Clinical trial results:
A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (KEYNOTE-181)

Summary

EudraCT number	2015-002782-32
Trial protocol	SE NO EE PT FI ES DE DK CZ NL FR IE IT
Global end of trial date	14 March 2022

Results information

Result version number	v1 (current)
This version publication date	10 March 2023
First version publication date	10 March 2023

Trial information

Trial identification

Sponsor protocol code	MK-3475-181

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02564263
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 163145

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	14 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2018
Global end of trial reached?	Yes
Global end of trial date	14 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this study, participants with advanced or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type I adenocarcinoma of the esophagogastric junction (EGJ) that had progressed after first-line standard therapy were randomized to receive either pembrolizumab (MK-3475) OR the Investigator's choice of standard chemotherapy with paclitaxel, docetaxel, or irinotecan.

The primary study hypothesis was that treatment with pembrolizumab would prolong overall survival (OS) as compared to treatment with standard chemotherapy.

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	01 December 2015
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: 3
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 80
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Ireland: 3

Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 152
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 76
Worldwide total number of subjects	628
EEA total number of subjects	189

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)	356
From 65 to 84 years	272
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At the time of the primary analysis data cut-off of 15-Oct-2018, 67 participants were ongoing in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg, intravenously (IV) on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 25 months).

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg administered as IV infusion on Day 1 of every 21-day cycle

Arm title	Chemotherapy

Arm description:

Participants received Investigator’s choice of paclitaxel 80-100 mg/m^2 IV on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR docetaxel 75 mg/m^2 IV on Day 1 of every 21-day (3-week) cycle, OR irinotecan 180 mg/m^2 IV on Day 1 of every 14-day (2-week) cycle (up to approximately 19 months).

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

Dosage and administration details:

80-100 mg/m^2 administered as IV infusion on Days 1, 8, and 15 of each 28-day cycle

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

Dosage and administration details:

180 mg/m^2 administered as IV infusion on Day 1 of every 14-day cycle

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

Dosage and administration details:

75 mg/m^2 administered as IV infusion on Day 1 of every 21-day cycle

Number of subjects in period 1	Pembrolizumab	Chemotherapy
Started	314	314
Treated	314	296
Received Second Course of Pembrolizumab	5	0
Completed	0	0
Not completed	314	314
Adverse event, serious fatal	270	262
Sponsor's decision	9	4
Consent withdrawn by subject	4	19
Adverse event, non-fatal	31	29

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg, intravenously (IV) on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 25 months).	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received Investigator's choice of paclitaxel 80-100 mg/m^2 IV on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR docetaxel 75 mg/m^2 IV on Day 1 of every 21-day (3-week) cycle, OR irinotecan 180 mg/m^2 IV on Day 1 of every 14-day (2-week) cycle (up to approximately 19 months).	

Reporting group values	Pembrolizumab	Chemotherapy	Total
Number of subjects	314	314	628
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	175	181	356
From 65-84 years	139	133	272
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	62.6	62.0	
standard deviation	± 9.4	± 9.6	-
Sex: Female, Male Units: Participants			
Female	41	43	84
Male	273	271	544
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	126	122	248
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	3	3	6
White	179	172	351
More than one race	2	4	6
Unknown or Not Reported	4	11	15
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	19	25	44
Not Hispanic or Latino	288	273	561

Unknown or Not Reported	7	16	23
Programmed Death-Ligand 1 (PD-L1) Status: Combined Positive Score (CPS)			
Participants were assessed for their PD-L1 tumor expression levels by immunohistochemistry assay on tumor tissue from a newly obtained biopsy. PD-L1 CPS was calculated as the number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes) divided by the total tumor cells and is expressed as a percentage. Participants were classified based on their PD-L1 tumor status as being either PD-L1 CPS ≥10 or PD-L1 CPS <10.			
Units: Subjects			
PD-L1 CPS ≥10	109	117	226
PD-L1 CPS <10	199	194	393
Not Evaluable	6	3	9
Geographic Region			
Participants were classified based on their geographic region of enrollment as either being from Asia or from outside of Asia (Rest of World [RoW]).			
Units: Subjects			
Asia	121	122	243
RoW	193	192	385
Tumor Histology			
Participants were classified based on their tumor histology (cell type) as either having squamous cell carcinoma or having adenocarcinoma of esophagus and esophagogastric junction (EGJ) Siewert type I.			
Units: Subjects			
Squamous cell carcinoma	199	204	403
Adenocarcinoma of esophagus & EGJ Siewert type I	115	110	225

End points

End points reporting groups

Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg, intravenously (IV) on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 25 months).	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received Investigator's choice of paclitaxel 80-100 mg/m^2 IV on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR docetaxel 75 mg/m^2 IV on Day 1 of every 21-day (3-week) cycle, OR irinotecan 180 mg/m^2 IV on Day 1 of every 14-day (2-week) cycle (up to approximately 19 months).	

Primary: Overall Survival (OS) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus

End point title	Overall Survival (OS) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus
End point description:	
OS was defined as the time from randomization to death due to any cause. The efficacy analysis population consisted of all randomized participants with SCC of the esophagus. Participants were included in the treatment group to which they were randomized. Median OS in participants with SCC of the esophagus is presented.	
End point type	Primary
End point timeframe:	
Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)	

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	203		
Units: Months				
median (confidence interval 95%)	8.2 (6.7 to 10.3)	7.1 (6.1 to 8.2)		

Statistical analyses

Statistical analysis title	OS in Participants with SCC of the Esophagus
Statistical analysis description:	
Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW)	
Comparison groups	Pembrolizumab v Chemotherapy

Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00894 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.96

Notes:

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

Primary: Overall Survival (OS) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point title	Overall Survival (OS) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point description:

OS was defined as the time from randomization to death due to any cause. The efficacy analysis population consisted of all randomized participants with a PD-L1 CPS ≥10. Participants were included in the treatment group to which they were randomized. Median OS in participants with a PD-L1 CPS ≥10 is presented.

End point type	Primary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	115		
Units: Months				
median (confidence interval 95%)	9.3 (6.6 to 12.5)	6.7 (5.1 to 8.2)		

Statistical analyses

Statistical analysis title	OS in Participants with PD-L1 CPS ≥10

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type 1 adenocarcinoma of the esophagogastric junction [EGJ])

Comparison groups	Pembrolizumab v Chemotherapy

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00855 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.94

Notes:

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

Primary: Overall Survival (OS) in All Participants

End point title	Overall Survival (OS) in All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. The efficacy analysis population consisted of all randomized participants. Participants were included in the treatment group to which they were randomized. Median OS in all participants is presented.

End point type	Primary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	314		
Units: Months				
median (confidence interval 95%)	7.1 (6.2 to 8.1)	7.1 (6.3 to 8.0)		

Statistical analyses

Statistical analysis title	OS in All Participants

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type 1 adenocarcinoma of the esophagogastric junction [EGJ])

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0531 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.05

Notes:

[3] - One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic & a weighted log-rank Fleming-Harrington (0,1) test statistic

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

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

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of ≥1 new lesions was also considered PD. The efficacy analysis population consisted of all randomized participants. Participants were included in the treatment group to which they were randomized. Median PFS as assessed by blinded independent central review per RECIST 1.1 in all participants is presented.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	314		
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 2.2)	3.4 (2.8 to 3.9)		

Statistical analyses

Statistical analysis title	PFS as Assessed by RECIST 1.1 in All Participants

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.31

Notes:

[4] - One-sided p-value based on stratified maximum weighted log rank test: the maximum of the log-rank test statistic & a weighted log-rank Fleming-Harrington (0,1) test statistic

Secondary: Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point title	Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

End point description:

ORR was defined as the percentage of participants 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) as assessed using RECIST 1.1. The efficacy analysis population consisted of all randomized participants. Participants were included in the treatment group to which they were randomized. The percentage of all participants who experienced a CR or PR is presented.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	314		
Units: Percentage of Participants				
number (confidence interval 95%)	13.1 (9.5 to 17.3)	6.7 (4.2 to 10.0)		

Statistical analyses

Statistical analysis title	ORR as Assessed by RECIST 1.1 in All Participants

Statistical analysis description:

Miettinen & Nurminen method stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type I adenocarcinoma of the EGJ)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 [5]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	6.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	11.2

Notes:

[5] - One-sided p-value for testing. H0: difference in %=0 versus; H1: difference in %>0.

Secondary: Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus

End point title	Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of ≥1 new lesions was also considered PD. The efficacy analysis population consisted of all randomized participants with SCC of the esophagus. Participants were included in the treatment group to which they were randomized. Median PFS as assessed by blinded independent central review per RECIST 1.1 is presented for participants with SCC of the esophagus.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	203		
Units: Months				
median (confidence interval 95%)	2.2 (2.1 to 3.2)	3.1 (2.2 to 3.9)		

Statistical analyses

Statistical analysis title	PFS in Participants with SCC of the Esophagus

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.216 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.13

Notes:

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

Secondary: Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point title	Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of ≥1 new lesions was also considered PD. The efficacy analysis population consisted of all randomized participants with a PD-L1 CPS ≥10. Participants were included in the treatment group to which they were randomized. Median PFS as assessed by blinded independent central review per RECIST 1.1 is presented for participants with a PD-L1 CPS ≥10.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	115		
Units: Months				
median (confidence interval 95%)	2.6 (2.1 to 4.1)	3.0 (2.1 to 3.7)		

Statistical analyses

Statistical analysis title	PFS in Participants with PD-L1 CPS ≥10

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.97

Notes:

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

Secondary: Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus

End point title	Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Squamous Cell Carcinoma (SCC) of the Esophagus

End point description:

ORR was defined as the percentage of participants 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) as assessed using RECIST 1.1. The efficacy analysis population consisted of all randomized participants with SCC of the esophagus. Participants were included in the treatment group to which they were randomized. The percentage of participants with SCC of the esophagus who experienced a CR or PR is presented.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	203		
Units: Percentage of Participants				
number (confidence interval 95%)	16.7 (11.8 to 22.6)	7.4 (4.2 to 11.9)		

Statistical analyses

Statistical analysis title	ORR in Participants with SCC of the Esophagus

Statistical analysis description:

Miettinen & Nurminen method stratified by geographic region (Asia vs RoW)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [8]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	9.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	15.8

Notes:

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

Secondary: Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point title	Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Participants with Programmed Death-Ligand 1 Combined Positive Score ≥10 (PD-L1 CPS ≥10)

End point description:

ORR was defined as the percentage of participants 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) as assessed using RECIST 1.1. The efficacy analysis population consisted of all randomized participants with a PD-L1 CPS ≥10. Participants were included in the treatment group to which they were randomized. The percentage of participants with a PD-L1 CPS ≥10 who experienced a CR or PR is presented.

End point type	Secondary

End point timeframe:

Through Final Analysis data cutoff date of 15-Oct-2018 (up to approximately 34 months)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	115		
Units: Percentage of Participants				
number (confidence interval 95%)	21.5 (14.1 to 30.5)	6.1 (2.5 to 12.1)		

Statistical analyses

Statistical analysis title	ORR in Participants with PD-L1 CPS ≥10

Statistical analysis description:

Miettinen & Nurminen method stratified by geographic region (Asia vs RoW) & tumor histology (SCC vs adenocarcinoma/Siewert type I adenocarcinoma of the EGJ)

Comparison groups	Pembrolizumab v Chemotherapy
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [9]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	15.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	24.7

Notes:

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

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

End point title	Number of Participants Experiencing 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 does 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 analysis population consisted of all randomized participants who received at least 1 dose of study treatment. Participants were included in the treatment group to which they were randomized. The number of participants who experienced ≥1 AE is presented.

End point type	Secondary

End point timeframe:

Through End-of-Trial Analysis data cutoff date of 14-Mar-2022 (up to approximately 6 years)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	296		
Units: Participants	301	288		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Discontinuing Study Treatment Due an Adverse Event (AE)

End point title	Number of Participants Discontinuing Study Treatment Due 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 does 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 analysis population consisted of all randomized participants who received at least 1 dose of study treatment. Participants were included in the treatment group to which they were randomized. The number of participants who discontinued study treatment due to an AE is presented.

End point type	Secondary

End point timeframe:

Through End-of-Trial Analysis data cutoff date of 14-Mar-2022 (up to approximately 6 years)

End point values	Pembrolizumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	296		
Units: Participants	40	42		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through End-of-Trial Analysis data cutoff date of 14-Mar-2022 (up to approximately 6 years)

Adverse event reporting additional description:

Deaths (all-causes) analysis population included all randomized participants (N=314, 314, 5). AE analysis population included all participants who received ≥1 dose of study treatment (N=314, 296, 5). MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Pembrolizumab First Course

Reporting group description:

Participants received pembrolizumab 200 mg, intravenously (IV) on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 25 months).

Reporting group title	Pembrolizumab Second Course

Reporting group description:

Qualified participants who received pembrolizumab as a first course and stopped the first course of pembrolizumab due to complete response (CR) or completed the first course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (approximately 1 year additional).

Reporting group title	Chemotherapy

Reporting group description:

Participants received Investigator’s choice of paclitaxel 80-100 mg/m^2 IV on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR docetaxel 75 mg/m^2 IV on Day 1 of every 21-day (3-week) cycle, OR irinotecan 180 mg/m^2 IV on Day 1 of every 14-day (2-week) cycle (up to approximately 19 months).

Serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	127 / 314 (40.45%)	1 / 5 (20.00%)	121 / 314 (38.54%)
number of deaths (all causes)	305	3	305
number of deaths resulting from adverse events	5	0	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed[1]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed[2]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Head and neck cancer			
subjects affected / exposed[3]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed[4]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed[5]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed[6]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed[7]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Shock haemorrhagic			
subjects affected / exposed[8]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed[9]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed[10]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed[11]	2 / 314 (0.64%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed[12]	5 / 314 (1.59%)	0 / 5 (0.00%)	10 / 296 (3.38%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 10
deaths causally related to treatment / all	1 / 5	0 / 0	0 / 10
Chest pain			
subjects affected / exposed[13]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Strangulated hernia			
subjects affected / exposed[14]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed[15]	4 / 314 (1.27%)	0 / 5 (0.00%)	4 / 296 (1.35%)
occurrences causally related to treatment / all	2 / 4	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed[16]	0 / 314 (0.00%)	1 / 5 (20.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed[17]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute respiratory distress syndrome			
subjects affected / exposed[18]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed[19]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed[20]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed[21]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed[22]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hiccups			
subjects affected / exposed[23]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed[24]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed[25]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed[26]	1 / 314 (0.32%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed[27]	7 / 314 (2.23%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed[28]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal fistula			
subjects affected / exposed[29]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed[30]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed[31]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary necrosis			
subjects affected / exposed[32]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed[33]	3 / 314 (0.96%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper airway obstruction			
subjects affected / exposed[34]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed[35]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Confusional state			
subjects affected / exposed[36]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed[37]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed[38]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed[39]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed[40]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Liver function test increased			
subjects affected / exposed[41]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed[42]	1 / 314 (0.32%)	0 / 5 (0.00%)	3 / 296 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
White blood cell count decreased			
subjects affected / exposed[43]	1 / 314 (0.32%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Weight decreased			
subjects affected / exposed[44]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			
subjects affected / exposed[45]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic fistula			
subjects affected / exposed[46]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed[47]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed[48]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femoral neck fracture			
subjects affected / exposed[49]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrostomy failure			
subjects affected / exposed[50]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body in gastrointestinal tract			
subjects affected / exposed[51]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed[52]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed[53]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed[54]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal injury			
subjects affected / exposed[55]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed[56]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			

subjects affected / exposed[57]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed[58]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed[59]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed[60]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed[61]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed[62]	2 / 314 (0.64%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed[63]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed[64]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Sinus tachycardia			
subjects affected / exposed[65]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed[66]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dystonia			
subjects affected / exposed[67]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed[68]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Demyelination			
subjects affected / exposed[69]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
subjects affected / exposed[70]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar stroke			
subjects affected / exposed[71]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bell's palsy			
subjects affected / exposed[72]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed[73]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed[74]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed[75]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed[76]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neuralgia			
subjects affected / exposed[77]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed[78]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed[79]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed[80]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			

subjects affected / exposed[81]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed[82]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed[83]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed[84]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[85]	2 / 314 (0.64%)	0 / 5 (0.00%)	5 / 296 (1.69%)
occurrences causally related to treatment / all	0 / 2	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed[86]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed[87]	1 / 314 (0.32%)	0 / 5 (0.00%)	22 / 296 (7.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	23 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed[88]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed[89]	0 / 314 (0.00%)	0 / 5 (0.00%)	4 / 296 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed[90]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed[91]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed[92]	3 / 314 (0.96%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed[93]	3 / 314 (0.96%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed[94]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed[95]	1 / 314 (0.32%)	0 / 5 (0.00%)	4 / 296 (1.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum oesophageal			
subjects affected / exposed[96]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed[97]	11 / 314 (3.50%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	1 / 12	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed[98]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed[99]	2 / 314 (0.64%)	0 / 5 (0.00%)	4 / 296 (1.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Gastrointestinal hypomotility			
subjects affected / exposed[100]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed[101]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Impaired gastric emptying			
subjects affected / exposed[102]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed[103]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed[104]	1 / 314 (0.32%)	0 / 5 (0.00%)	3 / 296 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal fistula			

subjects affected / exposed[105]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed[106]	4 / 314 (1.27%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 4	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed[107]	3 / 314 (0.96%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal perforation			
subjects affected / exposed[108]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed[109]	2 / 314 (0.64%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed[110]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed[111]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal adhesions			
subjects affected / exposed[112]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed[113]	0 / 314 (0.00%)	0 / 5 (0.00%)	3 / 296 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Vomiting			
subjects affected / exposed[114]	2 / 314 (0.64%)	0 / 5 (0.00%)	5 / 296 (1.69%)
occurrences causally related to treatment / all	1 / 2	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed[115]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed[116]	3 / 314 (0.96%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed[117]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed[118]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic function abnormal			
subjects affected / exposed[119]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed[120]	2 / 314 (0.64%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			

subjects affected / exposed[121]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed[122]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed[123]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed[124]	2 / 314 (0.64%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed[125]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed[126]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed[127]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed[128]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed[129]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyositis			
subjects affected / exposed[130]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed[131]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula inflammation			
subjects affected / exposed[132]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed[133]	0 / 314 (0.00%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Beta haemolytic streptococcal infection			
subjects affected / exposed[134]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed[135]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed[136]	1 / 314 (0.32%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed[137]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			
subjects affected / exposed[138]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed[139]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed[140]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed[141]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed[142]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed[143]	1 / 314 (0.32%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed[144]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed[145]	0 / 314 (0.00%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed[146]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed[147]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mediastinitis			
subjects affected / exposed[148]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia aspiration			
subjects affected / exposed[149]	12 / 314 (3.82%)	0 / 5 (0.00%)	5 / 296 (1.69%)
occurrences causally related to treatment / all	1 / 13	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 5	0 / 0	1 / 1
Pneumonia			
subjects affected / exposed[150]	14 / 314 (4.46%)	0 / 5 (0.00%)	22 / 296 (7.43%)
occurrences causally related to treatment / all	3 / 15	0 / 0	12 / 26
deaths causally related to treatment / all	0 / 3	0 / 0	1 / 5
Pneumonia bacterial			
subjects affected / exposed[151]	0 / 314 (0.00%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia necrotising			

subjects affected / exposed[152]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed[153]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed[154]	4 / 314 (1.27%)	0 / 5 (0.00%)	3 / 296 (1.01%)
occurrences causally related to treatment / all	0 / 4	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Respiratory tract infection			
subjects affected / exposed[155]	3 / 314 (0.96%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed[156]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Subcutaneous abscess			
subjects affected / exposed[157]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site infection			
subjects affected / exposed[158]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed[159]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy infection			

subjects affected / exposed[160]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed[161]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed[162]	2 / 314 (0.64%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed[163]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed[164]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[165]	2 / 314 (0.64%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed[166]	2 / 314 (0.64%)	0 / 5 (0.00%)	4 / 296 (1.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed[167]	1 / 314 (0.32%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed[168]	3 / 314 (0.96%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed[169]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed[170]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed[171]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed[172]	0 / 314 (0.00%)	0 / 5 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed[173]	0 / 314 (0.00%)	0 / 5 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed[174]	1 / 314 (0.32%)	0 / 5 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

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

Non-serious adverse events	Pembrolizumab First Course	Pembrolizumab Second Course	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	285 / 314 (90.76%)	5 / 5 (100.00%)	281 / 314 (89.49%)
Investigations			
Blood creatinine increased			
subjects affected / exposed[175]	8 / 314 (2.55%)	1 / 5 (20.00%)	3 / 296 (1.01%)
occurrences (all)	11	1	4
Aspartate aminotransferase increased			
subjects affected / exposed[176]	26 / 314 (8.28%)	1 / 5 (20.00%)	14 / 296 (4.73%)
occurrences (all)	33	1	16
Alanine aminotransferase increased			
subjects affected / exposed[177]	22 / 314 (7.01%)	0 / 5 (0.00%)	10 / 296 (3.38%)
occurrences (all)	26	0	16
Blood sodium decreased			
subjects affected / exposed[178]	0 / 314 (0.00%)	1 / 5 (20.00%)	1 / 296 (0.34%)
occurrences (all)	0	1	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed[179]	3 / 314 (0.96%)	1 / 5 (20.00%)	3 / 296 (1.01%)
occurrences (all)	4	1	3
Lymphocyte count decreased			
subjects affected / exposed[180]	9 / 314 (2.87%)	1 / 5 (20.00%)	9 / 296 (3.04%)
occurrences (all)	10	1	15
Weight decreased			

subjects affected / exposed[181]	39 / 314 (12.42%)	1 / 5 (20.00%)	34 / 296 (11.49%)
occurrences (all)	39	1	43
Neutrophil count decreased			
subjects affected / exposed[182]	2 / 314 (0.64%)	0 / 5 (0.00%)	50 / 296 (16.89%)
occurrences (all)	2	0	113
White blood cell count decreased			
subjects affected / exposed[183]	1 / 314 (0.32%)	0 / 5 (0.00%)	52 / 296 (17.57%)
occurrences (all)	1	0	114
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed[184]	0 / 314 (0.00%)	1 / 5 (20.00%)	0 / 296 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed[185]	6 / 314 (1.91%)	0 / 5 (0.00%)	25 / 296 (8.45%)
occurrences (all)	7	0	28
Peripheral sensory neuropathy			
subjects affected / exposed[186]	3 / 314 (0.96%)	0 / 5 (0.00%)	52 / 296 (17.57%)
occurrences (all)	3	0	53
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[187]	52 / 314 (16.56%)	1 / 5 (20.00%)	83 / 296 (28.04%)
occurrences (all)	60	2	110
Neutropenia			
subjects affected / exposed[188]	0 / 314 (0.00%)	0 / 5 (0.00%)	36 / 296 (12.16%)
occurrences (all)	0	0	65
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed[189]	67 / 314 (21.34%)	0 / 5 (0.00%)	87 / 296 (29.39%)
occurrences (all)	70	0	121
Asthenia			
subjects affected / exposed[190]	45 / 314 (14.33%)	0 / 5 (0.00%)	43 / 296 (14.53%)
occurrences (all)	48	0	58
Malaise			
subjects affected / exposed[191]	15 / 314 (4.78%)	0 / 5 (0.00%)	19 / 296 (6.42%)
occurrences (all)	18	0	26
Oedema peripheral			

subjects affected / exposed[192]	19 / 314 (6.05%)	0 / 5 (0.00%)	19 / 296 (6.42%)
occurrences (all)	20	0	19
Pyrexia			
subjects affected / exposed[193]	31 / 314 (9.87%)	0 / 5 (0.00%)	45 / 296 (15.20%)
occurrences (all)	41	0	58
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed[194]	7 / 314 (2.23%)	1 / 5 (20.00%)	2 / 296 (0.68%)
occurrences (all)	7	1	2
Abdominal pain			
subjects affected / exposed[195]	34 / 314 (10.83%)	0 / 5 (0.00%)	27 / 296 (9.12%)
occurrences (all)	36	0	32
Abdominal pain upper			
subjects affected / exposed[196]	14 / 314 (4.46%)	0 / 5 (0.00%)	17 / 296 (5.74%)
occurrences (all)	16	0	19
Diarrhoea			
subjects affected / exposed[197]	38 / 314 (12.10%)	1 / 5 (20.00%)	79 / 296 (26.69%)
occurrences (all)	65	1	120
Constipation			
subjects affected / exposed[198]	56 / 314 (17.83%)	0 / 5 (0.00%)	56 / 296 (18.92%)
occurrences (all)	63	0	63
Dyspepsia			
subjects affected / exposed[199]	6 / 314 (1.91%)	1 / 5 (20.00%)	11 / 296 (3.72%)
occurrences (all)	7	1	13
Dysphagia			
subjects affected / exposed[200]	40 / 314 (12.74%)	1 / 5 (20.00%)	26 / 296 (8.78%)
occurrences (all)	44	1	27
Nausea			
subjects affected / exposed[201]	59 / 314 (18.79%)	0 / 5 (0.00%)	83 / 296 (28.04%)
occurrences (all)	66	0	110
Stomatitis			
subjects affected / exposed[202]	9 / 314 (2.87%)	0 / 5 (0.00%)	28 / 296 (9.46%)
occurrences (all)	9	0	30
Vomiting			
subjects affected / exposed[203]	37 / 314 (11.78%)	0 / 5 (0.00%)	53 / 296 (17.91%)
occurrences (all)	45	0	74

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed[204]	31 / 314 (9.87%)	0 / 5 (0.00%)	17 / 296 (5.74%)
occurrences (all)	36	0	21
Cough			
subjects affected / exposed[205]	40 / 314 (12.74%)	0 / 5 (0.00%)	30 / 296 (10.14%)
occurrences (all)	46	0	33
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed[206]	4 / 314 (1.27%)	0 / 5 (0.00%)	88 / 296 (29.73%)
occurrences (all)	4	0	88
Pruritus			
subjects affected / exposed[207]	23 / 314 (7.32%)	1 / 5 (20.00%)	8 / 296 (2.70%)
occurrences (all)	27	1	8
Rash			
subjects affected / exposed[208]	20 / 314 (6.37%)	0 / 5 (0.00%)	25 / 296 (8.45%)
occurrences (all)	24	0	27
Psychiatric disorders			
Insomnia			
subjects affected / exposed[209]	25 / 314 (7.96%)	0 / 5 (0.00%)	16 / 296 (5.41%)
occurrences (all)	25	0	42
Irritability			
subjects affected / exposed[210]	0 / 314 (0.00%)	1 / 5 (20.00%)	1 / 296 (0.34%)
occurrences (all)	0	1	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed[211]	37 / 314 (11.78%)	1 / 5 (20.00%)	7 / 296 (2.36%)
occurrences (all)	40	1	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed[212]	24 / 314 (7.64%)	0 / 5 (0.00%)	19 / 296 (6.42%)
occurrences (all)	26	0	22
Back pain			
subjects affected / exposed[213]	38 / 314 (12.10%)	0 / 5 (0.00%)	24 / 296 (8.11%)
occurrences (all)	40	0	27
Myalgia			

subjects affected / exposed[214]	8 / 314 (2.55%)	0 / 5 (0.00%)	25 / 296 (8.45%)
occurrences (all)	10	0	31
Pain in extremity			
subjects affected / exposed[215]	8 / 314 (2.55%)	1 / 5 (20.00%)	8 / 296 (2.70%)
occurrences (all)	10	1	9
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed[216]	12 / 314 (3.82%)	1 / 5 (20.00%)	13 / 296 (4.39%)
occurrences (all)	17	2	15
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[217]	76 / 314 (24.20%)	1 / 5 (20.00%)	76 / 296 (25.68%)
occurrences (all)	82	1	97
Gout			
subjects affected / exposed[218]	1 / 314 (0.32%)	1 / 5 (20.00%)	0 / 296 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed[219]	16 / 314 (5.10%)	0 / 5 (0.00%)	14 / 296 (4.73%)
occurrences (all)	21	0	14
Hyperkalaemia			
subjects affected / exposed[220]	8 / 314 (2.55%)	1 / 5 (20.00%)	6 / 296 (2.03%)
occurrences (all)	13	1	7
Hypoalbuminaemia			
subjects affected / exposed[221]	17 / 314 (5.41%)	0 / 5 (0.00%)	15 / 296 (5.07%)
occurrences (all)	23	0	16
Hypokalaemia			
subjects affected / exposed[222]	15 / 314 (4.78%)	0 / 5 (0.00%)	29 / 296 (9.80%)
occurrences (all)	15	0	40
Hyponatraemia			
subjects affected / exposed[223]	19 / 314 (6.05%)	0 / 5 (0.00%)	17 / 296 (5.74%)
occurrences (all)	27	0	24
Iron deficiency			
subjects affected / exposed[224]	1 / 314 (0.32%)	1 / 5 (20.00%)	1 / 296 (0.34%)
occurrences (all)	1	1	1

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[222] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[223] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[224] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis population includes all participants who received at least 1 dose of study treatment.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	Amendment 02: Primary reason for amendment was to incorporate revisions to descriptions of gene expression profile (GEP) cut-off and how objectives and endpoints would be met and analyzed, respectively.
07 April 2017	Amendment 03: Primary reason for amendment was to incorporate revisions to the enrollment period to achieve the required sample size of the China Cohort.
30 August 2017	Amendment 04: Primary reason for amendment was to incorporate revisions to primary objectives, based on recommendations from emerging data.
09 March 2018	Amendment 05: Primary reason for amendment was to incorporate revisions to statistical tests for testing the OS and PFS hypotheses in all subjects.
26 August 2021	Amendment 06: Primary reason for amendment was to incorporate revisions to update the dose modification and toxicity management guidelines for immune-related AEs and to clarify the concomitant use of COVID-19 vaccines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported