Clinical trial results:
A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-Negative Breast Cancer (mTNBC) – (KEYNOTE-086)

Summary

EudraCT number	2015-000294-13
Trial protocol	ES DE BE FR
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	01 January 2021
First version publication date	01 January 2021

Trial information

Trial identification

Sponsor protocol code	MK-3475-086

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02447003
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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2019
Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a two-part study of pembrolizumab monotherapy in participants with metastatic triple-negative breast cancer (mTNBC). Part 1 of the study will examine the efficacy and safety of pembrolizumab monotherapy as first line or above treatment in participants who have received either no prior systemic treatment or at least one prior systemic treatment for metastatic breast cancer. Part 2 of the study, if done, will expand the investigation of pembrolizumab treatment in a subgroup of participants from Part 1 and will only start after enrollment in Part 1 has been completed. There will be no hypothesis testing in this study.

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. The following additional measure defined for this individual study was in place for the protection of trial subjects: subjects were permitted to be given rescue medication for management of infusion reactions, including but not limited to the following: intravenous (IV) fluids, antihistamines, nonsteroidal anti inflammatory drugs (NSAIDS), acetaminophen, narcotics, oxygen, pressors, corticosteroids, epinephrine. These medications would be administered according to local standards and practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2015
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	Australia: 21
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 77

Worldwide total number of subjects	254
EEA total number of subjects	87

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)	188
From 65 to 84 years	64
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Per protocol, response or progression during the second pembrolizumab course was not counted towards efficacy outcome measures, and adverse events during the second pembrolizumab course were not counted towards safety outcome measures. Based on protocol-specified inclusion criteria and outcome analyses requirements, Part 2 was not conducted.

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

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Pembrolizumab

Arm description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (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:

IV infusion of 200 mg.

Arm title	Cohort B: Pembrolizumab

Arm description:

Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W), for up to 17 cycles (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:

IV infusion of 200 mg.

Number of subjects in period 1	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab
Started	170	84
Completed	0	0
Not completed	170	84
Consent withdrawn by subject	4	3
Physician decision	-	1
Site discontinued	-	2
Death	154	63
Progressive Disease	1	-
Unknown	-	4
Sponsor Decision	6	11
Lost to follow-up	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: Pembrolizumab
Reporting group description:	
Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).	
Reporting group title	Cohort B: Pembrolizumab
Reporting group description:	
Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).	

Reporting group values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab	Total
Number of subjects	170	84	254
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	126	62	188
From 65-84 years	43	21	64
85 years and over	1	1	2
Age Continuous Units: Years			
arithmetic mean	54.6	54.2	
standard deviation	± 12.8	± 14.1	-
Sex: Female, Male Units: Participants			
Female	170	84	254
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	6	16
Not Hispanic or Latino	146	74	220
Unknown or Not Reported	14	4	18
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1

Asian	24	15	39
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	12	14	26
White	129	53	182
More than one race	3	0	3
Unknown or Not Reported	1	2	3

End points

End points reporting groups

Reporting group title	Cohort A: Pembrolizumab

Reporting group description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Reporting group title	Cohort B: Pembrolizumab

Reporting group description:

Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years). Qualified participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W), for up to 17 cycles (up to ~1 year).

Subject analysis set title	Cohort A: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort B: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort A: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort A: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort B: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort A: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Subject analysis set title	Cohort A: Pembrolizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Primary: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Central Imaging Vendor (CIV) in All Cohort A Participants

End point title	Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Central Imaging Vendor (CIV) in All Cohort A Participants[1]

End point description:

ORR was defined as the percentage of participants who had Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: ≥30% decrease in sum of diameters [SOD] of target lesions) per RECIST 1.1 by CIV. ORR was estimated by Agresti-Coull (A-C) method. The percentage of participants who had CR or PR is reported here as the protocol-specified ORR for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort, for all participants in Cohort A who got ≥1 dose of study drug. Per protocol final ORR analysis in all Cohort A participants was done at the time of final statistical efficacy analysis with a 10-November (Nov)-2017 cutoff. Per protocol ORR per RECIST 1.1 by CIV in all Cohort A participants was planned and conducted as a pre-specified primary outcome analysis and ORR per RECIST 1.1 by CIV in all Cohort B participants was analyzed separately as a pre-specified secondary outcome analysis and reported later in the record.

End point type	Primary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparisons between reported cohorts of the current study were planned for this endpoint.

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	0[2]		
Units: Percentage of participants				
number (confidence interval 95%)	5.3 (2.7 to 9.9)	(to)		

Notes:

[2] - Per protocol ORR in Cohort B was analyzed separately and reported later in the record.

Statistical analyses

No statistical analyses for this end point

Primary: ORR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with Programmed Cell Death- Ligand 1 (PD-L1) Positive Tumor Expression

End point title	ORR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with Programmed Cell Death- Ligand 1 (PD-L1) Positive Tumor Expression[3]

End point description:

ORR was defined as the percentage of participants who had a CR (disappearance of all target lesions) or a PR (≥30% decrease in SOD of target lesions) per RECIST 1.1 by CIV. ORR was estimated by A-C method. The percentage of participants who had CR or PR is reported here as the protocol-specified ORR, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort for the subgroup of Cohort A participants with tumor immunohistochemistry (IHC) defined-PD-L1 positive expression (PD-L1+) who got ≥1 dose of study drug. Per protocol final ORR analysis in the Cohort A PD-L1+ subgroup was done at the time of final statistical efficacy analysis with a 10-Nov-2017

cutoff. Per protocol all Cohort B participants were PD-L1+ and ORR per RECIST 1.1 by CIV in all Cohort B participants was analyzed separately as a pre-specified secondary outcome analysis and reported later in the record.

End point type	Primary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

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: No statistical comparisons between reported cohorts of the current study were planned for this endpoint.

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[4]	105		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	5.7 (2.4 to 12.2)		

Notes:

[4] - Per protocol ORR in Cohort B was analyzed separately and reported later in the record.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced at Least One Adverse Event (AE)

End point title	Number of Participants Who Experienced at Least One Adverse Event (AE)[5]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which 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 or protocol-specified procedure. Any worsening of a pre-existing condition that is temporally associated with the use of the Sponsor's product is also an AE. Per protocol the number of participants who experienced at least one AE, for the first pembrolizumab course, was assessed from enrollment/treatment initiation of a participant and analyzed by Cohort and is reported here for all participants in Cohort A and Cohort B who received ≥1 dose of study drug.

End point type	Primary

End point timeframe:

Up to ~31 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparisons between reported cohorts of the current study were planned for this endpoint.

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	84		
Units: Participants	161	83		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Drug Due to an AE

End point title	Number of Participants Who Discontinued Study Drug Due to an AE[6]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which 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 or protocol-specified procedure. Any worsening of a pre-existing condition that is temporally associated with the use of the Sponsor's product is also an AE. Per protocol the number of participants who discontinued study drug due to an AE, in the first pembrolizumab course, was assessed from enrolment/treatment initiation of a participant and analyzed by Cohort and is reported here for all participants in Cohort A and Cohort B who received ≥1 dose of study drug.

End point type	Primary

End point timeframe:

Up to ~31 months

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparisons between reported cohorts of the current study were planned for this endpoint.

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	84		
Units: Participants	8	3		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR per RECIST 1.1 by CIV in All Cohort B Participants

End point title	ORR per RECIST 1.1 by CIV in All Cohort B Participants

End point description:

ORR was defined as the percentage of participants who had a CR (disappearance of all target lesions) or a PR (≥30% decrease in SOD of target lesions) per RECIST 1.1 by CIV. ORR was estimated by A-C method. The percentage of participants who had CR or PR is reported here as the protocol-specified ORR, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort for all participants in Cohort B who got ≥1 dose of study drug. Per protocol final ORR analysis in all Cohort B participants was done at the time of final statistical efficacy analysis, with a 10-Nov-2017 cutoff. Per protocol ORR per RECIST 1.1 by CIV in all Cohort B participants was planned and conducted as a pre-specified secondary outcome analysis. Per protocol ORR per RECIST 1.1 by CIV in all Cohort A participants was analyzed separately as a pre-specified primary outcome analysis and reported earlier in the record.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	84		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	21.4 (13.9 to 31.4)		

Notes:

[7] - Per protocol ORR in Cohort A was analyzed separately and reported earlier in the record.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point title	Duration of Response (DOR) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point description:

For participants who had CR (disappearance of all target lesions) or PR (≥30% target lesion SOD decrease) per RECIST 1.1 by CIV, DOR was defined as time from first documented CR or PR until progressive disease (PD: ≥20% target lesion SOD increase, ≥5 mm absolute SOD increase; PD is also ≥1 new lesion appearance) or death. DOR for those who didn't progress/die at time of analysis was censored at last tumor assessment. Per protocol DOR for the first pembrolizumab course, assessed from enrolment/treatment initiation, estimated by Kaplan-Meier (KM) method and analyzed by cohort is reported here for all participants in Cohort A and Cohort B who had CR or PR per RECIST 1.1 by CIV and got ≥1 dose of study drug. Per protocol final DOR analysis in all Cohort A and Cohort B participants was done at the time of final statistical efficacy analysis with a 10-Nov-2017 cutoff. "99999" indicates no PD by last assessment.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	18		
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	10.4 (4.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point title	DOR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point description:

For participants who had CR (disappearance of all target lesions) or PR (≥30% target lesion SOD

decrease) per RECIST 1.1 by CIV, DOR was the time from first CR or PR until PD (≥20% target lesion SOD increase, ≥5 mm absolute SOD increase; PD is also ≥1 new lesion appearance) or death. DOR for those who didn't progress by analysis was censored at last assessment. Per protocol DOR for first pembrolizumab course assessed from enrolment/treatment initiation, estimated by KM method and analyzed by Cohort is reported for subgroup of Cohort A participants with tumor IHC defined-PD-L1 positive expression (PD-L1+) and CR/PR per RECIST 1.1 by CIV who got ≥1 dose of study drug. Per protocol final DOR analysis in Cohort A PD-L1+ subgroup was done with a final statistical efficacy analysis cutoff of 10-Nov-2017. Per protocol all Cohort B participants were PD-L1+; DOR in all Cohort B participants was analyzed separately and reported earlier in the record. "99999" indicates no PD by last assessment.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[8]	6		
Units: Months				
median (full range (min-max))	(to)	99999 (6.3 to 99999)		

Notes:

[8] - Per protocol DOR in Cohort B was analyzed separately and reported earlier in the record.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point title	Disease Control Rate (DCR) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point description:

DCR was defined as the percentage of participants in the analysis population who have CR (disappearance of all target lesions) or PR (≥30% target lesion SOD decrease) or SD (not sufficient shrinkage for PR or sufficient increase for PD [≥20% target lesion SOD increase, ≥5 mm absolute SOD increase; PD is also ≥1 new lesion appearance]) for ≥24 weeks per RECIST 1.1 by CIV. Per protocol percentage of participants who had CR, PR or SD per RECIST 1.1 by CIV is reported here as DCR, for the first pembrolizumab course, assessed from enrolment/treatment initiation, estimated by A-C method and analyzed by Cohort, for all participants in Cohort A and Cohort B who got ≥1 dose of study drug. Per protocol final DCR analysis in all Cohort A and Cohort B participants was done at the time of final statistical efficacy analysis, with a 10-Nov-2017 cutoff.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	84		
Units: Percentage of participants				
number (confidence interval 95%)	7.6 (4.4 to 12.7)	23.8 (15.9 to 34.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point title	DCR per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point description:

DCR was the percentage of participants who have CR (disappearance of all target lesions) or PR (≥30% target lesion SOD decrease) or SD (not sufficient shrinkage for PR or sufficient increase for PD [≥20% target lesion SOD increase, ≥5 mm absolute SOD increase; PD is also ≥1 new lesion appearance]) for ≥24 weeks per RECIST 1.1 by CIV. Per protocol percentage of participants who had CR, PR or SD per RECIST 1.1 by CIV is reported as DCR for the first pembrolizumab course assessed from enrolment/treatment initiation, estimated by A-C method and analyzed by Cohort for subgroup of Cohort A participants with tumor IHC defined-PD-L1 positive expression (PD-L1+) who got ≥1 dose of study drug. Per protocol final DCR analysis in Cohort A PD-L1+ subgroup was done with a final statistical efficacy analysis cutoff of 10-Nov-2017. Per protocol all Cohort B participants were PD-L1+; DCR per RECIST 1.1 by CIV in all Cohort B participants was analyzed separately and reported earlier in the record.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[9]	105		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	9.5 (5.1 to 16.8)		

Notes:

[9] - Per protocol DCR in Cohort B was analyzed separately and reported earlier in the record.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point title	Progression Free Survival (PFS) per RECIST 1.1 by CIV in All Cohort A and Cohort B Participants

End point description:

PFS was defined as the time from first dose of study drug to the first documented PD per RECIST 1.1 by CIV, or death due to any cause, whichever occurred first. Per RECIST 1.1 PD was defined as ≥20% increase in SOD of target lesions and absolute SOD increase of ≥5 mm. Appearance of ≥1 new lesion is also PD. PFS was estimated by KM method. Per protocol PFS, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort is reported here for all participants in Cohort A and Cohort B who got ≥1 dose of study drug. Per protocol final PFS analysis in all Cohort A and Cohort B participants was done at the time of final statistical efficacy analysis with a 10-Nov-2017 cutoff.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified final statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	84		
Units: Months				
median (confidence interval 95%)	2.0 (1.9 to 2.0)	2.1 (2.0 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point title	PFS per RECIST 1.1 by CIV in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point description:

PFS was defined as the time from first dose of study drug to the first documented PD per RECIST 1.1 by CIV, or death due to any cause, whichever occurred first. Per RECIST 1.1 PD was defined as ≥20% increase in SOD of target lesions and absolute SOD increase of ≥5 mm. Appearance of ≥1 new lesion is also PD. PFS was estimated by KM method. Per protocol PFS, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort is reported here for the subgroup of Cohort A participants with tumor IHC defined-PD-L1 positive expression (PD-L1+) who got ≥1 dose of study drug. Per protocol final PFS analysis in the Cohort A PD-L1+ subgroup was done at the time of final statistical efficacy analysis with a 10-Nov-2017 cutoff. Per protocol all Cohort B participants were PD-L1+ and PFS per RECIST 1.1 by CIV in all Cohort B participants was analyzed separately and reported earlier in the record.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[10]	105		
Units: Months				
median (confidence interval 95%)	(to)	2.0 (1.9 to 2.1)		

Notes:

[10] - Per protocol PFS in Cohort B was analyzed separately and reported earlier in the record.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in All Cohort A and Cohort B Participants

End point title	Overall Survival (OS) in All Cohort A and Cohort B Participants

End point description:

OS was defined as the time from the first dose of study drug to death due to any cause. OS was estimated by KM method. Per protocol OS, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort is reported here for all participants in Cohort A and Cohort B who got ≥1 dose of study drug. Per protocol final OS analysis in all Cohort A and Cohort B participants was done at the time of final statistical efficacy analysis with a 10-Nov-2017 cutoff.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort A: Pembrolizumab	Cohort B: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	84		
Units: Months				
median (confidence interval 95%)	9.0 (7.6 to 11.2)	18.0 (12.9 to 23.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point title	OS in Subgroup of Cohort A Participants with PD-L1 Positive Tumor Expression

End point description:

OS was defined as the time from the first dose of study drug to death due to any cause. OS was estimated by KM method. Per protocol OS, for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort, is reported here for the subgroup of Cohort A participants with tumor IHC defined-PD-L1 positive expression (PD-L1+) who got ≥1 dose of study drug. Per protocol final OS analysis in the Cohort A PD-L1+ subgroup was done at the time of final statistical efficacy analysis with a 10-Nov-2017 cutoff. Per protocol all Cohort B participants were PD-L1+ and OS in all Cohort B participants was analyzed separately and reported earlier in the record.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[11]	105		
Units: Months				
median (confidence interval 95%)	(to)	8.8 (7.1 to 11.2)		

Notes:

[11] - Per protocol OS in Cohort B was analyzed separately and reported earlier in the record.

Statistical analyses

No statistical analyses for this end point

Secondary: Odds Ratio of Association Between PD-L1 Tumor Expression and Objective Response (OR) per RECIST 1.1 by CIV in Cohort A Participants

End point title	Odds Ratio of Association Between PD-L1 Tumor Expression and Objective Response (OR) per RECIST 1.1 by CIV in Cohort A Participants

End point description:

OR comprises CR (disappearance of all target lesions) or PR (≥30% target lesion SOD decrease) per RECIST 1.1 by CIV. PD-L1 expression is assessed by IHC-defined combined positive score (CPS). Association between (b/w) PD-L1 CPS and OR was assessed by odds ratio by a logistic regression model and calculated as ratio of odds of OR per unit CPS increase in a single arm (odds ratio=1: no association; odds ratio<1: negative association [increase in CPS lowers odds of OR]; odds ratio >1: positive association [increase in CPS raises odds of OR]). Per protocol odds ratio for the first pembrolizumab course, assessed from enrolment/treatment initiation and analyzed by Cohort is reported here in a single arm of Cohort A participants with PD-L1 CPS who got ≥1 dose of study drug. Per protocol odds ratio was analyzed with a final statistical efficacy analysis cutoff of 10-Nov-2017. Per protocol odds ratio of association b/w PD-L1 expression and OR was not planned or done in Cohort B participants.

End point type	Secondary

End point timeframe:

Up to ~28 months (through pre-specified statistical analysis cut-off date of 10-Nov-2017)

End point values	Cohort B: Pembrolizumab	Cohort A: Pembrolizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[12]	169		
Units: Odds Ratio				
number (confidence interval 95%)	(to)	1.017 (0.991 to 1.043)		

Notes:

[12] - Per protocol odds ratio analysis was not planned or done in Cohort B.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Safety: Up to ~31 months for pembrolizumab first course; up to additional ~15 months for second course (SAEs: up to 90 days post treatment; NSAEs: up to 30 days post treatment); All-cause mortality (ACM): Up to ~54 months for first and second course

Adverse event reporting additional description:

Safety, ACM were analyzed by Cohort (A, B) and course (first, second) in participants assessed from treatment initiation, who got ≥1 study drug dose. Per protocol disease progression (DP) wasn't an AE unless related to study drug; MedDRA preferred terms "Neoplasm progression (NP)", "Malignant NP", "DP" unrelated to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Cohort A: Pembrolizumab First Course

Reporting group description:

Participants in Cohort A previously received at least one prior systemic treatment for metastatic breast cancer. Participants were administered pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Reporting group title	Cohort B: Pembrolizumab First Course

Reporting group description:

Participants in Cohort B previously received no prior systemic treatment for metastatic breast cancer AND had a programmed cell death-ligand 1 (PD-L1) positive tumor expression. Participants were administered pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles (up to ~2 years).

Reporting group title	Cohort A: Pembrolizumab Second Course

Reporting group description:

Qualified Cohort A participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 each 3-week cycle (Q3W) for up to 17 cycles (up to ~1 year).

Reporting group title	Cohort B: Pembrolizumab Second Course

Reporting group description:

Qualified Cohort B participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 17 cycles (up to ~1 year).

Serious adverse events	Cohort A: Pembrolizumab First Course	Cohort B: Pembrolizumab First Course	Cohort A: Pembrolizumab Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 170 (27.06%)	19 / 84 (22.62%)	0 / 1 (0.00%)
number of deaths (all causes)	154	63	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed	1 / 170 (0.59%)	1 / 84 (1.19%)	0 / 1 (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
Colorectal cancer			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Infected neoplasm			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Neoplasm malignant			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Hypotension			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 170 (1.18%)	0 / 84 (0.00%)	0 / 1 (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

Pain			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Pyrexia			
subjects affected / exposed	1 / 170 (0.59%)	1 / 84 (1.19%)	0 / 1 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 170 (1.18%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	8 / 170 (4.71%)	3 / 84 (3.57%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 170 (1.18%)	0 / 84 (0.00%)	0 / 1 (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	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Pulmonary embolism			
subjects affected / exposed	3 / 170 (1.76%)	0 / 84 (0.00%)	0 / 1 (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

Pulmonary oedema			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Pulmonary thrombosis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Product issues			
Device failure			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Liver function test abnormal			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Infusion related reaction			

subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Postoperative ileus			
subjects affected / exposed	0 / 170 (0.00%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Myocarditis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Pericardial effusion			
subjects affected / exposed	2 / 170 (1.18%)	1 / 84 (1.19%)	0 / 1 (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
Pericarditis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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			
Encephalopathy			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Intracranial pressure increased			

subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Loss of consciousness			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Migraine			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Febrile neutropenia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Diarrhoea			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Gastroenteritis eosinophilic			

subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Intestinal obstruction			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Nausea			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Subileus			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Hepatocellular injury			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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

Renal failure			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 170 (0.59%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Pain in extremity			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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			
Appendicitis			
subjects affected / exposed	2 / 170 (1.18%)	1 / 84 (1.19%)	0 / 1 (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

Bacteraemia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Infected skin ulcer			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 170 (2.94%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Septic shock			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Staphylococcal infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Superinfection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	2 / 170 (1.18%)	0 / 84 (0.00%)	0 / 1 (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
Wound infection			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Hyperglycaemia			
subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (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
Hyponatraemia			
subjects affected / exposed	2 / 170 (1.18%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B: Pembrolizumab Second Course		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected neoplasm				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neoplasm malignant				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pyrexia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pulmonary thrombosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device failure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative ileus				

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis eosinophilic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Drug eruption				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infected skin ulcer				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superinfection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A: Pembrolizumab First Course	Cohort B: Pembrolizumab First Course	Cohort A: Pembrolizumab Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 170 (86.47%)	79 / 84 (94.05%)	1 / 1 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 170 (4.71%)	6 / 84 (7.14%)	0 / 1 (0.00%)
occurrences (all)	8	6	0
Lymphoedema			
subjects affected / exposed	9 / 170 (5.29%)	4 / 84 (4.76%)	0 / 1 (0.00%)
occurrences (all)	10	4	0
Hypertension			
subjects affected / exposed	2 / 170 (1.18%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	2	3	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	19 / 170 (11.18%)	8 / 84 (9.52%)	0 / 1 (0.00%)
occurrences (all)	20	9	0
Chest pain			
subjects affected / exposed	11 / 170 (6.47%)	6 / 84 (7.14%)	0 / 1 (0.00%)
occurrences (all)	13	7	0
Fatigue			
subjects affected / exposed	49 / 170 (28.82%)	30 / 84 (35.71%)	0 / 1 (0.00%)
occurrences (all)	59	40	0
Oedema peripheral			
subjects affected / exposed	15 / 170 (8.82%)	7 / 84 (8.33%)	0 / 1 (0.00%)
occurrences (all)	18	8	0
Pain			
subjects affected / exposed	5 / 170 (2.94%)	5 / 84 (5.95%)	0 / 1 (0.00%)
occurrences (all)	5	5	0
Pyrexia			
subjects affected / exposed	19 / 170 (11.18%)	10 / 84 (11.90%)	0 / 1 (0.00%)
occurrences (all)	25	12	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 170 (22.94%)	20 / 84 (23.81%)	0 / 1 (0.00%)
occurrences (all)	45	22	0
Dyspnoea			
subjects affected / exposed	25 / 170 (14.71%)	17 / 84 (20.24%)	0 / 1 (0.00%)
occurrences (all)	26	21	0
Pleural effusion			
subjects affected / exposed	9 / 170 (5.29%)	3 / 84 (3.57%)	0 / 1 (0.00%)
occurrences (all)	11	5	0
Bronchial wall thickening			
subjects affected / exposed	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	5 / 170 (2.94%)	2 / 84 (2.38%)	0 / 1 (0.00%)
occurrences (all)	5	2	0
Sneezing			

subjects affected / exposed	1 / 170 (0.59%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	2 / 170 (1.18%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Wheezing			
subjects affected / exposed	4 / 170 (2.35%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	4	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 170 (6.47%)	3 / 84 (3.57%)	0 / 1 (0.00%)
occurrences (all)	11	3	0
Depression			
subjects affected / exposed	8 / 170 (4.71%)	5 / 84 (5.95%)	0 / 1 (0.00%)
occurrences (all)	8	5	0
Insomnia			
subjects affected / exposed	6 / 170 (3.53%)	7 / 84 (8.33%)	0 / 1 (0.00%)
occurrences (all)	6	7	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 170 (3.53%)	6 / 84 (7.14%)	0 / 1 (0.00%)
occurrences (all)	7	7	0
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 170 (7.06%)	8 / 84 (9.52%)	0 / 1 (0.00%)
occurrences (all)	14	9	0
Weight decreased			
subjects affected / exposed	10 / 170 (5.88%)	4 / 84 (4.76%)	0 / 1 (0.00%)
occurrences (all)	10	4	0
Platelet count decreased			
subjects affected / exposed	3 / 170 (1.76%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	3	1	0
Weight increased			
subjects affected / exposed	1 / 170 (0.59%)	1 / 84 (1.19%)	1 / 1 (100.00%)
occurrences (all)	1	1	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	11 / 170 (6.47%)	10 / 84 (11.90%)	0 / 1 (0.00%)
occurrences (all)	11	11	0
Headache			
subjects affected / exposed	13 / 170 (7.65%)	16 / 84 (19.05%)	0 / 1 (0.00%)
occurrences (all)	16	18	0
Paraesthesia			
subjects affected / exposed	4 / 170 (2.35%)	9 / 84 (10.71%)	0 / 1 (0.00%)
occurrences (all)	4	11	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 170 (10.59%)	10 / 84 (11.90%)	0 / 1 (0.00%)
occurrences (all)	22	12	0
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 170 (1.76%)	5 / 84 (5.95%)	0 / 1 (0.00%)
occurrences (all)	3	5	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 170 (4.71%)	9 / 84 (10.71%)	0 / 1 (0.00%)
occurrences (all)	8	14	0
Constipation			
subjects affected / exposed	33 / 170 (19.41%)	9 / 84 (10.71%)	0 / 1 (0.00%)
occurrences (all)	36	11	0
Diarrhoea			
subjects affected / exposed	22 / 170 (12.94%)	16 / 84 (19.05%)	0 / 1 (0.00%)
occurrences (all)	32	24	0
Dry mouth			
subjects affected / exposed	11 / 170 (6.47%)	2 / 84 (2.38%)	0 / 1 (0.00%)
occurrences (all)	11	2	0
Nausea			
subjects affected / exposed	34 / 170 (20.00%)	23 / 84 (27.38%)	0 / 1 (0.00%)
occurrences (all)	41	29	0
Vomiting			
subjects affected / exposed	19 / 170 (11.18%)	11 / 84 (13.10%)	0 / 1 (0.00%)
occurrences (all)	24	21	0
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	21 / 170 (12.35%)	8 / 84 (9.52%)	0 / 1 (0.00%)
occurrences (all)	21	10	0
Rash			
subjects affected / exposed	12 / 170 (7.06%)	14 / 84 (16.67%)	0 / 1 (0.00%)
occurrences (all)	14	23	0
Rash maculo-papular			
subjects affected / exposed	3 / 170 (1.76%)	5 / 84 (5.95%)	0 / 1 (0.00%)
occurrences (all)	3	8	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 170 (1.18%)	0 / 84 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	9 / 170 (5.29%)	4 / 84 (4.76%)	0 / 1 (0.00%)
occurrences (all)	9	5	0
Hypothyroidism			
subjects affected / exposed	19 / 170 (11.18%)	9 / 84 (10.71%)	0 / 1 (0.00%)
occurrences (all)	20	10	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 170 (17.06%)	15 / 84 (17.86%)	0 / 1 (0.00%)
occurrences (all)	38	20	0
Back pain			
subjects affected / exposed	17 / 170 (10.00%)	16 / 84 (19.05%)	0 / 1 (0.00%)
occurrences (all)	17	19	0
Musculoskeletal chest pain			
subjects affected / exposed	13 / 170 (7.65%)	4 / 84 (4.76%)	0 / 1 (0.00%)
occurrences (all)	14	4	0
Musculoskeletal pain			
subjects affected / exposed	12 / 170 (7.06%)	6 / 84 (7.14%)	0 / 1 (0.00%)
occurrences (all)	14	7	0
Myalgia			
subjects affected / exposed	12 / 170 (7.06%)	9 / 84 (10.71%)	0 / 1 (0.00%)
occurrences (all)	14	10	0

Pain in extremity			
subjects affected / exposed	15 / 170 (8.82%)	7 / 84 (8.33%)	1 / 1 (100.00%)
occurrences (all)	18	9	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 170 (3.53%)	6 / 84 (7.14%)	0 / 1 (0.00%)
occurrences (all)	8	6	0
Urinary tract infection			
subjects affected / exposed	4 / 170 (2.35%)	7 / 84 (8.33%)	0 / 1 (0.00%)
occurrences (all)	4	7	0
Pneumonia			
subjects affected / exposed	3 / 170 (1.76%)	1 / 84 (1.19%)	0 / 1 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 170 (16.47%)	12 / 84 (14.29%)	0 / 1 (0.00%)
occurrences (all)	30	14	0

Non-serious adverse events	Cohort B: Pembrolizumab Second Course		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Chest pain			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Bronchial wall thickening			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Upper-airway cough syndrome			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rash			

subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2016	The primary reasons for amendment were increase in Cohort B participant number and updates to primary efficacy objectives.
12 January 2018	The primary reason for amendment was updates to dose modifications and survival assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported