Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590)

Summary

EudraCT number	2017-000958-19
Trial protocol	DE GB ES FR DK RO
Global end of trial date	10 July 2023

Results information

Result version number	v1 (current)
This version publication date	19 June 2024
First version publication date	19 June 2024

Trial information

Trial identification

Sponsor protocol code	3475-590

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03189719
WHO universal trial number (UTN)	-
Other trial identifiers	MK-3475-590: Merck

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	10 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2020
Global end of trial reached?	Yes
Global end of trial date	10 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to evaluate efficacy and safety of pembrolizumab plus standard of care (SOC) chemotherapy with cisplatin and 5-fluorouracil (5-FU) versus placebo plus SOC chemotherapy with cisplatin and 5-FU as first-line treatment in participants with locally advanced or metastatic esophageal carcinoma.

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	25 July 2017
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: 13
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Chile: 16
Country: Number of subjects enrolled	China: 106
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Costa Rica: 7
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Guatemala: 20
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Japan: 141
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Peru: 9

Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Thailand: 20
Country: Number of subjects enrolled	Türkiye: 25
Country: Number of subjects enrolled	Taiwan: 43
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	South Africa: 7
Worldwide total number of subjects	749
EEA total number of subjects	92

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)	427
From 65 to 84 years	319
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

749 participants were randomized 1:1 to receive either pembrolizumab plus standard of care (SOC) chemotherapy, or placebo plus SOC chemotherapy.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + SOC

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus standard of care (SOC) chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

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

Dosage and administration details:

200 mg administered IV Q3W on Day 1 of each 3-week cycle, up to 35 administrations.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg/m^2/day (4000 mg/m^2 total per cycle) administered as continuous IV infusion on Days 1 to 5 (120 hours) of each 3-week cycle, or per local standard for 5-FU administration, up to 35 administrations.

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

Dosage and administration details:

80 mg/m^2 administered IV Q3W on Day 1 of each 3-week cycle. Duration of cisplatin treatment will be capped at 6 doses.

Arm title	Placebo + SOC

Arm description:

Participants received placebo to pembrolizumab (saline) IV Q3W plus SOC chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours)

Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to pembrolizumab (saline) administered IV Q3W on Day 1 of each 3-week cycle, up to 35 administrations.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg/m^2/day (4000 mg/m^2 total per cycle) administered as continuous IV infusion on Days 1 to 5 (120 hours) of each 3-week cycle, or per local standard for 5-FU administration, up to 35 administrations.

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

Dosage and administration details:

80 mg/m^2 administered IV Q3W on Day 1 of each 3-week cycle. Duration of cisplatin treatment will be capped at 6 doses.

Number of subjects in period 1	Pembrolizumab + SOC	Placebo + SOC
Started	373	376
Treated	370	370
Completed	0	0
Not completed	373	376
Adverse event, serious fatal	325	361
Physician decision	1	-
Consent withdrawn by subject	7	3
Sponsor Decision	40	12

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + SOC
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus standard of care (SOC) chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.	
Reporting group title	Placebo + SOC
Reporting group description:	
Participants received placebo to pembrolizumab (saline) IV Q3W plus SOC chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.	

Reporting group values	Pembrolizumab + SOC	Placebo + SOC	Total
Number of subjects	373	376	749
Age categorical Units: Subjects			
Adults (18-64 years)	201	226	427
From 65-84 years	171	148	319
85 years and over	1	2	3
Age Continuous Units: Years			
arithmetic mean	62.8	62.0	
standard deviation	± 9.8	± 9.2	-
Sex: Female, Male Units: Participants			
Female	67	57	124
Male	306	319	625
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	9	12	21
Asian	201	199	400
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	2	7
White	139	139	278
More than one race	5	9	14
Unknown or Not Reported	14	15	29
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	42	57	99
Not Hispanic or Latino	315	296	611
Unknown or Not Reported	16	23	39
Geographic Region			
Participants were stratified according to Geographic Region of enrolling site (Asia versus Rest of World)			
Units: Subjects			
Asia	196	197	393

Rest of World	177	179	356
Histology			
Participants were stratified according to baseline Histology (adenocarcinoma versus squamous cell carcinoma)			
Units: Subjects			
Adenocarcinoma	99	102	201
Squamous Cell Carcinoma	274	274	548
Eastern Cooperative Group Performance Status (ECOG PS)			
ECOG PS 0 = Fully active, able to carry on all pre-disease performance without restriction), ECOG PS 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ECOG PS 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours. Participants were stratified according to baseline ECOG PS (0 versus 1).			
Units: Subjects			
ECOG PS 0	149	150	299
ECOG PS 1	223	225	448
ECOG PS 2	1	1	2

End points

End points reporting groups

Reporting group title	Pembrolizumab + SOC

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus standard of care (SOC) chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

Reporting group title	Placebo + SOC

Reporting group description:

Participants received placebo to pembrolizumab (saline) IV Q3W plus SOC chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

Primary: OS in Participants With ESCC

End point title	OS in Participants With ESCC

End point description:

Overall survival was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS is reported here for all participants of the ITT population (all randomized) who had ESCC.

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	274		
Units: Months				
median (confidence interval 95%)	12.6 (10.2 to 14.3)	9.8 (8.6 to 11.1)		

Statistical analyses

Statistical analysis title	OS in ESCC

Statistical analysis description:

OS in ESCC participants of the pembrolizumab + SOC arm was compared to OS in ESCC participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.88

Primary: Overall Survival (OS) in Participants With Esophageal Squamous Cell Carcinoma (ESCC) Whose Tumors Are Programmed Cell Death-Ligand 1 (PD-L1) Biomarker-Positive (Combined Positive Score [CPS] ≥10)

End point title	Overall Survival (OS) in Participants With Esophageal Squamous Cell Carcinoma (ESCC) Whose Tumors Are Programmed Cell Death-Ligand 1 (PD-L1) Biomarker-Positive (Combined Positive Score [CPS] ≥10)

End point description:

Overall survival was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS is reported here for all participants of the Intent-To-Treat (ITT) population (all randomized) who had ESCC and who were PD-L1 CPS ≥10.

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	143		
Units: Months				
median (confidence interval 95%)	13.9 (11.1 to 17.7)	8.8 (7.8 to 10.5)		

Statistical analyses

Statistical analysis title	OS in ESCC PD-L1 CPS ≥10

Statistical analysis description:

OS in ESCC PD-L1 CPS ≥10 participants of the pembrolizumab + SOC arm was compared to OS in ESCC PD-L1 CPS ≥10 participants of the placebo + SOC arm based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.75

Primary: OS in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	OS in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

Overall survival was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS is reported here for all participants of the ITT population (all randomized) who were PD-L1 CPS ≥10.

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	197		
Units: Months				
median (confidence interval 95%)	13.5 (11.1 to 15.6)	9.4 (8.0 to 10.7)		

Statistical analyses

Statistical analysis title	OS in PD-L1 CPS ≥10

Statistical analysis description:

OS in PD-L1 CPS ≥10 participants of the pembrolizumab + SOC arm was compared to OS in PD-L1 CPS ≥10 participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.78

Primary: OS in All Participants

End point title	OS in All Participants

End point description:

Overall survival was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS is reported here for all participants of the ITT population (all randomized).

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	376		
Units: Months				
median (confidence interval 95%)	12.4 (10.5 to 14.0)	9.8 (8.8 to 10.8)		

Statistical analyses

Statistical analysis title	OS in all participants

Statistical analysis description:

OS in all participants of the pembrolizumab + SOC arm was compared to OS in all participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World), tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma), and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.86

Primary: Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed By Investigator in Participants With ESCC

End point title	Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed By Investigator in Participants With ESCC

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 as assessed by the investigator, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS is reported here for all participants of the ITT population (all randomized) who had ESCC.

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	274		
Units: Months				
median (confidence interval 95%)	6.3 (6.2 to 6.9)	5.8 (5.0 to 6.1)		

Statistical analyses

Statistical analysis title	PFS in ESCC

Statistical analysis description:

PFS in ESCC participants of the pembrolizumab + SOC arm was compared to PFS in ESCC participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.78

Primary: PFS Per RECIST 1.1 As Assessed By Investigator in All Participants

End point title	PFS Per RECIST 1.1 As Assessed By Investigator in All Participants

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 as assessed by the investigator, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS is reported here for all participants of the ITT population (all randomized).

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	376		
Units: Months				
median (confidence interval 95%)	6.3 (6.2 to 6.9)	5.8 (5.0 to 6.0)		

Statistical analyses

Statistical analysis title	PFS in all participants

Statistical analysis description:

PFS in all participants of the pembrolizumab + SOC arm was compared to PFS in all participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World), tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma), and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.76

Primary: PFS Per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	PFS Per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 as assessed by the investigator, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS is reported here for all participants of the ITT population (all randomized) who were PD-L1 CPS ≥10.

End point type	Primary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	197		
Units: Months				
median (confidence interval 95%)	7.5 (6.2 to 8.2)	5.5 (4.3 to 6.0)		

Statistical analyses

Statistical analysis title	PFS in PD-L1 CPS ≥10

Statistical analysis description:

PFS in PD-L1 CPS ≥10 participants of the pembrolizumab + SOC arm was compared to PFS in PD-L1 CPS ≥10 participants of the placebo + SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.65

Secondary: ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

ORR 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) per RECIST 1.1. as assessed by the investigator. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, the percentage of participants who experienced CR or PR is reported here as the ORR for all participants of the ITT population (all randomized) who had ESCC and who were PD-L1 CPS ≥10.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	143		
Units: Percentage of Participants				
number (confidence interval 95%)	51.0 (42.6 to 59.5)	28.0 (20.8 to 36.1)		

Statistical analyses

Statistical analysis title	ORR in ESCC PD-L1 CPS ≥10

Statistical analysis description:

ORR in ESCC PD-L1 CPS ≥10 participants of the pembrolizumab + SOC arm was compared to ORR in ESCC PD-L1 CPS ≥10 participants of the placebo + SOC arm based on the Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	One-sided p-value
Parameter estimate	Difference in Percentage
Point estimate	22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.6
upper limit	33.4

Secondary: Objective Response Rate (ORR) Per RECIST 1.1 As Assessed By Investigator in All Participants

End point title	Objective Response Rate (ORR) Per RECIST 1.1 As Assessed By Investigator in All Participants

End point description:

ORR 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) per RECIST 1.1. as assessed by the investigator. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, the percentage of participants who experienced CR or PR is reported here as the ORR for all participants of the ITT population (all randomized).

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	376		
Units: Percentage of Participants				
number (confidence interval 95%)	45.0 (39.9 to 50.2)	29.3 (24.7 to 34.1)		

Statistical analyses

Statistical analysis title	ORR in all participants

Statistical analysis description:

ORR in all participants of the pembrolizumab + SOC arm was compared to ORR in all participants of the placebo + SOC arm based on the Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World), tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma), and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	One-sided p-value
Parameter estimate	Difference in Percentage
Point estimate	15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	22.5

Secondary: ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC

End point title	ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC

End point description:

ORR 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) per RECIST 1.1. as assessed by the investigator. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, the percentage of participants who experienced CR or PR is reported here as the ORR for all participants of the ITT population (all randomized) who had ESCC.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	274		
Units: Percentage of Participants				
number (confidence interval 95%)	43.8 (37.8 to 49.9)	31.0 (25.6 to 36.9)		

Statistical analyses

Statistical analysis title	ORR in ESCC

Statistical analysis description:

ORR in ESCC participants of the pembrolizumab + SOC arm was compared to ORR in ESCC participants of the placebo + SOC arm based on the Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009
Method	One-sided p-value
Parameter estimate	Difference in Percentage
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	20.7

Secondary: Duration of Response (DOR) per RECIST 1.1 As Assessed By Investigator in All Participants

End point title	Duration of Response (DOR) per RECIST 1.1 As Assessed By Investigator in All Participants

End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by the investigator, DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death due to any cause, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Per protocol, DOR is reported here for all participants of the ITT population (all randomized) who had CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	110		
Units: Months				
median (confidence interval 95%)	8.3 (6.4 to 10.4)	6.0 (4.4 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	ORR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

ORR 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) per RECIST 1.1. as assessed by the investigator. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, the percentage of participants who experienced CR or PR is reported here as the ORR for all participants of the ITT population (all randomized) who were PD-L1 CPS ≥10.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	197		
Units: Percentage of Participants				
number (confidence interval 95%)	51.1 (43.7 to 58.5)	26.9 (20.8 to 33.7)		

Statistical analyses

Statistical analysis title	ORR in PD-L1 CPS ≥10

Statistical analysis description:

ORR in PD-L1 CPS ≥10 participants of the pembrolizumab + SOC arm was compared to ORR in PD-L1 CPS ≥10 participants of the placebo + SOC arm based on the Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	One-sided p-value
Parameter estimate	Difference in Percentage
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	33.2

Secondary: DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by the investigator, DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death due to any cause, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Per protocol, DOR is reported here for all participants of the ITT population (all randomized) who had CR or PR, and who had ESCC and were PD-L1 CPS ≥10.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	40		
Units: Months				
median (confidence interval 95%)	10.4 (8.0 to 16.2)	4.4 (4.1 to 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	DOR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by the investigator, DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death due to any cause, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Per protocol, DOR is reported here for all participants of the ITT population (all randomized) who had CR or PR, and were PD-L1 CPS ≥10.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	53		
Units: Months				
median (confidence interval 95%)	10.4 (6.7 to 14.5)	5.6 (4.3 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC

End point title	DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC

End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by the investigator, DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death due to any cause, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. Per protocol, DOR is reported here for all participants of the ITT population (all randomized) who had CR or PR, and who had ESCC.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	85		
Units: Months				
median (confidence interval 95%)	9.1 (6.6 to 12.3)	6.1 (4.4 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Adverse Event (AE)

End point title	Number of Participants with an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable 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 medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The number of participants that experienced at least one AE was reported for each treatment arm. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370	370		
Units: Participants	370	368		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Discontinuing Study Treatment Due to an AE

End point title	Number of Participants Discontinuing Study Treatment Due to an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable 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 medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The number of participants that discontinued any study drug due to an AE was reported for each treatment arm. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 27 months

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370	370		
Units: Participants	90	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline To Week 18 in the European Organization for the

Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) Combined Score in All Participants

End point title	Change from Baseline To Week 18 in the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) Combined Score in All Participants

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the Global Health Status (GHS) question "How would you rate your overall health during the past week?" (Item 29) and the Quality of Life (QoL) question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was reported by treatment arm as a pre-specified secondary analysis for all participants. All randomized participants who received at least one dose of study treatment and completed at least 1 EORTC-QLQ-C30 assessment were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	363		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-1.74 (-4.24 to 0.75)	-1.64 (-4.21 to 0.92)		

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL combined score

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between treatment arms based on a constrained longitudinal data analysis (cLDA) model with the EORTC-QLQ-C30 GHS/QoL scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	729
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.953
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.2

Secondary: Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the Global Health Status (GHS) question "How would you rate your overall health during the past week?" (Item 29) and the Quality of Life (QoL) question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was reported by treatment arm as a pre-specified secondary analysis for all participants who had ESCC and who were PD-L1 CPS ≥10. All randomized participants who received at least one dose of study treatment, completed at least 1 EORTC-QLQ-C30 assessment, who had ESCC, and who were PD-L1 CPS ≥10 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	138		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-2.36 (-6.58 to 1.87)	-0.40 (-4.86 to 4.05)		

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL combined score

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between treatment arms based on a cLDA model with the EORTC-QLQ-C30 GHS/QoL scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5053
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.72
upper limit	3.82

Secondary: Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the Global Health Status (GHS) question "How would you rate your overall health during the past week?" (Item 29) and the Quality of Life (QoL) question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was reported by treatment arm as a pre-specified secondary analysis for all participants who were PD-L1 CPS ≥10. All randomized participants who received at least one dose of study treatment, completed at least 1 EORTC-QLQ-C30 assessment, and who were PD-L1 CPS ≥10 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-1.73 (-5.50 to 2.04)	0.04 (-3.77 to 3.85)		

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL combined score

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between treatment arms based on a cLDA model with the EORTC-QLQ-C30 GHS/QoL scores as the response

variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.481
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.71
upper limit	3.17

Secondary: Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants With ESCC

End point title	Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score in Participants With ESCC

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the Global Health Status (GHS) question "How would you rate your overall health during the past week?" (Item 29) and the Quality of Life (QoL) question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was reported by treatment arm as a pre-specified secondary analysis for all participants who had ESCC. All randomized participants who received at least one dose of study treatment, completed at least 1 EORTC-QLQ-C30 assessment, and who had ESCC were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	264		
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-2.00 (-4.90 to 0.89)	-1.94 (-4.93 to 1.06)		

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL combined score

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between treatment arms based on a cLDA model with the EORTC-QLQ-C30 GHS/QoL scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9742
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	3.81

Secondary: Change from Baseline in the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) Subscale Scores in All Participants

End point title	Change from Baseline in the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) Subscale Scores in All Participants

End point description:

The EORTC QLQ-OES18 is a disease-specific questionnaire developed and validated to address measurements specific to esophageal cancer and contains 18 items assessing symptoms of dysphagia, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste, body image, and hair loss. For the purposes of this study, the Dysphagia subscale (3 items), Pain subscale (3 items), and Reflux subscale (2 items) were evaluated. All subscale items were scored using a four-point Likert scale with the following response choices: 1=not at all, 2=a little, 3=quite a bit, 4=very much. Raw scores for the subscales were standardized into a range of 0 to 100 by linear transformation, with higher symptom scores represent a higher ("worse") level of symptoms. Per protocol, change from baseline to Week 18 in the Dysphagia, Pain, and Reflux subscales was reported for all randomized participants who received at least one dose of study treatment and completed at least 1 EORTC QLQ-OES18 assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	359		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Dysphagia subscale	-3.18 (-7.19 to 0.82)	2.36 (-1.77 to 6.49)		
Pain subscale	-4.78 (-7.01 to -2.56)	-1.85 (-4.14 to 0.45)		
Reflux subscale	-0.22 (-2.81 to 2.36)	0.71 (-1.96 to 3.38)		

Statistical analyses

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

DYSPHAGIA: Change from baseline to Week 18 in EORTC QLQ-OES18 Dysphagia subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0436
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-5.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.93
upper limit	-0.16

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

REFLUX: Change from baseline to Week 18 in EORTC QLQ-OES18 Reflux subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5932
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	2.49

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

PAIN: Change from baseline to Week 18 in EORTC QLQ-OES18 Pain subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0487
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	-0.02

Secondary: Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

EORTC QLQ-OES18 is a disease-specific questionnaire developed and validated to address measurements specific to esophageal cancer containing 18 items assessing symptoms of dysphagia, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste, body image, and hair loss. For the purposes of this study, the Dysphagia subscale (3 items), Pain subscale (3 items), and Reflux subscale (2 items) were evaluated. All subscale items scored using a 4-point Likert scale with the following response choices: 1=not at all, 2=a little, 3=quite a bit, 4=very much. Raw scores for subscales were standardized into a range of 0-100 by linear transformation, with higher symptom scores representing a higher ("worse") level of symptoms. Change from baseline to Week 18 in the Dysphagia, Pain, and Reflux subscales reported for all randomized participants with ESCC and PD-L1 CPS≥10 in each treatment arm who received ≥1 dose of study treatment and completed at least 1 EORTC QLQ-OES18 assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	135		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Dysphagia subscale	-5.11 (-11.51 to 1.30)	3.57 (-3.22 to 10.36)		
Pain subscale	-2.55 (-6.11 to 1.01)	-0.42 (-4.20 to 3.36)		
Reflux subscale	-0.16 (-4.43 to 4.11)	4.94 (0.43 to 9.46)		

Statistical analyses

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

DYSPHAGIA: Change from baseline to Week 18 in EORTC QLQ-OES18 Dysphagia subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0564
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-8.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.59
upper limit	0.24

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

REFLUX: Change from baseline to Week 18 in EORTC QLQ-OES18 Reflux subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0816
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-5.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.86
upper limit	0.65

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

PAIN: Change from baseline to Week 18 in EORTC QLQ-OES18 Pain subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3813
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.93
upper limit	2.66

Secondary: Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point title	Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10)

End point description:

EORTC QLQ-OES18 is a disease-specific questionnaire developed and validated to address measurements specific to esophageal cancer and contains 18 items assessing symptoms of dysphagia, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste, body image, and hair loss. For the purposes of this study, the Dysphagia subscale (3 items), Pain subscale (3 items), and Reflux subscale (2 items) were evaluated. All subscale items were scored using a 4-point Likert scale with the following response choices: 1=not at all, 2=a little, 3=quite a bit, 4=very much. Raw scores for the subscales were standardized into a range of 0 to 100 by linear transformation, with higher symptom scores representing a higher ("worse") level of symptoms. Change from baseline to Week 18 in the Dysphagia, Pain, and Reflux subscales was reported for all randomized PD-L1 CPS≥10 participants in each treatment arm who received ≥1 dose of study treatment and completed ≥1 EORTC QLQ-OES18 assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	187		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Dysphagia subscale	-7.18 (-12.76 to -1.60)	1.02 (-4.66 to 6.70)		
Pain subscale	-3.51 (-6.69 to -0.33)	0.07 (-3.18 to 3.31)		
Reflux subscale	-0.52 (-4.17 to 3.14)	4.25 (0.52 to 7.97)		

Statistical analyses

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

DYSPHAGIA: Change from baseline to Week 18 in EORTC QLQ-OES18 Dysphagia subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0317
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.67
upper limit	-0.73

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

REFLUX: Change from baseline to Week 18 in EORTC QLQ-OES18 Reflux subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0555
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-4.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.64
upper limit	0.11

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

PAIN: Change from baseline to Week 18 in EORTC QLQ-OES18 Pain subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0945
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.77
upper limit	0.62

Secondary: Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants With ESCC

End point title	Change from Baseline in the EORTC QLQ-OES18 Subscale Scores in Participants With ESCC

End point description:

EORTC QLQ-OES18 is a disease-specific questionnaire developed and validated to address measurements specific to esophageal cancer and contains 18 items assessing symptoms of dysphagia, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste, body image, and hair loss. For the purposes of this study, the Dysphagia subscale (3 items), Pain subscale (3 items), and Reflux subscale (2 items) were evaluated. All subscale items were scored using a four-point Likert scale with the following response choices: 1=not at all, 2=a little, 3=quite a bit, 4=very much. Raw scores for the subscales were standardized into a range of 0 to 100 by linear transformation, with higher symptom scores representing a higher ("worse") level of symptoms. Change from baseline to Week 18 in the Dysphagia, Pain, and Reflux subscales was reported for all randomized participants with ESCC in each treatment arm who received ≥1 dose of study treatment and completed ≥1 EORTC QLQ-OES18 assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + SOC	Placebo + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	261		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Dysphagia subscale	-1.18 (-5.82 to 3.47)	3.32 (-1.50 to 8.13)		
Pain subscale	-4.03 (-6.64 to -1.43)	-2.33 (-5.02 to 0.37)		
Reflux subscale	-0.40 (-3.39 to 2.59)	1.09 (-2.01 to 4.19)		

Statistical analyses

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

DYSPHAGIA: Change from baseline to Week 18 in EORTC QLQ-OES18 Dysphagia subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1632
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-4.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.81
upper limit	1.83

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

REFLUX: Change from baseline to Week 18 in EORTC QLQ-OES18 Reflux subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC

Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4598
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.47
upper limit	2.48

Statistical analysis title	EORTC QLQ-OES18- Dysphagia + Pain + Reflux

Statistical analysis description:

PAIN: Change from baseline to Week 18 in EORTC QLQ-OES18 Pain subscale was compared between treatment arms based on a cLDA model with EORTC QLQ-OES18 scores as the response variable with covariates for treatment by study visit interaction, and stratification factors including geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Comparison groups	Pembrolizumab + SOC v Placebo + SOC
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3259
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	1.71

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 70 months

Adverse event reporting additional description:

Serious and Non serious AE tables include all treated participants. Per protocol, disease progression of cancer on study was not considered an AE unless considered related to study drug. Thus, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug were excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + SOC

Reporting group description:

Participants received placebo to pembrolizumab (saline) IV Q3W along with SOC chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

Reporting group title	Pembrolizumab + SOC

Reporting group description:

Participants received pembrolizumab 200 mg IV Q3W plus SOC chemotherapy with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours) Q3W. All treatments were administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.

Serious adverse events	Placebo + SOC	Pembrolizumab + SOC	
Total subjects affected by serious adverse events			
subjects affected / exposed	204 / 370 (55.14%)	207 / 370 (55.95%)	
number of deaths (all causes)	363	331	
number of deaths resulting from adverse events	38	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal submucosal tumour			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm swelling			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 370 (0.81%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Asthenia			
subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	7 / 370 (1.89%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	1 / 7	0 / 2	
Fatigue			
subjects affected / exposed	6 / 370 (1.62%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	5 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	4 / 370 (1.08%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 370 (0.27%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device occlusion			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			

subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Emphysema			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 370 (1.89%)	7 / 370 (1.89%)	
occurrences causally related to treatment / all	1 / 7	2 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 370 (0.00%)	12 / 370 (3.24%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleuritic pain			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 370 (0.27%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Tracheal stenosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 370 (0.81%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 370 (0.54%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 370 (0.54%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 370 (0.54%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	6 / 370 (1.62%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	6 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	4 / 370 (1.08%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	10 / 370 (2.70%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	10 / 13	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration error			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic stenosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy tube site complication			
subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic fistula			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 370 (0.27%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 370 (0.54%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 370 (0.81%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 370 (0.81%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cognitive disorder			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 370 (2.70%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	6 / 10	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	13 / 370 (3.51%)	9 / 370 (2.43%)	
occurrences causally related to treatment / all	12 / 13	9 / 9	
deaths causally related to treatment / all	1 / 1	1 / 1	
Neutropenia			
subjects affected / exposed	3 / 370 (0.81%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 370 (0.81%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 370 (1.35%)	7 / 370 (1.89%)	
occurrences causally related to treatment / all	2 / 5	5 / 7	
deaths causally related to treatment / all	0 / 1	1 / 1	
Abdominal distension			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 370 (0.27%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	13 / 370 (3.51%)	17 / 370 (4.59%)	
occurrences causally related to treatment / all	2 / 13	2 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 370 (1.08%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	3 / 370 (0.81%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 370 (0.54%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	7 / 370 (1.89%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	7 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	3 / 370 (0.81%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	4 / 370 (1.08%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	5 / 370 (1.35%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	6 / 370 (1.62%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Vomiting			
subjects affected / exposed	6 / 370 (1.62%)	9 / 370 (2.43%)	
occurrences causally related to treatment / all	7 / 7	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatous liver disease			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			

subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cold sweat			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 370 (1.62%)	11 / 370 (2.97%)	
occurrences causally related to treatment / all	5 / 6	8 / 12	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic kidney disease			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 370 (0.81%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graves' disease			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Polymyalgia rheumatica			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Giardiasis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	2 / 370 (0.54%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 370 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 370 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	32 / 370 (8.65%)	38 / 370 (10.27%)	
occurrences causally related to treatment / all	3 / 36	13 / 40	
deaths causally related to treatment / all	0 / 10	1 / 6	
Pneumonia aspiration			
subjects affected / exposed	7 / 370 (1.89%)	11 / 370 (2.97%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pneumonia influenzal			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 370 (0.00%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 370 (1.35%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	1 / 3	0 / 0	
Septic shock			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myositis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 370 (0.27%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 370 (0.54%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 370 (2.16%)	6 / 370 (1.62%)	
occurrences causally related to treatment / all	4 / 9	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	6 / 370 (1.62%)	6 / 370 (1.62%)	
occurrences causally related to treatment / all	4 / 6	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypocalcaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	6 / 370 (1.62%)	7 / 370 (1.89%)	
occurrences causally related to treatment / all	3 / 6	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	2 / 370 (0.54%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	6 / 370 (1.62%)	7 / 370 (1.89%)	
occurrences causally related to treatment / all	2 / 6	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	3 / 370 (0.81%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + SOC	Pembrolizumab + SOC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	364 / 370 (98.38%)	367 / 370 (99.19%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 370 (7.84%)	23 / 370 (6.22%)	
occurrences (all)	35	24	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	122 / 370 (32.97%)	147 / 370 (39.73%)	
occurrences (all)	182	231	
Asthenia			
subjects affected / exposed	44 / 370 (11.89%)	58 / 370 (15.68%)	
occurrences (all)	71	103	
Chest pain			

subjects affected / exposed	20 / 370 (5.41%)	28 / 370 (7.57%)	
occurrences (all)	21	39	
Pyrexia			
subjects affected / exposed	44 / 370 (11.89%)	53 / 370 (14.32%)	
occurrences (all)	60	72	
Oedema peripheral			
subjects affected / exposed	29 / 370 (7.84%)	16 / 370 (4.32%)	
occurrences (all)	34	20	
Oedema			
subjects affected / exposed	20 / 370 (5.41%)	22 / 370 (5.95%)	
occurrences (all)	50	59	
Mucosal inflammation			
subjects affected / exposed	65 / 370 (17.57%)	59 / 370 (15.95%)	
occurrences (all)	116	114	
Malaise			
subjects affected / exposed	42 / 370 (11.35%)	45 / 370 (12.16%)	
occurrences (all)	63	75	
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	24 / 370 (6.49%)	22 / 370 (5.95%)	
occurrences (all)	24	27	
Oropharyngeal pain			
subjects affected / exposed	12 / 370 (3.24%)	19 / 370 (5.14%)	
occurrences (all)	12	21	
Hiccups			
subjects affected / exposed	53 / 370 (14.32%)	56 / 370 (15.14%)	
occurrences (all)	102	112	
Dyspnoea			
subjects affected / exposed	29 / 370 (7.84%)	34 / 370 (9.19%)	
occurrences (all)	29	39	
Cough			
subjects affected / exposed	56 / 370 (15.14%)	59 / 370 (15.95%)	
occurrences (all)	64	71	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	44 / 370 (11.89%)	49 / 370 (13.24%)	
occurrences (all)	56	59	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	21 / 370 (5.68%)	24 / 370 (6.49%)	
occurrences (all)	47	52	
Blood creatinine increased			
subjects affected / exposed	77 / 370 (20.81%)	78 / 370 (21.08%)	
occurrences (all)	115	130	
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 370 (7.30%)	25 / 370 (6.76%)	
occurrences (all)	33	43	
Alanine aminotransferase increased			
subjects affected / exposed	26 / 370 (7.03%)	24 / 370 (6.49%)	
occurrences (all)	32	43	
Neutrophil count decreased			
subjects affected / exposed	107 / 370 (28.92%)	138 / 370 (37.30%)	
occurrences (all)	235	279	
White blood cell count decreased			
subjects affected / exposed	67 / 370 (18.11%)	96 / 370 (25.95%)	
occurrences (all)	154	215	
Weight decreased			
subjects affected / exposed	89 / 370 (24.05%)	87 / 370 (23.51%)	
occurrences (all)	110	97	
Platelet count decreased			
subjects affected / exposed	57 / 370 (15.41%)	59 / 370 (15.95%)	
occurrences (all)	96	100	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 370 (8.11%)	36 / 370 (9.73%)	
occurrences (all)	38	42	
Dysgeusia			
subjects affected / exposed	32 / 370 (8.65%)	39 / 370 (10.54%)	
occurrences (all)	35	46	
Headache			

subjects affected / exposed	25 / 370 (6.76%)	30 / 370 (8.11%)	
occurrences (all)	30	56	
Peripheral sensory neuropathy			
subjects affected / exposed	30 / 370 (8.11%)	36 / 370 (9.73%)	
occurrences (all)	32	36	
Neuropathy peripheral			
subjects affected / exposed	37 / 370 (10.00%)	37 / 370 (10.00%)	
occurrences (all)	43	41	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	37 / 370 (10.00%)	28 / 370 (7.57%)	
occurrences (all)	57	54	
Neutropenia			
subjects affected / exposed	90 / 370 (24.32%)	95 / 370 (25.68%)	
occurrences (all)	179	190	
Leukopenia			
subjects affected / exposed	29 / 370 (7.84%)	25 / 370 (6.76%)	
occurrences (all)	72	56	
Anaemia			
subjects affected / exposed	199 / 370 (53.78%)	185 / 370 (50.00%)	
occurrences (all)	295	288	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	27 / 370 (7.30%)	36 / 370 (9.73%)	
occurrences (all)	30	38	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	53 / 370 (14.32%)	46 / 370 (12.43%)	
occurrences (all)	66	56	
Constipation			
subjects affected / exposed	149 / 370 (40.27%)	147 / 370 (39.73%)	
occurrences (all)	210	238	
Abdominal pain upper			
subjects affected / exposed	27 / 370 (7.30%)	20 / 370 (5.41%)	
occurrences (all)	41	21	
Abdominal pain			

subjects affected / exposed	18 / 370 (4.86%)	28 / 370 (7.57%)	
occurrences (all)	21	33	
Nausea			
subjects affected / exposed	231 / 370 (62.43%)	245 / 370 (66.22%)	
occurrences (all)	507	523	
Stomatitis			
subjects affected / exposed	93 / 370 (25.14%)	97 / 370 (26.22%)	
occurrences (all)	146	160	
Vomiting			
subjects affected / exposed	114 / 370 (30.81%)	121 / 370 (32.70%)	
occurrences (all)	200	226	
Diarrhoea			
subjects affected / exposed	120 / 370 (32.43%)	129 / 370 (34.86%)	
occurrences (all)	190	226	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	26 / 370 (7.03%)	44 / 370 (11.89%)	
occurrences (all)	33	56	
Pruritus			
subjects affected / exposed	12 / 370 (3.24%)	31 / 370 (8.38%)	
occurrences (all)	13	33	
Dry skin			
subjects affected / exposed	10 / 370 (2.70%)	20 / 370 (5.41%)	
occurrences (all)	10	21	
Alopecia			
subjects affected / exposed	39 / 370 (10.54%)	55 / 370 (14.86%)	
occurrences (all)	40	55	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	24 / 370 (6.49%)	40 / 370 (10.81%)	
occurrences (all)	27	46	
Hyperthyroidism			
subjects affected / exposed	3 / 370 (0.81%)	19 / 370 (5.14%)	
occurrences (all)	4	19	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	30 / 370 (8.11%)	27 / 370 (7.30%)	
occurrences (all)	35	34	
Arthralgia			
subjects affected / exposed	24 / 370 (6.49%)	30 / 370 (8.11%)	
occurrences (all)	26	38	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	23 / 370 (6.22%)	12 / 370 (3.24%)	
occurrences (all)	26	15	
Upper respiratory tract infection			
subjects affected / exposed	18 / 370 (4.86%)	19 / 370 (5.14%)	
occurrences (all)	19	19	
Pneumonia			
subjects affected / exposed	22 / 370 (5.95%)	20 / 370 (5.41%)	
occurrences (all)	23	21	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	72 / 370 (19.46%)	63 / 370 (17.03%)	
occurrences (all)	108	95	
Hypomagnesaemia			
subjects affected / exposed	23 / 370 (6.22%)	34 / 370 (9.19%)	
occurrences (all)	29	43	
Hypokalaemia			
subjects affected / exposed	68 / 370 (18.38%)	64 / 370 (17.30%)	
occurrences (all)	109	107	
Hypocalcaemia			
subjects affected / exposed	19 / 370 (5.14%)	27 / 370 (7.30%)	
occurrences (all)	25	34	
Hypoalbuminaemia			
subjects affected / exposed	49 / 370 (13.24%)	34 / 370 (9.19%)	
occurrences (all)	69	43	
Hyperkalaemia			
subjects affected / exposed	29 / 370 (7.84%)	26 / 370 (7.03%)	
occurrences (all)	42	47	
Hyperglycaemia			

subjects affected / exposed	19 / 370 (5.14%)	18 / 370 (4.86%)	
occurrences (all)	29	25	
Dehydration			
subjects affected / exposed	25 / 370 (6.76%)	27 / 370 (7.30%)	
occurrences (all)	25	32	
Decreased appetite			
subjects affected / exposed	138 / 370 (37.30%)	162 / 370 (43.78%)	
occurrences (all)	239	283	
Hypophosphataemia			
subjects affected / exposed	22 / 370 (5.95%)	20 / 370 (5.41%)	
occurrences (all)	25	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2018	The major change of Amendment 2 (AM 2) was a change in the primary biomarker from GEP to PD-L1; clarification of the 5-FU dosing; an update to the Statistical Analysis Plan; and a reduction in PK/ADA sampling.
21 December 2018	The major change of AM 5 was to extend the enrollment period beyond the Global Cohort to achieve the required sample size of the China Cohort to investigate efficacy and safety in Chinese participants.
10 February 2020	Major changes of AM 8 included addition of 3 primary objectives and corresponding hypotheses (OS in ESCC participants, OS in ESCC participants with PD-L1 CPS ≥10, and PFS in ESCC participants), update of secondary objectives (ORR and DOR endpoints in the ESCC and ESCC PD-L1 CPS ≥10 populations) and exploratory objectives (PFS per immune related RECIST in the ESCC and ESCC PD-L1 CPS ≥10 populations), merging of the Global Cohort and the China Extension Study Cohort into the Global Study group, and inclusion of assessment of DOR, QoL (C30) and QoL (OES18) in all prespecified populations.
14 July 2020	Major changes of AM 9 included a change in the primary PFS endpoint from BICR-assessed to investigator-assessed, and elimination of one of the two planned efficacy interim analyses.
01 July 2021	The major change of AM 10 was to update the dose modification and toxicity management guidelines for immune-related AEs.
28 November 2022	The major change of AM 11 was to update the name of the Sponsor from “Merck Sharp & Dohme Corp.” to “Merck Sharp & Dohme LLC”.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported