Clinical trial results:
A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)

Summary

EudraCT number	2014-001473-14
Trial protocol	SE CZ LT LV PT PL EE BG HU
Global end of trial date	02 February 2023

Results information

Result version number	v1 (current)
This version publication date	23 September 2023
First version publication date	23 September 2023

Trial information

Trial identification

Sponsor protocol code	3475-042

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02220894
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	02 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2018
Global end of trial reached?	Yes
Global end of trial date	02 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) in subjects with TPS≥50%, advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies, to compare the OS in subjects with TPS≥20%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies and to compare the OS in subjects with TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

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	30 October 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	Argentina: 40
Country: Number of subjects enrolled	Brazil: 113
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Chile: 42
Country: Number of subjects enrolled	China: 92
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Czechia: 39
Country: Number of subjects enrolled	Estonia: 12
Country: Number of subjects enrolled	Guatemala: 11
Country: Number of subjects enrolled	Hong Kong: 13
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Japan: 93
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Latvia: 49
Country: Number of subjects enrolled	Lithuania: 30
Country: Number of subjects enrolled	Malaysia: 35
Country: Number of subjects enrolled	Mexico: 32

Country: Number of subjects enrolled	Peru: 23
Country: Number of subjects enrolled	Philippines: 22
Country: Number of subjects enrolled	Poland: 90
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Romania: 26
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 16
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 52
Country: Number of subjects enrolled	Turkey: 109
Country: Number of subjects enrolled	Ukraine: 91
Country: Number of subjects enrolled	Viet Nam: 2
Worldwide total number of subjects	1274
EEA total number of subjects	270

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)	707
From 65 to 84 years	554
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Of the 1275 participants randomized (pembrolizumab=638, chemotherapy=637), 1 participant assigned to receive pembrolizumab died prior to randomization and was randomized in error. The intent to treat population was defined as participants alive at the time of randomization, so the actual randomized population included 637 participants in each arm.

Pre-assignment

Screening details:

Pembrolizumab-treated participants, who attained a complete response (CR) or who stopped treatment after 35 administrations for reasons other than disease progression or intolerability may have been eligible for re-treatment with pembrolizumab after they had experienced radiographic disease as per protocol-defined criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.

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

Dosage and administration details:

200 mg on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments

Arm title	Chemotherapy (Standard of Care [SOC] Treatment)

Arm description:

Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W

Arm type	Active comparator
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose

900 mg)

Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	ALIMTA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m^2 IV on Day 1 Q3W for a maximum of 6 cycles

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	TAXOL®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m^2 IV on Day 1 of every 21-day cycle (Q3W) for a maximum of 6 cycles

Number of subjects in period 1	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)
Started	637	637
Treated	636	615
Completed	0	0
Not completed	637	637
Adverse event, serious fatal	418	508
Consent withdrawn by subject	10	9
Adverse event, non-fatal	127	74
Withdrawal by Parent/Guardian	-	1
Site Terminated by Sponsor	2	-
Participation in Study Terminated by Sponsor	80	41
Lost to follow-up	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.	
Reporting group title	Chemotherapy (Standard of Care [SOC] Treatment)
Reporting group description:	
Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W	

Reporting group values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)	Total
Number of subjects	637	637	1274
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	62.5	63.1	
standard deviation	± 9.9	± 9.4	-
Sex: Female, Male Units: Participants			
Female	187	185	372
Male	450	452	902
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	10	5	15
Asian	189	187	376
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	10	13	23
White	398	412	810
More than one race	30	19	49
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			
ECOG PS=0	197	192	389
ECOG PS=1	439	445	884
ECOG PS=2	1	0	1
Programmed Cell Death-Ligand 1 (PD-L1) Tumor Status			
Participants were assessed for their PD-L1 tumor expression status by immunohistochemistry assay using tumor tissue from an archival or newly obtained biopsy. Participants with a tumor proportion score (TPS) were classified as follows: ≥50% = PD-L1 strongly positive; 1-49% = PD-L1 weakly positive; and <1% = PD-L1 negative.			
Units: Subjects			
TPS=≥50%	299	300	599
TPS=20-49%	114	105	219
TPS=1-19%	224	232	456
TPS=<1%	0	0	0
Tumor Histology			
Participants were classified according to tumor histology: Squamous or Non-squamous. The tumor histology determined potential treatment regimen.			
Units: Subjects			
Squamous	242	249	491
Non-squamous	395	388	783

End points

End points reporting groups

Reporting group title	Pembrolizumab

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) for a maximum of 35 cycles (21-day cycles). Some participants may have been eligible for re-treatment with pembrolizumab monotherapy after they had experienced radiographic disease as per protocol-defined criteria.

Reporting group title	Chemotherapy (Standard of Care [SOC] Treatment)

Reporting group description:

Participants received carboplatin at target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W

Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point title	Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point description:

OS was determined for participants with a TPS of ≥50% and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The OS for participants with a TPS ≥50% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥50%.

End point type	Primary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Months				
median (confidence interval 95%)	20.0 (15.9 to 24.2)	12.2 (10.4 to 14.6)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.86

Notes:

[1] - One-sided p-value based on stratified log-rank test

Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point title	Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point description:

OS was determined for participants with a TPS of ≥20% and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The OS for participants with a TPS ≥20% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥20%.

End point type	Primary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	405		
Units: Months				
median (confidence interval 95%)	18.0 (15.4 to 21.9)	13.0 (11.6 to 15.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	818
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.91

Notes:

[2] - One-sided p-value based on stratified log-rank test

Primary: Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point title	Overall Survival (OS) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point description:

OS was determined for participants with a TPS of ≥1% and was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was OS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The OS for participants with a TPS ≥1% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥1%.

End point type	Primary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	637	637		
Units: Months				
median (confidence interval 95%)	16.4 (14.0 to 19.7)	12.1 (11.3 to 13.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.93

Notes:

[3] - One-sided p-value based on stratified log-rank test

Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point title	Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point description:

PFS was determined for participants with a TPS of ≥50% and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The PFS for participants with a TPS ≥50% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥50%.

End point type	Secondary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Months				
median (confidence interval 95%)	6.5 (5.9 to 8.5)	6.4 (6.2 to 7.2)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1

Notes:

[4] - One-sided p-value based on stratified log-rank test

Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point title	Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point description:

PFS was determined for participants with a TPS of ≥20% and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The PFS for participants with a TPS ≥20% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥20%.

End point type	Secondary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	405		
Units: Months				
median (confidence interval 95%)	6.2 (5.1 to 7.4)	6.7 (6.3 to 8.0)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	818
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2134 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.1

Notes:

[5] - One-sided p-value based on stratified log-rank test

Secondary: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point title	Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point description:

PFS was determined for participants with a TPS of ≥1% and was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of 1 or more new lesions was also considered PD. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was PFS in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The PFS for participants with a TPS ≥1% is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥1%.

End point type	Secondary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	637	637		
Units: Months				
median (confidence interval 95%)	5.4 (4.3 to 6.2)	6.6 (6.3 to 7.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

Hazard ratio based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS=≥50% vs. TPS=1-49%) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7964 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.19

Notes:

[6] - One-sided p-value based on stratified log-rank test

Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥50%

End point description:

ORR was determined for participants with a TPS of ≥50%. ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if

the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The percentage of participants who had a TPS ≥50% and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥50%.

End point type	Secondary
End point timeframe:	
Up to 45 months	

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Percentage of participants				
number (confidence interval 95%)	39.1 (33.6 to 44.9)	32.0 (26.8 to 37.6)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC
Statistical analysis description:	
Difference in Percentage (DP) for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. nonsquamous).	
Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0353 [7]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Difference in Percentage (DP)
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	14.6

Notes:

[7] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥20%

End point description:

ORR was determined for participants with a TPS of ≥20%. ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The percentage of participants who had a TPS ≥20% and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥20%.

End point type	Secondary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	405		
Units: Percentage of participants				
number (confidence interval 95%)	33.2 (28.6 to 37.9)	28.9 (24.5 to 33.6)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

DP for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS=≥50% vs. TPS=1-
49%) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	818
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0744 [8]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Difference in Percentage (DP)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	10.9

Notes:

[8] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in

Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with a Tumor Proportion Score (TPS) of ≥1%

End point description:

ORR was determined for participants with a TPS of ≥1%. ORR was determined per RECIST 1.1 and was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The efficacy hypothesis was analyzed using a sequential testing strategy that involved testing a hypothesis only if the superiority of pembrolizumab over chemotherapy was established for all the preceding hypotheses. The order of testing was ORR in participants with TPS≥50%, then with TPS≥20%, and finally with TPS≥1%. The percentage of participants who had a TPS ≥1% and who experienced a CR or PR is presented. The analysis population included all participants who were alive at the time of randomization and had a TPS of ≥1%.

End point type	Secondary

End point timeframe:

Up to 45 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	637	637		
Units: Percentage of participants				
number (confidence interval 95%)	27.2 (23.7 to 30.8)	26.5 (23.1 to 30.1)		

Statistical analyses

Statistical analysis title	Pembrolizumab vs SOC

Statistical analysis description:

DP for pembrolizumab vs. chemotherapy based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1), PD-L1 expression status (TPS=≥50% vs. TPS=1-49%) and histology (squamous vs. non-squamous).

Comparison groups	Pembrolizumab v Chemotherapy (Standard of Care [SOC] Treatment)
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.406 [9]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Difference in Percentage (DP)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	5.4

Notes:

[9] - One-sided p-value for testing. H0: difference in percentages=0 vs. H1: difference in percentages >0

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

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

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 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 participants who experienced at least one AE is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 93 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	636	615		
Units: Participants	608	606		

Statistical analyses

No statistical analyses for this end point

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

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

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 participants who discontinued study treatment due to an AE is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 93 months

End point values	Pembrolizumab	Chemotherapy (Standard of Care [SOC] Treatment)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	636	615		
Units: Participants	126	93		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 93 months

Adverse event reporting additional description:

Population: All participants receiving ≥1 dose of study treatment. Per protocol, progression of cancer under study was not considered an AE unless related to study drug. Therefore, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" not related 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

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 Q3W for a maximum of 35 cycles (21-day cycles)

Reporting group title	Pembrolizumab Second Course

Reporting group description:

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	Chemotherapy (SOC Treatment)

Reporting group description:

Participants received carboplatin at target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles) OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W for a maximum of 6 cycles (21-day cycles). Participants with non-squamous histologies received optional additional maintenance treatment with pemetrexed 500 mg/m^2 by IV infusion on Day 1 Q3W.

Serious adverse events	Pembrolizumab	Pembrolizumab Second Course	Chemotherapy (SOC Treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	261 / 636 (41.04%)	8 / 34 (23.53%)	193 / 615 (31.38%)
number of deaths (all causes)	528	18	582
number of deaths resulting from adverse events	13	0	14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Metastases to bone			

subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Oesophageal carcinoma			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	0 / 615 (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
Adenocarcinoma gastric			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Keratoacanthoma			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Cancer pain			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Gastric cancer			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Infected neoplasm			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Anogenital warts			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Lung cancer metastatic			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous cell carcinoma			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Tumour necrosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	1 / 636 (0.16%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Aortic aneurysm			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial thrombosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Embolism			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	9 / 636 (1.42%)	0 / 34 (0.00%)	5 / 615 (0.81%)
occurrences causally related to treatment / all	1 / 9	0 / 0	0 / 5
deaths causally related to treatment / all	1 / 9	0 / 0	0 / 5
Fatigue			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 636 (0.63%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental death			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Asthenia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	4 / 615 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ill-defined disorder			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Performance status decreased			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Prosthetic cardiac valve thrombosis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Sudden death			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
General physical health deterioration			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media allergy			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Ovarian cyst torsion			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	6 / 6	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	5 / 615 (0.81%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	7 / 636 (1.10%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	14 / 636 (2.20%)	0 / 34 (0.00%)	5 / 615 (0.81%)
occurrences causally related to treatment / all	8 / 16	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	13 / 636 (2.04%)	0 / 34 (0.00%)	11 / 615 (1.79%)
occurrences causally related to treatment / all	2 / 13	0 / 0	5 / 11
deaths causally related to treatment / all	1 / 5	0 / 0	1 / 5
Respiratory failure			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	4 / 615 (0.65%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 3
Acute respiratory failure			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Acute pulmonary oedema			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Asthma			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Atelectasis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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 chronic			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Chronic respiratory failure			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pleurisy			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hydrothorax			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Lung disorder			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagobronchial fistula			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	7 / 636 (1.10%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	2 / 8	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Pneumonitis			
subjects affected / exposed	25 / 636 (3.93%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	26 / 26	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pulmonary fistula			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pulmonary thrombosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tracheal stenosis			

subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Pulmonary haemorrhage			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 2
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Delirium			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Completed suicide			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	5 / 615 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			

subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	1 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood prolactin increased			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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 bilirubin increased			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Blood calcium decreased			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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 pressure increased			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Bilirubin conjugated increased			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Cervical vertebral fracture			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Femur fracture			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Radius fracture			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 636 (0.00%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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			
Coronary artery disease			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Myocardial infarction			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute myocardial infarction			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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 failure			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Arrhythmia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Atrial flutter			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Aortic valve stenosis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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 failure acute			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	0 / 615 (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
Cardio-respiratory arrest			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocarditis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pericarditis			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Sinus tachycardia			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pericardial effusion			
subjects affected / exposed	6 / 636 (0.94%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhage intracranial			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Dizziness			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Altered state of consciousness			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	0 / 615 (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
Coma			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Embolic stroke			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Encephalopathy			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	16 / 615 (2.60%)
occurrences causally related to treatment / all	0 / 3	0 / 0	21 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	8 / 615 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	6 / 615 (0.98%)
occurrences causally related to treatment / all	1 / 1	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Leukopenia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	16 / 615 (2.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	14 / 17
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Normochromic anaemia			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 636 (0.79%)	1 / 34 (2.94%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	3 / 5	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Abdominal pain			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	6 / 636 (0.94%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	5 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Duodenal perforation			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Enterocolitis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Gastritis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glossitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Haematemesis			

subjects affected / exposed	0 / 636 (0.00%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ileus paralytic			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Melaena			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Nausea			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 636 (0.00%)	1 / 34 (2.94%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal fistula			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pancreatic mass			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Rectal ulcer			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Stomatitis			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (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
Neutropenic colitis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Vomiting			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			

subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hepatitis acute			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hepatitis toxic			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Immune-mediated hepatitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Rash			
subjects affected / exposed	1 / 636 (0.16%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Acute kidney injury			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	4 / 615 (0.65%)
occurrences causally related to treatment / all	1 / 3	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Glomerulonephritis membranous			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hydronephrosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Nephropathy			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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			
Adrenal insufficiency			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hypophysitis			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hypothyroidism			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Neck pain			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Myalgia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pain in extremity			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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			

Upper respiratory tract infection			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Lung abscess			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	49 / 636 (7.70%)	2 / 34 (5.88%)	34 / 615 (5.53%)
occurrences causally related to treatment / all	1 / 54	0 / 2	14 / 41
deaths causally related to treatment / all	0 / 10	0 / 0	4 / 7
Septic shock			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	4 / 615 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	2 / 2
Lymph gland infection			
subjects affected / exposed	0 / 636 (0.00%)	1 / 34 (2.94%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abscess jaw			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Amoebiasis			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amoebic dysentery			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Anal abscess			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchitis			
subjects affected / exposed	8 / 636 (1.26%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	1 / 8	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Candida infection			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Cystitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Device related infection			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Diverticulitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Infectious pleural effusion			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
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	2 / 636 (0.31%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	3 / 636 (0.47%)	1 / 34 (2.94%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	1 / 4	0 / 0	3 / 4
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Pseudomembranous colitis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 2
Respiratory tract infection			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access site infection			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	3 / 615 (0.49%)
occurrences causally related to treatment / all	1 / 4	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			

subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Diabetes mellitus			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 636 (0.00%)	0 / 34 (0.00%)	1 / 615 (0.16%)
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	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 636 (0.31%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	0 / 615 (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
Hypoglycaemia			

subjects affected / exposed	1 / 636 (0.16%)	0 / 34 (0.00%)	2 / 615 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pembrolizumab	Pembrolizumab Second Course	Chemotherapy (SOC Treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	535 / 636 (84.12%)	21 / 34 (61.76%)	577 / 615 (93.82%)
Vascular disorders			
Hypertension			
subjects affected / exposed	41 / 636 (6.45%)	1 / 34 (2.94%)	14 / 615 (2.28%)
occurrences (all)	49	1	17
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	15 / 636 (2.36%)	1 / 34 (2.94%)	32 / 615 (5.20%)
occurrences (all)	15	1	49
Asthenia			
subjects affected / exposed	69 / 636 (10.85%)	2 / 34 (5.88%)	81 / 615 (13.17%)
occurrences (all)	92	3	110
Chest pain			
subjects affected / exposed	56 / 636 (8.81%)	1 / 34 (2.94%)	43 / 615 (6.99%)
occurrences (all)	61	1	52
Fatigue			
subjects affected / exposed	101 / 636 (15.88%)	0 / 34 (0.00%)	129 / 615 (20.98%)
occurrences (all)	129	0	193
Pyrexia			
subjects affected / exposed	64 / 636 (10.06%)	1 / 34 (2.94%)	52 / 615 (8.46%)
occurrences (all)	82	1	63
Oedema peripheral			
subjects affected / exposed	32 / 636 (5.03%)	1 / 34 (2.94%)	36 / 615 (5.85%)
occurrences (all)	33	1	50
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	107 / 636 (16.82%)	2 / 34 (5.88%)	66 / 615 (10.73%)
occurrences (all)	128	2	72
Dyspnoea			
subjects affected / exposed	105 / 636 (16.51%)	1 / 34 (2.94%)	72 / 615 (11.71%)
occurrences (all)	120	1	81
Haemoptysis			
subjects affected / exposed	45 / 636 (7.08%)	3 / 34 (8.82%)	23 / 615 (3.74%)
occurrences (all)	62	4	25
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 636 (5.35%)	0 / 34 (0.00%)	45 / 615 (7.32%)
occurrences (all)	38	0	51
Investigations			
Weight decreased			
subjects affected / exposed	67 / 636 (10.53%)	4 / 34 (11.76%)	48 / 615 (7.80%)
occurrences (all)	71	4	49
Platelet count decreased			
subjects affected / exposed	7 / 636 (1.10%)	0 / 34 (0.00%)	65 / 615 (10.57%)
occurrences (all)	7	0	144
Neutrophil count decreased			
subjects affected / exposed	6 / 636 (0.94%)	0 / 34 (0.00%)	89 / 615 (14.47%)
occurrences (all)	6	0	239
Aspartate aminotransferase increased			
subjects affected / exposed	62 / 636 (9.75%)	3 / 34 (8.82%)	57 / 615 (9.27%)
occurrences (all)	83	3	87
Alanine aminotransferase increased			
subjects affected / exposed	66 / 636 (10.38%)	3 / 34 (8.82%)	72 / 615 (11.71%)
occurrences (all)	89	4	97
White blood cell count decreased			
subjects affected / exposed	5 / 636 (0.79%)	1 / 34 (2.94%)	77 / 615 (12.52%)
occurrences (all)	7	1	228
Blood alkaline phosphatase increased			
subjects affected / exposed	39 / 636 (6.13%)	2 / 34 (5.88%)	30 / 615 (4.88%)
occurrences (all)	46	2	35
Nervous system disorders			

Dizziness			
subjects affected / exposed	25 / 636 (3.93%)	0 / 34 (0.00%)	39 / 615 (6.34%)
occurrences (all)	28	0	49
Headache			
subjects affected / exposed	44 / 636 (6.92%)	2 / 34 (5.88%)	51 / 615 (8.29%)
occurrences (all)	58	2	62
Neuropathy peripheral			
subjects affected / exposed	5 / 636 (0.79%)	0 / 34 (0.00%)	52 / 615 (8.46%)
occurrences (all)	6	0	62
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 636 (0.63%)	0 / 34 (0.00%)	43 / 615 (6.99%)
occurrences (all)	5	0	55
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	6 / 636 (0.94%)	0 / 34 (0.00%)	59 / 615 (9.59%)
occurrences (all)	7	0	86
Neutropenia			
subjects affected / exposed	6 / 636 (0.94%)	0 / 34 (0.00%)	85 / 615 (13.82%)
occurrences (all)	9	0	177
Anaemia			
subjects affected / exposed	102 / 636 (16.04%)	2 / 34 (5.88%)	253 / 615 (41.14%)
occurrences (all)	124	2	332
Leukopenia			
subjects affected / exposed	10 / 636 (1.57%)	1 / 34 (2.94%)	35 / 615 (5.69%)
occurrences (all)	17	1	63
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	74 / 636 (11.64%)	3 / 34 (8.82%)	78 / 615 (12.68%)
occurrences (all)	94	5	107
Constipation			
subjects affected / exposed	78 / 636 (12.26%)	3 / 34 (8.82%)	131 / 615 (21.30%)
occurrences (all)	98	3	168
Nausea			
subjects affected / exposed	73 / 636 (11.48%)	1 / 34 (2.94%)	195 / 615 (31.71%)
occurrences (all)	98	1	407
Vomiting			

subjects affected / exposed	50 / 636 (7.86%)	0 / 34 (0.00%)	106 / 615 (17.24%)
occurrences (all)	62	0	167
Stomatitis			
subjects affected / exposed	16 / 636 (2.52%)	0 / 34 (0.00%)	33 / 615 (5.37%)
occurrences (all)	18	0	40
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 636 (0.47%)	0 / 34 (0.00%)	138 / 615 (22.44%)
occurrences (all)	4	0	139
Pruritus			
subjects affected / exposed	67 / 636 (10.53%)	2 / 34 (5.88%)	22 / 615 (3.58%)
occurrences (all)	83	4	23
Rash			
subjects affected / exposed	72 / 636 (11.32%)	1 / 34 (2.94%)	43 / 615 (6.99%)
occurrences (all)	82	4	52
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	76 / 636 (11.95%)	3 / 34 (8.82%)	10 / 615 (1.63%)
occurrences (all)	99	5	10
Hyperthyroidism			
subjects affected / exposed	37 / 636 (5.82%)	1 / 34 (2.94%)	4 / 615 (0.65%)
occurrences (all)	38	1	4
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	31 / 636 (4.87%)	0 / 34 (0.00%)	34 / 615 (5.53%)
occurrences (all)	36	0	40
Myalgia			
subjects affected / exposed	32 / 636 (5.03%)	1 / 34 (2.94%)	70 / 615 (11.38%)
occurrences (all)	37	1	135
Back pain			
subjects affected / exposed	61 / 636 (9.59%)	1 / 34 (2.94%)	43 / 615 (6.99%)
occurrences (all)	70	1	51
Arthralgia			
subjects affected / exposed	86 / 636 (13.52%)	3 / 34 (8.82%)	87 / 615 (14.15%)
occurrences (all)	109	3	162
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	46 / 636 (7.23%)	1 / 34 (2.94%)	32 / 615 (5.20%)
occurrences (all)	62	1	41
Pneumonia			
subjects affected / exposed	39 / 636 (6.13%)	1 / 34 (2.94%)	30 / 615 (4.88%)
occurrences (all)	40	1	35
Nasopharyngitis			
subjects affected / exposed	26 / 636 (4.09%)	3 / 34 (8.82%)	21 / 615 (3.41%)
occurrences (all)	37	4	26
Bronchitis			
subjects affected / exposed	30 / 636 (4.72%)	3 / 34 (8.82%)	23 / 615 (3.74%)
occurrences (all)	34	4	25
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	21 / 636 (3.30%)	1 / 34 (2.94%)	32 / 615 (5.20%)
occurrences (all)	26	1	43
Decreased appetite			
subjects affected / exposed	108 / 636 (16.98%)	3 / 34 (8.82%)	134 / 615 (21.79%)
occurrences (all)	127	3	209

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2016	Updated Statistical Analysis Plan and Inclusion/Exclusion Criteria
11 May 2017	Updates to the primary, secondary, and exploratory objectives/hypothesis
01 March 2018	Expanded dose modification guidelines
20 April 2021	Added language regarding the enrollment of participants in a pembrolizumab extension study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported