



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	

Results information

Result version number	v1
This version publication date	18 May 2018
First version publication date	18 May 2018

Trial information

Trial identification

Sponsor protocol code	MK-3475-040
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252042
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	Interim
Date of interim/final analysis	15 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2017
Global end of trial reached?	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	287

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:

This results disclosure is based on a data cutoff date of 15 May 2017, at which time 99 participants were ongoing in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

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

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

Dosage and administration details:

200 mg via intravenous (IV) infusion

Arm title	Active Comparator
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Arm description:

Participants received methotrexate 40 mg/m² IV (may have been escalated to 60 mg/m² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m² IV loading dose on Day 1 and 250 mg/m² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m² 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/m² IV infusion

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/m² via IV infusion

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/m² via IV infusion

Number of subjects in period 1	Pembrolizumab	Active Comparator
Started	247	248
Treated	246	234
Completed	0	0
Not completed	247	248
Adverse event, serious fatal	170	192
Consent withdrawn by subject	13	20
Physician decision	-	1
Ongoing in study	64	35

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.	
Reporting group title	Active Comparator
Reporting group description:	
Participants received methotrexate 40 mg/m ² IV (may have been 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	Active Comparator	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: Subjects			
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	207	207	414
More than one race	4	3	7
Unknown or Not Reported	16	15	31
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	67	138
EGOG PS=1	176	180	356
EGOG 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	58	119
Negative HPV Status	186	190	376
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

End points

End points reporting groups

Reporting group title	Pembrolizumab
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Reporting group description:

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

Reporting group title	Active Comparator
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Reporting group description:

Participants received methotrexate 40 mg/m² IV (may have been escalated to 60 mg/m² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m² IV loading dose on Day 1 and 250 mg/m² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m² on Days 1, 8, and 15 of each subsequent 3-week cycle.

Subject analysis set title	Pembrolizumab with PD-L1 ≥ 1% CPS
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants who received Pembrolizumab and had PD-L1 ≥ 1% CPS. Participants are included in the treatment arm to which they were randomized.

Subject analysis set title	Active Comparator with PD-L1 ≥ 1% CPS
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants with PD-L1 ≥ 1% CPS who received Active Comparator. Participants are included in the treatment group to which they were randomized.

Subject analysis set title	Pembrolizumab with CR or PR
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants who received Pembrolizumab and demonstrated a Complete Response (CR) or Partial Response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Participants are included in the treatment arm to which they were randomized.

Subject analysis set title	Active Comparator with CR or PR
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants who received Active Comparator and demonstrated a CR or PR according to RECIST 1.1. Participants are included in the treatment arm to which they were randomized.

Subject analysis set title	Pembrolizumab with PD-L1 ≥ 1% CPS and CR or PR
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants who received Pembrolizumab, had PD-L1 ≥ 1% CPS and experienced a CR or PR. Participants are included in the treatment arm to which they were randomized.

Subject analysis set title	Active Comparator with PD-L1 ≥ 1% CPS and CR or PR
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All randomized participants who received Active Comparator, had PD-L1 ≥ 1% CPS and experienced a CR or PR. Participants are included in the treatment arm to which they were randomized.

Primary: Overall Survival (OS) for All Participants

End point title	Overall Survival (OS) for All Participants
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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. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

End point type	Primary
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End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Active Comparator		
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	Hazard Ratio
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator.	
Comparison groups	Pembrolizumab v Active Comparator
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01605
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

Secondary: OS for Participants With PD-L1-Positive Expression Defined by $\geq 1\%$ CPS (PD-L1 $\geq 1\%$ CPS)

End point title	OS for Participants With PD-L1-Positive Expression Defined by $\geq 1\%$ CPS (PD-L1 $\geq 1\%$ 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 will be censored at the date of the last follow-up. The OS for all participants with PD-L1 expression $\geq 1\%$ CPS is presented. The efficacy population consisted of all randomized participants with PD-L1 $\geq 1\%$ 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 with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
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 Hazard Ratio, CPS \geq 1% CPS
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator.	
Comparison groups	Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
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: 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 progressive disease (PD) per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. The PFS per RECIST 1.1 for all participants is presented. 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	Active Comparator		
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	Hazard Ratio
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator.	
Comparison groups	Pembrolizumab v Active Comparator
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
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: 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 PD per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. The PFS per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. 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 with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
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	Hazard Ratio
Statistical analysis description: Cox regression model with treatment as a single covariate. Pembrolizumab is the numerator; Active Comparator is the denominator.	
Comparison groups	Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
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 blinded central imaging vendor review. The ORR per RECIST 1.1 for all participants is presented. 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	Active Comparator		
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	Difference in Percentages
Statistical analysis description:	
Stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). H0: difference in % = 0; H1: difference in % > 0.	
Comparison groups	Pembrolizumab v Active Comparator
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
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 CR (Disappearance of all target lesions) or a PR (At least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1 based on blinded central imaging vendor review. The ORR per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. 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 with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
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	Difference in Percentages
Statistical analysis description:	
Stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). H0: difference in % = 0; H1: difference in % > 0	
Comparison groups	Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
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: 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 CR or PR, DOR was defined as the time from first documented evidence of CR or PR per RECIST 1.1 until PD per RECIST 1.1 or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. DOR assessments were based on blinded central imaging vendor review. The DOR per RECIST 1.1 for all participants who experienced a CR or PR is presented. The efficacy population consisted of all randomized participants who demonstrated CR or PR. 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 with CR or PR	Active Comparator with CR or PR		
Subject group type	Subject analysis set	Subject analysis set		
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: DOR per RECIST 1.1 in Participants With PD-L1 \geq 1% CPS

End point title	DOR per RECIST 1.1 in Participants With PD-L1 \geq 1% CPS
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End point description:

For participants who demonstrated CR or PR, DOR was defined as the time from first documented evidence of CR or PR per RECIST 1.1 until PD per RECIST 1.1 or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. DOR assessments were based on blinded central imaging vendor review. The DOR per RECIST 1.1 for all participants with PD-L1 \geq 1% CPS who experienced a CR or PR is presented. The efficacy population consisted of all randomized participants with PD-L1 \geq 1% CPS who demonstrated CR or PR. Participants are included in the treatment group to which they were randomized.

End point type	Secondary
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End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab with PD-L1 \geq 1% CPS and CR or PR	Active Comparator with PD-L1 \geq 1% CPS and CR or PR		
Subject group type	Subject analysis set	Subject analysis set		
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: 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
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End point description:

TTP was defined as the time from randomization to the first documented PD based on assessments by the blinded central imaging vendor review per RECIST 1.1. Per RECIST 1.1, PD 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 PD. The TTP per RECIST 1.1 for all participants is presented. 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	Active Comparator		
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	Hazard Ratio
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Statistical analysis description:

Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

Comparison groups	Pembrolizumab v Active Comparator
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14545 ^[1]
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:

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

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
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End point description:

TTP was defined as the time from randomization to the first documented PD based on assessments by the blinded central imaging vendor review per RECIST 1.1. Per RECIST 1.1, PD 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 PD. The TTP per RECIST 1.1 for all participants with PD-L1 ≥1% CPS is presented. 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 with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
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	Hazard Ratio
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)	
Comparison groups	Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05851 ^[2]
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:

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

Secondary: PFS per Modified RECIST in All Participants

End point title	PFS per Modified RECIST in All Participants
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End point description:

PFS was defined as the time from randomization to the first documented PD on per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. Modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) 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. 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	Active Comparator		
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	Hazard Ratio
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator.	
Comparison groups	Pembrolizumab v Active Comparator
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
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 PD per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD 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 PD. Modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) 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. 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 with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
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	Hazard Ratio
Statistical analysis description: Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly. Pembrolizumab is the numerator; Active Comparator is the denominator. Positive).	
Comparison groups	Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
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
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment 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, 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 is temporally associated with the use of study treatment, is 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 27 months	

End point values	Pembrolizumab	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	234		
Units: Participants	238	227		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants Who Experienced At Least One AE in Participants With PD-L1 $\geq 1\%$ CPS
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment 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, 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 is temporally associated with the use of study treatment, is also an AE. The number of all participants with PD-L1 $\geq 1\%$ CPS who experienced at least one AE is presented. The safety population consisted of all randomized participants with PD-L1 $\geq 1\%$ CPS who received at least one dose of study treatment.

End point type	Secondary
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End point timeframe:

Up to approximately 27 months

End point values	Pembrolizumab with PD-L1 $\geq 1\%$ CPS	Active Comparator with PD-L1 $\geq 1\%$ CPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	195	183		
Units: Participants	192	178		

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
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End point description:

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
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End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	234		
Units: Participants	28	37		

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 \geq 1% CPS

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

The number of all participants with PD-L1 \geq 1% CPS who discontinued study treatment due to an AE is presented. The safety population consisted of all randomized participants with PD-L1 \geq 1% CPS who received at least one dose of study treatment.

End point type	Secondary
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End point timeframe:

Up to approximately 2 years

End point values	Pembrolizumab with PD-L1 \geq 1% CPS	Active Comparator with PD-L1 \geq 1% CPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	195	183		
Units: Participants	24	30		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 27 months (Up to 90 days after last dose of study drug)

Adverse event reporting additional description:

The Safety Population consisted of all randomized participants who received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Active Comparator
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Reporting group description:

Participants received methotrexate 40 mg/m² IV (may have been escalated to 60 mg/m² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m² IV loading dose on Day 1 and 250 mg/m² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m² on Days 1, 8, and 15 of each subsequent 3-week cycle.

Reporting group title	Pembrolizumab
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Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle.

Serious adverse events	Active Comparator	Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 234 (39.32%)	110 / 246 (44.72%)	
number of deaths (all causes)	25	20	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 234 (0.85%)	9 / 246 (3.66%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 2	
Tumour pain			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 234 (1.71%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 4	1 / 5	
Euthanasia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Face oedema			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ill-defined disorder			

subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 234 (0.85%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 234 (1.28%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Aspiration			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 234 (0.43%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eosinophilic pneumonia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal fistula			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 234 (1.28%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	1 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 234 (1.28%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	0 / 3	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			

subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 234 (1.28%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femoral neck fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site ulcer			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 234 (0.85%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	9 / 234 (3.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	8 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 234 (0.43%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 234 (0.85%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	2 / 2	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 234 (1.28%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malignant dysphagia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			

subjects affected / exposed	3 / 234 (1.28%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral discharge			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 234 (1.28%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			

subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungating wound			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	2 / 234 (0.85%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Kyphosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue haemorrhage			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 234 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disseminated tuberculosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 234 (0.43%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 234 (0.85%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral bacterial infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	2 / 234 (0.85%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 234 (6.84%)	20 / 246 (8.13%)	
occurrences causally related to treatment / all	4 / 17	1 / 21	
deaths causally related to treatment / all	1 / 5	0 / 6	
Pulmonary sepsis			

subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 234 (1.28%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stoma site infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 234 (0.85%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 234 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 234 (0.00%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 234 (1.28%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 234 (0.43%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 234 (0.00%)	7 / 246 (2.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 234 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Comparator	Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 234 (89.74%)	212 / 246 (86.18%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	7 / 234 (2.99%)	13 / 246 (5.28%)	
occurrences (all)	8	13	
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 234 (5.13%)	12 / 246 (4.88%)	
occurrences (all)	16	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	41 / 234 (17.52%)	37 / 246 (15.04%)	
occurrences (all)	52	47	
Fatigue			
subjects affected / exposed	63 / 234 (26.92%)	48 / 246 (19.51%)	
occurrences (all)	81	51	
Mucosal inflammation			
subjects affected / exposed	36 / 234 (15.38%)	17 / 246 (6.91%)	
occurrences (all)	51	21	
Pyrexia			
subjects affected / exposed	25 / 234 (10.68%)	24 / 246 (9.76%)	
occurrences (all)	35	38	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 234 (15.38%)	42 / 246 (17.07%)	
occurrences (all)	39	47	
Dyspnoea			
subjects affected / exposed	26 / 234 (11.11%)	30 / 246 (12.20%)	
occurrences (all)	31	32	
Haemoptysis			
subjects affected / exposed	6 / 234 (2.56%)	13 / 246 (5.28%)	
occurrences (all)	8	15	
Productive cough			

subjects affected / exposed occurrences (all)	5 / 234 (2.14%) 7	14 / 246 (5.69%) 14	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 234 (2.56%)	13 / 246 (5.28%)	
occurrences (all)	6	13	
Insomnia			
subjects affected / exposed	17 / 234 (7.26%)	22 / 246 (8.94%)	
occurrences (all)	17	22	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 234 (5.56%)	10 / 246 (4.07%)	
occurrences (all)	18	10	
Neutrophil count decreased			
subjects affected / exposed	24 / 234 (10.26%)	4 / 246 (1.63%)	
occurrences (all)	29	11	
Platelet count decreased			
subjects affected / exposed	13 / 234 (5.56%)	7 / 246 (2.85%)	
occurrences (all)	19	7	
Weight decreased			
subjects affected / exposed	26 / 234 (11.11%)	21 / 246 (8.54%)	
occurrences (all)	26	22	
White blood cell count decreased			
subjects affected / exposed	12 / 234 (5.13%)	2 / 246 (0.81%)	
occurrences (all)	15	3	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 234 (9.40%)	21 / 246 (8.54%)	
occurrences (all)	24	25	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	51 / 234 (21.79%)	62 / 246 (25.20%)	
occurrences (all)	70	77	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	12 / 234 (5.13%)	9 / 246 (3.66%)	
occurrences (all)	12	9	
Constipation			
subjects affected / exposed	37 / 234 (15.81%)	43 / 246 (17.48%)	
occurrences (all)	43	49	
Diarrhoea			
subjects affected / exposed	41 / 234 (17.52%)	36 / 246 (14.63%)	
occurrences (all)	50	54	
Dry mouth			
subjects affected / exposed	6 / 234 (2.56%)	15 / 246 (6.10%)	
occurrences (all)	6	15	
Dysphagia			
subjects affected / exposed	15 / 234 (6.41%)	21 / 246 (8.54%)	
occurrences (all)	16	23	
Nausea			
subjects affected / exposed	44 / 234 (18.80%)	34 / 246 (13.82%)	
occurrences (all)	52	43	
Stomatitis			
subjects affected / exposed	26 / 234 (11.11%)	7 / 246 (2.85%)	
occurrences (all)	34	9	
Vomiting			
subjects affected / exposed	23 / 234 (9.83%)	23 / 246 (9.35%)	
occurrences (all)	34	27	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 234 (11.54%)	1 / 246 (0.41%)	
occurrences (all)	27	1	
Dermatitis acneiform			
subjects affected / exposed	18 / 234 (7.69%)	0 / 246 (0.00%)	
occurrences (all)	28	0	
Dry skin			
subjects affected / exposed	17 / 234 (7.26%)	4 / 246 (1.63%)	
occurrences (all)	19	4	
Pruritus			
subjects affected / exposed	17 / 234 (7.26%)	18 / 246 (7.32%)	
occurrences (all)	40	22	

Rash subjects affected / exposed occurrences (all)	38 / 234 (16.24%) 81	25 / 246 (10.16%) 32	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	9 / 234 (3.85%) 9	37 / 246 (15.04%) 40	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	5 / 234 (2.14%) 6 8 / 234 (3.42%) 8 17 / 234 (7.26%) 17	19 / 246 (7.72%) 20 23 / 246 (9.35%) 24 19 / 246 (7.72%) 19	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypercalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	43 / 234 (18.38%) 48 13 / 234 (5.56%) 14 19 / 234 (8.12%) 21 20 / 234 (8.55%) 25 16 / 234 (6.84%) 17 12 / 234 (5.13%) 14	31 / 246 (12.60%) 37 14 / 246 (5.69%) 16 23 / 246 (9.35%) 27 10 / 246 (4.07%) 11 12 / 246 (4.88%) 14 15 / 246 (6.10%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2015	Amendment 01: Increased sample size from 466 to 600 participants, added hypotheses, and added statistical analyses for the PD-L1 Strong Positive (TPS >50% PD-L1) population; Inclusion/Exclusion criteria modifications were made to align with program standards.
16 April 2016	Amendment 10: Decreased the sample size from 600 to 466 subjects, downgraded OS in the PD-L1 positive subjects and PFS from primary hypotheses to key secondary hypotheses, replaced hypotheses on the PD-L1 population with hypotheses on the CPS ≥ 1 population, promoted ORR to the key secondary endpoints, updated language to include PD-L1 status masking, and included the role of unblended Sponsor personnel.
02 November 2016	Amendment 11: Updated, in the Statistical Analysis Plan, 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	Amendment 12: Added text and updated Dose Modification Guidelines for Pembrolizumab and added text to enable survival follow-up activities throughout the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported