Clinical trial results:
A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab

Summary

EudraCT number	2014-002447-18
Trial protocol	NO DK
Global end of trial date	18 June 2021

Results information

Result version number	v2 (current)
This version publication date	27 July 2022
First version publication date	11 June 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	3475-055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02255097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, 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	18 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2016
Global end of trial reached?	Yes
Global end of trial date	18 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study of single-agent pembrolizumab (MK-3475) in participants with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) who have progressed on platinum-based and cetuximab therapy. The primary study hypothesis is that pembrolizumab will provide a clinically meaningful objective response rate (ORR).

With protocol amendment 05 (02-Jan-2018), once study participants have achieved the study objective or the study has ended, participants will be discontinued from this study and enrolled in an extension study to continue protocol-defined assessments and treatment.

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	24 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	172
EEA total number of subjects	6

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)	108
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were eligible to receive second course treatment with pembrolizumab if they met criteria for re-treatment. Per protocol, data collected during the second course were not counted towards efficacy or safety outcome measures.

Pre-assignment

Screening details:

Final analyses for all primary outcome measures were done at the protocol-specified primary outcome measure met date. The analyses for all secondary outcome measures and the collection of adverse events were done at the end of study date.

One participant allocated to receive pembrolizumab was not treatment and was not eligible for analysis.

Period 1

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

Arms

Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg administered by IV infusion on Day 1 of each 3-week cycle for up to 24 months

Number of subjects in period 1	Pembrolizumab
Started	172
Treated	171
Received Second Course of Pembrolizumab	3
Completed	0
Not completed	172
Adverse event, serious fatal	151
Consent withdrawn by subject	7
Allocated but not treated	1
Lost to follow-up	5

Participation in Study Discontinued by Sponsor	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.	

Reporting group values	Overall Study	Total	
Number of subjects	172	172	
Age categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	108	108	
From 65-84 years	63	63	
85 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	61.1		
standard deviation	± 9.9	-	
Sex: Female, Male Units: Participants			
Female	34	34	
Male	138	138	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	7	7	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	11	11	
White	153	153	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	153	153	
Unknown or Not Reported	10	10	
Programmed Cell Death-Ligand 1 (PD-L1) Tumor Status			

Participants were assessed for their PD-L1 tumor expression status by immunohistochemistry assay using tumor tissue from an archival or newly obtained biopsy. Participants with a tumor proportion score (TPS) were classified as follows: ≥50% = PD-L1 strongly positive; 1-49% = PD-L1 weakly positive; and <1% = PD-L1 negative.			
Units: Subjects			
≥50%	44	44	
≥1 - <50%	77	77	
<1%	46	46	
Unknown	5	5	

End points reporting groups

Reporting group title	Pembrolizumab

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

Subject analysis set title	Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Pembrolizumab First Course
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Pembrolizumab Second Course
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 1 year of treatment.

Subject analysis set title	Strong PD-L1 TPS Positive Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with strong programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) ≥50%, received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	PD-L1 TPS Positive Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) ≥1%, received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	PD-L1 CPS Positive Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 combined positive score (CPS) ≥1%, received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Participants With a HPV-positive Tumor Biopsy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a human papillomavirus (HPV) tumor biopsy received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Duplicate Pembrolizumab Arm
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

Subject analysis set title	Duplicate Strong PD-L1 TPS Positive Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with strong programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) ≥50%, received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

Subject analysis set title	Duplicate PD-L1 TPS Positive Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) ≥1%, received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

Subject analysis set title	Duplicate Participants With a HPV-positive Tumor Biopsy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a human papillomavirus (HPV) tumor biopsy received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

Primary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point title	Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point description:

ORR was assessed by RECIST 1.1 by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a Complete Response (CR) defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or Partial Response (PR) defined as at least a 30% decrease in the sum of diameters (SPD) of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1

dose of study treatment.

End point type	Primary

End point timeframe:

Up to 36 months

End point values	Pembrolizumab	Duplicate Pembrolizumab Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171	171		
Units: Percentage of participants				
number (confidence interval 95%)	16.4 (11.2 to 22.8)	16.4 (11.2 to 22.8)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	Pembrolizumab v Duplicate Pembrolizumab Arm
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	exact binomial distribution

Notes:

[1] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Primary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a strong PD-L1 expression status were evaluated for ORR by RECIST 1.1. The expression of PD-L1 was determined by immunohistochemistry (IHC) and strong PD-L1 positive was defined as a PD-L1 tumor proportion score (TPS) ≥50%. ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment with a TPS ≥50%.

End point type	Primary

End point timeframe:

Up to 36 months

End point values	Strong PD-L1 TPS Positive Participants	Duplicate Strong PD-L1 TPS Positive Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Percentage of participants				
number (confidence interval 95%)	27.3 (15.0 to 42.8)	27.3 (15.0 to 42.8)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	Strong PD-L1 TPS Positive Participants v Duplicate Strong PD-L1 TPS Positive Participants
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	exact binomial distribution

Notes:

[2] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Primary: Number of Participants Experiencing an Adverse Event (AE)

End point title	Number of Participants Experiencing an Adverse Event (AE)[3]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Worsening of a preexisting condition temporally associated with the use of the product was also an AE. A serious adverse event was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, or was another important medical event. Per protocol, analysis for this outcome measure was performed during the initial (first) course of therapy. The analysis included all participants who received ≥1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 27 months

Notes:

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

End point values	Pembrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Participants	166			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Discontinuing Study Drug Due to an AE

End point title	Number of Participants Discontinuing Study Drug Due to an

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Worsening of a preexisting condition temporally associated with the use of the product was also an AE. A serious adverse event was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, or was another important medical event. Per protocol, analysis for this outcome measure was performed during the initial (first) course of therapy. The analysis included all participants who received ≥1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 24 months

Notes:

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

End point values	Pembrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Participants	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Human Papillomavirus (HPV) Positive Tumors

End point title	Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Human Papillomavirus (HPV) Positive Tumors

End point description:

Participants with a HPV-positive tumor biopsy were evaluated for ORR by RECIST 1.1. ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference.

Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment with a HPV-positive tumor.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Participants With a HPV-positive Tumor Biopsy	Duplicate Participants With a HPV-positive Tumor Biopsy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: Percentage of participants				
number (confidence interval 95%)	14.1 (7.0 to 24.4)	14.1 (7.0 to 24.4)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	Participants With a HPV-positive Tumor Biopsy v Duplicate Participants With a HPV-positive Tumor Biopsy
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027 [5]
Method	exact binomial distribution

Notes:

[5] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Secondary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a positive PD-L1 expression status were evaluated for ORR by RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 TPS ≥1%. ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment with a TPS ≥1%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	PD-L1 TPS Positive Participants	Duplicate PD-L1 TPS Positive Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	121		
Units: Percentage of participants				
number (confidence interval 95%)	18.2 (11.8 to 26.2)	18.2 (11.8 to 26.2)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	PD-L1 TPS Positive Participants v Duplicate PD-L1 TPS Positive Participants
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	exact binomial distribution

Notes:

[6] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point title	Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point description:

ORR was assessed by modified RECIST 1.1 by performing imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the sum of diameters of target lesions, using the baseline SPD as a reference. If imaging shows disease progression (PD) imaging was repeated 4 weeks later for confirmation. PD was defined as ≥20% increase in SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Pembrolizumab	Duplicate Pembrolizumab Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171	171		
Units: Percentage of participants				
number (confidence interval 95%)	16.4 (11.2 to 22.8)	16.4 (11.2 to 22.8)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	Pembrolizumab v Duplicate Pembrolizumab Arm
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	exact binomial distribution

Notes:

[7] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a positive PD-L1 expression status were evaluated for ORR by modified RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a TPS ≥1%. ORR was assessed by imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. If imaging shows PD imaging was repeated 4 weeks later for confirmation. PD was defined as ≥20% increase in the SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment with a tumor proportion score ≥1%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	PD-L1 TPS Positive Participants	Duplicate PD-L1 TPS Positive Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	121		
Units: Percentage of participants				
number (confidence interval 95%)	18.2 (11.8 to 26.2)	18.2 (11.8 to 26.2)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	PD-L1 TPS Positive Participants v Duplicate PD-L1 TPS Positive Participants
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	exact binomial distribution

Notes:

[8] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a strong positive PD-L1 expression status were evaluated for ORR by modified RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a TPS ≥50%. ORR was assessed by imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. If imaging shows PD imaging was repeated 4 weeks later for confirmation. PD was defined as ≥20% increase in the SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received ≥1 dose of study treatment with a tumor proportion score ≥50%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Strong PD-L1 TPS Positive Participants	Duplicate Strong PD-L1 TPS Positive Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Percentage of participants				
number (confidence interval 95%)	27.3 (15.0 to 42.8)	27.3 (15.0 to 42.8)		

Statistical analyses

Statistical analysis title	ORR Comparison to Fixed Efficacy Target

Statistical analysis description:

ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution.

Comparison groups	Strong PD-L1 TPS Positive Participants v Duplicate Strong PD-L1 TPS Positive Participants
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	exact binomial distribution

Notes:

[9] - null hypothesis (H0): p ≤0.05 versus alternate hypothesis (H1): p >0.05

Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a positive PD-L1 expression status were evaluated for DOR based on RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score ≥1%. DOR was measured from the time of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received ≥1 dose of study treatment with a combined positive score ≥1% and a best overall response as confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	PD-L1 CPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: Months				
median (full range (min-max))	15.7 (2.8 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point title	Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point description:

DOR was based on RECIST 1.1 and measured from the time of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received ≥1 dose of study treatment with a best overall response as confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Pembrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Months				
median (full range (min-max))	15.7 (2.8 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

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

End point description:

PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as

either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of >5 mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Pembrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a strong PD-L1 expression status were evaluated for DOR based n RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor proportion score ≥50%. DOR was measured from the of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received ≥1dose of study treatment with a tumor proportion score ≥50% and a best overall response as confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Strong PD-L1 TPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Months				
median (full range (min-max))	22.8 (4.2 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a positive PD-L1 expression status were evaluated for PFS. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score ≥1%. PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of >5 mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1 dose of study treatment with a combined positive score ≥1%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	PD-L1 CPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: Months				
median (confidence interval 95%)	2.1 (2.0 to 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a strong PD-L1 expression status were evaluated for PFS by modified RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor

proportion score ≥50%. PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of >5 mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1 dose of study treatment with a tumor proportion score ≥50%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Strong PD-L1 TPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: Months				
median (confidence interval 95%)	2.1 (1.8 to 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Overall Survival (OS) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a positive PD-L1 expression status were evaluated for OS. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score ≥1%. OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1 dose of study treatment with a combined positive score ≥1%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	PD-L1 CPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: Months				
median (confidence interval 95%)	9.0 (6.2 to 11.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in All Participants

End point title	Overall Survival (OS) in All Participants

End point description:

OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Pembrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Months				
median (confidence interval 95%)	8.5 (6.6 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point title	Overall Survival (OS) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

End point description:

Participants with a strong PD-L1 expression status were evaluated for OS. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor proportion score ≥50%. OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received ≥1dose of study treatment with a tumor proportion score ≥50%.

End point type	Secondary

End point timeframe:

Up to 76.9 months

End point values	Strong PD-L1 TPS Positive Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: Months				
median (confidence interval 95%)	6.9 (4.0 to 11.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First Course: Up to 76.9 months
Second Course: Up to 53.3 months
First and second course dosing occurred concurrently

Adverse event reporting additional description:

All-cause mortality (ACM)=all allocated participants (n=172); AEs=all participants who received ≥1 dose of study treatment (n=171). Per protocol, Medical Dictionary for Regulatory Activities (MedDRA) terms neoplasm progression (NP), malignant NP, and disease progression not related to treatment were excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Pembrolizumab Second Course

Reporting group description:

Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 1 year of treatment.

Reporting group title	Pembrolizumab First Course

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

Serious adverse events	Pembrolizumab Second Course	Pembrolizumab First Course	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	87 / 171 (50.88%)	
number of deaths (all causes)	2	153	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendix cancer			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Death			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased upper airway secretion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	8 / 171 (4.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	4 / 171 (2.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	4 / 171 (2.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mental status changes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Clostridium test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Traumatic fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve paralysis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	4 / 171 (2.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary duct inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperthyroidism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteomyelitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	15 / 171 (8.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 3 (0.00%)	5 / 171 (2.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 171 (2.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pembrolizumab Second Course	Pembrolizumab First Course	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	158 / 171 (92.40%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	16 / 171 (9.36%)	
occurrences (all)	0	17	
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	11 / 171 (6.43%)	
occurrences (all)	0	17	
Lymphoedema			
subjects affected / exposed	1 / 3 (33.33%)	2 / 171 (1.17%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	67 / 171 (39.18%)	
occurrences (all)	0	71	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	10 / 171 (5.85%)	
occurrences (all)	0	11	
Oedema peripheral			

subjects affected / exposed	0 / 3 (0.00%)	11 / 171 (6.43%)	
occurrences (all)	0	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	38 / 171 (22.22%)	
occurrences (all)	0	39	
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	23 / 171 (13.45%)	
occurrences (all)	1	26	
Rhinitis allergic			
subjects affected / exposed	1 / 3 (33.33%)	2 / 171 (1.17%)	
occurrences (all)	1	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	18 / 171 (10.53%)	
occurrences (all)	0	19	
Depression			
subjects affected / exposed	1 / 3 (33.33%)	7 / 171 (4.09%)	
occurrences (all)	1	7	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	11 / 171 (6.43%)	
occurrences (all)	0	13	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	19 / 171 (11.11%)	
occurrences (all)	0	20	
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	33 / 171 (19.30%)	
occurrences (all)	0	33	
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	10 / 171 (5.85%)	
occurrences (all)	0	10	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3 (33.33%)	9 / 171 (5.26%)	
occurrences (all)	1	9	
Injury, poisoning and procedural			

complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	9 / 171 (5.26%)	
occurrences (all)	0	10	
Stoma site erythema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	18 / 171 (10.53%)	
occurrences (all)	0	21	
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	9 / 171 (5.26%)	
occurrences (all)	0	9	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	20 / 171 (11.70%)	
occurrences (all)	0	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	32 / 171 (18.71%)	
occurrences (all)	0	35	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	42 / 171 (24.56%)	
occurrences (all)	1	46	
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	12 / 171 (7.02%)	
occurrences (all)	0	12	
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	24 / 171 (14.04%)	
occurrences (all)	0	38	
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	23 / 171 (13.45%)	
occurrences (all)	0	24	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	15 / 171 (8.77%)	
occurrences (all)	0	15	

Nausea			
subjects affected / exposed	0 / 3 (0.00%)	34 / 171 (19.88%)	
occurrences (all)	0	37	
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	9 / 171 (5.26%)	
occurrences (all)	0	13	
Lip dry			
subjects affected / exposed	1 / 3 (33.33%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	1 / 171 (0.58%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	14 / 171 (8.19%)	
occurrences (all)	0	14	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	17 / 171 (9.94%)	
occurrences (all)	0	20	
Psoriasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	6 / 171 (3.51%)	
occurrences (all)	1	7	
Dermatitis acneiform			
subjects affected / exposed	1 / 3 (33.33%)	4 / 171 (2.34%)	
occurrences (all)	1	4	
Decubitus ulcer			
subjects affected / exposed	1 / 3 (33.33%)	2 / 171 (1.17%)	
occurrences (all)	1	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	32 / 171 (18.71%)	
occurrences (all)	0	34	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	27 / 171 (15.79%)	
occurrences (all)	0	33	
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	13 / 171 (7.60%)	
occurrences (all)	0	13	
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	13 / 171 (7.60%)	
occurrences (all)	0	14	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	9 / 171 (5.26%)	
occurrences (all)	0	9	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 3 (33.33%)	2 / 171 (1.17%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	12 / 171 (7.02%)	
occurrences (all)	0	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	30 / 171 (17.54%)	
occurrences (all)	0	36	
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	14 / 171 (8.19%)	
occurrences (all)	0	23	
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	13 / 171 (7.60%)	
occurrences (all)	0	15	
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	16 / 171 (9.36%)	
occurrences (all)	0	20	
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	29 / 171 (16.96%)	
occurrences (all)	1	41	
Hypomagnesaemia			

subjects affected / exposed	0 / 3 (0.00%)	14 / 171 (8.19%)	
occurrences (all)	0	17	
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	11 / 171 (6.43%)	
occurrences (all)	0	16	
Hypoalbuminaemia			
subjects affected / exposed	1 / 3 (33.33%)	11 / 171 (6.43%)	
occurrences (all)	1	16	
Hypoglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 171 (0.58%)	
occurrences (all)	1	2	
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	11 / 171 (6.43%)	
occurrences (all)	0	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	Amendment 01 removed the option to discontinue pharmacokinetics (PK) sampling after the assessment of the first 65-70 participants and instituted PK analysis for all participants. In addition, language was added to clarify that PK samples will also be used to explore the exposure-response relationships for pembrolizumab and measures of anti-tumor activity/efficacy, toxicity, and pharmacodynamics in the proposed population of participants.
06 May 2015	Amendment 02 modified the objective response rate (ORR) endpoint to specify analyses in a Programmed Cell Death Ligand-1 (PD-L1) strong positive subgroup instead of any PD-L1 positivity. The analysis of any PD-L1 positivity is now a secondary objective.
22 March 2016	Amendment 03 unblinded the Sponsor to the PD-L1 data, after the cut-point for PD-L1 strong positive was determined, in support of the upcoming analyses.
08 December 2017	Amendment 04 revised the survival status activities to enable flexibility and ensure that current and complete survival data are available at the time of database locks. In addition, the dose modification guidelines were replaced to provide current comprehensive guidelines for management of immune-related adverse events associated with pembrolizumab.
04 April 2018	Amendment 05 made a correction to the trial diagram.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported