Clinical trial results:
A Phase III, Randomized, Open-label Clinical trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-line Therapy with Platinum and Fluoropyrimidine

Summary

EudraCT number	2014-005241-45
Trial protocol	FI IT EE ES IE DE GB DK BE PL
Global end of trial date	10 June 2021

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	3475-061

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02370498
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC: 152988

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2017
Global end of trial reached?	Yes
Global end of trial date	10 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study for participants with advanced gastric or gastroesophageal junction adenocarcinoma who have had tumor progression after first-line treatment with platinum and fluoropyrimidine doublet therapy. The primary study hypotheses are that pembrolizumab (MK-3475) prolongs progression free survival (PFS) and overall survival (OS) for participants with tumors that show positive programmed cell death ligand 1 (PD-L1) expression. As of 20-March-2016, enrollment will be limited to PD-L1 positive participants.

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	11 May 2015
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: 17
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Estonia: 11
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Guatemala: 10
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 2

Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Hong Kong: 1
Worldwide total number of subjects	592
EEA total number of subjects	213

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)	353
From 65 to 84 years	237
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

After 20 March 2016, enrollment was limited to programmed cell death ligand 1 (PD-L1) positive participants.

Pre-assignment

Screening details:

Of 592 participants that were randomized to trial, 570 received treatment. At the time of the primary analysis data cut-off, 89 participants were ongoing in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).

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

Dosage and administration details:

200 mg IV Day 1 of each 3-week cycle

Arm title	Paclitaxel

Arm description:

Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	TAXOL®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m^2 on Days 1, 8, and 15 of each 4-week cycle

Number of subjects in period 1	Pembrolizumab	Paclitaxel
Started	296	296
Treated	294	276
PD-L1 Positive Participants	196	199
Completed	0	0
Not completed	296	296
Adverse event, serious fatal	10	8
Sponsor's decision	15	9
Consent withdrawn by subject	7	12
Death	263	265
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).	
Reporting group title	Paclitaxel
Reporting group description:	
Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.	

Reporting group values	Pembrolizumab	Paclitaxel	Total
Number of subjects	296	296	592
Age categorical Units: Participants			
Adults (18-64 years)	170	183	353
From 65-84 years	125	112	237
85 years and over	1	1	2
Age Continuous Units: Years			
arithmetic mean	60.7	59.6	
standard deviation	± 12.0	± 11.7	-
Sex: Female, Male Units: Participants			
Female	94	88	182
Male	202	208	410
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	3	7
Asian	93	91	184
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	2	6
White	193	198	391
More than one race	2	2	4
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	27	24	51
Not Hispanic or Latino	269	272	541
Unknown or Not Reported	0	0	0
PD-L1 Status Units: Subjects			
Positive	196	199	395
Negative	99	96	195
Unknown	1	1	2
Region of Enrollment Units: Subjects			

Europe/Israel/North America/Australia	190	187	377
Asia	88	89	177
Rest of World	18	20	38
Time To Progression (TTP) on first-line therapy Units: Subjects			
<6 months	186	182	368
≥6 months	110	114	224

End points

End points reporting groups

Reporting group title	Pembrolizumab
Reporting group description:	
Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).	
Reporting group title	Paclitaxel
Reporting group description:	
Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.	

Primary: Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants

End point title	Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants
End point description:	
PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. According to RECIST 1.1, progressive disease (PD) was defined as a 20% relative increase in the sum of diameters (SOD) of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% confidence interval [CI]) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.	
End point type	Primary
End point timeframe:	
Up to 30 months (through database cut-off date of 26 Oct 2017)	

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	1.5 (1.4 to 2.0)	4.1 (3.1 to 4.2)		

Statistical analyses

Statistical analysis title	PFS per RECIST 1.1 - PD-L1 positive participants
Statistical analysis description:	
Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms.	
Comparison groups	Paclitaxel v Pembrolizumab

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.98358 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.57

Notes:

[1] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (< 6 months vs. >= 6 months).

Primary: Overall Survival (OS) in PD-L1 Positive Participants

End point title	Overall Survival (OS) in PD-L1 Positive Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. OS was analyzed using the Kaplan-Meier method and median OS (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	9.1 (6.2 to 10.7)	8.3 (7.6 to 9.0)		

Statistical analyses

Statistical analysis title	OS - PD-L1 positive participants

Statistical analysis description:

Treatment difference in OS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04205 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.03

Notes:

[2] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (< 6 months vs. >= 6 months).

Secondary: PFS According to RECIST 1.1 Based on BICR in All Participants

End point title	PFS According to RECIST 1.1 Based on BICR in All Participants

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	1.5 (1.4 to 1.6)	4.1 (3.2 to 4.2)		

Statistical analyses

Statistical analysis title	PFS per RECIST 1.1 - all participants

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.99999 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	1.77

Notes:

[3] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

Secondary: OS in All Participants

End point title	OS in All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. OS was analyzed using the Kaplan-Meier method and median OS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	6.7 (5.4 to 8.9)	8.3 (7.7 to 8.8)		

Statistical analyses

Statistical analysis title	OS - all participants

Statistical analysis description:

Treatment difference in OS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.24463 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.12

Notes:

[4] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative).

Secondary: PFS According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point title	PFS According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	1.6 (1.5 to 2.7)	3.1 (2.8 to 4.0)		

Statistical analyses

Statistical analysis title	PFS per RECIST 1.1 - PD-L1 positive participants

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.41331 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.21

Notes:

[5] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

Secondary: PFS According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point title	PFS According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	1.6 (1.5 to 1.9)	3.2 (2.9 to 4.0)		

Statistical analyses

Statistical analysis title	PFS per RECIST 1.1 - all participants

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.97481 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.42

Notes:

[6] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative).

Secondary: PFS According to Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Based on BICR in PD-L1 Positive Participants

End point title	PFS According to Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Based on BICR in PD-L1 Positive Participants

End point description:

PFS defined as time from randomization to first documented PD per irRECIST based on BICR, or death due to any cause, whichever occurs first. Following initial PD by RECIST 1.1 (20% relative increase in SOD of target lesions), participants were assessed according to irRECIST: tumor assessment repeated ≥4 weeks later to confirm PD with option of continuing treatment until scan was obtained for clinically stable participants. If PD confirmed, participant was discontinued from treatment unless investigator found benefit. If repeat scan showed stable disease (SD; neither sufficient shrinkage or increase of lesion), partial response (PR; ≥30% decrease in SOD of lesions), or complete response (CR; disappearance of all non-nodal lesions), participant could continue treatment at investigator's discretion. PFS using Kaplan-Meier and median PFS (95% CI) in months was reported. All randomized PD-L1 positive participants were analyzed and included in treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	1.9 (1.4 to 3.0)	4.2 (3.5 to 4.4)		

Statistical analyses

Statistical analysis title	PFS per irRECIST - PD-L1 positive participants

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.80696 [7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.38

Notes:

[7] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

Secondary: PFS According to irRECIST Based on BICR in All Participants

End point title	PFS According to irRECIST Based on BICR in All Participants

End point description:

PFS defined as time from randomization to first documented PD per irRECIST based on BICR, or death due to any cause, whichever occurs first. Following initial PD by RECIST 1.1 (20% relative increase in SOD of target lesions), participants were assessed according to irRECIST: tumor assessment was repeated ≥4 weeks later to confirm PD with option of continuing treatment until this scan was obtained for clinically stable participants. If PD confirmed, participant was discontinued from treatment unless investigator determined benefit. If repeat scan indicated SD (neither sufficient shrinkage or increase of target lesion), PR (≥30% decrease in the SOD of target lesions), or CR (disappearance of all non-nodal target lesions), participant could continue treatment at investigator's discretion. PFS analyzed using Kaplan-Meier method and median PFS (95% CI) in months was reported. All randomized participants were analyzed and included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	1.6 (1.5 to 2.5)	4.2 (4.0 to 4.4)		

Statistical analyses

Statistical analysis title	PFS per irRECIST - all participants

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.99932 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	1.6

Notes:

[8] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

Secondary: Time to Tumor Progression (TTP) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point title	Time to Tumor Progression (TTP) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	1.6 (1.4 to 2.7)	4.0 (3.1 to 4.2)		

Statistical analyses

Statistical analysis title	TTP per RECIST 1.1 - PD-L1 positive participants

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.99661 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.89

Notes:

[9] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

Secondary: TTP According to RECIST 1.1 Based on BICR in All Participants

End point title	TTP According to RECIST 1.1 Based on BICR in All Participants

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	1.5 (1.4 to 1.8)	4.1 (3.2 to 4.2)		

Statistical analyses

Statistical analysis title	TTP per RECIST 1.1 - all participants

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 1 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	2.2

Notes:

[10] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

Secondary: TTP According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point title	TTP According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: months				
median (confidence interval 95%)	2.1 (1.5 to 3.0)	3.3 (2.9 to 4.1)		

Statistical analyses

Statistical analysis title	TTP per RECIST 1.1 - all participants

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3928 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.23

Notes:

[11] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

Secondary: TTP According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point title	TTP According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: months				
median (confidence interval 95%)	1.6 (1.5 to 2.7)	3.8 (3.0 to 4.1)		

Statistical analyses

Statistical analysis title	TTP per RECIST 1.1 - all participants

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.97033 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.47

Notes:

[12] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

Secondary: Objective Response Rate (ORR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point title	Objective Response Rate (ORR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: Percentage of participants				
number (confidence interval 95%)	15.8 (11.0 to 21.7)	13.6 (9.1 to 19.1)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - PD-L1 positive participants

Statistical analysis description:

Stratified Miettinen and Nurminen's (MN) method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.28967 [13]
Method	Miettinen and Nurminen method
Parameter estimate	Difference in Percentage
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	9.1

Notes:

[13] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months) weighting by sample size.

Secondary: ORR According to RECIST 1.1 Based on BICR in All Participants

End point title	ORR According to RECIST 1.1 Based on BICR in All Participants

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: Percentage of participants				
number (confidence interval 95%)	11.1 (7.8 to 15.3)	12.5 (9.0 to 16.8)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - all participants

Statistical analysis description:

Stratified MN method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6901 [14]
Method	Miettinen and Nurminen method
Parameter estimate	Difference in Percentage
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	4

Notes:

[14] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative) weighting by sample size

Secondary: ORR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point title	ORR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	199		
Units: Percentage of participants				
number (confidence interval 95%)	17.3 (12.3 to 23.4)	15.6 (10.8 to 21.4)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - PD-L1 positive participants

Statistical analysis description:

Stratified MN method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3322 [15]
Method	Miettinen and Nurminen method
Parameter estimate	Difference in Percentage
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	9.1

Notes:

[15] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months), weighting by sample size.

Secondary: ORR According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point title	ORR According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	296		
Units: Percentage of participants				
number (confidence interval 95%)	12.2 (8.7 to 16.4)	15.2 (11.3 to 19.8)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - all participants

Statistical analysis description:

Stratified Miettinen and Nurminen's method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm is provided.

Comparison groups	Pembrolizumab v Paclitaxel

Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.85922 [16]
Method	Miettinen and Nurminen method
Parameter estimate	Difference in Percentage
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	2.6

Notes:

[16] - Stratification factors included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative) weighting by sample size.

Secondary: Duration of Response (DOR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point title	Duration of Response (DOR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

End point description:

For PD-L1 positive participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for PD-L1 positive participants with response by treatment group. The subset of all randomized PD-L1 positive participants that showed a CR or PR according to RECIST 1.1 and based on BICR were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	27		
Units: months				
median (full range (min-max))	18.0 (1.4 to 26.0)	5.2 (1.3 to 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR According to RECIST 1.1 Based on BICR in All Participants

End point title	DOR According to RECIST 1.1 Based on BICR in All Participants

End point description:

For participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for all participants with response by treatment group. The subset of all randomized participants that showed a CR or PR according to RECIST 1.1 and based on BICR were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	37		
Units: months				
median (full range (min-max))	18.0 (1.4 to 26.0)	5.5 (1.3 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point title	DOR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

End point description:

For PD-L1 positive participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for PD-L1 positive participants with response by treatment group. The subset of all randomized PD-L1 positive participants that showed a CR or PR according to RECIST 1.1 and based on investigator assessment were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	31		
Units: months				
median (full range (min-max))	15.7 (2.7 to 23.7)	4.3 (1.8 to 19.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point title	DOR According to RECIST 1.1 Based on Investigator Assessment in All Participants

End point description:

For participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for all participants with response by treatment group. The subset of all randomized participants that showed a CR or PR according to RECIST 1.1 and based on investigator assessment were analyzed. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	45		
Units: months				
median (full range (min-max))	15.7 (2.7 to 23.7)	4.3 (1.3 to 19.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PD-L1 Positive Participants Who Experienced an Adverse Event (AE)

End point title	Percentage of PD-L1 Positive Participants Who Experienced an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE

could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants with at least one AE was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants who received at least 1 dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to 71 months (through database cut-off date of 10 Jun 2021)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	188		
Units: Percentage of participants				
number (not applicable)	93.3	97.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of All Participants Who Experienced an AE

End point title	Percentage of All Participants Who Experienced an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants with at least one AE was reported for all participants by treatment group. All randomized participants who received at least 1 dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to 71 months (through database cut-off date of 10 Jun 2021)

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	276		
Units: Percentage of participants				
number (not applicable)	93.9	97.1		

Statistical analyses

Statistical analysis title	All participants

Statistical analysis description:

Between-treatment differences (Pembrolizumab vs. Paclitaxel) in the percentage of participants with events and accompanying 95% confidence intervals were based on the Miettinen and Nurminen method. Negative values correspond to a greater percentage of events for Paclitaxel.

Comparison groups	Pembrolizumab v Paclitaxel
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	0.2

Secondary: Percentage of PD-L1 Positive Participants that Discontinued Study Treatment Due to AE

End point title	Percentage of PD-L1 Positive Participants that Discontinued Study Treatment Due to AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants that discontinued study treatment due to an AE was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants who received at least 1 dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 26.4 months

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	188		
Units: Percentage of participants				
number (not applicable)	4.1	8.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of All Participants that Discontinued Study Treatment Due to

AE

End point title	Percentage of All Participants that Discontinued Study Treatment Due to AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product was also an AE. The percentage of participants that discontinued study treatment due to an AE was reported for all participants by treatment group. All randomized participants who received at least 1 dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 26.4 months

End point values	Pembrolizumab	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	276		
Units: Percentage of participants				
number (not applicable)	4.8	9.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 71 months (through database cut-off date of 10 Jun 2021)

Adverse event reporting additional description:

Deaths (all-causes) analysis population included all randomized participants (N=296, 296, 3). AE analysis population included all participants who received ≥1 dose of study treatment (N=294, 276, 3). MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Pembrolizumab First Course

Reporting group description:

Participants receive 200 mg IV pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).

Reporting group title	Pembrolizumab Second Course

Reporting group description:

Qualified participants who received pembrolizumab as a first course and stopped the first course of pembrolizumab due to complete response (CR) or completed the first course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (approximately 1 year additional).

Reporting group title	Paclitaxel

Reporting group description:

Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 296 (36.49%)	1 / 3 (33.33%)	68 / 296 (22.97%)
number of deaths (all causes)	278	2	287
number of deaths resulting from adverse events	3	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed[1]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed[2]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed[3]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed[4]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Vascular compression			
subjects affected / exposed[5]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed[6]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed[7]	2 / 294 (0.68%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed[8]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed[9]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1

Fatigue			
subjects affected / exposed[10]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
General physical health deterioration			
subjects affected / exposed[11]	3 / 294 (1.02%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed[12]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Oedema peripheral			
subjects affected / exposed[13]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Pyrexia			
subjects affected / exposed[14]	5 / 294 (1.70%)	0 / 3 (0.00%)	4 / 276 (1.45%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed[15]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed[16]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Cough			
subjects affected / exposed[17]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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

Dyspnoea			
subjects affected / exposed[18]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed[19]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Interstitial lung disease			
subjects affected / exposed[20]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Pleural effusion			
subjects affected / exposed[21]	3 / 294 (1.02%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed[22]	3 / 294 (1.02%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed[23]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Pneumothorax			
subjects affected / exposed[24]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed[25]	1 / 294 (0.34%)	0 / 3 (0.00%)	4 / 276 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory failure			

subjects affected / exposed[26]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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			
Completed suicide			
subjects affected / exposed[27]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Confusional state			
subjects affected / exposed[28]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic disorder			
subjects affected / exposed[29]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed[30]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Device occlusion			
subjects affected / exposed[31]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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			
Alanine aminotransferase increased			
subjects affected / exposed[32]	2 / 294 (0.68%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed[33]	2 / 294 (0.68%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased			
subjects affected / exposed[34]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Weight decreased			
subjects affected / exposed[35]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed[36]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed[37]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed[38]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed[39]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Muscle strain			
subjects affected / exposed[40]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin wound			
subjects affected / exposed[41]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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

Toxicity to various agents			
subjects affected / exposed[42]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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 stoma complication			
subjects affected / exposed[43]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed[44]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed[45]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed[46]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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 disorders			
Cerebral infarction			
subjects affected / exposed[47]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed[48]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Depressed level of consciousness			
subjects affected / exposed[49]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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

Epilepsy			
subjects affected / exposed[50]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial mass			
subjects affected / exposed[51]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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[52]	11 / 294 (3.74%)	0 / 3 (0.00%)	5 / 276 (1.81%)
occurrences causally related to treatment / all	3 / 14	0 / 0	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed[53]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Febrile neutropenia			
subjects affected / exposed[54]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed[55]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed[56]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed[57]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (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

Eye disorders			
Cataract			
subjects affected / exposed[58]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed[59]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed[60]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed[61]	8 / 294 (2.72%)	1 / 3 (33.33%)	4 / 276 (1.45%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed[62]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed[63]	4 / 294 (1.36%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed[64]	4 / 294 (1.36%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed[65]	1 / 294 (0.34%)	0 / 3 (0.00%)	3 / 276 (1.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Constipation			
subjects affected / exposed[66]	5 / 294 (1.70%)	0 / 3 (0.00%)	4 / 276 (1.45%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed[67]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Dyspepsia			
subjects affected / exposed[68]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed[69]	2 / 294 (0.68%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed[70]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Gastric hypomotility			
subjects affected / exposed[71]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric stenosis			
subjects affected / exposed[72]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Gastrointestinal haemorrhage			
subjects affected / exposed[73]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Gastrointestinal perforation			

subjects affected / exposed[74]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Gastrosplenic fistula			
subjects affected / exposed[75]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (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
Haematemesis			
subjects affected / exposed[76]	0 / 294 (0.00%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal perforation			
subjects affected / exposed[77]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus			
subjects affected / exposed[78]	4 / 294 (1.36%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed[79]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed[80]	1 / 294 (0.34%)	0 / 3 (0.00%)	4 / 276 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed[81]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed[82]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Mechanical ileus			
subjects affected / exposed[83]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed[84]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed[85]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed[86]	0 / 294 (0.00%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed[87]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed[88]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic failure			
subjects affected / exposed[89]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed[90]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed[91]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed[92]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed[93]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed[94]	3 / 294 (1.02%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed[95]	6 / 294 (2.04%)	0 / 3 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed[96]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Bile duct stenosis			
subjects affected / exposed[97]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Biliary obstruction			

subjects affected / exposed[98]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Cholangitis			
subjects affected / exposed[99]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed[100]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Cholelithiasis			
subjects affected / exposed[101]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed[102]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Hyperbilirubinaemia			
subjects affected / exposed[103]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Jaundice cholestatic			
subjects affected / exposed[104]	2 / 294 (0.68%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed[105]	3 / 294 (1.02%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			

subjects affected / exposed[106]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed[107]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed[108]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed[109]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed[110]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Renal failure			
subjects affected / exposed[111]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Renal injury			
subjects affected / exposed[112]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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 retention			
subjects affected / exposed[113]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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 obstruction			

subjects affected / exposed[114]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's disease			
subjects affected / exposed[115]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed[116]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed[117]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Hypothyroidism			
subjects affected / exposed[118]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed[119]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Muscle disorder			
subjects affected / exposed[120]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Infections and infestations			
Aspergillus infection			
subjects affected / exposed[121]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacteraemia			
subjects affected / exposed[122]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Bacterial sepsis			
subjects affected / exposed[123]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Biliary sepsis			
subjects affected / exposed[124]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Escherichia infection			
subjects affected / exposed[125]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter infection			
subjects affected / exposed[126]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed[127]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed[128]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Infection			
subjects affected / exposed[129]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed[130]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Influenza			
subjects affected / exposed[131]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Lower respiratory tract infection			
subjects affected / exposed[132]	1 / 294 (0.34%)	0 / 3 (0.00%)	3 / 276 (1.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site infection			
subjects affected / exposed[133]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Otitis media			
subjects affected / exposed[134]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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[135]	9 / 294 (3.06%)	0 / 3 (0.00%)	7 / 276 (2.54%)
occurrences causally related to treatment / all	1 / 9	0 / 0	3 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed[136]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed[137]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Respiratory tract infection			

subjects affected / exposed[138]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed[139]	2 / 294 (0.68%)	0 / 3 (0.00%)	3 / 276 (1.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed[140]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed[141]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[142]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Dehydration			
subjects affected / exposed[143]	4 / 294 (1.36%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed[144]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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
Hyperglycaemia			
subjects affected / exposed[145]	1 / 294 (0.34%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed[146]	0 / 294 (0.00%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed[147]	2 / 294 (0.68%)	0 / 3 (0.00%)	0 / 276 (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
Type 2 diabetes mellitus			
subjects affected / exposed[148]	1 / 294 (0.34%)	0 / 3 (0.00%)	0 / 276 (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

Notes:

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

Non-serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	256 / 296 (86.49%)	3 / 3 (100.00%)	260 / 296 (87.84%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed[149]	30 / 294 (10.20%)	1 / 3 (33.33%)	38 / 276 (13.77%)
occurrences (all)	41	1	63
Fatigue			
subjects affected / exposed[150]	77 / 294 (26.19%)	1 / 3 (33.33%)	89 / 276 (32.25%)
occurrences (all)	95	1	132
Mucosal inflammation			
subjects affected / exposed[151]	2 / 294 (0.68%)	0 / 3 (0.00%)	16 / 276 (5.80%)
occurrences (all)	4	0	19
Pyrexia			
subjects affected / exposed[152]	32 / 294 (10.88%)	2 / 3 (66.67%)	30 / 276 (10.87%)
occurrences (all)	40	2	38
Oedema peripheral			
subjects affected / exposed[153]	24 / 294 (8.16%)	0 / 3 (0.00%)	29 / 276 (10.51%)
occurrences (all)	25	0	37
Immune system disorders			
Seasonal allergy			
subjects affected / exposed[154]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed[155]	18 / 294 (6.12%)	0 / 3 (0.00%)	28 / 276 (10.14%)
occurrences (all)	18	0	34
Dyspnoea			
subjects affected / exposed[156]	25 / 294 (8.50%)	0 / 3 (0.00%)	19 / 276 (6.88%)
occurrences (all)	27	0	22
Dyspnoea exertional			
subjects affected / exposed[157]	1 / 294 (0.34%)	1 / 3 (33.33%)	2 / 276 (0.72%)
occurrences (all)	1	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed[158]	16 / 294 (5.44%)	0 / 3 (0.00%)	24 / 276 (8.70%)
occurrences (all)	16	0	26
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed[159]	18 / 294 (6.12%)	0 / 3 (0.00%)	18 / 276 (6.52%)
occurrences (all)	19	0	26
Aspartate aminotransferase increased			
subjects affected / exposed[160]	24 / 294 (8.16%)	0 / 3 (0.00%)	16 / 276 (5.80%)
occurrences (all)	26	0	22
Blood alkaline phosphatase increased			
subjects affected / exposed[161]	21 / 294 (7.14%)	0 / 3 (0.00%)	9 / 276 (3.26%)
occurrences (all)	21	0	12
Neutrophil count decreased			
subjects affected / exposed[162]	2 / 294 (0.68%)	0 / 3 (0.00%)	36 / 276 (13.04%)
occurrences (all)	5	0	70
Weight decreased			
subjects affected / exposed[163]	22 / 294 (7.48%)	1 / 3 (33.33%)	17 / 276 (6.16%)
occurrences (all)	23	1	21
White blood cell count decreased			
subjects affected / exposed[164]	3 / 294 (1.02%)	0 / 3 (0.00%)	19 / 276 (6.88%)
occurrences (all)	6	0	45
Nervous system disorders			
Dizziness			
subjects affected / exposed[165]	14 / 294 (4.76%)	0 / 3 (0.00%)	15 / 276 (5.43%)
occurrences (all)	15	0	18

Headache			
subjects affected / exposed[166]	10 / 294 (3.40%)	0 / 3 (0.00%)	15 / 276 (5.43%)
occurrences (all)	12	0	20
Neuropathy peripheral			
subjects affected / exposed[167]	8 / 294 (2.72%)	0 / 3 (0.00%)	42 / 276 (15.22%)
occurrences (all)	8	0	45
Peripheral sensory neuropathy			
subjects affected / exposed[168]	5 / 294 (1.70%)	0 / 3 (0.00%)	37 / 276 (13.41%)
occurrences (all)	5	0	43
Sciatica			
subjects affected / exposed[169]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed[170]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[171]	44 / 294 (14.97%)	1 / 3 (33.33%)	68 / 276 (24.64%)
occurrences (all)	56	1	86
Neutropenia			
subjects affected / exposed[172]	5 / 294 (1.70%)	0 / 3 (0.00%)	31 / 276 (11.23%)
occurrences (all)	5	0	62
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed[173]	17 / 294 (5.78%)	0 / 3 (0.00%)	12 / 276 (4.35%)
occurrences (all)	17	0	12
Abdominal pain			
subjects affected / exposed[174]	40 / 294 (13.61%)	0 / 3 (0.00%)	49 / 276 (17.75%)
occurrences (all)	42	0	57
Abdominal pain upper			
subjects affected / exposed[175]	17 / 294 (5.78%)	1 / 3 (33.33%)	16 / 276 (5.80%)
occurrences (all)	21	1	17
Ascites			
subjects affected / exposed[176]	19 / 294 (6.46%)	0 / 3 (0.00%)	12 / 276 (4.35%)
occurrences (all)	19	0	14
Constipation			

subjects affected / exposed[177]	56 / 294 (19.05%)	0 / 3 (0.00%)	53 / 276 (19.20%)
occurrences (all)	62	0	71
Diarrhoea			
subjects affected / exposed[178]	40 / 294 (13.61%)	1 / 3 (33.33%)	72 / 276 (26.09%)
occurrences (all)	42	2	104
Dyspepsia			
subjects affected / exposed[179]	18 / 294 (6.12%)	0 / 3 (0.00%)	11 / 276 (3.99%)
occurrences (all)	18	0	13
Dysphagia			
subjects affected / exposed[180]	19 / 294 (6.46%)	0 / 3 (0.00%)	17 / 276 (6.16%)
occurrences (all)	20	0	22
Melaena			
subjects affected / exposed[181]	6 / 294 (2.04%)	1 / 3 (33.33%)	1 / 276 (0.36%)
occurrences (all)	6	1	1
Nausea			
subjects affected / exposed[182]	65 / 294 (22.11%)	1 / 3 (33.33%)	77 / 276 (27.90%)
occurrences (all)	75	1	119
Oesophageal pain			
subjects affected / exposed[183]	2 / 294 (0.68%)	1 / 3 (33.33%)	1 / 276 (0.36%)
occurrences (all)	2	1	1
Stomatitis			
subjects affected / exposed[184]	7 / 294 (2.38%)	0 / 3 (0.00%)	19 / 276 (6.88%)
occurrences (all)	7	0	22
Vomiting			
subjects affected / exposed[185]	49 / 294 (16.67%)	1 / 3 (33.33%)	47 / 276 (17.03%)
occurrences (all)	59	1	65
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed[186]	1 / 294 (0.34%)	0 / 3 (0.00%)	116 / 276 (42.03%)
occurrences (all)	1	0	120
Dermatitis bullous			
subjects affected / exposed[187]	0 / 294 (0.00%)	1 / 3 (33.33%)	0 / 276 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed[188]	29 / 294 (9.86%)	0 / 3 (0.00%)	18 / 276 (6.52%)
occurrences (all)	29	0	25

Rash			
subjects affected / exposed[189]	29 / 294 (9.86%)	0 / 3 (0.00%)	22 / 276 (7.97%)
occurrences (all)	34	0	30
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed[190]	22 / 294 (7.48%)	0 / 3 (0.00%)	1 / 276 (0.36%)
occurrences (all)	25	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed[191]	23 / 294 (7.82%)	0 / 3 (0.00%)	24 / 276 (8.70%)
occurrences (all)	29	0	46
Back pain			
subjects affected / exposed[192]	33 / 294 (11.22%)	0 / 3 (0.00%)	23 / 276 (8.33%)
occurrences (all)	37	0	29
Groin pain			
subjects affected / exposed[193]	1 / 294 (0.34%)	1 / 3 (33.33%)	1 / 276 (0.36%)
occurrences (all)	2	1	1
Myalgia			
subjects affected / exposed[194]	9 / 294 (3.06%)	0 / 3 (0.00%)	25 / 276 (9.06%)
occurrences (all)	10	0	31
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed[195]	7 / 294 (2.38%)	0 / 3 (0.00%)	17 / 276 (6.16%)
occurrences (all)	9	0	21
Skin infection			
subjects affected / exposed[196]	1 / 294 (0.34%)	1 / 3 (33.33%)	1 / 276 (0.36%)
occurrences (all)	1	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[197]	76 / 294 (25.85%)	0 / 3 (0.00%)	79 / 276 (28.62%)
occurrences (all)	83	0	99
Hyperglycaemia			
subjects affected / exposed[198]	7 / 294 (2.38%)	1 / 3 (33.33%)	2 / 276 (0.72%)
occurrences (all)	8	1	21
Hypoalbuminaemia			

subjects affected / exposed[199]	19 / 294 (6.46%)	0 / 3 (0.00%)	6 / 276 (2.17%)
occurrences (all)	20	0	7
Hypokalaemia			
subjects affected / exposed[200]	15 / 294 (5.10%)	0 / 3 (0.00%)	10 / 276 (3.62%)
occurrences (all)	17	0	11

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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2015	Amendment 02: Primary reason for amendment was to enable to better monitor disease response and progression based on evolving gastric cancer studies. Additionally, increasing the imaging interval after median progression may artificially lengthen the progression time in a substantial number of patients. Disease stratification factors (time to progression on first-line therapy and PD-L1 expression status) may help predict response in second-line gastric cancer treatment and consequently overall survival in gastric cancer patients.
25 November 2015	Amendment 05: Primary reason for amendment was due to the higher than anticipated prevalence rate for PD-L1+ patients, the interim futility analysis for PD-L1 patients is no longer necessary.
24 August 2016	Amendment 07: Primary reason for amendment was based on the recommendations from the external Data Monitoring Committee to no longer enroll PD-L1 negative participants as of 20-MAR-2016.
06 September 2017	Amendment 09: Primary reason for amendment was to update the timing to allow for adequate follow-up time before the final analysis in order to account for a potential delayed treatment effect on overall survival.
15 November 2017	Amendment 11: Primary reason for amendment was to clarify language in alignment with the labels – USPI and SmPC and the core data sheet and to add guidelines for the management of myocarditis to the table based upon health authority feedback; and to allow flexibility in the entire follow-up period beyond just the current survival follow-up portion to enable more frequent follow-ups as necessary.
20 April 2020	Amendment 13: Primary reason for amendment was to include an extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported