Clinical trial results:
A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-119)

Summary

EudraCT number	2015-001020-27
Trial protocol	DE SE NL BE FR GB PL ES IT
Global end of trial date	10 November 2020

Results information

Result version number	v1 (current)
This version publication date	25 November 2021
First version publication date	25 November 2021

Trial information

Trial identification

Sponsor protocol code	3475-119

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02555657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2019
Global end of trial reached?	Yes
Global end of trial date	10 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this study, participants with metastatic triple negative breast cancer (mTNBC) were randomly assigned to receive either single agent pembrolizumab or single agent chemotherapy chosen by the treating physician (Treatment of Physician's Choice, TPC) in accordance with local regulations and guidelines, consisting of either capecitabine, eribulin, gemcitabine, or vinorelbine. The primary study hypothesis was that pembrolizumab extends overall survival compared to TPC.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 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	Argentina: 7
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Guatemala: 5
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Japan: 90
Country: Number of subjects enrolled	Korea, Republic of: 32
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Peru: 8

Country: Number of subjects enrolled	Philippines: 9
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	622
EEA total number of subjects	177

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)	524
From 65 to 84 years	97
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Per protocol, response/progression or adverse events during the second pembrolizumab course were not counted towards efficacy outcome measures or safety outcome measures respectively.

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 received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (up to ~2 years). Qualified participants who received first course of pembrolizumab but continued to experience disease progression may have, at investigator's discretion, initiated a second course of pembrolizumab at 200 mg IV Q3W for up to 17 administrations (up to ~1 year).

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

Dosage and administration details:

Participants receive pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (up to ~2 years). Qualified participants who received first course of pembrolizumab but continued to experience disease progression may have, at investigator's discretion, initiated a second course of pembrolizumab at 200 mg IV Q3W for up to 17 administrations (up to ~1 year).

Arm title	Chemotherapy

Arm description:

Participants received capecitabine, eribulin, gemcitabine, or vinorelbine as single agent chemotherapy chosen by the treating physician (Treatment of Physician's Choice, TPC) in accordance with local regulations and guidelines.

Arm type	Active comparator
Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	XELODA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants receive capecitabine as TPC in accordance with local regulations and guidelines.

Investigational medicinal product name	eribulin
Investigational medicinal product code	
Other name	HALAVEN®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: Participants receive eribulin as TPC in accordance with local regulations and guidelines.	
Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	GEMZAR®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Participants receive gemcitabine as TPC in accordance with local regulations and guidelines.	
Investigational medicinal product name	vinorelbine
Investigational medicinal product code	
Other name	NAVELBINE®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Participants receive vinorelbine as TPC in accordance with local regulations and guidelines.	

Number of subjects in period 1	Pembrolizumab	Chemotherapy
Started	312	310
Treated	309	292
Completed	0	0
Not completed	312	310
Consent withdrawn by subject	11	32
Physician decision	-	1
Death	274	262
Sponsor Decision	27	15

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (up to ~2 years). Qualified participants who received first course of pembrolizumab but continued to experience disease progression may have, at investigator's discretion, initiated a second course of pembrolizumab at 200 mg IV Q3W for up to 17 administrations (up to ~1 year).	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received capecitabine, eribulin, gemcitabine, or vinorelbine as single agent chemotherapy chosen by the treating physician (Treatment of Physician's Choice, TPC) in accordance with local regulations and guidelines.	

Reporting group values	Pembrolizumab	Chemotherapy	Total
Number of subjects	312	310	622
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	51.4	52.6	
standard deviation	± 11.4	± 11.2	-
Sex: Female, Male Units: Participants			
Female	312	308	620
Male	0	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	4	8
Asian	87	101	188
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	13	4	17
White	183	180	363
More than one race	12	12	24
Unknown or Not Reported	13	9	22

End points

End points reporting groups

Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (up to ~2 years). Qualified participants who received first course of pembrolizumab but continued to experience disease progression may have, at investigator's discretion, initiated a second course of pembrolizumab at 200 mg IV Q3W for up to 17 administrations (up to ~1 year).	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received capecitabine, eribulin, gemcitabine, or vinorelbine as single agent chemotherapy chosen by the treating physician (Treatment of Physician's Choice, TPC) in accordance with local regulations and guidelines.	

Primary: Overall Survival in Participants With Programmed Cell Death Ligand 1 (PD-L1) With Combined Positive Score (CPS) ≥10

End point title	Overall Survival in Participants With Programmed Cell Death Ligand 1 (PD-L1) With Combined Positive Score (CPS) ≥10
End point description:	
Overall survival (OS) was defined as the time from randomization to death due to any cause. The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥10 who were included in a treatment group at randomization.	
End point type	Primary
End point timeframe:	
Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)	

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: Months				
median (confidence interval 95%)	12.7 (9.9 to 16.3)	11.6 (8.3 to 13.7)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Comparison groups	Chemotherapy v Pembrolizumab
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0574
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.06

Primary: Overall Survival in Participants With PD-L1 CPS ≥1

End point title	Overall Survival in Participants With PD-L1 CPS ≥1

End point description:

Overall survival (OS) was defined as the time from randomization to death due to any cause. The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥1 who were included in a treatment group at randomization.

End point type	Primary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	202		
Units: Months				
median (confidence interval 95%)	10.7 (9.3 to 12.5)	10.2 (7.9 to 12.6)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0728
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.06

Primary: Overall Survival in All Participants

End point title	Overall Survival in All Participants

End point description:

Overall survival (OS) was defined as the time from randomization to death due to any cause. The analysis population for this endpoint consisted of all participants who were included in a treatment group at randomization.

End point type	Primary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	310		
Units: Months				
median (confidence interval 95%)	9.9 (8.3 to 11.4)	10.8 (9.1 to 12.6)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3802
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.15

Secondary: Overall Response Rate per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants With PD-L1 CPS ≥10

End point title	Overall Response Rate per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants With PD-L1 CPS ≥10

End point description:

Overall Response Rate (ORR), based on a Blinded Independent Central Review (BICR) assessment per RECIST 1.1, was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions). The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥10 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: Percentage of participants				
number (confidence interval 95%)	17.7 (10.7 to 26.8)	9.2 (4.3 to 16.7)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0457
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	18.4

Secondary: Overall Response Rate per RECIST 1.1 in Participants With PD-L1 CPS ≥1

End point title	Overall Response Rate per RECIST 1.1 in Participants With PD-L1 CPS ≥1

End point description:

Overall Response Rate (ORR), based on BICR assessment per RECIST 1.1, was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions). The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥1 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	202		
Units: Percentage of participants				
number (confidence interval 95%)	12.3 (8.1 to 17.6)	9.4 (5.8 to 14.3)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1752
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	9.2

Secondary: Overall Response Rate per RECIST 1.1 in All Participants

End point title	Overall Response Rate per RECIST 1.1 in All Participants

End point description:

Overall Response Rate (ORR), based on BICR assessment per RECIST 1.1, was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions). The analysis population for this endpoint consisted of all participants who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	310		
Units: Percentage of participants				
number (confidence interval 95%)	9.6 (6.6 to 13.4)	10.6 (7.4 to 14.6)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6629
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	3.8

Secondary: Progression-Free Survival per RECIST 1.1 in Participants With PD-L1 CPS ≥10

End point title	Progression-Free Survival per RECIST 1.1 in Participants With PD-L1 CPS ≥10

End point description:

Progression-Free Survival (PFS), based on BICR assessment per RECIST 1.1, was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥10 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: Months				
median (confidence interval 95%)	2.1 (2.0 to 2.5)	3.4 (2.3 to 4.1)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7936
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.59

Secondary: Progression-Free Survival per RECIST 1.1 in Participants With PD-L1 CPS ≥1

End point title	Progression-Free Survival per RECIST 1.1 in Participants With PD-L1 CPS ≥1

End point description:

Progression-Free Survival (PFS), based on BICR assessment per RECIST 1.1, was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥1 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	202		
Units: Months				
median (confidence interval 95%)	2.1 (2.0 to 2.1)	3.1 (2.3 to 4.0)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Comparison groups	Pembrolizumab v Chemotherapy

Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9964
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.68

Secondary: Progression-Free Survival per RECIST 1.1 in All Participants

End point title	Progression-Free Survival per RECIST 1.1 in All Participants

End point description:

Progression-Free Survival (PFS), based on BICR assessment per RECIST 1.1, was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The analysis population for this endpoint consisted of all participants who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	310		
Units: Months				
median (confidence interval 95%)	2.1 (2.0 to 2.1)	3.3 (2.7 to 4.0)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	1.92

Secondary: Duration of Response per RECIST 1.1 in Participants With PD-L1 CPS ≥10 Who Had a Confirmed Response

End point title	Duration of Response per RECIST 1.1 in Participants With PD-L1 CPS ≥10 Who Had a Confirmed Response

End point description:

For participants with PD-L1 CPS ≥10 who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, Duration of Response (DOR) was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least a 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD. DOR assessments were based on BICR. The analysis population for this endpoint consisted of all randomized participants with PD-L1 CPS ≥10, whether or not they received study treatment, who demonstrated a confirmed response (CR or PR). Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (from time of first documented evidence of CR or PR through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	9		
Units: Months				
median (full range (min-max))	9999 (2.2 to 9999)	7.1 (3.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response per RECIST 1.1 in Participants With PD-L1 CPS ≥1 Who Had a Confirmed Response

End point title	Duration of Response per RECIST 1.1 in Participants With PD-L1 CPS ≥1 Who Had a Confirmed Response

End point description:

For participants with PD-L1 CPS ≥1 who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, Duration of Response (DOR) was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least a 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD. DOR assessments were based on BICR. The analysis population for this endpoint

consisted of all randomized participants with PD-L1 CPS ≥1, regardless of whether or not they received study treatment, who demonstrated a confirmed response (CR or PR). Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (from time of first documented evidence of CR or PR through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	19		
Units: Months				
median (full range (min-max))	12.2 (2.2 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response per RECIST 1.1 in All Participants Who Had a Confirmed Response

End point title	Duration of Response per RECIST 1.1 in All Participants Who Had a Confirmed Response

End point description:

For participants who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, Duration of Response (DOR) was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least a 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD. DOR assessments were based on BICR. The analysis population for this endpoint consisted of all randomized participants, regardless of whether or not they received study treatment, who demonstrated a confirmed response (CR or PR). Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (from time of first documented evidence of CR or PR through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	33		
Units: Months				
median (full range (min-max))	12.2 (2.2 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate per RECIST 1.1 in Participants With PD-L1 CPS ≥10

End point title	Disease Control Rate per RECIST 1.1 in Participants With PD-L1 CPS ≥10

End point description:

Disease Control Rate (DCR), based on BICR assessment per RECIST 1.1, was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) or Stable Disease for at least 24 weeks (SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease [PD: At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD.]) The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥10 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: Percentage of participants				
number (confidence interval 95%)	19.8 (12.4 to 29.2)	17.3 (10.4 to 26.3)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3388
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	13.5

Secondary: Disease Control Rate per RECIST 1.1 in Participants With PD-L1 CPS ≥1

End point title	Disease Control Rate per RECIST 1.1 in Participants With PD-L1

	CPS ≥1

End point description:

Disease Control Rate (DCR), based on BICR assessment per RECIST 1.1, was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) or Stable Disease for at least 24 weeks (SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease [PD: At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD.]) The analysis population for this endpoint consisted of all participants with PD-L1 CPS ≥1 who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	202		
Units: Percentage of participants				
number (confidence interval 95%)	14.3 (9.8 to 19.9)	15.8 (11.1 to 21.6)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6701
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	5.5

Secondary: Disease Control Rate per RECIST 1.1 in All Participants

End point title	Disease Control Rate per RECIST 1.1 in All Participants

End point description:

Disease Control Rate (DCR), based on BICR assessment per RECIST 1.1, was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) or Stable Disease for at least 24 weeks (SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease [PD: At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered

PD.]) The analysis population for this endpoint consisted of all participants who were included in a treatment group at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (through Final Analysis database cutoff date of 11-April-2019)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	310		
Units: Percentage of participants				
number (confidence interval 95%)	12.2 (8.8 to 16.3)	18.7 (14.5 to 23.5)		

Statistical analyses

Statistical analysis title	Difference in Percentages
Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9877
Method	Miettinen & Nurminen method
Parameter estimate	Difference in percentages
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	-0.8

Secondary: Number of Participants Who Experienced One or More Adverse Events

End point title	Number of Participants Who Experienced One or More Adverse Events

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The analysis population for this endpoint consisted of all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 60 months

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	292		
Units: Participants	285	281		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The analysis population for this endpoint consisted of all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 60 months

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	292		
Units: Participants	14	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality and Adverse Events (including first and second courses): Up to approximately 60 months

Adverse event reporting additional description:

All-cause mortality includes all randomized participants. Serious and other AEs include participants who received at least 1 dose of study treatment. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to drug were excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Pembrolizumab First Course

Reporting group description:

Participants received pembrolizumab 200 mg IV Q3W for up to 35 administrations (up to ~2 years).

Reporting group title	Chemotherapy

Reporting group description:

Participants received capecitabine, eribulin, gemcitabine, or vinorelbine as TPC in accordance with local regulations and guidelines.

Reporting group title	Pembrolizumab Second Course

Reporting group description:

Qualified participants who received the first course of pembrolizumab 200 mg IV Q3W for up to 35 administrations (up to ~2 years), but experienced disease progression, initiated a second course of pembrolizumab at the investigator's discretion, at 200 mg IV Q3W for up to 17 administrations (up to ~1 year).

Serious adverse events	Pembrolizumab First Course	Chemotherapy	Pembrolizumab Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 309 (21.04%)	60 / 292 (20.55%)	1 / 8 (12.50%)
number of deaths (all causes)	283	289	0
number of deaths resulting from adverse events	1	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 309 (0.97%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infected neoplasm			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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

Inflammatory carcinoma of the breast			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic neoplasm			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Tumour associated fever			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 309 (0.32%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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

Thrombosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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			
Chest pain			
subjects affected / exposed	0 / 309 (0.00%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 309 (0.00%)	4 / 292 (1.37%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Fatigue			
subjects affected / exposed	3 / 309 (0.97%)	0 / 292 (0.00%)	0 / 8 (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
Hyperthermia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Influenza like illness			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Malaise			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Mucosal inflammation			
subjects affected / exposed	0 / 309 (0.00%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oedema peripheral			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Pyrexia			
subjects affected / exposed	4 / 309 (1.29%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Dyspnoea			
subjects affected / exposed	3 / 309 (0.97%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Oropharyngeal pain			

subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Pleural effusion			
subjects affected / exposed	8 / 309 (2.59%)	3 / 292 (1.03%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 8	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 309 (0.65%)	0 / 292 (0.00%)	0 / 8 (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
Pneumothorax			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Pulmonary embolism			
subjects affected / exposed	2 / 309 (0.65%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Depression			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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	2 / 309 (0.65%)	0 / 292 (0.00%)	0 / 8 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Blood corticotrophin abnormal			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Femur fracture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Post procedural complication			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Radiation associated pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Cardio-respiratory arrest			
subjects affected / exposed	2 / 309 (0.65%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Sinus tachycardia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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			
Brain oedema			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Headache			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Horner's syndrome			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Lethargy			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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

Neuralgia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Post herpetic neuralgia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Seizure			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Syncope			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 309 (0.65%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	1 / 309 (0.32%)	5 / 292 (1.71%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 309 (0.32%)	4 / 292 (1.37%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Colitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 309 (0.32%)	3 / 292 (1.03%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 309 (0.32%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			

subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Oesophageal achalasia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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 perforation			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Vomiting			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Cholecystitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Liver disorder			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	0 / 309 (0.00%)	0 / 292 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Rash maculo-papular			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Urticaria			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 309 (0.00%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Flank pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Muscular weakness			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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			
Bronchitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Cellulitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Device related infection			

subjects affected / exposed	2 / 309 (0.65%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Enterococcal sepsis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Gastroenteritis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Klebsiella infection			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Liver abscess			

subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 309 (0.32%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 309 (1.94%)	8 / 292 (2.74%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 6	2 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 309 (0.65%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Systemic candida			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Wound infection			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Decreased appetite			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Dehydration			

subjects affected / exposed	0 / 309 (0.00%)	2 / 292 (0.68%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Hypercalcaemia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Hyperglycaemia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 292 (0.34%)	0 / 8 (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
Hypocalcaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (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
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 309 (0.32%)	0 / 292 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pembrolizumab First Course	Chemotherapy	Pembrolizumab Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	259 / 309 (83.82%)	263 / 292 (90.07%)	4 / 8 (50.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 309 (11.65%)	38 / 292 (13.01%)	0 / 8 (0.00%)
occurrences (all)	40	42	0
Malaise			

subjects affected / exposed	9 / 309 (2.91%)	15 / 292 (5.14%)	0 / 8 (0.00%)
occurrences (all)	9	17	0
Fatigue			
subjects affected / exposed	55 / 309 (17.80%)	54 / 292 (18.49%)	1 / 8 (12.50%)
occurrences (all)	67	61	2
Oedema peripheral			
subjects affected / exposed	16 / 309 (5.18%)	14 / 292 (4.79%)	0 / 8 (0.00%)
occurrences (all)	17	17	0
Mucosal inflammation			
subjects affected / exposed	1 / 309 (0.32%)	22 / 292 (7.53%)	0 / 8 (0.00%)
occurrences (all)	1	22	0
Pyrexia			
subjects affected / exposed	35 / 309 (11.33%)	34 / 292 (11.64%)	0 / 8 (0.00%)
occurrences (all)	46	49	0
Influenza like illness			
subjects affected / exposed	3 / 309 (0.97%)	4 / 292 (1.37%)	1 / 8 (12.50%)
occurrences (all)	4	4	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	53 / 309 (17.15%)	31 / 292 (10.62%)	0 / 8 (0.00%)
occurrences (all)	60	33	0
Dyspnoea			
subjects affected / exposed	37 / 309 (11.97%)	32 / 292 (10.96%)	0 / 8 (0.00%)
occurrences (all)	41	39	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 309 (2.91%)	17 / 292 (5.82%)	0 / 8 (0.00%)
occurrences (all)	9	18	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 309 (7.12%)	24 / 292 (8.22%)	1 / 8 (12.50%)
occurrences (all)	25	43	1
Aspartate aminotransferase increased			
subjects affected / exposed	32 / 309 (10.36%)	28 / 292 (9.59%)	1 / 8 (12.50%)
occurrences (all)	39	51	1
Neutrophil count decreased			

subjects affected / exposed	3 / 309 (0.97%)	44 / 292 (15.07%)	0 / 8 (0.00%)
occurrences (all)	8	144	0
White blood cell count decreased			
subjects affected / exposed	5 / 309 (1.62%)	30 / 292 (10.27%)	0 / 8 (0.00%)
occurrences (all)	11	103	0
Weight decreased			
subjects affected / exposed	10 / 309 (3.24%)	16 / 292 (5.48%)	0 / 8 (0.00%)
occurrences (all)	10	16	0
Blood bilirubin increased			
subjects affected / exposed	3 / 309 (0.97%)	8 / 292 (2.74%)	1 / 8 (12.50%)
occurrences (all)	3	9	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 309 (4.53%)	20 / 292 (6.85%)	0 / 8 (0.00%)
occurrences (all)	15	21	0
Headache			
subjects affected / exposed	44 / 309 (14.24%)	34 / 292 (11.64%)	0 / 8 (0.00%)
occurrences (all)	61	43	0
Neuropathy peripheral			
subjects affected / exposed	4 / 309 (1.29%)	26 / 292 (8.90%)	0 / 8 (0.00%)
occurrences (all)	4	28	0
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 309 (1.94%)	19 / 292 (6.51%)	0 / 8 (0.00%)
occurrences (all)	6	20	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 309 (9.06%)	46 / 292 (15.75%)	0 / 8 (0.00%)
occurrences (all)	31	80	0
Neutropenia			
subjects affected / exposed	2 / 309 (0.65%)	61 / 292 (20.89%)	0 / 8 (0.00%)
occurrences (all)	2	146	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 309 (5.83%)	15 / 292 (5.14%)	0 / 8 (0.00%)
occurrences (all)	18	18	0
Constipation			

subjects affected / exposed	50 / 309 (16.18%)	51 / 292 (17.47%)	0 / 8 (0.00%)
occurrences (all)	56	59	0
Diarrhoea			
subjects affected / exposed	29 / 309 (9.39%)	60 / 292 (20.55%)	1 / 8 (12.50%)
occurrences (all)	34	83	1
Nausea			
subjects affected / exposed	50 / 309 (16.18%)	89 / 292 (30.48%)	0 / 8 (0.00%)
occurrences (all)	63	117	0
Vomiting			
subjects affected / exposed	23 / 309 (7.44%)	33 / 292 (11.30%)	0 / 8 (0.00%)
occurrences (all)	30	44	0
Stomatitis			
subjects affected / exposed	6 / 309 (1.94%)	23 / 292 (7.88%)	0 / 8 (0.00%)
occurrences (all)	7	24	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 309 (0.65%)	43 / 292 (14.73%)	0 / 8 (0.00%)
occurrences (all)	2	44	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 309 (0.65%)	36 / 292 (12.33%)	0 / 8 (0.00%)
occurrences (all)	2	47	0
Pruritus			
subjects affected / exposed	35 / 309 (11.33%)	12 / 292 (4.11%)	0 / 8 (0.00%)
occurrences (all)	44	12	0
Rash			
subjects affected / exposed	23 / 309 (7.44%)	13 / 292 (4.45%)	0 / 8 (0.00%)
occurrences (all)	25	14	0
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 309 (0.00%)	0 / 292 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	25 / 309 (8.09%)	4 / 292 (1.37%)	0 / 8 (0.00%)
occurrences (all)	26	4	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	37 / 309 (11.97%)	24 / 292 (8.22%)	1 / 8 (12.50%)
occurrences (all)	46	28	1
Back pain			
subjects affected / exposed	22 / 309 (7.12%)	30 / 292 (10.27%)	0 / 8 (0.00%)
occurrences (all)	24	33	0
Pain in extremity			
subjects affected / exposed	19 / 309 (6.15%)	24 / 292 (8.22%)	1 / 8 (12.50%)
occurrences (all)	20	28	1
Muscular weakness			
subjects affected / exposed	4 / 309 (1.29%)	4 / 292 (1.37%)	1 / 8 (12.50%)
occurrences (all)	4	4	1
Musculoskeletal chest pain			
subjects affected / exposed	11 / 309 (3.56%)	4 / 292 (1.37%)	1 / 8 (12.50%)
occurrences (all)	11	4	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 309 (5.83%)	14 / 292 (4.79%)	0 / 8 (0.00%)
occurrences (all)	22	20	0
Urinary tract infection			
subjects affected / exposed	16 / 309 (5.18%)	20 / 292 (6.85%)	0 / 8 (0.00%)
occurrences (all)	18	24	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 309 (9.71%)	38 / 292 (13.01%)	0 / 8 (0.00%)
occurrences (all)	31	43	0
Hyperglycaemia			
subjects affected / exposed	12 / 309 (3.88%)	17 / 292 (5.82%)	0 / 8 (0.00%)
occurrences (all)	14	21	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2016	Amendment 1: The primary reason for this amendment was to update the description and proper formulation of eribulin in the Investigational Products section.
08 September 2017	Amendment 2: The primary reasons for this amendment were to revise the primary and secondary objectives, statistical analysis plan, and trial design of this study.
25 October 2017	Amendment 3: The primary reason for this amendment was to update the timing of the interim/final analysis and the target events for final analysis and sample size and power calculation in the Statistical Analysis Plan Summary section.
22 December 2017	Amendment 4: The primary reasons for this amendment were to update the Trial Summary, Trial Design, and several other sections of the protocol.
03 April 2018	Amendment 5: The primary reasons for this amendment were to revise the study objectives, hypotheses, and statistical analysis plan to include participants with PD-L1 positive tumors with a higher combined positive score (CPS) cutoff of ≥10 (CPS ≥10).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported