29
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	21 / 245 (8.57%)	2 / 50 (4.00%)	21 / 246 (8.54%)
occurrences (all)	22	2	24
Cough			
subjects affected / exposed	41 / 245 (16.73%)	5 / 50 (10.00%)	32 / 246 (13.01%)
occurrences (all)	54	5	36
Psychiatric disorders			

Insomnia			
subjects affected / exposed	23 / 245 (9.39%)	1 / 50 (2.00%)	17 / 246 (6.91%)
occurrences (all)	24	1	17
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 245 (7.76%)	4 / 50 (8.00%)	13 / 246 (5.28%)
occurrences (all)	26	5	14
Blood creatinine increased			
subjects affected / exposed	24 / 245 (9.80%)	3 / 50 (6.00%)	20 / 246 (8.13%)
occurrences (all)	32	3	23
Aspartate aminotransferase increased			
subjects affected / exposed	55 / 245 (22.45%)	3 / 50 (6.00%)	55 / 246 (22.36%)
occurrences (all)	98	3	83
Alanine aminotransferase increased			
subjects affected / exposed	60 / 245 (24.49%)	3 / 50 (6.00%)	58 / 246 (23.58%)
occurrences (all)	96	5	82
Lymphocyte count decreased			
subjects affected / exposed	16 / 245 (6.53%)	0 / 50 (0.00%)	11 / 246 (4.47%)
occurrences (all)	20	0	12
Neutrophil count decreased			
subjects affected / exposed	90 / 245 (36.73%)	2 / 50 (4.00%)	113 / 246 (45.93%)
occurrences (all)	236	2	282
Platelet count decreased			
subjects affected / exposed	49 / 245 (20.00%)	0 / 50 (0.00%)	52 / 246 (21.14%)
occurrences (all)	81	0	94
Weight decreased			
subjects affected / exposed	24 / 245 (9.80%)	3 / 50 (6.00%)	16 / 246 (6.50%)
occurrences (all)	29	3	18
White blood cell count decreased			
subjects affected / exposed	71 / 245 (28.98%)	2 / 50 (4.00%)	87 / 246 (35.37%)
occurrences (all)	211	2	259
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 245 (11.84%)	0 / 50 (0.00%)	31 / 246 (12.60%)
occurrences (all)	32	0	33
Dysgeusia			

subjects affected / exposed	16 / 245 (6.53%)	0 / 50 (0.00%)	6 / 246 (2.44%)
occurrences (all)	35	0	7
Dizziness			
subjects affected / exposed	22 / 245 (8.98%)	1 / 50 (2.00%)	23 / 246 (9.35%)
occurrences (all)	42	1	38
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	99 / 245 (40.41%)	4 / 50 (8.00%)	110 / 246 (44.72%)
occurrences (all)	161	4	177
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 245 (3.67%)	2 / 50 (4.00%)	15 / 246 (6.10%)
occurrences (all)	9	2	15
Nausea			
subjects affected / exposed	96 / 245 (39.18%)	4 / 50 (8.00%)	107 / 246 (43.50%)
occurrences (all)	242	4	237
Diarrhoea			
subjects affected / exposed	24 / 245 (9.80%)	0 / 50 (0.00%)	18 / 246 (7.32%)
occurrences (all)	27	0	23
Constipation			
subjects affected / exposed	81 / 245 (33.06%)	1 / 50 (2.00%)	76 / 246 (30.89%)
occurrences (all)	124	1	103
Vomiting			
subjects affected / exposed	48 / 245 (19.59%)	5 / 50 (10.00%)	44 / 246 (17.89%)
occurrences (all)	61	5	55
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	12 / 245 (4.90%)	3 / 50 (6.00%)	14 / 246 (5.69%)
occurrences (all)	17	3	16
Pruritus			
subjects affected / exposed	17 / 245 (6.94%)	3 / 50 (6.00%)	13 / 246 (5.28%)
occurrences (all)	18	3	15
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	13 / 245 (5.31%)	0 / 50 (0.00%)	3 / 246 (1.22%)
occurrences (all)	25	0	4
Hypothyroidism			

subjects affected / exposed	14 / 245 (5.71%)	3 / 50 (6.00%)	6 / 246 (2.44%)
occurrences (all)	18	3	9
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	10 / 245 (4.08%)	0 / 50 (0.00%)	17 / 246 (6.91%)
occurrences (all)	10	0	19
Back pain			
subjects affected / exposed	25 / 245 (10.20%)	3 / 50 (6.00%)	25 / 246 (10.16%)
occurrences (all)	36	3	29
Arthralgia			
subjects affected / exposed	19 / 245 (7.76%)	4 / 50 (8.00%)	21 / 246 (8.54%)
occurrences (all)	20	4	22
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 245 (4.49%)	2 / 50 (4.00%)	18 / 246 (7.32%)
occurrences (all)	12	2	21
Urinary tract infection			
subjects affected / exposed	18 / 245 (7.35%)	0 / 50 (0.00%)	13 / 246 (5.28%)
occurrences (all)	19	0	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	64 / 245 (26.12%)	4 / 50 (8.00%)	61 / 246 (24.80%)
occurrences (all)	81	4	79
Hyperglycaemia			
subjects affected / exposed	14 / 245 (5.71%)	2 / 50 (4.00%)	18 / 246 (7.32%)
occurrences (all)	16	2	32
Hypokalaemia			
subjects affected / exposed	16 / 245 (6.53%)	3 / 50 (6.00%)	13 / 246 (5.28%)
occurrences (all)	25	3	19
Hypoalbuminaemia			
subjects affected / exposed	11 / 245 (4.49%)	3 / 50 (6.00%)	12 / 246 (4.88%)
occurrences (all)	13	3	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2018	Amendment 3: Updated the Inclusion Criteria regarding creatinine clearance in order to align with regulatory safety labeling for pemetrexed.
24 March 2020	Amendment 4: Based on better understanding of survival outcomes for this population, planned statistical analyses were modified to relax superiority statistics without the need to alter population size. Part of the changes included removal of the Objective Response Rate-only interim analysis.
23 February 2021	Amendment 5: The control assumption for the planned Overall Survival analysis was updated to better reflect the characteristics of the population that was actually enrolled. The number and timing of analyses has also been updated based on actual enrollment timing.
19 July 2021	Amendment 6: The dose modification and toxicity management guidelines for immune-related adverse events (irAEs) were updated.
11 October 2022	Amendment 7: Text was added to specify that interim analysis 3 would become the final analysis if the observed number of events was too close to the target number of events for final analysis.
23 August 2023	Amendment 8: Text was added to allow participants to rollover to the extension study (MK-3475-587).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported