Clinical trial results:
A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer

Summary

EudraCT number	2014-001749-26
Trial protocol	IE LT DE BE PT NL HU IT ES FR PL SE
Global end of trial date	15 August 2022

Results information

Result version number	v3 (current)
This version publication date	05 August 2023
First version publication date	18 May 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	3475-040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252042
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	15 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2017
Global end of trial reached?	Yes
Global end of trial date	15 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study of pembrolizumab (MK-3475) versus standard treatment (methotrexate, docetaxel or cetuximab) for the treatment of recurrent or metastatic head and neck squamous cell cancer (HNSCC). Participants will be randomly assigned to receive either pembrolizumab or Investigator's choice of standard treatment.

The primary study hypothesis is that pembrolizumab treatment prolongs Overall Survival (OS) when compared to standard 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	17 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 3

Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	United States: 94
Worldwide total number of subjects	495
EEA total number of subjects	233

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)	332
From 65 to 84 years	162
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

495 participants were randomized 1:1 to receive either pembrolizumab or standard treatment. Per protocol, response/progression or adverse events (AEs) that occurred during the second course of pembrolizumab were not counted towards efficacy outcome measures or safety outcome measures, respectively.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475, Keytruda®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenous (IV) on Day 1 of each 3-week cycle.

Arm title	Standard Treatment

Arm description:

Participants received standard treatment of either methotrexate 40 mg/m^2 IV (could be escalated to 60 mg/m^2 maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m^2 IV on Day 1 of each 3- week cycle; or cetuximab 400 mg/m^2 IV loading dose on Day 1 and 250 mg/m^2 IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m^2 on Days 1, 8, and 15 of each subsequent 3-week cycle.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	OTREXUP™, RASUVO®, RHEUMATREX®, TREXALL™
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/m^2 IV (may be escalated to 60 mg/m^2 maximum dose) on Days 1, 8, and 15 of each 3-week cycle

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	ERBITUX®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: 400 mg/m^2 IV loading dose on Day 1 and 250 mg/m^2 IV on Days 8 and 15 of Cycle 1, followed by 250 mg/m^2 on Days 1, 8, and 15 of each subsequent 3-week cycle.	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	TAXOTERE®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m^2 IV on Day 1 of each 3- week cycle	

Number of subjects in period 1	Pembrolizumab	Standard Treatment
Started	247	248
Received First Course of Pembrolizumab	246	234
Received Second Course of Pembrolizumab	2	0
Completed	0	0
Not completed	247	248
Consent withdrawn by subject	15	20
Physician decision	-	2
Adverse event, non-fatal	9	6
Death	209	217
Transferred to Extension Study	7	1
Did Not Continue on Extension Study	7	2

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.	
Reporting group title	Standard Treatment
Reporting group description:	
Participants received standard treatment of either methotrexate 40 mg/m^2 IV (could be escalated to 60 mg/m^2 maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m^2 IV on Day 1 of each 3- week cycle; or cetuximab 400 mg/m^2 IV loading dose on Day 1 and 250 mg/m^2 IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m^2 on Days 1, 8, and 15 of each subsequent 3-week cycle.	

Reporting group values	Pembrolizumab	Standard Treatment	Total
Number of subjects	247	248	495
Age categorical Units: Subjects			
Adults (18-64 years)	165	167	332
From 65-84 years	81	81	162
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	60.3	60.2	
standard deviation	± 9.8	± 8.6	-
Sex: Female, Male Units: Participants			
Female	40	43	83
Male	207	205	412
Programmed Cell Death-Ligand 1 (PD-L1) Expression Level: Tumor Proportion Score (TPS)			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Participants with a TPS ≥50% were classified as PD-L1 strongly positive and participants with a TPS <50% were classified as not strongly positive.			
Units: Subjects			
TPS = 0%	103	93	196
1% ≤ TPS <50%	79	87	166
TPS ≥ 50%	64	65	129
Missing	1	3	4
Race (NIH/OMB)			
The race of participants is presented.			
Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	15	16	31
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	7	10
White	206	207	413

More than one race	4	3	7
Unknown or Not Reported	17	15	32
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Participants were assessed for ECOG PS: Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or sedentary nature; Grade 2: Ambulatory & capable of all selfcare but unable to carry out any work activities, up & about more than 50% of waking hours; Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled, cannot carry on any selfcare, totally confined to bed or chair or Grade 5: Dead.			
Units: Subjects			
EGOG PS=0	71	68	139
ECOG PS=1	176	179	355
ECOG PS=2	0	1	1
Human Papillomavirus (HPV) Tumor Status			
Participants were assessed for the presence or absence of HPV in their tumors.			
Units: Subjects			
Positive HPV Status	61	57	118
Negative HPV Status	186	191	377
PD-L1 Combined Positive Score (CPS) Status			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Participants with a CPS ≥1 were classified as PD-L1 positive and participants with a CPS <1 were classified as PD-L1 negative.			
Units: Subjects			
PD-L1 CPS <1	50	54	104
PD-L1 CPS ≥1	196	191	387
Missing	1	3	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21	12	33
Not Hispanic or Latino	182	195	377
Unknown or Not Reported	44	41	85

End points

End points reporting groups

Reporting group title	Pembrolizumab

Reporting group description:

Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Standard Treatment

Reporting group description:

Participants received standard treatment of either methotrexate 40 mg/m^2 IV (could be escalated to 60 mg/m^2 maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m^2 IV on Day 1 of each 3- week cycle; or cetuximab 400 mg/m^2 IV loading dose on Day 1 and 250 mg/m^2 IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m^2 on Days 1, 8, and 15 of each subsequent 3-week cycle.

Primary: Initial Overall Survival (OS) for All Participants

End point title	Initial Overall Survival (OS) for All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were to be censored at the date of the last follow-up. The OS for all participants is presented. These initial OS results are based on a data cut-off date of 15-May-2017 with a database lock date of 04-Jun-2017. At the time of the database lock of 04-Jun-2017, there was incomplete collection of survival data for 12 participants. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)	8.4 (6.5 to 9.4)	7.1 (5.9 to 8.1)		

Statistical analyses

Statistical analysis title	OS: All Participants (Initial Analysis)
Comparison groups	Pembrolizumab v Standard Treatment

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0316
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.01

Primary: Updated Final OS for All Participants

End point title	Updated Final OS for All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were to be censored at the date of the last follow-up. The updated OS for all participants is presented. These OS results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)	8.4 (6.4 to 9.4)	6.9 (5.9 to 8.0)		

Statistical analyses

Statistical analysis title	OS: All Participants (Updated Final Analysis)
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01605 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.98

Notes:

[1] - Nominal p-value

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

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

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent central review (BICR) or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered progression. The PFS per RECIST 1.1 for all participants is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 2.3)	2.3 (2.1 to 2.8)		

Statistical analyses

Statistical analysis title	PFS: All Participants
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.32504
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.16

Secondary: OS for Participants With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Expression Defined by ≥1% Combined Positive Score (CPS)(PD-L1 ≥1% CPS)

End point title	OS for Participants With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Expression Defined by ≥1% Combined Positive Score (CPS)(PD-L1 ≥1% CPS)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. The OS for all participants with PD-L1 expression ≥1% CPS was presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: Months				
median (confidence interval 95%)	8.7 (6.9 to 11.4)	7.1 (5.7 to 8.3)		

Statistical analyses

Statistical analysis title	OS: PD-L1 ≥1% CPS
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00493
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.93

Secondary: PFS per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point title	PFS per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered progression. The PFS per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: Months				
median (confidence interval 95%)	2.2 (2.1 to 3.0)	2.3 (2.1 to 3.0)		

Statistical analyses

Statistical analysis title	PFS: PD-L1 ≥1% CPS
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.07736
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.06

Secondary: Objective Response Rate (ORR) per RECIST 1.1 in All Participants	
End point title	Objective Response Rate (ORR) per RECIST 1.1 in All Participants

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 based on BICR with or without confirmation. The ORR per RECIST 1.1 for all participants is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Percentage of Participants				
number (confidence interval 95%)	14.6 (10.4 to 19.6)	10.1 (6.6 to 14.5)		

Statistical analyses

Statistical analysis title	ORR: All Participants
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.061
Method	Logrank
Parameter estimate	Difference in percentages
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	10.6

Secondary: ORR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS	
End point title	ORR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1 based on BICR with or without confirmation. The ORR per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: Percentage of Participants				
number (confidence interval 95%)	17.3 (12.3 to 23.4)	9.9 (6.1 to 15.1)		

Statistical analyses

Statistical analysis title	ORR: PD-L1 ≥1% CPS
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0171
Method	Logrank
Parameter estimate	Difference in percentages
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	14.6

Secondary: Time to Progression (TTP) per RECIST 1.1 in All Participants

End point title	Time to Progression (TTP) per RECIST 1.1 in All Participants

End point description:

TTP was defined as the time from randomization to the first documented disease progression based on assessments by BICR per RECIST 1.1. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered progression. The TTP per RECIST 1.1 for all participants is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy

population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)	2.2 (2.1 to 3.3)	2.2 (2.1 to 3.4)		

Statistical analyses

Statistical analysis title	TTP: All Participants
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.14545 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.12

Notes:

[2] - p-value stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

Secondary: DOR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point title	DOR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point description:

For participants who demonstrated a confirmed CR or PR per RECIST 1.1, DOR was defined as time from first documented evidence of a confirmed CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as a ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered progression. DOR assessments were based on BICR with confirmation. The DOR per RECIST 1.1 for all participants with PD-L1 ≥1% CPS who experienced a confirmed CR or PR is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. All randomized PD-L1 ≥1% CPS participants with confirmed CR or PR were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	15		
Units: Months				
median (full range (min-max))	18.4 (2.7 to 18.4)	9.6 (1.4 to 18.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per RECIST 1.1 in All Participants

End point title	Duration of Response (DOR) per RECIST 1.1 in All Participants

End point description:

For participants who demonstrated a confirmed CR or PR per RECIST 1.1, DOR was defined as the time from first documented evidence of a confirmed CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. DOR assessments were based on BICR with confirmation. The DOR per RECIST 1.1 for all participants who experienced a confirmed CR or PR is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. All randomized participants with confirmed CR or PR were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	18		
Units: Months				
median (full range (min-max))	18.4 (2.7 to 18.4)	5.0 (1.4 to 18.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per Modified RECIST in All Participants

End point title	PFS per Modified RECIST in All Participants

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. Modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (>4 weeks after the initial PD) is required for participants who remain on treatment following a documented PD per RECIST 1.1. The PFS per modified RECIST for all participants is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. All randomized participants were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)	3.5 (3.1 to 4.4)	4.8 (4.1 to 5.7)		

Statistical analyses

Statistical analysis title	PFS per mRECIST: All Participants
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.65759
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.27

Secondary: PFS per Modified RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point title	PFS per Modified RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Modified RECIST is similar to RECIST 1.1 with the

exception that a confirmation assessment of PD (>4 weeks after the initial PD) is required for participants who remain on treatment following a documented PD per RECIST 1.1. The PFS per modified RECIST for all participants with PD-L1 ≥1% CPS is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. All randomized participants with PD-L1 ≥1% CPS were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: Months				
median (confidence interval 95%)	3.6 (3.1 to 4.6)	4.8 (4.1 to 5.7)		

Statistical analyses

Statistical analysis title	PFS per mRECIST: PD-L1 ≥1% CPS
Comparison groups	Pembrolizumab v Standard Treatment
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.51982
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.26

Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE) in All Participants

End point title	Number of Participants Who Experienced At Least One Adverse Event (AE) in All Participants

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of all participants who experienced at least one AE is presented. The safety population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	234		
Units: Participants	240	227		

Statistical analyses

No statistical analyses for this end point

Secondary: TTP per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point title	TTP per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

End point description:

TTP was defined as the time from randomization to the first documented disease progression based on assessments by BICR per RECIST 1.1. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered progression. The TTP per RECIST 1.1 for all participants with PD-L1 ≥1% CPS is presented. These efficacy results were reported after complete acquisition of all outstanding survival data using a 15-May-2017 data cut-off date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: Months				
median (full range (min-max))	2.7 (2.1 to 3.5)	2.3 (2.1 to 3.4)		

Statistical analyses

Statistical analysis title	TTP: PD-L1 ≥1% CPS
Comparison groups	Pembrolizumab v Standard Treatment

Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.05851 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.06

Notes:

[3] - p-value stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

Secondary: Number of Participants Who Experienced At Least One AE in Participants With PD-L1 ≥1% CPS

End point title	Number of Participants Who Experienced At Least One AE in Participants With PD-L1 ≥1% CPS

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of all participants with PD-L1 ≥1% CPS who experienced at least one AE is presented. The safety population consisted of all randomized participants with PD-L1 ≥1% CPS who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	183		
Units: Participants	193	178		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE in Participants With PD-L1 ≥1% CPS

End point title	Number of Participants Who Discontinued Study Treatment Due to an AE in Participants With PD-L1 ≥1% CPS

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment

and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of all participants with PD-L1 ≥1% CPS who discontinued study treatment due to an AE is presented. The safety population consisted of all randomized participants with PD-L1 ≥1% CPS who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	183		
Units: Participants	25	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE in All Participants

End point title	Number of Participants Who Discontinued Study Treatment Due to an AE in All Participants

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of study treatment, was also an AE. The number of all participants who discontinued study treatment due to an AE is presented. The safety population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab	Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	234		
Units: Participants	30	36		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 92 months

Adverse event reporting additional description:

Deaths (all-causes) reported for all randomized participants (N=247, 248, 2). Serious and NonSerious AEs reported for all randomized participants who received ≥1 dose of study treatment. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to study drug are excluded as AEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Pembrolizumab First Course

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to approximately 24 months.

Reporting group title	Pembrolizumab Second Course

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to approximately 24 months) with SD or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to approximately 1 additional year.

Reporting group title	Standard Treatment First Course

Reporting group description:

Participants received standard treatment of either methotrexate 40 mg/m^2 IV (could be escalated to 60 mg/m^2 maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m^2 IV on Day 1 of each 3- week cycle; or cetuximab 400 mg/m^2 IV loading dose on Day 1 and 250 mg/m^2 IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m^2 on Days 1, 8, and 15 of each subsequent 3-week cycle.

Serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Standard Treatment First Course
Total subjects affected by serious adverse events			
subjects affected / exposed	110 / 247 (44.53%)	0 / 2 (0.00%)	92 / 248 (37.10%)
number of deaths (all causes)	228	2	243
number of deaths resulting from adverse events	23	0	25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed[1]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed[2]	9 / 246 (3.66%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 10	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Rectal cancer			
subjects affected / exposed[3]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Paraneoplastic syndrome			
subjects affected / exposed[4]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Malignant neoplasm progression			
subjects affected / exposed[5]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Infected neoplasm			
subjects affected / exposed[6]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Basal cell carcinoma			
subjects affected / exposed[7]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astrocytoma, low grade			
subjects affected / exposed[8]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Malignant melanoma in situ			
subjects affected / exposed[9]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Squamous cell carcinoma of skin			

subjects affected / exposed[10]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Oropharyngeal neoplasm			
subjects affected / exposed[11]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Angiodysplasia			
subjects affected / exposed[12]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Deep vein thrombosis			
subjects affected / exposed[13]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Haemorrhage			
subjects affected / exposed[14]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Jugular vein thrombosis			
subjects affected / exposed[15]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed[16]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Ill-defined disorder			
subjects affected / exposed[17]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed[18]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed[19]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed[20]	5 / 246 (2.03%)	0 / 2 (0.00%)	4 / 234 (1.71%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 4
deaths causally related to treatment / all	1 / 5	0 / 0	0 / 4
Asthenia			
subjects affected / exposed[21]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Malaise			
subjects affected / exposed[22]	1 / 246 (0.41%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed[23]	1 / 246 (0.41%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed[24]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed[25]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Anaphylactic reaction			

subjects affected / exposed[26]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed[27]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Eosinophilic pneumonia			
subjects affected / exposed[28]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed[29]	4 / 246 (1.63%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed[30]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aspiration			
subjects affected / exposed[31]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asphyxia			
subjects affected / exposed[32]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed[33]	1 / 246 (0.41%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			

subjects affected / exposed[34]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed[35]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed[36]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed[37]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed[38]	5 / 246 (2.03%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract haemorrhage			
subjects affected / exposed[39]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung disorder			
subjects affected / exposed[40]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal stenosis			
subjects affected / exposed[41]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Laryngeal obstruction			

subjects affected / exposed[42]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Hypoxia			
subjects affected / exposed[43]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Haemoptysis			
subjects affected / exposed[44]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Pleural effusion			
subjects affected / exposed[45]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Oropharyngeal fistula			
subjects affected / exposed[46]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed[47]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed[48]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
White blood cell count decreased			
subjects affected / exposed[49]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			

subjects affected / exposed[50]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Neutrophil count decreased			
subjects affected / exposed[51]	0 / 246 (0.00%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed[52]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed[53]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Platelet count decreased			
subjects affected / exposed[54]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed[55]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed[56]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed[57]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			

subjects affected / exposed[58]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site haemorrhage			
subjects affected / exposed[59]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site ulcer			
subjects affected / exposed[60]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Accidental overdose			
subjects affected / exposed[61]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed[62]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed[63]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fever			
subjects affected / exposed[64]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural hypotension			
subjects affected / exposed[65]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed[66]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed[67]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed[68]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Cerebrovascular accident			
subjects affected / exposed[69]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed[70]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed[71]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed[72]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Vocal cord paresis			
subjects affected / exposed[73]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed[74]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[75]	5 / 246 (2.03%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed[76]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Febrile neutropenia			
subjects affected / exposed[77]	0 / 246 (0.00%)	0 / 2 (0.00%)	9 / 234 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node haemorrhage			
subjects affected / exposed[78]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed[79]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Incarcerated inguinal hernia			
subjects affected / exposed[80]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed[81]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Large intestine perforation			

subjects affected / exposed[82]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Malignant dysphagia			
subjects affected / exposed[83]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed[84]	4 / 246 (1.63%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gastrointestinal inflammation			
subjects affected / exposed[85]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed[86]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed[87]	3 / 246 (1.22%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed[88]	5 / 246 (2.03%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	5 / 7	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed[89]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed[90]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed[91]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed[92]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed[93]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed[94]	2 / 246 (0.81%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed[95]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral discharge			
subjects affected / exposed[96]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed[97]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed[98]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed[99]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed[100]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Cholelithiasis			
subjects affected / exposed[101]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Cirrhosis alcoholic			
subjects affected / exposed[102]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed[103]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Fungating wound			
subjects affected / exposed[104]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Pruritus			
subjects affected / exposed[105]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed[106]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Stevens-Johnson syndrome			
subjects affected / exposed[107]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed[108]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Urinary retention			
subjects affected / exposed[109]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed[110]	3 / 246 (1.22%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Kyphosis			
subjects affected / exposed[111]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Soft tissue haemorrhage			
subjects affected / exposed[112]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed[113]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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

Arthralgia			
subjects affected / exposed[114]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed[115]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected fistula			
subjects affected / exposed[116]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed[117]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiglottitis			
subjects affected / exposed[118]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed[119]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed[120]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed[121]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed[122]	3 / 246 (1.22%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida sepsis			
subjects affected / exposed[123]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Bronchitis			
subjects affected / exposed[124]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed[125]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed[126]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed[127]	4 / 246 (1.63%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed[128]	22 / 246 (8.94%)	0 / 2 (0.00%)	17 / 234 (7.26%)
occurrences causally related to treatment / all	1 / 23	0 / 0	5 / 19
deaths causally related to treatment / all	0 / 6	0 / 0	1 / 6
Pneumocystis jirovecii pneumonia			
subjects affected / exposed[129]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			

subjects affected / exposed[130]	0 / 246 (0.00%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed[131]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neutropenic sepsis			
subjects affected / exposed[132]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection bacterial			
subjects affected / exposed[133]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Klebsiella infection			
subjects affected / exposed[134]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed[135]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed[136]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Oral bacterial infection			
subjects affected / exposed[137]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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
Stoma site infection			

subjects affected / exposed[138]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed[139]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed[140]	1 / 246 (0.41%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed[141]	1 / 246 (0.41%)	0 / 2 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed[142]	2 / 246 (0.81%)	0 / 2 (0.00%)	0 / 234 (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
Wound infection			
subjects affected / exposed[143]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed[144]	6 / 246 (2.44%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 7	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed[145]	7 / 246 (2.85%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			

subjects affected / exposed[146]	0 / 246 (0.00%)	0 / 2 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed[147]	2 / 246 (0.81%)	0 / 2 (0.00%)	3 / 234 (1.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed[148]	4 / 246 (1.63%)	0 / 2 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed[149]	3 / 246 (1.22%)	0 / 2 (0.00%)	0 / 234 (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
Hypophagia			
subjects affected / exposed[150]	1 / 246 (0.41%)	0 / 2 (0.00%)	0 / 234 (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

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

Non-serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Standard Treatment First Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 247 (87.04%)	0 / 2 (0.00%)	211 / 248 (85.08%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed[151]	13 / 246 (5.28%)	0 / 2 (0.00%)	7 / 234 (2.99%)
occurrences (all)	13	0	8
Vascular disorders			
Hypotension			
subjects affected / exposed[152]	13 / 246 (5.28%)	0 / 2 (0.00%)	12 / 234 (5.13%)
occurrences (all)	13	0	16
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed[153]	24 / 246 (9.76%)	0 / 2 (0.00%)	25 / 234 (10.68%)
occurrences (all)	38	0	36
Mucosal inflammation			
subjects affected / exposed[154]	17 / 246 (6.91%)	0 / 2 (0.00%)	36 / 234 (15.38%)
occurrences (all)	21	0	51
Fatigue			
subjects affected / exposed[155]	49 / 246 (19.92%)	0 / 2 (0.00%)	63 / 234 (26.92%)
occurrences (all)	53	0	81
Asthenia			
subjects affected / exposed[156]	40 / 246 (16.26%)	0 / 2 (0.00%)	42 / 234 (17.95%)
occurrences (all)	50	0	54
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed[157]	15 / 246 (6.10%)	0 / 2 (0.00%)	5 / 234 (2.14%)
occurrences (all)	16	0	7
Haemoptysis			
subjects affected / exposed[158]	13 / 246 (5.28%)	0 / 2 (0.00%)	7 / 234 (2.99%)
occurrences (all)	15	0	9
Dyspnoea			
subjects affected / exposed[159]	31 / 246 (12.60%)	0 / 2 (0.00%)	26 / 234 (11.11%)
occurrences (all)	33	0	31
Cough			
subjects affected / exposed[160]	43 / 246 (17.48%)	0 / 2 (0.00%)	37 / 234 (15.81%)
occurrences (all)	49	0	40
Psychiatric disorders			
Insomnia			
subjects affected / exposed[161]	22 / 246 (8.94%)	0 / 2 (0.00%)	18 / 234 (7.69%)
occurrences (all)	22	0	18
Anxiety			
subjects affected / exposed[162]	13 / 246 (5.28%)	0 / 2 (0.00%)	7 / 234 (2.99%)
occurrences (all)	13	0	7
Investigations			
Weight decreased			
subjects affected / exposed[163]	21 / 246 (8.54%)	0 / 2 (0.00%)	25 / 234 (10.68%)
occurrences (all)	24	0	25

Platelet count decreased			
subjects affected / exposed[164]	7 / 246 (2.85%)	0 / 2 (0.00%)	13 / 234 (5.56%)
occurrences (all)	7	0	19
Neutrophil count decreased			
subjects affected / exposed[165]	4 / 246 (1.63%)	0 / 2 (0.00%)	24 / 234 (10.26%)
occurrences (all)	11	0	29
Aspartate aminotransferase increased			
subjects affected / exposed[166]	10 / 246 (4.07%)	0 / 2 (0.00%)	13 / 234 (5.56%)
occurrences (all)	10	0	18
Lymphocyte count decreased			
subjects affected / exposed[167]	13 / 246 (5.28%)	0 / 2 (0.00%)	10 / 234 (4.27%)
occurrences (all)	16	0	13
Nervous system disorders			
Headache			
subjects affected / exposed[168]	21 / 246 (8.54%)	0 / 2 (0.00%)	23 / 234 (9.83%)
occurrences (all)	25	0	25
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[169]	61 / 246 (24.80%)	0 / 2 (0.00%)	53 / 234 (22.65%)
occurrences (all)	77	0	72
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed[170]	7 / 246 (2.85%)	0 / 2 (0.00%)	26 / 234 (11.11%)
occurrences (all)	9	0	34
Nausea			
subjects affected / exposed[171]	36 / 246 (14.63%)	0 / 2 (0.00%)	44 / 234 (18.80%)
occurrences (all)	45	0	52
Abdominal pain			
subjects affected / exposed[172]	9 / 246 (3.66%)	0 / 2 (0.00%)	12 / 234 (5.13%)
occurrences (all)	12	0	12
Dry mouth			
subjects affected / exposed[173]	15 / 246 (6.10%)	0 / 2 (0.00%)	6 / 234 (2.56%)
occurrences (all)	15	0	6
Diarrhoea			
subjects affected / exposed[174]	37 / 246 (15.04%)	0 / 2 (0.00%)	42 / 234 (17.95%)
occurrences (all)	57	0	51

Constipation			
subjects affected / exposed[175]	43 / 246 (17.48%)	0 / 2 (0.00%)	37 / 234 (15.81%)
occurrences (all)	49	0	43
Dysphagia			
subjects affected / exposed[176]	21 / 246 (8.54%)	0 / 2 (0.00%)	15 / 234 (6.41%)
occurrences (all)	22	0	16
Vomiting			
subjects affected / exposed[177]	24 / 246 (9.76%)	0 / 2 (0.00%)	23 / 234 (9.83%)
occurrences (all)	28	0	34
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed[178]	26 / 246 (10.57%)	0 / 2 (0.00%)	41 / 234 (17.52%)
occurrences (all)	33	0	92
Pruritus			
subjects affected / exposed[179]	19 / 246 (7.72%)	0 / 2 (0.00%)	17 / 234 (7.26%)
occurrences (all)	24	0	40
Dry skin			
subjects affected / exposed[180]	4 / 246 (1.63%)	0 / 2 (0.00%)	17 / 234 (7.26%)
occurrences (all)	4	0	19
Dermatitis acneiform			
subjects affected / exposed[181]	0 / 246 (0.00%)	0 / 2 (0.00%)	18 / 234 (7.69%)
occurrences (all)	0	0	28
Alopecia			
subjects affected / exposed[182]	1 / 246 (0.41%)	0 / 2 (0.00%)	27 / 234 (11.54%)
occurrences (all)	1	0	27
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed[183]	41 / 246 (16.67%)	0 / 2 (0.00%)	10 / 234 (4.27%)
occurrences (all)	45	0	10
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed[184]	20 / 246 (8.13%)	0 / 2 (0.00%)	17 / 234 (7.26%)
occurrences (all)	20	0	17
Back pain			
subjects affected / exposed[185]	23 / 246 (9.35%)	0 / 2 (0.00%)	8 / 234 (3.42%)
occurrences (all)	24	0	8

Arthralgia			
subjects affected / exposed[186]	23 / 246 (9.35%)	0 / 2 (0.00%)	12 / 234 (5.13%)
occurrences (all)	24	0	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[187]	31 / 246 (12.60%)	0 / 2 (0.00%)	45 / 234 (19.23%)
occurrences (all)	37	0	50
Hypercalcaemia			
subjects affected / exposed[188]	14 / 246 (5.69%)	0 / 2 (0.00%)	13 / 234 (5.56%)
occurrences (all)	16	0	14
Hypokalaemia			
subjects affected / exposed[189]	23 / 246 (9.35%)	0 / 2 (0.00%)	19 / 234 (8.12%)
occurrences (all)	27	0	21
Hypophosphataemia			
subjects affected / exposed[190]	15 / 246 (6.10%)	0 / 2 (0.00%)	12 / 234 (5.13%)
occurrences (all)	21	0	14
Hyponatraemia			
subjects affected / exposed[191]	12 / 246 (4.88%)	0 / 2 (0.00%)	16 / 234 (6.84%)
occurrences (all)	14	0	17
Hypomagnesaemia			
subjects affected / exposed[192]	10 / 246 (4.07%)	0 / 2 (0.00%)	20 / 234 (8.55%)
occurrences (all)	11	0	25

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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2015	Major changes of Amendment (AM) 1 include increasing the sample size from 466 to 600 participants, adding hypotheses, revising eligibility criteria, and adding statistical analyses for the PD-L1 Strong Positive (TPS >50% PD-L1) population.
20 April 2016	Major changes of Amendment AM 10 include decreasing the sample size from 600 to 466, keeping OS in all participants as the single primary hypothesis and downgrading OS in the biomarker positive participants and PFS hypotheses to key secondary hypotheses, replacing hypotheses on the PD-L1 population with hypotheses on the CPS ≥1 population, promoting ORR to a key secondary endpoint, updating language to include PD-L1 status masking, and including the role of unblinded Sponsor personnel.
07 November 2016	Major changes of Amendment AM 11 include updating the alpha-spending language, power calculation, and timing of the final analysis to reflect the change to the number of death events at the final analysis.
20 February 2018	Major changes of Amendment AM 12 included updating the dose modification guidelines for pembrolizumab (for the management of myocarditis), updating the trial flow chart to enable survival follow-up activities throughout the study, and updating the plan for pharmacokinetic and anti-drug antibodies.
31 May 2021	Major changes of Amendment AM 13 included updating the dose modification and toxicity management guidelines for immune-related AEs.
10 December 2021	Major changes of Amendment AM 14 included adding language indicating that participants may be enrolled in a pembrolizumab extension trial upon trial completion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported