Clinical trial results:
A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Summary

EudraCT number	2015-000972-88
Trial protocol	LT DE LV NL ES CZ FR AT HU BE PL IT
Global end of trial date	06 June 2022

Results information

Result version number	v1 (current)
This version publication date	05 May 2023
First version publication date	05 May 2023

Trial information

Trial identification

Sponsor protocol code	3475-062

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02494583
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2019
Global end of trial reached?	Yes
Global end of trial date	06 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a study of pembrolizumab as first-line treatment for participants with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. Participants whose tumors expressed programmed death-ligand 1 (PD-L1) were randomly assigned to one of the three treatment arms of the study: pembrolizumab as monotherapy [pembro mono], pembrolizumab plus standard of care (SOC) chemotherapy with cisplatin plus 5-fluorouracil (5-FU) or capecitabine [pembro combo], or placebo plus SOC chemotherapy with cisplatin plus 5-fluorouracil (5-FU) or capecitabine [SOC].

The primary hypotheses compared pembrolizumab plus SOC chemotherapy OR pembrolizumab monotherapy with SOC chemotherapy alone in terms of Progression-free Survival (PFS) and Overall Survival (OS) in participants with PD-L1 Combined Positive Score (CPS) ≥1 and participants with PD-L1 CPS ≥10.

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	31 July 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: 9
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Chile: 44
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Guatemala: 22
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Japan: 103

Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Latvia: 23
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	South Africa: 21
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 69
Worldwide total number of subjects	763
EEA total number of subjects	227

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)	445
From 65 to 84 years	315
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who were programmed death-ligand 1 (PD-L1)-positive (Combined Positive Score [CPS]≥1) and human epidermal growth factor receptor 2 (HER2/neu)-negative were recruited to the study.

Pre-assignment

Screening details:

763 were randomized 1:1:1 to pembrolizumab monotherapy (pembro mono), pembrolizumab plus standard of care (SOC) chemotherapy (pembro combo), or placebo plus SOC. Per protocol, response/progression or adverse events (AEs) occurring during second course not counted towards efficacy outcome measures or safety outcome measures, respectively.

Period 1

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

Blinding implementation details:

For pembrolizumab (monotherapy); the participant, the trial site personnel, the Sponsor and/or designee were not blinded to
this treatment arm since only one type of trial medication was administered on this arm.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab Monotherapy (Pembro Mono)

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/kg IV, administered Q3W

Arm title	Pembrolizumab + SOC Chemotherapy (Pembro Combo)

Arm description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-fluorouracil (5-FU) 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Arm type	Experimental

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/kg IV, administered Q3W

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1000 mg/m^2 twice daily by oral tablet on Day 1-14 of each 3-week cycle.

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:

5-FU 800 mg/m^2/day IV continuous from Day 1-5 of each 3-week cycle.

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 IV on Day 1 of each week in 3-week cycles (6 cycle maximum per local country guidelines).

Arm title	Placebo + SOC Chemotherapy (SOC)

Arm description:

Participants received placebo IV Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

Arm type	Experimental
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:

Normal saline IV on Day 1 of each week in 3-week cycles for up to 35 cycles (approximately 2 years).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1000 mg/m^2 twice daily by oral tablet on Day 1-14 of each 3-week cycle.

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:

5-FU 800 mg/m^2/day IV continuous from Day 1-5 of each 3-week cycle.

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 IV on Day 1 of each week in 3-week cycles (6 cycle maximum per local country guidelines).

Number of subjects in period 1	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)
Started	256	257	250
Received First Course of Pembrolizumab	254	250	244
Received Second Course of Pembrolizumab	4	5	0
Completed	0	0	0
Not completed	256	257	250
Consent withdrawn by subject	7	15	15
Screen Failure	-	1	-
Transferred to Extension Study	15	15	6
Death	224	214	225
Lost to follow-up	1	-	-
Did Not Continue on Extension Study	8	10	4
Protocol deviation	1	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab Monotherapy (Pembro Mono)
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.	
Reporting group title	Pembrolizumab + SOC Chemotherapy (Pembro Combo)
Reporting group description:	
Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-fluorouracil (5-FU) 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.	
Reporting group title	Placebo + SOC Chemotherapy (SOC)
Reporting group description:	
Participants received placebo IV Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.	

Reporting group values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)
Number of subjects	256	257	250
Age categorical Units: Subjects			
Adults (18-64 years)	154	152	139
From 65-84 years	102	105	108
85 years and over	0	0	3
Age Continuous Units: Years			
arithmetic mean	59.9	60.9	60.7
standard deviation	± 11.6	± 11.6	± 12.7
Sex: Female, Male Units: Participants			
Female	76	62	71
Male	180	195	179
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	9	7	13
Asian	69	71	67
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	4	4	5
White	164	167	154
More than one race	9	6	7
Unknown or Not Reported	0	2	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	45	54	46

Not Hispanic or Latino	206	196	197
Unknown or Not Reported	5	7	7
Region of Enrollment			
Participants were stratified according to geographic region of enrolling site: Europe (including Israel)/North America/Australia, Asia (including East Asia [South Korea, Hong Kong, Taiwan], South East Asia [Malaysia], Thailand, Singapore, Japan), or Rest of the World (including South America).			
Units: Subjects			
Europe/North America/Australia	148	148	147
Asia	62	64	61
Rest of the World	46	45	42
Disease Status			
Participants were stratified according to gastric cancer disease status as either locally advanced unresectable or metastatic disease.			
Units: Subjects			
Locally advanced	10	12	13
Metastatic	245	243	235
Missing	1	2	2
Fluoropyrimidine Treatment			
Participants receiving SOC chemotherapy were stratified according to fluoropyrimidine treatment (5-FU or capecitabine).			
Units: Subjects			
5-FU	97	98	95
Capecitabine	159	159	155

Reporting group values	Total		
Number of subjects	763		
Age categorical			
Units: Subjects			
Adults (18-64 years)	445		
From 65-84 years	315		
85 years and over	3		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	209		
Male	554		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	29		
Asian	207		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	13		
White	485		
More than one race	22		
Unknown or Not Reported	5		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	145		
Not Hispanic or Latino	599		

Unknown or Not Reported	19		
Region of Enrollment			
Participants were stratified according to geographic region of enrolling site: Europe (including Israel)/North America/Australia, Asia (including East Asia [South Korea, Hong Kong, Taiwan], South East Asia [Malaysia], Thailand, Singapore, Japan), or Rest of the World (including South America).			
Units: Subjects			
Europe/North America/Australia	443		
Asia	187		
Rest of the World	133		
Disease Status			
Participants were stratified according to gastric cancer disease status as either locally advanced unresectable or metastatic disease.			
Units: Subjects			
Locally advanced	35		
Metastatic	723		
Missing	5		
Fluoropyrimidine Treatment			
Participants receiving SOC chemotherapy were stratified according to fluoropyrimidine treatment (5-FU or capecitabine).			
Units: Subjects			
5-FU	290		
Capecitabine	473		

End points reporting groups

Reporting group title	Pembrolizumab Monotherapy (Pembro Mono)

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Pembrolizumab + SOC Chemotherapy (Pembro Combo)

Reporting group description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-fluorouracil (5-FU) 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Placebo + SOC Chemotherapy (SOC)

Reporting group description:

Participants received placebo IV Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

Primary: Pembro Combo vs SOC: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Combo vs SOC: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

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

Per protocol, PFS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the Intent-To-Treat (ITT) population. PFS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, PFS was compared separately between CPS ≥1 participants of the pembro mono arm and SOC arm and is presented later in the record.

All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 36 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	257	250	
Units: Months				
median (confidence interval 95%)	(to)	6.9 (5.7 to 7.3)	6.4 (5.7 to 7.0)	

Notes:

[1] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	PFS: Pembro Combo vs SOC, CPS ≥1

Statistical analysis description:

PFS in CPS ≥1 participants of the pembro combo arm was compared to PFS in CPS ≥1 participants of the SOC arm to address the first primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and fluoropyrimidine treatment.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.03918 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.02

Notes:

[2] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Combo vs SOC: Overall Survival (OS) in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Combo vs SOC: Overall Survival (OS) in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, OS was compared separately between CPS ≥1 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	257	250	
Units: Months				
median (confidence interval 95%)	(to)	12.5 (10.8 to 13.9)	11.1 (9.2 to 12.8)	

Notes:

[3] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	OS: Pembro Combo vs SOC, CPS ≥1

Statistical analysis description:

OS in CPS ≥1 participants of the pembro combo arm was compared to OS in CPS ≥1 participants of the SOC arm to address the second primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04611 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.03

Notes:

[4] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Combo vs SOC: OS in Participants With PD-L1 CPS ≥10

End point title	Pembro Combo vs SOC: OS in Participants With PD-L1 CPS ≥10

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥10. Per protocol, OS was compared separately between CPS ≥10 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥10 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	99	90	
Units: Months				
median (confidence interval 95%)	(to)	12.3 (9.5 to 14.8)	10.8 (8.5 to 13.8)	

Notes:

[5] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	OS: Pembro Combo vs SOC, CPS ≥10

Statistical analysis description:

OS in CPS ≥10 participants of the pembro combo arm was compared to OS in CPS ≥10 participants of the SOC arm to address the third primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.15804 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.17

Notes:

[6] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, OS was compared separately between CPS ≥1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	256	0[7]	250	
Units: Months				
median (confidence interval 95%)	10.6 (7.7 to 13.8)	(to)	11.1 (9.2 to 12.8)	

Notes:

[7] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	OS non-inferiority: Pembro Mono vs SOC, CPS ≥1

Statistical analysis description:

OS in CPS ≥1 participants of the pembro mono arm was compared to OS in CPS ≥1 participants of the SOC arm to address the fourth primary hypothesis (non-inferiority to SOC). The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.69
upper limit	1.18

Statistical analysis title	OS superiority: Pembro Mono vs SOC, CPS ≥1

Statistical analysis description:

OS in CPS ≥1 participants of the pembro mono arm was compared to OS in CPS ≥1 participants of the SOC arm to address the fifth primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)

Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.16205 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.1

Notes:

[8] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥10

End point title	Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥10

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥10. Per protocol, OS was compared separately between CPS ≥10 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥10 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	0[9]	90	
Units: Months				
median (confidence interval 95%)	17.4 (9.1 to 23.1)	(to)	10.8 (8.5 to 13.8)	

Notes:

[9] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	OS: Pembro Mono vs SOC, CPS ≥10

Statistical analysis description:

OS in CPS ≥10 participants of the pembro mono arm was compared to OS in CPS ≥10 participants of the SOC arm to address the sixth primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01491 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.97

Notes:

[10] - One-sided p-value based on log-rank test with stratification.

Secondary: Pembro Combo vs SOC: Objective Response Rate (ORR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Combo vs SOC: Objective Response Rate (ORR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

ORR was defined as the percentage of participants in the analysis population who have 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. based upon BICR. Per protocol, ORR in the pembro combo arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. The percentage of participants who experienced CR or PR is reported here as the ORR for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	257	250	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	48.6 (42.4 to 54.9)	37.2 (31.2 to 43.5)	

Notes:

[11] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	ORR: Pembro Combo vs SOC, CPS ≥1

Statistical analysis description:

ORR in CPS ≥1 participants of the pembro combo arm was compared to ORR in CPS ≥1 participants of the SOC arm based on Miettinen & Nurminen method stratified by geographic region, disease status,

and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00447 [12]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	20

Notes:

[12] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs SOC: Duration of Response (DOR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Combo vs SOC: Duration of Response (DOR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death, 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. All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm and who demonstrated a confirmed CR or PR were analyzed. Values of 9999 indicate that the median DOR and DOR range lower and upper limits were not reached (no progressive disease by time of last disease assessment). Per protocol, DOR was compared separately between CPS ≥1 responders of the pembro mono arm and SOC arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	125	93	
Units: Months				
median (full range (min-max))	(to)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Notes:

[13] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs SOC: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Mono vs SOC: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. based upon BICR. Per protocol, ORR in the pembro mono arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. The percentage of participants who experienced CR or PR is reported here as the ORR for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	256	0[14]	250	
Units: Percentage of Participants				
number (confidence interval 95%)	14.8 (10.7 to 19.8)	(to)	37.2 (31.2 to 43.5)	

Notes:

[14] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	ORR: Pembro Mono vs SOC, CPS ≥1

Statistical analysis description:

ORR in CPS ≥1 participants of the pembro mono arm was compared to ORR in CPS ≥1 participants of the SOC arm based on Miettinen & Nurminen method stratified by geographic region, disease status, and Fluoropyrimidine treatment.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.99999 [15]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	-22.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.6
upper limit	-14.9

Notes:

[15] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs SOC: DOR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Mono vs SOC: DOR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death, 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. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm and who demonstrated a confirmed CR or PR were analyzed. Values of 9999 indicate that the median DOR and DOR range lower and upper limits were not reached (no progressive disease by time of last disease assessment). Per protocol, DOR was compared separately between CPS ≥1 responders of the pembro combo arm and SOC arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	0[16]	93	
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	(to)	9999 (9999 to 9999)	

Notes:

[16] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs SOC: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point title	Pembro Mono vs SOC: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

End point description:

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

Per protocol, PFS in the pembro mono arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. PFS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, PFS was compared separately between CPS ≥1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

End point type	Secondary
End point timeframe:	
Up to approximately 42 months	

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	256	0[17]	250	
Units: Months				
median (confidence interval 95%)	2.0 (1.5 to 2.8)	(to)	6.4 (5.7 to 7.1)	

Notes:

[17] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	ORR: Pembro Mono vs SOC, CPS ≥1

Statistical analysis description:

PFS in CPS ≥1 participants of the pembro mono arm was compared to PFS in CPS ≥1 participants of the SOC arm based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and fluoropyrimidine treatment.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	
P-value	= 1 [18]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	1.98

Notes:

[18] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs SOC: Change from Baseline to Week 18 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point title	Pembro Mono vs SOC: Change from Baseline to Week 18 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score

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. Participants in the pembro mono arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-C30 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro combo arm and SOC arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	251	0[19]	243	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-1.91 (-5.81 to 1.98)	(to)	-1.75 (-5.17 to 1.66)	

Notes:

[19] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL: Pembro Mono vs SOC

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro mono arm and the SOC arm. Comparison based on constrained longitudinal data analysis (cLDA) model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.948 [20]
Method	cLDA
Parameter estimate	Difference in LS Means
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.01
upper limit	4.69

Notes:

[20] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs SOC: Change from Baseline to Week 18 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point title	Pembro Combo vs SOC: Change from Baseline to Week 18 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

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 GHS question "How would you rate your overall health during the past week?" (Item 29) and the 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. Participants in the pembro combo arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-C30 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro mono arm and SOC arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[21]	245	243	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	-0.09 (-3.36 to 3.19)	-2.07 (-5.43 to 1.29)	

Notes:

[21] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	EORTC-QLQ-C30 GHS/QoL: Pembro Combo vs SOC

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro combo arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)

Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.368 [22]
Method	cLDA
Parameter estimate	Difference in LS Means
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	6.31

Notes:

[22] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-Module for Gastric Cancer (STO22) Pain Symptom Subscale Score

End point title	Pembro Mono vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-Module for Gastric Cancer (STO22) Pain Symptom Subscale Score

End point description:

EORTC-QLQ-STO22 is a 22-item questionnaire developed to assess QoL of gastric cancer participants. It consists of 5 multi-item subscales that assess dysphagia (3 items), dietary restriction (4 items), pain (4 items), upper gastro-esophageal symptoms (3 items), and emotional problems (3 items), and questions on dry mouth, taste, body image, and hair loss. Participant responses to the Pain symptom subscale (Items 34-37) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Participants in the pembro mono arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-STO22 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the EORTC-QLQ-STO22 Pain score was compared separately between the pembro combo arm and SOC arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	251	0[23]	243	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	-1.14 (-4.67 to 2.39)	(to)	-3.49 (-6.60 to -0.38)	

Notes:

[23] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	EORTC-QLQ-STO22: Pembro Mono vs SOC

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-STO22 Pain symptom subscale score was compared between all participants of the pembro mono arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.308 [24]
Method	cLDA
Parameter estimate	Difference in LS Means
Point estimate	2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	6.89

Notes:

[24] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-STO22 Pain Symptom Subscale Score

End point title	Pembro Combo vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-STO22 Pain Symptom Subscale Score

End point description:

EORTC-QLQ-STO22 is a 22-item questionnaire developed to assess QoL of gastric cancer participants. It consists of 5 multi-item subscales that assess dysphagia (3 items), dietary restriction (4 items), pain (4 items), upper gastro-esophageal symptoms (3 items), and emotional problems (3 items), and questions on dry mouth, taste, body image, and hair loss. Participant responses to the Pain symptom subscale (Items 34-37) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Participants in the pembro combo arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-STO22 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the EORTC-QLQ-STO22 Pain score was compared separately between the pembro mono arm and SOC arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	245	243	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	-10.12 (-13.08 to -7.17)	-3.56 (-6.61 to -0.51)	

Notes:

[25] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Statistical analysis title	EORTC-QLQ-STO22: Pembro Combo vs SOC

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-STO22 Pain symptom subscale score was compared between all participants of the pembro combo arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

Comparison groups	Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC)
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001 [26]
Method	cLDA
Parameter estimate	Difference in LS Means
Point estimate	-6.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.55
upper limit	-2.58

Notes:

[26] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

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 did not necessarily 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 adverse event. The number of participants who experienced an AE was reported for each arm according to the treatment received. All randomized participants who received at least 1 dose of trial treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 33 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	254	250	244	
Units: Participants	242	244	240	

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 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 adverse event. The number of participants who discontinued study treatment due to an AE was reported for each arm according to the treatment received. All randomized participants who received at least 1 dose of trial treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + SOC Chemotherapy (Pembro Combo)	Placebo + SOC Chemotherapy (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	254	250	244	
Units: Participants	29	85	58	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 78 months

Adverse event reporting additional description:

All-Cause Mortality reported for all randomized participants. Serious AEs and Other AEs were reported for all randomized participants who received at least 1 dose of study treatment. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Pembrolizumab Monotherapy (Pembro Mono) First Course

Reporting group description:

Participants received pembrolizumab 200 mg IV Q3W.

Reporting group title	Pembrolizumab + SOC Chemotherapy (Pembro Combo)-First Course

Reporting group description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

Reporting group title	Pembrolizumab + SOC Chemotherapy-Second Course

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to 35 treatments [approximately 2 years]) administered in combination with SOC chemotherapy, and experienced Stable Disease (SD) or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (up to approximately 1 additional year).

Reporting group title	Pembrolizumab Monotherapy Second Course

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to 35 treatments [approximately 2 years]) with Stable Disease (SD) or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (up to approximately 1 additional year).

Reporting group title	Placebo + SOC Chemotherapy (SOC)-First Course

Reporting group description:

Participants received placebo IV Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

Serious adverse events	Pembrolizumab Monotherapy (Pembro Mono) First Course	Pembrolizumab + SOC Chemotherapy (Pembro Combo)-First Course	Pembrolizumab + SOC Chemotherapy-Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 254 (36.61%)	122 / 250 (48.80%)	0 / 5 (0.00%)
number of deaths (all causes)	229	232	1
number of deaths resulting from adverse events	3	5	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Oncologic complication			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Rectal cancer			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Malignant neoplasm progression			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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

Hypertension			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Hypotension			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial vein thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 254 (0.00%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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

Non-cardiac chest pain			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 254 (0.79%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Fatigue			
subjects affected / exposed	1 / 254 (0.39%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	6 / 254 (2.36%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 6	0 / 3	0 / 0
Pain			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 254 (0.79%)	5 / 250 (2.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Epistaxis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 254 (0.79%)	8 / 250 (3.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 2	6 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Pneumonitis			
subjects affected / exposed	3 / 254 (1.18%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 254 (0.79%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Completed suicide			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood calcium decreased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood magnesium decreased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Lower limb fracture			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Anastomotic stenosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Procedural pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Arrhythmia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Bradycardia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Pericardial effusion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Extrasystoles			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Cardiac failure			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Cerebral infarction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Cerebral thrombosis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral venous sinus thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Dizziness postural			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Ischaemic stroke			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Presyncope			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Seizure			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 254 (0.00%)	9 / 250 (3.60%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	8 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Anaemia			
subjects affected / exposed	3 / 254 (1.18%)	12 / 250 (4.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 3	11 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 254 (0.00%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Hypochromic anaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Thrombocytopenia			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 254 (0.39%)	6 / 250 (2.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 254 (0.39%)	4 / 250 (1.60%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Abdominal pain lower			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Abdominal distension			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Abdominal pain			
subjects affected / exposed	1 / 254 (0.39%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 254 (0.79%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Gastric haemorrhage			
subjects affected / exposed	5 / 254 (1.97%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	2 / 254 (0.79%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Dysphagia			
subjects affected / exposed	2 / 254 (0.79%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 254 (0.39%)	7 / 250 (2.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	6 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	3 / 254 (1.18%)	0 / 250 (0.00%)	0 / 5 (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
Constipation			
subjects affected / exposed	1 / 254 (0.39%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 254 (0.00%)	5 / 250 (2.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Oesophageal obstruction			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	2 / 254 (0.79%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated hiatus hernia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Inguinal hernia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Intestinal perforation			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Mechanical ileus			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Pancreatitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 254 (1.18%)	6 / 250 (2.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 3	3 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 254 (1.18%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary hypersecretion			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Peritoneocutaneous fistula			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Subileus			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Cholangitis acute			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Hepatitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Cholangitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Jaundice cholestatic			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Jaundice			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Hypertransaminasaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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 disorder			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 254 (1.57%)	8 / 250 (3.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 4	5 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Autoimmune nephritis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 254 (0.79%)	0 / 250 (0.00%)	0 / 5 (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
Prerenal failure			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	1 / 254 (0.39%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			

subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Compartment syndrome			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Myalgia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Myositis			
subjects affected / exposed	2 / 254 (0.79%)	0 / 250 (0.00%)	0 / 5 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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

Appendicitis perforated			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Appendicitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Amoebiasis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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 sepsis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Biliary tract infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida sepsis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Endocarditis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Device related infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 254 (0.79%)	0 / 250 (0.00%)	0 / 5 (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
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Meningitis tuberculous			

subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis bacterial			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Pneumonia			
subjects affected / exposed	5 / 254 (1.97%)	7 / 250 (2.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 5	3 / 7	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Prostate infection			

subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Pulmonary tuberculosis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Urosepsis			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Wound infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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			
Cachexia			
subjects affected / exposed	2 / 254 (0.79%)	0 / 250 (0.00%)	0 / 5 (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
Decreased appetite			
subjects affected / exposed	3 / 254 (1.18%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 254 (0.00%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			

subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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
Dehydration			
subjects affected / exposed	1 / 254 (0.39%)	7 / 250 (2.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	6 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 254 (0.39%)	2 / 250 (0.80%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 254 (0.00%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	5 / 254 (1.97%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	2 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refeeding syndrome			

subjects affected / exposed	0 / 254 (0.00%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 254 (0.39%)	1 / 250 (0.40%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 254 (0.00%)	1 / 250 (0.40%)	0 / 5 (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
Malnutrition			
subjects affected / exposed	1 / 254 (0.39%)	0 / 250 (0.00%)	0 / 5 (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

Serious adverse events	Pembrolizumab Monotherapy Second Course	Placebo + SOC Chemotherapy (SOC)-First Course	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	117 / 244 (47.95%)	
number of deaths (all causes)	2	240	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mucosal inflammation			

subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	5 / 244 (2.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	13 / 244 (5.33%)	
occurrences causally related to treatment / all	0 / 0	9 / 13	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Depression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anastomotic stenosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
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	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 4 (0.00%)	7 / 244 (2.87%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	10 / 244 (4.10%)	
occurrences causally related to treatment / all	0 / 0	12 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	5 / 244 (2.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	9 / 244 (3.69%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 4 (0.00%)	5 / 244 (2.05%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hiatus hernia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
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	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	12 / 244 (4.92%)	
occurrences causally related to treatment / all	0 / 0	11 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneocutaneous fistula			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	8 / 244 (3.28%)	
occurrences causally related to treatment / all	0 / 0	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebiasis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	8 / 244 (3.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pneumonia aspiration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	4 / 244 (1.64%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	5 / 244 (2.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	5 / 244 (2.05%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	7 / 244 (2.87%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refeeding syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 4 (0.00%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pembrolizumab Monotherapy (Pembro Mono) First Course	Pembrolizumab + SOC Chemotherapy (Pembro Combo)-First Course	Pembrolizumab + SOC Chemotherapy-Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	216 / 254 (85.04%)	239 / 250 (95.60%)	5 / 5 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 254 (4.33%)	10 / 250 (4.00%)	1 / 5 (20.00%)
occurrences (all)	12	13	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 254 (1.57%)	14 / 250 (5.60%)	0 / 5 (0.00%)
occurrences (all)	6	16	0
Fatigue			
subjects affected / exposed	49 / 254 (19.29%)	105 / 250 (42.00%)	0 / 5 (0.00%)
occurrences (all)	63	156	0
Mucosal inflammation			
subjects affected / exposed	3 / 254 (1.18%)	41 / 250 (16.40%)	0 / 5 (0.00%)
occurrences (all)	5	57	0
Oedema peripheral			
subjects affected / exposed	13 / 254 (5.12%)	16 / 250 (6.40%)	0 / 5 (0.00%)
occurrences (all)	14	16	0
Pyrexia			
subjects affected / exposed	25 / 254 (9.84%)	32 / 250 (12.80%)	0 / 5 (0.00%)
occurrences (all)	33	38	0
Asthenia			

subjects affected / exposed	30 / 254 (11.81%)	41 / 250 (16.40%)	0 / 5 (0.00%)
occurrences (all)	33	53	0
Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	1 / 254 (0.39%)	16 / 250 (6.40%)	0 / 5 (0.00%)
occurrences (all)	1	20	0
Epistaxis			
subjects affected / exposed	0 / 254 (0.00%)	5 / 250 (2.00%)	1 / 5 (20.00%)
occurrences (all)	0	5	1
Dyspnoea			
subjects affected / exposed	11 / 254 (4.33%)	19 / 250 (7.60%)	0 / 5 (0.00%)
occurrences (all)	16	23	0
Dysphonia			
subjects affected / exposed	3 / 254 (1.18%)	1 / 250 (0.40%)	1 / 5 (20.00%)
occurrences (all)	3	1	1
Cough			
subjects affected / exposed	19 / 254 (7.48%)	24 / 250 (9.60%)	0 / 5 (0.00%)
occurrences (all)	23	26	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 254 (8.27%)	18 / 250 (7.20%)	1 / 5 (20.00%)
occurrences (all)	21	19	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 254 (3.15%)	30 / 250 (12.00%)	0 / 5 (0.00%)
occurrences (all)	8	52	0
Alanine aminotransferase increased			
subjects affected / exposed	13 / 254 (5.12%)	7 / 250 (2.80%)	0 / 5 (0.00%)
occurrences (all)	16	8	0
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 254 (7.09%)	9 / 250 (3.60%)	0 / 5 (0.00%)
occurrences (all)	22	10	0
White blood cell count decreased			
subjects affected / exposed	4 / 254 (1.57%)	30 / 250 (12.00%)	0 / 5 (0.00%)
occurrences (all)	6	71	0
Weight decreased			

subjects affected / exposed	28 / 254 (11.02%)	54 / 250 (21.60%)	0 / 5 (0.00%)
occurrences (all)	28	63	0
Platelet count decreased			
subjects affected / exposed	3 / 254 (1.18%)	23 / 250 (9.20%)	0 / 5 (0.00%)
occurrences (all)	3	38	0
Neutrophil count decreased			
subjects affected / exposed	4 / 254 (1.57%)	59 / 250 (23.60%)	0 / 5 (0.00%)
occurrences (all)	15	120	0
Blood uric acid increased			
subjects affected / exposed	2 / 254 (0.79%)	0 / 250 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 254 (5.51%)	20 / 250 (8.00%)	0 / 5 (0.00%)
occurrences (all)	18	21	0
Headache			
subjects affected / exposed	16 / 254 (6.30%)	24 / 250 (9.60%)	0 / 5 (0.00%)
occurrences (all)	18	26	0
Neuropathy peripheral			
subjects affected / exposed	0 / 254 (0.00%)	31 / 250 (12.40%)	0 / 5 (0.00%)
occurrences (all)	0	36	0
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 254 (1.18%)	34 / 250 (13.60%)	0 / 5 (0.00%)
occurrences (all)	3	37	0
Dysgeusia			
subjects affected / exposed	4 / 254 (1.57%)	16 / 250 (6.40%)	0 / 5 (0.00%)
occurrences (all)	4	18	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 254 (24.02%)	112 / 250 (44.80%)	0 / 5 (0.00%)
occurrences (all)	73	150	0
Leukopenia			
subjects affected / exposed	0 / 254 (0.00%)	21 / 250 (8.40%)	0 / 5 (0.00%)
occurrences (all)	0	52	0
Neutropenia			

subjects affected / exposed	1 / 254 (0.39%)	95 / 250 (38.00%)	0 / 5 (0.00%)
occurrences (all)	2	201	0
Thrombocytopenia			
subjects affected / exposed	2 / 254 (0.79%)	27 / 250 (10.80%)	0 / 5 (0.00%)
occurrences (all)	5	38	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 254 (0.00%)	22 / 250 (8.80%)	0 / 5 (0.00%)
occurrences (all)	0	24	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	13 / 254 (5.12%)	9 / 250 (3.60%)	0 / 5 (0.00%)
occurrences (all)	21	11	0
Abdominal discomfort			
subjects affected / exposed	2 / 254 (0.79%)	6 / 250 (2.40%)	0 / 5 (0.00%)
occurrences (all)	2	7	0
Abdominal pain			
subjects affected / exposed	46 / 254 (18.11%)	41 / 250 (16.40%)	1 / 5 (20.00%)
occurrences (all)	56	49	1
Abdominal pain upper			
subjects affected / exposed	23 / 254 (9.06%)	24 / 250 (9.60%)	0 / 5 (0.00%)
occurrences (all)	26	27	0
Ascites			
subjects affected / exposed	6 / 254 (2.36%)	8 / 250 (3.20%)	0 / 5 (0.00%)
occurrences (all)	7	8	0
Constipation			
subjects affected / exposed	36 / 254 (14.17%)	71 / 250 (28.40%)	0 / 5 (0.00%)
occurrences (all)	43	108	0
Diarrhoea			
subjects affected / exposed	35 / 254 (13.78%)	83 / 250 (33.20%)	0 / 5 (0.00%)
occurrences (all)	60	153	0
Dyspepsia			
subjects affected / exposed	16 / 254 (6.30%)	13 / 250 (5.20%)	0 / 5 (0.00%)
occurrences (all)	18	18	0
Dysphagia			

subjects affected / exposed	11 / 254 (4.33%)	15 / 250 (6.00%)	0 / 5 (0.00%)
occurrences (all)	11	17	0
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 254 (3.15%)	6 / 250 (2.40%)	0 / 5 (0.00%)
occurrences (all)	8	7	0
Nausea			
subjects affected / exposed	49 / 254 (19.29%)	162 / 250 (64.80%)	0 / 5 (0.00%)
occurrences (all)	59	295	0
Stomatitis			
subjects affected / exposed	5 / 254 (1.97%)	33 / 250 (13.20%)	0 / 5 (0.00%)
occurrences (all)	6	49	0
Vomiting			
subjects affected / exposed	49 / 254 (19.29%)	84 / 250 (33.60%)	0 / 5 (0.00%)
occurrences (all)	64	148	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	20 / 254 (7.87%)	31 / 250 (12.40%)	1 / 5 (20.00%)
occurrences (all)	23	41	1
Pruritus			
subjects affected / exposed	22 / 254 (8.66%)	21 / 250 (8.40%)	1 / 5 (20.00%)
occurrences (all)	27	25	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 254 (0.00%)	60 / 250 (24.00%)	0 / 5 (0.00%)
occurrences (all)	0	69	0
Dry skin			
subjects affected / exposed	6 / 254 (2.36%)	15 / 250 (6.00%)	0 / 5 (0.00%)
occurrences (all)	6	16	0
Alopecia			
subjects affected / exposed	2 / 254 (0.79%)	19 / 250 (7.60%)	0 / 5 (0.00%)
occurrences (all)	2	19	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 254 (0.00%)	3 / 250 (1.20%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	21 / 254 (8.27%)	28 / 250 (11.20%)	0 / 5 (0.00%)
occurrences (all)	21	29	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 254 (7.48%)	22 / 250 (8.80%)	0 / 5 (0.00%)
occurrences (all)	20	25	0
Back pain			
subjects affected / exposed	30 / 254 (11.81%)	13 / 250 (5.20%)	0 / 5 (0.00%)
occurrences (all)	32	14	0
Pain in extremity			
subjects affected / exposed	4 / 254 (1.57%)	17 / 250 (6.80%)	0 / 5 (0.00%)
occurrences (all)	4	23	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 254 (3.15%)	13 / 250 (5.20%)	0 / 5 (0.00%)
occurrences (all)	8	13	0
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	3 / 254 (1.18%)	34 / 250 (13.60%)	0 / 5 (0.00%)
occurrences (all)	11	43	0
Hyponatraemia			
subjects affected / exposed	15 / 254 (5.91%)	12 / 250 (4.80%)	0 / 5 (0.00%)
occurrences (all)	16	21	0
Hypophosphataemia			
subjects affected / exposed	2 / 254 (0.79%)	15 / 250 (6.00%)	0 / 5 (0.00%)
occurrences (all)	2	21	0
Hypokalaemia			
subjects affected / exposed	11 / 254 (4.33%)	35 / 250 (14.00%)	0 / 5 (0.00%)
occurrences (all)	16	49	0
Hypocalcaemia			
subjects affected / exposed	9 / 254 (3.54%)	14 / 250 (5.60%)	0 / 5 (0.00%)
occurrences (all)	10	20	0
Hypoalbuminaemia			
subjects affected / exposed	18 / 254 (7.09%)	17 / 250 (6.80%)	0 / 5 (0.00%)
occurrences (all)	21	21	0

Dehydration			
subjects affected / exposed	7 / 254 (2.76%)	11 / 250 (4.40%)	0 / 5 (0.00%)
occurrences (all)	7	14	0
Decreased appetite			
subjects affected / exposed	48 / 254 (18.90%)	94 / 250 (37.60%)	0 / 5 (0.00%)
occurrences (all)	53	135	0

Non-serious adverse events	Pembrolizumab Monotherapy Second Course	Placebo + SOC Chemotherapy (SOC)-First Course	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	234 / 244 (95.90%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	12 / 244 (4.92%)	
occurrences (all)	2	17	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	7 / 244 (2.87%)	
occurrences (all)	0	7	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	75 / 244 (30.74%)	
occurrences (all)	0	112	
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	34 / 244 (13.93%)	
occurrences (all)	0	62	
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	19 / 244 (7.79%)	
occurrences (all)	0	22	
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	25 / 244 (10.25%)	
occurrences (all)	0	26	
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	47 / 244 (19.26%)	
occurrences (all)	0	81	
Respiratory, thoracic and mediastinal disorders			

Hiccups			
subjects affected / exposed	0 / 4 (0.00%)	12 / 244 (4.92%)	
occurrences (all)	0	21	
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	10 / 244 (4.10%)	
occurrences (all)	0	12	
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	9 / 244 (3.69%)	
occurrences (all)	0	11	
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	0 / 4 (0.00%)	23 / 244 (9.43%)	
occurrences (all)	0	26	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	22 / 244 (9.02%)	
occurrences (all)	0	24	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	34 / 244 (13.93%)	
occurrences (all)	0	59	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	9 / 244 (3.69%)	
occurrences (all)	0	9	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	11 / 244 (4.51%)	
occurrences (all)	0	12	
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	25 / 244 (10.25%)	
occurrences (all)	0	52	
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	33 / 244 (13.52%)	
occurrences (all)	0	33	
Platelet count decreased			

subjects affected / exposed	0 / 4 (0.00%)	17 / 244 (6.97%)	
occurrences (all)	0	21	
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	40 / 244 (16.39%)	
occurrences (all)	0	79	
Blood uric acid increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 244 (0.41%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	15 / 244 (6.15%)	
occurrences (all)	0	22	
Headache			
subjects affected / exposed	0 / 4 (0.00%)	16 / 244 (6.56%)	
occurrences (all)	0	22	
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	16 / 244 (6.56%)	
occurrences (all)	0	17	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	16 / 244 (6.56%)	
occurrences (all)	0	18	
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	20 / 244 (8.20%)	
occurrences (all)	0	21	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 4 (75.00%)	108 / 244 (44.26%)	
occurrences (all)	3	144	
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	26 / 244 (10.66%)	
occurrences (all)	0	51	
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	102 / 244 (41.80%)	
occurrences (all)	0	222	
Thrombocytopenia			

subjects affected / exposed	0 / 4 (0.00%)	26 / 244 (10.66%)	
occurrences (all)	0	33	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	20 / 244 (8.20%)	
occurrences (all)	0	20	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	10 / 244 (4.10%)	
occurrences (all)	0	10	
Abdominal discomfort			
subjects affected / exposed	1 / 4 (25.00%)	2 / 244 (0.82%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	41 / 244 (16.80%)	
occurrences (all)	0	54	
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	23 / 244 (9.43%)	
occurrences (all)	0	25	
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	14 / 244 (5.74%)	
occurrences (all)	0	15	
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	68 / 244 (27.87%)	
occurrences (all)	0	83	
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	71 / 244 (29.10%)	
occurrences (all)	0	106	
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	11 / 244 (4.51%)	
occurrences (all)	0	13	
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	16 / 244 (6.56%)	
occurrences (all)	0	20	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 4 (0.00%)	13 / 244 (5.33%)	
occurrences (all)	0	14	
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	129 / 244 (52.87%)	
occurrences (all)	0	236	
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	35 / 244 (14.34%)	
occurrences (all)	0	39	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	79 / 244 (32.38%)	
occurrences (all)	0	142	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	15 / 244 (6.15%)	
occurrences (all)	0	18	
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	8 / 244 (3.28%)	
occurrences (all)	1	11	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 4 (0.00%)	46 / 244 (18.85%)	
occurrences (all)	0	57	
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	15 / 244 (6.15%)	
occurrences (all)	0	15	
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	11 / 244 (4.51%)	
occurrences (all)	0	11	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)	2 / 244 (0.82%)	
occurrences (all)	1	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	10 / 244 (4.10%)	
occurrences (all)	0	11	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	7 / 244 (2.87%)	
occurrences (all)	0	7	
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	14 / 244 (5.74%)	
occurrences (all)	0	15	
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	8 / 244 (3.28%)	
occurrences (all)	0	9	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 244 (0.82%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	32 / 244 (13.11%)	
occurrences (all)	0	48	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	20 / 244 (8.20%)	
occurrences (all)	0	26	
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	9 / 244 (3.69%)	
occurrences (all)	0	16	
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	42 / 244 (17.21%)	
occurrences (all)	0	61	
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	14 / 244 (5.74%)	
occurrences (all)	0	16	
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	23 / 244 (9.43%)	
occurrences (all)	0	28	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	16 / 244 (6.56%)	
occurrences (all)	0	19	
Decreased appetite			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	90 / 244 (36.89%) 127	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2016	Major changes of Amendment (AM) 3 include clarification of Inclusion and Exclusion Criteria and revision of Withdrawal/Discontinuation Criteria.
06 October 2016	Major changes of AM 5 include revision of Inclusion and Exclusion Criteria.
08 March 2017	Major changes of AM 6 include removing primary PFS hypothesis comparing pembrolizumab monotherapy to SOC, and adding primary OS hypothesis evaluating non-inferiority of pembrolizuman monotherapy. Secondary ORR hypothesis comparing pembrolizumab plus SOC vs. SOC was added.
15 January 2018	Major changes of AM 8 included revising dose modification language and adding survival status follow-up to the study.
11 May 2018	Major changes of AM 10 included the addition of 2 primary hypotheses for OS: pembrolizumab plus SOC vs. SOC, and pembrolizumab monotherapy vs. SOC in participants with CPS≥10.
22 January 2019	Major changes of AM 12 included revision of Prohibited Concomitant Medication language and safety follow-up language.
02 August 2021	Major changes of AM 14 included the revision of sections of the protocol including the Trial Summary and Study Diagram to include study extension language, and updating the Dose Modification and Toxicity Management Guidelines for immune response AEs per Food and Drug Administration request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported